

Human Herpes Viruses (HHV)

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KSU

HERPES VIRUS INFECTIONS

- objectives:

- To know the clinically important HHVs.
- To know the common characteristics of HHVs.
- To know the common modes of transmission of different HHVs
- To know the clinical features of these infections, diagnostic methods and treatment.

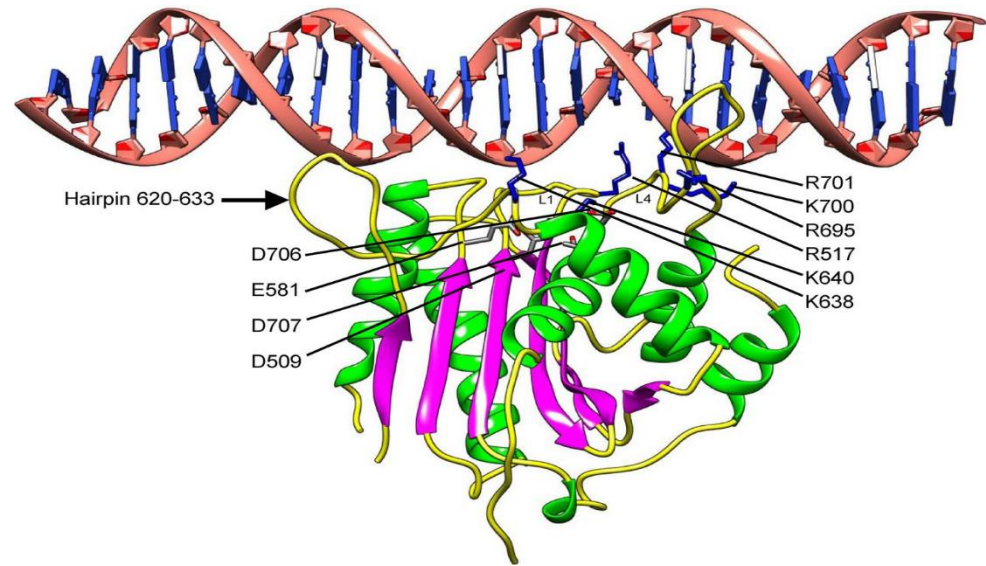
HERPES VIRUSES

- **Herpes Simplex Virus type1 (HSV-1)**
- **Herpes Simplex Virus type2 (HSV-2)**
- **Varicella Zoster Virus (VZV)**
- **Cytomegalovirus (CMV)**
- **Epstein-Barr Virus (EBV)**
- **Human Herpes Virus 6 (HHS-6)**
- **Human Herpes Virus 7 (HHS-7)**
- **Human Herpes Virus 8 (HHS-8)**

HERPES VIRUSES

Characteristics:

- All DNA viruses
- All encapsulated
- All have latency after the initial infection
- Mostly require close contact for transmission



Virus	Infection
<p align="center">HSV Type 1</p>	<p>Herpes labialis ('cold sores')</p> <p>Keratoconjunctivitis</p> <p>Finger infections ('whitlows')</p> <p>Encephalitis</p> <p>Primary stomatitis</p> <p>Genital infections</p>
<p align="center">HSV Type 2</p>	<p>Genital infections</p> <p>Neonatal infection (acquired during vaginal delivery)</p>
<p align="center">Varicella zoster virus (VZV)</p>	<p>Chickenpox</p> <p>Shingles (herpes zoster)</p>
<p align="center">Cytomegalovirus (CMV)</p>	<p>Congenital infection</p> <p>Disease in immunocompromised patients</p> <p>Pneumonitis</p> <p>Retinitis</p> <p>Colitis</p> <p>systemic infection</p>
<p align="center">Epstein-Barr virus (EBV)</p>	<p>Infectious mononucleosis</p> <p>Burkitt's lymphoma</p> <p>Nasopharyngeal carcinoma</p> <p>Oral hairy Cell leucoplakia (AIDS patients)</p>
<p align="center">Human herpes virus 6 (HHV-6) and 7 (HHV-7) Roseolovirus</p>	<p>Exanthem subitum (Roseola): three day fever</p> <p>Disease in immunocompromised patients, Bell's Palsy</p>
<p align="center">Human herpes virus 8 (HHV-8)</p>	<p>Associated with Kaposi's sarcoma</p>

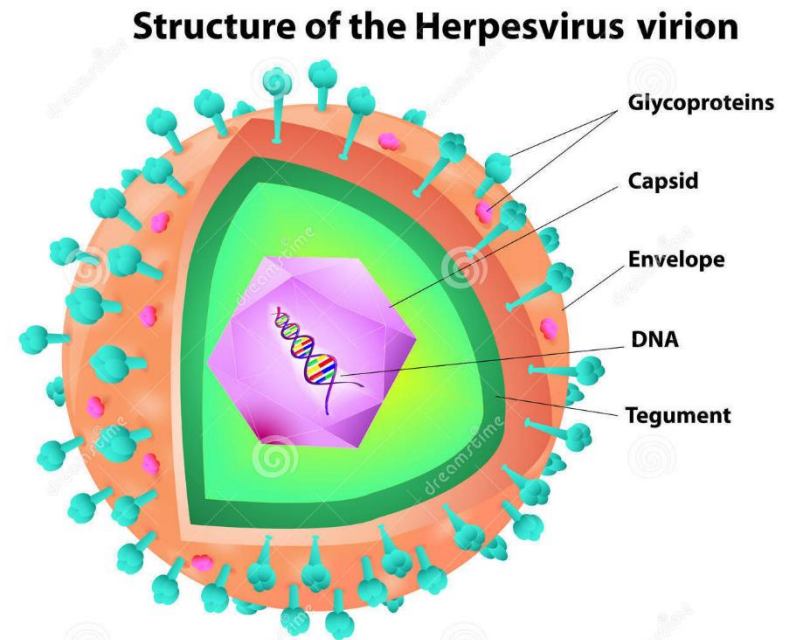
Herpes simiae (Herpes B or Monkey B Virus)

Fatal human cases of myelitis and hemorrhagic encephalitis have been reported following bites, scratches, or eye inoculation of saliva from monkeys.

HERPES VIRUSES

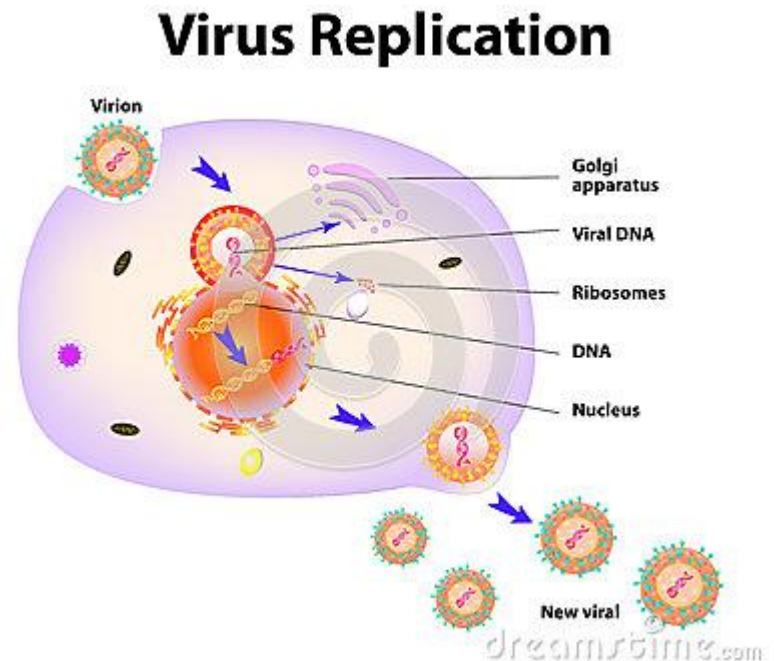
Structure

- Herpesviruses have a unique four-layered **structure**:
 - A core containing the large double-stranded DNA genome
 - Genome is enclosed by an icosapentahedral capsid which is composed of capsomers
 - The capsid is surrounded by an amorphous protein coat called the tegument
 - It is encased in a glycoprotein-bearing lipid bilayer envelope



Viral Replication

- Upon entry into the host cell nucleus, three distinct phases of gene transcription and protein synthesis are initiated producing the immediate-early, early, and late proteins
- Viral nucleocapsid assembly occurs within the host cell nucleus.
- The virus acquires its final envelope by budding into cytoplasmic vesicles



HERPES SIMPLEX VIRUSES

- **HSV-1 vs HSV-2**

- Oral (HSV-1) vs Genital Herpes infection(HSV-2)

- Primary and Recurrent infections (both)

- Encephalitis (HSV-1)

- Neonatal infection (HSV-2)

But both can cause similar illness: e.g. oral sex may transmit HSV-1 to genitals

HERPES SIMPLEX VIRUSES

- Transmission is by close contact with body secretions
- Exposure to HSV at mucosal surfaces or abraded skin sites permits entry of virus and initiation of its replication in cells of the epidermis and dermis
- After initial infection the virus infects the sensory and autonomic nerves and become dormant in the ganglion (trigeminal nerve for HSV-1 and sacral root for HSV-2)
- Incubation period 2-12 days, lesions last 3- 4 weeks

HSV-1 Gingivostomatitis

- Gingivostomatitis and pharyngitis are the most frequent clinical manifestations of first-episode HSV-1 infection
- Fever, sore throat, painful blisters around mouth and in oral mucosa, tender cervical lymphadenopathy



Herpes Labialis (cold sores)

- Recurrent herpes labialis is the most frequent clinical manifestation of reactivation HSV infection
- Disease usually less severe than first episode
- Symptoms typically include a burning pain followed by small blisters or sores

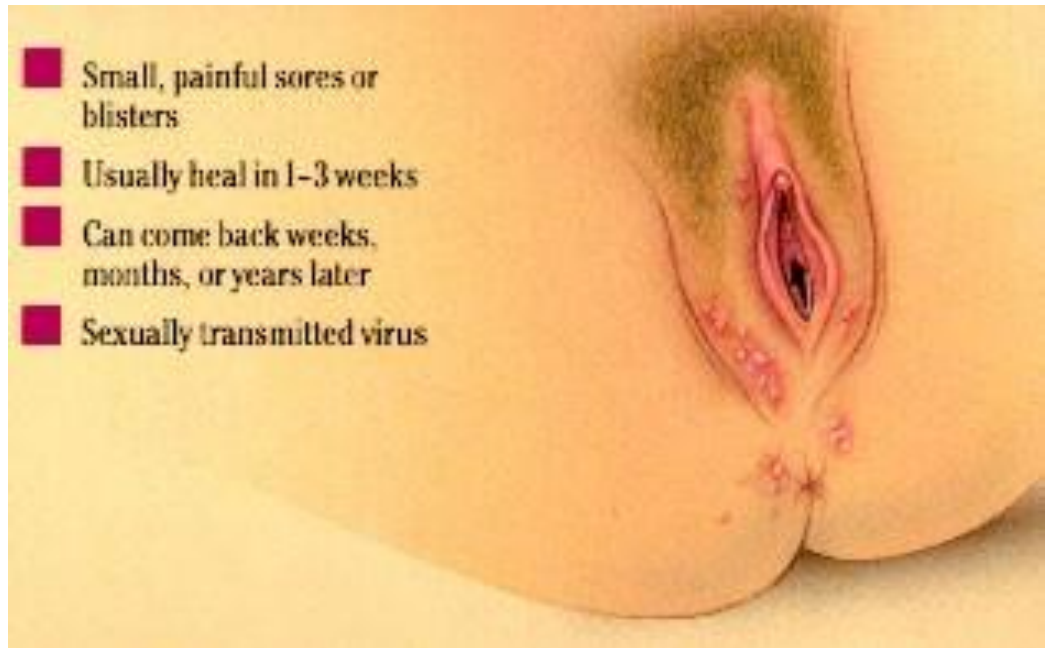


Oral HSV-1 infection



GENITAL HSV-2

- First attack: Fever, headache, malaise, and myalgia. Pain, itching, dysuria, vaginal and urethral discharge, and tender inguinal lymphadenopathy
- Recurrent attacks : no systemic symptoms



Genital HSV-2



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Herpetic ulceration of the vulva



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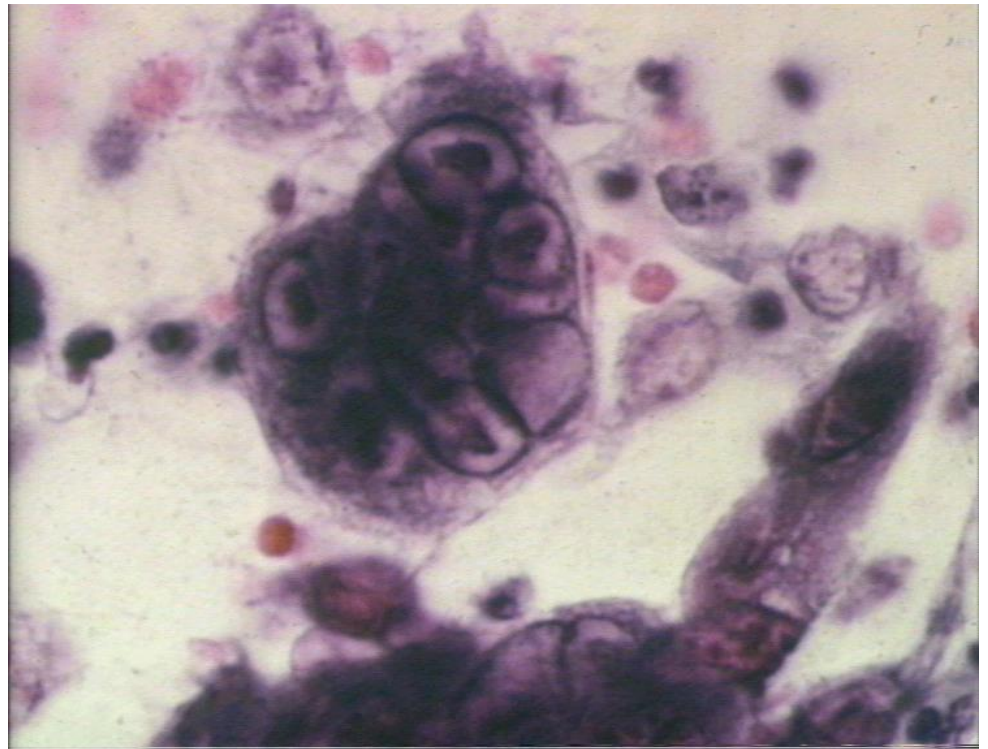
Penile herpes simplex (HSV-2) infection

GENITAL HSV-2



Diagnosis of HSV

- Clinical picture
- Viral culture
- Cytology
- Serology
- PCR

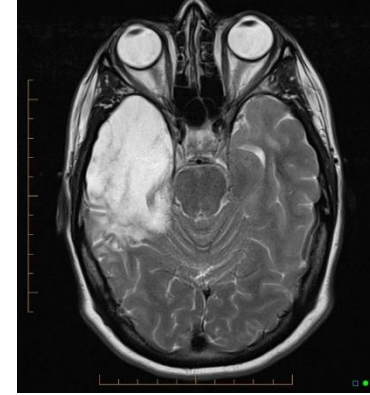


HSV TREATMENT

- Start treatment with prodrome symptoms (tingling/burning) before lesions appear
 - Acyclovir 400 mg po 5 x/day (q4h while awake) x 5 days
 - Famciclovir 500 mg po bid x 7 days
 - Valacyclovir 2 gm po q12h x 1 day
- Topical treatment (mild cases)
 - Penciclovir 1% cream q2h during day x 4 days
 - Acyclovir 5% cream 6x/day (q3h) x 7 days



Herpes Encephalitis



- Clinical Setting:
 - HSV-1 is most common cause of sporadic encephalitis
 - Risk factor: use of natalizumab for treatment of multiple sclerosis or Crohn's disease
 - Survival and recovery from neurological sequelae are related to mental status at time of initiation of therapy
 - Early diagnosis and treatment imperative
- Etiologies:
 - HSV-1
 - HSV-2 causes occasional cases
- Diagnosis:
 - PCR analysis of CSF for HSV-1 DNA is 100% specific and 75–98% sensitive
 - 25% CSF samples drawn before day 3 are negative by PCR
 - Negative PCR is associated with decreased protein and <10 WBC/mm³ in CSF
- Treatment:
 - Acyclovir IV 12.5 mg/kg IV (infuse over 1 hr) q8h x21 days

Case 1

- 36 Y/O Indian professor presents to ID clinic with recurrent oral vesicular lesions that lasts for 10 to 14 days
- 4 to 5 lesion around his lip, slightly painful, interferes with his lecturing
- No fever, no oral cavity lesions
- Gets these episodes almost on a monthly basis,
- Previously diagnosed with HSV-1, took acyclovir on occasion with good results
- Brought on occasionally with stress

- You recommend ?
 - Chronic suppressive therapy with acyclovir

Case 2

- 32 Y/O 40 weeks pregnant lady who is in labor
- O.B. found her to have genital vesicular lesions suspected to be HSV-2
- She had similar genital lesions twice in the past 4 years
- O.B. calls for medical opinion. You recommend:
 - C-Section if possible
 - IV acyclovir till delivery
 - Refer baby to neonatal ID once born

VARICILLA ZOSTER VIRUS (VZV)

- Clinical syndromes:
 - Chickenpox
 - Shingles (single dermatomal or multiple dermatomes)
 - Disseminated VZV disease/organ involvement
 - Emerging data suggests VZV may cause vasculopathy of cerebral , temporal, and other arteries
 - Suggested as possible cause of Giant Cell arteritis
- Varicella (VAR) vaccine at a minimum age of 1 yr
 - 2-dose series: 12–15 months and 4–6 years

VARICILLA ZOSTER VIRUS (VZV)

- The virus is spread by the respiratory route (airborne and contact) and replicates in the nasopharynx or upper respiratory tract
- Followed by localized replication at an undefined site, which leads to seeding of the reticuloendothelial system and viremia
- The virus establishes latency within the dorsal root ganglia
- Chickenpox incubation period: 10 to 21 days

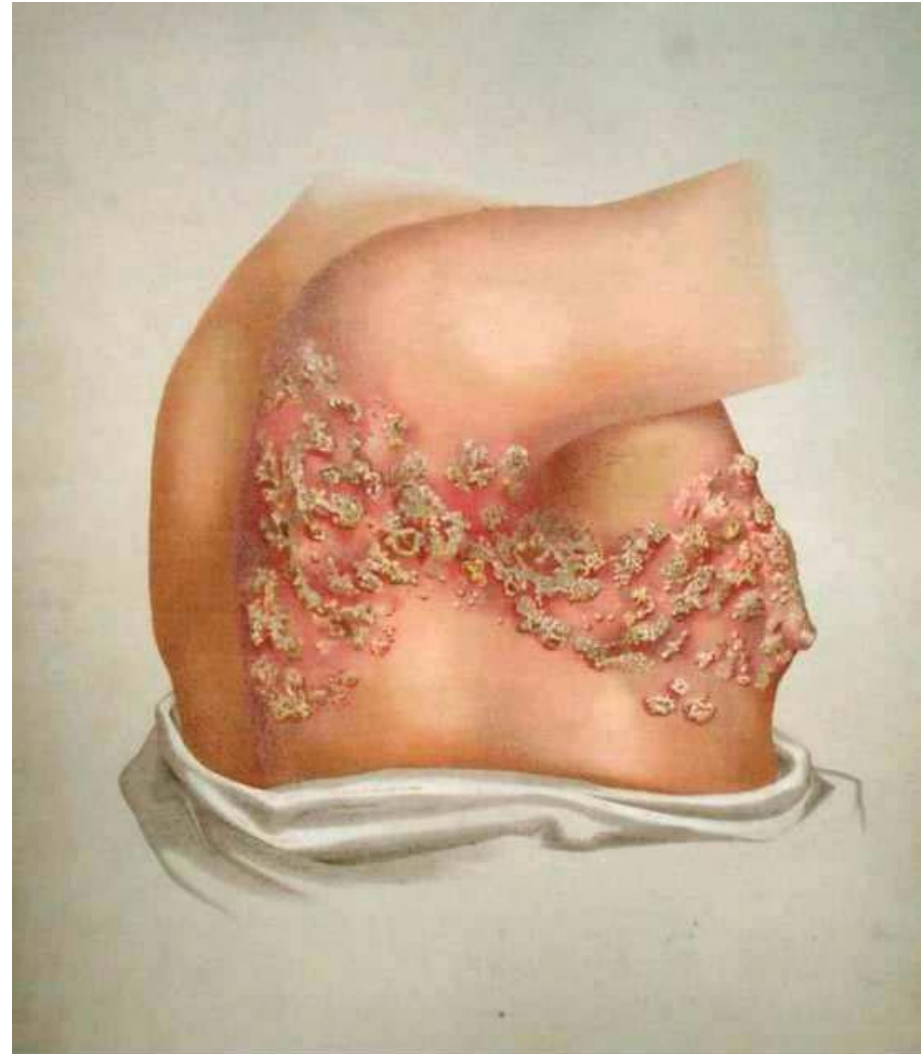
CHICKENPOX

- Overall, chickenpox is a disease of childhood, because 90% of cases occur in children younger than 13 years of age
- Highly contagious
- Symptoms: fever, headache, malaise, itchy, blister-like vesicular rash: appears first on chest, back, and face, and then spreads over the entire body
- Recover in 2 wks: rash scabs over
- Complications: rare
 - Pneumonia
 - Encephalitis
 - Bacterial skin and soft tissue infections



VARICILLA ZOSTER

Reactivation of VZV leads to VZ



VARICILLA ZOTER



VARICILLA ZOSTER



VARICILLA ZOSTER



VARICILLA ZOTER



VZV Diagnosis

- Clinical picture
- Viral culture
- PCR
- Serology



Chickenpox Treatment

- Acyclovir 800 mg po 5x/day x 5–7 days (start within 24 hrs of rash)
- Valacyclovir 1000 mg po tid x 5 days
- Famciclovir 500 mg po tid

- Immunocompromised:
 - Acyclovir 10–12 mg/kg IV (infused over 1 hour) q8h x 7 days

VZV Prevention & Post-exposure Prophylaxis

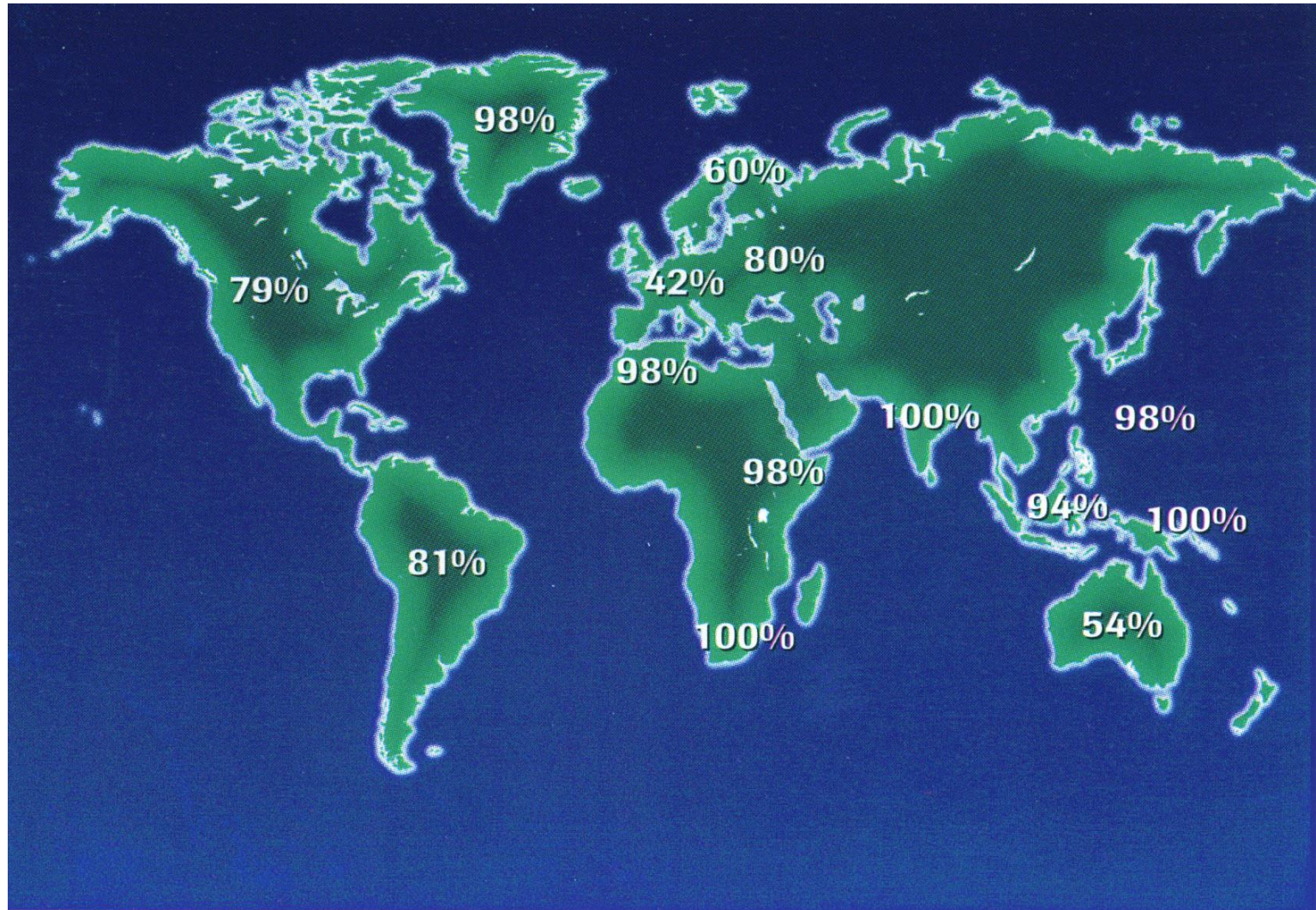
- Admitted patients should be on Airborne Infection Isolation (AII) and contact precautions
- <5% of cases of varicella but >50% of varicella-related deaths occur in adults >20 yrs of age:
 - Varicella-zoster immune globulin (VZIG) (125 units/10 kg) in susceptible persons at greater risk for complications (immunocompromised such as HIV, malignancies, pregnancy, and steroid therapy) as soon as possible after exposure (<96 hrs)
 - If varicella develops, initiate treatment quickly (<24 hrs of rash) with Acyclovir
- Susceptible adults should be vaccinated
 - Check antibody in adults with negative or uncertain history of varicella (10–30% will be Ab-neg.) and vaccinate those who are Ab-negative

Cytomegalovirus (CMV)

- The largest virus that infects human beings
- World wide distribution
- Latency after primary infection
- Infection ranges from asymptomatic to severe multisystemic disease

CMV

Seroepidemiology

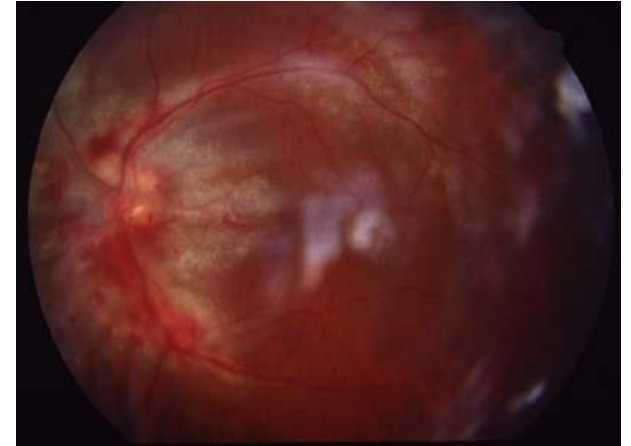


Cytomegalovirus (CMV)

Primary infection

- Asymptomatic
- Infectious mononucleosis

**Secondary infections in
Immunocompromised, esp.
solid organ transplant (SOT)
and hematopoietic stem cell
transplant (HCT) recipients:**



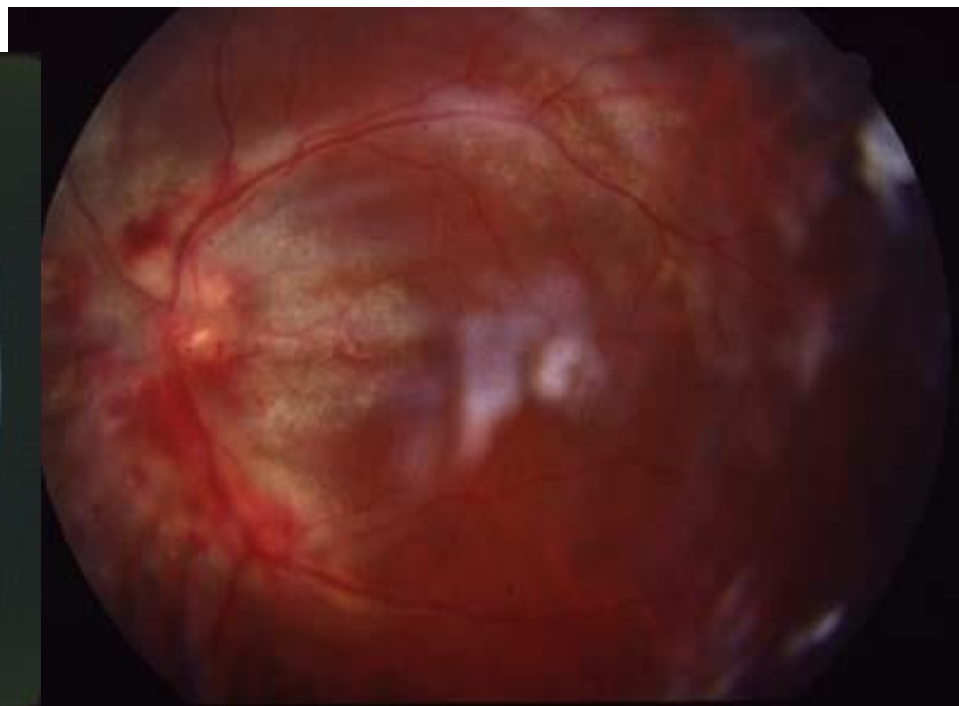
Cytomegalovirus in Transplant Recipients

- SOT recipient's disease onset was early post-transplant (first 100 days) but with the use of effective prophylaxis disease is now often "late-onset" and occurs following the discontinuation of prophylaxis
- Risk factors:
 - SOT: Seropositive donor (D+) and seronegative recipient (R-); Lymphocyte depleting antibody therapy (thymoglobulin, ATG, OKT-3, alemtuzumab)
 - HCT: Seronegative donor (D-) and seropositive recipient (R+); T-cell depleted or cord blood transplants; Graft versus host diseases (GVHD)

Cytomegalovirus in Transplant Recipients

- Clinical disease:
 - "CMV syndrome" (fever, leukopenia, and thrombocytopenia w/o other end-organ disease)
 - Gastrointestinal disease (colitis, esophagitis, enteritis)
 - Hepatitis
 - Pneumonitis
 - CNS disease (meningoencephalitis, myelitis)
 - Other (cystitis, retinitis, nephritis, etc.)
- Diagnostic strategies:
 - PCR (most common test, used on serum, CSF, tissue)
 - pp65 antigen (less commonly used, not recommended in neutropenic patients)
 - Culture (from tissue, lacks specificity)
 - Histopathology (gold standard to confirm end-organ disease)

CMV Retinitis



Cytomegalovirus (CMV) Treatment

- **Ganciclovir 5 mg/kg IV q12h OR**
- **Valganciclovir 900 mg po q12h**

- Foscarnet 90 mg/kg IV q12h
- Cidofovir 5 mg/kg IV once weekly

- Treatment duration should be individualized: Continue treatment until:
 - CMV PCR or antigenemia has become undetectable
 - Clinical evidence of disease has resolved
 - At least 2-3 weeks of treatment

Epstein-Barr Virus (EBV)

- Ubiquitous human herpes virus.
- By adulthood 90 to 95% of most populations are positive.
- Spread occurs by intimate contact between susceptible individuals and asymptomatic shedders of EBV.
- Mostly causes asymptomatic infections.
- Strong association with African Burkitt's lymphoma and Nasopharyngeal carcinoma.

Epstein-Barr Virus (EBV)

Infectious mononucleosis

Clinical

Fever, Sore throat ,Lymphadenopathy

Hematologic

>50% mononuclear cells

>10% atypical lymphocytes

Serologic

Transient appearance of heterophile antibodies (weak antibodies)

Permanent emergence of antibodies to EBV

Epstein-Barr Virus (EBV)

Diagnosis:

Heterophile Antibodies (monospot test) 70–92% sensitivity and 96–100% specificity

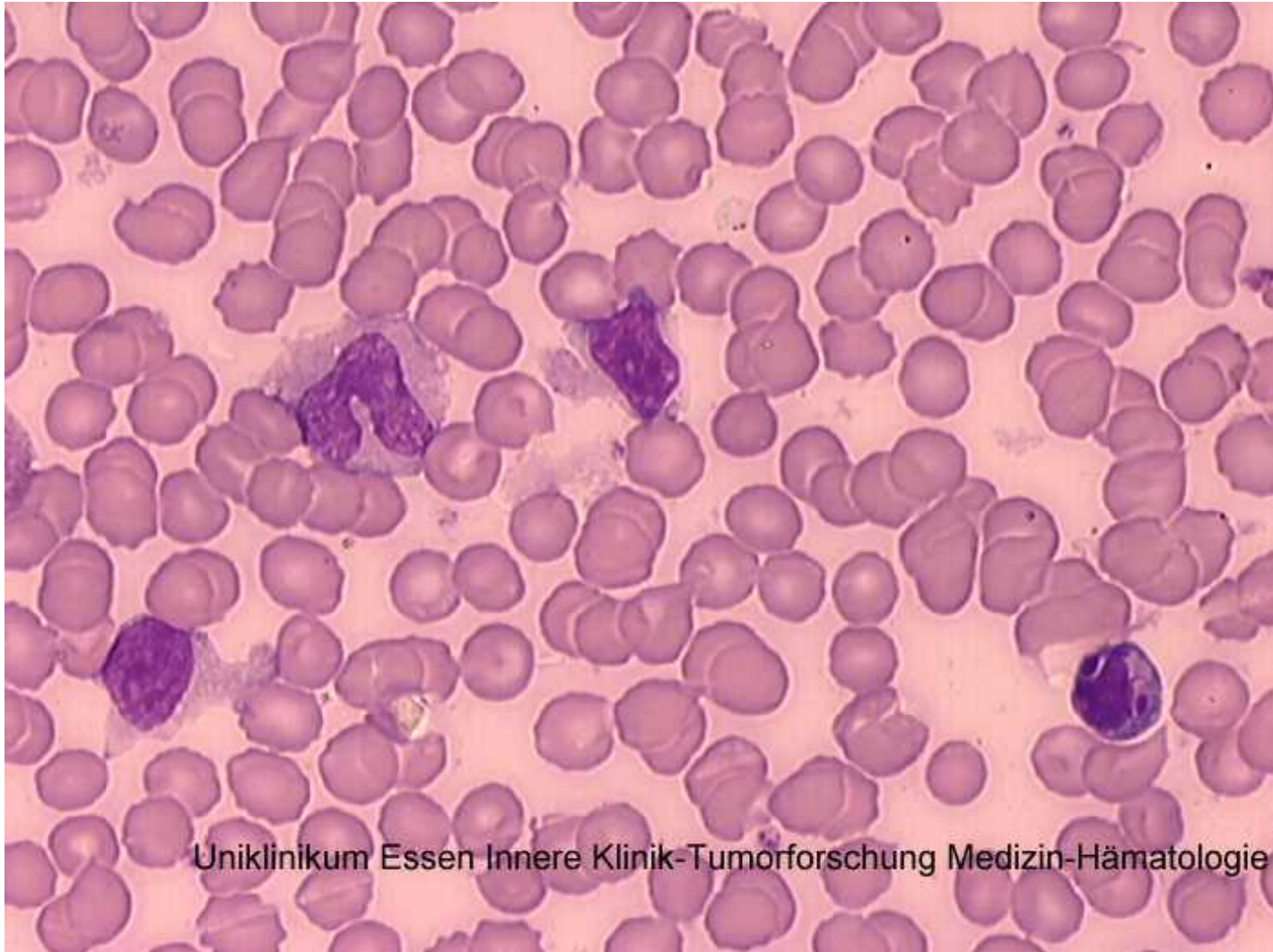
Hematologic Findings

Lymphocytosis, neutropenia , thrombocytopenia

EBV specific antibodies

EBV Infection

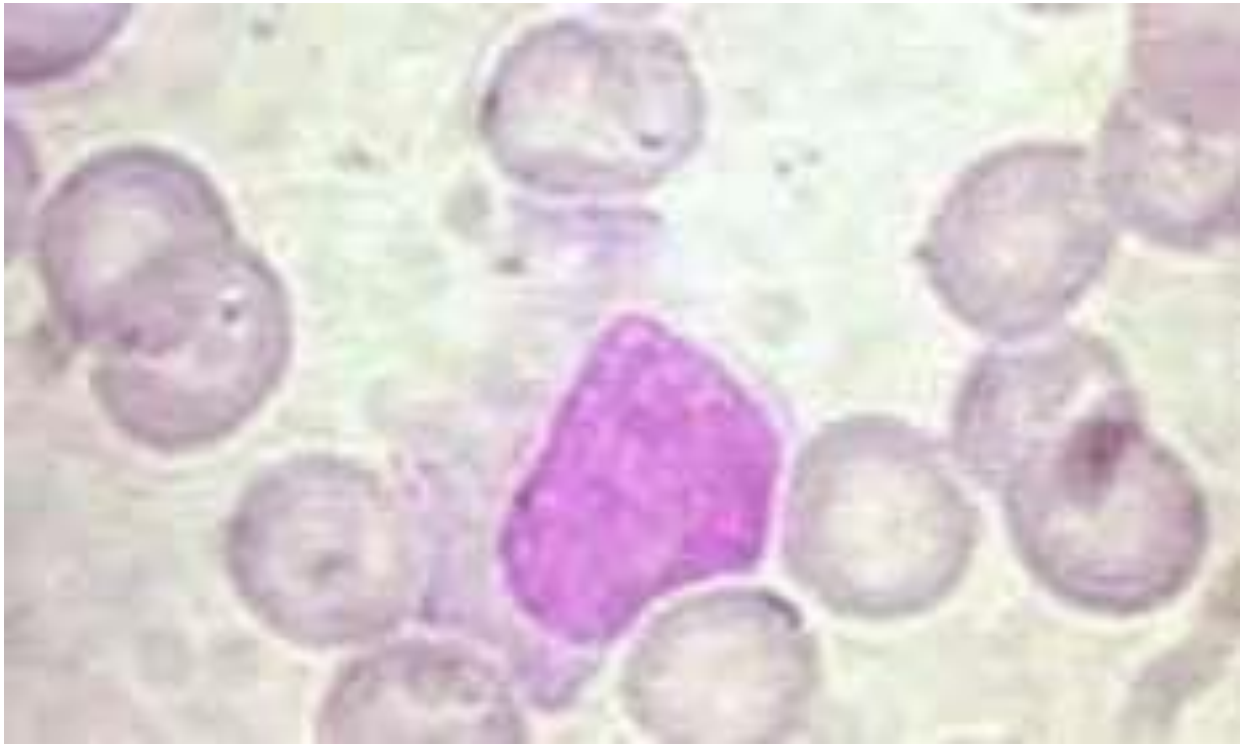
Atypical Lymphocytes



Uniklinikum Essen Innere Klinik-Tumorforschung Medizin-Hämatologie

EBV Infection

Atypical Lymphocytes



EBV Infection

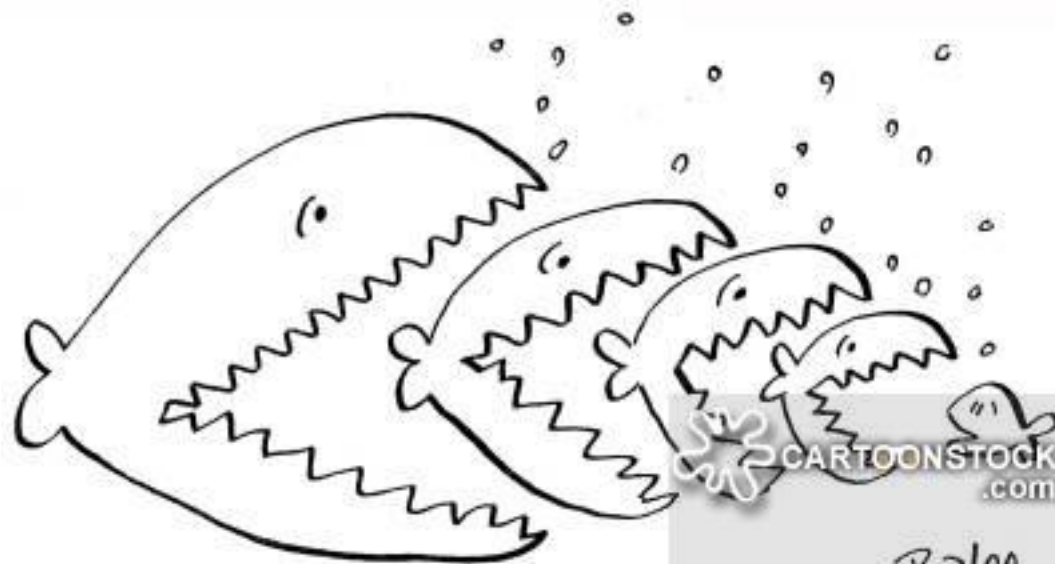


Epstein-Barr Virus (EBV)

Treatment:

Treatment of infectious mononucleosis is largely supportive because more than 95% of the patients recover uneventfully without specific therapy

Corticosteroids



Baloo
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"I'm warning you guys —
I've got herpes!"