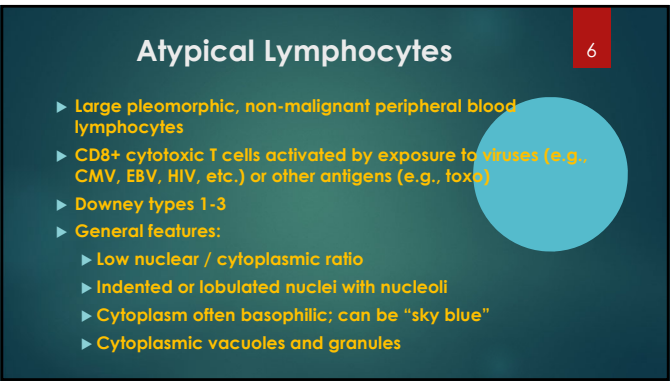
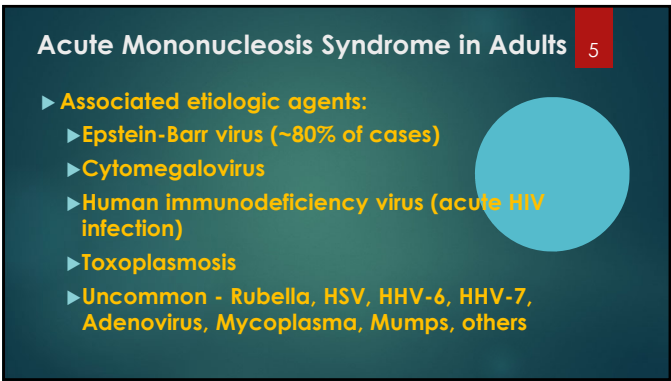
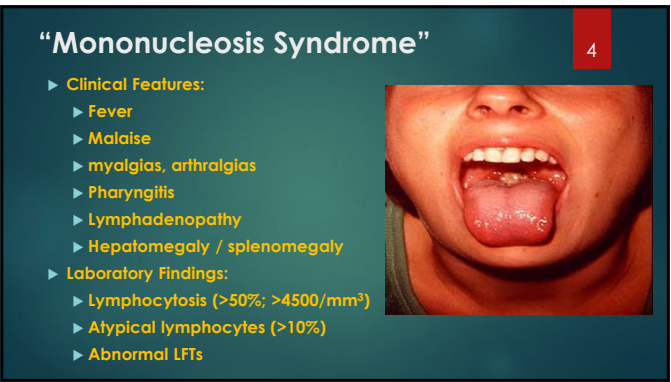
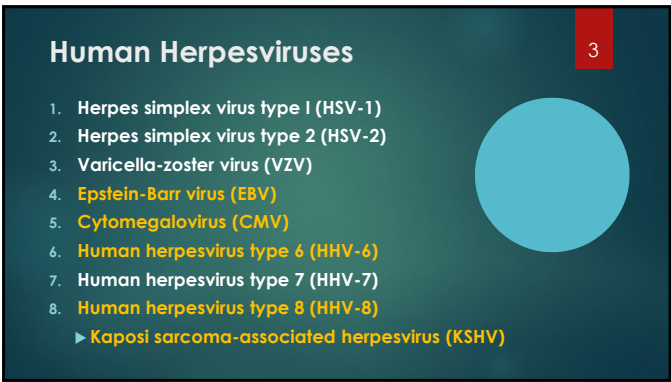
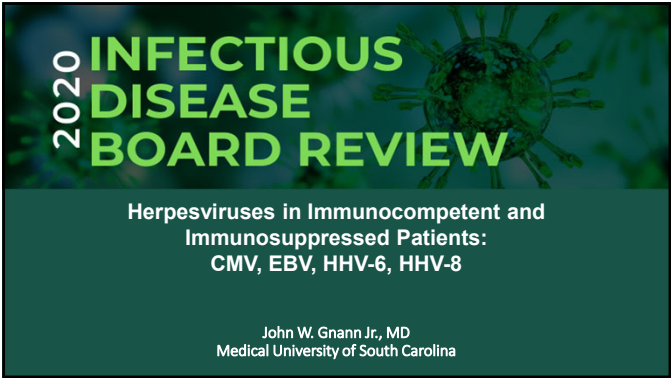
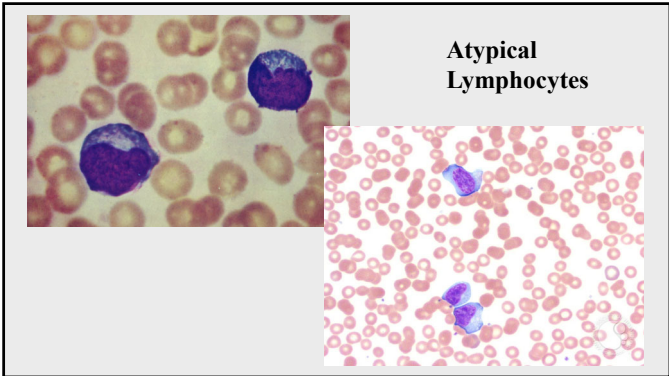


**16 – Herpes Viruses in Immunocompetent and Immunosuppressed Patients;
CMV, EBV, HHV 6, HHV 8**
Speaker: John Gnann, MD



16 – Herpes Viruses in Immunocompetent and Immunosuppressed Patients; CMV, EBV, HHV 6, HHV 8

Speaker: John Gnann, MD



	EBV	CMV	Toxo	HIV
Fever	++++	++++	++	++++
Myalgias / Arthralgias	++	+++	+	+++
Lymphadenopathy	++++	+	++++	+++
Sore throat	++++	++	+	+++
Exudative pharyngitis	++++	+	0	0
Headache	+++	++	+	++
Rash	+	+	+	+++
Splenomegaly	+++	++	+	++
Hepatomegaly	+	++	+	0
Atypical lymphocytes	++++	+++	+	++
Elevated LFTs	++++	+++	0	+

Question #1

9

A previously healthy 24 year old man presents complaining of the acute onset of fever and myalgias. He is married and has an 18 month old child. On exam, he has no adenopathy, pharyngeal exudate or rash. His AST and ALT are 2.5X normal. Peripheral smear is below:

<http://library.med.utah.edu/WinPath/HEM/HTML/HEM0913.html>

The likeliest pathogen is:

- A. CMV
- B. EBV
- C. HIV
- D. HHV-6
- E. HHV-7

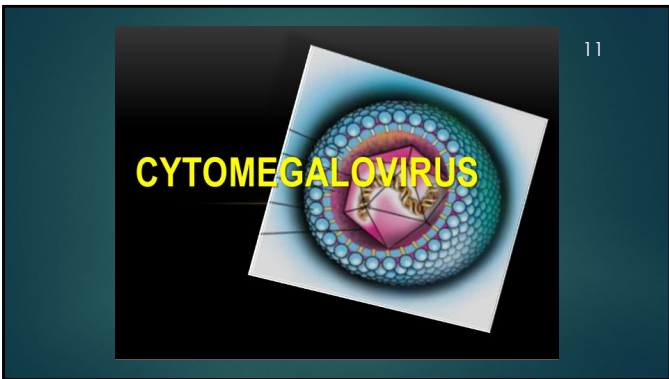
Question #1 - Answer

10

▶ The correct answer is A – CMV

▶ The image demonstrates atypical lymphocytes.

▶ All of these viruses can cause a mononucleosis-like syndrome. Compared with EBV, CMV tends to cause less pharyngitis and less lymphadenopathy. The presence of a young child in the household is a strong epidemiologic clue for CMV.



Pathogenesis of CMV Infection (1)

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- ▶ Beta herpesvirus
- ▶ Infection transmitted via:
 - ▶ body fluids (urine, semen, cervical secretions, saliva, breast milk)
 - ▶ transplanted tissue (blood, organs)
- ▶ Primary infection is usually asymptomatic (<10% report symptoms)
- ▶ Viral replication in WBCs, epithelial cells (kidney, salivary glands, etc.)
- ▶ T cell immune responses control infection, but do not prevent establishment of latency

16 – Herpes Viruses in Immunocompetent and Immunosuppressed Patients; CMV, EBV, HHV 6, HHV 8

Speaker: John Gnann, MD

Pathogenesis of CMV Infection (2)

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- ▶ Following primary infection, prolonged viremia (weeks) and viremia (months) persist despite humoral and cellular immune responses. Important factor in transmission.
- ▶ Lifelong latent viral infection
 - ▶ Latency is primarily in mononuclear cells
 - ▶ Reactivation disease (symptomatic) is rare in immunocompetent host
 - ▶ CMV can reactivate with immunosuppression later in life, causing disease
- ▶ Re-infection with novel exogenous CMV strains has been documented; clinical significance uncertain.
- ▶ No vaccine available

Epidemiology of CMV Infection

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- ▶ Age-specific peaks in incidence:
 - ▶ Children:
 - ▶ 10-15% infected before age 5
 - ▶ 30-40% infected by age 12 years
 - ▶ Young adults at onset of sexual activity
- ▶ Seroprevalence of CMV correlates inversely with socioeconomic development. In the developing world, CMV seroprevalence approaches 100%.
- ▶ U.S. seroprevalence (age 6-49 years) varies with demographics:
 - ▶ Non-Hispanic whites – 40%
 - ▶ Non-Hispanic blacks – 71%
 - ▶ Latin-Americans – 77%

CMV Routes of Transmission

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- ▶ Children
 - ▶ Congenital - most common virus transmitted *in utero*
 - ▶ Perinatal - intra-partum or post-partum; breast feeding
 - ▶ Horizontal transmission - e.g., daycare (chronic asymptomatic viral shedding in urine; stable on fomites for 1-6 hours)
- ▶ Adults
 - ▶ Sexual - heterosexual, male homosexual
 - ▶ Horizontal - child-to-parent; child-to-daycare worker (low risk among health care providers)
- ▶ Nosocomial
 - ▶ Blood transfusion – reduced with serologic screening and routine use of WBC-depleted pRBCs
 - ▶ Banked breast milk
 - ▶ Organ transplantation

CMV: Three Main Clinical Syndromes

16

1. Congenital infection
 - Primary maternal CMV infection - 30-40% risk
 - Reactivation maternal CMV infection - 0.9-1.5% risk
2. Mononucleosis syndrome
 - Primary CMV infection causing "heterophile-negative mononucleosis."
3. Invasive visceral organ disease
 - Usually in immunocompromised patients
 - CMV colitis has been described in otherwise immunocompetent adults receiving corticosteroid therapy
 - Primary infection or re-activation of latent CMV

CMV Mononucleosis Syndrome

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- ▶ CMV causes ~20% of mono syndrome cases in adults
- ▶ Presentation: fever, myalgias, atypical lymphocytosis.
 - ▶ High fever ("typhoidal"). Pharyngitis and lymphadenopathy (13-17%) less common than with EBV IM (80%).
 - ▶ Rash in up to 30% (variety of appearances)
 - ▶ However, may be clinically indistinguishable from mono syndrome caused by other pathogens
 - ▶ Complications: colitis, hepatitis, encephalitis, GBS, anterior uveitis
- ▶ Symptoms may persist ≥ 8 weeks
- ▶ Diagnosis: IgG seroconversion or CMV blood PCR
- ▶ Antiviral therapy not indicated (except for severe complications)

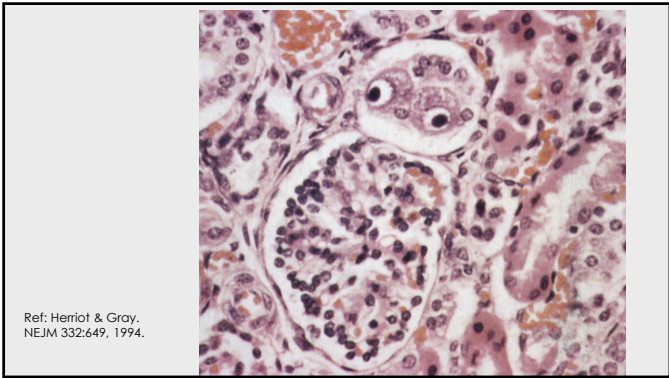
Laboratory Diagnosis of CMV (1) –

How to distinguish CMV infection (common) from CMV disease (uncommon)?

18

- ▶ Molecular diagnostics
 - ▶ Quantitative PCR - Detection of CMV DNA in blood, other fluids, tissues
 - ▶ Lower sensitivity of blood PCR for CMV pneumonitis, retinitis, or GI disease
 - ▶ Antigen detection in blood neutrophils (pp65 antigen)
 - ▶ Less sensitive than PCR; not useful in neutropenia
 - ▶ Largely replaced by PCR
- ▶ Histopathology of biopsied tissue
 - ▶ Presence of basophilic intranuclear inclusion bodies surrounded by a clear halo – "owl's eye" cells. Low sensitivity.
 - ▶ Cytology, e.g., BAL
 - ▶ CMV-specific immunohistochemical stains
 - ▶ In situ hybridization of tissue – research tool

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Laboratory Diagnosis of CMV (2) –
How to distinguish CMV infection (common) from CMV disease (uncommon)?

20

- ▶ **Serology**
 - ▶ To diagnose acute infection, detect IgM or document IgG seroconversion
 - ▶ High rate of false-positives with CMV IgM
 - ▶ IgG very useful to establish D/R sero-status in transplantation
- ▶ **Viral culture**
 - ▶ Specimens: PBMCs, BAL, biopsy, etc.
 - ▶ Tissue culture: slow; cytopathic effect in 3-21 days (shell vial technique is faster); expensive; sensitivity is not optimal
 - ▶ Positive CMV culture (except for blood) is highly specific for infection, not for disease
 - ▶ Positive culture from a distant site is non-specific (e.g., recovering CMV from urine does not diagnose CMV pneumonia)
 - ▶ No longer routinely used

Human Herpesvirus Type 6

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- ▶ Beta herpesvirus, discovered in 1986
- ▶ Two subgroups:
 - ▶ HHV-6A – uncommon pathogen
 - ▶ HHV-6B – very common pathogen, frequent infections in healthy children, etiology of roseola (exanthem subitem)
- ▶ Replicates and establishes latency in mononuclear cells, esp. activated T-lymphocytes
- ▶ Can integrate into human germline cells; chromosomally inherited
- ▶ Primary infection common in first year of life, >60% infected by 12 months. Seroprevalence >80% by age 5 yr.
 - ▶ Common cause of febrile illness 6-18 mo. infants
- ▶ Transmission by saliva; incubation period ~9 days (5-15 days)
- ▶ No vaccine available

Human Herpesvirus Type 6

22

- ▶ **Associated diseases:**
 - ▶ Exanthem subitum (roseola infantum, sixth disease)
 - ▶ children <4 y.o.; usually benign disease
 - ▶ high fever for 5 days (febrile seizures), followed by a rash
 - ▶ Primary infection in adults (rare) - Mono syndrome
 - ▶ Reactivation disease in transplant patients, esp. encephalitis and pneumonitis. Syndromes not well defined
 - ▶ Mesial temporal lobe epilepsy
- ▶ **Diagnosis**
 - ▶ IgG seroconversion
 - ▶ PCR from target organ tissue or cell-free plasma. Problem of distinguishing latent infection (very common) from active disease.
- ▶ **Therapy**
 - ▶ Supportive care
 - ▶ Antivirals? Anecdotal reports of GCV benefit (esp. encephalitis in immunocompromised patients), but no controlled data. Efficacy unproven.

Exanthem subitum (roseola, sixth disease)

23

Epstein-Barr Virus

24

16 – Herpes Viruses in Immunocompetent and Immunosuppressed Patients;
CMV, EBV, HHV 6, HHV 8
Speaker: John Gnann, MD

EBV Infection: Pathogenesis

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- ▶ Gamma herpesvirus; HHV-4
- ▶ Infectious virus intermittently shed from oropharyngeal epithelial cells.
- ▶ Transmission by saliva ("kissing disease")
- ▶ Long incubation period – 4 to 8 weeks
- ▶ Usual site of latency is peripheral blood mononuclear cells, esp. B lymphocytes. EBV is capable of transforming B lymphocytes, resulting in malignancy.
- ▶ EBV reactivation not usually assoc. with symptomatic disease.

Epstein-Barr Virus: Epidemiology

26

- ▶ Asymptomatic infection in early childhood
- ▶ Adolescent seroprevalence:
 - ▶ Developing countries >90%
 - ▶ Developed countries 40-50%
- ▶ Primary infection in adolescents or adults results in symptomatic dz (infectious mononucleosis) in 50% of cases
- ▶ IM in US - 45 cases/100,000 population/year
- ▶ Occasionally transmitted by transfusion or transplantation

Epstein-Barr Virus Diseases

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- ▶ Infectious mononucleosis (IM)
 - ▶ Variants with severe, prolonged IM symptoms, progression to lymphoma
 - ▶ Chronic active EBV (rare, more common in Asia and SA)
 - ▶ X-linked lymphoproliferative disease; XLMN syndrome
- ▶ EBV-associated malignancies, including:
 - ▶ Burkitt lymphoma (Africa). Malaria as a co-factor.
 - ▶ Nasopharyngeal carcinoma (southern China).
 - ▶ Malignancies in HIV+ persons. NHL (usually B cell); leiomyosarcomas (children)
 - ▶ Post-transplant lymphoproliferative diseases (PTLD)
 - ▶ T cell lymphoma
 - ▶ Hodgkin lymphoma
- ▶ Oral hairy leukoplakia (in HIV)



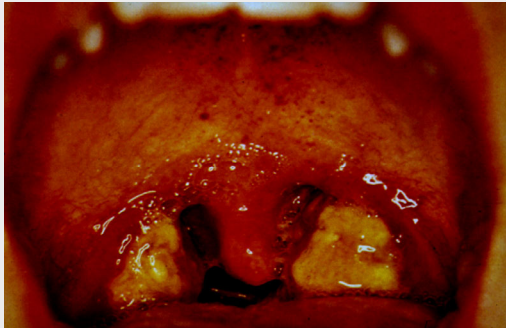
Burkitt lymphoma in an African child

Infectious Mononucleosis

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- ▶ Etiology - 1^o Epstein-Barr virus infection
- ▶ Transmission - saliva (EBV shed >6 mo. after IM)
- ▶ Clinical – prodrome of fever, malaise, HA.
 - ▶ Pharyngitis with tonsillar exudate
 - ▶ Symmetrical cervical adenopathy, posterior > anterior
 - ▶ Acute symptoms persist 1-2 weeks, fatigue can last for months
 - ▶ Rash with ampicillin
- ▶ Lab - lymphocytosis with atypical lymphocytes
- ▶ Diagnosis - serologic. Non-specific heterophile Ab ("monospot"); specific Ab (VCA, EBNA)
- ▶ Therapy - supportive, no antiviral therapy
- ▶ Prevention - no vaccine

Exudative Pharyngitis in a Patient with EBV Infectious Mononucleosis



Clinical Findings in EBV Infectious Mononucleosis

30

Symptoms	%	Signs	%
Sore throat	82%	Lymphadenopathy	100%
Malaise	57%	Fever	98%
Headache	51%	Pharyngitis	85%
Anorexia	21%	Splenomegaly	52%
Myalgias	20%	Hepatomegaly	12%
Chills	15%	Palatal petechiae	11%
Nausea	12%	Rash	10%
Abdominal pain	9%	Jaundice	9%

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Complications of EBV Infectious Mononucleosis

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- ▶ Splenic rupture. 1 to 2 events/1000 cases, male > female
- ▶ Airway obstruction 2° to massive adenopathy
- ▶ Hepatitis, including acute liver failure
- ▶ Neurologic syndromes: encephalitis, myelitis, G-B syndrome, CN palsies, optic neuritis, etc.
- ▶ Heme syndromes: cytopenias, TTP-HUS, DIC
- ▶ Hemophagocytic lymphohistiocytosis (HLH)
- ▶ Pneumonitis
- ▶ Prolonged fatigue/malaise (>6 mo. in 13%)

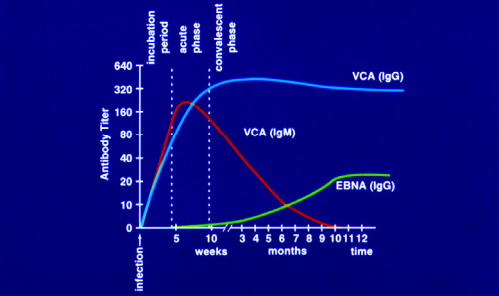
Laboratory Findings in EBV Infectious Mononucleosis

32

- ▶ CBC shows lymphocytosis
 - ▶ WBC = 12,000 - 18,000/mm³, 60-70% mononuclear
 - ▶ Atypical lymphocytes = 30% (range 10-90%)
- ▶ Elevated liver function tests
 - ▶ AST, ALT (90%), alkaline phosphatase (60%), bilirubin (45%, but jaundice in <10%)
- ▶ Positive heterophile antibodies ("monospot")
 - ▶ Non-specific IgM against animal RBCs
 - ▶ Positive in 90% of cases, disappear within 1 year
- ▶ EBV-specific antibodies. Acute infection defined by:
 - ▶ Positive viral capsid antigen (VCA) IgG and IgM
 - ▶ Negative EBV nuclear antigen (EBNA) IgG
- ▶ PCR - not necessary for routine IM, may be useful in transplant patients

EBV Antibody Responses in Infectious Mononucleosis

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Management of EBV Infectious Mononucleosis

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- Supportive care
- Corticosteroids only for life-threatening manifestations (e.g., liver failure, hemolytic anemia, airway obstruction)
- Avoid contact sports for a minimum of 4 weeks
- Antiviral therapy: acyclovir, ganciclovir, valganciclovir?
 - *In vitro* activity demonstrated during lytic phase of EBV replication; no activity on latent phase of EBV
 - **Not** indicated for IM; no benefit in clinical trials
 - Anecdotal reports of benefit from ACV in EBV-induced HLH

Question #2

35

An 18-year-old woman presents to your office with signs and symptoms consistent with acute infectious mononucleosis. However, her heterophile antibody test (Monospot) is negative. In addition to other tests, you order EBV-specific serology.

Which EBV-specific antibody profile would confirm a diagnosis of acute infectious mononucleosis?

- A. VCA IgM positive, VCA IgG positive, EBNA IgG positive
- B. VCA IgM positive, VCA IgG positive, EBNA IgG negative
- C. VCA IgM negative, VCA IgG positive, EBNA IgG positive
- D. VCA IgM positive, VCA IgG negative, EBNA IgG positive
- E. VCA IgM negative, VCA IgG negative, EBNA IgG negative

Question #2 - Answer

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The correct answer is B - VCA IgM positive, VCA IgG positive, EBNA IgG negative.

Antibodies directed against the viral capsid antigen (VCA), both IgM and IgG, are usually detectable at the time of symptom onset. VCA IgG persists for life, while VCA IgM disappears after about a year. Epstein-Barr nuclear antigen (EBNA) IgG does not appear for several weeks after symptom onset and also persists for life.

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Human Herpesvirus Type 8

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- ▶ Kaposi sarcoma-associated herpesvirus (KSHV)
- ▶ Gamma herpesvirus, discovered 1995
- ▶ Partial sequence homology with EBV
- ▶ KS previously known to be endemic in Africa, Mediterranean regions
- ▶ HHV-8 seroprevalence in the US:
 - ▶ Blood donor populations: 1-5%
 - ▶ MSM: 8-25%
 - ▶ HIV-positive MSM: 30-77%
 - ▶ HIV-positive with KS: 90%
- ▶ Route of transmission unknown – Sexual, saliva? Transmission via SOT documented (rare).
- ▶ 1° infection usually asymptomatic. Febrile rash syndrome described.

HHV-8 Associated Diseases

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- ▶ Kaposi sarcoma. 4 types:
 - ▶ Classic. Leg lesions in elderly men of Mediterranean or Ashkenazi Jewish origin
 - ▶ Endemic, Sub-Saharan Africa, not assoc. with immune deficiency
 - ▶ Transplant-associated. Usually (but not always) donor-derived
 - ▶ Epidemic (AIDS-related)
- ▶ Primary effusion lymphoma (body cavity-based lymphoma)
 - ▶ Non-Hodgkin B-cell lymphoma, usually in HIV+. Involves pleural, pericardial, or peritoneal spaces
- ▶ Castleman's disease. Seen in HIV positive and negative patients
 - ▶ Unicentric or Multicentric; hyaline vascular or plasma cell variants – all HHV-8 related. Fever, hepatomegaly, splenomegaly, massive lymphadenopathy
- ▶ KSHV Inflammatory Cytokine Syndrome (KICS) in HIV+.
 - ▶ Fever, elevated IL-6 & IL-10, high HHV-8 VL. High mortality rate.

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Thank you for your attention!

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CMV Reactivation in Critically Ill Patients

- ▶ Multiple studies have demonstrated CMV reactivation in 25-30% of immunocompetent patients requiring ICU care.
- ▶ Clinical significance uncertain
 - ▶ Some studies have shown positive association between CMV reactivation and duration of ICU stay, duration of ventilator support, and mortality. Association not supported by other studies.
 - ▶ One study of CMV antiviral prophylaxis in this setting failed to show benefit.

Chronic Active EBV Infection

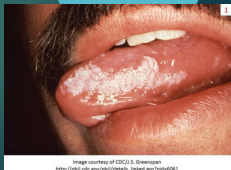
- ▶ Persistent IM sx; rare; maybe more common in Asian and SA populations
- ▶ Diagnosis: Persistent IM sx (fever, lymphadenopathy, H-Smegaly) with EBV viremia, cytopenias, transaminitis, hypogammaglobulinemia, clonal proliferation of lymphocyte population (B, T, or NK)
- ▶ Therapy: Steroids, ganciclovir, proteasome inhibitors (e.g., bortezomib, ixazomib, etc.)
- ▶ Prognosis: Poor 2° to lymphocytic infiltration of tissues, HLH, liver failure, coronary artery aneurysms
- ▶ Note: Not to be confused with the unsubstantiated link between "chronic EBV" and myalgic encephalomyelitis/ CFS

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EBV-Associated Lymphoproliferative Disorders

- ▶ **X-linked lymphoproliferative disease**
 - ▶ XMEN syndrome (with magnesium deficiency)
- ▶ Post-transplant lymphoproliferative disease (PTLD)
- ▶ Hemophagocytic lymphohistiocytosis (HLH)
- ▶ Lymphomatoid granulomatosis

- ▶ **Miscellaneous: Oral hairy leukoplakia** (usually in HIV+)



EBV-Associated Malignancies

- ▶ **B cell NHL**, esp. in HIV+
- ▶ **Burkitt lymphoma**. Most common childhood malignancy in Africa. Usually jaw. Malaria as a co-factor
- ▶ **Nasopharyngeal carcinoma**. Among most common cancers in southern China. Incidence 55 cases/100,000 population/yr.
- ▶ **Nasal angiocentric lymphoma**. Rare NK cell lymphoma. Described mostly in Asia, SA
- ▶ **T cell lymphoma**. May follow acute EBV infection
- ▶ **Hodgkin Disease**. Complex epidemiologic association, varying with geography and EBV sub-type
- ▶ **Leiomyosarcoma**, esp. in HIV+ children

Human Herpesvirus Type 7

45

- ▶ **Beta herpesvirus**, discovered in 1990, closely related to HHV-6
- ▶ **Tropism for CD4+ T-lymphocytes**
- ▶ **High frequency of asymptomatic infection during childhood** (50% by age 3). Over 95% of adults are seropositive. Route of transmission unclear.
- ▶ **Infection diagnosed by seroconversion**
- ▶ **Disease associations are not well-defined:**
 - ▶ Likely causes a pediatric febrile rash illness similar to roseola; febrile seizures?
 - ▶ other dermatologic dz (pityriasis rosea, lichen planus)?
 - ▶ possible pathogen in organ transplant patients

Management of HHV-8 Disease

Diagnosis

1. PCR (blood)

- Limited for diagnosis of KS by frequent low copy number positivity due to latent virus in at-risk populations
- Has diagnostic and prognostic value for HHV-8 associated lymphoproliferative diseases

2. Serology

- Moderate sensitivity and specificity
- Positive result indicates infection, not necessarily disease

Antiviral Therapy

- GCV, CDV, FOS, NFV have *in vitro* activity against HHV-8
- Therapy may reduce HHV-8 shedding in saliva, but no impact on blood VL
- No evidence for clinical benefit after malignant transformation
- In HIV+, dramatic response of HHV-8 disease to effective ART