Goal: To help guide providers caring for children receiving solid organ transplants (SOT) to prevent HSV and VZV infection or reactivation.

Definitions:

- **Suppression**: Using an antiviral medication to prevent recurrence of HSV or VZV disease in a patient known to be infected with one of these viruses and with prior clinical manifestations. Suppression is typically considered for patients who have had previous recurrent HSV or VZV disease (such as HSV gingivostomatitis or zoster rash).
- **Prophylaxis**: Using an antiviral medication to prevent occurrence of HSV or VZV disease in a patient known to be infected with one of these viruses (most often determined by positive IgG on serologic testing). Patients receiving prophylaxis for HSV or VZV typically have not had prior disease caused by either of these viruses, but have the potential to develop disease because of their immunosuppressed state.

In this protocol we will only address PROPHYLAXIS for HSV or VZV. Patients with a known history of HSV or VZV disease should be evaluated by the Immunocompromised Hosts (ICH) ID team or in ICH ID clinic for consideration of suppressive therapy prior to transplantation. In addition, it should be noted that the doses of antiviral agents used for suppressive therapy are often significantly higher than the doses used for prophylaxis.

Overview:

- HSV-1 is a commonly acquired infection among young children, leading to a seroprevalence rate of approximately 40% in 12-19 year-olds and >80% in those over age 60. HSV-2 seroprevalence is estimated to be approximately 22% in the population over age 12, but is likely rising.
- Greater than 95% of adults are VZV seropositive at the time of transplantation, but with the use of the varicella vaccine in childhood many children have not had natural infection and seropositivity rates vary. Children with a positive IgG to VZV either due to vaccination or natural infection are candidates for prophylaxis.
- Pathogenesis in transplant-associated infections: unlike CMV or EBV, which are transmitted from donor to recipient via the transplanted organ, HSV/VZV are NOT typically transmitted to the recipient during transplantation. HSV-1 establishes latency in the trigeminal ganglion, HSV-2 in the sacral ganglion, and VZV in the dorsal root ganglion. Since the site of HSV/VZV latency is not transplanted, donor to recipient transmission would not be expected unless the donor is viremic and/or has organ involvement with the infection at the time of organ harvest. The overwhelming majority of HSV and VZV disease reported among SOT recipients is due to reactivation of the individual’s own latent virus, with donor transmissions reported only in case reports.

Clinical manifestations of HSV or VZV disease (usually early, in first month post-transplant and in setting of anti-rejection therapy):

- Typically localized disease (e.g. stomatitis, localized zoster rash), more commonly in individuals with history of previous clinical disease
- Hepatitis, pneumonia, and disseminated visceral disease can occur. Patients with VZV disease may develop neurologic symptoms including encephalitis.
- Probably more fulminant disease in donor-derived infections
- Risk of pneumonitis is higher in heart-lung recipients
- Primary varicella disease more significant concern in pediatric SOT recipients after discharge depending on immunization status and community vaccination/exposures

Risk Assessment:

- Designation of intermediate vs. high risk not typically considered in adult SOT because almost all disease is due to reactivation. All patients who are known to be positive for HSV/VZV prior to transplant receive antivirals. There is little data about practice at pediatric transplant centers, although centers do typically test for HSV/VZV in recipients.
Screening Strategy (FIGURES 1 and 2):
• All pediatric patients listed for SOT should be tested for HSV I/II and VZV antibody using the same testing strategy for CMV (at time of transplant listing and if negative, repeat at time of transplant)
• Infants less than 18 months should be considered HSV-infected if their HSV IgG is positive as we are unable to distinguish between maternal antibody vs. true infection in this population (no shell vial equivalent as with CMV).
• Donor serum testing for HSV and VZV is not routine and not required when recipients are known to be HSV or VZV seropositive. Donor serum testing can be considered on a case-by-case basis in patients who test negative for HSV and VZV if there is clinical concern for potential donor to recipient transmission. Donor testing is not required if the recipient will be receiving prophylaxis against CMV anyway.
• Separate testing for HSV I and HSV II is not routinely needed because the prophylaxis is the same for both.

Prophylaxis considerations (TABLE 1):
• Patients receiving CMV prophylaxis do not need separate HSV/VZV prophylaxis as CMV active agents (ganciclovir, valganciclovir) also protect against HSV/VZV
• Consider acyclovir prophylaxis in those patients who are known to be HSV or VZV seropositive and are CMV D-/R-
• If CMV D-/R- patients are HSV D-/R- and VZV D-/R-, they do not need any antiviral prophylaxis
• Prophylaxis does not need to be initiated in very small subset of patients who are CMV and HSV negative and for whom donor serologies are pending. If donor serologies return positive, prophylaxis can be initiated at that time.
• Drug of choice for prophylaxis is acyclovir. The acyclovir dose that is used for prophylaxis is a very low dose with minimal toxicity and low cost. There is no need for additional hydration with this dose (see dosing below).
• Ganciclovir/valganciclovir should NOT be used routinely in CMV D-/R- patients for HSV prophylaxis simply due to concerns about nephrotoxicity, as ganciclovir has other significant toxicities that must be considered. The acyclovir dose used for HSV/VZV prophylaxis is associated with minimal toxicities compared to ganciclovir, valganciclovir, or treatment doses of acyclovir.
• Patients with history of recurrent HSV stomatitis, recurrent genital HSV, or zoster (shingles) should initiate suppressive therapy with acyclovir/valacyclovir prior to transplant as this is likely more effective than episodic therapy. Patients who need an antiviral agent for suppression will require higher doses and potentially more frequent dosing than those receiving prophylaxis. These patients should continue to receive their appropriate suppressive doses post-SOT to minimize recurrences. They should not follow the dosing for prophylaxis.

Duration of prophylaxis (TABLE 1):
• All patients should receive prophylaxis for 3 months as the greatest period of disease risk for HSV and VZV is in the early post-transplant time period (unlike CMV/EBV).
• Longer duration of prophylaxis may be needed in some patients, based on patient-specific factors.
• Patients receiving suppressive therapy will likely need to continue their antiviral agent for a longer period of time, typically at least 1 year post-SOT.

Dosing, formulation, and renal considerations (TABLE 2):
• The dose of acyclovir used for HSV/VZV prophylaxis is 100mg/m2 IV every 12 hours (or 10mg/kg/dose orally twice daily up to a maximum dose of 400mg twice daily)
• Valacyclovir is used as an alternative antiviral agent to oral acyclovir, particularly for treatment of HSV/VZV infections because of its greater bioavailability which allows it to be given less frequently than oral acyclovir. In the setting of prophylaxis, however, there is no benefit to replacing acyclovir with valacyclovir because both must be given twice daily and valacyclovir is substantially more expensive than acyclovir. In addition, there is no liquid formulation for valacyclovir, therefore the liquid must be compounded for patients who cannot swallow pills. The compounded liquid must also be kept refrigerated.
• Nephrotoxicity associated with acyclovir is typically dose-dependent. The low, twice-daily dose of acyclovir used for prophylaxis has not historically been associated with nephrotoxicity among our patients who were previously receiving acyclovir routinely for antiviral prophylaxis.
• Acyclovir dose may need to be adjusted for those patients with renal function impairment.
Appendices:
Figure 1. Pre-transplant HSV screening algorithm
Figure 2. Pre-transplant VZV screening algorithm
Table 1. Recommendations for HSV/VZV Prophylaxis depending on recipient/donor CMV status
Table 2. Agents for HSV/VZV Prophylaxis

References:

Protocol developed by the Pediatric Transplant Virology Working Group at Boston Children's Hospital:

Lynne Lewis, RN, MS, CPNP
Transplant Infectious Diseases Coordinator
Division of Pediatric Infectious Diseases
Section on Immunocompromised Hosts

Jennifer Gilarde, PharmD
Clinical Pharmacy Specialist – Solid Organ Transplant

Sarah Jones, PharmD, BCPS
Clinical Pharmacy Specialist – Infectious Diseases

Lakshmi Ganapathi, MD
Attending Faculty
Immunocompromised Hosts – Infectious Diseases Service
Division of Pediatric Infectious Diseases

Tanvi Sharma, MD, MPH
Attending Faculty
Immunocompromised Hosts – Infectious Diseases Service
Division of Pediatric Infectious Diseases

Disclaimer:
This protocol is not intended to replace the advice of the immunocompromised infectious diseases service or the pharmacy team. Additional guidance should be sought from these sources as needed, particularly when a potential variation from the protocol is being considered or dosing adjustments are needed. Patients who develop HSV or VZV infection or disease should be managed in conjunction with the immunocompromised infectious diseases service.
Figure 1. Pre-transplant HSV Screening Algorithm

*Infants under 18 months of age may have positive HSV IgG due to maternal antibody or due to true infection. Because antibody testing cannot reliably distinguish between these scenarios, the most conservative approach is to consider a positive IgG as evidence of infection and give prophylaxis.
*Less than 2 doses of VZV vaccination may not render adequate immunity even if IgG is detected.
**Table 1.** Recommendations for HSV/VZV Prophylaxis depending on recipient/donor CMV status for all organs

<table>
<thead>
<tr>
<th>HSV/VZV Status</th>
<th>CMV Recipient/Donor Serostatus</th>
<th>Prophylaxis agent</th>
<th>Duration of prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not infected</td>
<td>R-/D-</td>
<td>None</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>R+/D-</td>
<td>IV ganciclovir</td>
<td>Refer to organ specific CMV prophylaxis protocol</td>
</tr>
<tr>
<td></td>
<td>R-/D+</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>R+/D+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infected</td>
<td>R-/D-</td>
<td>IV ganciclovir</td>
<td>3 months</td>
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<tr>
<td></td>
<td>R+/D-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infected</td>
<td>R-/D+</td>
<td>IV ganciclovir</td>
<td>Refer to organ-specific CMV prophylaxis protocol</td>
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<td></td>
<td>R+/D+</td>
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**Table 2.** Agents for HSV/VZV Prophylaxis

<table>
<thead>
<tr>
<th>Agent</th>
<th>Description</th>
<th>Route of administration</th>
<th>Dosing for prophylaxis</th>
</tr>
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<tbody>
<tr>
<td>Acyclovir</td>
<td>Antiviral</td>
<td>IV</td>
<td>100mg/m2 IV every 12 hours</td>
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<tr>
<td>Acyclovir</td>
<td>Antiviral</td>
<td>PO</td>
<td>10mg/kg/dose orally twice daily (maximum dose of 400mg twice daily)</td>
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</tbody>
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