24
Cytomegalovirus Infection After Stem Cell Transplantation

Morgan Hakki and Per Ljungman

24.1 Virus Structure and Replication

Human cytomegalovirus (CMV) is a member of the beta (β) herpesvirus subfamily, along with human herpesvirus (HHV)-6 and HHV-7. The CMV virion shares structural similarities with other herpesviridae. Namely, the double-stranded DNA genome is encased within an icosahedral capsid, which in turn is surrounded by a proteinaceous tegument (or matrix). A lipid membrane containing surface viral glycoproteins that function in host cell binding and entry is the outermost component of the virion.

The CMV genome is approximately 230 kb, making CMV one of the largest among human viruses, and is organized into unique long (UL) and unique short (US) segments that are flanked by inverted genomic repeats. Most CMV genes are named according to their position within the genome based on the reference strain AD169 [1]. For example, UL97 is the 97th open reading frame (ORF) in the UL segment and US28 is the 28th ORF in the US segment. CMV genes may also have names that reflect historical usage, function, or homology to genes of other herpesviruses.

Like all herpesviruses, CMV establishes latency after primary infection, during which replication-competent virus remains present in the infected cell but evidence of viral replication is undetectable until triggered to reactivate. The viral and host factors that regulate latency and reactivation are poorly understood [2]. The site(s) of latency are not well defined but bone marrow stem cells of the myeloid lineage such as CD34+ and CD14+ cells have been shown to be one site of CMV latency [3, 4]. It has also been shown that the allogeneic effect can contribute to reactivation from peripheral blood mononuclear cells [5]. Since CMV can be transmitted from donor to recipient during solid organ transplant [6], parenchymal cells in these organs may also harbor latent virus.

24.2 CMV and the Host Immune System

24.2.1 Adaptive Immunity

Infection with CMV is associated with pronounced induction of $CD4^+$ and $CD8^+$ T cell responses. Immunodominant T cells responses are directed primarily against the gene products of UL123 (IE-1) and UL83 (pp65) [7–12]. However, CMV-specific T-cell immunity is now recognized as complex due to the large numbers of antigens, both lytic and latency-associated, that have been found to be targeted by T-cell responses [13–16]. Numerous studies have documented the importance of both CMV-specific $CD8^+$ and $CD4^+$ responses in determining the incidence and outcome CMV infection after allogeneic HCT [17–26]. Similar findings have been observed after newer HCT techniques such as haploidentical HCT [27] and umbilical cord blood transplant (CBT) [28–30].

The contribution of humoral immunity in controlling CMV replication is less clear. Antibodies to glycoprotein B (gB) and glycoprotein H (gH) predominate during infection [31–33], but while such antibodies may neutralize virus in tissue culture, their capacity to prevent primary infection is not well defined. While evidence suggests that antibody may serve to limit CMV dissemination and disease severity [34–36], lack of antibody does not alter the course of the primary MCMV infection in murine models [36]. Thus, the contribution of antibody to the control of CMV infection remains poorly understood.

24.2.2 Innate Immunity

Innate immunity plays a critical role in controlling herpesvirus infections through the production of inflammatory cytokines such as type I interferons (IFN α and β), interleukin 12

P. Ljungman et al. (eds.), *Transplant Infections*, DOI 10.1007/978-3-319-28797-3_24

(IL-12), and tumor necrosis factor (TNF) that exert a direct antiviral effect and induce adaptive immunity [37, 38]. The CMV glycoproteins gB and gH trigger the toll-like receptor 2 (TLR2) upon binding to the target cell [39–41]. In addition, viral DNA triggers TLR3 and TLR9 as well as the DNA sensor ZBP1 [42–47]. Attempts to correlate polymorphisms in donor and recipient TLRs and other innate immune sensors with CMV infection after HCT have yielded conflicting results that require further study [48–52].

Expansion of natural killer (NK) cells during CMV infection has been reported in both immunocompetent humans and after HCT [53–58]. While NK cells have been shown to limit MCMV replication in mice [59–63], their role in controlling CMV infection in humans is less clear although associative evidence strongly indicates an important contribution [22, 64, 65]. In addition, the genotype of the donor activating KIR (aKIR) has been demonstrated to influence the development of CMV infection after allogeneic HCT [66–68]. The mechanistic basis underlying these correlative findings is not well defined.

γδ T cells represent a minority (<6%) subset of circulating T cells in healthy individuals but are more prominent in peripheral sites such as mucosal surfaces [69]. Marked by the expression of receptors composed of γ and δ chains [38], as opposed to α and β chains associated with CD4+ and CD8+ responses, they respond to CMV infection with both in both innate- and adaptive- type immune function [70, 71]. CMV infection stimulates γδ T cell proliferation in both humans and mice, and deficient γδ T cell function has been associated with impaired regulation of CMV infection [70, 72–74].

24.2.3 Immune Evasion Mechanisms

As a successful human pathogen, CMV has necessarily evolved numerous mechanisms to evade and counteract virtually all aspects of the host immune response. Starting at the earliest stages of infection, CMV utilizes virion-associated and immediate-early proteins to effectively prevent host cell apoptosis, interferon-mediated pathways, and other innate immune responses such as shutoff of host cell protein synthesis in response to viral nucleic acid accumulation [75–79]. Multiple CMV proteins as well as the noncoding viral microRNAs miR-UL122 and miR-112 inhibit NK cell function [80–82].

A hallmark of CMV immune evasion is the blunting of CTL responses by inhibiting MHC-I restricted antigen presentation [83]. A number of CMV proteins contribute to this, including the tegument protein pp65 and genes of the US2-11 region [84–92]

Finally, CMV encodes several homologues of cellular proteins, including MHC class-I molecules, chemokine receptors, IL-10, TNF receptors, and CXC-1 homologues, that function to evade the host immune response [93–97].

24.3 Diagnostic Methods

The serologic determination of IgG and IgM has an important role in determining a patient's risk for CMV infection after HCT (see below, "Risk Factors") but is not useful in the diagnosis of active CMV infection or disease.

Histopathologic examination of tissue specimens remains the "gold standard" in the diagnosis of invasive CMV disease. In addition to observing nonspecific viral cytopathic effect in tissue, immunohistochemical techniques are used to identify CMV antigens (Figure 24-1a left and middle panels).

Growth of CMV in tissue culture takes several weeks, limiting its clinical usefulness as a diagnostic tool. Culture-proven viremia is highly predictive of CMV disease, but is of limited utility for screening since this finding frequently coincides with the onset of symptomatic disease [98–100].

The shell vial technique, in which monoclonal antibodies are used to detect CMV immediate-early proteins in cultured cells, can be performed within 18–24 h after inoculation. This assay is not sensitive enough to use for routine blood monitoring [99], but is highly useful on bronchoalveolar lavage (BAL) fluid in the diagnosis of CMV pneumonia due to its established specificity in this setting [101]. Many laboratories have abandoned culture-based techniques in favor of nucleic acid testing so that today these techniques have limited availability in many parts of the world.

The detection of the CMV pp65 tegument phosphoprotein in peripheral blood leukocytes offers a rapid, sensitive, and specific method of diagnosing and roughly quantitating CMV viremia. In the transplant setting, a positive or quantitatively increasing CMV pp65 assay has been shown to predict the development of invasive disease [102, 103] but is not always positive in the setting of proven end-organ disease, particularly gastrointestinal tract disease [104–107]. The predictive value of this assay has not been validated when performed on other body fluids such as BAL fluid. Since this assay relies on the detection of pp65 in circulating leukocytes, it may not be reliable in patients with profound leukopenia, such as in the pre-engraftment stage after HCT. At most centers, this assay has been replaced by nucleic acid testing primarily using quantitative polymerase chain reaction (qPCR).

qPCR relies on the amplification and quantitative measurement of CMV DNA. PCR is the most sensitive method for detecting CMV [108], while at the same time maintains high specificity. In addition, it is very rapid, with results usually available within 24 h, and does not rely on the presence of circulating leukocytes as does the pp65 antigenemia assay. qPCR provides a direct quantitative measurement of circulating CMV viral load, which is an accurate predictor of CMV disease after transplantation in most cases [109–113]. Like the pp65 antigenemia assay, serum or blood PCR may be negative in the setting of visceral disease [104, 106,

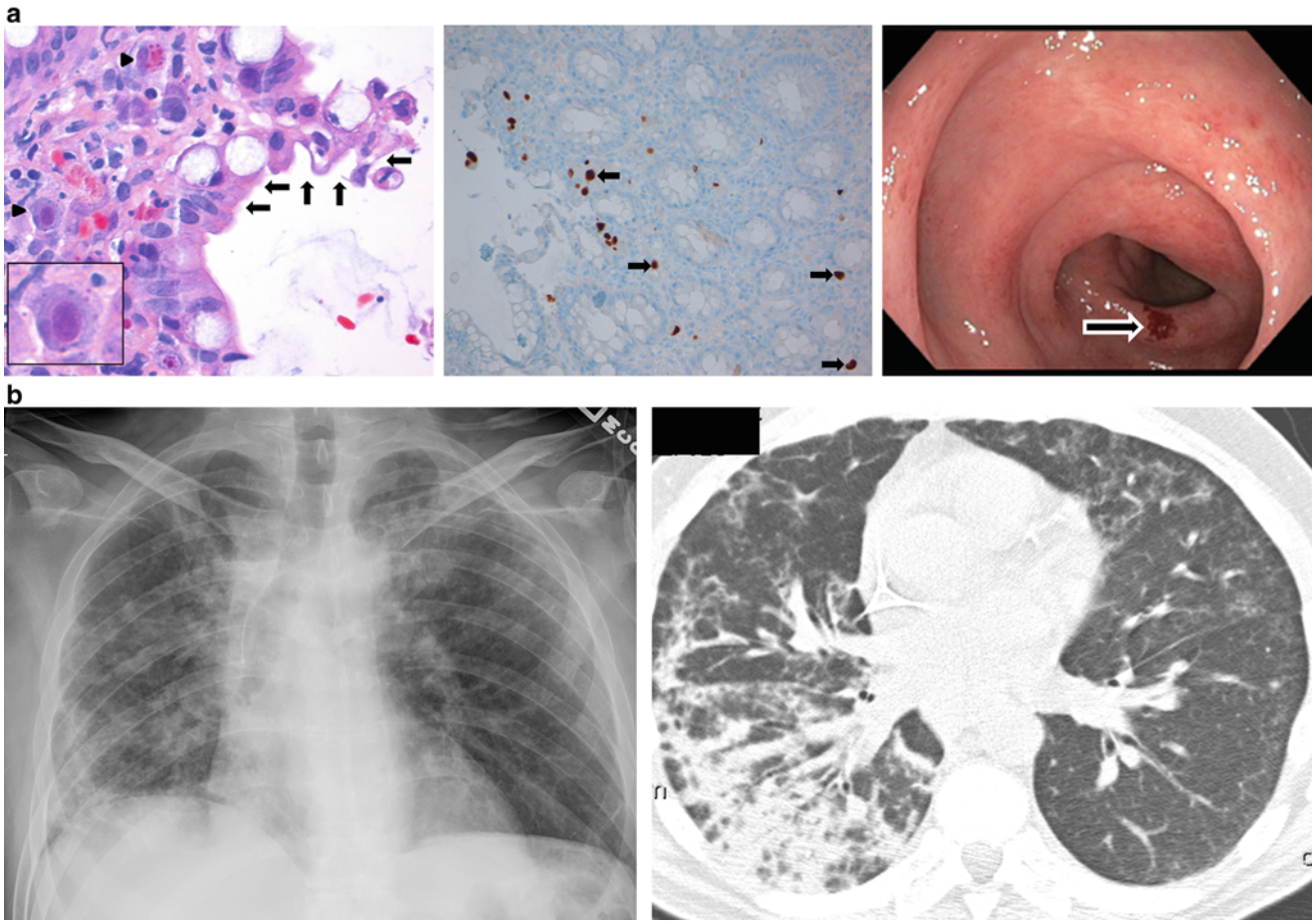

FIGURE 24-1. (**a**) CMV colitis in a CBT recipient. *Left panel*: histopathologic examination of ulcer biopsy specimen showing loss of superficial mucosal integrity (*arrows*) and viral inclusions (*arrowheads*). Inset shows higher magnification view of viral inclusion. *Middle panel*: immunohistochemistry demonstrating CMV-infected cells in biopsy specimen using an antibody recognizing the CMV gB protein. *Right panel*: endoscopic visualization of mucosal ulceration (*arrow*). Microscopy images courtesy of Dr. John Fortune, Department of Pathology, Oregon Health and Science University. (**b**) Chest X-ray (*left panel*) and computed tomography (*right panel*) of an allogeneic HCT recipient demonstrating bilateral interstitial infiltrates typical of CMV pneumonia.

107]. qPCR values of circulating CMV in plasma versus whole blood in a given patient may vary [114]; therefore, it is important to use the same blood component for testing when following serial viral loads. Although PCR has been used on BAL fluid [115], viral-load cutoffs have not been defined, and while the sensitivity and negative predictive values are very high, the specificity and positive predictive values are not known. Similarly, the significance of detection of CMV DNA by PCR in tissue samples such as lung, colon, or liver biopsy specimens for the diagnosis of CMV end-organ disease is not well established and will require further development and evaluation. PCR testing of CSF is specific and strongly indicative of CMV replication in the CNS. PCR testing of vitreous fluid strengthens the diagnosis of CMV retinitis.

The detection of CMV mRNA by PCR amplification on blood samples is equivalent to utilizing DNA PCR or p65 antigenemia to guide preemptive therapy after HCT [116, 117]. However, this method has not been as widely adopted as DNA-based PCR assays.

24.4 Clinical Manifestations

Defining the fundamental concepts of CMV "infection" and "disease" has been tremendously useful in the care of the individual patient and also in patient-centered clinical research. First developed and published in 1993, CMV definitions were updated in 1995 and 2002 to reflect advances in diagnostics and recognition of the "indirect effects" of CMV infection [118]. CMV "infection" simply indicates the detection of CMV, typically by DNA or messenger ribonucleic acid (mRNA) PCR, or pp65 antigenemia, from plasma or whole blood. CMV "disease" was

historically limited to "proven," as defined by the presence of symptoms and signs compatible with CMV end-organ involvement along with the detection of CMV in tissue from the relevant organ by histopathology, immunohistochemistry, or DNA hybridization [118]. Only retinitis was defined based solely on symptoms and/or signs when assessed by an experienced ophthalmologist. These definitions are being revised and expanded to include "probable" disease categorization based on new diagnostic techniques, primarily PCR-based (Table 24-1). Since CMV infection and disease are generally managed differently (see below), distinguishing between the two is critical.

24.4.1 Direct Effects

Almost any organ can be affected by CMV in the HCT recipient. Since the introduction of effective antivirals such as ganciclovir and sensitive monitoring techniques such as PCR, the overall incidence of CMV disease in the first year after HCT has fallen from approximately 30–35 to 5–10% among seropositive recipients [119]. Gastrointestinal disease and pneumonia are the most common manifestations of CMV end-organ disease after HCT.

Pneumonia is the most important clinical manifestation of CMV disease due to its high associated mortality. Prior to the

Table 24-1. Definitions of CMV disease in HCT recipients

	Classification	
Disease manifestation	Proven[a]	Probable[a]
Pneumonia	Tissue CMV positive by: Immunohistochemistry or Histopathology or DNA hybridization *Or* BAL: culture/shell vial	BAL or lung tissue CMV positive by: qPCR value above established threshold
Gastrointestinal[b]	Macroscopic mucosal lesions *And* Tissue CMV positive by: Immunohistochemistry *or* Histopathology *or* DNA hybridization	Tissue CMV positive by: Immunohistochemistry *or* Histopathology *or* DNA hybridization
Hepatitis	Abnormal serum transaminases *And* Tissue CMV positive by: Immunohistochemistry *or* Histopathology *or* DNA hybridization *And* Absence of other cause of hepatitis	Not defined
Retinitis	Ophthalmological signs[c] Vitreal fluid CMV PCR positive[d]	Not defined
CNS[e]	Tissue CMV positive by: Immunohistochemistry *or* Histopathology *or* DNA hybridization *or* Culture *or* PCR	CSF CMV positive by PCR[f]

[a]Both require the presence of the appropriate symptoms and/or signs of CMV disease.
[b]Esophagitis, gastritis, small or large bowel disease.
[c]As determined by an experienced ophthalmologist.
[d]Use as supporting evidence if clinical presentation is atypical.
[e]Ventriculitis, encephalitis.
[f]Requires absence of significant (visible) bloody contamination in CSF sample obtained.

development of effective preemptive and prophylactic strategies, the incidence of CMV pneumonia ranged from 1 to 6% after autologous HCT and 10 to 30% after allogeneic HCT [120]. Currently, CMV pneumonia accounts for approximately one-third of the cases of CMV disease [121]. The vast majority of cases occur after allogeneic HCT and typically within the first 60 days, but up to 30% of cases occur after day +100 [109, 122]. CMV pneumonia often manifests with fever, nonproductive cough, and hypoxia. It is important to recognize that fever may be absent in patients receiving high-dose immune suppression. The onset of symptoms can occur over 1–2 weeks, often times with rapid progression to respiratory failure and the requirement for mechanical ventilation. Although there are no specific radiologic changes, the most common radiographic findings consist of bilateral, ground-glass interstitial infiltrates (Figure 24-1b); small centrilobular nodules and air-space consolidations may also be present [123, 124].

The diagnosis of CMV pneumonia is established ("proven") by detection of CMV by shell-vial, culture, or histology in BAL or lung biopsy specimens in the presence of compatible clinical signs and symptoms (Table 24-1). Pulmonary shedding of CMV is common, but CMV detection in BAL by shell vial assay from asymptomatic patients who underwent routine BAL screening at day 35 after HCT was predictive of subsequent CMV pneumonia in approximately two-thirds of cases [125]. In centers where these techniques are no longer available, quantification of CMV DNA by qPCR in BAL fluid at a level above the threshold established by the center is indicative of "probable" CMV pneumonia (Table 24-1). Due to the high negative predictive value afforded by its high sensitivity, a negative PCR result can be used to rule out the diagnosis of CMV pneumonia [115].

Prior to effective antiviral therapy, the mortality rate of CMV pneumonia after HCT approached 100% [126]. The introduction of agents with potent anti-CMV activity resulted in improved outcomes but mortality rates remain in the range of 30–50% [126–131]. In the current era of preemptive antiviral therapy, lymphopenia and requirement for mechanical ventilation predict both overall and infection-attributable mortality [131].

Gastrointestinal disease is now the most common end-organ manifestation of CMV infection after HCT [104]. As with pneumonia, most cases occur within the first 3 months after allogeneic HCT [132]; however, direct infection-attributable mortality with GI tract disease is uncommon.

Any part of the gastrointestinal tract can be affected, from the esophagus to the colon. Esophagitis typically results in odynophagia, while gastritis often presents with epigastric abdominal pain and nausea. Hematochezia, diarrhea, and diffuse abdominal pain may occur with colitis. As none of these symptoms are pathognomic for CMV infection, endoscopy with tissue biopsy of abnormal areas is required for diagnosis (Table 24-1). Ulcers are often seen on endoscopy (Figure 24-1a, right panel), and visual differentiation of these lesions from other processes that may affect the gastrointestinal tract in these populations, such as graft-versus-host disease (GVHD), is often difficult. Therefore, the diagnosis of gastrointestinal disease ultimately relies on detection of CMV in biopsy specimens by histology combined with immunohistochemistry or DNA hybridization techniques (Figure 24-1a, left and middle panels) or with viral culture (if available). Notably, gastrointestinal disease can occur in the absence of CMV detection in the blood [105, 106, 133]. It should also be noted that GVHD and CMV gastrointestinal disease frequently occur together and therefore each condition's relative contribution to the patient's symptoms might be difficult to assess.

CMV hepatitis is less common than GI tract disease. Based on presenting features alone, it is difficult to distinguish hepatitis caused by CMV from other causes of hepatitis encountered after HCT, including GVHD. Therefore, liver biopsy is required to establish the diagnosis.

Retinitis is relatively uncommon after HCT [134–137]. Patients will often present with decreased visual acuity or blurred vision, and approximately 60% will have involvement of both eyes [135]. Most cases present later than day 100 after transplantation and are associated with prior CMV reactivation, delayed lymphocyte engraftment, and GVHD [135]. The diagnosis of CMV retinitis can often be made by an experienced ophthalmologist based on signs and symptoms alone. Detection of CMV in vitreal fluid by PCR can give supportive evidence for the diagnosis (Table 24-1).

CMV infection of the central nervous system (CNS) is less common after HCT than in the setting of advanced human immunodeficiency virus (HIV) infection. As opposed to pneumonia and GI tract disease, the onset of CNS disease is often late (after day +100) after HCT [138]. The most common disease manifestations are typical of encephalitis, with cognitive dysfunction and confusion [138–140]. The diagnosis of CMV CNS disease is made by detecting CMV in cerebrospinal fluid (CSF) by PCR or culture, or in brain tissue by culture or histopathology, in the appropriate clinical setting (Table 24-1) [118].

CMV rarely causes end-organ disease including, but not limited to, nephritis, cystitis, pancreatitis, and myocarditis; these additional disease categories are defined by the presence of compatible symptoms and signs, and documentation of CMV by biopsy.

24.4.2 Indirect Effects

In addition to the direct end-organ effects of CMV infection, CMV appears to be associated with consequences indirectly related to active infection [141]. After HCT, CMV infection has been associated with an increased risk of invasive bacterial and fungal infections [142]. CMV infection has also been suggested to be a risk factor for subsequent both acute and chronic GVHD after HCT [143–145] similar to the associative finding with rejection after solid organ transplant [146–149]. These findings have been attributed largely to modulation of the host immune system during infection.

Recently, there has been great interest in the role of CMV on disease relapse after HCT. The first hint of an effect came with the observation that patients with CMV infection had less relapse of leukemia compared with patients who had no CMV infection after BMT [150]. This finding was confirmed in a pediatric population in which CMV donor (D) seronegative/recipient (R) seronegative HCT was associated with an increased risk of relapse compared to D+ or R+ HCT [151]. A subsequent study in adults undergoing allogeneic HCT for AML found that early CMV reactivation was associated with a significant reduction in risk of leukemic relapse at 10 years after HCT [152]. Evaluation of a larger cohort of adults found that CMV reactivation was associated with a decreased risk of relapse at day +100 among patients with AML, and was associated with a decreased risk of relapse at 1 year in all patients when analyzed together [153]. Finally, a protective effect of CMV reactivation on relapse was observed in a small cohort of patients who underwent transplant for CML [154]. A large CIBMTR study assessing CMV infection and relapse after HCT is now underway. The mechanisms underlying these findings are poorly understood. An interesting hypothesis is that CMV reactivation stimulates γδ T cells that cross-recognize leukemic cells [155]. Other proposed mechanisms are through stimulation of NK-cell mediated clearance of leukemic cells, or by direct induction of apoptosis in leukemic cells [156–159]. However, any potential benefit of CMV reactivation in terms of disease relapse is almost certainly outweighed by the negative effect of CMV serostatus and reactivation on non-relapse and overall mortality [104, 153, 160–162].

24.5 Risk Factors for CMV Infection and Disease

24.5.1 Allogeneic HCT Recipients

In the setting of allogeneic HCT, the most important risk factor is the serological status of the donor and recipient [161]; both should be routinely assessed prior to HCT. CMV D−/R− transplants have a very low risk of primary infection in the recipient. Primary infection can still occur if CMV is transmitted in transfused blood products or is acquired via contact with another individual with active CMV infection.

Approximately 20–30% of seronegative recipients who receive stem cells from a seropositive donor will develop primary CMV infection due most likely to transmission of latent CMV via the allograft [163, 164]. The risk of transmission is directly related to the allograft nucleated white blood cell count [163], consistent with hematopoietic myeloid lineage cells acting as a reservoir of latent CMV [2]. CMV D+/R− mismatching negatively impacts the overall survival and increases the transplant-related mortality, especially those caused by bacterial and fungal infections [142, 165]. More recent studies performed in the modern diagnostic and therapeutic era have confirmed the negative effect of CMV D+/R− mismatching [160]. Recently, a large study found a strong negative effect on overall survival, relapse-free survival, and transplant- related mortality in CMV D+/R− *unrelated* HCT but a much smaller negative effect for human leukocyte antigen (HLA)-identical sibling D+/R− HCT, and no effect in patients receiving mismatched related donor grafts [166]. Thus the impact of D+/R− sero-mismatching may be influenced by the type of HCT.

Without prophylaxis, approximately 60–70% of CMV-seropositive patients will experience CMV infection after allogeneic peripheral blood or bone marrow HCT. It is well-established that a CMV-seropositive recipient is at higher risk for mortality than a seronegative recipient after HCT [167–170].

Unlike the situation of D+/R− HCT, in which the negative impact of a seropositive donor is well-described, the impact of donor serostatus when the recipient in seropositive has been the subject of controversy. Some studies reported a beneficial effect of having seropositive donor with regard to a reduction in relapse- or nonrelapse-related mortality (NRM), whereas other studies found no such benefit [117, 151, 169, 171–179].

To reconcile these differences, a large retrospective analysis of over 29,000 patients from the European Society for Blood and Marrow Transplantation (EBMT) registry was performed [166]. Seropositive patients receiving grafts from seropositive unrelated donors had improved overall survival compared with seronegative donors if they had received myeloablative, but not reduced-intensity, conditioning, perhaps due to loss of CMV-specific T cell function after myeloablative conditioning. No effect was observed when they received allograft from HLA identical sibling donors. Thus, the negative effect of CMV D−/R+ mismatching may be limited to high-risk transplant settings.

In addition to the effects on non-relapse mortality and overall survival, the D−/R+ serological combination has been reported as a risk factor for delayed CMV specific immune reconstitution [180–183], CMV reactivation [181, 184], late CMV recurrence [185], and CMV disease [113, 181, 186].

Other risk factors for CMV infection after allogeneic HCT include the use of steroids at doses greater than 1 mg/kg body weight/day, T-cell depletion (either ex vivo or in vivo), acute and chronic GVHD, the use of total body irradiation $CD4^+$ lymphopenia, and the use of mismatched or unrelated donors [110, 113, 186–190]. Whether the source of stem cells (peripheral blood versus bone marrow) has a significant impact on the development of CMV infection and disease is not clear, as several studies have yielded conflicting results [186, 190–192]. Interestingly, the use of sirolimus for GVHD prophylaxis appears to protect against CMV infection, possibly due to the inhibition of cellular signaling pathways that are co-opted by CMV during infection for synthesis of viral proteins [186, 193, 194].

The use of HLA-matched, related nonmyeloablative conditioning regimens generally results in a less CMV infection and disease early after HCT compared to standard myeloablative regimens [195]. However, by 1 year after HCT, the risk of CMV infection and disease is equal among nonmyeloablative and myeloablative groups [194, 196].

Umbilical cord blood transplantation (CBT) is a technique that is now utilized when a suitable donor for bone marrow or peripheral blood stem cell transplantation is not available [197]. Since most infants are born without CMV infection, the transplanted allograft is almost always CMV-negative. CMV seropositive CBT recipients are at particularly high risk for infection compared to GSCF-mobilized peripheral blood stem cell transplant recipients due to delayed T cell immune reconstitution [198] and failure of functional CMV-specific T cells to achieve sufficient numbers to control CMV reactivation after CBT [29]. The reported rate of CMV reactivation after CBT varies widely, from 21 to 100%, while disease occurs in ~5–28% of recipients [190, 199–208]. The variability in reported infection rates likely reflects differences in conditioning regimens, inclusion of low-risk CMV seronegative recipients in certain data cohorts, and approaches to CMV prevention after CBT. One center reported a markedly high rate of CMV disease, particularly during the pre-engraftment period, and associated mortality after CBT [205], prompting a change in their preventative approach after CBT (discussed below).

An alternative stem cell source for patients who do not have matched donors is the HLA-haploidentical 2 or 3-loci mismatched family donor [209]. Such haploidentical transplantation has traditionally been associated with a high incidence of severe GVHD and graft rejection, prompting the implementation of T cell depletion strategies to reduce these adverse alloreactive events [209]. While T cell depletion does prevent GVHD, the consequent delayed immune reconstitution led to increased risk of infection [210–212]. High rates of CMV disease, antiviral drug resistance, and infection-attributable mortality have been reported in this population [213]. Performing T-cell-replete haploidentical HCT with posttransplant cyclophosphamide to induce immune tolerance [214] may reduce the incidence of CMV infection and disease compared to T-cell depletion [215, 216].

24.5.2 Autologous HCT

After autologous transplantation, approximately 40% of seropositive patients will have detectable CMV infection [217, 218]. While CMV disease is rare after autologous transplantation [191, 219–221], the outcome of CMV pneumonia is similar to that after allogeneic HCT [217, 222, 223]. Risk factors for CMV disease after autologous transplantation include CD34+ selection, high-dose corticosteroids, and the use of total-body irradiation or fludarabine as part of the conditioning regimen [191]. Therefore, while CMV is not typically considered a significant pathogen after autologous HCT, certain patients who are at high risk for CMV in this setting merit routine surveillance and preemptive therapy.

24.5.3 Late CMV Infection After Allogeneic HCT

Whereas CMV was typically seen by 100 days after allogeneic HCT [224], it has become recognized as a significant problem after day 100 as well [109, 185, 225]. Several factors predict the development of late CMV infection, including prolonged or repeated CMV infection and/or disease before day +100, use of antiviral prophylaxis during the early posttransplant period, slow response to antiviral therapy, qualitative or quantitative lymphopenia, cord blood transplants, patients with severe acute or chronic GVHD, and HLA-mismatched transplant [19, 20, 109, 113, 185, 186, 226]. Patients, who have experienced prolonged or repeated CMV episodes before day 100, cord blood transplant recipients, and patients with significant immunosuppression should have continued weekly surveillance to reduce the risk of late CMV disease.

24.6 Antiviral Agents

Agents licensed for the treatment or prevention of CMV infection include ganciclovir (GCV) and its oral prodrug valganciclovir (vGCV), foscarnet (FOS), and cidofovir (CDV) (Table 24-2). All exert their antiviral effect by inhibiting viral DNA synthesis through targeting of the viral DNA polymerase encoded by the UL54 gene. Acyclovir (ACV) and its oral prodrug valacyclovir (vACV) do not possess potent activity against CMV and therefore cannot be used for treatment of infection but have shown efficacy when used as prophylaxis (discussed below).

Table 24-2. Agents licensed for the treatment or prevention of CMV infection and disease

Agent	Target	Route of administration	Dose[a]		Toxicities[b]	Resistance mutations
			Induction	Maintenance		
Ganciclovir	UL54	IV	5 mg/kg bid	5 mg/kg/day	Neutropenia, anemia, thrombocytopenia, diarrhea, fever	UL97, UL54
Valganciclovir	UL54	oral	900 mg bid (≥40 kg)	900 mg/day (≥40 kg)	Same as ganciclovir	UL97, UL54
Foscarnet	UL54	IV	90 mg/kg bid	90 mg/kg/day	Nephrotoxicity, electrolyte, wasting, nausea, urethral ulceration, paresthesia, hallucination	UL54
Cidofovir	UL54	IV	5 mg/kg/week	5 mg/kg every other week	Nephrotoxicity, neutropenia, headache, nausea, uveitis/iritis, diarrhea, ocular hypotony	UL54

[a]All agents require dose adjustment in the setting of renal dysfunction.
[b]For full listing of toxicities, please refer to the summary of product characteristics (SPC) for each agent.

GCV is a nucleoside analogue of guanosine that acts as a competitive inhibitor of deoxyguanosine triphosphate incorporation into viral DNA by the viral DNA polymerase UL54. A CMV gene, UL97, encodes a kinase that phosphorylates GCV to GCV monophosphate, a necessary step in conversion of GCV to its active form. Cellular kinases then phosphorylate GCV monophosphate to the active triphosphate form. GCV is currently the first-line agent for CMV prophylaxis, preemptive treatment, and treatment of CMV disease, barring contraindications. Neutropenia occurs in up to 30% of HCT recipients during GCV therapy [227], thereby placing the patient at risk of invasive bacterial and fungal infections [227, 228]. vGCV achieves serum concentrations at least equivalent to intravenous GCV [229, 230] and the toxicity profile appears similar. However, drug levels can be unpredictable, especially in patients with gastrointestinal tract GVHD, and therapeutic drug monitoring can therefore be a useful tool in managing patients on vGCV therapy. Neutropenia often responds to dose reduction and support with granulocyte-colony stimulating factor, but occasionally discontinuation of GCV or vGCV is required, in which case FOS is typically the second-line agent of choice.

FOS is a pyrophosphate analogue that binds directly to and competitively inhibits the CMV DNA polymerase UL54. Although a randomized, controlled trial showed similar efficacy and rate of side effects for GCV and FOS when used as preemptive therapy [231], practical issues such as the need for intensive hydration along with the electrolyte wasting that accompany FOS have resulted in its use mostly as a second-line agent when GCV or vGCV are contraindicated or not tolerated, or there is suspicion of GCV resistance (see below).

CDV is a cytosine nucleotide analogue that, like FOS, does not require phosphorylation by the CMV UL97 kinase for antiviral activity. Instead, cellular enzymes convert CDV to CDV triphosphate, which then inhibits the CMV DNA polymerase. The long half-life of cidofovir allows a once-per-week dosing schedule. However, the major toxicity with CDV—renal tubular damage—limits its utility after HCT and it should therefore be considered third-line therapy after GCV and FOS.

24.6.1 Antiviral Resistance

Drug resistance is relatively uncommon after peripheral blood or bone marrow HCT [232] but the risk has been reported to be increased after T-cell-depleted haploidentical HCT [213]. Resistance typically occurs in the setting of ongoing, intermittent or recurrent viral replication in the presence of drug. This situation arises most often due to profound host immunosuppression and/or suboptimal drug levels. Therefore, reducing immune suppression and optimization of drug delivery are important aspects of management. CBT or T-cell-depleted transplant recipients and those on augmented immune suppression for GVHD should be considered at increased risk for resistance. Inadequate drug delivery may occur in a patient receiving vGCV during GI GVHD, or when dosages are improperly adjusted for renal dysfunction. When available, therapeutic drug level monitoring may be of benefit.

Drug resistance should be suspected in patients with some or all of the above risk factors who have a rising viral load after at least 2 weeks of antiviral therapy or who experience worsening or relapse of clinical disease or viremia while on prolonged therapy. In general, resistance requires accumulated drug exposure; in treatment-naïve patients, no decrease or even a moderate increase in the viral load will occur in many patients within the first 2 weeks of starting therapy that is likely due to the underlying immunosuppression, not true

drug resistance [103]. Thus, this situation does usually not warrant change of therapy. The duration of drug exposure required to select for resistance and the increase in viral load that should prompt testing for resistance after HCT are not well defined and likely depend on the above mentioned host factors, viral loads during therapy, and genetic barrier to resistance for the drug in question.

Since GCV/vGCV is typically used as a first-line agent for CMV infection and disease, resistance to this antiviral is the most commonly encountered problem. A general approach to the patient with suspected GCV resistance is presented in Figure 24-2. GCV resistance is usually due to mutations in the UL97 gene; mutations in UL54 may follow UL97 mutations with continued GCV exposure. UL97 and UL54 mutations that confer GCV resistance have been determined and genotypic assays are available for diagnostic analysis in reference laboratories [232]. Since different UL97 mutations confer varying degrees of GCV resistance, some cases of genotypically defined GCV -resistant CMV may still respond to high-dose GCV therapy (i.e., twice standard induction dose) if they confer low-level (two- to threefold) resistance [232]. However, if there is evidence of CMV disease or the viral load is increasing rapidly, a switch to FOS is recommended [232].

Since neither FOS nor CDV activity are dependent on phosphorylation by the UL97 gene product, CMV that has acquired GCV resistance due to UL97 mutations will still be susceptible to these agents. Due to its relatively favorable toxicity profile compared to CDV, FOS is most often used as the agent of choice in the setting of GCV resistance. Studies evaluating the utility of combination therapy of FOS and GCV for GCV-resistant CMV disease have been inconclusive, and therefore, this strategy is not routinely recommended [233].

Mutations in UL54 may confer resistance to GCV, FOS, CDV, or cross-resistance to combinations thereof. Cross-resistance between FOS and GCV due to UL54 mutations rarely occurs, while on the other hand most UL54 mutations that confer GCV resistance also result in CDV resistance [232]. Rarely, mutations in UL54 that confer resistance to all three agents—GCV, FOS, and CDV—are encountered [232]. Therapeutic options in such situations are limited and highlight the need for antiviral agents with targets other than UL54. The use of a sirolimus-based regimen for GVHD prophylaxis may provide some benefit for reasons discussed above but should be viewed as an adjunct to, not a substitute for, direct antiviral therapy.

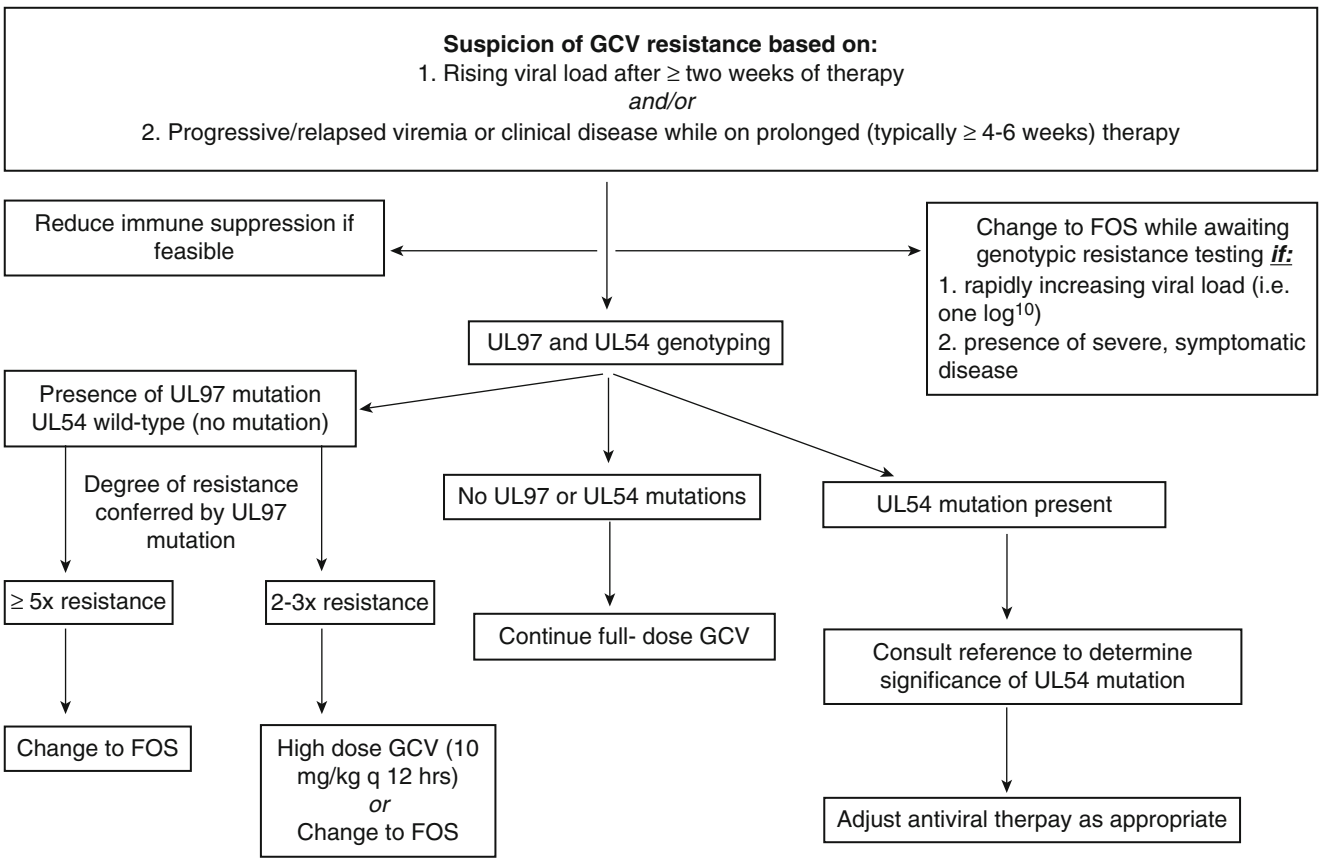

FIGURE 24-2. Approach to the patient with suspected GCV resistance.

24.6.2 Antiviral Agents in Development

Maribavir (MBV) (Table 24-3) is an oral agent that inhibits the CMV UL97 kinase and potently inhibits CMV replication in vitro [234]. Due to its mechanism of action, MBV is active against CMV strains resistant to GCV, FOS, and CDV [235] but antagonizes the antiviral activity of GCV [236]. After promising results phase I and II clinical trials, MBV failed to effectively prevent CMV infection compared to placebo after HCT when used as prophylaxis in a phase III trial [237–239]. The reason(s) underlying the failure of MBV in the phase III study are not clear but the use of too low a dose of MBV is often cited [240]. A phase II dose-ranging trial comparing higher doses of MBV to standard of care GCV (or vGCV) as preemptive therapy after allogeneic HCT (EudraCT: 2010-024247-32) has been completed. In addition, MBV has demonstrated efficacy in the treatment of refractory or resistant CMV infections after transplantation [241, 242] and a phase II study for this indication has been completed (ClinicalTrials.gov NCT01611974). Results from these two phase II trials are forthcoming. MBV resistance due to mutations in UL97 has occurred in patients treated with this agent [243, 244].

Letermovir (Table 24-3) inhibits the activity of the essential CMV UL56/UL89 DNA terminase complex [245]. Letermovir is active against wild-type and drug-resistant CMV in tissue culture [245]. Experience using letermovir for multidrug-resistant CMV disease in vivo is promising but very limited [246]. A phase II study of letermovir as prophylaxis in CMV-seropositive HCT recipients showed a dose-dependent reduction of prophylaxis failure (defined as discontinuation of letermovir or placebo because of CMV antigen or DNA detection, end-organ disease, or any other cause) compared to placebo [247]. A phase III randomized multicenter trial as prophylaxis in seropositive HCT recipients has completed patient enrollment (ClinicalTrials.gov NCT02137772). Letermovir appears to be very well tolerated, with few demonstrable side effects or toxicities [247]. Resistance mutations mapping to UL56 can be selected for in tissue culture [248]; whether similar mutations will be arise in patients treated with letermovir remains to be seen. Demonstration of an additive antiviral effect when combined with DNA polymerase inhibitors [249] raises the possibility of combination therapy similar to strategies currently employed for the treatment of hepatitis C and HIV.

Brincidofovir (CMX-001) (Table 24-3) is a lipid-conjugated nucleotide analogue of CDV that has a high oral bioavailability and long half-life. It has activity against most DNA viruses, including CMV [250]. In contrast to CDV, brincidofovir is not associated with significant nephrotoxicity. Brincidofovir at a dose of 100 mg twice daily was shown to be effective in preventing CMV infection after HCT when used as prophylaxis in a phase II placebo-controlled study [251]. However, diarrhea and acute gastrointestinal GVHD were reported more frequently in the group that received this dose compared to placebo or lower dose brincidofovir, and gastrointestinal side effects were dose-limiting at 200 mg twice weekly. A phase III randomized multicenter trial using a dose of 100 mg twice weekly as prophylaxis in seropositive HCT recipients (ClinicalTrials.gov NCT01769170) has been completed, and results are forthcoming. While resistance to brincidofovir has not been well characterized, it is expected that mutations in UL54 conferring CDV resistance will also result in brincidofovir resistance [252].

While reports of leflunomide and the antimalarial artesunate having anti-CMV activity exist [253–255], neither of these have conclusively demonstrated benefit and are not approved by European or American regulatory authorities for the treatment of CMV; therefore, their routine use cannot be recommended. The immunosuppressive drug sirolimus inhibits CMV replication in tissue culture by regulating key cellular signaling pathways and has been shown to reduce the risk of CMV reactivation after HCT and renal transplantation [186, 193, 256]. Thus, this agent may be a useful adjunct when ongoing immune suppressive therapy is required in the setting of refractory CMV infection.

TABLE 24-3. CMV antiviral agents in development

Agent	Target	Route of administration	Dose	Toxicities	Resistance mutations
Maribavir	UL97 kinase	Oral	400–1200 mg twice daily	Taste disturbance	UL97, UL27[a]
Letermovir (AIC-246)	UL56/UL89 terminase complex	Oral, IV	240 mg daily[b], 480 mg daily[c]	None apparent	UL56[a]
Brincidofovir (CMX-001)	UL54 DNA polymerase	Oral	100 mg twice weekly[b]	Gastrointestinal[d]	Not described

[a]Found only in tissue culture thus far.
[b]Dose chosen for phase III studies.
[c]In patients receiving cyclosporine for GVHD prophylaxis.
[d]Diarrhea, nausea, vomiting, abdominal pain, aGVHD, elevated ALT.

24.7 Prevention of Infection and Disease

24.7.1 Choice of Donor

Recipients who are CMV seronegative before allogeneic HCT should ideally receive a graft from a CMV seronegative donor to prevent primary infection via the allograft. No data exists indicating whether HLA-matching is more important compared to CMV serostatus in affecting a good outcome for the patient. Given the choice, an antigen-matched donor for HLA-A, B, or DR would most likely be preferred to a CMV-negative donor. For lesser degrees of mismatch, (allele-mismatches or mismatches on HLA-C, DQ, or DP), the CMV-serostatus of donor should be considered a factor even if the match was poorer. Compared to other donor factors such as donor age or blood group, a CMV-seronegative donor would have preference. If the patient is CMV seropositive, it has been shown that a CMV seropositive unrelated donor confers a survival advantage if the patient will receive myeloablative conditioning [166]. Similar to the situation with a CMV seronegative patient, an antigen-match on A, B, and DR is the major selection criterion but CMV-status should be weighed among other factors with lesser degrees of HLA-mismatch.

24.7.2 Transmission via Blood Products

Previously, the transfusion of blood products represents a significant source for CMV infection in seronegative transplant recipients. Today preventive measures such as using blood products from CMV seronegative donors or leukocyte-reduced, filtered blood products are widely used and greatly reduce this risk [257–259]. It is not clear which strategy is the most effective [260, 261] and no controlled study has investigated whether there is an extra benefit from the use of both methods.

24.7.3 Immune Therapy

Intravenous immune globulin (IVIG) is not reliably effective as prophylaxis against primary CMV infection. One study demonstrated a reduction in the rate of CMV infection but not disease, while another study was unable to confirm protection from infection [262, 263]. Similarly negative results were observed using a CMV-specific monoclonal antibody [264]. Likewise, the effect of immunoglobulin on reducing CMV infection in seropositive patients is modest, and no survival benefit among those receiving immunoglobulin has been reported in any study or meta-analysis [265–270]. Therefore, the prophylactic use of IVIG is not recommended.

24.7.4 Chemoprevention

The strategies of prophylactic or preemptive use of antiviral agents after HCT have markedly reduced the incidence of CMV disease and improved survival among at-risk populations. All centers performing allogeneic transplants should therefore have one of these strategies in place for all allogeneic HCT recipients at risk for CMV infection (seropositive recipients, or seronegative recipients of a seropositive donor graft) [271]. Studies in the eras of pp65 and qPCR monitoring have documented the equivalence of prophylaxis and preemptive therapy in terms of preventing CMV infection and disease after HCT [127, 272]. Most transplant centers have moved towards preemptive strategies as pp65 antigenemia and qPCR-based diagnostics techniques have become readily available [273]. DNA qPCR has become the standard for monitoring at many institutions as it is more sensitive than pp65 antigenemia [127] and technically easier to perform than mRNA detection. Additionally, it has been reported that qPCR-based initial viral load and viral load kinetics are important as risk factors for CMV disease [111].

Prophylaxis denotes the routine administration of antivirals to all at-risk patients regardless of the presence of active CMV infection, typically until day +100 after HCT. ACV and its vACV, while not approved for the treatment of CMV, are used at some centers for CMV prophylaxis after HCT [273]. High dose ACV and vACV have demonstrated efficacy in reducing the risk for CMV infection and disease after HCT [220, 274–276]. Routine monitoring for CMV infection is still required if vACV or ACV prophylaxis is used, and therapy with GCV or vGCV is indicated if CMV is detected. GCV prophylaxis, begun at engraftment and continued until day +100, has been demonstrated to reduce the risk of CMV infection and disease after HCT compared to placebo, although its use is limited by toxicity, primarily marrow suppression [127, 228, 277]. Data regarding vGCV prophylaxis is more limited. A recent randomized, double-blind study of vGCV prophylaxis compared to preemptive therapy for the prevention of late CMV infection after HCT demonstrated reduced CMV viremia in the prophylaxis group but no difference in CMV disease [272].

Preemptive therapy, on the other hand, withholds antiviral therapy until CMV infection is detected in whole blood or plasma samples. This strategy mandates sensitive, specific, and rapid turnaround laboratory tests to detect circulating CMV in order to enable initiation of antiviral therapy prior to the development of CMV end-organ disease. All patients who have undergone allogeneic HCT should be monitored at least once per week beginning either at the time of transplant or ~day +10 and extending to at least day +100 after HCT [271]. Surveillance should be extended past day +100 in those at risk for late infection and disease

(discussed above). The ideal duration and frequency of CMV monitoring in the later transplantation periods have not been defined [195, 278].

Although CMV infection is rare in D−/R− patients, such a monitoring strategy is effective in identifying CMV infection and preventing disease in a large cohort of such patients [279]. Routine monitoring of autologous HCT recipients is not recommended, with the exception being high-risk patients as described above.

In all patients in whom viremia is detected, a thorough evaluation of the patient in order to assess for signs and symptoms of CMV disease is necessary. Initiation of induction-dose preemptive antiviral therapy is generally recommended [271]. However, it has been clearly shown that most patients with low viral loads can be safely spared preemptive antiviral therapy unless there are special high risk features [104, 113, 280]. Currently, there are no validated universal viral load thresholds for starting preemptive therapy, and such thresholds are difficult to establish due to differences in assay performance and testing material (i.e., whole blood versus plasma) [281]; the development of an international standard for CMV qPCR calibration [282] may eventually allow for this. Additionally, thresholds for initiating preemptive therapy need to account for underlying patient characteristics which determine the risk for progression to CMV disease.

Currently, considerable variation in practice exists pertaining to the duration of induction dose preemptive treatment [273]. In general, this should be continued for a minimum of 1–2 weeks and a decrease in viral load has been documented by qPCR, followed by maintenance therapy until the CMV viral load is undetectable [271] or below a center's established cutoff. After discontinuation of preemptive therapy, routine weekly screening until day +100 or later if risk factors for late infection are present are still necessary to monitor for recurrence of viremia [271]. If less sensitive markers than qPCR, such as the pp65 antigenemia assay, are used, then preemptive therapy should be continued until 2 negative assays are obtained [231].

GCV is considered the first-line agent for preemptive therapy [271]. While FOS has demonstrated equivalence to GCV when used in a preemptive manner [231], practical aspects of its administration relegate its use to situations when GCV is contraindicated or not tolerated. The results of several uncontrolled studies suggest that vGCV is comparable to intravenous GCV in terms of efficacy and safety when used as preemptive therapy after allogeneic HCT [283–288]. A prospective, randomized trial comparing vGCV to intravenous GCV supported these observations [289]. Thus, in the HCT recipient who is able to tolerate oral therapy and in whom no barriers to efficient absorption of an oral agent exist, vGCV appears to be a reasonable alternative to intravenous GCV for preemptive therapy.

There has been great interest in utilizing methods to determine CMV-specific immune reconstitution after HCT as an additional means to stratify risk of CMV infection and disease ("immune monitoring") and further tailor surveillance and preemptive therapy strategies. The types of assays used, their strengths and limitations, and their predictive value in terms of CMV infection and disease after transplantation have been extensively reviewed elsewhere [69, 290]. While promising, the use of immune monitoring in this fashion requires validation in large, randomized trials before it can be recommended.

24.7.5 Vaccination

Given the costs and toxicities associated with antiviral therapy, a vaccine to prevent CMV infection would be of substantial benefit. Indeed, the Institute of Medicine has given the development of a CMV vaccine highest priority [291]. Historically, most vaccine candidates yielded mixed results [292]. Recently, the safety and efficacy of a DNA vaccine expressing the CMV immunogenic proteins gB and pp65 was evaluated in a phase II, placebo controlled trial in CMV seropositive allogeneic HCT recipients [293]. While no difference in initiation of preemptive anti-CMV therapy or duration of antiviral therapy was observed between the groups, the group receiving the vaccine had fewer episodes of viremia, lower viral loads, and was more likely to be viremia-free at 1 year after HCT. No differences in CMV disease were observed but the overall incidence of disease was low (7.5% in vaccine group vs. 8.8% in placebo group). A phase III study of this vaccine in a similar patient population is currently underway (ClinicalTrials.gov NCT01877655). CMV peptide vaccines designed to elicit pp65-specific CTL were found to be safe and immunogenic in healthy adults [294] and a phase II study in HCT recipients is under way (ClinicalTrials.gov NCT02396134).

24.7.6 Special Populations

Patients with CMV disease occurring prior to planned allogeneic HCT have a very high risk of death after transplantation [295]. After transplantation, a patient with documented pretransplant CMV disease should either be monitored for CMV very closely (i.e., twice weekly), or be given prophylaxis with GCV or FOS.

The CMV seropositive CBT recipient population may benefit from more intensive prevention strategies. The reactivation rate in CMV seropositive CBT recipients in the absence of high-dose ACV/vACV or anti-CMV prophylaxis has been reported at 70–100% [205, 207, 208, 296]. A combination approach of high-dose vACV prophylaxis coupled with continued monitoring and preemptive therapy was

associated with rates of CMV reactivation and disease similar to those seen after allogeneic BMT or PBSCT [190]. Other studies have described successful vGCV or GCV prophylaxis and preemptive treatment strategies after CBT using protocols similar to other allogeneic HCT recipients [208, 297]. More recently, an aggressive approach of pretransplant GCV along with posttransplant high dose ACV/vACV prophylaxis and biweekly monitoring was demonstrated to reduce the incidence of CMV infection and disease after CBT [205]; the relatively contributions of these interventions towards CMV prevention are unclear. Thus, the optimal approach to CMV after CBT has not been determined.

24.8 Management of CMV Disease

As mentioned earlier, the diagnosis of CMV disease requires documenting the presence of CMV in the appropriate diagnostic specimen, coupled with symptoms and signs consistent with CMV. GCV is considered first-line therapy for end-organ disease, with FOS reserved as an alternative if neutropenia or other factors precluding GCV use are present. As opposed to preemptive therapy, the treatment of end-organ disease requires longer courses of induction-dosing antiviral therapy. For gastrointestinal disease, standard therapy generally entails induction treatment with an intravenous antiviral, most often GCV, for 3–4 weeks followed by several weeks of maintenance. Shorter courses of induction therapy (2 weeks) are not as effective [298]. Recurrence of GI disease may occur in approximately 30% of patients in the setting of continued immunosuppression and such patients may benefit from secondary prophylaxis with maintenance antivirals until immunosuppression has been reduced. Similar to GI tract disease, the treatment of CMV pneumonia involves induction-dose GCV for 3–4 weeks, followed by a period of maintenance therapy.

The role of vGCV in the management of CMV disease after HCT is not well established. vGCV has been shown to be noninferior to IV GCV in the treatment of non-life threatening CMV disease after solid-organ transplant, primarily kidney transplant recipients [299]. However, similar studies have not been performed in HCT recipients. Therefore, IV anti-CMV therapy remains the standard of care, although oral vGCV may be considered for patients with mild or moderate, non-life threatening disease after an initial period of IV therapy to bring disease under control and suppress viremia. In general, vGCV should only be used if there are no factors that would impair the absorption of an orally administered medication, such as severe gastrointestinal GVHD.

The role of IVIG as an adjunct to antiviral therapy for CMV disease remains controversial due to the lack of prospective, randomized trials evaluating the additional benefit of this intervention over antiviral therapy alone [122]. There does not appear to be a specific advantage of CMV-specific immune globulin (CMV-Ig) compared to pooled immunoglobulin [300]. While there is no role for IVIG in the treatment of gastrointestinal disease [301], it has been considered as standard-of-care at many centers in the management of CMV pneumonia based on small studies showing improved survival rates with the addition of IVIG compared to historical controls using antiviral therapy alone [302–304]. On the other hand, a recent, large retrospective analysis was unable to demonstrate an improvement in overall or infection-attributable mortality with the addition of IVIG to antiviral therapy [131]. Thus, the role of IVIG in the management of CMV pneumonia remains unclear.

CMV retinitis is typically treated with systemic therapy, with or without intraocular GCV injections or implants [135, 305–307]. The optimal duration of therapy is not well established, but in general longer courses are needed in order to prevent recurrence.

Other manifestations of CMV disease, such as hepatitis and encephalitis, are uncommon and are typically managed with intravenous therapy. The duration of therapy for these manifestations has not been well established and should be tailored to the individual patient.

24.9 Adoptive Immunotherapy

Due to the importance of CMV-specific functional T cells in the control of CMV infection after HCT [23], there has been intense interest in promoting CMV immune reconstitution via the adoptive transfer of CMV-reactive T cells [308]. This topic is discussed in more detail elsewhere in this book.

References

1. Chee MS, Bankier AT, Beck S, Bohni R, Brown CM, Cerny R, et al. Analysis of the protein-coding content of the sequence of human cytomegalovirus strain AD169. Curr Top Microbiol Immunol. 1990;154:125–69.
2. Goodrum F, Caviness K, Zagallo P. Human cytomegalovirus persistence. Cell Microbiol. 2012;14(5):644–55.
3. Bolovan-Fritts CA, Mocarski ES, Wiedeman JA. Peripheral blood CD14(+) cells from healthy subjects carry a circular conformation of latent cytomegalovirus genome. Blood. 1999;93(1):394–8.
4. Slobedman B, Mocarski ES. Quantitative analysis of latent human cytomegalovirus. J Virol. 1999;73(6):4806–12.
5. Soderberg-Naucler C, Fish KN, Nelson JA. Reactivation of latent human cytomegalovirus by allogeneic stimulation of blood cells from healthy donors. Cell. 1997;91(1):119–26.
6. Fishman JA. Infection in solid-organ transplant recipients. N Engl J Med. 2007;357(25):2601–14.
7. Kern F, Bunde T, Faulhaber N, Kiecker F, Khatamzas E, Rudawski IM, et al. Cytomegalovirus (CMV) phosphoprotein 65 makes a large contribution to shaping the T cell repertoire

in CMV-exposed individuals. J Infect Dis. 2002;185(12): 1709–16.
8. Kern F, Surel IP, Faulhaber N, Frommel C, Schneider-Mergener J, Schonemann C, et al. Target structures of the CD8(+)-T-cell response to human cytomegalovirus: the 72-kilodalton major immediate-early protein revisited. J Virol. 1999;73(10):8179–84.
9. Khan N, Best D, Bruton R, Nayak L, Rickinson AB, Moss PA. T cell recognition patterns of immunodominant cytomegalovirus antigens in primary and persistent infection. J Immunol. 2007;178(7):4455–65.
10. Khan N, Bruton R, Taylor GS, Cobbold M, Jones TR, Rickinson AB, et al. Identification of cytomegalovirus-specific cytotoxic T lymphocytes in vitro is greatly enhanced by the use of recombinant virus lacking the US2 to US11 region or modified vaccinia virus Ankara expressing individual viral genes. J Virol. 2005;79(5):2869–79.
11. Khan N, Cobbold M, Keenan R, Moss PA. Comparative analysis of CD8+ T cell responses against human cytomegalovirus proteins pp 65 and immediate early 1 shows similarities in precursor frequency, oligoclonality, and phenotype. J Infect Dis. 2002;185(8):1025–34.
12. Kondo E, Akatsuka Y, Kuzushima K, Tsujimura K, Asakura S, Tajima K, et al. Identification of novel CTL epitopes of CMV-pp 65 presented by a variety of HLA alleles. Blood. 2004;103(2):630–8.
13. Elkington R, Walker S, Crough T, Menzies M, Tellam J, Bharadwaj M, et al. Ex vivo profiling of CD8+–T-cell responses to human cytomegalovirus reveals broad and multispecific reactivities in healthy virus carriers. J Virol. 2003;77(9):5226–40.
14. 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(5):673–85.
15. Manley TJ, Luy L, Jones T, Boeckh M, Mutimer H, Riddell SR. Immune evasion proteins of human cytomegalovirus do not prevent a diverse CD8+ cytotoxic T-cell response in natural infection. Blood. 2004;104(4):1075–82.
16. Tey SK, Goodrum F, Khanna R. CD8+ T-cell recognition of human cytomegalovirus latency-associated determinant pUL138. J Gen Virol. 2010;91(Pt 8):2040–8.
17. Einsele H, Roosnek E, Rufer N, Sinzger C, Riegler S, Loffler J, et al. Infusion of cytomegalovirus (CMV)-specific T cells for the treatment of CMV infection not responding to antiviral chemotherapy. Blood. 2002;99(11):3916–22.
18. Hebart H, Daginik S, Stevanovic S, Grigoleit U, Dobler A, Baur M, et al. Sensitive detection of human cytomegalovirus peptide-specific cytotoxic T-lymphocyte responses by interferon-gamma-enzyme-linked immunospot assay and flow cytometry in healthy individuals and in patients after allogeneic stem cell transplantation. Blood. 2002;99(10):3830–7.
19. Krause H, Hebart H, Jahn G, Muller CA, Einsele H. Screening for CMV-specific T cell proliferation to identify patients at risk of developing late onset CMV disease. Bone Marrow Transplant. 1997;19(11):1111–6.
20. Li CR, Greenberg PD, Gilbert MJ, Goodrich JM, Riddell SR. Recovery of HLA-restricted cytomegalovirus (CMV)-specific T-cell responses after allogeneic bone marrow transplant: correlation with CMV disease and effect of ganciclovir prophylaxis. Blood. 1994;83(7):1971–9.
21. Ljungman P, Aschan J, Azinge JN, Brandt L, Ehrnst A, Hammarstrom V, et al. Cytomegalovirus viraemia and specific T-helper cell responses as predictors of disease after allogeneic marrow transplantation. Br J Haematol. 1993;83(1):118–24.
22. Quinnan Jr GV, Kirmani N, Rook AH, Manischewitz JF, Jackson L, Moreschi G, et al. Cytotoxic t cells in cytomegalovirus infection: HLA-restricted T-lymphocyte and non-T-lymphocyte cytotoxic responses correlate with recovery from cytomegalovirus infection in bone-marrow-transplant recipients. N Engl J Med. 1982;307(1):7–13.
23. Reusser P, Riddell SR, Meyers JD, Greenberg PD. Cytotoxic T-lymphocyte response to cytomegalovirus after human allogeneic bone marrow transplantation: pattern of recovery and correlation with cytomegalovirus infection and disease. Blood. 1991;78(5):1373–80.
24. Tormo N, Solano C, Benet I, Nieto J, de la Camara R, Lopez J, et al. Reconstitution of CMV pp 65 and IE-1-specific IFN-gamma CD8(+) and CD4(+) T-cell responses affording protection from CMV DNAemia following allogeneic hematopoietic SCT. Bone Marrow Transplant. 2011;46(11):1437–43.
25. Widmann T, Sester U, Gartner BC, Schubert J, Pfreundschuh M, Kohler H, et al. Levels of CMV specific CD4 T cells are dynamic and correlate with CMV viremia after allogeneic stem cell transplantation. PLoS One. 2008;3(11), e3634.
26. Eid AJ, Brown RA, Hogan WJ, Lahr BD, Eckel-Passow JE, Litzow MR, et al. Kinetics of interferon-gamma producing cytomegalovirus (CMV)-specific CD4+ and CD8+ T lymphocytes and the risk of subsequent CMV viremia after allogeneic hematopoietic stem cell transplantation. Transpl Infect Dis. 2009;11(6):519–28.
27. Peccatori J, Forcina A, Clerici D, Crocchiolo R, Vago L, Stanghellini MT, et al. Sirolimus-based graft-versus-host disease prophylaxis promotes the in vivo expansion of regulatory T cells and permits peripheral blood stem cell transplantation from haploidentical donors. Leukemia. 2015;29(2):396–405.
28. Brown JA, Stevenson K, Kim HT, Cutler C, Ballen K, McDonough S, et al. Clearance of CMV viremia and survival after double umbilical cord blood transplantation in adults depends on reconstitution of thymopoiesis. Blood. 2010;115(20):4111–9.
29. McGoldrick SM, Bleakley ME, Guerrero A, Turtle CJ, Yamamoto TN, Pereira SE, et al. Cytomegalovirus-specific T cells are primed early after cord blood transplant but fail to control virus in vivo. Blood. 2013;121(14):2796–803.
30. Ruggeri A, Peffault de Latour R, Carmagnat M, Clave E, Douay C, Larghero J, et al. Outcomes, infections, and immune reconstitution after double cord blood transplantation in patients with high-risk hematological diseases. Transpl Infect Dis. 2011;13(5):456–65.
31. Britt WJ, Vugler L, Butfiloski EJ, Stephens EB. Cell surface expression of human cytomegalovirus (HCMV) gp55-116 (gB): use of HCMV-recombinant vaccinia virus-infected cells in analysis of the human neutralizing antibody response. J Virol. 1990;64(3):1079–85.
32. Marshall GS, Rabalais GP, Stout GG, Waldeyer SL. Antibodies to recombinant-derived glycoprotein B after natural human cytomegalovirus infection correlate with neutralizing activity. J Infect Dis. 1992;165(2):381–4.
33. Rasmussen L, Matkin C, Spaete R, Pachl C, Merigan TC. Antibody response to human cytomegalovirus glycoproteins

gB and gH after natural infection in humans. J Infect Dis. 1991;164(5):835–42.
34. Boppana SB, Britt WJ. Antiviral antibody responses and intrauterine transmission after primary maternal cytomegalovirus infection. J Infect Dis. 1995;171(5):1115–21.
35. Jonjic S, Pavic I, Lucin P, Rukavina D, Koszinowski UH. Efficacious control of cytomegalovirus infection after long-term depletion of CD8+ T lymphocytes. J Virol. 1990;64(11): 5457–64.
36. Jonjic S, Pavic I, Polic B, Crnkovic I, Lucin P, Koszinowski UH. Antibodies are not essential for the resolution of primary cytomegalovirus infection but limit dissemination of recurrent virus. J Exp Med. 1994;179(5):1713–7.
37. Paludan SR, Bowie AG, Horan KA, Fitzgerald KA. Recognition of herpesviruses by the innate immune system. Nat Rev Immunol. 2011;11(2):143–54.
38. Smith C, Khanna R. Immune regulation of human herpesviruses and its implications for human transplantation. Am J Transplant. 2013;13 Suppl 3:9–23. quiz.
39. Boehme KW, Guerrero M, Compton T. Human cytomegalovirus envelope glycoproteins B and H are necessary for TLR2 activation in permissive cells. J Immunol. 2006;177(10): 7094–102.
40. Compton T, Kurt-Jones EA, Boehme KW, Belko J, Latz E, Golenbock DT, et al. Human cytomegalovirus activates inflammatory cytokine responses via CD14 and Toll-like receptor 2. J Virol. 2003;77(8):4588–96.
41. Juckem LK, Boehme KW, Feire AL, Compton T. Differential initiation of innate immune responses induced by human cytomegalovirus entry into fibroblast cells. J Immunol. 2008;180(7):4965–77.
42. Delale T, Paquin A, Asselin-Paturel C, Dalod M, Brizard G, Bates EE, et al. MyD88-dependent and -independent murine cytomegalovirus sensing for IFN-alpha release and initiation of immune responses in vivo. J Immunol. 2005;175(10): 6723–32.
43. Tabeta K, Georgel P, Janssen E, Du X, Hoebe K, Crozat K, et al. Toll-like receptors 9 and 3 as essential components of innate immune defense against mouse cytomegalovirus infection. Proc Natl Acad Sci U S A. 2004;101(10):3516–21.
44. DeFilippis VR, Alvarado D, Sali T, Rothenburg S, Fruh K. Human cytomegalovirus induces the interferon response via the DNA sensor ZBP1. J Virol. 2010;84(1):585–98.
45. DeFilippis VR, Sali T, Alvarado D, White L, Bresnahan W, Fruh KJ. Activation of the interferon response by human cytomegalovirus occurs via cytoplasmic double-stranded DNA but not glycoprotein B. J Virol. 2010;84(17):8913–25.
46. Krug A, French AR, Barchet W, Fischer JA, Dzionek A, Pingel JT, et al. TLR9-dependent recognition of MCMV by IPC and DC generates coordinated cytokine responses that activate antiviral NK cell function. Immunity. 2004;21(1):107–19.
47. Varani S, Cederarv M, Feld S, Tammik C, Frascaroli G, Landini MP, et al. Human cytomegalovirus differentially controls B cell and T cell responses through effects on plasmacytoid dendritic cells. J Immunol. 2007;179(11):7767–76.
48. Bravo D, Solano C, Gimenez E, Remigia MJ, Corrales I, Amat P, et al. Effect of the IL28B Rs12979860 C/T polymorphism on the incidence and features of active cytomegalovirus infection in allogeneic stem cell transplant patients. J Med Virol. 2014;86(5):838–44.
49. Corrales I, Gimenez E, Solano C, Amat P, de la Camara R, Nieto J, et al. Incidence and dynamics of active cytomegalovirus infection in allogeneic stem cell transplant patients according to single nucleotide polymorphisms in donor and recipient CCR5, MCP-1, IL-10, and TLR9 genes. J Med Virol. 2015;87(2):248–55.
50. Loeffler J, Steffens M, Arlt EM, Toliat MR, Mezger M, Suk A, et al. Polymorphisms in the genes encoding chemokine receptor 5, interleukin-10, and monocyte chemoattractant protein 1 contribute to cytomegalovirus reactivation and disease after allogeneic stem cell transplantation. J Clin Microbiol. 2006;44(5):1847–50.
51. Mezger M, Steffens M, Semmler C, Arlt EM, Zimmer M, Kristjanson GI, et al. Investigation of promoter variations in dendritic cell-specific ICAM3-grabbing non-integrin (DC-SIGN) (CD209) and their relevance for human cytomegalovirus reactivation and disease after allogeneic stem-cell transplantation. Clin Microbiol Infect. 2008;14(3):228–34.
52. Xiao HW, Luo Y, Lai XY, Shi JM, Tan YM, He JS, et al. Donor TLR9 gene tagSNPs influence susceptibility to aGVHD and CMV reactivation in the allo-HSCT setting without polymorphisms in the TLR4 and NOD2 genes. Bone Marrow Transplant. 2014;49(2):241–7.
53. Della Chiesa M, Falco M, Podesta M, Locatelli F, Moretta L, Frassoni F, et al. Phenotypic and functional heterogeneity of human NK cells developing after umbilical cord blood transplantation: a role for human cytomegalovirus? Blood. 2012;119(2):399–410.
54. Guma M, Angulo A, Vilches C, Gomez-Lozano N, Malats N, Lopez-Botet M. Imprint of human cytomegalovirus infection on the NK cell receptor repertoire. Blood. 2004;104(12):3664–71.
55. Guma M, Budt M, Saez A, Brckalo T, Hengel H, Angulo A, et al. Expansion of CD94/NKG2C+ NK cells in response to human cytomegalovirus-infected fibroblasts. Blood. 2006;107(9):3624–31.
56. Malmberg KJ, Beziat V, Ljunggren HG. Spotlight on NKG2C and the human NK-cell response to CMV infection. Eur J Immunol. 2012;42(12):3141–5.
57. Muntasell A, Vilches C, Angulo A, Lopez-Botet M. Adaptive reconfiguration of the human NK-cell compartment in response to cytomegalovirus: a different perspective of the host-pathogen interaction. Eur J Immunol. 2013;43(5):1133–41.
58. Della Chiesa M, Falco M, Bertaina A, Muccio L, Alicata C, Frassoni F, et al. Human cytomegalovirus infection promotes rapid maturation of NK cells expressing activating killer Ig-like receptor in patients transplanted with NKG2C−/− umbilical cord blood. J Immunol. 2014;192(4):1471–9.
59. Bukowski JF, Warner JF, Dennert G, Welsh RM. Adoptive transfer studies demonstrating the antiviral effect of natural killer cells in vivo. J Exp Med. 1985;161(1):40–52.
60. Bukowski JF, Woda BA, Habu S, Okumura K, Welsh RM. Natural killer cell depletion enhances virus synthesis and virus-induced hepatitis in vivo. J Immunol. 1983;131(3):1531–8.
61. Polic B, Hengel H, Krmpotic A, Trgovcich J, Pavic I, Luccaronin P, et al. Hierarchical and redundant lymphocyte subset control precludes cytomegalovirus replication during latent infection. J Exp Med. 1998;188(6):1047–54.
62. Scalzo AA, Fitzgerald NA, Simmons A, La Vista AB, Shellam GR. Cmv-1, a genetic locus that controls murine cytomegalo-

virus replication in the spleen. J Exp Med. 1990;171(5): 1469–83.
63. Scalzo AA, Fitzgerald NA, Wallace CR, Gibbons AE, Smart YC, Burton RC, et al. The effect of the Cmv-1 resistance gene, which is linked to the natural killer cell gene complex, is mediated by natural killer cells. J Immunol. 1992;149(2):581–9.
64. Kuijpers TW, Baars PA, Dantin C, van den Burg M, van Lier RA, Roosnek E. Human NK cells can control CMV infection in the absence of T cells. Blood. 2008;112(3):914–5.
65. Biron CA, Byron KS, Sullivan JL. Severe herpesvirus infections in an adolescent without natural killer cells. N Engl J Med. 1989;320(26):1731–5.
66. Chen C, Busson M, Rocha V, Appert ML, Lepage V, Dulphy N, et al. Activating KIR genes are associated with CMV reactivation and survival after non-T-cell depleted HLA-identical sibling bone marrow transplantation for malignant disorders. Bone Marrow Transplant. 2006;38(6):437–44.
67. Cook M, Briggs D, Craddock C, Mahendra P, Milligan D, Fegan C, et al. Donor KIR genotype has a major influence on the rate of cytomegalovirus reactivation following T-cell replete stem cell transplantation. Blood. 2006;107(3):1230–2.
68. Zaia JA, Sun JY, Gallez-Hawkins GM, Thao L, Oki A, Lacey SF, et al. The effect of single and combined activating killer immunoglobulin-like receptor genotypes on cytomegalovirus infection and immunity after hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2009;15(3):315–25.
69. Crough T, Khanna R. Immunobiology of human cytomegalovirus: from bench to bedside. Clin Microbiol Rev. 2009;22(1):76–98.
70. Sell S, Dietz M, Schneider A, Holtappels R, Mach M, Winkler TH. Control of murine cytomegalovirus infection by gammadelta T cells. PLoS Pathog. 2015;11(2), e1004481.
71. Turchinovich G, Pennington DJ. T cell receptor signalling in gammadelta cell development: strength isn't everything. Trends Immunol. 2011;32(12):567–73.
72. Lafarge X, Merville P, Cazin MC, Berge F, Potaux L, Moreau JF, et al. Cytomegalovirus infection in transplant recipients resolves when circulating gammadelta T lymphocytes expand, suggesting a protective antiviral role. J Infect Dis. 2001;184(5):533–41.
73. Ninomiya T, Takimoto H, Matsuzaki G, Hamano S, Yoshida H, Yoshikai Y, et al. Vgamma1+ gammadelta T cells play protective roles at an early phase of murine cytomegalovirus infection through production of interferon-gamma. Immunology. 2000;99(2):187–94.
74. Pitard V, Roumanes D, Lafarge X, Couzi L, Garrigue I, Lafon ME, et al. Long-term expansion of effector/memory Vdelta2-gammadelta T cells is a specific blood signature of CMV infection. Blood. 2008;112(4):1317–24.
75. Abate DA, Watanabe S, Mocarski ES. Major human cytomegalovirus structural protein pp 65 (ppUL83) prevents interferon response factor 3 activation in the interferon response. J Virol. 2004;78(20):10995–1006.
76. Child SJ, Hakki M, De Niro KL, Geballe AP. Evasion of cellular antiviral responses by human cytomegalovirus TRS1 and IRS1. J Virol. 2004;78(1):197–205.
77. Taylor RT, Bresnahan WA. Human cytomegalovirus immediate-early 2 gene expression blocks virus-induced beta interferon production. J Virol. 2005;79(6):3873–7.
78. Taylor RT, Bresnahan WA. Human cytomegalovirus immediate-early 2 protein IE86 blocks virus-induced chemokine expression. J Virol. 2006;80(2):920–8.
79. Goldmacher VS, Bartle LM, Skaletskaya A, Dionne CA, Kedersha NL, Vater CA, et al. A cytomegalovirus-encoded mitochondria-localized inhibitor of apoptosis structurally unrelated to Bcl-2. Proc Natl Acad Sci U S A. 1999;96(22):12536–41.
80. Nachmani D, Lankry D, Wolf DG, Mandelboim O. The human cytomegalovirus microRNA miR-UL112 acts synergistically with a cellular microRNA to escape immune elimination. Nat Immunol. 2010;11(9):806–13.
81. Stern-Ginossar N, Elefant N, Zimmermann A, Wolf DG, Saleh N, Biton M, et al. Host immune system gene targeting by a viral miRNA. Science. 2007;317(5836):376–81.
82. Wilkinson GW, Tomasec P, Stanton RJ, Armstrong M, Prod'homme V, Aicheler R, et al. Modulation of natural killer cells by human cytomegalovirus. J Clin Virol. 2008;41(3):206–12.
83. Basta S, Bennink JR. A survival game of hide and seek: cytomegaloviruses and MHC class I antigen presentation pathways. Viral Immunol. 2003;16(3):231–42.
84. Ahn K, Gruhler A, Galocha B, Jones TR, Wiertz EJ, Ploegh HL, et al. The ER-luminal domain of the HCMV glycoprotein US6 inhibits peptide translocation by TAP. Immunity. 1997;6(5):613–21.
85. Furman MH, Dey N, Tortorella D, Ploegh HL. The human cytomegalovirus US10 gene product delays trafficking of major histocompatibility complex class I molecules. J Virol. 2002;76(22):11753–6.
86. Gilbert MJ, Riddell SR, Plachter B, Greenberg PD. Cytomegalovirus selectively blocks antigen processing and presentation of its immediate-early gene product. Nature. 1996;383(6602):720–2.
87. Jones TR, Sun L. Human cytomegalovirus US2 destabilizes major histocompatibility complex class I heavy chains. J Virol. 1997;71(4):2970–9.
88. Jones TR, Wiertz EJ, Sun L, Fish KN, Nelson JA, Ploegh HL. Human cytomegalovirus US3 impairs transport and maturation of major histocompatibility complex class I heavy chains. Proc Natl Acad Sci U S A. 1996;93(21):11327–33.
89. Miller DM, Rahill BM, Boss JM, Lairmore MD, Durbin JE, Waldman JW, et al. Human cytomegalovirus inhibits major histocompatibility complex class II expression by disruption of the Jak/Stat pathway. J Exp Med. 1998;187(5):675–83.
90. Miller DM, Zhang Y, Rahill BM, Waldman WJ, Sedmak DD. Human cytomegalovirus inhibits IFN-alpha-stimulated antiviral and immunoregulatory responses by blocking multiple levels of IFN-alpha signal transduction. J Immunol. 1999;162(10): 6107–13.
91. Tomazin R, Boname J, Hegde NR, Lewinsohn DM, Altschuler Y, Jones TR, et al. Cytomegalovirus US2 destroys two components of the MHC class II pathway, preventing recognition by CD4+ T cells. Nat Med. 1999;5(9):1039–43.
92. Wiertz EJ, Jones TR, Sun L, Bogyo M, Geuze HJ, Ploegh HL. The human cytomegalovirus US11 gene product dislocates MHC class I heavy chains from the endoplasmic reticulum to the cytosol. Cell. 1996;84(5):769–79.
93. Benedict CA, Butrovich KD, Lurain NS, Corbeil J, Rooney I, Schneider P, et al. Cutting edge: a novel viral TNF receptor superfamily member in virulent strains of human cytomegalovirus. J Immunol. 1999;162(12):6967–70.
94. Chapman TL, Heikeman AP, Bjorkman PJ. The inhibitory receptor LIR-1 uses a common binding interaction to recognize class I MHC molecules and the viral homolog UL18. Immunity. 1999;11(5):603–13.

95. Gao JL, Murphy PM. Human cytomegalovirus open reading frame US28 encodes a functional beta chemokine receptor. J Biol Chem. 1994;269(46):28539–42.
96. Kotenko SV, Saccani S, Izotova LS, Mirochnitchenko OV, Pestka S. Human cytomegalovirus harbors its own unique IL-10 homolog (cmvIL-10). Proc Natl Acad Sci U S A. 2000;97(4):1695–700.
97. Penfold ME, Dairaghi DJ, Duke GM, Saederup N, Mocarski ES, Kemble GW, et al. Cytomegalovirus encodes a potent alpha chemokine. Proc Natl Acad Sci U S A. 1999;96(17):9839–44.
98. Boeckh M, Boivin G. Quantitation of cytomegalovirus: methodologic aspects and clinical applications. Clin Microbiol Rev. 1998;11(3):533–54.
99. Einsele H, Ehninger G, Hebart H, Wittkowski KM, Schuler U, Jahn G, et al. Polymerase chain reaction monitoring reduces the incidence of cytomegalovirus disease and the duration and side effects of antiviral therapy after bone marrow transplantation. Blood. 1995;86(7):2815–20.
100. Meyers JD, Ljungman P, Fisher LD. Cytomegalovirus excretion as a predictor of cytomegalovirus disease after marrow transplantation: importance of cytomegalovirus viremia. J Infect Dis. 1990;162(2):373–80.
101. Crawford SW, Bowden RA, Hackman RC, Gleaves CA, Meyers JD, Clark JG. Rapid detection of cytomegalovirus pulmonary infection by bronchoalveolar lavage and centrifugation culture. Ann Intern Med. 1988;108(2):180–5.
102. Boeckh M, Bowden RA, Goodrich JM, Pettinger M, Meyers JD. Cytomegalovirus antigen detection in peripheral blood leukocytes after allogeneic marrow transplantation. Blood. 1992;80(5):1358–64.
103. Nichols WG, Corey L, Gooley T, Drew WL, Miner R, Huang M, et al. Rising pp 65 antigenemia during preemptive anticytomegalovirus therapy after allogeneic hematopoietic stem cell transplantation: risk factors, correlation with DNA load, and outcomes. Blood. 2001;97(4):867–74.
104. Green ML, Leisenring W, Stachel D, Pergam SA, Sandmaier BM, Wald A, et al. Efficacy of a viral load-based, risk-adapted, preemptive treatment strategy for prevention of cytomegalovirus disease after hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2012;18(11):1687–99.
105. Jang EY, Park SY, Lee EJ, Song EH, Chong YP, Lee SO, et al. Diagnostic performance of the cytomegalovirus (CMV) antigenemia assay in patients with CMV gastrointestinal disease. Clin Infect Dis. 2009;48(12):e121–4.
106. Mori T, Mori S, Kanda Y, Yakushiji K, Mineishi S, Takaue Y, et al. Clinical significance of cytomegalovirus (CMV) antigenemia in the prediction and diagnosis of CMV gastrointestinal disease after allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant. 2004;33(4):431–4.
107. Ruell J, Barnes C, Mutton K, Foulkes B, Chang J, Cavet J, et al. Active CMV disease does not always correlate with viral load detection. Bone Marrow Transplant. 2007;40(1):55–61.
108. Boeckh M, Huang M, Ferrenberg J, Stevens-Ayers T, Stensland L, Nichols WG, et al. Optimization of quantitative detection of cytomegalovirus DNA in plasma by real-time PCR. J Clin Microbiol. 2004;42(3):1142–8.
109. Boeckh M, Leisenring W, Riddell SR, Bowden RA, Huang ML, Myerson D, et al. Late cytomegalovirus disease and mortality in recipients of allogeneic hematopoietic stem cell transplants: importance of viral load and T-cell immunity. Blood. 2003;101(2):407–14.
110. Einsele H, Hebart H, Kauffmann-Schneider C, Sinzger C, Jahn G, Bader P, et al. Risk factors for treatment failures in patients receiving PCR-based preemptive therapy for CMV infection. Bone Marrow Transplant. 2000;25(7):757–63.
111. Emery VC, Sabin CA, Cope AV, Gor D, Hassan-Walker AF, Griffiths PD. Application of viral-load kinetics to identify patients who develop cytomegalovirus disease after transplantation. Lancet. 2000;355(9220):2032–6.
112. Gor D, Sabin C, Prentice HG, Vyas N, Man S, Griffiths PD, et al. Longitudinal fluctuations in cytomegalovirus load in bone marrow transplant patients: relationship between peak virus load, donor/recipient serostatus, acute GVHD and CMV disease. Bone Marrow Transplant. 1998;21(6):597–605.
113. Ljungman P, Perez-Bercoff L, Jonsson J, Avetisyan G, Sparrelid E, Aschan J, et al. Risk factors for the development of cytomegalovirus disease after allogeneic stem cell transplantation. Haematologica. 2006;91(1):78–83.
114. Lisboa LF, Asberg A, Kumar D, Pang X, Hartmann A, Preiksaitis JK, et al. The clinical utility of whole blood versus plasma cytomegalovirus viral load assays for monitoring therapeutic response. Transplantation. 2011;91(2):231–6.
115. Cathomas G, Morris P, Pekle K, Cunningham I, Emanuel D. Rapid diagnosis of cytomegalovirus pneumonia in marrow transplant recipients by bronchoalveolar lavage using the polymerase chain reaction, virus culture, and the direct immunostaining of alveolar cells. Blood. 1993;81(7):1909–14.
116. Gerna G, Lilleri D, Baldanti F, Torsellini M, Giorgiani G, Zecca M, et al. Human cytomegalovirus immediate-early mRNAemia versus pp 65 antigenemia for guiding pre-emptive therapy in children and young adults undergoing hematopoietic stem cell transplantation: a prospective, randomized, open-label trial. Blood. 2003;101(12):5053–60.
117. Hebart H, Ljungman P, Klingebiel T, Loeffler J, Lewensohhn-Fuchs I, Barkholt L, et al. Prospective comparison of PCR-based versus late mRNA-based preemptive antiviral therapy for HCMV infection in patients after allogeneic stem cell transplantation. Blood. 2003;102(11):195a.
118. Ljungman P, Griffiths P, Paya C. Definitions of cytomegalovirus infection and disease in transplant recipients. Clin Infect Dis. 2002;34(8):1094–7.
119. Boeckh M, Ljungman P. How we treat cytomegalovirus in hematopoietic cell transplant recipients. Blood. 2009;113(23):5711–9.
120. Kotloff RM, Ahya VN, Crawford SW. Pulmonary complications of solid organ and hematopoietic stem cell transplantation. Am J Respir Crit Care Med. 2004;170(1):22–48.
121. Travi G, Pergam SA. Cytomegalovirus pneumonia in hematopoietic stem cell recipients. J Intensive Care Med. 2013;29(4):200–12.
122. Ariza-Heredia EJ, Nesher L, Chemaly RF. Cytomegalovirus diseases after hematopoietic stem cell transplantation: a mini-review. Cancer Lett. 2014;342(1):1–8.
123. Franquet T, Lee KS, Muller NL. Thin-section CT findings in 32 immunocompromised patients with cytomegalovirus pneumonia who do not have AIDS. AJR Am J Roentgenol. 2003;181(4):1059–63.
124. Gasparetto EL, Ono SE, Escuissato D, Marchiori E, Roldan L, Marques HL, et al. Cytomegalovirus pneumonia after bone

marrow transplantation: high resolution CT findings. Br J Radiol. 2004;77(921):724–7.
125. Schmidt GM, Horak DA, Niland JC, Duncan SR, Forman SJ, Zaia JA. A randomized, controlled trial of prophylactic ganciclovir for cytomegalovirus pulmonary infection in recipients of allogeneic bone marrow transplants; The City of Hope-Stanford-Syntex CMV Study Group. N Engl J Med. 1991;324(15):1005–11.
126. Ljungman P. Cytomegalovirus pneumonia: presentation, diagnosis, and treatment. Semin Respir Infect. 1995;10(4):209–15.
127. Boeckh M, Gooley TA, Myerson D, Cunningham T, Schoch G, Bowden RA. Cytomegalovirus pp 65 antigenemia-guided early treatment with ganciclovir versus ganciclovir at engraftment after allogeneic marrow transplantation: a randomized double-blind study. Blood. 1996;88(10):4063–71.
128. Konoplev S, Champlin RE, Giralt S, Ueno NT, Khouri I, Raad I, et al. Cytomegalovirus pneumonia in adult autologous blood and marrow transplant recipients. Bone Marrow Transplant. 2001;27(8):877–81.
129. Horger MS, Pfannenberg C, Einsele H, Beck R, Hebart H, Lengerke C, et al. Cytomegalovirus pneumonia after stem cell transplantation: correlation of CT findings with clinical outcome in 30 patients. AJR Am J Roentgenol. 2006;187(6): W636–43.
130. Vigil KJ, Adachi JA, Chemaly RF. Viral pneumonias in immunocompromised adult hosts. J Intensive Care Med. 2010;25(6): 307–26.
131. Erard V, Guthrie KA, Seo S, Smith J, Huang M, Chien J, et al. Reduced mortality of cytomegalovirus pneumonia after hematopoietic cell transplantation due to antiviral therapy and changes in transplantation practices. Clin Infect Dis. 2015;61(1):31–9.
132. van Burik JA, Lawatsch EJ, DeFor TE, Weisdorf DJ. Cytomegalovirus enteritis among hematopoietic stem cell transplant recipients. Biol Blood Marrow Transplant. 2001;7(12):674–9.
133. Mori T, Okamoto S, Matsuoka S, Yajima T, Wakui M, Watanabe R, et al. Risk-adapted pre-emptive therapy for cytomegalovirus disease in patients undergoing allogeneic bone marrow transplantation. Bone Marrow Transplant. 2000;25(7):765–9.
134. Coskuncan NM, Jabs DA, Dunn JP, Haller JA, Green WR, Vogelsang GB, et al. The eye in bone marrow transplantation. VI. Retinal complications. Arch Ophthalmol. 1994;112(3):372–9.
135. Crippa F, Corey L, Chuang EL, Sale G, Boeckh M. Virological, clinical, and ophthalmologic features of cytomegalovirus retinitis after hematopoietic stem cell transplantation. Clin Infect Dis. 2001;32(2):214–9.
136. Eid AJ, Bakri SJ, Kijpittayarit S, Razonable RR. Clinical features and outcomes of cytomegalovirus retinitis after transplantation. Transpl Infect Dis. 2008;10(1):13–8.
137. Larsson K, Lonnqvist B, Ringden O, Hedquist B, Ljungman P. CMV retinitis after allogeneic bone marrow transplantation: a report of five cases. Transpl Infect Dis. 2002;4(2):75–9.
138. Wolf DG, Lurain NS, Zuckerman T, Hoffman R, Satinger J, Honigman A, et al. Emergence of late cytomegalovirus central nervous system disease in hematopoietic stem cell transplant recipients. Blood. 2003;101(2):463–5.
139. Ando T, Mitani N, Yamashita K, Takahashi T, Ohama E, Miyata H, et al. Cytomegalovirus ventriculoencephalitis in a reduced-intensity conditioning cord blood transplant recipient. Transpl Infect Dis. 2010;12(5):441–5.
140. Reddy SM, Winston DJ, Territo MC, Schiller GJ. CMV central nervous system disease in stem-cell transplant recipients: an increasing complication of drug-resistant CMV infection and protracted immunodeficiency. Bone Marrow Transplant. 2010;45(6):979–84.
141. Razonable R. Direct and indirect effects of cytomegalovirus: can we prevent them? Enferm Infecc Microbiol Clin. 2010;28(1):1–5.
142. Nichols WG, Corey L, Gooley T, Davis C, Boeckh M. High risk of death due to bacterial and fungal infection among cytomegalovirus (CMV)-seronegative recipients of stem cell transplants from seropositive donors: evidence for indirect effects of primary CMV infection. J Infect Dis. 2002;185(3):273–82.
143. Cantoni N, Hirsch HH, Khanna N, Gerull S, Buser A, Bucher C, et al. Evidence for a bidirectional relationship between cytomegalovirus replication and acute graft-versus-host disease. Biol Blood Marrow Transplant. 2010;16(9):1309–14.
144. Jacobsen N, Andersen HK, Skinhoj P, Ryder LP, Platz P, Jerne D, et al. Correlation between donor cytomegalovirus immunity and chronic graft-versus-host disease after allogeneic bone marrow transplantation. Scand J Haematol. 1986;36(5):499–506.
145. Lonnqvist B, Ringden O, Wahren B, Gahrton G, Lundgren G. Cytomegalovirus infection associated with and preceding chronic graft-versus-host disease. Transplantation. 1984;38(5):465–8.
146. Helantera I, Koskinen P, Finne P, Loginov R, Kyllonen L, Salmela K, et al. Persistent cytomegalovirus infection in kidney allografts is associated with inferior graft function and survival. Transpl Int. 2006;19(11):893–900.
147. Kliem V, Fricke L, Wollbrink T, Burg M, Radermacher J, Rohde F. Improvement in long-term renal graft survival due to CMV prophylaxis with oral ganciclovir: results of a randomized clinical trial. Am J Transplant. 2008;8(5):975–83.
148. Reischig T, Jindra P, Hes O, Bouda M, Kormunda S, Treska V. Effect of cytomegalovirus viremia on subclinical rejection or interstitial fibrosis and tubular atrophy in protocol biopsy at 3 months in renal allograft recipients managed by preemptive therapy or antiviral prophylaxis. Transplantation. 2009;87(3): 436–44.
149. Snydman DR. The case for cytomegalovirus prophylaxis in solid organ transplantation. Rev Med Virol. 2006;16(5):289–95.
150. Lonnqvist B, Ringden O, Ljungman P, Wahren B, Gahrton G. Reduced risk of recurrent leukaemia in bone marrow transplant recipients after cytomegalovirus infection. Br J Haematol. 1986;63(4):671–9.
151. Behrendt CE, Rosenthal J, Bolotin E, Nakamura R, Zaia J, Forman SJ. Donor and recipient CMV serostatus and outcome of pediatric allogeneic HSCT for acute leukemia in the era of CMV-preemptive therapy. Biol Blood Marrow Transplant. 2009;15(1):54–60.
152. Elmaagacli AH, Steckel NK, Koldehoff M, Hegerfeldt Y, Trenschel R, Ditschkowski M, et al. Early human cytomegalovirus replication after transplantation is associated with a decreased relapse risk: evidence for a putative virus-versus-leukemia effect in acute myeloid leukemia patients. Blood. 2011;118(5):1402–12.
153. Green ML, Leisenring WM, Xie H, Walter RB, Mielcarek M, Sandmaier BM, et al. CMV reactivation after allogeneic HCT and relapse risk: evidence for early protection in acute myeloid leukemia. Blood. 2013;122(7):1316–24.

154. Ito S, Pophali P, Co W, Koklanaris EK, Superata J, Fahle GA, et al. CMV reactivation is associated with a lower incidence of relapse after allo-SCT for CML. Bone Marrow Transplant. 2013;48(10):1313–6.
155. Scheper W, van Dorp S, Kersting S, Pietersma F, Lindemans C, Hol S, et al. GammadeltaT cells elicited by CMV reactivation after allo-SCT cross-recognize CMV and leukemia. Leukemia. 2013;27(6): 1328–38.
156. Foley B, Cooley S, Verneris MR, Pitt M, Curtsinger J, Luo X, et al. Cytomegalovirus reactivation after allogeneic transplantation promotes a lasting increase in educated NKG2C+ natural killer cells with potent function. Blood. 2012;119(11):2665–74.
157. Koldehoff M, Lindemann M, Opalka B, Bauer S, Ross RS, Elmaagacli AH. Cytomegalovirus induces apoptosis in acute leukemia cells as a virus-versus-leukemia function. Leuk Lymphoma. 2015;1–25.
158. Challa-Malladi M, Lieu YK, Califano O, Holmes AB, Bhagat G, Murty VV, et al. Combined genetic inactivation of beta2-Microglobulin and CD58 reveals frequent escape from immune recognition in diffuse large B cell lymphoma. Cancer Cell. 2011;20(6):728–40.
159. Ruggeri L, Capanni M, Urbani E, Perruccio K, Shlomchik WD, Tosti A, et al. Effectiveness of donor natural killer cell alloreactivity in mismatched hematopoietic transplants. Science. 2002;295(5562):2097–100.
160. Schmidt-Hieber M, Labopin M, Beelen D, Volin L, Ehninger G, Finke J, et al. CMV serostatus still has an important prognostic impact in de novo acute leukemia patients after allogeneic stem cell transplantation: a report from the Acute Leukemia Working Party of EBMT. Blood. 2013;122(19):3359–64.
161. George B, Pati N, Gilroy N, Ratnamohan M, Huang G, Kerridge I, et al. Pre-transplant cytomegalovirus (CMV) serostatus remains the most important determinant of CMV reactivation after allogeneic hematopoietic stem cell transplantation in the era of surveillance and preemptive therapy. Transpl Infect Dis. 2010;12(4):322–9.
162. Hiwarkar P, Gaspar HB, Gilmour K, Jagani M, Chiesa R, Bennett-Rees N, et al. Impact of viral reactivations in the era of pre-emptive antiviral drug therapy following allogeneic haematopoietic SCT in paediatric recipients. Bone Marrow Transplant. 2013;48(6):803–8.
163. Pergam SA, Xie H, Sandhu R, Pollack M, Smith J, Stevens-Ayers T, et al. Efficiency and risk factors for CMV transmission in seronegative hematopoietic stem cell recipients. Biol Blood Marrow Transplant. 2012;18(9):1391–400.
164. Ljungman P. The role of cytomegalovirus serostatus on outcome of hematopoietic stem cell transplantation. Curr Opin Hematol. 2014;21(6):466–9.
165. Bowden RA, Sayers M, Flournoy N, Newton B, Banaji M, Thomas ED, et al. Cytomegalovirus immune globulin and seronegative blood products to prevent primary cytomegalovirus infection after marrow transplantation. N Engl J Med. 1986;314(16):1006–10.
166. Ljungman P, Brand R, Hoek J, de la Camara R, Cordonnier C, Einsele H, et al. Donor cytomegalovirus status influences the outcome of allogeneic stem cell transplant: a study by the European group for blood and marrow transplantation. Clin Infect Dis. 2014;59(4):473–81.
167. Broers AE, van Der Holt R, van Esser JW, Gratama JW, Henzen-Logmans S, Kuenen-Boumeester V, et al. Increased transplant-related morbidity and mortality in CMV-seropositive patients despite highly effective prevention of CMV disease after allogeneic T-cell-depleted stem cell transplantation. Blood. 2000;95(7):2240–5.
168. Craddock C, Szydlo RM, Dazzi F, Olavarria E, Cwynarski K, Yong A, et al. Cytomegalovirus seropositivity adversely influences outcome after T-depleted unrelated donor transplant in patients with chronic myeloid leukaemia: the case for tailored graft-versus-host disease prophylaxis. Br J Haematol. 2001;112(1):228–36.
169. Boeckh M, Nichols WG. The impact of cytomegalovirus serostatus of donor and recipient before hematopoietic stem cell transplantation in the era of antiviral prophylaxis and preemptive therapy. Blood. 2004;103(6):2003–8.
170. Zhou W, Longmate J, Lacey SF, Palmer JM, Gallez-Hawkins G, Thao L, et al. Impact of donor CMV-status on viral infection and reconstitution of multi-function CMV-specific T-cells in CMV-positive transplant recipients. Blood. 2009; 113(25):6465–76.
171. Bordon V, Bravo S, Van Renterghem L, de Moerloose B, Benoit Y, Laureys G, et al. Surveillance of cytomegalovirus (CMV) DNAemia in pediatric allogeneic stem cell transplantation: incidence and outcome of CMV infection and disease. Transpl Infect Dis. 2008;10(1):19–23.
172. Cwynarski K, Roberts IA, Iacobelli S, van Biezen A, Brand R, Devergie A, et al. Stem cell transplantation for chronic myeloid leukemia in children. Blood. 2003;102(4):1224–31.
173. Erard V, Guthrie KA, Riddell S, Boeckh M. Impact of HLA A2 and cytomegalovirus serostatus on outcomes in patients with leukemia following matched-sibling myeloablative allogeneic hematopoietic cell transplantation. Haematologica. 2006;91(10):1377–83.
174. Grob JP, Grundy JE, Prentice HG, Griffiths PD, Hoffbrand AV, Hughes MD, et al. Immune donors can protect marrow-transplant recipients from severe cytomegalovirus infections. Lancet. 1987;1(8536):774–6.
175. Jacobsen N, Badsberg JH, Lonnqvist B, Ringden O, Volin L, Rajantie J, et al. Graft-versus-leukaemia activity associated with CMV-seropositive donor, post-transplant CMV infection, young donor age and chronic graft-versus-host disease in bone marrow allograft recipients. The Nordic Bone Marrow Transplantation Group. Bone Marrow Transplant. 1990;5(6):413–8.
176. Kollman C, Howe CW, Anasetti C, Antin JH, Davies SM, Filipovich AH, et al. Donor characteristics as risk factors in recipients after transplantation of bone marrow from unrelated donors: the effect of donor age. Blood. 2001;98(7):2043–51.
177. Nachbaur D, Clausen J, Kircher B. Donor cytomegalovirus seropositivity and the risk of leukemic relapse after reduced-intensity transplants. Eur J Haematol. 2006;76(5):414–9.
178. Gustafsson Jernberg A, Remberger M, Ringden O, Winiarski J. Risk factors in pediatric stem cell transplantation for leukemia. Pediatr Transplant. 2004;8(5):464–74.
179. Ljungman P, Einsele H, Frassoni F, Niederwieser D, Cordonnier C. Donor CMV serological status influences the outcome of CMVseropositive recipients after unrelated donor stem cell transplantation. An EBMT Megafile analysis. Blood. 2003;102:4255–60.

180. Avetisyan G, Aschan J, Hagglund H, Ringden O, Ljungman P. Evaluation of intervention strategy based on CMV-specific immune responses after allogeneic SCT. Bone Marrow Transplant. 2007;40(9):865–9.
181. Ganepola S, Gentilini C, Hilbers U, Lange T, Rieger K, Hofmann J, et al. Patients at high risk for CMV infection and disease show delayed CD8+ T-cell immune recovery after allogeneic stem cell transplantation. Bone Marrow Transplant. 2007;39(5):293–9.
182. Lilleri D, Fornara C, Chiesa A, Caldera D, Alessandrino EP, Gerna G. Human cytomegalovirus-specific CD4+ and CD8+ T-cell reconstitution in adult allogeneic hematopoietic stem cell transplant recipients and immune control of viral infection. Haematologica. 2008;93(2):248–56.
183. Moins-Teisserenc H, Busson M, Scieux C, Bajzik V, Cayuela JM, Clave E, et al. Patterns of cytomegalovirus reactivation are associated with distinct evolutive profiles of immune reconstitution after allogeneic hematopoeitic stem cell transplantation. J Infect Dis. 2008;198(6):818–26.
184. Lin TS, Zahrieh D, Weller E, Alyea EP, Antin JH, Soiffer RJ. Risk factors for cytomegalovirus reactivation after CD6+ T-cell-depleted allogeneic bone marrow transplantation. Transplantation. 2002;74(1):49–54.
185. Ozdemir E, Saliba R, Champlin R, Couriel D, Giralt S, de Lima M, et al. Risk factors associated with late cytomegalovirus reactivation after allogeneic stem cell transplantation for hematological malignancies. Bone Marrow Transplant. 2007;40(2):125–36.
186. Marty FM, Bryar J, Browne SK, Schwarzberg T, Ho VT, Bassett IV, et al. Sirolimus-based graft-versus-host disease prophylaxis protects against cytomegalovirus reactivation after allogeneic hematopoietic stem cell transplantation: a cohort analysis. Blood. 2007;110(2):490–500.
187. Ljungman P, Aschan J, Lewensohn-Fuchs I, Carlens S, Larsson K, Lonnqvist B, et al. Results of different strategies for reducing cytomegalovirus-associated mortality in allogeneic stem cell transplant recipients. Transplantation. 1998;66(10):1330–4.
188. Martino R, Rovira M, Carreras E, Solano C, Jorge S, De La Rubia J, et al. Severe infections after allogeneic peripheral blood stem cell transplantation: a matched-pair comparison of unmanipulated and CD34+ cell-selected transplantation. Haematologica. 2001;86(10):1075–86.
189. Miller W, Flynn P, McCullough J, Balfour Jr HH, Goldman A, Haake R, et al. Cytomegalovirus infection after bone marrow transplantation: an association with acute graft-v-host disease. Blood. 1986;67(4):1162–7.
190. Walker CM, van Burik JA, De For TE, Weisdorf DJ. Cytomegalovirus infection after allogeneic transplantation: comparison of cord blood with peripheral blood and marrow graft sources. Biol Blood Marrow Transplant. 2007;13(9):1106–15.
191. Holmberg LA, Boeckh M, Hooper H, Leisenring W, Rowley S, Heimfeld S, et al. Increased incidence of cytomegalovirus disease after autologous CD34-selected peripheral blood stem cell transplantation. Blood. 1999;94(12):4029–35.
192. Trenschel R, Ross S, Husing J, Ottinger H, Elmaagacli A, Roggendorf M, et al. Reduced risk of persisting cytomegalovirus pp 65 antigenemia and cytomegalovirus interstitial pneumonia following allogeneic PBSCT. Bone Marrow Transplant. 2000;25(6):665–72.
193. Kudchodkar SB, Yu Y, Maguire TG, Alwine JC. Human cytomegalovirus infection alters the substrate specificities and rapamycin sensitivities of raptor- and rictor-containing complexes. Proc Natl Acad Sci U S A. 2006;103(38):14182–7.
194. Kornblit B, Maloney DG, Storer BE, Maris MB, Vindelov L, Hari P, et al. A randomized phase II trial of tacrolimus, mycophenolate mofetil and sirolimus after non-myeloablative unrelated donor transplantation. Haematologica. 2014;99(10):1624–31.
195. Junghanss C, Boeckh M, Carter RA, Sandmaier BM, Maris MB, Maloney DG, et al. Incidence and outcome of cytomegalovirus infections following nonmyeloablative compared with myeloablative allogeneic stem cell transplantation, a matched control study. Blood. 2002;99(6):1978–85.
196. Nakamae H, Kirby KA, Sandmaier BM, Norasetthada L, Maloney DG, Maris MB, et al. Effect of conditioning regimen intensity on CMV infection in allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2009;15(6):694–703.
197. Schoemans H, Theunissen K, Maertens J, Boogaerts M, Verfaillie C, Wagner J. Adult umbilical cord blood transplantation: a comprehensive review. Bone Marrow Transplant. 2006;38(2):83–93.
198. Jacobson CA, Turki AT, McDonough SM, Stevenson KE, Kim HT, Kao G, et al. Immune reconstitution after double umbilical cord blood stem cell transplantation: comparison with unrelated peripheral blood stem cell transplantation. Biol Blood Marrow Transplant. 2012;18(4):565–74.
199. Montesinos P, Sanz J, Cantero S, Lorenzo I, Martin G, Saavedra S, et al. Incidence, risk factors, and outcome of cytomegalovirus infection and disease in patients receiving prophylaxis with oral valganciclovir or intravenous ganciclovir after umbilical cord blood transplantation. Biol Blood Marrow Transplant. 2009;15(6):730–40.
200. Mikulska M, Raiola AM, Bruzzi P, Varaldo R, Annunziata S, Lamparelli T, et al. CMV infection after transplant from cord blood compared to other alternative donors: the importance of donor-negative CMV serostatus. Biol Blood Marrow Transplant. 2012;18(1):92–9.
201. Beck JC, Wagner JE, DeFor TE, Brunstein CG, Schleiss MR, Young JA, et al. Impact of cytomegalovirus (CMV) reactivation after umbilical cord blood transplantation. Biol Blood Marrow Transplant. 2010;16(2):215–22.
202. Sauter C, Abboud M, Jia X, Heller G, Gonzales AM, Lubin M, et al. Serious infection risk and immune recovery after double-unit cord blood transplantation without antithymocyte globulin. Biol Blood Marrow Transplant. 2011;17(10):1460–71.
203. Albano MS, Taylor P, Pass RF, Scaradavou A, Ciubotariu R, Carrier C, et al. Umbilical cord blood transplantation and cytomegalovirus: posttransplantation infection and donor screening. Blood. 2006;108(13):4275–82.
204. Matsumura T, Narimatsu H, Kami M, Yuji K, Kusumi E, Hori A, et al. Cytomegalovirus infections following umbilical cord blood transplantation using reduced intensity conditioning regimens for adult patients. Biol Blood Marrow Transplant. 2007;13(5):577–83.
205. Milano F, Pergam SA, Xie H, Leisenring WM, Gutman JA, Riffkin I, et al. Intensive strategy to prevent CMV disease in seropositive umbilical cord blood transplant recipients. Blood. 2011;118(20):5689–96.

206. Saavedra S, Sanz GF, Jarque I, Moscardo F, Jimenez C, Lorenzo I, et al. Early infections in adult patients undergoing unrelated donor cord blood transplantation. Bone Marrow Transplant. 2002;30(12):937–43.
207. Takami A, Mochizuki K, Asakura H, Yamazaki H, Okumura H, Nakao S. High incidence of cytomegalovirus reactivation in adult recipients of an unrelated cord blood transplant. Haematologica. 2005;90(9):1290–2.
208. Tomonari A, Iseki T, Ooi J, Takahashi S, Shindo M, Ishii K, et al. Cytomegalovirus infection following unrelated cord blood transplantation for adult patients: a single institute experience in Japan. Br J Haematol. 2003;121(2):304–11.
209. Reisner Y, Hagin D, Martelli MF. Haploidentical hematopoietic transplantation: current status and future perspectives. Blood. 2011;118(23):6006–17.
210. Aversa F, Tabilio A, Velardi A, Cunningham I, Terenzi A, Falzetti F, et al. Treatment of high-risk acute leukemia with T-cell-depleted stem cells from related donors with one fully mismatched HLA haplotype. N Engl J Med. 1998;339(17):1186–93.
211. Aversa F, Terenzi A, Tabilio A, Falzetti F, Carotti A, Ballanti S, et al. Full haplotype-mismatched hematopoietic stem-cell transplantation: a phase II study in patients with acute leukemia at high risk of relapse. J Clin Oncol. 2005;23(15):3447–54.
212. Mehta J, Singhal S, Gee AP, Chiang KY, Godder K, Rhee Fv F, et al. Bone marrow transplantation from partially HLA-mismatched family donors for acute leukemia: single-center experience of 201 patients. Bone Marrow Transplant. 2004;33(4):389–96.
213. Shmueli E, Or R, Shapira MY, Resnick IB, Caplan O, Bdolah-Abram T, et al. High rate of cytomegalovirus drug resistance among patients receiving preemptive antiviral treatment after haploidentical stem cell transplantation. J Infect Dis. 2014;209(4):557–61.
214. Luznik L, O'Donnell PV, Fuchs EJ. Post-transplantation cyclophosphamide for tolerance induction in HLA-haploidentical bone marrow transplantation. Semin Oncol. 2012;39(6):683–93.
215. Luznik L, O'Donnell PV, Symons HJ, Chen AR, Leffell MS, Zahurak M, et al. HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide. Biol Blood Marrow Transplant. 2008;14(6):641–50.
216. Raiola AM, Dominietto A, di Grazia C, Lamparelli T, Gualandi F, Ibatici A, et al. Unmanipulated haploidentical transplants compared with other alternative donors and matched sibling grafts. Biol Blood Marrow Transplant. 2014;20(10):1573–9.
217. Boeckh M, Stevens-Ayers T, Bowden RA. Cytomegalovirus pp 65 antigenemia after autologous marrow and peripheral blood stem cell transplantation. J Infect Dis. 1996;174(5):907–12.
218. Hebart H, Schroder A, Loffler J, Klingebiel T, Martin H, Wassmann B, et al. Cytomegalovirus monitoring by polymerase chain reaction of whole blood samples from patients undergoing autologous bone marrow or peripheral blood progenitor cell transplantation. J Infect Dis. 1997;175(6):1490–3.
219. Bilgrami S, Aslanzadeh J, Feingold JM, Bona RD, Clive J, Dorsky D, et al. Cytomegalovirus viremia, viruria and disease after autologous peripheral blood stem cell transplantation: no need for surveillance. Bone Marrow Transplant. 1999;24(1):69–73.
220. Boeckh M, Gooley TA, Reusser P, Buckner CD, Bowden RA. Failure of high-dose acyclovir to prevent cytomegalovirus disease after autologous marrow transplantation. J Infect Dis. 1995;172(4):939–43.
221. Singhal S, Powles R, Treleaven J, Horton C, Pinkerton CR, Meller S, et al. Cytomegaloviremia after autografting for leukemia: clinical significance and lack of effect on engraftment. Leukemia. 1997;11(6):835–8.
222. Enright H, Haake R, Weisdorf D, Ramsay N, McGlave P, Kersey J, et al. Cytomegalovirus pneumonia after bone marrow transplantation. Risk factors and response to therapy. Transplantation. 1993;55(6):1339–46.
223. Reusser P, Fisher LD, Buckner CD, Thomas ED, Meyers JD. Cytomegalovirus infection after autologous bone marrow transplantation: occurrence of cytomegalovirus disease and effect on engraftment. Blood. 1990;75(9):1888–94.
224. Einsele H, Steidle M, Vallbracht A, Saal JG, Ehninger G, Muller CA. Early occurrence of human cytomegalovirus infection after bone marrow transplantation as demonstrated by the polymerase chain reaction technique. Blood. 1991;77(5):1104–10.
225. Nguyen Q, Champlin R, Giralt S, Rolston K, Raad I, Jacobson K, et al. Late cytomegalovirus pneumonia in adult allogeneic blood and marrow transplant recipients. Clin Infect Dis. 1999;28(3):618–23.
226. Perez-Bercoff L, Vudattu NK, Byrareddy SN, Mattsson J, Maeurer M, Ljungman P. Reduced IL-7 responsiveness defined by signal transducer and activator of transcription 5 phosphorylation in T cells may be a marker for increased risk of developing cytomegalovirus disease in patients after hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2014;20(1):128–32.
227. Salzberger B, Bowden RA, Hackman RC, Davis C, Boeckh M. Neutropenia in allogeneic marrow transplant recipients receiving ganciclovir for prevention of cytomegalovirus disease: risk factors and outcome. Blood. 1997;90(6):2502–8.
228. Goodrich JM, Bowden RA, Fisher L, Keller C, Schoch G, Meyers JD. Ganciclovir prophylaxis to prevent cytomegalovirus disease after allogeneic marrow transplant. Ann Intern Med. 1993;118(3):173–8.
229. Einsele H, Reusser P, Bornhauser M, Kalhs P, Ehninger G, Hebart H, et al. Oral valganciclovir leads to higher exposure to ganciclovir than intravenous ganciclovir in patients following allogeneic stem cell transplantation. Blood. 2006;107(7):3002–8.
230. Winston DJ, Baden LR, Gabriel DA, Emmanouilides C, Shaw LM, Lange WR, et al. Pharmacokinetics of ganciclovir after oral valganciclovir versus intravenous ganciclovir in allogeneic stem cell transplant patients with graft-versus-host disease of the gastrointestinal tract. Biol Blood Marrow Transplant. 2006;12(6):635–40.
231. Reusser P, Einsele H, Lee J, Volin L, Rovira M, Engelhard D, et al. Randomized multicenter trial of foscarnet versus ganciclovir for preemptive therapy of cytomegalovirus infection after allogeneic stem cell transplantation. Blood. 2002;99(4):1159–64.
232. Lurain NS, Chou S. Antiviral drug resistance of human cytomegalovirus. Clin Microbiol Rev. 2010;23(4):689–712.
233. Drew WL. Is combination antiviral therapy for CMV superior to monotherapy? J Clin Virol. 2006;35(4):485–8.

234. Biron KK, Harvey RJ, Chamberlain SC, Good SS, Smith 3rd AA, Davis MG, et al. Potent and selective inhibition of human cytomegalovirus replication by 1263W94, a benzimidazole L-riboside with a unique mode of action. Antimicrob Agents Chemother. 2002;46(8):2365–72.
235. Drew WL, Miner RC, Marousek GI, Chou S. Maribavir sensitivity of cytomegalovirus isolates resistant to ganciclovir, cidofovir or foscarnet. J Clin Virol. 2006;37(2):124–7.
236. Chou S, Marousek GI. Maribavir antagonizes the antiviral action of ganciclovir on human cytomegalovirus. Antimicrob Agents Chemother. 2006;50(10):3470–2.
237. Marty FM, Ljungman P, Papanicolaou GA, Winston DJ, Chemaly RF, Strasfeld L, et al. Maribavir prophylaxis for prevention of cytomegalovirus disease in recipients of allogeneic stem-cell transplants: a phase 3, double-blind, placebo-controlled, randomised trial. Lancet Infect Dis. 2011;11(4):284–92.
238. Wang LH, Peck RW, Yin Y, Allanson J, Wiggs R, Wire MB. Phase I safety and pharmacokinetic trials of 1263W94, a novel oral anti-human cytomegalovirus agent, in healthy and human immunodeficiency virus-infected subjects. Antimicrob Agents Chemother. 2003;47(4):1334–42.
239. Winston DJ, Young JA, Pullarkat V, Papanicolaou GA, Vij R, Vance E, et al. Maribavir prophylaxis for prevention of cytomegalovirus infection in allogeneic stem-cell transplant recipients: a multicenter, randomized, double-blind, placebo-controlled, dose-ranging study. Blood. 2008;111:5403–10.
240. Marty FM, Boeckh M. Maribavir and human cytomegalovirus—what happened in the clinical trials and why might the drug have failed? Curr Opin Virol. 2011;1(6):555–62.
241. Alain S, Revest M, Veyer D, Essig M, Rerolles JP, Rawlinson W, et al. Maribavir use in practice for cytomegalovirus infection in French transplantation centers. Transplant Proc. 2013;45(4):1603–7.
242. Avery RK, Marty FM, Strasfeld L, Lee I, Arrieta A, Chou S, et al. Oral maribavir for treatment of refractory or resistant cytomegalovirus infections in transplant recipients. Transpl Infect Dis. 2010;12(6):489–96.
243. Schubert A, Ehlert K, Schuler-Luettmann S, Gentner E, Mertens T, Michel D. Fast selection of maribavir resistant cytomegalovirus in a bone marrow transplant recipient. BMC Infect Dis. 2013;13:330.
244. Strasfeld L, Lee I, Villano S, Chou S. Virologic characterization of multi-drug-resistant cytomegalovirus infection in two transplant recipients treated with maribavir. J Infect Dis. 2010;202(1):104–8.
245. Lischka P, Hewlett G, Wunberg T, Baumeister J, Paulsen D, Goldner T, et al. In vitro and in vivo activities of the novel anticytomegalovirus compound AIC246. Antimicrob Agents Chemother. 2010;54(3):1290–7.
246. Kaul DR, Stoelben S, Cober E, Ojo T, Sandusky E, Lischka P, et al. First report of successful treatment of multidrug-resistant cytomegalovirus disease with the novel anti-CMV compound AIC246. Am J Transplant. 2011;11(5):1079–84.
247. Chemaly RF, Ullmann AJ, Stoelben S, Richard MP, Bornhauser M, Groth C, et al. Letermovir for cytomegalovirus prophylaxis in hematopoietic-cell transplantation. N Engl J Med. 2014;370(19):1781–9.
248. Goldner T, Hempel C, Ruebsamen-Schaeff H, Zimmermann H, Lischka P. Geno- and phenotypic characterization of human cytomegalovirus mutants selected in vitro after letermovir (AIC246) exposure. Antimicrob Agents Chemother. 2014;58(1):610–3.
249. Wildum S, Zimmermann H, Lischka P. In vitro drug combination studies of Letermovir (AIC246, MK-8228) with approved anti-human cytomegalovirus (HCMV) and anti-HIV compounds in inhibition of HCMV and HIV replication. Antimicrob Agents Chemother. 2015;59(6):3140–8.
250. Dropulic LK, Cohen JI. Update on new antivirals under development for the treatment of double-stranded DNA virus infections. Clin Pharmacol Ther. 2010;88(5):610–9.
251. Marty FM, Winston DJ, Rowley SD, Vance E, Papanicolaou GA, Mullane KM, et al. CMX001 to prevent cytomegalovirus disease in hematopoietic-cell transplantation. N Engl J Med. 2013;369(13):1227–36.
252. Hakki M, Chou S. The biology of cytomegalovirus drug resistance. Curr Opin Infect Dis. 2011;24(6):605–11.
253. Avery RK, Bolwell BJ, Yen-Lieberman B, Lurain N, Waldman WJ, Longworth DL, et al. Use of leflunomide in an allogeneic bone marrow transplant recipient with refractory cytomegalovirus infection. Bone Marrow Transplant. 2004;34(12):1071–5.
254. Efferth T, Marschall M, Wang X, Huong SM, Hauber I, Olbrich A, et al. Antiviral activity of artesunate towards wild-type, recombinant, and ganciclovir-resistant human cytomegaloviruses. J Mol Med. 2002;80(4):233–42.
255. Efferth T, Romero MR, Wolf DG, Stamminger T, Marin JJ, Marschall M. The antiviral activities of artemisinin and artesunate. Clin Infect Dis. 2008;47(6):804–11.
256. Kudchodkar SB, Yu Y, Maguire TG, Alwine JC. Human cytomegalovirus infection induces rapamycin-insensitive phosphorylation of downstream effectors of mTOR kinase. J VIrol. 2004;78(20):11030–9.
257. Bowden R, Cays M, Schoch G, Sayers M, Slichter S, Welk K, et al. Comparison of filtered blood (FB) to seronegative blood products (SB) for prevention of cytomegalovirus (CMV) infection after marrow transplant. Blood. 1995;86:3598–603.
258. Ljungman P, Larsson K, Kumlien G, Aschan J, Barkholt L, Gustafsson-Jernberg A, et al. Leukocyte depleted, unscreened blood products give a low risk for CMV infection and disease in CMV seronegative allogeneic stem cell transplant recipients with seronegative stem cell donors. Scand J Infect Dis. 2002; 34(5):347–50.
259. Nichols WG, Price TH, Gooley T, Corey L, Boeckh M. Transfusion-transmitted cytomegalovirus infection after receipt of leukoreduced blood products. Blood. 2003;101(10):4195–200.
260. Blajchman MA, Goldman M, Freedman JJ, Sher GD. Proceedings of a consensus conference: prevention of post-transfusion CMV in the era of universal leukoreduction. Transfus Med Rev. 2001;15(1):1–20.
261. Ratko TA, Cummings JP, Oberman HA, Crookston KP, DeChristopher PJ, Eastlund DT, et al. Evidence-based recommendations for the use of WBC-reduced cellular blood components. Transfusion. 2001;41(10):1310–9.
262. Bowden RA, Fisher LD, Rogers K, Cays M, Meyers JD. Cytomegalovirus (CMV)-specific intravenous immunoglobulin for the prevention of primary CMV infection and disease after marrow transplant [see comments]. J Infect Dis. 1991;164(3):483–7.
263. Ruutu T, Ljungman P, Brinch L, Lenhoff S, Lonnqvist B, Ringden O, et al. No prevention of cytomegalovirus infection

by anti-cytomegalovirus hyperimmune globulin in seronegative bone marrow transplant recipients. The Nordic BMT Group. Bone Marrow Transplant. 1997;19(3):233–6.
264. Boeckh M, Bowden R, Storer B, Chao N, Spielberger R, Tierney D, et al. Randomized, placebo-controlled, double-blind study of a cytomegalovirus-specific monoclonal antibody (MSL-109) for prevention of cytomegalovirus infection after allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2001;7(6):343–51.
265. Bass E, Powe N, Goodman S, Graziano S, Griffiths R, Kickler T, et al. Efficacy of immune globulin in preventing complications of bone marrow transplantation: a meta-analysis. Bone Marrow Transplant. 1993;12:179–83.
266. Messori A, Rampazzo R, Scroccaro G, Martini N. Efficacy of hyperimmune anti-cytomegalovirus immunoglobulins for the prevention of cytomegalovirus infection in recipients of allogeneic bone marrow transplantation: a meta analysis. Bone Marrow Transplant. 1994;13:163–8.
267. Raanani P, Gafter-Gvili A, Paul M, Ben-Bassat I, Leibovici L, Shpilberg O. Immunoglobulin prophylaxis in hematopoietic stem cell transplantation: systematic review and meta-analysis. J Clin Oncol. 2009;27(5):770–81.
268. Sullivan KM, Kopecky KJ, Jocom J, Fisher L, Buckner CD, Meyers JD, et al. Immunomodulatory and antimicrobial efficacy of intravenous immunoglobulin in bone marrow transplantation. N Engl J Med. 1990;323(11):705–12.
269. Winston DJ, Ho WG, Lin CH, Bartoni K, Budinger MD, Gale RP, et al. Intravenous immune globulin for prevention of cytomegalovirus infection and interstitial pneumonia after bone marrow transplantation. Ann Intern Med. 1987;106(1):12–8.
270. Zikos P, Van Lint MT, Lamparelli T, Gualandi F, Occhini D, Mordini N, et al. A randomized trial of high dose polyvalent intravenous immunoglobulin (HDIgG) vs. Cytomegalovirus (CMV) hyperimmune IgG in allogeneic hemopoietic stem cell transplants (HSCT). Haematologica. 1998;83(2):132–7.
271. Tomblyn M, Chiller T, Einsele H, Gress R, Sepkowitz K, Storek J, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant. 2009;15(10):1143–238.
272. Boeckh M, Nichols WG, Chemaly RF, Papanicolaou GA, Wingard JR, Xie H, et al. Valganciclovir for the prevention of complications of late cytomegalovirus infection after allogeneic hematopoietic cell transplantation: a randomized trial. Ann Intern Med. 2015;162(1):1–10.
273. Pollack M, Heugel J, Xie H, Leisenring W, Storek J, Young JA, et al. An international comparison of current strategies to prevent herpesvirus and fungal infections in hematopoietic cell transplant recipients. Biol Blood Marrow Transplant. 2011;17(5):664–73.
274. Ljungman P, De La Camara R, Milpied N, Volin L, Russell CA, Webster A, et al. A randomised study of valaciclovir as prophylaxis against CMV reactivation in allogeneic bone marrow transplant recipients. Blood. 2002;73:930–6.
275. Meyers JD, Reed EC, Shepp DH, Thornquist M, Dandliker PS, Vicary CA, et al. Acyclovir for prevention of cytomegalovirus infection and disease after allogeneic marrow transplantation. N Engl J Med. 1988;318(2):70–5.
276. Prentice HG, Gluckman E, Powles RL, Ljungman P, Milpied N, Fernandez Ranada JM, et al. Impact of long-term acyclovir on cytomegalovirus infection and survival after allogeneic bone marrow transplantation. European Acyclovir for CMV Prophylaxis Study Group. Lancet. 1994;343(8900):749–53.
277. Winston DJ, Ho WG, Bartoni K, Du Mond C, Ebeling DF, Buhles WC, et al. Ganciclovir prophylaxis of cytomegalovirus infection and disease in allogeneic bone marrow transplant recipients. Results of a placebo-controlled, double-blind trial. Ann Intern Med. 1993;118(3):179–84.
278. Peggs KS, Preiser W, Kottaridis PD, McKeag N, Brink NS, Tedder RS, et al. Extended routine polymerase chain reaction surveillance and pre-emptive antiviral therapy for cytomegalovirus after allogeneic transplantation. Br J Haematol. 2000;111(3):782–90.
279. Nichols WG, Price T, Boeckh M. Donor serostatus and CMV infection and disease among recipients of prophylactic granulocyte transfusions. Blood. 2003;101(12):5091–2. author reply 2.
280. Lilleri D, Gerna G, Furione M, Bernardo ME, Giorgiani G, Telli S, et al. Use of a DNAemia cut-off for monitoring human cytomegalovirus infection reduces the number of preemptively treated children and young adults receiving hematopoietic stem-cell transplantation compared with qualitative pp65 antigenemia. Blood. 2007;110(7):2757–60.
281. Pang XL, Fox JD, Fenton JM, Miller GG, Caliendo AM, Preiksaitis JK. Interlaboratory comparison of cytomegalovirus viral load assays. Am J Transplant. 2009;9(2):258–68.
282. Kraft CS, Armstrong WS, Caliendo AM. Interpreting quantitative cytomegalovirus DNA testing: understanding the laboratory perspective. Clin Infect Dis. 2012;54(12):1793–7.
283. Ruiz-Camps I, Len O, de la Camara R, Gurgui M, Martino R, Jarque I, et al. Valganciclovir as pre-emptive therapy for cytomegalovirus infection in allogeneic haematopoietic stem cell transplant recipients. Antivir Ther. 2011;16(7):951–7.
284. Allice T, Busca A, Locatelli F, Falda M, Pittaluga F, Ghisetti V. Valganciclovir as pre-emptive therapy for cytomegalovirus infection post-allogenic stem cell transplantation: implications for the emergence of drug-resistant cytomegalovirus. J Antimicrob Chemother. 2009;63(3):600–8.
285. Ayala E, Greene J, Sandin R, Perkins J, Field T, Tate C, et al. Valganciclovir is safe and effective as pre-emptive therapy for CMV infection in allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant. 2006;37(9):851–6.
286. Busca A, de Fabritiis P, Ghisetti V, Allice T, Mirabile M, Gentile G, et al. Oral valganciclovir as preemptive therapy for cytomegalovirus infection post allogeneic stem cell transplantation. Transpl Infect Dis. 2007;9(2):102–7.
287. Takenaka K, Eto T, Nagafuji K, Kamezaki K, Matsuo Y, Yoshimoto G, et al. Oral valganciclovir as preemptive therapy is effective for cytomegalovirus infection in allogeneic hematopoietic stem cell transplant recipients. Int J Hematol. 2009;89(2):231–7.
288. van der Heiden PL, Kalpoe JS, Barge RM, Willemze R, Kroes AC, Schippers EF. Oral valganciclovir as pre-emptive therapy has similar efficacy on cytomegalovirus DNA load reduction as intravenous ganciclovir in allogeneic stem cell transplantation recipients. Bone Marrow Transplant. 2006;37(7):693–8.
289. Volin L, Barkholt L, Nihtinen A, Aschan J, Uotinen H, Hagglund H, et al. An open-label randomised study of oral valganciclovir versus intravenous ganciclovir for pre-emptive therapy of cytomegalovirus infection after allogeneic stem cell transplantation. 34th Annual Meeting of the European Group for Blood and Marrow Transplantation, March 30–April 2. Florence, Italy, 2008

290. Lacey SF, Diamond DJ, Zaia JA. Assessment of cellular immunity to human cytomegalovirus in recipients of allogeneic stem cell transplants. Biol Blood Marrow Transplant. 2004;10(7):433–47.
291. Arvin AM, Fast P, Myers M, Plotkin S, Rabinovich R. Vaccine development to prevent cytomegalovirus disease: report from the National Vaccine Advisory Committee. Clin Infect Dis. 2004;39(2):233–9.
292. Adler SP. Human CMV, vaccine trials: what if CMV caused a rash? J Clin Virol. 2008;41(3):231–6.
293. Kharfan-Dabaja MA, Boeckh M, Wilck MB, Langston AA, Chu AH, Wloch MK, et al. A novel therapeutic cytomegalovirus DNA vaccine in allogeneic haemopoietic stem-cell transplantation: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Infect Dis. 2012;12(4):290–9.
294. La Rosa C, Longmate J, Lacey SF, Kaltcheva T, Sharan R, Marsano D, et al. Clinical evaluation of safety and immunogenicity of PADRE-cytomegalovirus (CMV) and tetanus-CMV fusion peptide vaccines with or without PF03512676 adjuvant. J Infect Dis. 2012;205(8):1294–304.
295. Fries BC, Riddell SR, Kim HW, Corey L, Dahlgren C, Woolfrey A, et al. Cytomegalovirus disease before hematopoietic cell transplantation as a risk for complications after transplantation. Biol Blood Marrow Transplant. 2005;11(2):136–48.
296. Parody R, Martino R, Rovira M, Vazquez L, Vazquez MJ, de la Camara R, et al. Severe infections after unrelated donor allogeneic hematopoietic stem cell transplantation in adults: comparison of cord blood transplantation with peripheral blood and bone marrow transplantation. Biol Blood Marrow Transplant. 2006;12(7):734–48.
297. Tomonari A, Takahashi S, Ooi J, Tsukada N, Konuma T, Kobayashi T, et al. Preemptive therapy with ganciclovir 5 mg/kg once daily for cytomegalovirus infection after unrelated cord blood transplantation. Bone Marrow Transplant. 2008;41(4):371–6.
298. Reed EC, Wolford JL, Kopecky KJ, Lilleby KE, Dandliker PS, Todaro JL, et al. Ganciclovir for the treatment of cytomegalovirus gastroenteritis in bone marrow transplant patients. A randomized, placebo-controlled trial. Ann Intern Med. 1990;112(7):505–10.
299. Asberg A, Humar A, Rollag H, Jardine AG, Mouas H, Pescovitz MD, et al. Oral valganciclovir is noninferior to intravenous ganciclovir for the treatment of cytomegalovirus disease in solid organ transplant recipients. Am J Transplant. 2007;7(9):2106–13.
300. Ljungman P, Engelhard D, Link H, Biron P, Brandt L, Brunet S, et al. Treatment of interstitial pneumonitis due to cytomegalovirus with ganciclovir and intravenous immune globulin: experience of European Bone Marrow Transplant Group. Clin Infect Dis. 1992;14(4):831–5.
301. Ljungman P, Cordonnier C, Einsele H, Bender-Gotze C, Bosi A, Dekker A, et al. Use of intravenous immune globulin in addition to antiviral therapy in the treatment of CMV gastrointestinal disease in allogeneic bone marrow transplant patients: a report from the European Group for Blood and Marrow Transplantation (EBMT). Infectious Diseases Working Party of the EBMT. Bone Marrow Transplant. 1998;21(5):473–6.
302. Emanuel D, Cunningham I, Jules-Elysee K, Brochstein JA, Kernan NA, Laver J, et al. Cytomegalovirus pneumonia after bone marrow transplantation successfully treated with the combination of ganciclovir and high-dose intravenous immune globulin. Ann Intern Med. 1988;109(10):777–82.
303. Reed EC, Bowden RA, Dandliker PS, Lilleby KE, Meyers JD. Treatment of cytomegalovirus pneumonia with ganciclovir and intravenous cytomegalovirus immunoglobulin in patients with bone marrow transplants. Ann Intern Med. 1988;109(10):783–8.
304. Alexander BT, Hladnik LM, Augustin KM, Casabar E, McKinnon PS, Reichley RM, et al. Use of cytomegalovirus intravenous immune globulin for the adjunctive treatment of cytomegalovirus in hematopoietic stem cell transplant recipients. Pharmacotherapy. 2010;30(6):554–61.
305. Chang M, Dunn JP. Ganciclovir implant in the treatment of cytomegalovirus retinitis. Expert Rev Med Devices. 2005;2(4):421–7.
306. Ganly PS, Arthur C, Goldman JM, Schulenburg WE. Foscarnet as treatment for cytomegalovirus retinitis following bone marrow transplantation. Postgrad Med J. 1988;64(751):389–91.
307. Okamoto T, Okada M, Mori A, Saheki K, Takatsuka H, Wada H, et al. Successful treatment of severe cytomegalovirus retinitis with foscarnet and intraocular infection of ganciclovir in a myelosuppressed unrelated bone marrow transplant patient. Bone Marrow Transplant. 1997;20(9):801–3.
308. Heslop HE, Leen AM. T-cell therapy for viral infections. Hematol Am Soc Hematol Educ Program. 2013;2013:342–7.