

Cytomegalovirus & Herpes Simplex Viruses

1. Virology

- Double stranded DNA viruses = low mutation rate
- Enveloped viruses = labile in the environment

2. Epidemiology

- Agents are ubiquitous
- No seasonality
- US adult seroprevalence
 - ◆ CMV = 58.9% (90.8% aged \geq 80 years)
 - ◆ HSV-1 = 57.7%
 - ◆ HSV-2 = 17.0%
- Racial/ethnic factors, socioeconomic status, and behavioral factors affect risk – racial and socioeconomic disparities

3. Cytomegalovirus

- Transmission – person-to-person
 - ◆ Intrauterine
 - ◆ Perinatal
 - ◆ Postnatal
 - ◆ Blood transfusion
 - ◆ Organ transplantation
- Pathogenesis
 - ◆ Primary infection: Virus entry via epithelium of the GU, upper GI or respiratory tract; or introduction via hematogenous route or organ transplantation. Virus spread via leukocytes to multiple tissues. Host immunity limits spread, cell-mediated immunity is critical. CMV encodes immune evasion genes but significance unknown.
 - ◆ Latent infection: Virus persistent indefinitely in host. Reservoir of non-replicating virus is probably bone marrow myelomonocytic stem cells and circulating monocytes. Reactivation of latent infection to produce productive viral replication is likely due to differentiation of latently infected monocytes into tissue macrophages caused by allogenic

stimulation (as can occur with transplantation) or proinflammatory cytokines (as can occur with intercurrent infections).

- ◆ Recurrent infections: Tend to be asymptomatic except in patients with impaired T-cell immunity.
- ◆ Re-infections: Unusual except in the profoundly immunocompromised patient
- **Common** clinical illnesses
 - ◆ Infectious mononucleosis
 - ◆ Congenital CMV infection (multi-organ involvement)
 - ◆ CMV infection in the immunocompromised host
 - Solid organ transplantation
 - Bone marrow transplantation
 - HIV/AIDS
- Putative associations
 - ◆ Atherosclerosis
- Diagnosis
 - ◆ Serology
 - IgG & IgM (potential anamnestic IgM response)
 - Virus isolation
 - Antigen (pp65) detection (in blood)
 - CMV DNA PCR
- Treatment
 - ◆ Mononucleosis
 - None
 - ◆ Congenital CMV infection
 - None
 - ◆ CMV infection in the immunocompromised host
 - Ganciclovir
 - Foscarnet
 - Cidofovir
- Prevention
 - ◆ Hand washing (*1-30% of hospitalized patients shed virus in urine or saliva*)
 - ◆ Use of CMV seronegative blood products
 - ◆ Use of CMV seronegative organ donors (impractical)
 - ◆ CMV immune globulin

- ◆ CMV vaccines (in development; among highest priority by IOM)

4. Herpes simplex viruses

- Transmission – person-to-person
 - ◆ Intrauterine
 - ◆ Perinatal
 - ◆ Postnatal
 - Oral-oral
 - Oral-facial
 - Oral-genital
 - Genital-genital
 - Skin-to-skin
- Pathogenesis – mucocutaneous infections

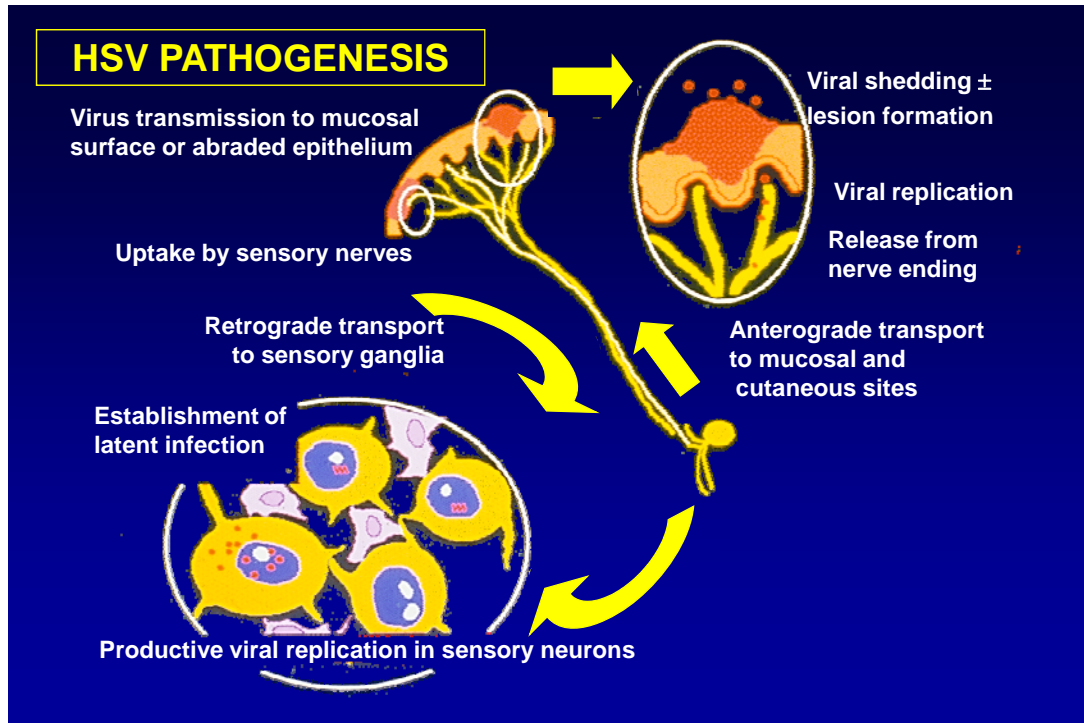
Primary infection: In the immunocompetent host the pathogenesis of HSV infection involves viral replication in skin and mucous membranes and replication and spread in neural tissue. Viral infection typically begins at a cutaneous portal of entry such as the oral cavity, genital mucosa, ocular conjunctiva, or breaks in keratinized epithelia. Virus replicates locally resulting in the death of the cell and sometimes produces clinically apparent inflammatory responses which facilitate the development of characteristic herpetic vesicles and ulcers. Virus also enters nerve endings and spreads beyond the portal of entry to sensory ganglia by intraneuronal transport. Virus replicates in some sensory neurons and the progeny virions are sent via intraneuronal transport mechanisms back to the periphery where they are released from nerve endings and replicate further in skin or mucosal surfaces. It is virus moving through this neural arc that is primarily responsible for the development of characteristic herpetic lesions although most HSV infections do not reach a threshold necessary to cause clinically recognizable disease.

Viremia or hematogenous spread of the virus does not appear to play a role in HSV infections of the immunocompetent host but can occur in neonates, individuals with eczema, and severely malnourished children. It is also seen in patients with depressed or defective cell-mediated immunity such as occurs with HIV infection or some immunosuppression regimens. With viremia there can be dissemination of the virus to visceral

organs including the liver and adrenals. Hematogenous dissemination of virus to the central nervous system appears to only occur in neonates. The pathogenesis of HSV infection in newborns is complicated by their relative immunological immaturity.

- ◆ Latent infection: While many sensory neurons become productively infected during the initial infection, some infected neurons do not initially support viral replication; in these the virus establishes a latent infection. HSV latency is a reversible interruption of the virus replication cycle in sensory neurons. The establishment and maintenance of the latent state appears to be a passive process in so far as no virus gene products are required, however, the host response may play a role. Latently infected neurons do not express viral antigens and most do not show evidence of transcription of the viral genome. Transcripts from a limited region of the genome are detectable in a subpopulation of latently infected neurons (latency-associated transcripts) (LAT). Latency associated transcription appears to facilitate reactivation from latency. Latent HSV-1 reactivates most efficiently and frequently from trigeminal ganglia, causing recurrent ocular and oral-facial lesions, while latent HSV-2 reactivates primarily from sacral ganglia causing recurrent genital lesions. These characteristic site-specific reactivation phenotypes appear to depend upon the latency-associated transcript region.
- ◆ Recurrent infections: Result from reactivation of latent infection. Intermittently throughout the life of the host undefined changes can occur in latently infected neurons that trigger the virus to begin to replicate. This occurs despite the host having established a variety of humoral and cellular immune responses which successfully controlled the initial infection. With reactivation of the latent neuron, progeny virions are produced and transported within nerve fibers back to cutaneous sites somewhere in the vicinity of the initial infection where further replication occurs causing recurrent infections. Recurrent infections may be symptomatic with typical or atypical herpetic lesions or the recurrences may be asymptomatic. Whichever the case, virus is shed at the site where cutaneous replication occurs and can be transmitted to other susceptible individuals who come in contact with the site or with associated contaminated secretions. Latency and reactivation are the mechanisms used by the virus to successfully maintain itself in the human population.

- ◆ Re-infections: Exogenous re-infection at an anatomic site previously infected is unusual except in the profoundly immunocompromised patient.



- **Common Clinical Illnesses**

Disease	Predominant Virus Type	Primary or Recurrent	Characteristics
Herpes gingivostomatitis	HSV-1	Primary	High fever, significant oral pain with associated difficulty swallowing, vesicular lesions throughout the oral cavity
Herpes pharyngitis	HSV-1	Primary	Moderate fever, persistent sore throat, vesicular lesions on tonsils and posterior pharynx

Herpes labialis	HSV-1	Recurrent	Small solitary or cluster of vesiculoculcerative lesions (fever blisters or cold sores) on or around the lip. The onset is sometimes heralded by tingling, itching, burning, or pain at the site where the lesions will develop
Herpes genitalis	HSV-1 or HSV-2 depending on geographic region	Primary or Recurrent although recurrent infections are almost due to HSV-2	Classically presentation is that of vesicles or genital ulcers. Lesions may be on the genitalia or on the buttocks, thighs, or around the anus. Mild infections may be non-classical with non-specific findings including tingling, burning, itching, erythematous patches and small skin fissures
Neonatal herpes	HSV-1 or HSV-2	Primary	Generally result from mother-to-infant transmission, the clinical manifestations broadly fall into one of three patterns of disease: (1) vesiculoulcerative lesions localized to the skin, eyes, or mouth; (2) encephalitis; or (3) disseminated infection.

- Less common clinical illness
 - ◆ Herpes encephalitis
 - ◆ Herpes keratitis
 - ◆ Herpes retinitis
 - ◆ Herpes whitlow
 - ◆ Herpes gladiatorum
 - ◆ Excema herpeticum
 - ◆ Herpes meningitis
 - ◆ Disseminated herpes
 - ◆ Erythema multiforme

- Putative associations
 - ◆ Schizophrenia
 - ◆ Alzheimer's Disease

- Diagnosis
 - ◆ Serology
 - IgG & IgM (potential anamnestic IgM response)
 - Virus isolation
 - Antigen detection (in tissue or scrapings)
 - HSV DNA PCR
 - ◆ *Clinical diagnosis is often unreliable*

- Treatment
 - ◆ Oral (non-life threatening infections)
 - Acyclovir
 - Valacyclovir (acyclovir prodrug)
 - Famciclovir (penciclovir prodrug)
 - ◆ Topical (non-life threatening infections)
 - Acyclovir
 - Penciclovir
 - ◆ Intravenous
 - Acyclovir



Gertude Elion

George Hitchings

Nobel Prize in Physiology or Medicine 1988

- Prevention
 - ◆ Neonatal herpes
 - Cesarean delivery
 - Antiviral in last four weeks of gestation (unproven)
 - ◆ Oral-facial herpes
 - Good hygiene (?)
 - ◆ Genital herpes
 - Condoms (limited benefit)
 - Valacyclovir (by infected partner)
 - Abstinence
 - Vaccines (in development)

