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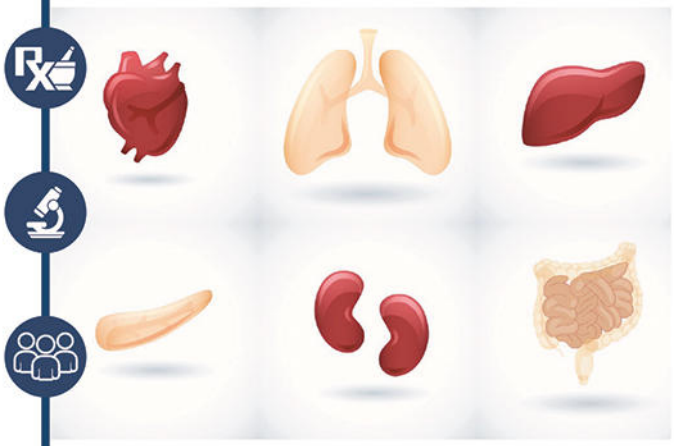

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SPECIAL ISSUE-TRANSPLANT INFECTIOUS DISEASES

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Herpes simplex virus infections in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

Dong H. Lee[1] | **Richard A. Zuckerman**[2] | **on behalf of the AST Infectious Diseases Community of Practice**

[1]Division of Infectious Diseases and HIV Medicine, College of Medicine, Drexel University, Philadelphia, Pennsylvania

[2]Infectious Disease Service for Transplant and Immunocompromised Hosts, Section of Infectious Disease and International Health, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire

Correspondence
Richard A. Zuckerman, MD, MPH, Infectious Disease Service for Transplant and Immunocompromised Hosts, Section of Infectious Disease and International Health, Dartmouth-Hitchcock Medical Center, Lebanon, NH.
Email: richard.a.zuckerman@hitchcock.org

Abstract

These updated guidelines from the Infectious Diseases Community of Practice of the American Society of Transplantation review the diagnosis, prevention, and management of HSV in the pre- and post-transplant period. A majority of transplant recipients are seropositive for HSV-1 or 2. Compared with immunocompetent persons, SOT recipients shed HSV more frequently, have more severe clinical manifestations, and are slower to respond to therapy. Most HSV infection is diagnosed on clinical grounds, but patients may present with atypical lesions and/or other clinical manifestations. Acquisition from the donor is rare. Polymerase chain reaction is the preferred diagnostic test unless culture is needed for resistance testing. For limited mucocutaneous lesions, oral therapy can be used; however, in severe, disseminated, visceral or CNS involvement, acyclovir doses of up to 10 mg/kg every 8 hours intravenously should be initiated. Acyclovir-resistant HSV is less common in SOT patients than in HSCT and can be treated with foscarnet, though other novel therapies are currently under investigation. HSV-specific prophylaxis should be considered for all HSV-1 and HSV-2–seropositive organ recipients who are not receiving antiviral medication for CMV prevention that has activity against HSV.

KEYWORDS
herpes simplex virus, prevention, transplantation, treatment, viral infection

1 | ETIOLOGY

Herpes simplex virus type-1 and 2 (HSV-1, HSV-2) are linear, double-stranded DNA, α-herpes viruses associated with infections involving mucocutaneous surfaces, the CNS, and visceral organs. Herpes simplex virus type-1 classically causes orolabial lesions, and HSV-2 has historically been associated with genital HSV. However, in recent years, HSV-1 is an increasing cause of genital lesions; though typically with less frequent reactivation.[1,2] HSV is acquired from contact with infected mucocutaneous surfaces, lesions, or rarely from infected donor material. The majority of HSV is acquired from asymptomatic individuals, as viral shedding is often asymptomatic. After primary infection, HSV establishes latency in sensory ganglia and persists lifelong with periodic reactivation.

2 | EPIDEMIOLOGY AND RISK FACTORS

Herpes simplex virus type-1 is acquired from early childhood through adulthood, whereas HSV-2 is very uncommon until the age of sexual debut, with an associated increase in seroprevalence thereafter. Recent data suggest declining seroprevalence of both HSV-1 and HSV-2 in the United States and elsewhere (Figure 1).[3,4] Herpes simplex virus type-1 seroprevalence ranges from 27% in

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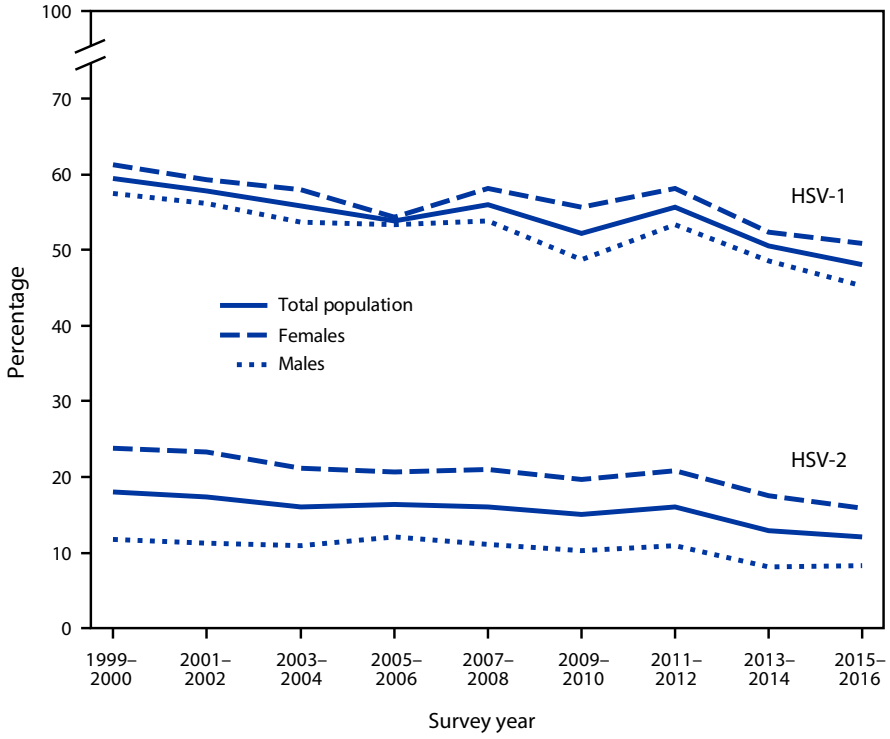

FIGURE 1 Age-adjusted trends in the prevalence of herpes simplex virus type-1 (HSV-1) and herpes simplex virus type-2 (HSV-2) among adolescents and adults aged 14-49 Years—United States, 1999-2000 through 2015-2016 (Source: NCHS Data Brief No. 304. https://www.cdc.gov/mmwr/volumes/67/wr/mm6706a7.htm)

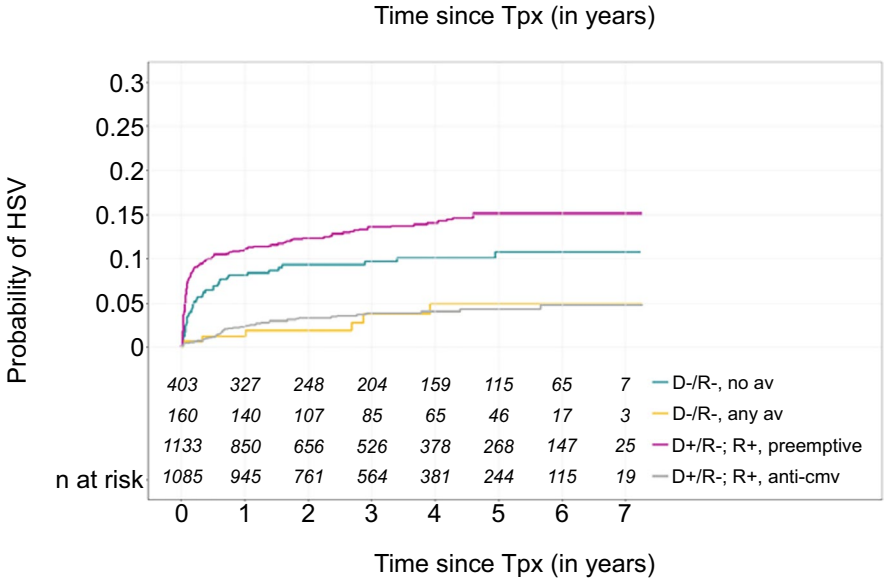

FIGURE 2 Probability of HSV infection after transplantation according to CMV serostatus and antiviral preventive strategy.[10] Probability of HSV infection in CMV D-/R- patients receiving antiviral (av) prophylaxis (yellow line), CMV D+/R− or R+ patients receiving antiviral prophylaxis (grey line), CMV D−/R− patients not receiving antiviral prophylaxis (green line), and CMV D+/R− or R+ followed by the preemptive CMV approach (magenta line) ($P < 0.001$, all four groups). Regardless of CMV prevention strategy, shows the effectiveness of antiviral prophylaxis on HSV reactivation

14- to 19-year-olds and 59.7% in 40- to 49-year-olds.[5] Herpes simplex virus type-2 has a seroprevalence of 0.8% of persons aged 14-19 years and 21.2% of persons aged 40-49 years in the United States. Many adult transplant patients are infected with HSV-1 or HSV-2, or both, with prevalence similar to the distribution by age in the general population.[6]

A minority of immunocompetent persons infected with HSV develop symptomatic lesions; however, most will shed virus on mucosal surfaces.[7] Compared with immunocompetent persons, solid organ transplant (SOT) recipients shed virus more frequently, have more severe clinical manifestations,[8,9] and are slower to respond to therapy. HSV-seronegative SOT recipients may acquire HSV from intimate contacts; however, most symptomatic HSV disease in adult transplant recipients results from reactivation of the previously acquired virus, particularly early after transplantation, or in the setting of anti-rejection therapy.[10-13] In a large cohort of SOT recipients, the incidence of symptomatic HSV during the first year after transplant was 3% in patients receiving antiviral prophylaxis versus 9.8% without prophylaxis (Figure 2). Most had mucocutaneous diseases. Female gender, HSV seropositivity, episodes of rejection, and use of a preemptive approach for CMV prevention were associated with a higher risk of symptomatic HSV

infection.[10] Primary infection from the allograft (donor derived infection) is described in liver, kidney, and other organ transplant types and can be quite severe due to lack of immunologic memory.[13-21] Knowledge of serostatus may be important to determine the possibility of primary HSV acquisition, either from the allograft or natural sources after transplant. It should be noted that there is limited utility in testing infants in the first 6-12 months of life when they still harbor maternal antibodies.

The association of HSV reactivation with specific immunosuppressive agents is complicated to assess given the varied regimens and the use of multiple medications simultaneously in the early post-transplant period when HSV reactivation is most common. Prior to modern antiviral prophylactic regimens, the use of anti-CD3 antibody muromonab (OKT3) and mycophenolate mofetil was associated with an increased risk of HSV reactivation,[13,22,23] Additionally, there was some suggestion that the use of the mTOR inhibitors (eg, rapamycin) with reduced calcineurin inhibitor exposure leads to reduced herpes virus infections.[24] However, a recent large retrospective analysis failed to show any association with induction therapy or various maintenance regimens on the risk for HSV reactivation.[10]

3 | CLINICAL MANIFESTATIONS

The most common clinical presentation of HSV is localized multiple painful lesions on orolabial, genital or perianal area.[10-12] Lesions can be vesicular or ulcerative and may extend locally.[25] Primary infection is characterized by an incubation period of 4-7 days, after which multiple painful vesicular lesions appear that crust-over in 1-3 weeks. In the normal host, symptomatic reactivation usually has a shorter course; however, in immunocompromised patients, HSV can be more persistent and can cause atypical lesions in both primary and reactivation disease. HSV lesions can occur at other body sites such as herpetic whitlow or gladiatorum. In normal and immunocompromised hosts, HSV can also reactivate in a retrograde fashion from the ganglion to the CNS to cause meningoencephalitis, transverse myelitis, or recurrent lymphocytic meningitis (Mollaret's meningitis).

TABLE 1 Laboratory Methods for Diagnosis of HSV[36]

Test	Advantage	Disadvantage
Direct fluorescent antibody (DFA)	• Rapidly available • Virus-specific	• Lower sensitivity (40%-90%) than PCR • Limited sample types (needs cells to stain; eg, not CSF)
PCR	• Most sensitive (98%) • Done on most sample types	• Not available at all centers • High cost • Positive result other than in CSF, requires interpretation
Culture (standard tissue based)	• Identify type-specific HSV • Able to isolate virus for drug susceptibility testing	• Turnaround time • Labor intensive • Sensitivity affected by storage and transport (30%-90%)
Culture (shell vial)	• Faster turnaround than tissue culture (24-48 hours) • Similar sensitivity to tissue culture	• Labor intensive • Does not grow virus for phenotypic sensitivity testing
Tzanck smear	• Rapid • Direct visualization	• Fresh lesion needed • Requires experience • Non-specific to HSV or VZV
Histopathology with immunohistochemistry	• Can prove tissue-invasive disease	• Samples more difficult to acquire • Long turnaround time
Serology	• Useful to guide pre-transplant risk stratification and prevention	• Insensitive marker for acute infection • False-positive IgM
Drug resistance phenotypic assay (plaque reduction assay)	• Clinically reliable • Can test multiple medications	• Need positive culture (see above re: sensitivity) • Turnaround time
Drug resistance genotypic assay	• Rapid	• Available for research use, commercial assays not readily available • Resistance mutations not completely characterized

More severe forms of HSV disease include disseminated mucocutaneous or visceral disease, esophagitis, hepatitis, and pneumonitis.[26-29] Fever, leukopenia, and hepatitis are the common presenting signs of disseminated disease. Pneumonitis is described in recipients of all organ types but is most common in heart-lung transplant recipients.[27] Severe visceral disease may initially present with absent or sparse mucocutaneous lesions, so prompt evaluation for HSV infection should be considered when confronted with hepatitis or other clinically appropriate syndromes of otherwise unclear etiology. Because severe HSV disease can occur in HSV-seropositive or in HSV-seronegative persons who newly acquire the infection, HSV infection should be considered in the differential diagnosis of clinically appropriate syndromes regardless of serostatus before transplantation.

Keratitis (infection of the cornea) is a manifestation of HSV in the eye that can result in visual disturbance or blindness.[30] Superficial ocular infection may result from HSV reactivation in the trigeminal nerve, and deeper infection of corneal tissues (eg, stromal keratitis) from the inflammatory reaction and/or immune-mediated responses to remaining antigen.[31] As ocular HSV disease can exist in several forms, it is useful to involve ophthalmologists to establish the diagnosis, assess the anatomic extent, and appropriately treat ocular HSV.

4 | DIAGNOSTIC STRATEGIES

Most patients present with typical orolabial and genital lesions and can be diagnosed on clinical grounds (Table 1). However, HSV in an immunocompromised host may present atypically so laboratory confirmation may be necessary to differentiate with other lesions. For sampling, the lesion should be unroofed and scraped for viral culture or polymerase chain reaction (PCR), both of which can differentiate type-specific HSV. The timing of sampling is important for yield with mucocutaneous lesions: for example, sampling of genital lesions >5 days old had a yield of <35%.[32] Direct fluorescent antibody (DFA) testing of mucocutaneous lesions, bronchoalveolar lavage (BAL), and other clinical samples can provide rapid results. Compared with tissue culture, the sensitivity is between 60% and 75% and specificity is 85 and 99%.[32-34] Polymerase chain reaction for HSV DNA is 4-fold more sensitive than tissue culture for diagnosing mucocutaneous HSV and has largely replaced culture and DFA for HSV diagnosis in most body sites.[35-41] However, culture should be done when drug-resistant HSV disease is suspected. HSV PCR testing availability has increased dramatically and is available at most medical centers though may be performed at an outside reference laboratory. Turnaround time may vary depending on availability, so alternative on-site laboratory tests (DFA, culture, Tzanck, histopathology) may be useful. Cerebrospinal fluid PCR is the gold standard for diagnosing HSV meningitis or meningoencephalitis with a sensitivity of 98% and specificity of 100%.[42] HSV DNA is also detected in the blood of immunocompetent patients with primary ulcerative infection[43] and in those with significant reactivation disease.[43,44] However, the clinical significance of finding HSV DNA in the blood outside of patients with clinical syndromes consistent with disseminated disease has not been well established.[45] Previously, HSV culture was via cell (tissue) culture with positive results available mostly within 2-5 days. Many laboratories now offer cultures via a centrifugation-enhanced technique (shell vial), which is nearly as sensitive and more rapid than traditional cell culture but may not provide enough viable virus for resistance testing, if warranted. Tissue histopathology can be helpful with immunocytochemistry for HSV and is recommended to confirm a diagnosis where PCR or other tests (eg, culture) may represent contamination from another site (eg, BAL contaminated from oropharynx). Serologic testing is rarely useful for diagnosing acute infection as most patients will be HSV seropositive, and increased IgM levels in HSV may occur with reactivation and not a new acquisition. HSV serologic testing is not routinely done in donors because the results will not affect clinical care. Immunity is not transferred, and donor serology does not predict the rare case of allograft transmission of HSV. Prior to transplant, recipient IgM level is not indicated because isolated IgM seropositivity may occur as a false-positive.[35,46] Nevertheless, recipient HSV IgG 1 and 2 serostatus should be determined prior to transplantation for appropriate post-transplant risk stratification. The nuances of HSV serologic testing are beyond the scope of this guideline, but are well summarized in the literature.[36]

Diagnosis of HSV keratitis remains primarily a clinical diagnosis based on characteristic features of the corneal lesion on slit lamp microscopy. Referral to an ophthalmologist is requisite for appropriate diagnosis and treatment of HSV ocular disease.[47]

Summary points:

- Most HSV infections are diagnosed on clinical grounds.
- Polymerase chain reaction is the preferred test for sampling lesions and CSF (strong, high). Polymerase chain reaction testing of other samples may be used as an adjunct to clinical, pathological, and other laboratory testing (weak, low).
- Culture and DFA may be helpful where PCR testing is not available. Culture may be helpful when nucleoside resistance is suspected.
- Early diagnosis is associated with improved outcomes (strong, low)

5 | TREATMENT

Limited mucocutaneous disease in the immunocompromised patient can be treated with nucleoside analogs: oral acyclovir, valacyclovir, or famciclovir (Table 2).[48-50] Therapy should be continued until complete healing of the lesions and a minimum of 5-7 days. More extensive mucocutaneous disease in the immunocompromised host can be treated with intravenous acyclovir. However, when there is disseminated, visceral, or CNS involvement, higher intravenous doses should be initiated. Prompt initiation of acyclovir

TABLE 2 Recommendations for HSV prevention and treatment in HSV-seropositive solid organ transplant recipients

Indication	Agents	Comments
Prevention		
Adult	CMV prophylaxis[a] or Acyclovir (400-800 mg twice a day) Valacyclovir (500 mg twice a day) Famciclovir (500 mg twice a day)	Administer for at least 1 mo During treatment of rejection episodes (for at least 1 mo) For recurrent infection: Lower doses for recurrent labialis, higher doses for recurrent genital or ocular disease.
Pediatric	<40 kg: Acyclovir (60-90 mg/kg PO in 3 divided doses) Valacyclovir (20 mg/kg PO twice a day, 3 mo to 11 y) For IV, 5 mg/kg every 8 h	
Treatment Mucocutaneous disease		
Adult	Acyclovir (400 mg 3 times a day) Valacyclovir (1000 mg twice a day) Famciclovir (500 mg twice a day) Acyclovir 5 mg/kg IV every 8 h (if unable to take PO or more extensive disease)	Because prompt initiation of therapy is associated with improved outcome, therapy should be started based on clinical diagnosis, pending laboratory confirmation Therapy should be continued until complete healing of all lesions or at least 5-7 d
Pediatric	Acyclovir (10 mg/kg IV every 8 h Acyclovir (80 mg/kg divided qid (not to exceed 800 mg/dose)	Severe mucocutaneous Limited disease, treat for 7-14 d.
Severe, visceral/disseminated/CNS disease		
Adult	Acyclovir IV (10 mg/kg every 8 h)	Intravenous therapy should be continued until resolution of disease, or 14 d, and then, oral medication may be given. For CNS infection may consider 21 d of IV therapy. Continue for 21 d for disseminated or CNS infection.
Pediatric	Acyclovir IV (45-60 mg/kg/d in 3 divided doses)	
HSV Keratitis	*Topical*: Ganciclovir 0.15% Trifluorothymidine 1% Acyclovir 3% ointment	Topical steroids should also be considered for stromal keratitis. Ganciclovir given 5× a day until healing then 3× daily for one week One drop every 2 hours for 2 weeks. Limited by epithelial toxicity
	Oral: Acyclovir (400 mg five times a day) Valacyclovir (1000 mg twice a day) Famciclovir (500 mg twice a day)	Avoids topical toxicity No comparative or dose finding studies.
Acyclovir-resistant HSV	Foscarnet (80-120 mg/kg/day IV in 2-3 divided doses) Cidofovir IV (5 mg/kg IV q wk give with probenecid) Topical cidofovir (1% gel qd) Topical trifluridine	Resistance should be laboratory-confirmed, although empiric therapy can be started Reduce immunosuppression, if possible

CMV, cytomegalovirus; HSV, herpes simplex virus; IV, intravenously; PO, orally; SOT, solid organ transplant.
[a]CMV prophylaxis with recommended doses of ganciclovir, valganciclovir, valacyclovir, or acyclovir is adequate for HSV prevention. If letermovir used for CMV prophylaxis, additional HSV-specific prophylaxis is necessary. Due to lack of SOT-specific studies, the level of evidence is extrapolated from populations of other patients with similar levels of immune compromise. Dosages are for GFR ≥ 50, and adjustment is necessary for renal insufficiency.[89]

therapy is associated with improved outcome for HSV disease in transplantation[16] and can be life-saving treatment in cases of HSV hepatitis or dissemination. Therapy in severe disease (eg, encephalitis) should be continued for a minimum of 14 days although some clinicians favor longer courses up to 21 days.[51-54] Reduction in immunosuppression should be considered for life-threatening HSV disease. Liver transplantation has been performed successfully in cases of fulminant HSV hepatitis without recurrence in the new organ.[55]

Children clear acyclovir more rapidly than adults and thus need higher doses of acyclovir. There have been no controlled clinical trials for dosing of anti-HSV medications in the pediatric solid organ transplant population. For significant mucocutaneous and CNS disease in children, acyclovir at doses up to 15 mg/kg/dose intravenously every 8 hours may be used, usually for a minimum of 14 (mucocutaneous) to 21 (CNS) days.[56] Rarely, doses up to 60 mg/kg/d may be used in children <12 years old, but with monitoring for toxicity (renal and hematologic). For less severe localized disease,

oral acyclovir may be used.[56] Data for oral valacyclovir come from healthy immunocompetent patients.[57] Valacyclovir is FDA approved for treatment of herpes labialis in children over 12 years of age and for children ≥2 years of age for the treatment of varicella infection. Treatment for genital herpes in the adolescent population is usually the same as dosing in the adult population. While acyclovir and valacyclovir are felt to have equivalent efficacy when dosed appropriately, there are no comparative studies of the relative efficacy of the oral antivirals in the pediatric transplant population. Penciclovir is generally not used in the pediatric population.

Herpes simplex virus keratitis treatment includes both topical and/or systemic therapy. The various forms of topical therapy appear equally effective.[58] Topical agents such as trifluridine solution and vidarabine ointment may result in epithelial toxicity with prolonged use. Topical ganciclovir gel has also been shown to be effective and has the advantage of less toxicity and less frequent applications. A study in immunocompetent individuals showed acyclovir at a dose of 400 mg five times a day was equivalent to topical therapy[59] and avoids the epithelial toxicity. Alternate HSV medications such as valacyclovir or famciclovir are possibly as effective as acyclovir but have not been studied in comparative trials.[60] Stromal keratitis and endotheliitis is treated with a combination of antivirals and topical steroids.[61]

5.1 | Resistance

The estimated prevalence of acyclovir resistance in immunocompromised hosts ranges from 2.1% to 10.9%[62] and needs to be considered in patients whose lesions are not responding clinically to appropriate doses of antiviral therapy, those with a history prior acyclovir exposure and recurrent disease. Acyclovir (and valganciclovir)-resistant HSV in solid organ transplant patients is rarely reported, compared to other immunocompromised groups such as HIV+ and HSCT patients.[62] Surveillance network data from 2004 identified a prevalence 2.5% of HSV isolates as resistant to acyclovir in organ recipients, including one patient whose sole antiviral exposure was ganciclovir for CMV treatment.[62] The most common mechanism of HSV resistance to nucleoside analogs is due to diminished or absent thymidine kinase (TK) activity from mutations in viral thymidine kinase encoded by the UL23 gene in HSV. Thus, drugs that utilize TK (acyclovir, famciclovir, valacyclovir, ganciclovir) are all affected. Initial evaluation should include laboratory confirmation of HSV disease including a viral culture as testing for acyclovir resistance generally relies on phenotypic assays—most commonly a plaque reduction assay. Given that testing relies on growth of the virus, results may be delayed for days to weeks. Genotypic testing may be performed more rapidly than phenotypic testing, but is not routinely available for clinical use and requires cautious interpretation.[63] When resistant virus is strongly suspected, typically based on history and lack of response to high-dose IV acyclovir, alternate therapy should be considered prior to confirmation of resistance.

Foscarnet and intravenous cidofovir are recommended for acyclovir-resistant HSV infections.[64] But these drugs are associated with significant renal toxicity and need close monitoring. Probenecid is used with cidofovir to protect against toxicity. Topical 5% imiquimod has been used for resistant HSV in immunocompromised hosts.[65-67] Topical cidofovir and trifluridine therapy have also been used.[68] Brincidofovir (CMX-001), oral bioavailable form of cidofovir, and helicase-primase inhibitors (eg, Amenamevir; ASP2151, Pritelivir; AIC316) are currently in later stages of development and may be available in the near future.[69-72] To the extent possible, doses of immunosuppressive therapy should be reduced in patients with acyclovir-resistant disease. Recurrent acyclovir-resistant HSV disease may require repeated courses of foscarnet. However, after complete healing, subsequent recurrences may be again susceptible to acyclovir therapy.[73]

5.2 | Chronic suppression

In patients who experience bothersome clinical recurrences (≥2) after discontinuation of antiviral therapy, suppressive antiviral therapy can be used until such time that level of immunosuppression can be decreased. For patients with frequent recurrences, suppressive therapy can be safely continued for many years and is associated with less frequent acyclovir-resistant HSV than episodic therapy in immunocompromised patients[74,75] and thus is the preferred approach. In patients who have frequent recurrences, chronic suppressive therapy can be used, but toxicity, cost, transmission, adherence, and psychosocial issues should be considered.[74,76] If cessation of prophylaxis is unsuccessful, then lifelong suppressive therapy may be attempted.

Summary points:

- For limited mucocutaneous lesions, oral therapy can be used and therapy should be continued for a minimum of 5-7 days or until complete healing of the lesions depending on the clinical circumstances (strong, high).
- For severe, disseminated, visceral or CNS involvement, doses of up to 10 mg/kg every 8 hours intravenously should be initiated (with adjustment for reduced GFR) (strong, high) and continued for at least 14 days.
- Nucleoside inhibitor resistance is suspected based on lack of response to treatment, at which point foscarnet (strong, high) therapy should be considered.
- Suppressive therapy can be safely continued for many years and is associated with less frequent acyclovir-resistant HSV than episodic therapy in immunocompromised patients and thus is the preferred approach (strong, moderate).

6 | PREVENTION

Many transplant recipients receive antiviral medication to prevent CMV replication (see CMV guidelines). Ganciclovir, acyclovir, valacyclovir, and valganciclovir prevent most HSV replication when given

in standard doses. HSV-specific prophylaxis should be considered for all HSV-1 and HSV-2–seropositive organ recipients who are not receiving antiviral medication for CMV replication.[77] Letermovir, although used for CMV prophylaxis, does not have activity against HSV, and additional HSV-specific prophylaxis is necessary.[78] In the unusual circumstance of a patient who is not receiving CMV antiviral prophylaxis and is also HSV seronegative, the risk of early post-transplant HSV infection is not well defined, though probable cases of HSV transmission from organs have been described.[16] This may be a more common scenario in the pediatric population, where recipients are more likely to be HSV seronegative and donors HSV seropositive. In this setting, clinicians may choose to give antiviral prophylaxis.

Immunosuppression intensification for organ rejection has been associated with HSV recurrence, though usually not life-threatening. Limited data suggest that prophylaxis during rejection episodes treated with OKT3 is effective,[22] and the utility of HSV prophylaxis is likely similar for other types of immunosuppressive regimens. If a patient is receiving antivirals with anti-HSV activity for CMV prevention during treatment of rejection, HSV-specific prophylaxis is not required. No study has evaluated the need for secondary prophylaxis after an episode of severe HSV disease. Clinicians should weigh the risks of further episodes of reactivation based on history of prior HSV reactivation, level of immunosuppression, and other host factors in choosing to continue preventive therapy.

Unfortunately, a vaccine to prevent primary or recurrent HSV infection has been elusive.[79] Current HSV prevention techniques are focused on behavioral and antiviral methods. Seronegative transplant recipients should be counseled regarding the risks of HSV-1 and HSV-2 acquisition. It is important to avoid contact with persons with active lesions, as these patients are highly infectious. However, persons may acquire HSV from asymptomatic individuals, so providers are encouraged to provide standard counseling to recipients regarding HSV acquisition. Condoms are effective, but do not completely protect against HSV transmission.[80] The virus can be acquired from persons who have never had lesions. Where appropriate, HSV-2-seronegative transplant recipients in new sexual relationships should consider having their partner tested for HSV serology. In serodiscordant couples, daily antiviral therapy taken by the seropositive partner can prevent HSV-2 transmission to the seronegative partner.[81] This may be considered as an option, but has not been evaluated in the SOT population. There are no controlled studies looking at the efficacy of post-exposure prophylaxis to prevent HSV acquisition, so it is not routinely recommended.

6.1 | Antiviral dosing for prophylaxis

Herpes simplex virus prophylaxis in SOT recipients is effective with acyclovir administered at doses of 200 mg three[12] or four[11] times a day. In a meta-analysis, comparing these regimens with higher doses of acyclovir and valacyclovir for CMV prevention, HSV was well-suppressed at all evaluated doses of acyclovir, with no difference between these "low-dose" (<1 g/d) and the higher dose regimens.[82] In this meta-analysis, the use of acyclovir resulted in a significant reduction in HSV disease.[82]

Compared with these initial HSV prevention trials in SOT, higher doses of acyclovir administered less frequently (eg, 400-800 mg twice a day) have been shown to be safe and effective in other similarly immunocompromised populations (eg, hematopoietic stem cell transplant, HIV) and are recommended for SOT recipients due to their safety and ease of administration. Because SOT-specific studies have not been done, the level of evidence reported herein is extrapolated from studies performed in populations of other patients with similar levels of immune compromise.[74,83,84] Patients with a history of frequent severe clinical HSV reactivations prior to transplant should be given higher doses. Valacyclovir given twice daily was found to be superior to once daily when used as prophylaxis against HSV in immunocompromised patients so once-daily administration is generally not recommended.[85] Dosage adjustment for renal insufficiency is necessary if GFR is <50. Famciclovir, the oral prodrug of penciclovir, is also effective in preventing recurrent HSV in immunocompromised hosts.[86,87]

Herpes simplex virus prophylaxis in pediatric patients is not universal. Dosing for seropositive patients or patients who have had prior occurrences is derived from studies of HIV positive and stem cell transplant recipients. For children ≥2 years of age requiring oral therapy, a typical quantity for infants, children, and adolescents <40 kg is 60-90 mg/kg/day orally in 2-3 divided doses; maximum daily dose: 800 mg twice daily; children and adolescents ≥40 kg orally 400-800 mg twice daily.[88] For intravenous therapy, 5 mg/kg every 8 hours is recommended.[56]

6.2 | Duration of prophylaxis

The majority of severe HSV disease occurs within the first month after transplant,[12] so antiviral prophylaxis should continue for at least a month. Resumption of prophylaxis can be considered for patients being treated for rejection (with T cell depleting agents). For patients receiving CMV antiviral prophylaxis active against HSV, additional prevention is not necessary.

Summary points:

- Patients on antivirals for CMV prevention with activity against HSV do not need additional antiviral prophylaxis (strong, high). HSV-specific prophylaxis should be considered for all HSV-1– and HSV-2–seropositive organ recipients who are not receiving antiviral medication for CMV replication (strong, moderate). Antiviral prophylaxis should continue for at least a month (weak, low).
- Persons may acquire HSV from asymptomatic individuals so care should be taken in intimate contact, particularly during periods of most intense immune suppression (weak. low).
- In serodiscordant couples, daily antiviral therapy taken by the seropositive partner can prevent HSV-2 transmission to the seronegative partner (strong, moderate).

- Resumption of prophylaxis can be considered for patients being treated for rejection (with T-cell–depleting agents) (weak, low).

7 | RESEARCH ISSUES

Research into the epidemiology and natural history of HSV, in addition to controlled treatment trials, are needed in the pediatric population. It is important to further elucidate the effects of different immunosuppressive regimens on the natural history of herpes simplex reactivation and disease, and the potential benefit of suppressive therapy during long-term immunosuppression. With the possibility for increased use of preemptive regimens for CMV prevention, it will be important to evaluate if there is changing incidence of HSV reactivation and resistance, and the need for HSV-specific prevention during periods without therapy active against HSV. Improved surveillance of the prevalence and risk factors for HSV antiviral resistance, including the use of ganciclovir and other new drugs for CMV prophylaxis is important moving forward. The utility and availability of genotypic resistance assays in monitoring early detection of drug-resistant HSV and the molecular diagnostic testing in tissue and fluids other than CSF (ie, blood, ascites, BAL) for diagnostic and monitoring purposes require additional research to establish its role in routine care. As new therapeutic agents become available for HSV, they should be evaluated in the setting of transplant and other immunocompromised hosts. Should a therapeutic or prophylactic vaccine become available, the efficacy and safety in the transplant population will need to be evaluated. The optimal method and duration for HSV prevention in seronegative recipients who are not taking CMV antiviral prophylaxis should be investigated.

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CONFLICT OF INTEREST

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