# Viral infections in acute graft-versus-host disease: A review of diagnostic and therapeutic approaches

Lana X. Tong, BA, and Scott D. Worswick, MD
*Los Angeles, California*

***Background:*** While immunosuppressive therapy for acute graft-versus-host disease (aGVHD) advances, viral reactivation has been found to be an increasingly common complication in these patients. Dermatologists may often be consulted on inpatient services for evaluation.

***Objective:*** We investigated the literature for the role of viral infections in aGVHD and review the current evidence regarding management.

***Methods:*** Articles in the public domain regarding aGVHD, cytomegalovirus, Epstein–Barr virus, varicella zoster virus, hepatitis viruses, parvovirus B19, and respiratory viruses were included.

***Results:*** Dermatologic findings vary between different viral antigens, and some infections may be a marker for the development of aGVHD or worsen prognosis.

***Limitations:*** The heterogeneous cohorts of the studies reviewed often preclude direct comparison between results.

***Conclusion:*** The relationship between viral reactivation and aGVHD may be bidirectional and is worthy of further exploration. Additional studies are needed to determine appropriate prophylaxis and treatment. (J Am Acad Dermatol 2015;72:696-702.)

***Key words:*** cytomegalovirus; Epstein–Barr virus; graft-versus-host disease; human herpesvirus 6; human herpesvirus 7; inpatient dermatology; transplant dermatology; viral infections.

Infections have become an increasingly common complication of acute graft-versus-host-disease (aGVHD), in part because advances in immunosuppressive therapy have resulted in increased survival rates of transplant patients.[1] However, aGVHD continues to be a major obstacle in clinical outcomes and mortality. aGVHD usually manifests with fever, diarrhea, an elevated bilirubin level, and a morbilliform eruption.[2] Erythematous macules and papules begin on the face, ears, and palmar and plantar surfaces and may have perifollicular accentuation. Confluent morbilliform patches can then develop, which occasionally progress to erythroderma and/or bulla and desquamation that mimic toxic epidermal necrolysis.

*Abbreviations used:*

| | |
|---|---|
| aGVHD: | acute graft-versus-host disease |
| CMV: | cytomegalovirus |
| EBV: | Epstein–Barr virus |
| HBV: | hepatitis B virus |
| HCV: | hepatitis C virus |
| HHV6: | human herpesvirus 6 |
| LAD: | lymphadenopathy |
| LCV: | leukocytoclastic vasculitis |
| RSV: | respiratory syncytial virus |
| VZV: | varicella virus |

Immunosuppressive management of aGVHD often results in hypergammaglobulinemia and impaired cell-mediated immunity; the reactivation of

From the Division of Dermatology, Department of Medicine, David Geffen School of Medicine at the University of California, Los Angeles.
Funding sources: None.
Conflicts of interest: None declared.
Accepted for publication December 1, 2014.
Correspondence to: Scott D. Worswick, MD, Division of Dermatology, Department of Medicine, David Geffen School of Medicine at UCLA, 200 Medical Plaza, Ste 450, Los Angeles, CA 90095. E-mail: sworswick@mednet.ucla.edu.
Published online January 10, 2015.
0190-9622/$36.00

http://dx.doi.org/10.1016/j.jaad.2014.12.002

viral infections occurs while the patient is in this immunosuppressive state, including cytomegalovirus (CMV), varicella zoster virus (VZV), Epstein–Barr virus (EBV), hepatitis viruses, parvovirus B19, and respiratory viruses. Antimicrobial prophylaxis and monitoring of diagnostic infectious markers are recommended (ie, viral DNA loads and cultures) in suspected reactivation, and aGVHD itself has been shown to be a significant risk factor in the development of viral coinfection.[3,4] We reviewed the literature regarding the role of viral infections in aGVHD and the current evidence for diagnostic workup and treatment to aid dermatologists in the management of complex inpatient cases and to improve patient outcomes.

## METHODS

Articles in the public domain were searched for the following terms between July and September 2014: "graft-versus-host disease," "acute," "viral infection," "virus," "Epstein–Barr virus," "adenovirus," "cytomegalovirus," "human herpesvirus-6," "hepatitis," "transplant," and "adenovirus." These search strings included the subcategories of "herpesvirus-4, human," "human herpesvirus-4," "Epstein," "Barr," "herpesvirus-3, human," "human herpesvirus-3," "chickenpox," "virus diseases," "adenoviridae," "infections," and "adenoviridae infections." Results were filtered to include only articles written in English. Bibliographies were used to search for more articles that met the inclusion criteria. A total of 67 articles were examined and summarized.

### Cytomegalovirus

CMV reactivation is potentially life threatening and is estimated to occur in 20% to 40% of patients with aGVHD (Table I).[5] It usually presents with fever, malaise, myalgias, cervical lymphadenopathy (LAD), and nonexudative pharyngitis.[6,7] CMV is associated with a generalized petechial exanthem and can progress to leukocytoclastic vasculitis (LCV). Reactivation typically occurs at a median of 38 days (range, 1-150 days) posttransplant.[8]

Serostatus of the recipient has been shown to be the most important risk factor for CMV reactivation. Immunosuppressive therapy used in the treatment of aGVHD is a known risk factor for CMV coinfection (hazard ratio [HR], 1.61 [95% confidence interval {CI}: 1.11-2.36]; $P = .01$), while CMV has been shown to increase the risk of developing aGVHD (HR, 2.18 [95% CI: 1.30-3.65]; $P < .01$), supporting a bidirectional relationship between CMV and aGVHD.[9]

If a patient is known to be CMV-seropositive, quantitative CMV testing should be performed weekly until at least 180 days posttransplant.[1] Patients who are at high risk for CMV reactivation should continue to be monitored with quantitative DNA–polymerase chain reaction (PCR) testing even if they have received treatment.[10] Many centers use prophylaxis with ganciclovir or valganciclovir because waiting until CMV viremia is detected to administer antiviral treatment results in a prolonged disease course.[11] Once viremia is detected, induction therapy with oral ganciclovir or valganciclovir should be administered for 1 to 2 weeks, followed by maintenance therapy at half the induction dose for >6 weeks. If infection is identified in an end organ, the induction stage of treatment should be extended by 3 to 4 weeks, for which intravenous ganciclovir is preferred because of potentially impaired gastrointestinal absorption.[1] Maribavir is a newer antiviral agent that is currently under investigation and has been shown to be effective in the treatment of CMV with a decreased risk of neutropenia when compared to ganciclovir or valganciclovir.[12] For CMV pneumonitis or end organ involvement, intravenous immunoglobulin may be used in addition to antiviral therapy every other day for 3 weeks during the induction stage.[13]

### Varicella zoster virus

VZV reactivation typically presents characteristically as painful, clear vesicles on an erythematous base in a dermatomal distribution, which eventually become crusted, hemorrhagic, umbilicated, or pustular.[14] Disseminated VZV is defined as the presence of >10 nondermatomal lesions. Lesions may initially begin as urticarial, erythematous papules. Although VZV is typically a clinical diagnosis, laboratory confirmation with a Tzanck smear, direct fluorescent antigen, viral culture, or DNA-PCR testing can be performed if the presentation is unusual or nondermatomal. Reactivation has been shown to occur at a median of 227 days (range, 45-346 days) posttransplant.[15] Prophylaxis with acyclovir or valacyclovir may be given for a year, although their effectiveness is controversial.[16,17] Other options include famciclovir and foscarnet in acyclovir-resistant cases.[18] Valacyclovir should be used with caution because of potential nephrotoxicity.

### Epstein–Barr virus

EBV reactivation typically presents with fever, cervical LAD, and pharyngitis.[19] Dermatologic findings typically involve a brawny, morbilliform eruption on the extremities, although it may also be urticarial or scarlatiniform. Periorbital edema and palatal petechiae can also be seen.[20] Its incidence has been estimated to be between 1% and 30% and is thought to occur at a median of 44 days (range, 19-84 days) posttransplant.[21] In addition, EBV is known to