CYTOMEGALOVIRUS & HERPES SIMPES VIRUSES

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Enveloped viruses are labile in the environment.

**Shedding and survival of herpes simplex virus from 'fever blisters'**

Ronald Turner, Ziad Shebad, Karen Osborne, J Owen Hendley

In nine adults with virus-positive herpes labialis, HSV was detected in the anterior oral pool of seven (78%) and on the hands of six (67%).

HSV isolated from patients with oral lesions were found to survive for as long as two hours on skin, three hours on cloth, and four hours on plastic.

*Pediatrics. 1982; 70:547-9*
Reactivation and Shedding of Cytomegalovirus in Astronauts during Spaceflight

S Metha, R Stowe, A Feiveson, S Tyring, D Pierson

The reactivation of cytomegalovirus (CMV) in 71 astronauts was investigated, using polymerase chain reaction. A significantly greater shedding frequency was found in urine samples from astronauts before spaceflight (10.6%) than in urine from the healthy control subject group (1.2%). Two of 4 astronauts studied during spaceflight shed CMV in urine.

J Infectious Dis 2000; 182:1761

HERPESVIRUS GENOMIC ORGANIZATION

Double stranded DNA genome – high fidelity replication
CMV & HSV EPIDEMIOLOGY

- Agents are ubiquitous
- No seasonality
- US adult seroprevalence
  - CMV = 58.9% (90.8% aged ≥ 80 years)
  - HSV-1 = 57.7%
  - HSV-2 = 17.0%
- Prevalence demonstrates racial and socioeconomic disparities
- Prevalence affected by behavioral factors

Longitudinal risk of HSV-1, HSV-2 and CMV infections among young adolescent girls

L R Stanberry, SL Rosenthal, L Mills, PA Succop, FM Biro, RA Morrow, DI Bernstein

A 3-yr longitudinal study of HSV-1, HSV-2, and CMV seroprevalence was conducted in a cohort of 174 adolescent girls.

By study end, 81% were CMV seropositive, 49% were HSV-1 seropositive, and 14% were HSV-2 seropositive. Among girls with a history of sexual activity 18.9% were HSV-2 seropositive.

The attack rates, based on the number of cases per 100 person-years, were 13.8 for CMV infection and 3.2 for HSV-1 infection (among all girls) and 4.4 for HSV-2 infection (among girls with a history of sexual activity).

Clinical Infectious Diseases 2004;39:1433–1438
CMV TRANSMISSION

• Transmission – person-to-person or via infected fomites
• Viral shedding
  • urine
  • saliva
  • In a daycare center study an average of 11.2% children shed CMV – Arch Med Res 2005; 36:590-3.
  • cervicovaginal secretions
  • breast milk
  • semen (?)

CMV TRANSMISSION

• Intrauterine
  • most common congenital infection
• Perinatal
• Postnatal
  • infants, parents of young infants, daycare workers, hospital workers
  • most common route of mother-to-baby transmission is via breast feeding
• Blood transfusion
  • prevented by using blood from CMV seronegative donors or cotton wool filtered blood (removes WBCs & platelets)
• Organ transplantation
  • CMV seropositive donor to CNV seronegative recipient
Cytomegaloviruses are over 200 million years old...no wonder they are so good at what they do

Human CMV (HCMV) has evolved with us since the beginning of our time (prior to invertebrate-vertebrate split).

For every defense mechanism we have, HCMV has at least one counter-mechanism...tit for tat

Unsuccessful viruses cannot overcome host defenses.

[CMV PATHOGENESIS diagram]

Infection of Endothelial Cells (GU, upper GI, Respiratory Tract)

Infection of Trafficking Leukocytes

Hematogenous Dissemination via Leukocytes to Multiple Tissues

Symptomatic Disease or Asymptomatic Infection

Latent infection in myelomonocytic stem cells & circulating monocytes

Cell-mediated immunity

Recovery

Reactivation

Symptomatic Disease or Asymptomatic Infection
### COMMON CMV INFECTIONS

**INFECTIOUS MONONUCLEOSIS**

<table>
<thead>
<tr>
<th>Clinical Manifestations</th>
<th>Laboratory Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Atypical Lymphocytes</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>Lymphocytosis</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>Mild Thrombocytopenia</td>
</tr>
<tr>
<td>Malaise and Fatigue</td>
<td>EBV or CMV antibodies</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>Heterophile antibodies</td>
</tr>
<tr>
<td>Pharyngitis/Sore Throat</td>
<td></td>
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<tr>
<td>Rash</td>
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CMV responsible for about 8% of IM cases

### COMMON CMV INFECTIONS

**CONGENITAL INFECTION**

<table>
<thead>
<tr>
<th>Clinical Manifestations</th>
<th>Laboratory Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatosplenomegaly</td>
<td>Elevated LFTs</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>Pneumonitis</td>
</tr>
<tr>
<td>Rash</td>
<td>CMV in body fluids</td>
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<tr>
<td>Microcephaly</td>
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</table>

Infection can cause brain damage that may result in mental retardation, spasticity, seizures, deafness and/or blindness
CMV IS THE MOST IMPORTANT POST TRANSPLANT VIRAL PATHOGEN

CMV DISEASES IN IMMUNOCOMPROMISED PATIENTS

<table>
<thead>
<tr>
<th>Manifestations</th>
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<tbody>
<tr>
<td>Fever</td>
<td>Myelosuppression</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>Encephalopathy</td>
</tr>
<tr>
<td>Retinitis</td>
<td>Colitis</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>Rejection</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>Graft v Host Disease</td>
</tr>
</tbody>
</table>

Disease likelihood determined by nature of the immunosuppression, solid organ transplantation, bone marrow transplantation or AIDS
PUTATIVE ASSOCIATIONS

- Atherosclerosis is an inflammatory disease
- Infection is a candidate inflammatory trigger
- Epidemiological studies link CMV infection with clinically manifest atherosclerotic disease
- CMV antigen and nucleic acid sequences in arterial smooth muscle cells of humans suggests that viral infection of the arterial wall may be common in the general population
- Some heart transplant recipients, who are immunosuppressed, and actively infected with CMV, are prone to develop accelerated atherosclerosis in the transplanted organ
- There may be a gene by environment interaction

CMV DIAGNOSIS

- Serology – IgG and IgM detection (anamnestic IgM responses can occur)
- Virus isolation
- Antigen (pp65) detection
- CMV DNA PCR
CMV TREATMENT
• Ganciclovir and Valganciclovir
• Foscarnet
• Cidofovir

- All are viral DNA polymerase inhibitors
- Used exclusively in the treatment of CMV infection in immunocompromised patients
- Used for pre-emptive and prophylactic therapy
- Ganciclovir resistance reported in 5-10% of patients

CMV PREVENTION
• Hand washing (1-30% of hospitalized patients and 100% of infected infants shed in urine and/or saliva)
• Use of CMV seronegative blood products
• Use of CMV seronegative organ donors (impractical)
• Antiviral prophylaxis
• CMV immune globulin
• Vaccines
HSV TRANSMISSION

- Transmission – person-to-person (rarely by fomites)
  - Intrauterine (very rare)
  - Perinatal
  - Skin-Skin
  - Genital-Genital
  - Oral-Genital
  - Oral-Oral
- Viral shedding
  - saliva
  - oro-facial lesions
  - genital lesions and secretions
  - tears (?)
- HSV-1 more commonly shed from oral cavity and HSV-2 more commonly from genital tract

HSV SITE-SPECIFIC RECURRENCES
**MUCOCUTANEOUS HSV PATHOGENESIS**

- Virus transmission to mucosal surface or abraded epithelium
- Uptake by sensory nerves
- Retrograde transport to sensory ganglia
- Establishment of latent infection
- Productive viral replication in sensory neurons
- Viral shedding
- Lesion formation
- Viral replication
- Release from nerve ending
- Anterograde transport to mucosal and cutaneous sites

**HSV INFECTIONS**

- Clinical manifestations are determined by portal of entry, immune status of the host, and whether the infection is primary or recurrent
- HSV is a neurotropic virus that infects sensory ganglia hence pain is a common manifestation of mucocutaneous HSV infections
HSV INFECTIONS

• Primary vs recurrent mucocutaneous infections
  • Primary oral-facial infection – herpes gingivostomatitis or pharyngitis
  • Recurrent oral-facial infection – herpes labialis

HSV INFECTIONS

• Primary vs recurrent genital infections
  • Primary genital herpes
  • Recurrent genital herpes
HSV INFECTIONS

- Neonatal herpes
  - Skin-eye-mouth
  - Central nervous system
  - Disseminated

HSV INFECTIONS

- Herpes encephalitis
- Herpes keratitis
- Herpes retinitis
- Herpes meningitis
HSV INFECTIONS

- Herpes gladiatorium
- Herpes whitlow
- Eczema herpeticum
- Disseminated herpes
- Erythema multiforme
- Bells palsy

PUTATIVE ASSOCIATIONS

- Infectious agents have been implicated in the pathogenesis of SCHIZOPHRENIA

- Herpes simplex virus (HSV) has been suggested as a putative cause of schizophrenia based on its tropism for the nervous system and epidemiological studies linking herpes infection in pregnancy with schizophrenia. Yolken R, Viruses and schizophrenia: a focus on herpes simplex virus. Herpes 2004; 11:83A.
HSV DIAGNOSIS

• Serology – IgG and IgM detection
  • Anamnestic IgM responses can occur; IgM tests unreliable; most tests cannot accurately distinguish HSV-1 and HSV-2
• Virus isolation
• Antigen detection
• HSV DNA PCR
• Tzacnk smear – unreliable
• Clinical diagnosis – unreliable
  • Langenberg, NEJM 1999, 341:1432

HSV TREATMENT

• Acyclovir and Valacyclovir
• Penciclovir and Famciclovir
• Foscarnet
• All are viral DNA polymerase inhibitors
• For life threatening HSV infections use on intravenous acyclovir
• Valacyclovir use has been shown to reduce risk of transmission of genital herpes from infected to susceptible partner
• Acyclovir resistance is rare but seen in profoundly immunocompromised patients
• Acyclovir, Valacyclovir and Famciclovir remarkably safe
HSV TREATMENT

• Nobel Prize in Physiology and Medicine 1988

“Gertrude Elion and George Hitchings demonstrated differences in nucleic acid metabolism between normal human cells, cancer cells, protozoa, bacteria and virus. On the basis of such differences a series of drugs were developed that block nucleic acid synthesis in cancer cells and noxious organisms without damaging the normal human cells. A recent, successful application of their research ideas is exemplified by acyclovir (1977), the first effective drug in the treatment of herpes virus infections.”

HERPES INFECTIONS
MISCELLANEOUS THERAPIES

• Phototherapy
• Burn therapy (laser/N₂)
• Application of ice
• X-rays
• Benzoin
• Topical epinephrine
• Hydrogen peroxide

• Vitamins
• Diet therapy
• Ginseng
• Aloe vera extracts
• Various herbs
• Red algae
• Lactobacillus tablets
### HERPES INFECTIONS
#### MISCELLANEOUS THERAPIES

- Dimethyl sulfoxide (DMSO)
- Lysine
- Blistex
- Camphophenique
- Pyrethins
- Antibiotics
- Steroid creams
- Tannic acid
- Mercurochrome
- Potassium permanganate
- Gentian violet
- Silver nitrate
- Iodine
- Lithium
- Red wine

### HSV PREVENTION

- Neonatal herpes
  - Cesarean delivery
  - Antivirals in final 4 weeks of gestation (unproven)
- Genital herpes
  - Abstinence
  - Valacyclovir use by infected partner
  - Condom use (limited benefit)
  - Vaccines (in development)
GSK HSV-2 VACCINE TRIALS

- Two double blind, randomized, placebo-controlled trials
- Study 1 (57 centers) enrolled 847 HSV-1 and HSV-2 seronegative partners of HSV-2 infected persons
- Study 2 (60 centers) enrolled 2491 (any serostatus) partners of HSV-2 infected persons
- Vaccinations: 0, 1, and 6 months – I.M. administration
- Follow-up period: 19 months
- Primary efficacy endpoint: Acquisition of HSV-2 disease

Study 1- GSK HSV-2 Vaccine
Genital Herpes Disease HSV 1/-2- Subjects

<table>
<thead>
<tr>
<th></th>
<th>Vaccine Efficacy</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Men</td>
<td>-10.9%</td>
<td>0.81</td>
</tr>
<tr>
<td>Women</td>
<td>73.2%</td>
<td>0.01</td>
</tr>
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Stanberry NEJM 2002;347:1652
Study 2 - GSK HSV-2 Vaccine
Genital Herpes Disease HSV 1/-2- Subjects

Men

Women

Vaccine Efficacy | p-value
---|---
32.2% | 0.47
74.4% | 0.02

Stanberry NEJM 2002;347:1652
**HSV-2 Vaccines: Key Questions**

- What might explain the gender effect?
- Why did the vaccine not protect HSV-1 seropositive women?
- Would an HSV vaccine to protect against HSV-2 genital herpes also protect against genital herpes caused by HSV-1?
- Would a genital herpes vaccine protect against non-genital HSV infections including gingivostomatitis, encephalitis, retinitis and neonatal herpes?

**CMV and HSV**

**Learning points**

- Common, clinically relevant, ubiquitous viruses
- Transmission is by person-to-person spread
- Cause self-limited limited acute infection that results in establishment of a persistent life-long infection
- Persistent infection can reanimate to cause recurrent infection
- Myriad different clinical illnesses
- Safe antiviral drugs are effective at controlling the acute infection but ineffective in eliminating the persistent infection
- Current prevention strategies have limited effectiveness
- Promising vaccines are in development