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Herpes Viruses

Infectious Diseases/Microbiology Sequence Course

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Spring 2010

University of Michigan
Medical School

Objectives

- **Know the common and unique features of herpes viruses**
- **Appreciate the roles of both lytic and latent replication cycles of herpes viruses**
- **Understand the interactions between herpes viruses and the immune system**
- **Know the transmission routes of the herpes viruses**
- **Know the laboratory methods used to diagnose particular herpes virus infections**

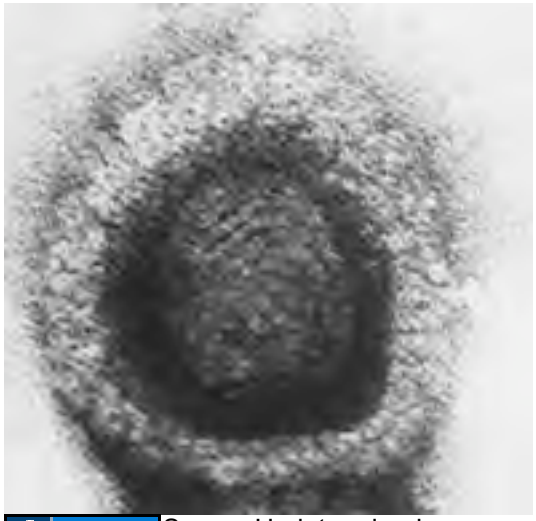
Reading assignment: Schaechter's 4th edition, chapters 41 and 42

Herpes viruses

	Subfamily	Transmission	Clinical Syndromes	Latency site	Diagnosis	Antiviral Rx	Vaccine
HSV	Alpha	Cutaneous	Cutaneous - localized (oral, genital) CNS	Neurons	Clinical PCR Culture/DFA	Acyclovir	No
VZV	Alpha	Respiratory	Cutaneous - disseminated and localized	Neurons	Clinical PCR Culture/DFA	Acyclovir	Yes
CMV	Beta	Secretions (oral, urogenital)	Systemic Ocular, GI, hematopoietic, respiratory	Monocytes, macrophages	Serology PCR Culture/DFA	Ganciclovir	No
EBV	Gamma	Secretions (oral)	Systemic Lymphoma	B cells	Serology, PCR Culture/DFA	None	No

Herpes viruses

- **Family: *Herpesviridae***
- **Large, enveloped virus**
- **Double-stranded DNA genome (100-150 proteins)**



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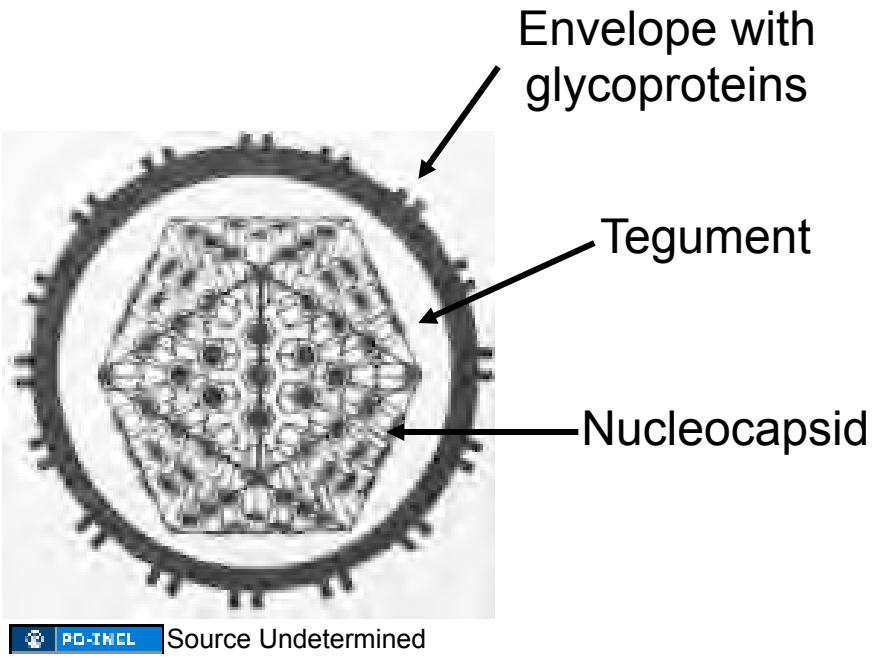

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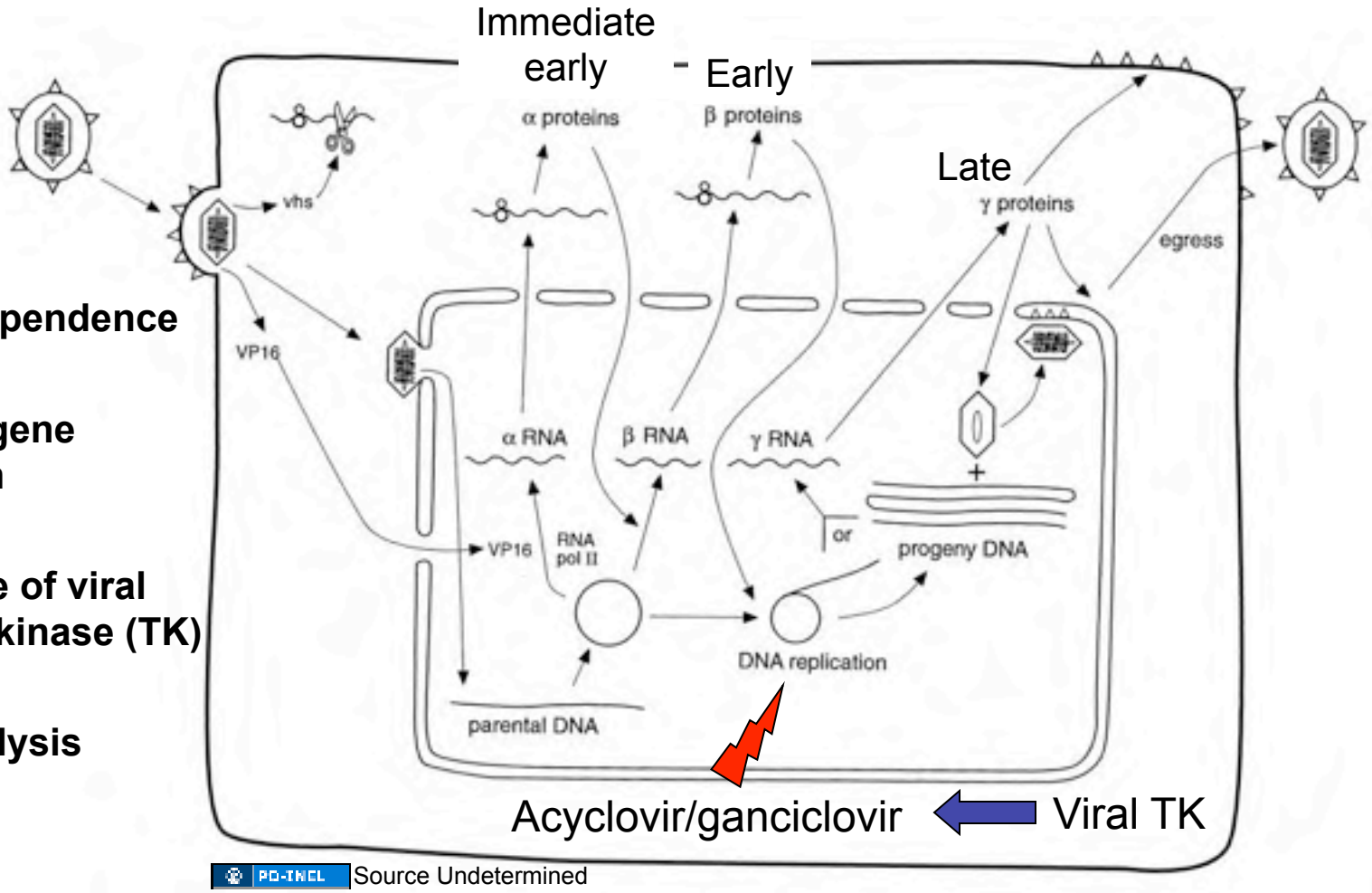
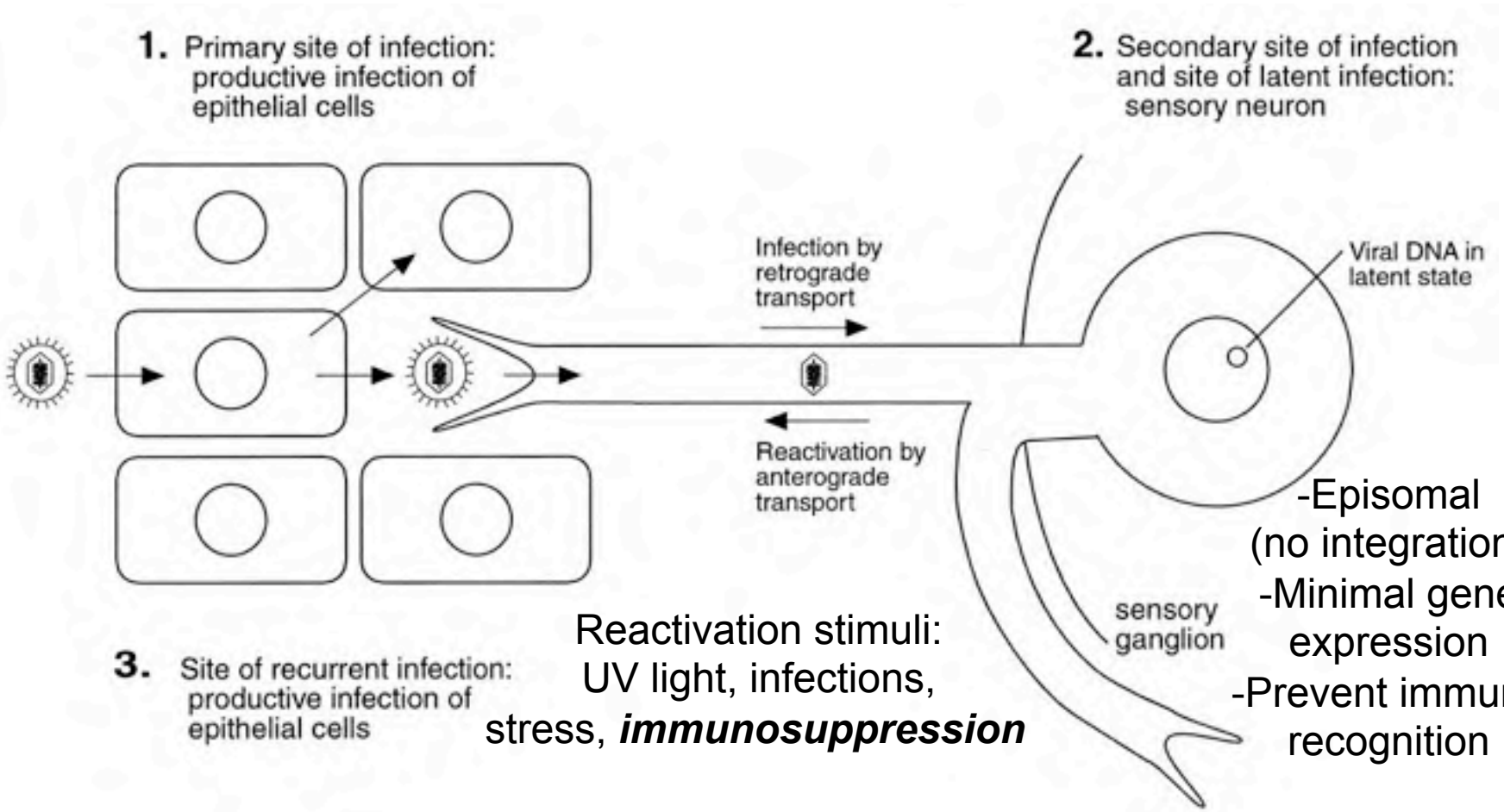
Herpesvirus life cycle (lytic)

- **Nuclear dependence**
- **Temporal gene expression**
- **Importance of viral thymidine kinase (TK)**
- **Direct cell lysis**



Herpesvirus life cycle (latent)



Reactivation stimuli:
UV light, infections,
stress, ***immunosuppression***

-Episomal (no integration)
-Minimal gene expression
-Prevent immune recognition

19 year old sexually active male college student presented to student health services with a two day history of painful ulcers on his penis. He had unprotected sexual intercourse with a female roommate several days prior to developing symptoms. The lesions initially progressed over one week and coalesced into larger shallow ulcers, but eventually resolved completely after another two weeks. Over the next two semesters he had recurrence of similar symptoms that weren't related to sexual activity.

19 year old *sexually active* male college student presented to student health services with a *two day* history of *painful ulcers on his penis*. He had *unprotected sexual intercourse* with a female roommate *several days prior* to developing symptoms. The lesions initially progressed over one week and *coalesced into larger shallow ulcers*, but eventually *resolved completely* after another two weeks. Over the next two semesters he had *recurrence of similar symptoms* that weren't related to sexual activity.

Diagnosis?

Herpes simplex

- **Alphaherpesvirus**
- **Two serotypes (HSV-1, 2)**
- **Direct contact transmission**
  - HSV-1: *primarily* oral
  - HSV-2: *primarily* genital
  - Asymptomatic transmission possible
- **Epidemiology**
  - HSV-1: 2/3 of adults seropositive
  - HSV-2: 1/5 of adults seropositive
    - Varies with sexual promiscuity

HSV clinical disease

- **Cutaneous lesion (*NOT* absolute)**
  - HSV-1: oral, perioral
  - HSV-2: genital
  - Can be asymptomatic (especially with reactivation)

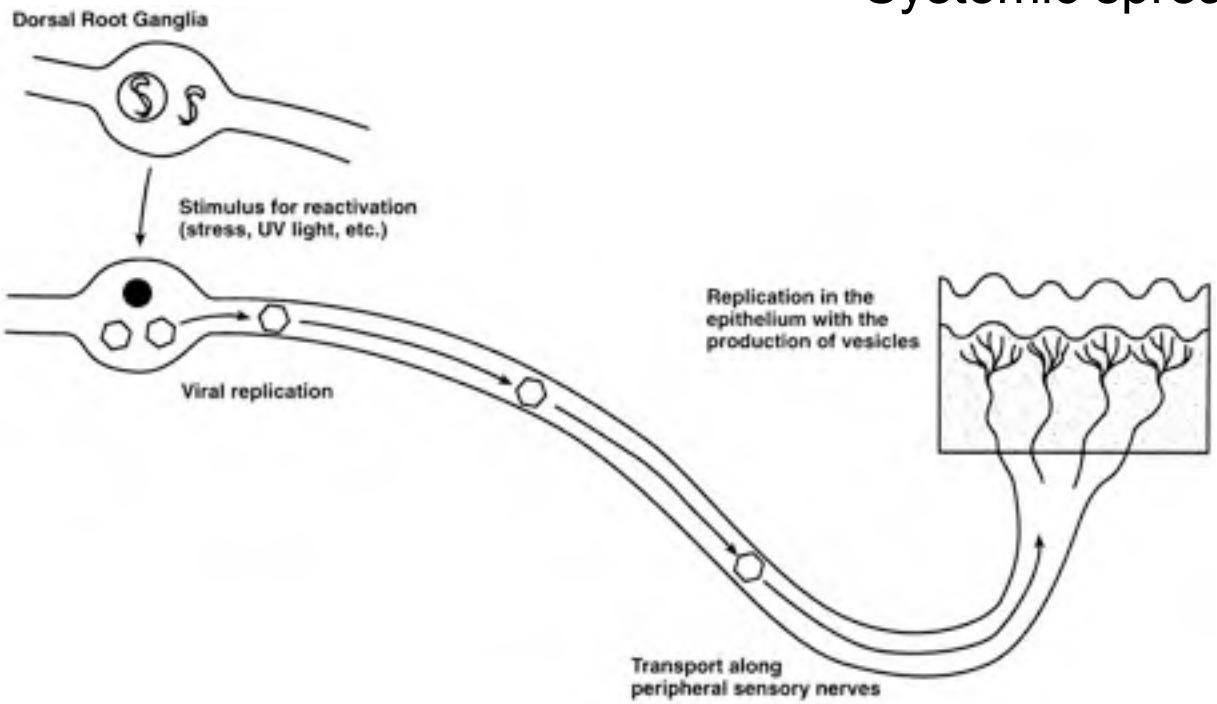
Source Undetermined

- **Pathogenesis**
  - Direct epithelial cell lysis and spread to adjacent cells

- **Complications**
  - Ocular disease
  - CNS involvement (encephalitis)
  - Dissemination

HSV latency

- **Establishment**
  - Retrograde transmission
  - Sensory ganglia nerve cells
- **Reactivation**
  - Anterograde transmission
  - UV light, stress, infection, menstruation
  - Systemic spread rare



HSV and immunity

- ***NO* viral clearance**
- **Immune system maturation crucial**
  - Neonatal HSV infections can be devastating
- **Control of reactivation**
  - Cell mediated immunity essential
  - Limited role of humoral immunity
- **Prevent systemic spread**
  - Immunosuppression greatly increases risk

HSV diagnosis

- **Clinical syndrome**
- **Virus detection**
  - Tzanck smear
  - Direct fluorescent antibody (DFA) test
  - PCR
  - Culture
- **Serologies not helpful**

Multinucleated giant cell with intranuclear inclusions

HSV treatment and prevention

- **Available drugs**
  - Acyclovir, valacylovir, famciclovir
- **Target groups**
  - Neonatal HSV infections
  - Immunosuppressed patients (localized or systemic)
  - CNS disease
  - Genital HSV lesions
- **Prophylaxis**
  - Immunosuppressed patients
  - Genital recurrences
- **No vaccine available**

55 year old male presented to his primary care physician with a two day history of painful blisters on his left chest wall. The area initially felt “tingly” several days before the blisters appeared, and he had a mild headache but no fevers or other systemic symptoms. The area increased in size with a coalescence of the small blisters, but the lesions never crossed the midline. The blisters eventually crusted over and resolved after about three weeks, but the area remained extremely tender, even to the slightest touch.

55 year old male presented to his primary care physician with a two day history of *painful blisters* on his left chest wall. The area initially *felt "tingly" several days before* the blisters appeared, and he had a *mild headache* but no fevers or other systemic symptoms. The area increased in size with a *coalescence of the small blisters*, but the lesions *never crossed the midline*. The blisters eventually crusted over and resolved after about three weeks, but the area *remained extremely tender*, even to the slightest touch.

Diagnosis?

Varicella zoster virus (VZV)

- **Alphaherpesvirus**
- **Aerosol/respiratory transmission**
  - Highly contagious
  - Direct inoculation unusual
- **Epidemiology**
  - >90% of adults seropositive
  - Vaccination program may change epidemiology

VSV clinical disease

- **Primary exposure**
  - *MOST* exposures produce symptomatic disease
  - Local respiratory lymph node replication
  - Primary viremia – secondary viremia (lymphocyte infection)
  - Cutaneous lesion development

- **Pathogenesis**
  - Direct epithelial cell lysis and spread to adjacent cells

- **Complications**
  - Pneumonia and CNS involvement
  - Immunosuppressed at highest risk
  - Ramsay-Hunt syndrome (CN VII palsy, loss of taste, auricle vesicles)

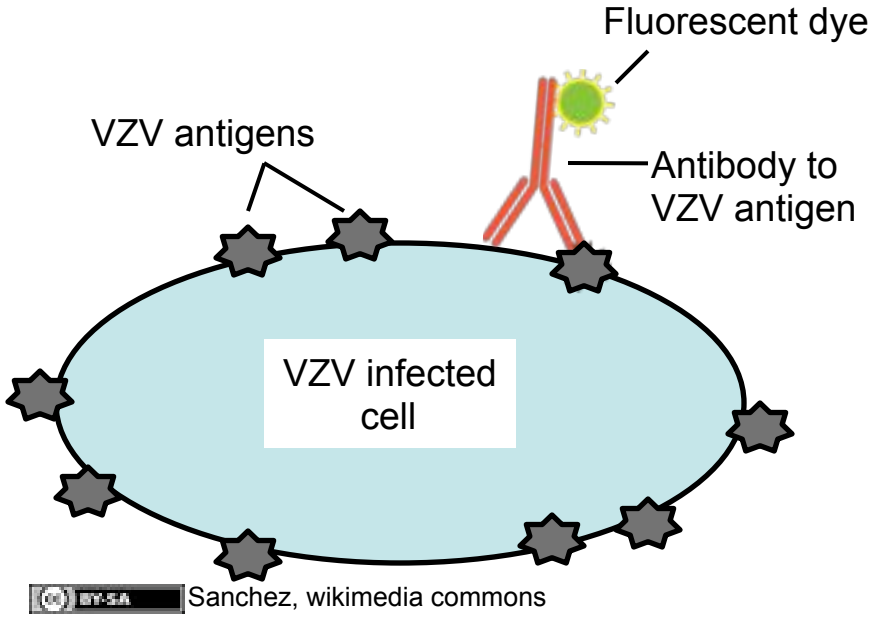
VZV latency

- **Establishment**
  - Dorsal root sensory ganglia nerve cells infected during *viremia*
  - *Contrast to HSV (direct retrograde spread)*

- **Reactivation (shingles)**
  - Anterograde transmission
  - Dermatomal distribution
    - Opthalmic division of trigeminal nerve - DANGER
  - Advancing age, immunosuppression
  - Systemic spread rare
  - Post-herpetic neuralgia most troublesome complication

VZV diagnosis

- **Clinical syndrome**
  - Simultaneous lesions at all stages
- **Virus detection**
  - Direct fluorescent antibody test (DFA)
  - PCR
  - Culture
- **Serologies helpful to determine exposure risk**



VZV treatment

- **HSV drugs (acyclovir) less active but still useful**

- **Target groups**
  - Immunosuppressed patients
  - CNS/ocular disease
  - Reactivation (reduce post-herpetic neuralgia)
  - Most effective if given <72 h from symptom onset
  - Prednisone efficacy for shingles questionable

VZV prevention

- **Effective vaccine available**
  - Live, attenuated virus

- **Target populations**
  - Routine childhood vaccination (VARIVAX®, ProQuad®)
  - Persons > 60 yo *regardless* of previous shingles history
  - Healthy adolescents and adults without evidence of immunity
    - High risk for VZV transmission (healthcare workers, teachers, childcare employees, chronic care facilities)
    - Non-pregnant women of childbearing age
  - Household contacts of immunocompromised persons

- **Contraindications**
  - Immunosuppression
  - Pregnancy

http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5604a1.htm

46 year old female had kidney transplant secondary to diabetic nephropathy three months ago. Her postoperative course was uneventful, and she was tolerating her immunosuppressive medications. She rarely left the house out of concern for picking up an infection, but over the past three weeks she developed fever, fatigue, and decreased appetite but no significant localizing symptoms. Blood tests showed a severely decreased white blood cell count.

46 year old female had *kidney transplant* secondary to diabetic nephropathy three months ago. Her postoperative course was uneventful, and she was tolerating her *immunosuppressive medications*. She rarely left the house out of concern for picking up an infection, but over the past three weeks she developed *fever, fatigue, and decreased appetite* but no significant localizing symptoms. Blood tests showed a severely *decreased white blood cell count*.

Diagnosis?

Cytomegalovirus (CMV)

- **Betaherpesvirus**

- **Direct contact transmission**
  - Saliva, breast milk, urogenital
  - Blood products, organ transplantation
  - Transplacental (“TORCH” infections)

- **Epidemiology**
  - Approximately 50% of adults in U.S. seropositive
  - >90% in underdeveloped countries

CMV clinical disease

- **Primary exposure**
  - Usually asymptomatic
  - Can produce “mono-like” syndrome (non-specific symptoms)

- **Complications**
  - Congenital CMV
    - CNS involvement (encephalomalacia, hydrocephalus, retinitis)
  - End-organ damage in immunc
    - Ocular (retinitis)
    - CNS (encephalitis)
    - Respiratory
    - Gastrointestinal
    - Bone marrow

PD-INCL University of Michigan Kellogg Eye Center

CMV latency

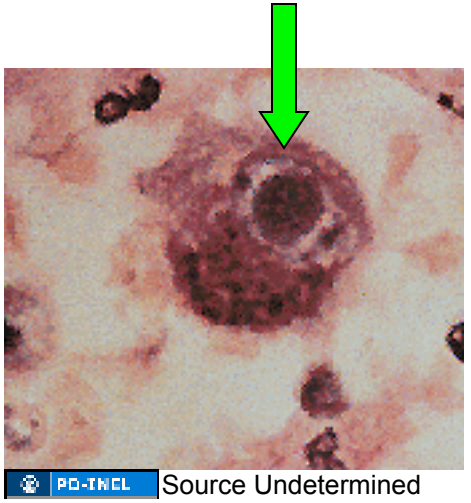
- **Establishment**
  - Monocytes and macrophages
  - Mechanisms poorly understood

- **Reactivation**
  - *DIRECTLY* linked with immune status
  - Replication in wide variety of cell types
    - Transplanted organs
  - Can *augment* immunosuppression

CMV diagnosis

- **Clinical syndrome *non-specific***
- **Virus detection**
  - PCR (quantitative)
  - Histopathology (“owl eye”)
  - Direct fluorescent antibody (DFA) test
  - Culture
- **Serologies helpful**
  - Assess risk for reactivation if immunosuppression anticipated

Large nuclear inclusion
With peripheral clear zone



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CMV treatment and prevention

- **Antiviral drugs available**
  - HSV drugs (acyclovir) less active
  - Ganciclovir (valganciclovir), foscarnet, cidofovir
  - Resistance problematic

- **Target groups**
  - *NOT* for primary infection in immunocompetent patient
  - Immunosuppressed patients
  - Pre-emptive therapy often used
    - CMV disease versus infection

- **Prevention**
  - No vaccine available
  - Prophylactic ganciclovir frequently used

18 year old student presented to his primary physician with one week history of fever, fatigue, sore throat, swollen glands. He recently started a new relationship with a classmate who had no symptoms. On physical exam, his oropharynx was erythematous without tonsillar exudate and he had prominent cervical lymphadenopathy. Rapid strep test was negative. Blood test showed an increased white blood cell count with atypical appearing lymphocytes. His symptoms eventually resolved over 2 weeks, but his fatigue persisted for 6 months.

18 year old student presented to his primary physician with one week history of *fever, fatigue, sore throat, swollen glands*. He recently started a *new relationship* with a classmate who had no symptoms. On physical exam, his *oropharynx was erythematous without tonsillar exudate* and he had prominent *cervical lymphadenopathy*. Rapid strep test was negative. Blood test showed an *increased white blood cell count* with *atypical appearing lymphocytes*. His symptoms eventually resolved over 2 weeks, but his *fatigue persisted* for 6 months.

Diagnosis?

Epstein-Barr virus (EBV)

- **Gammaherpesvirus**
- **Direct contact transmission**
  - Saliva, respiratory secretions
  - Transfusion, transplantation
- **Epidemiology**
  - Approximately 50-70% of adults in U.S. seropositive
  - >90% in underdeveloped countries

EBV clinical disease

- **Primary exposure**
  - Often asymptomatic
  - Typically produce mononucleosis syndrome
    - Fever, sore throat, fatigue (prolonged)
    - Hematologic abnormalities, hepatitis

- **Complications (malignancies)**
  - Linked to immune status and latency in B cells
  - Post-transplant lymphoproliferative disorder (PTLD)
  - Lymphoma
    - Nasopharyngeal carcinoma
    - Burkitt's lymphoma (Africa)
    - Primary CNS lymphoma (HIV/AIDS)
    - Hodgkin's disease

EBV diagnosis

- **Clinical syndrome *non-specific***
- **Virus detection**
  - PCR
  - Direct fluorescent antibody (DFA) test
  - Culture
- **Serologies helpful**
  - Assess risk for reactivation
  - Monospot test
    - Heterophil antibodies directed against RBC from other *species* (NOT EBV-specific)

EBV treatment and prevention

- **Antiviral drugs (acyclovir, ganciclovir)**
  - In vitro activity but no evidence for effectiveness in patients

Correct underlying immunosuppressed status

- **Prevention**
  - No vaccine available

Other herpesviruses

- **Human herpes virus 6 (HHV6)**
  - Betaherpesvirus (similar to CMV)
  - Etiology of roseola infanatum

- **HHV8**
  - Gammaherpesvirus (similar to EBV)
  - Also called Kaposi's sarcoma herpes virus (KSHV)

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