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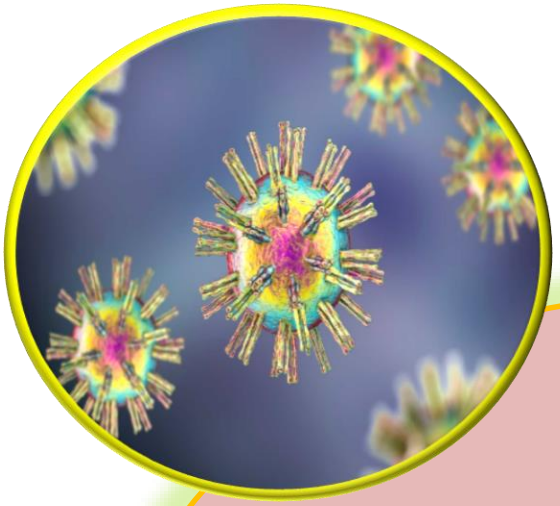

HSV And VZV In Renal Transplant

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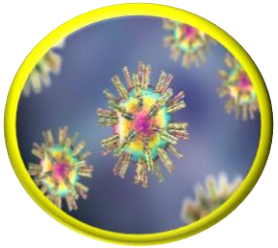
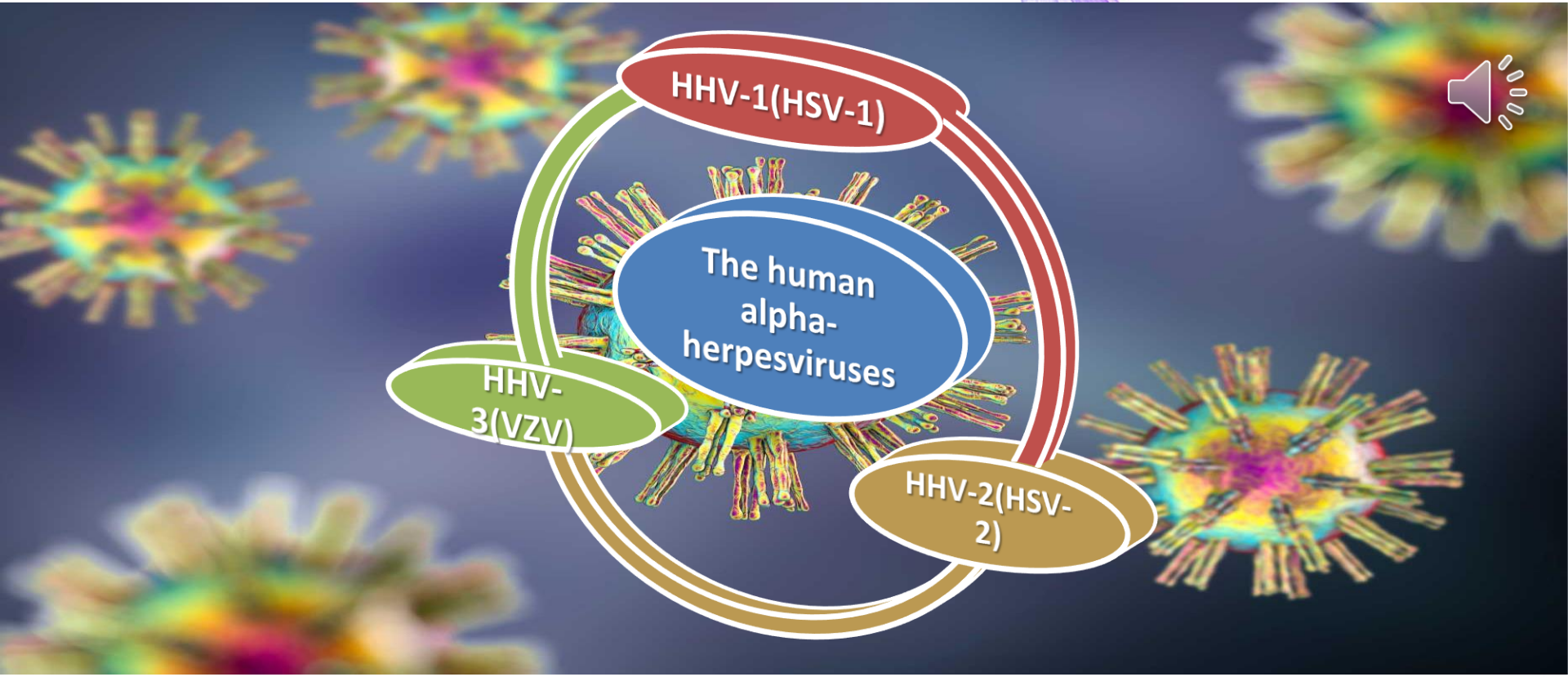
Nephrologist

Herpesviride

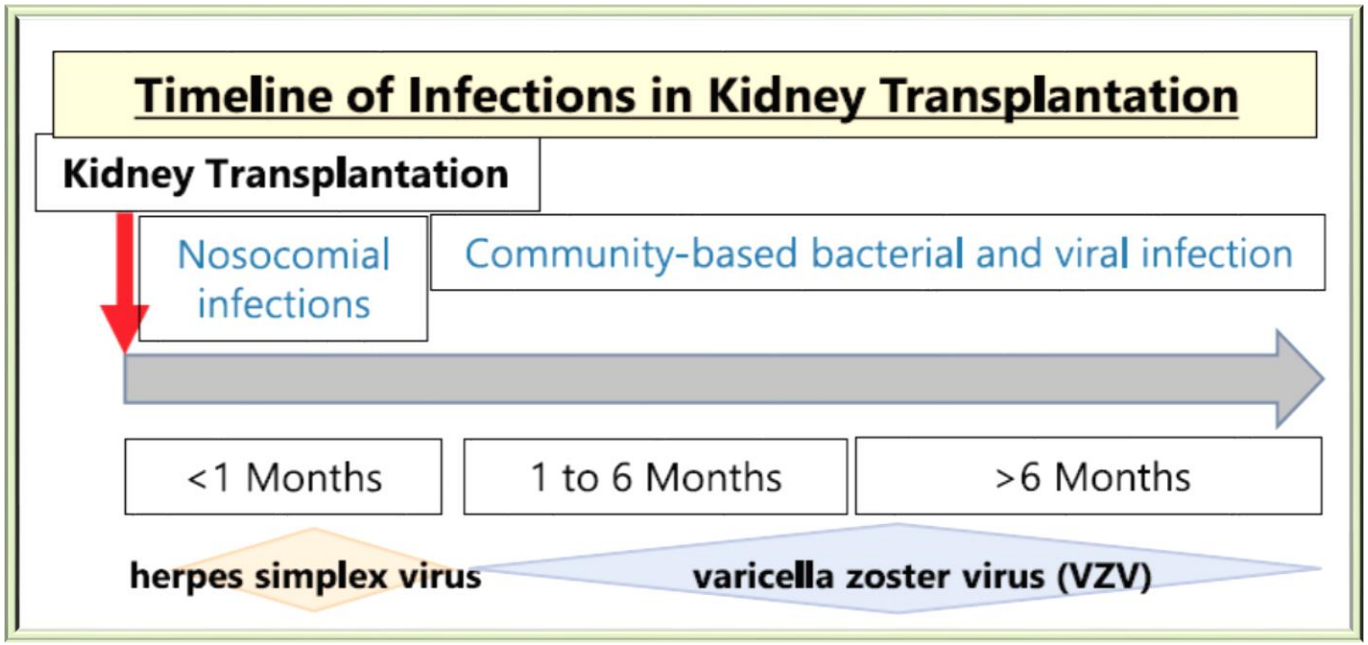
Subfamily	Biological properties	
Alphaherpesvirinae α	➢Variable host range ➢Rapid reproductive cycle ➢Establish latent infections in neurons	➢Herpes simplex virus type 1 (HSV-1) ➢Herpes simplex virus type 2 (HSV-2) ➢Varicella-Zoster virus (VZV) HHV-3
Betaherpesvirinae β	➢Generally restricted host range ➢Slow reproductive cycle ➢Cytomegalic ➢Establish latency in lymphocytes, monocytes, SG, kidney.	➢Human cytomegalovirus (HCMV) HHV-5 ➢Human herpesvirus-6 (HHV-6) ➢Human herpesvirus-7 (HHV-7)
Gammaherpesvirinae γ	➢Restricted host range ➢Lymphotropic, lymphproliferative. ➢Establish latent infections in lymphoid cells	➢Epstein-Barr virus (EBV-HHV-4) ➢Human herpesvirus-8 (HHV-8)





The human alpha-herpesviruses.

Type	Common name	Major syndromes	Site of Latency	Means of spread
HHV–1	Herpes simplex virus-1 (HSV-1)	Oral herpes, genital herpes (predominantly orofacial	Sensory and cranial nerve ganglia	Close contact (sexually transmitted disease)
HHV-2	Herpes simplex virus-2 (HSV-2)	Oral and/or genital herpes (predominantly genital)	Sensory and cranial nerve ganglia	Close contact (sexually transmitted disease)
HHV-3	Varicella zoster virus (VZV)	Chickenpox and shingles	Sensory and cranial nerve ganglia	Respiratory and close contact (including sexually transmitted disease)



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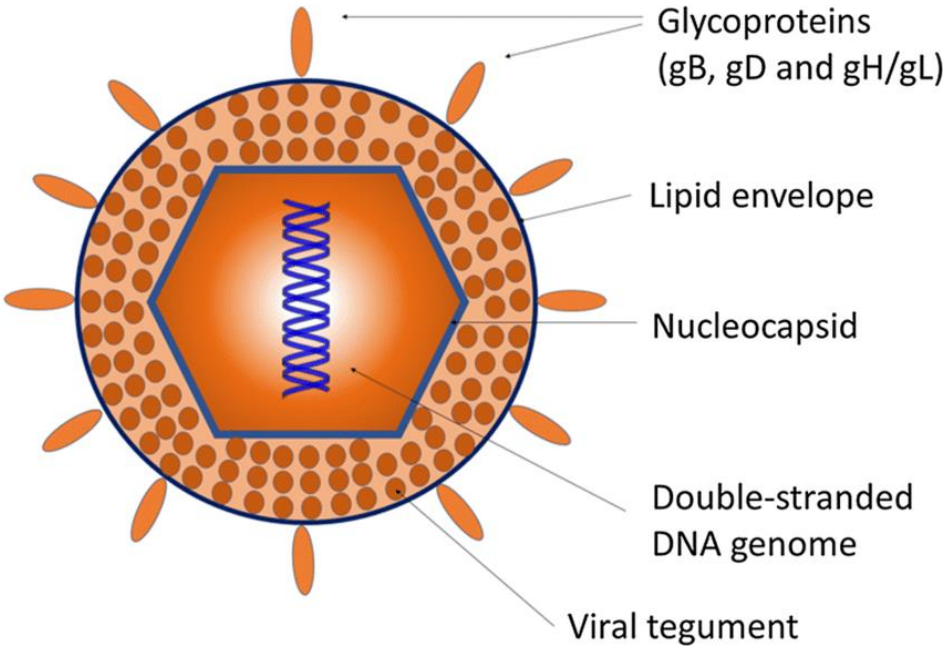
HSV(1 & 2)

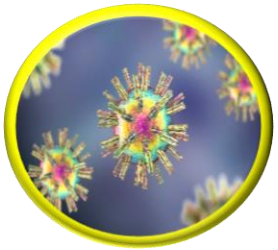


Herpes simplex virus type-1 and 2 (HSV-1, HSV-2) are linear , double stranded DNA, α-herpes viruses associated with infections involving

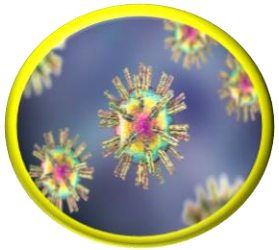
mucocutaneous surfaces, the CNS, and visceral organs.

Clinical Manifestations Of HSV

HSV-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.



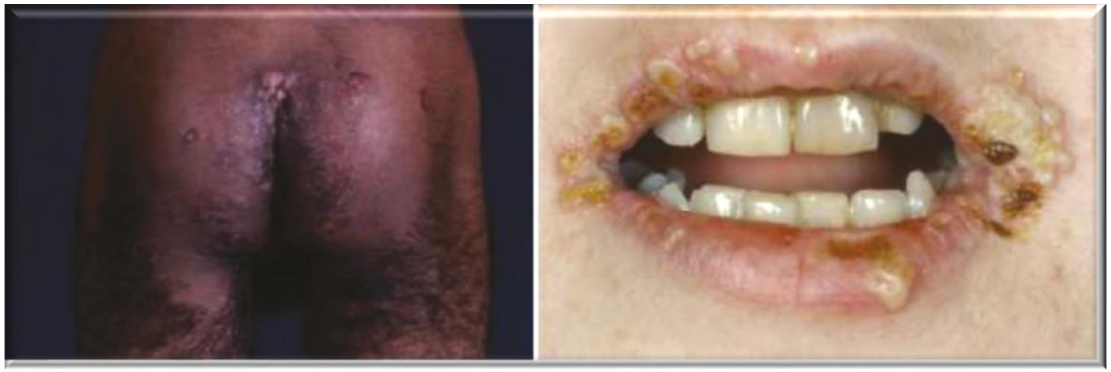
Compared with immunocompetent persons, solid organ transplant (SOT) recipients shed virus more frequently, have more severe clinical manifestations, and are slower to respond to therapy.

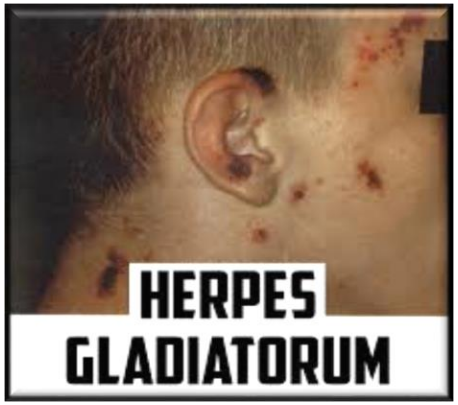


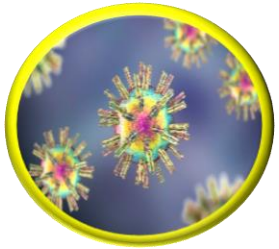
Clinical Manifestations Of HSV

The most common clinical presentation of HSV is localized multiple painful lesions on orolabial, genital or perianal area.

Lesions can be vesicular or ulcerative and may extend locally.



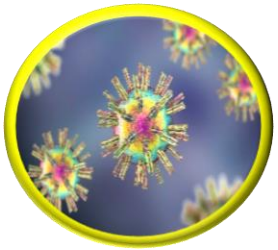




Clinical Manifestations Of HSV

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.

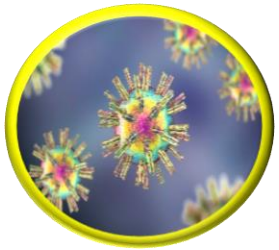


HSV can also reactivate in a retrograde fashion from the ganglion to the CNS to cause meningoencephalitis, transverse myelitis, or recurrent lymphocytic meningitis (Mollaret's meningitis)

More severe forms of HSV disease

- Disseminated mucocutaneous or visceral disease
- Esophagitis
- Hepatitis
- Pneumonitis.

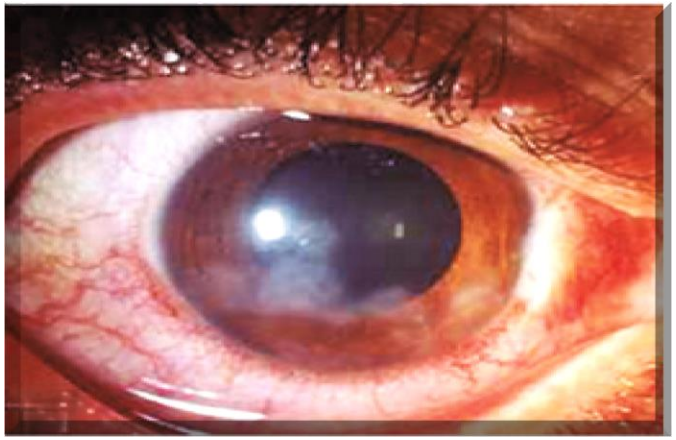
Severe visceral disease may initially present with absent or sparse mucocutaneous lesions, so prompt evaluation for HSV infection should be considered when confronted with hepatitis or other clinically appropriate syndromes of otherwise unclear etiology.

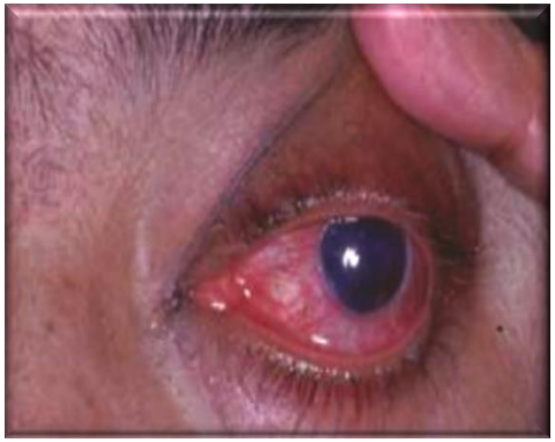


HSV Keratitis

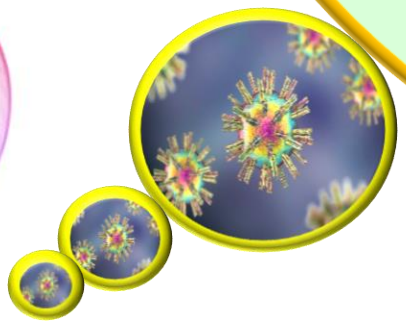
A manifestation of HSV in the eye that can result in visual disturbance or blindness. Superficial ocular infection may result from HSV reactivation in the trigeminal nerve, and deeper infection of corneal tissues (eg, stromal keratitis)
from the inflammatory reaction and/or immune-mediated responses to remaining antigen.

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.





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.



Diagnosis Of HSV

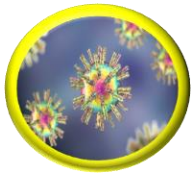
- Most HSV infections are diagnosed on clinical grounds.
- Polymerase chain reaction(PCR) is the preferred test for sampling lesions and CSF (strong, high).

PCR 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)



Drug Therapy in HSV-Seropositive SOT Recipients

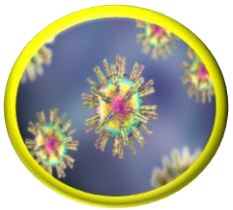
Treatment Mucocutaneous disease		
Adult	Acyclovir (400 mg 3 times a day) Valacyclovir (1000 mg twice a day) Famciclovir (500 mg twice a day) Acyclovir 5 mg/kg IV every 8 h (if unable to take PO or more extensive disease)	Because prompt initiation of therapy is associated with improved outcome, therapy 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%	Topical steroids should also be considered for stromal keratitis.
	Trifluorothymidine 1% Acyclovir 3% ointment	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

Resistance

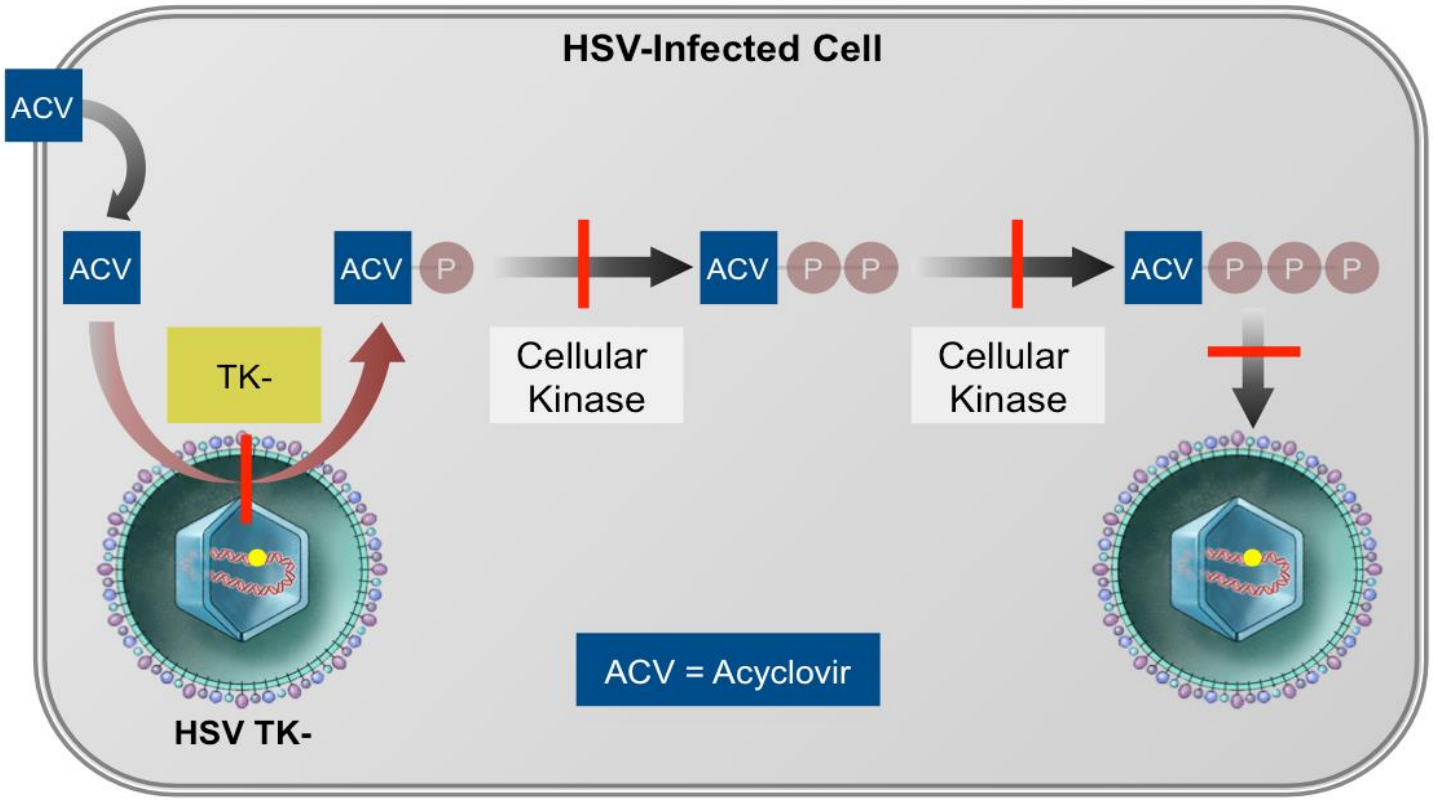
The estimated prevalence of acyclovir resistance in immunocompromised hosts ranges from 2.1% to 10.9% and needs to be considered in patients whose lesions are not responding clinically to appropriate doses of antiviral therapy,

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.



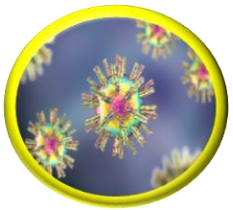
Antiviral-resistant HSV most often results from absent or decreased production of viral thymidine kinase (TK-negative mutants)



Most acyclovir-resistant HSV occurs via the mechanism of decreased or absent production of thymidine kinase (TK) by HSV. The strains are referred to as HSV TK-mutants. With inadequate production of TK, acyclovir does not undergo the mandatory initial phosphorylation step, and HSV replication proceeds uninhibited.

Resistance

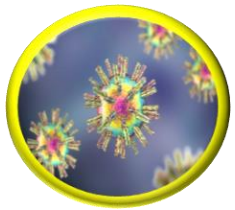
When resistant virus is strongly suspected, typically based on history and lack of response to high-dose IV acyclovir, alternate therapy should be considered prior to confirmation of resistance. Foscarnet and intravenous cidofovir are recommended for acyclovir-resistant HSV infections. But these drugs are associated with significant renal toxicity and need close monitoring.



Prevention

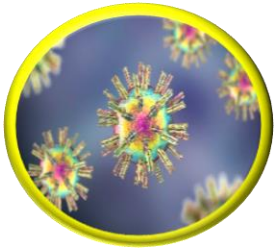
Many transplant recipients receive antiviral medication to prevent CMV replication.Ganciclovir, acyclovir, valacyclovir, and valganciclovir prevent most HSV replication when given in standard doses. HSV-specific prophylaxis should be considered for all HSV-1 and HSV-2–seropositive organ recipients who are not receiving antiviral medication for CMV replication.

Current HSV prevention techniques are focused on behavioral and antiviral methods



Prevention

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	



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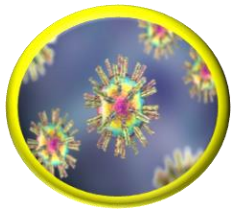
SPECIAL ISSUE-TRANSPLANT INFECTIOUS DISEASES

WILEY Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research

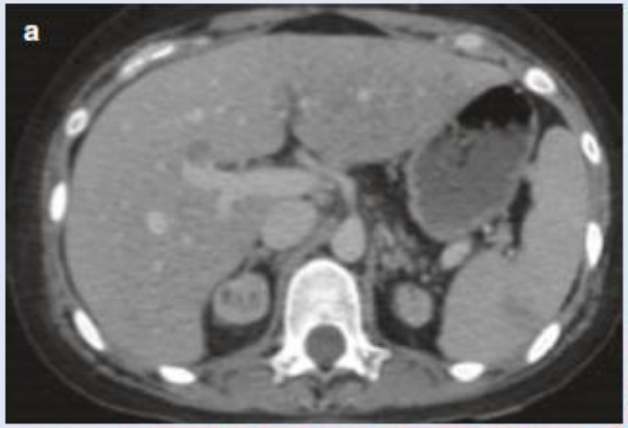
Herpes simplex virus infections in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

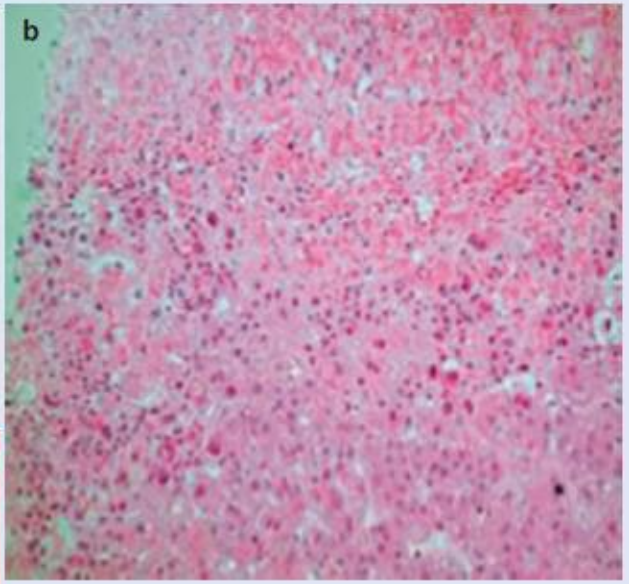
Dong H. Lee[1] | Richard A. Zuckerman[2] | on behalf of the AST Infectious Diseases Community of Practice

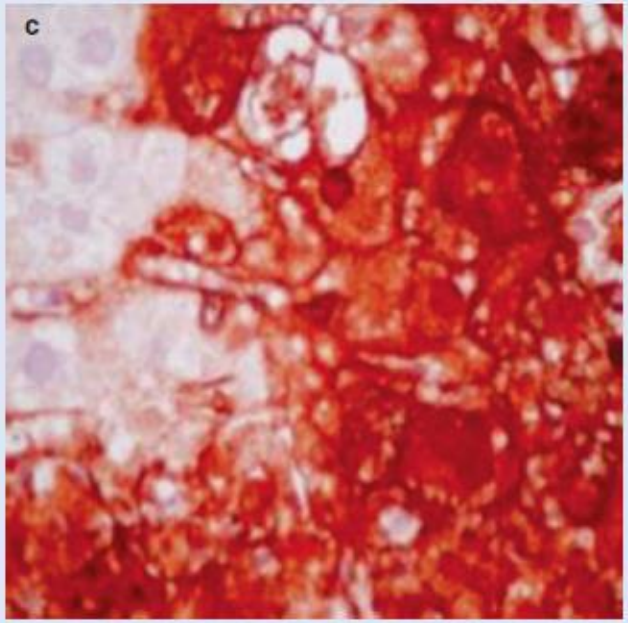


Case Presentation

A 30-y/o woman underwent a deceased donor transplant. Initially things went well but she developed a fever and a progressive rise in CRP 6 days posttransplant. There was no obvious focus, multiple cultures were negative and the patient appeared well, but her liver function tests became increasingly abnormal with a marked coagulopathy. A CT scan demonstrated multiple microabscesses. She rapidly deteriorated and a laparoscopic liver biopsy demonstrated an acute hepatitis which was positive for HSV on immunoperoxidase.

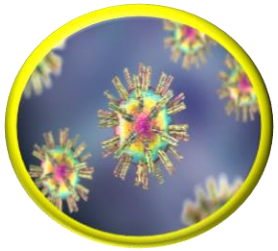






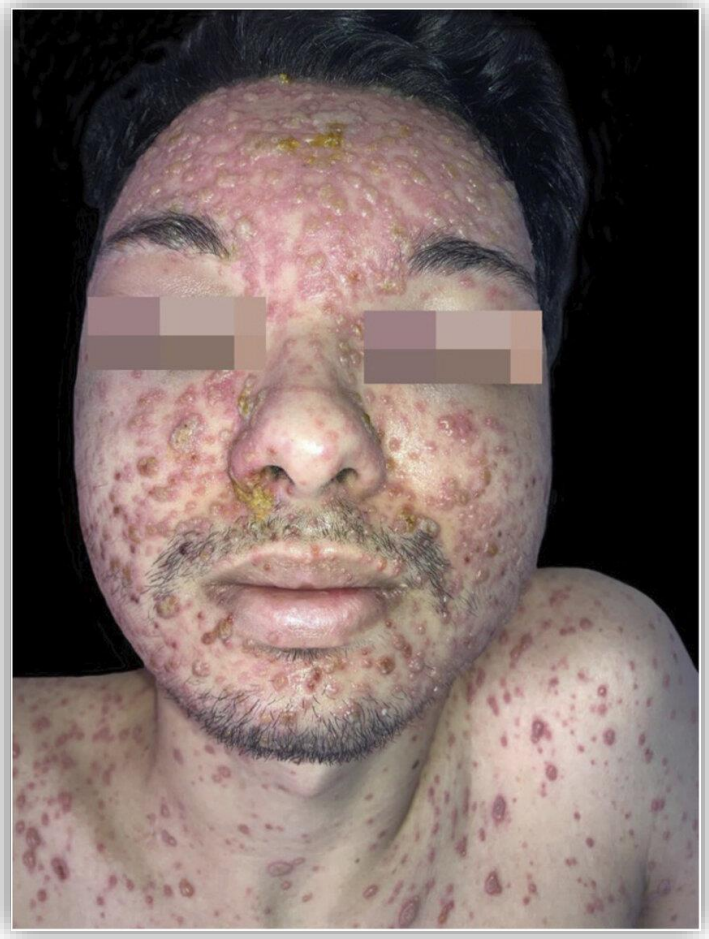
CT demonstrating multiple “microabscesses” secondary to HSV necrosis. **b** Liver biopsy demonstrating multinucleate giant cells, apoptotic cells and necrotic areas. **c** Liver biopsy Immunoperoxidase with livid staining for HSV

The recipient, and donor, were HSV negative and despite the absence of an obvious source she was started on acyclovir prior to the liver biopsy and the patient made a fully and rapid recovery. However, this case illustrates that while fulminant hepatic failure from primary HSV is very rare, herpes virus infections can be very dangerous when acquired posttransplant. HSV negative patients should receive anti-viral prophylaxis at the time of transplant.



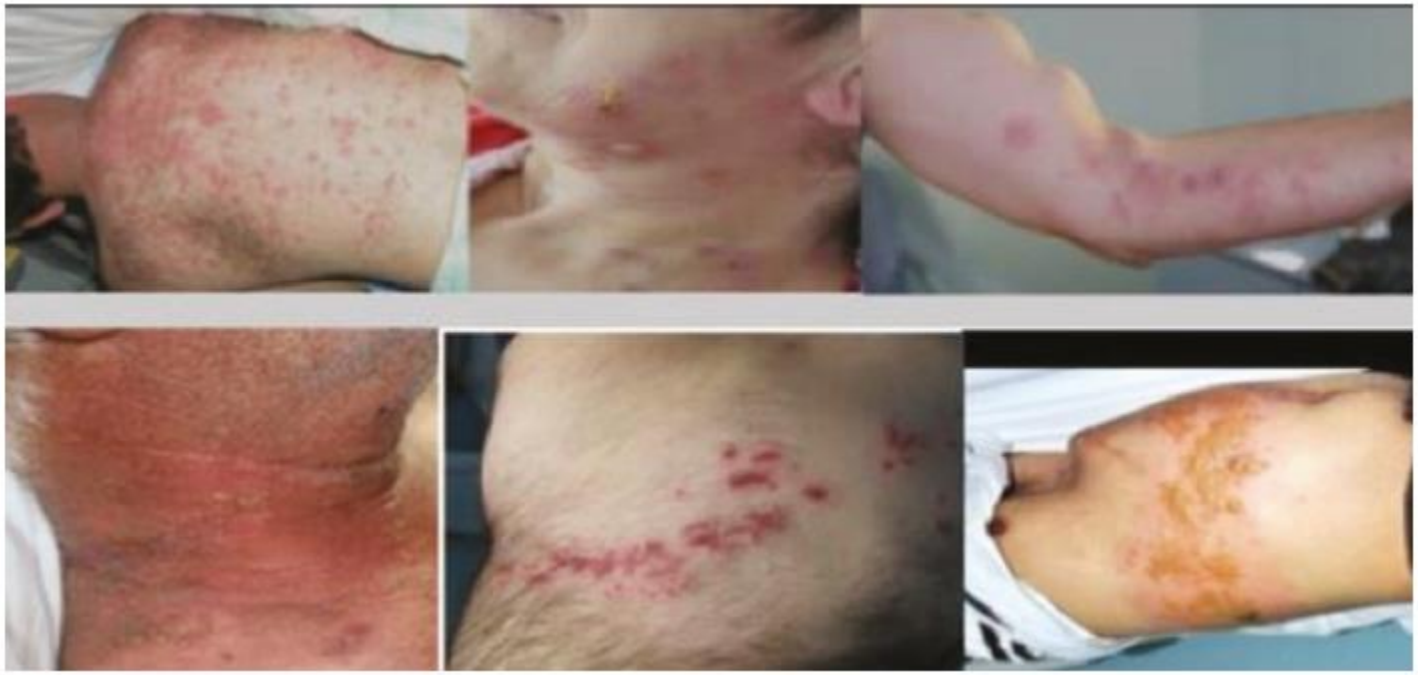
VZV

- Primary Varicella
- Herpes Zoster



Primary Varicella in a renal transplant patient

10.1016/j.abd.2022.10.013



appearance of Herpes Zoster Lesions in Different Dermatomes in Solid-Organ Transplant Recipients

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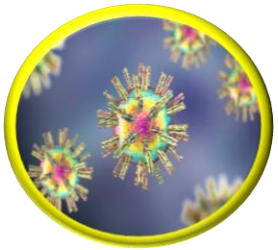

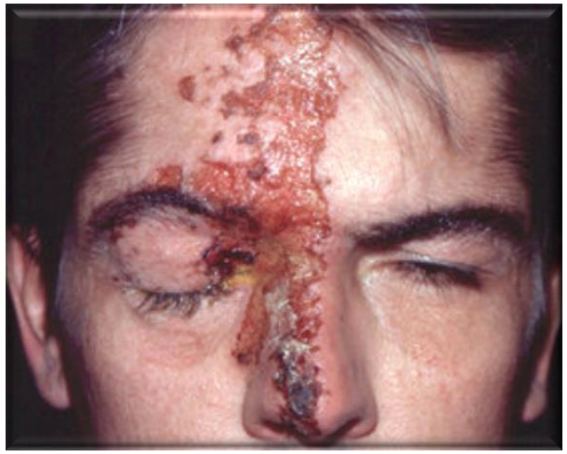

herpes zoster ophthalmicus

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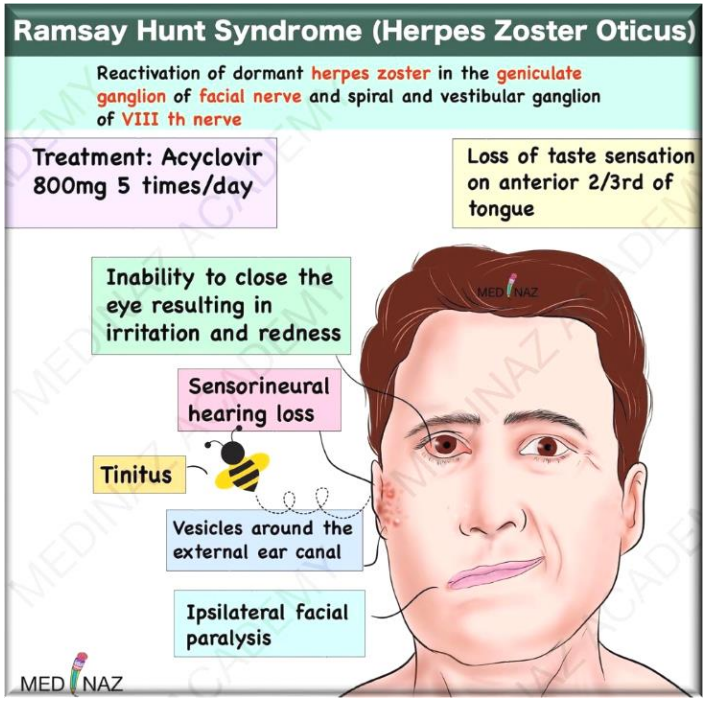

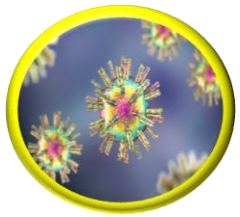

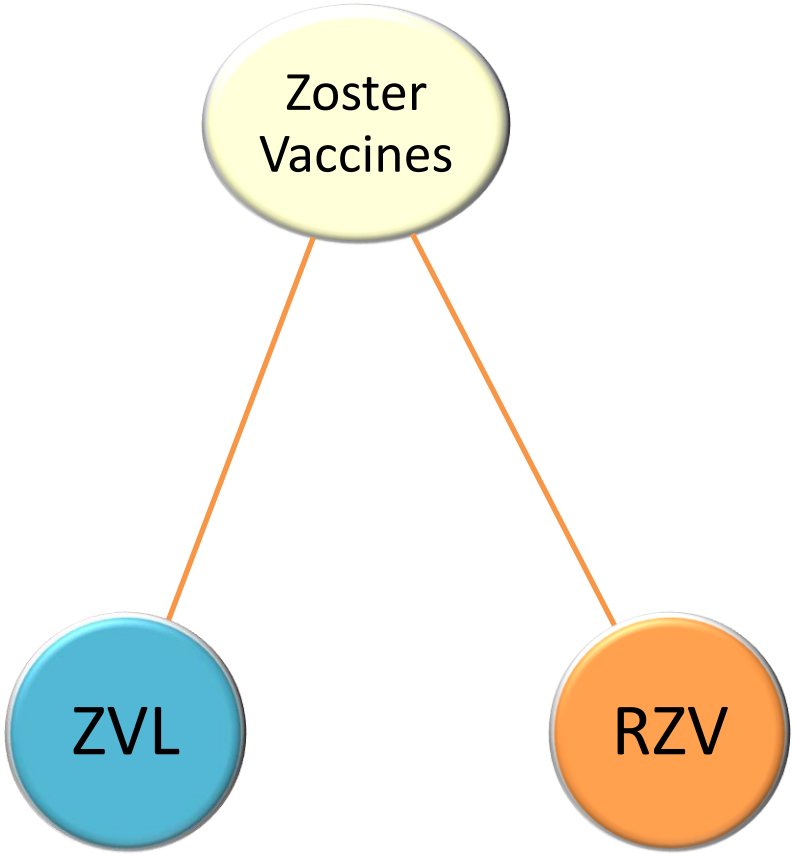
Zoster Vaccines
ZVL
RZV

Table 1: Recommendations for VZV treatment in solid organ transplant recipients

Disease	Treatment	Evidence	Comments
Outpatient treatment			
Herpes zoster localized (dermatomal)	**Acyclovir** 800 mg PO five times daily (adults and children ≥12 years) OR **Valacyclovir** 1 gram PO three times daily (adults) 20 mg/kg PO four times daily (children ≥2 and ≤18) years)[1] OR **Famciclovir** 500 mg PO three times daily (adults only)	Evidence II-1	• Oral therapy is not recommended for young children <2 years of age, or patients with evidence of dissemination, tissue invasion, HZ ophthalmicus or oticus, or those with severe symptoms. These patients should be treated with IV therapy (see below) • Antivirals are typically given for at least 7 days or until lesions have crusted over, which may be delayed in immunocompromised hosts • Valacyclovir and Famciclovir are not FDA approved for treatment of herpes zoster, but are commonly used in clinical practice • Valacyclovir is only recommended for children ≥2–18 years of age • IV acyclovir is recommended in children <2 yrs of age or those who cannot tolerate oral therapy (see below for dosing) • Careful monitoring of renal function is needed while on high-dose acyclovir therapy, and dosing should be adjusted for renal insufficiency

Table 1: Recommendations for VZV treatment in solid organ transplant recipients

Disease	Treatment	Evidence	Comments
Inpatient treatment			
Acute varicella	**Acyclovir** 30 mg/kg IV in 3 divided doses (adults and children <1 year) OR 1500 mg/m^2 IV per day in 3 divided doses (children ≥ 1 year of age)[2]	Evidence I	• IV therapy can be changed to oral therapy once the patient has significantly improved • Careful monitoring of renal function is needed while on IV therapy, and dosing should be adjusted for renal insufficiency
Herpes zoster Disseminated or Invasive disease or Herpes zoster ophthalmicus or Ramsay-Hunt syndrome/ Herpes zoster oticus	**Acyclovir** 30 mg/kg IV in 3 divided doses (adults and children)		• In disseminated disease IV therapy should be given for at for at least 7 days, but may need to be given for longer in patients with extensive involvement or CNS disease • Ophthalmology consultation is recommended for patients with ophthalmic involvement • Consideration for switch to oral therapy dependent on patient's clinical status • Careful monitoring of renal function is needed while on IV therapy, and dosing should be adjusted for renal insufficiency

For nonimmune solid organ transplant recipients who have been exposed to a patient with VZV (varicella or herpes zoster) infection, we recommend prophylaxis with VariZIG and/or antiviral therapy.


THANKS FOR YOUR ATTENTION