

The Clinical Spectrum of Herpesvirus Infections

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Objectives

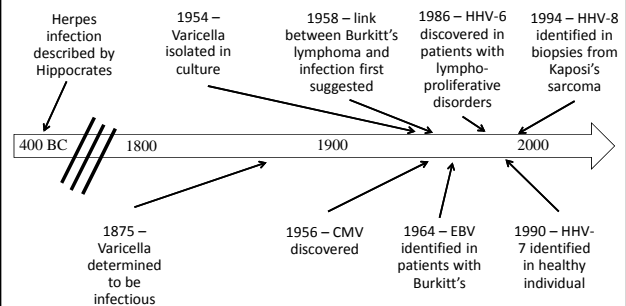
- Recognize the herpesviruses that cause disease in humans
- Understand the clinical presentations of herpesvirus infections

Herpesviruses overview

- > 100 known herpesvirus
 - 8 human herpesviruses
- Greek word *herpein* – "to creep or crawl"
 - referring to the latent, recurring nature
- All herpesviruses can establish latent infection within specific tissues, characteristic for each virus



History of herpesviruses



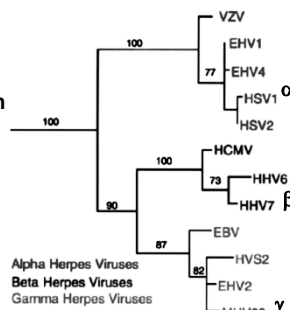
Herpesviridae Subfamilies

Alphaherpesvirinae (HSV-1, HSV-2, VZV)

- Broad host range
- Rapid reproductive cycle,
- Cytopathic effect and spread in culture
- Latent infections: Neuronal (sensory ganglia)

Betaherpesvirinae (HCMV, HHV-6,7)

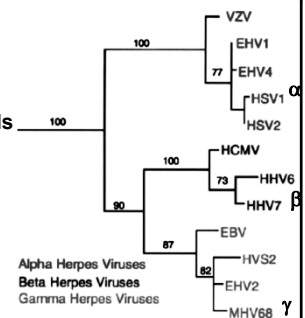
- Restricted host range
- Slow reproductive cycle
- Latent virus: Leukocytes (CD34+), Hematopoietic stem cells, and secretory glands (Salivary glands, and renal tubule).



Herpesviridae Subfamilies

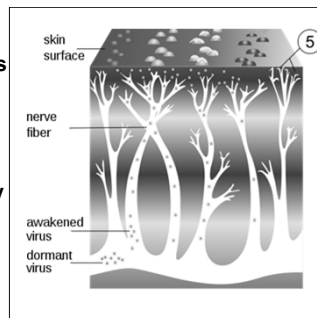
Gammaherpesvirinae (EBV, KHSV)

- Most Restricted Host Range
- Replicate in lymphoblastoid Cells
- Viruses specific for B or T cells
- Latent or lytic infection



Shared properties of human herpesviruses

- Code for unique enzymes involved in the biosynthesis of viral nucleic acids
- Synthesis and assembly of viral DNA is initiated in the nucleus
- Release of progeny virus from the is accompanied by cell death
- Establish latent infection within tissues



HHVs can cause severe and atypical disease in immunocompromised patients

Immunosuppression

- Medications
- HIV
- Cancer/ Transplant

Host Barrier defects (MUCOSITIS, Eczema, Burns)

Immune defects

- Neonates
- Pregnancy
- Elderly
- Cellular defects

Diagnosis of Herpesviruses

- Isolation virus through culture and/or detection of viral genes or gene products
- Direct visualization
- Serology
- Polymerase chain reaction



Case #1

- A 4 year old F presents to your office with a swollen, painful, right index finger. You notice multiple fluid-filled lesions on the finger, as well as some small ulcers on her tongue and bleeding around her gums. What's the diagnosis?



Image courtesy of Dwight Powell

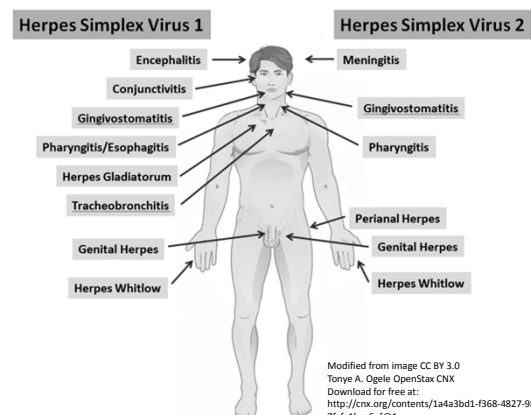
HSV - Pathogenesis

Primary infection: high titer and prolonged infection

Establish Latency: provide reservoir and viral template for future secondary infections

Secondary Reactivation: lower titer and shorter duration but there are some who have more prolonged disease

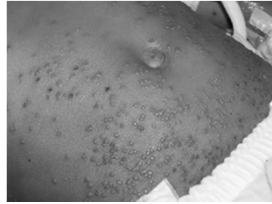
Clinical Manifestations of HSV



Diseases Caused by HSV: Oral & Cutaneous



Images courtesy of
Dwight Powell



HSV Gingivostomatitis in Immunocompromised

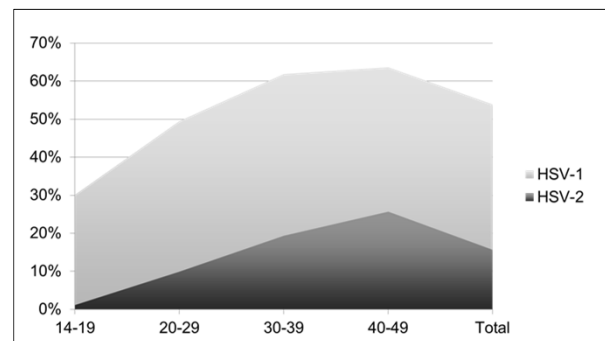


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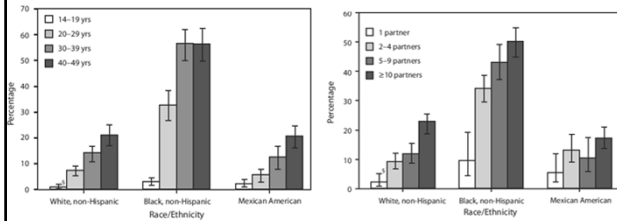
Images courtesy of
Dwight Powell

Percent of U.S. population positive for herpes viruses: 2005-2010



Bradley et al, JID 2013

HSV-2 seroprevalence by race & sexual partners

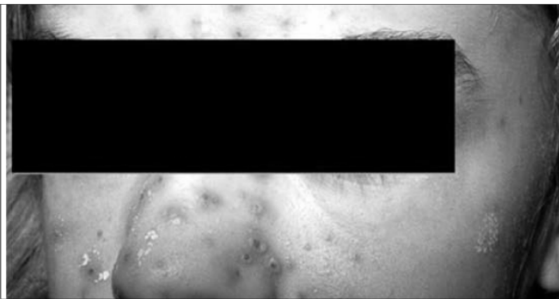


Centers for Disease
Control and Prevention

Case #2

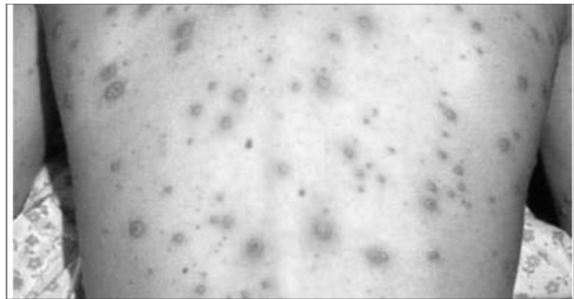
- An unimmunized, previously healthy 25-year-old woman presents to your office with a 24-hour history of fever, malaise, and a generalized pruritic rash. Physical examination reveals a temperature of 38.6°C, respiratory rate of 25 breaths/min, heart rate of 88 beats/min, and blood pressure of 110/62 mm Hg. She has a papulovesicular rash over her face, trunk, and extremities that involves her scalp but spares her palms and soles. The remainder of her exam is normal. What is your diagnosis?

Case #2: Papulovesicular Facial Rash*



*Courtesy of Red Book Online.© 2009

Case #2: Papulovesicular Truncal Rash*



*Courtesy of Red Book Online.© 2009

Varicella-Zoster Virus (VZV) Pathogenesis Primary infection

- **Entry:** Respiratory route
 - Local replication
- **Primary viremia:** seeds liver/spleen
 - T cells and Antibodies limit primary viremia in people with prior immunity
- **Secondary replication cycle**
 - Amplification Liver and Spleen
- **Secondary viremia** hematogenous dissemination to cutaneous sites.
- Immunity: T-cell response and resolution of lesions, IgG present
- Virus establishes latent virus in dorsal root ganglia

Day 0 Infection of conjunctiva and/or mucosa of upper respiratory tract

Day 4-6 Viral replication in regional lymph nodes
Primary viremia in bloodstream
Further viral replication in liver and spleen

Day 10 Secondary viremia
Infection of skin and appearance of vesicular rash

Varicella-Zoster Virus

- **Transmission:** direct contact or aerosol
- **Incubation**
 - Mean 14-16 days (10-21 days)
 - Contagious 1-2 days before rash and until lesions crusted
- **Increased severity**
 - Immune compromised
 - Older age
 - Pregnancy
- **250-500 lesions wild-type infection; in immunized, ≤ 50 lesions**

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Herpes Zoster

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GABHS periorbital cellulitis and necrotizing fasciitis complicating varicella

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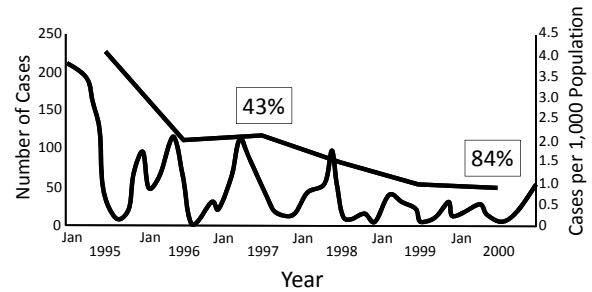
Necrotizing Fasciitis



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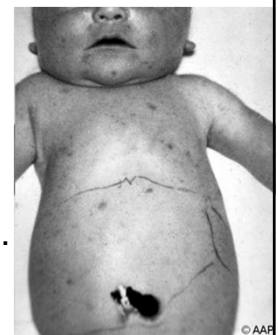
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Varicella disease after introduction of Varicella vaccine in West Philadelphia 1995-2000



Case #3

- A 1 day old male is born to a mother with no significant prenatal history. Delivery is uncomplicated but initial examination reveals hepatosplenomegaly and a "blueberry muffin" rash. Labs show thrombocytopenia and elevated liver enzymes. What's your diagnosis?



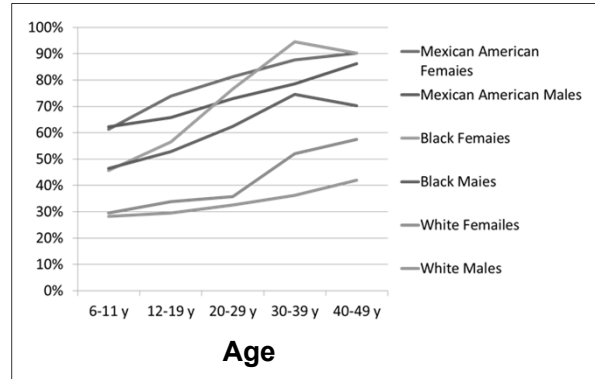
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Cytomegalovirus Clinical Syndromes

- Congenital infection
- Mononucleosis syndrome
- Immunocompromised hosts: may develop life-threatening disseminated disease

CMV Seroprevalence



Clin Infect Dis. 2010 Jun 1;50(11):1439-47

Congenital CMV

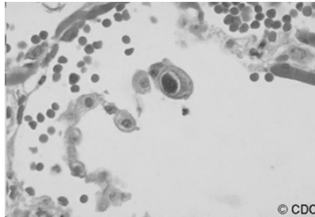
- Hepatosplenomegaly
- Retinitis
- Rash
- Central nervous system involvement
- Leading nongenetic cause of sensorineural hearing loss in US
 - Up to 50% of symptomatic infants
 - Up to 15% of asymptomatic infants

CMV Clinical Manifestations

- 90% asymptomatic
- Mononucleosis syndrome (20-50% cases)
 - Fever - most prominent
 - Increased SGOT/SGPT (90%)
 - Rash, particularly following ampicillin (EBV > CMV)
 - Atypical lymphocytosis
 - Exudative pharyngitis (EBV >> CMV)
 - Hepatosplenomegaly (EBV > CMV)
 - Adenopathy (EBV > CMV)
 - Aseptic meningitis, encephalitis, G B Syndrome

CMV – Immunocompromised Hosts

- Arthralgia
- Leukopenia
- Pneumonitis
- Retinitis
- Enterocolitis
- Polyradiculopathy
- Deterioration of graft function



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Case #4

- A 15yo male presents to your office with fever, sore throat, and swollen glands in the neck. Exam reveals exudative pharyngitis, bilateral cervical adenopathy, and mild hepatosplenomegaly. What's your diagnosis?



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Epstein-Barr Virus

- Present in human populations from all part of the world
 - Acquisition occurs at an earlier age in underdeveloped countries
- Adolescent seroprevalence:
- Undeveloped: >90%
 - Developed: 40-50%

EBV

Clinical Manifestations - Acute

- Asymptomatic (frequency inversely related to age)
- Mononucleosis syndrome
- Neurologic/Neuropsychiatric
 - Nerve palsy, esp. Bell's palsy
 - Guillain-Barré Syndrome
 - Aseptic meningoencephalitis
 - Transverse myelitis
 - "Alice-in-Wonderland" Syndrome
- Thrombocytopenia/purpura

EBV Mononucleosis Syndrome

- Fever
- Lymphadenopathy
- Pharyngitis
- Splenomegaly
- Hepatitis
- Skin rash
- Pneumonitis
- Neurologic
- Myocarditis/pericarditis
- Thrombocytopenia
- Anemia
- Granulocytopenia



EBV Complications

- Splenic rupture
- Airway obstruction
- Fulminant hepatitis
- Myopericarditis
- Meningoencephalitis
- Thrombocytopenia
- Hemolytic anemia
- Orchitis

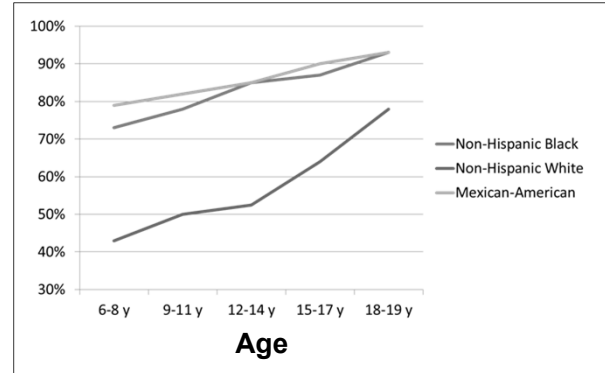
EBV in Immunocompromised Hosts

- X-linked lymphoproliferative syndrome
- Post-transplant B cell lymphoproliferative disorders
- HIV-associated B cell lymphoma
- HIV-associated oral “hairy” leukoplakia
- HIV-associated LIP
- HIV-associated leiomyosarcoma

EBV-associated malignancies

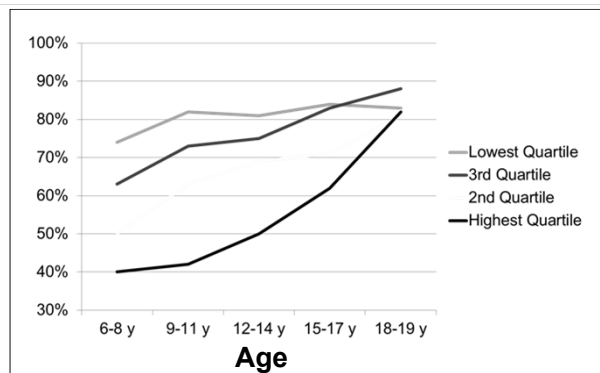
- Burkitt lymphoma
- Nasopharyngeal carcinoma
- Hodgkin's disease (some are EBV-associated)
- HIV-associated
 - B cell, non-Hodgkin lymphoma
 - Smooth muscle (leiomyoma, and leiomyosarcoma)
- Lymphoma

EBV Seroprevalence



PLoS One. 2013; 8(5): e64921

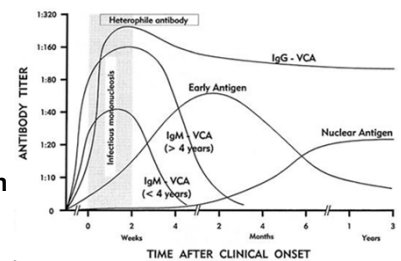
EBV Seroprevalence



PLoS One. 2013; 8(5): e64921

Diagnosis of EBV

- Direct visualization
- Serology
- Polymerase chain reaction



*Courtesy of Red Book Online.® 2009

Case #5

- A 13-month-old female developed high fever that persisted for 4 days without recognized cause. The child appeared relatively well and the fever subsided to be followed by a maculopapular rash that began on the trunk and spread to involve the face and extremities. What's your diagnosis?



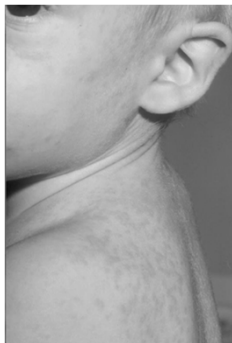
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Human Herpesvirus 6 & 7

- Human herpes viruses 6 and 7 are associated with exanthem subitem (roseola) and rejection of transplanted kidneys
- Antibodies to this HHV-6 present in almost everyone by age 5
- HHV-7 ubiquitous: >95% of adults seropositive
- HHV-6 can also be recovered in vivo from a broad range of tissues

HHV-6 Clinical Manifestations

- High fever
- Irritability
- Adenopathy (cervical and occipital)
- Maculopapular rash
- Inflamed tympanic membranes
- URI symptoms
- GI symptoms: vomiting and diarrhea
- Bulging anterior fontanelle
- Febrile seizures (15%)



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HHV-6 Less Common Manifestations

- Arthritis
- Hepatitis
- Heterophile - negative mononucleosis (primarily adults)
- Intussusception
- Thrombocytopenia
- Neurologic (aseptic meningitis, meningoencephalitis, multiple sclerosis)
- Syndromes in immunocompromised patients
 - Suppression of marrow in BMT
 - Interstitial pneumonitis in BMT/HIV
 - Organ dysfunction/graft rejection
 - Skin rash

HHV-7 Clinical Manifestations

- Fever
- Maculopapular rash
- Irritability
- Lymphadenopathy
- Mild diarrhea
- Hepatitis

Case #6

- A 34 year old HIV+ male presents to your office with complaints of a lump in his mouth. He has been noncompliant with medications, his viral load is >2 million copies/ml and his CD4 lymphocyte count is 143 cells/mm³. Exam reveals a firm, fleshy lump on the hard palate.
- What's your presumptive diagnosis?



Human Herpesvirus 8

- Kaposi's sarcoma-associated herpesvirus (KSHV)
- Manifestations of 1° infection not well characterized
- HHV-8 is implicated as the etiologic agent of:
 - Kaposi's sarcoma (HIV+/HIV-) (found in 95%)
 - Monoclonal B cell lymphomas in HIV
 - Multicentric Castleman's disease



HHV-8 Epidemiology

| <u>Population</u> | <u>Seropositivity Rate</u> |
|------------------------|----------------------------|
| US Children | 2 - 8% |
| US adults | 25% |
| US HIV+ IDU | 23% |
| US HIV+ women | 21% |
| US HIV+ homosexual men | 90% |
| US HIV+/KS+ | 96% |
| African endemic KS | 100% |

The take-home message...

