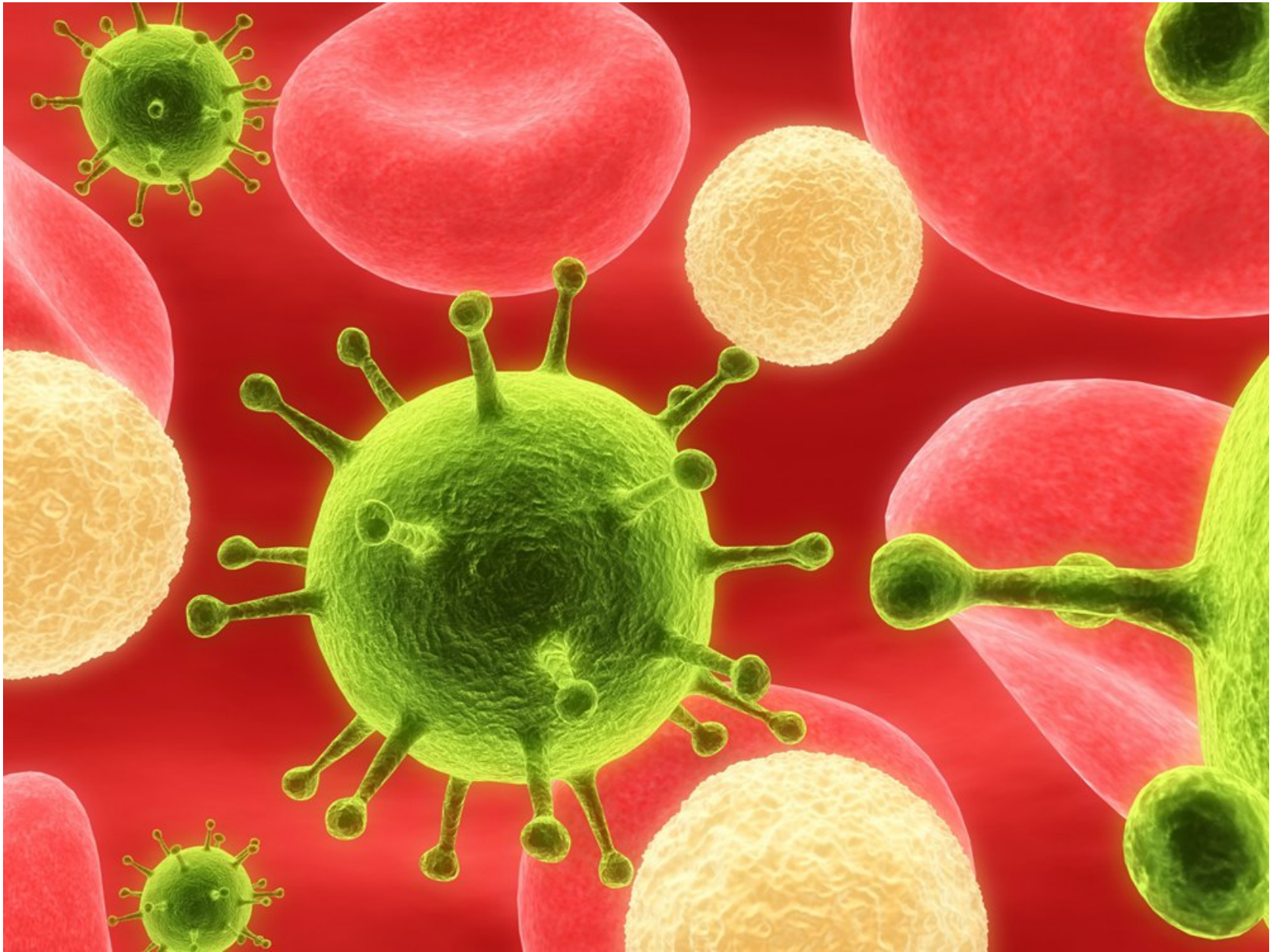


DNA Enveloped Viruses



Herpes Viruses

1. DNA Enveloped Viruses Herpesviruses

- a) HSV1
- b) HSV2
- c) VZV
- d) CMV
- e) EBV
- f) Human herpes virus 8

1. Herpesviruses

Herpesviruses

No.	Virus	Associated with Vesicular Rash
a	Herpes simplex virus types 1	Yes
b	Herpes simplex virus types 2	
c	Varicella-zoster virus	
d	Cytomegalovirus	No
e	Epstein-Barr virus	
f	Human herpes virus 8 (the cause of Kaposi's sarcoma).	

Characters of Herpesviruses

All herpesviruses are:

Structurally similar.

Capsid: an icosahedral core surrounded by a lipoprotein envelope.

Core: linear double-stranded DNA.

Envelope: derived from nuclear membrane of the host cell & contains viral glycoproteins

The virion does not contain a polymerase.

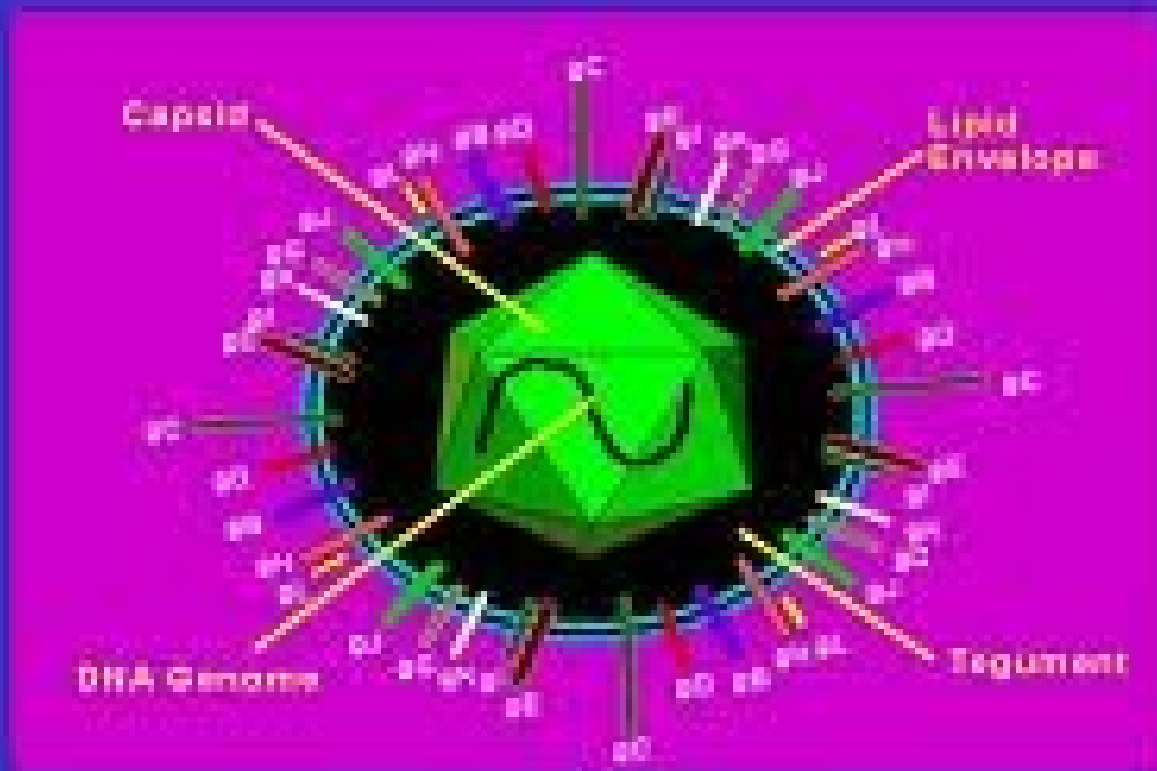
They are large (120–200 nm in diameter), second in size only to poxviruses.

General Characters of Herpesviruses

All herpesviruses are:

1. Most infections are asymptomatic
2. They remain latent in the host after recovery of primary infection
3. They can be reactivated by the following factors
 - a. Physical: long exposure to sunlight
 - b. Physiological: menstruation, stress or pregnancy
 - c. Pathological: high fever, common cold & low immunity.
4. In tissue culture, they produce
 - a) Intranuclear inclusion bodies
 - b) Cytopathic effects in the form of ballooning & rounding of cells followed by necrosis (multinucleated giant cells).

Herpes Simplex Virus



Latency & Reactivation

Latent phase

In the latent phase, the virus is 'quiescent' (a state in which the virus is not replicating).

Reactivation

It is well known that many triggers can provoke a recurrence. These include;

1. Stress – trauma, physical, or psychological
2. Pneumococcal infection
3. Meningococcal infection
4. Fever
5. Irradiation, including sunlight
6. Hormonal changes as menstruation
7. Patients receiving cytotoxic drug therapy
8. Organ graft recipients
9. HIV carriers

Important Features of Common Herpes virus Infections

Virus	Primary infection	Usual Site of Latency	Recurrent Infection	Transmission
HSV1	Gingivo-stomatitis ¹	Cranial sensory ganglia	Herpes labialis, ² encephalitis, keratitis	Respiratory secretions & saliva
HSV2	Herpes genitalis, perinatal disseminated disease	Lumbar or sacral sensory ganglia	Herpes genitalis	Sexual contact, perinatal infection
VZV	Varicella	Cranial or thoracic sensory ganglia	Zoster ²	Respiratory secretions

¹Primary infection is often asymptomatic.

²In immunocompromised patients, dissemination is common.

Important Features of Common Herpes virus Infections

Virus	Primary infection	Usual Site of	Recurrent	Transmission
EBV	Infectious mononucleosis ¹	B lymphocytes	None ³	Via respiratory secretions and
CMV	Congenital infection (in utero) ⁶	Uncertain ⁴	Asymptomatic shedding ²	Intrauterine infection
HHV8 ⁵	Uncertain ⁶	Uncertain	Kaposi's sarcoma	Sexual or organ transplantation

¹Primary infection is often asymptomatic.

³The relationship of EBV infection to "chronic fatigue syndrome" and B-cell neoplasms is unclear. (e.g., saliva & urine)

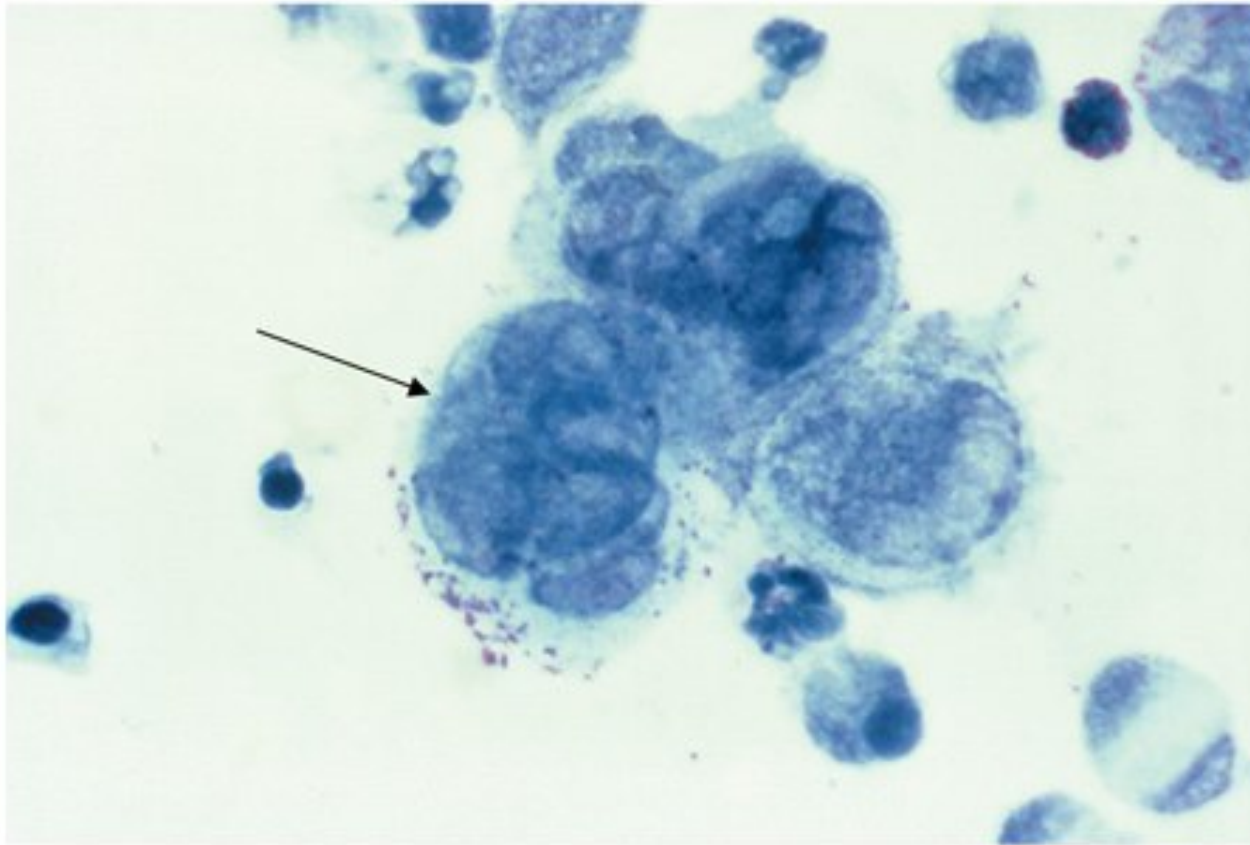
⁴CMV may be latent within circulating lymphoid cells or epithelial cells.

⁵Also known as Kaposi's sarcoma-associated herpesvirus.

⁶A mononucleosis-like syndrome has been described. KS itself also can result from a primary infection.

Four herpesviruses, namely herpes HSV 1 & 2, VZV, & CMV, induce the formation of **multinucleated giant cells**, which can be seen microscopically in the lesions.

Herpes
simplex
type-2



Multinucleated giant cells in Tzanck smear. Arrow points to a multinucleated giant cell with approximately eight nuclei.

HSV1



HSV2



Herpes simplex virus



Electron micrograph. 3 HSV virions are visible.

Short arrow points to the envelope of an HSV virion.

Long arrow points to the nucleocapsid of the virion.

Dark area between the inner nucleocapsid and the outer envelope is the tegument

important differences between the diseases caused by HSV-1 & HSV-2.

Site	Disease Caused by HSV- 1	Disease Caused by HSV- 2
Skin	Vesicular lesions above the waist	Vesicular lesions below the waist
Mouth	Gingivo- stomatitis	Rare
Eye	Kerato- conjunctivitis	Rare
CNS	Encephalitis (temporal lobe)	Meningitis
Neonate	Rare ¹	Skin lesions, encephalitis, & disseminated infection ²
Dissemination to viscera in immunocompromised patients	Yes	Rare

¹ Infection acquired after birth from HSV- 1 –infected person.

² Infection acquired during passage through birth canal.

Transmission

HSV-1 is transmitted primarily in saliva, whereas HSV-2 is transmitted by sexual contact.

HSV-1 infections occur mainly on the face, whereas HSV-2 lesions occur in the genital area.

However, oral–genital sexual practices can result in HSV-1 infections of the genitals & HSV-2 lesions in the oral cavity (this occurs in about 10–20% of cases).

Although transmission occurs most often when active lesions are present, asymptomatic shedding of both HSV-1 & HSV-2 does occur & plays an important role in transmission.

Epidemiology

The number of HSV-2 infections has markedly increased in recent years, whereas that of HSV-1 infections has not.

Roughly 80% of people in the USA are infected with HSV-1 & 40% have recurrent herpes labialis.

Most primary infections by HSV-1 occur in childhood, as evidenced by the early appearance of antibody.

In contrast, antibody to HSV-2 does not appear until the age of sexual activity.

Pathogenesis

The virus replicates in the skin or mucous membrane at the initial site of infection, then

Migrates up the neuron by retrograde axonal flow & becomes latent in the sensory ganglion cells.

HSV-1 becomes latent in the trigeminal ganglia, whereas HSV-2 becomes latent in the lumbar & sacral ganglia.

During latency, most—if not all—viral DNA is located in the cytoplasm rather than integrated into nuclear DNA.

The virus can be reactivated from the latent state by a variety of inducers, at which time it migrates down the neuron & replicates in the skin, causing lesions.

Pathogenesis

The typical skin lesion is a vesicle that contains serous fluid filled with virus particles & cell debris.

When the vesicle ruptures, virus is liberated & can be transmitted to other individuals.

Multinucleated giant cells are typically found at the base of herpesvirus lesions.

Immunity

Immunity is type-specific, but some cross-protection exists.

Immunity is incomplete, & both re-infection & reactivation occur in the presence of circulating IgG.

CMI is important in limiting herpesviruses, because its suppression often results in

Reactivation

Spread

Severe disease.

Clinical Findings

HSV-1 causes primary & recurrent disease

1. Gingivostomatitis

Occur primarily in children & is characterized by fever, irritability, & vesicular lesions in the mouth.

The primary disease is more severe & lasts longer than recurrences.

The lesions heal spontaneously in 2 to 3 weeks.

Many children have asymptomatic primary infections.



Gingivostomatitis

Clinical Findings

HSV-1 causes primary & recurrent disease

2. Herpes labialis (fever blisters or cold sores)

Is the milder, recurrent form & is characterized by crops of vesicles

usually at the mucocutaneous junction of the lips or nose.

Recurrences frequently reappear at the same site.



Small, painful, fluid-filled blisters on the mouth or nose, cold sores are caused by the herpes simplex virus. Lasting about 10 days, cold sores are very contagious

Clinical Findings

HSV-1 causes primary & recurrent disease

3. Keratoconjunctivitis

Is characterized by corneal ulcers & lesions of the conjunctival epithelium.

Recurrences can lead to scarring & blindness.



Source: [National Eye Institute](#)

Keratoconjunctivitis

Clinical Findings

HSV-1 causes primary & recurrent disease

4. Herpetic whitlow

Is a pustular lesion of the skin of the finger or hand. It can occur in medical personnel as a result of contact with patient's lesions.

5. Herpes gladiatorum

As the name implies, occurs in wrestlers & others who have close body contact. It is caused primarily by HSV-1 & is characterized by vesicular lesions on the head, neck, & trunk.

6. Disseminated infections

Such as esophagitis & pneumonia, occur in immunocompromised patients with depressed T-cell function.



Herpetic whitlow

Clinical Findings

HSV-1 causes primary & recurrent disease

7. Encephalitis

Caused by HSV-1 is characterized by a necrotic lesion in one temporal lobe.

Fever, headache, vomiting, seizures, & altered mental status are typical clinical features.

The onset may be acute or protracted over several days.

Occurs as a result of either a primary infection or a recurrence.

MRI imaging often reveals the lesion.

Examination of the spinal fluid typically shows a moderate increase of lymphocytes, a moderate elevation in the amount of protein, & a normal amount of glucose.

HSV-1 encephalitis has a high mortality rate & causes severe neurologic sequelae in those who survive .

HSV 2

Genital Herpes

Clinical Findings

HSV-2 causes primary & recurrent

Genital Herpes

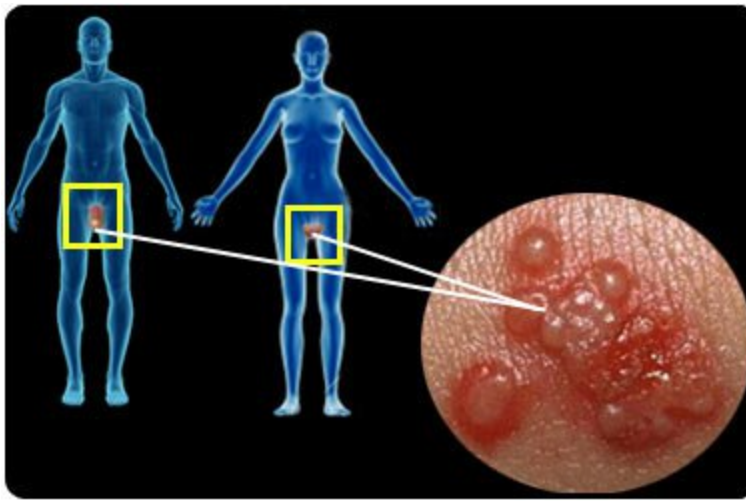
Is characterized by painful vesicular lesions of the male & female genitals & anal area.

The lesions are more severe & protracted in primary disease than in recurrences.

Primary infections are associated with fever & inguinal adenopathy.

Asymptomatic infections occur in both men (in the prostate or urethra) & women (in the cervix) & can be a source of infection of other individuals.

Many infections are asymptomatic, i.e., many people have antibody to HSV-2 but have no history of disease.



Genital Herpes



Photomicrograph of HSV-1 (Dr. J. A. Fleming & J. A. Jones, 1981)



Clinical Findings

HSV-2 causes primary & recurrent

Neonatal Herpes

Originates chiefly from contact with vesicular lesions within the birth canal.

In some cases, although there are no visible lesions, HSV-2 is shed into the birth canal (asymptomatic shedding) & can infect the child during birth.

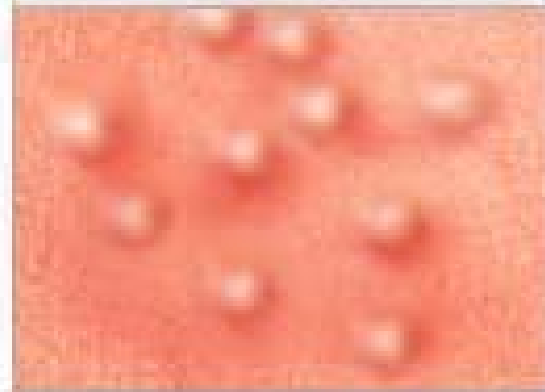
Neonatal herpes varies from severe disease (e.g., disseminated lesions or encephalitis) to milder local lesions (skin, eye, mouth) to asymptomatic infection.

Neonatal disease may be prevented by performing cesarean section on women with either active lesions or positive viral cultures.

Mother with
active herpes infection
(although active infection
may not be apparent)



Blisters due to
congenital
herpes



Clinical Findings

HSV-2 causes primary & recurrent

Both HSV-1 & HSV-2 can cause severe neonatal infections that are acquired after birth from carriers handling the child.

Despite their association with neonatal infections, neither HSV-1 nor HSV-2 causes congenital abnormalities to any significant degree.

Clinical Findings

HSV-2 causes primary & recurrent

Serious neonatal infection is more likely to occur when the mother is experiencing a primary herpes infection than a recurrent infection for two reasons:

- (1) the amount of virus produced during a primary infection is greater than during a secondary infection
- (2) mothers who have been previously infected can pass IgG across the placenta, which can protect the neonate from serious disseminated infection.

Aseptic meningitis

Caused by HSV-2 is usually a mild, self-limited disease with few sequelae.

Clinical Findings

HSV-2 causes primary & recurrent

Erythema multiforme

Both HSV-1 & HSV-2 infections are associated with erythema multiforme.

The lesions are typically macular or papular & occur symmetrically on the trunk, hands, & feet.

The rash is thought to be an immune-mediated reaction to the presence of HSV antigens.

Acyclovir is useful in preventing recurrent episodes of erythema multiforme, probably by reducing the amount of HSV antigens.

Erythema Multiforme

Central red area surrounded
by a ring of normal skin
outside of which is a red ring

("target" or
"bull's eye"
lesion).



Clinical Findings

HSV-2 causes primary & recurrent

Erythema multiforme

Many drugs, especially

Sulfonamides among the antimicrobial drugs, commonly cause erythema multiforme.

Other prominent infectious causes include

Mycoplasma pneumoniae

Viruses such as HBV & HCV

Clinical Findings

HSV-2 causes primary & recurrent

Stevens-Johnson syndrome

Erythema multiforme major, also known as Stevens-Johnson syndrome, is characterized by

- Fever

- Erosive oral lesions

- Extensive desquamating skin lesions.

M. pneumoniae infection is the most common infectious cause of Stevens-Johnson syndrome.



Stevens-Johnson syndrome

Laboratory Diagnosis

1. Cell culture
2. Tzanck smear
3. Polymerase Chain Reaction (PCR) assay
4. Serologic tests such as the neutralization test

Laboratory Diagnosis

Cell culture

A diagnostic procedure is isolation of the virus from the lesion by growth in cell culture.

The typical cytopathic effect occurs in 1 to 3 days, after which the virus is identified by:

Fluorescent antibody staining of the infected cells or by
Detecting virus-specific glycoproteins in ELISAs.

Laboratory Diagnosis

Tzanck smear

Cells from the base of the vesicle are stained with Giemsa stain.

The presence of multinucleated giant cells suggests herpesvirus infection.

Laboratory Diagnosis

Polymerase Chain Reaction (PCR) assay

A rapid diagnosis of **encephalitis** can be made by detecting HSV-1 DNA in the spinal fluid by using a PCR assay, but virus is rarely recovered from the spinal fluid.

Diagnosis of **neonatal herpes infection** typically involves the use of:
Viral cultures or
PCR assay.

PCR is the most sensitive test for HSV diagnosis.

Laboratory Diagnosis

Serologic tests such as the neutralization test

Can be used in the diagnosis of **primary infections** because a significant rise in antibody titer is readily observed. However,

They are of no use in the diagnosis of recurrent infections because many adults already have circulating antibodies & recurrences rarely cause a rise in antibody titer.

Treatment

1. Acyclovir (Zovirax)
2. Valacyclovir (Valtrex)
3. Famciclovir (Famvir)
4. Penciclovir (a derivative of acyclovir) or
5. Docosanol (a long-chain saturated alcohol)
6. Trifluridine (Viroptic)
7. Foscarnet

Treatment

Acyclovir (Zovirax)

Is the treatment of choice for

- Encephalitis & systemic disease caused by HSV-1.

- Primary & recurrent genital herpes; it shortens the duration of the lesions & reduces the extent of shedding of the virus.

- Neonatal infections caused by HSV-2.

Valacyclovir (Valtrex) & famciclovir (Famvir)

Used in the treatment of genital herpes & in the suppression of recurrences.

Treatment

Penciclovir (a derivative of acyclovir) or docosanol (a long-chain saturated alcohol)

Used to treat recurrences of orolabial HSV-1 infections in immunocompetent adults.

Trifluridine (Viroptic)

Topical use for HSV-1 eye infections

Treatment

Foscarnet

Used for mutants of HSV-1 resistant to acyclovir.

No drug treatment of the primary infection prevents recurrences.

Drugs have no effect on the latent state, but prophylactic, long-term administration of acyclovir, valacyclovir, or famciclovir can suppress clinical recurrences.

Prevention

Avoiding contact with the vesicular lesion or ulcer.

Cesarean section is recommended for women who are at term & who have genital lesions or positive viral cultures.

Circumcision reduces the risk of infection by HSV-2.

Vaccine formed of purified HSV glycoproteins given before the primary infection



Most people with genital herpes don't know it.

True

False

About 16% of people aged 14-49 in the U.S. are infected with the herpes simplex virus-2 (HSV-2) that causes genital herpes, but as many as 81% of them had not received the diagnosis.

Most people with genital herpes don't know it.

True

False

True

About 16% of people aged 14-49 in the U.S. are infected with the herpes simplex virus-2 (HSV-2) that causes genital herpes, but as many as 81% of them had not received the diagnosis.

How many people in the U.S. are estimated to have genital herpes?

1 million

10 million

30 million

45 million

How many people in the U.S. are estimated to have genital herpes?

45 million

Genital herpes is very common, infecting at least 45 million people aged 12 and older in the United States.

Genital herpes caused by HSV-2 is found more frequently in women than in men.

True

False

Genital herpes caused by HSV-2 is found more frequently in women than in men.

True

About one in five women between the ages of 14 and 49 have genital herpes caused by HSV-2, while about one in nine men in that same age range are infected.

You can get genital herpes from a toilet seat.

True

False

You can get genital herpes from a toilet seat.

False

As with other sexually transmitted diseases, herpes can be spread by close contact or sexual activity. It is highly unlikely to be spread by a toilet seat or other objects.

You can get genital herpes from someone who doesn't have visible sores.

True

False

You can get genital herpes from someone who doesn't have visible sores.

True

Genital herpes can be transmitted even if the infected partner has no symptoms or visible signs or doesn't know he or she is infected.

Washing the genital area before and after sex can help prevent the transmission of genital herpes.

True

False

Washing the genital area before and after sex can help prevent the transmission of genital herpes.

False

Washing the genital area doesn't help prevent any sexually transmitted disease (STD), including genital herpes.

The best way to prevent any STD is to abstain from sex or engage in sex only with someone you know is not infected.

Condoms are not guaranteed to prevent infection, but research has shown that they provide some protection.

A pregnant woman can give herpes to her unborn baby.

True

False

A pregnant woman can give herpes to her unborn baby.

True

The estimated number of pregnant women infected with HSV-2 is 880,000.

Most transmission to newborns occurs during vaginal delivery.

If a woman had genital herpes before getting pregnant, her baby may be infected but the chance is very low -- less than 1%.

However, the risk of infecting the baby is much higher (25% to 50%) when a woman is newly infected late in pregnancy.

If pregnant women think infected, she has to tell her doctor right away.

Women with genital herpes are examined carefully for any symptoms before giving birth.

If sores or signs that an outbreak is coming are present at the time of delivery, the baby may be delivered by cesarean section (C-section).

A blood test can determine if someone has genital herpes.

True

False

A blood test can determine if someone has genital herpes.

True

To find out if you have genital herpes, a doctor can take a sample from a sore and test it in the laboratory.

There is also a blood test that looks for antibodies to the virus that your immune system would have made.

HSV-2 almost always infects the genitals, so if antibodies to HSV-2 are detected in your blood, you probably have genital herpes.

A blood test that shows antibodies to HSV-1 means you could have genital or oral herpes. That's because oral herpes, typically caused by HSV-1, can be spread to the genitals during oral sex.

New or initial genital herpes infections

- a) Tend to be the most severe
- b) May produce fever and flu-like symptoms
- c) Can cause genital itching, burning, and painful genital blisters
- d) All of the above

New or initial genital herpes infections

- a) All of the above

When do the sores associated with genital herpes typically heal after the first outbreak?

- a) Within a week
- b) Within one to two weeks
- c) Within two to four weeks
- d) Within five to six weeks

When do the sores associated with genital herpes typically heal after the first outbreak?

a) Within two to four weeks

The classic symptom of genital herpes is small fluid-filled blisters that break, forming painful sores that crust and heal. These may appear four to seven days after the initial virus transmission.

Genital herpes outbreaks increase in frequency over time.

True

False

Genital herpes outbreaks increase in frequency over time.

False

Genital herpes typically causes several outbreaks (four or five) within a year of the first outbreak, with fewer and less severe outbreaks over time.

Which of these is NOT a commonly reported trigger of a genital herpes outbreak?

- a) Vigorous sex
- b) Stress
- c) Surgery
- d) Perspiration

Which of these is NOT a commonly reported trigger of a genital herpes outbreak?

a) Perspiration

Some commonly reported triggers for genital herpes outbreaks include stress, illness, surgery, vigorous sex, diet, and menstrual periods.

Varicella-Zoster Virus (VZV)



VZV Disease

1. Varicella (chickenpox) is the primary disease
2. Zoster (shingles) is the recurrent form.

Important Properties

VZV is structurally & morphologically similar to other herpes viruses but is antigenically different.

It has a single serotype.

The same virus causes both varicella & zoster.

Humans are the natural hosts.

Summary of Replicative Cycle

The cycle is similar to that of HSV.

VZV Disease

Transmission

Respiratory droplets

Direct contact with the lesions.

There is infectious VZV in zoster vesicles

This virus can be transmitted, usually by direct contact, to children & can cause varicella.

Varicella is a highly contagious disease of childhood.

VZV Disease Epidemiology

Varicella occurs worldwide.

> 90% of people in the USA have antibody by age 10 years.

Prior to 2001, there were more cases of chickenpox than any other notifiable disease, but the widespread use of the vaccine has significantly reduced the number of cases.

The appearance of either varicella or zoster in a hospital is a major infection control problem because

The virus can be transmitted to immunocompromised patients & cause life-threatening disseminated infection .

Pathogenesis

VZV infects the mucosa of the upper respiratory tract, then spreads via the blood to the skin, where the typical vesicular rash occurs.

Multinucleated giant cells with intranuclear inclusions are seen in the base of the lesions.

The virus infects sensory neurons & is carried by retrograde axonal flow into the cells of the dorsal root ganglia where the virus becomes latent.

In latently infected cells, VZV DNA is located in the nucleus & is not integrated into cellular DNA.

Later in life, frequently at times of reduced cell-mediated immunity or local trauma, the virus is activated & causes the vesicular skin lesions & nerve pain of zoster.

Immunity

Immunity following varicella is lifelong:

A person gets varicella only once, but zoster can occur despite this immunity to varicella.

Zoster usually occurs only once.

The frequency of zoster increases with advancing age, perhaps as a consequence of waning immunity.

Clinical Findings: Varicella

IP of 14 to 21 days.

Brief prodromal symptoms of fever & malaise occur.

A papulovesicular rash then appears in crops on the trunk & spreads to the head & extremities.

The rash evolves from papules to vesicles, pustules, & finally, crusts.

Itching is a prominent symptom, especially when vesicles are present.

Varicella is mild in children but more severe in adults.

Varicella pneumonia & encephalitis are the major rare complications, occurring more often in adults.

Reye's syndrome, characterized by encephalopathy & liver degeneration, is associated with VZV & influenza B virus infection, especially in children given aspirin.



Photo Courtesy of CDC - Joe Miller

Early lesion



Photo Courtesy of CDC

Evolving lesion

Chicken Pox



Chicken Pox



Adults with chickenpox typically have a more complicated course with more widespread rash, prolonged fever, & a higher incidence of pneumonia.

Clinical Findings: Zoster

The occurrence of painful vesicles along the course of a sensory nerve of the head or trunk is the usual picture.

The pain can last for weeks, and post-zoster neuralgia (also known as post-herpetic neuralgia) can be debilitating.

In immunocompromised patients, life-threatening disseminated infections such as pneumonia can occur.

Shingles (Herpes Zoster)



Shingles starts with burning, tingling, or very sensitive skin. A rash of raised dots develops into painful blisters that last about 2 weeks.

Shingles often occurs on the trunk & buttocks, but can appear anywhere.

Most people recover, but pain, numbness, & itching linger for many & may last for months, years, or the rest of their lives.



Herpes Zoster



Ramsay Hunt syndrome, or herpes zoster oticus, is a reactivation of VZV that involves the facial nerve. Cranial nerves V, VI, VIII, and IX may also be involved.



Herpes zoster ophthalmicus is a latent VZV infection involving the ophthalmic division of the trigeminal nerve. It accounts for 10%-25% of all cases of shingles.

Laboratory Diagnosis

Although most diagnoses are made clinically, laboratory tests are available.

A **presumptive diagnosis** can be made by using the Tzanck smear. Multinucleated giant cells are seen in VZV as well as HSV lesions.

The **definitive diagnosis** is made by isolation of the virus in cell culture & identification with specific antiserum.

A rise in antibody titer can be used to diagnose varicella but is less useful in the diagnosis of zoster, since antibody is already present.

Treatment

Immunocompetent children

No antiviral therapy is necessary for chickenpox or zoster .

Immunocompetent adults

With either moderate or severe cases of chickenpox or zoster often are treated with acyclovir because it can reduce the duration & severity of symptoms.

Immunocompromised children & adults

With chickenpox, zoster, or disseminated disease should be treated with acyclovir

Disease caused by acyclovir-resistant strains of VZV

Can be treated with foscarnet .

Treatment

Two drugs similar to acyclovir

1. Famciclovir (Famvir)
2. Valacyclovir (Valtrex)

Can be used in patients with zoster to accelerate healing of the lesions.

None of these drugs can cure the latent state & none have any effect on post-zoster neuralgia.

Prevention Vaccines

There are two vaccines against VZV

1. Varivax to prevent varicella.

The varicella vaccine is recommended for children between the ages of 1 & 12 years

2. Zostavax to prevent zoster

The zoster vaccine is recommended for people older than 60 years & who have had varicella.

Both contain live, attenuated VZV, but the zoster vaccine contains 14 times more virus than the varicella vaccine.

The zoster vaccine is effective in preventing the symptoms of zoster, but does not eradicate the latent state of VZV.

Because these vaccines contain live virus, they should not be given to immunocompromised people or pregnant women.

Prevention Chemoprophylaxis

Acyclovir

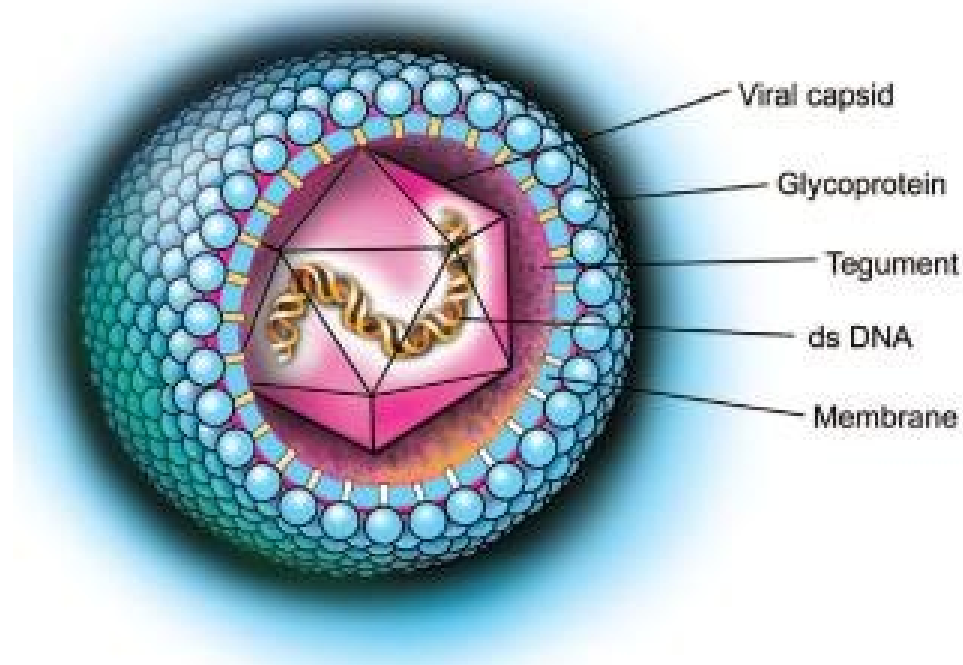
Is useful in preventing varicella & disseminated zoster in immunocompromised people exposed to the virus.

Prevention Immunoprophylaxis

Varicella-zoster immune globulin (VZIG)

Contains a high titer of antibody to the virus

Cytomegalovirus (CMV)



HCMV Human Cytomegalovirus

CMV

Important Properties

CMV is structurally & morphologically similar to other herpes.

viruses but is antigenically different.

It has a single serotype.

Humans are the natural hosts

Animal CMV strains do not infect humans.

Giant cells are formed, hence the name " cytomegalo."

CMV: Diseases

CMV causes cytomegalic inclusion disease (especially congenital abnormalities) in neonates.

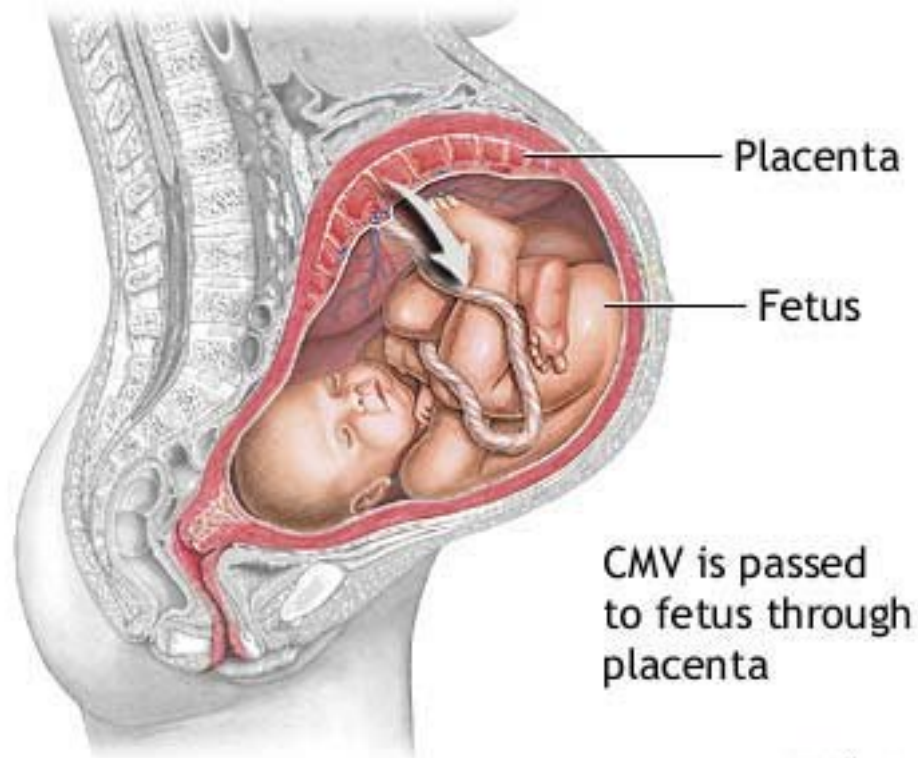
It is the most common cause of congenital abnormalities in the USA.

CMV is a very important cause of pneumonia & other diseases in immunocompromised patients such as recipients of bone marrow & solid organ transplants.

It also causes heterophil-negative mononucleosis in immunocompetent individuals.

CMV Transmission

Early in life it is transmitted across the placenta, within the birth canal, & quite commonly in breast milk.



CMV Transmission

In young children, its most common mode of transmission is via saliva.

Later in life it is transmitted sexually; it is present in both semen & cervical secretions.

It can also be transmitted during blood transfusions & organ transplants.

CMV Epidemiology

CMV infection occurs worldwide, & more than 80% of adults have antibody against this virus.

CMV Pathogenesis & Immunity

CMV has a specific mechanism of "immune evasion" that allows it to maintain the latent state for long periods.

Killing by cytotoxic T cells does not occur because

- a. In CMV-infected cells, assembly of the MHC class I–viral peptide complex is unstable, so viral antigens are not displayed on the cell surface.
- b. CMV encodes several micro RNAs, one of which binds to & prevents the translation of the cell's mRNA for the class-I MHC protein.

CMV infection causes an immunosuppressive effect by inhibiting T cells.

CMV Pathogenesis & Immunity

Host defenses against CMV infection include both circulating antibody & cell-mediated immunity.

Cellular immunity is more important, because its suppression can lead to systemic disease.

Clinical Findings

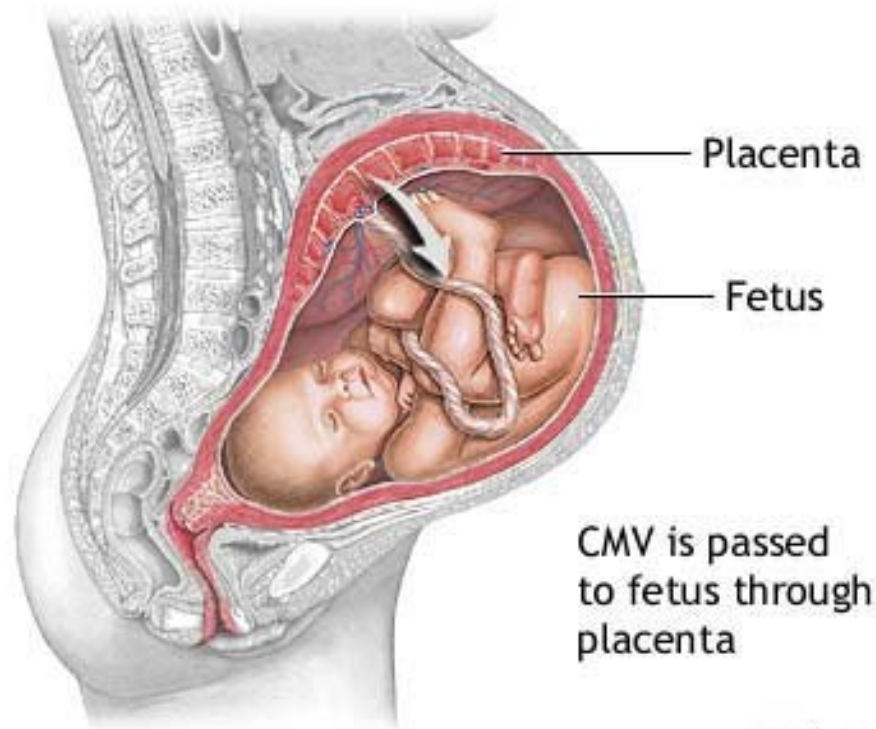
Congenital CMV Infection

Acquired CMV Infection

Clinical Findings

Congenital CMV Infection

1. Intrauterine death & abortion
2. Congenital cytomegalic inclusion disease in neonates



CMV Congenital CMV Infection

1. Intrauterine death & abortion

Infection of the fetus occurs mainly:

When a primary infection occurs in the pregnant woman, i.e.,

When she has no antibodies that will neutralize the virus before it can infect the fetus.

The fetus usually will not be infected if the pregnant woman has antibodies against the virus.

CMV Congenital CMV Infection

1. Intrauterine death & abortion

Congenital abnormalities are more common when a fetus is infected during the 1st trimester than later in gestation; Because the 1st trimester is when development of organs occurs & the death of any precursor cells can result in congenital defects.

Clinical Findings

Congenital CMV Infection

2. Congenital cytomegalic inclusion disease in neonates

Approximately 20% of infants infected with CMV during gestation show clinically apparent manifestations of cytomegalic inclusion disease such as

- a. Mental retardation (It is the most common cause).
- b. Microcephaly
- c. Seizures
- d. Deafness
- e. Jaundice & purpura.
- f. Hepatosplenomegaly (very common).

Infected infants can continue to excrete CMV, especially in the urine, for several years.

Clinical Findings

Acquired CMV Infection

Infections of children & adults are usually asymptomatic, except in immunocompromised individuals.

In immunocompetent adults

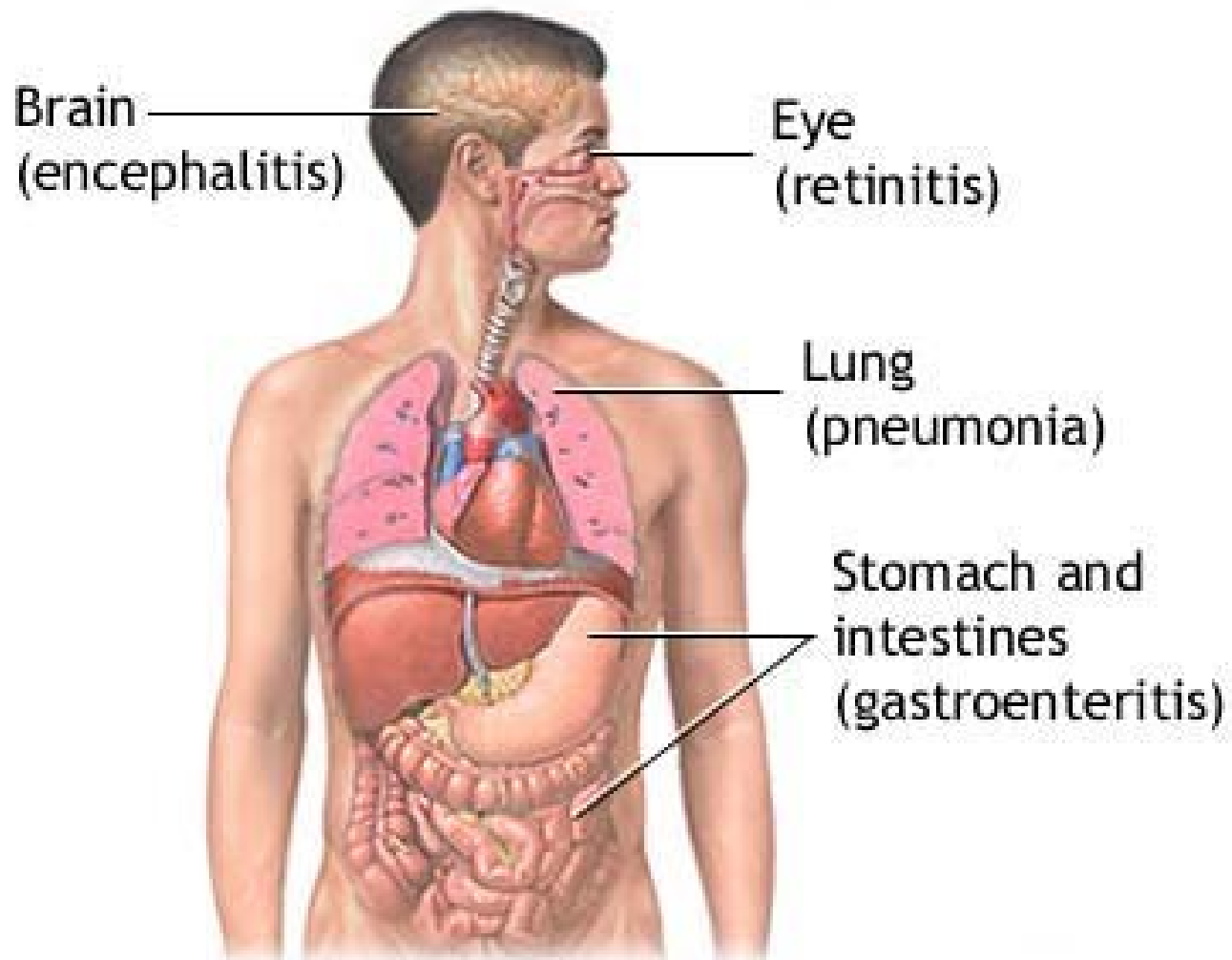
CMV can cause heterophil-negative mononucleosis characterized by:
Fever, lethargy, & the presence of abnormal lymphocytes in peripheral blood smears.

In immunosuppressed patients (renal & bone marrow transplants).
Systemic CMV infections, especially pneumonitis & hepatitis

In AIDS patients

- a. CMV commonly infects the intestinal tract & causes intractable colitis with diarrhea.
- b. CMV also causes retinitis in AIDS patients, which can lead to blindness.

CMV (cytomegalovirus)



CMV Latency

CMV enters a latent state in leukocytes & can be reactivated when CMI is decreased.

CMV can also persist in kidneys for years.

Reactivation of CMV from the latent state in cervical cells can result in

Infection of the newborn during passage through the birth canal.

Laboratory Diagnosis

1. Direct demonstration of virus structures

Examination of desquamated cells in urine, lymphocytes or tissue for the detection of:

Intranuclear inclusion bodies in giant cells (oval in shape (owl's eye) seen by light microscope

Viral DNA by DNA hybridization

2. Virus isolation

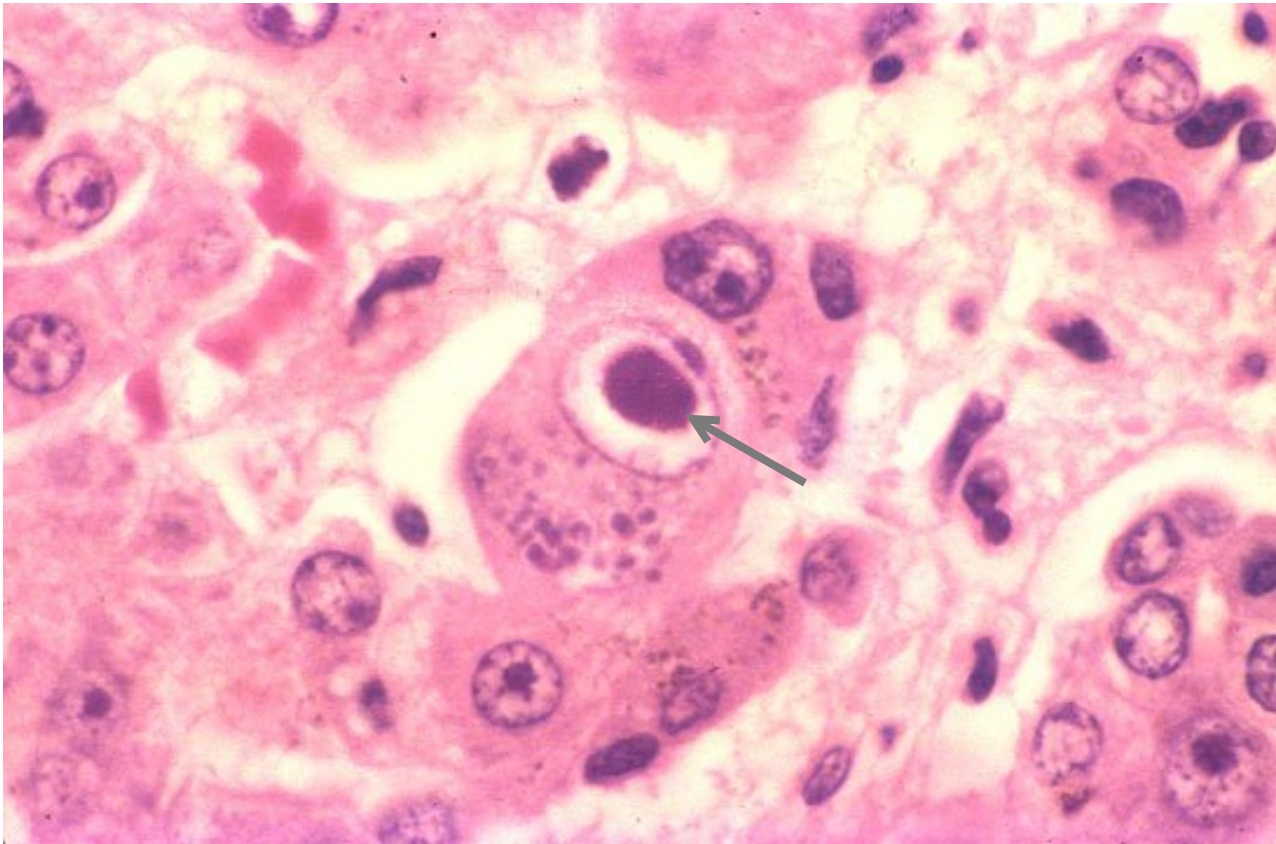
Specimen: throat washings or urine

Culture: human fibroblast cell

Detection: viral antigen in cell culture

3. Detection of specific antibodies

Anti CMV IgM by ELIZA or IFT



Cytomegalovirus—Owl's-eye inclusion body. Arrow points to an "owl's-eye" inclusion body in the nucleus of an infected cell

Laboratory Diagnosis

The preferred approach involves culturing in special tubes called shell vials coupled with the use of immunofluorescent antibody, which can make a diagnosis in 72 hours.



The virus obtained from the culture can be used to determine the drug susceptibility to ganciclovir.

Laboratory Diagnosis

A fourfold or greater rise in antibody titer is also diagnostic.

PCR-based assays for CMV DNA in tissue or body fluids, such as spinal fluid, & amniotic fluid are also very useful.

Treatment

Ganciclovir (Cytovene)

Is moderately effective in the treatment of CMV retinitis & pneumonia in patients with AIDS.

Valganciclovir,

Can be taken orally, is also effective against CMV retinitis.

CMV resistant to ganciclovir & valganciclovir have emerged, mostly due to mutations in the UL97 gene that encodes the phosphokinase.

Drug susceptibility testing can be done.

Treatment

Foscarnet (Foscavir)

Is also effective but causes more side effects.

Cidofovir (Vistide)

Is also useful in the treatment of CMV retinitis.

Fomivirsen (Vitravene)

Is an antisense DNA approved for the intraocular treatment of CMV retinitis. It is the first &, at present, the only antisense molecule to be approved for the treatment of human disease.

Unlike HSV & VZV, CMV is largely resistant to acyclovir.

Prevention

There is no vaccine.

Ganciclovir can suppress progressive retinitis in AIDS patients.

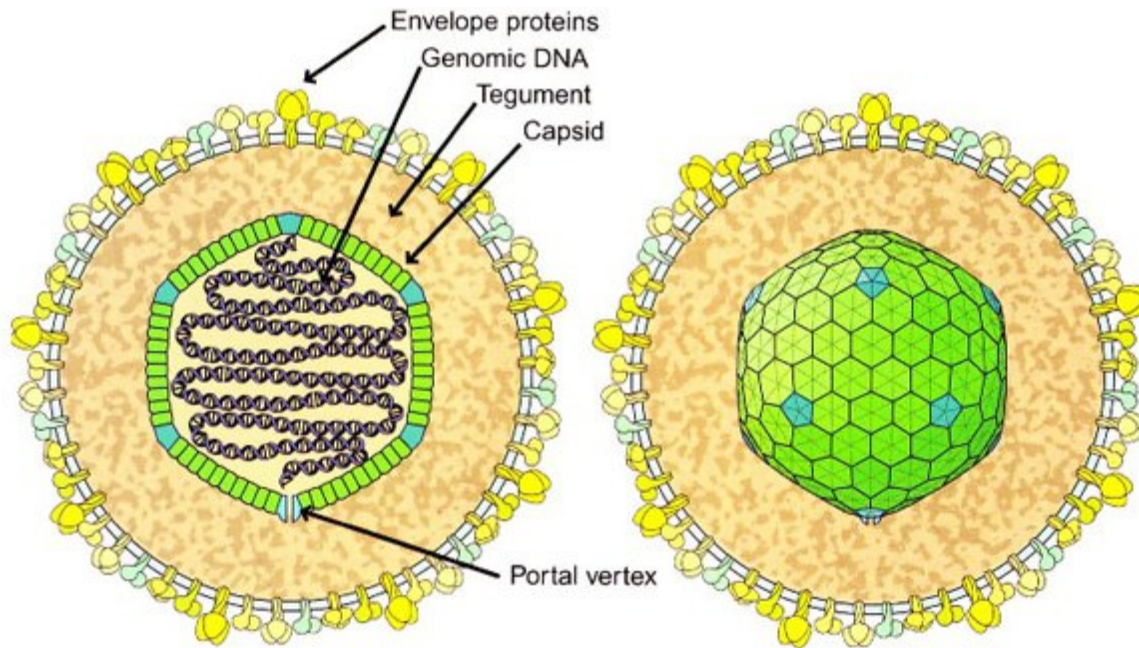
Infants with cytomegalic inclusion disease who are shedding virus in their urine should be kept isolated from other infants.

Blood for transfusion to newborns should be CMV antibody-negative.

Only organs from CMV antibody-negative donors should be transplanted to antibody-negative recipients.

A high-titer immune globulin preparation (CytoGam) is used to prevent disseminated CMV infections in organ transplant patients.

Epstein-Barr Virus (EBV)



EBV is structurally & morphologically similar to other herpesviruses but is antigenically different.

EBV Diseases

EBV causes

Infectious mononucleosis.

Associated with Burkitt's lymphoma

Associated with other B-cell lymphomas

Associated with nasopharyngeal carcinoma.

Causes hairy leukoplakia.

EBV Antigens

Viral capsid antigen (VCA)

It is the most important antigen because it is used most often in diagnostic tests.

The early antigens (EA)

Are produced prior to viral DNA synthesis

Nuclear antigen (EBNA)

Is located in the nucleus bound to chromosomes, are sometimes diagnostically helpful as well.

Lymphocyte-determined membrane antigen

Viral membrane antigen

Neutralizing activity is directed against the viral membrane antigen.

EBV Important Properties

Humans are the natural hosts.

EBV infects mainly lymphoid cells, primarily B lymphocytes.

In latently infected cells, EBV DNA is in the nucleus & is not integrated into cellular DNA.

Some, but not all, genes are transcribed, & only a subset of those are translated into protein.

EBV Transmission

kissing Disease

EBV is transmitted primarily by the exchange of saliva, e.g., during kissing. It is not highly contagious

The saliva of people with

Reactivation of a latent infection

Active infection can serve as a source of the virus.

In contrast to CMV, blood transmission of EBV is very rare.

EBV Epidemiology

EBV infection is one of the most common infections worldwide

More than 90% of adults in the USA have antibody.

Infection in the first few years of life is usually asymptomatic.

Early infection tends to occur in individuals in lower socioeconomic groups.

The frequency of clinically apparent infectious mononucleosis, is highest in those who are exposed to the virus later in life, e.g., college students.

EBV Pathogenesis

The infection first occurs in the oropharynx & then spreads to the blood, where it infects B lymphocytes.

Cytotoxic T lymphocytes react against the infected B cells.

The T cells are the "atypical lymphs" seen in the blood smear.

EBV remains latent within B lymphocytes.

EBV Pathogenesis & Immunity

Specific Antibodies

The immune response to EBV infection consists first of IgM antibody to the VCA.

IgG antibody to the VCA follows & persists for life.

The IgM response is therefore useful for diagnosing acute infection

The IgG response is best for revealing prior infection.

Lifetime immunity against second episodes of infectious mononucleosis is based on antibody to the viral membrane antigen.

EBV Pathogenesis & Immunity

Nonspecific Antibodies

1. Heterophil antibodies are found.

The term "heterophil" refers to antibodies that are detected by tests using antigens different from the antigens that induced them.

The heterophil antibodies formed in infectious mononucleosis agglutinate sheep or horse red blood cells in the laboratory.

2. Cross-reacting Forssman antibodies in human serum are removed by adsorption with guinea pig kidney extract prior to agglutination.

EBV Pathogenesis & Immunity

These antibodies do not react with any component of EBV.

It seems likely that EBV infection modifies a cell membrane constituent such that it becomes antigenic & induces the heterophil antibody.

Heterophil antibodies usually disappear within 6 months after recovery.

These antibodies are not specific for EBV infection & are also seen in individuals with

Hepatitis B

Serum sickness.

EBV Clinical Findings

Infectious mononucleosis is characterized primarily by

IP ranges from 4 to 6 weeks

Fever

Sore throat

Lymphadenopathy

Splenomegaly

Anorexia & lethargy are prominent.

Hepatitis is frequent

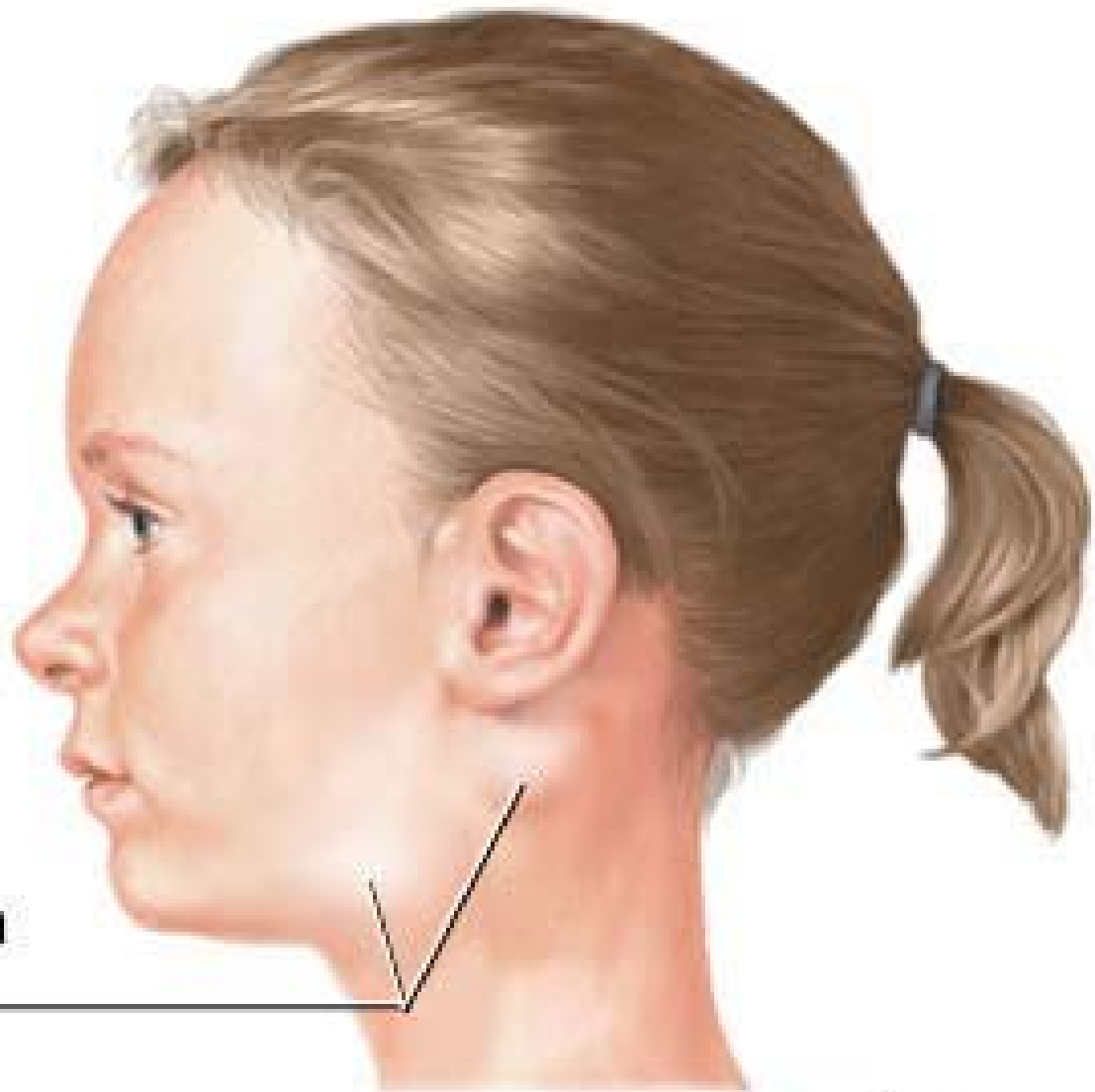
Encephalitis occurs in some patients.

Splenic rupture, associated with contact sports such as football, is a feared but rare complication of the splenomegaly.

Spontaneous recovery usually occurs in 2 to 3 weeks.

Mononucleosis causes:

- Fever
- Fatigue
- Sore throat
- Swollen lymph glands





Mononucleosis - mouth



A very reddened throat and tonsils & swollen lymph nodes in the neck.

The tonsils have a whitish coating in at least one-third of the cases

EBV Chronic fatigue syndrome

A feeling of fatigue or tiredness may persist for months following the acute phase of the illness.

It is recommended that patients with mono avoid participation in any contact sports during the first six to eight weeks following the onset to prevent trauma to the enlarged spleen.

Patients can continue to have virus particles present in their saliva for as long as 18 months after the initial infection.

EBV Clinical Findings

EBV infection & X-linked lymphoproliferative syndrome

EBV causes a severe, often fatal, progressive form of infectious mononucleosis that occurs in children with an inherited immunodeficiency called X-linked lymphoproliferative syndrome.

The mutated gene encodes a signal transduction protein required for both T-cell & NK-cell function.

The mortality rate is 75% by age 10.

Bone marrow or cord blood transplants may cure the underlying immunodeficiency.

EBV Clinical Findings

EBV causes hairy leukoplakia (nonmalignant)

A whitish lesion with an irregular "hairy" surface on the lateral side of the tongue.

It occurs in immunocompromised individuals, especially AIDS patients.

EBV Clinical Findings

EBV-associated disease is Posttransplant lymphoproliferative disorder (PTLD) (nonmalignant).

"Associated" refers to the observation that EBV infection is the initiating event that causes the cells to divide.

It requires additional steps for malignant transformation to occur.

Reduced CMI predisposes to the uncontrolled growth of the EBV infected cells.

The most common form of PTLD is a B-cell lymphoma.

PTLD occurs following both bone marrow transplants & solid organ transplants.

The main predisposing factor to PTLD is the immunosuppression required to prevent rejection of the graft.

The lymphoma will regress if the degree of immunosuppression is reduced.

EBV Clinical Findings

EBV infection is associated with several cancers

- Burkitt's lymphoma,

- Some forms of Hodgkin's lymphoma

- Nasopharyngeal carcinoma.

- Thymic carcinoma.

EBV

EBV infection is associated with cancers of lymphoid origin:

1. Burkitt's lymphoma in African children,
2. Other B-cell lymphomas
3. Nasopharyngeal carcinoma in the Chinese population
4. Thymic carcinoma in the USA

EBV

The initial evidence of an association of EBV infection with Burkitt's lymphoma was the production of EBV by the lymphoma cells in culture.

This was how EBV was discovered by Epstein and Barr in 1964. Additional evidence includes the finding of EBV DNA & EBNA in the tumor cells.

EBV DNA & antigens are found in nasopharyngeal & thymic carcinoma cells also.

EBV can induce malignant transformation in B lymphocytes in vitro. The role of EBV in carcinogenesis is unclear.



Burkitt's lymphoma in African child

EBV Laboratory Diagnosis

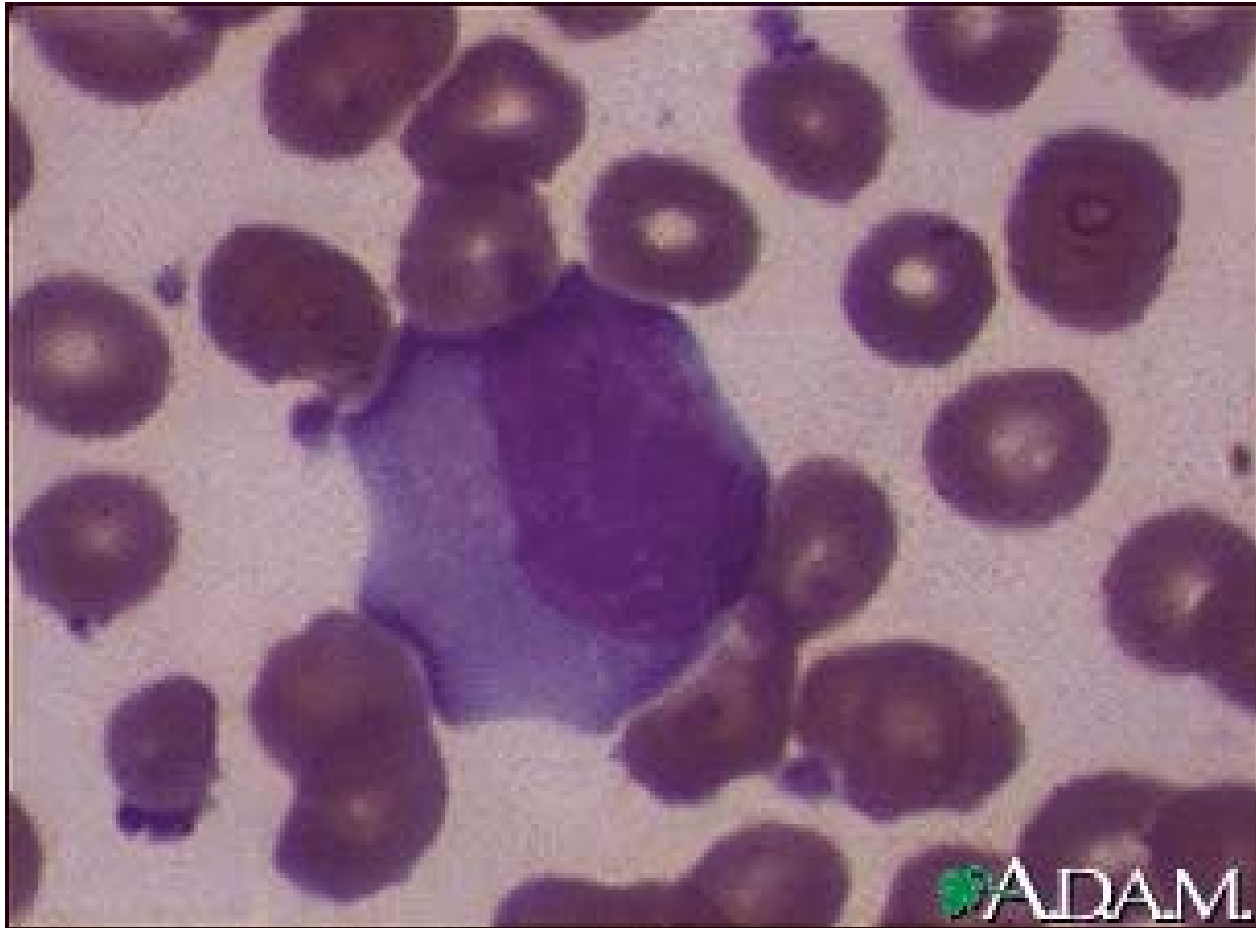
hematologic approach

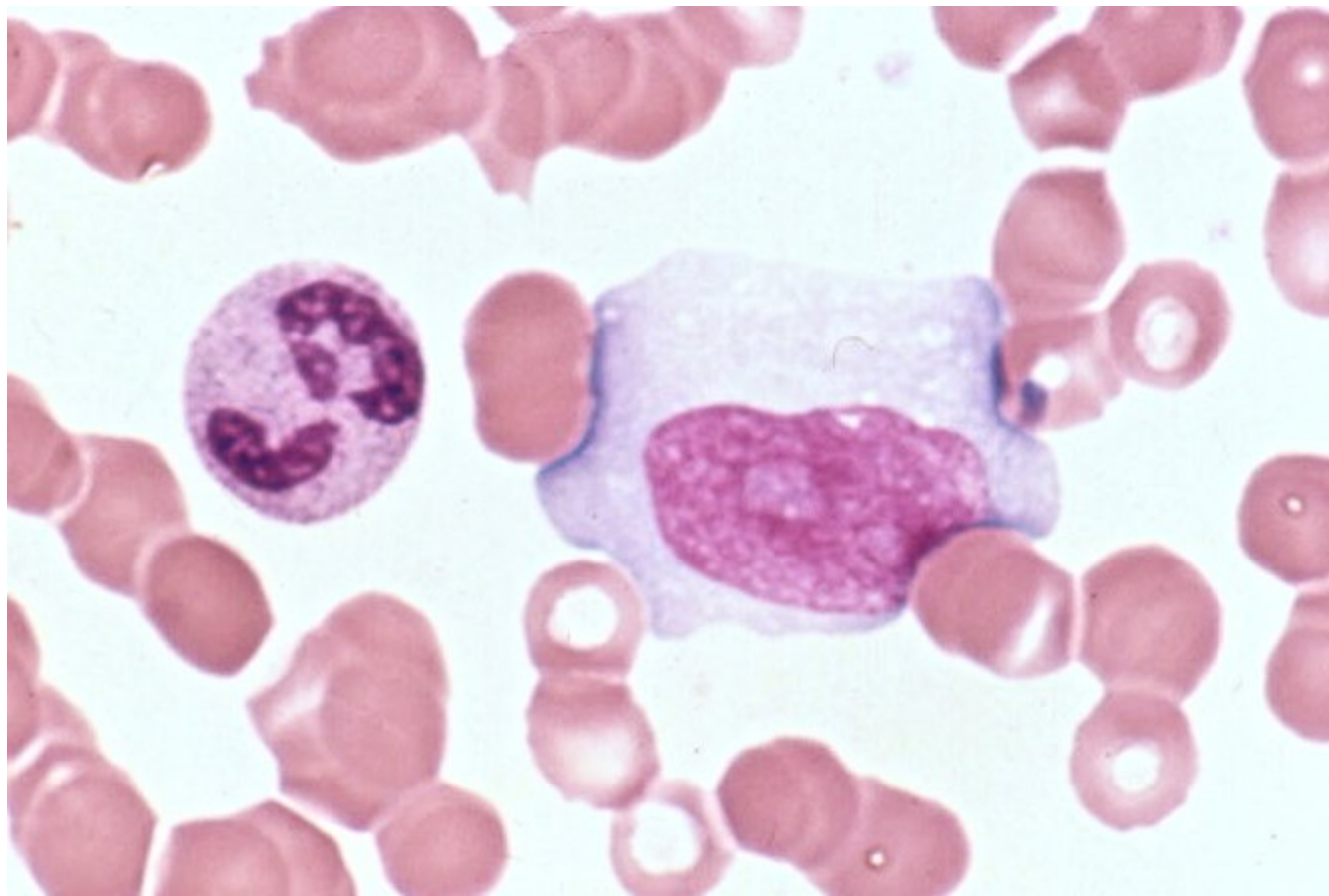
The white cell count is usually moderately elevated, usually somewhere in the range of 16-20. It rarely goes above 35 .

Absolute lymphocytosis occurs & as many as 30% abnormal lymphocytes are seen on a smear.

These atypical lymphs are large & have a lobulated nucleus & a vacuolated, basophilic cytoplasm.

They are cytotoxic T cells that are reacting against the EBV-infected B cells.





EBV Laboratory Diagnosis

immunologic approach

There are two types of serologic tests:

(a) Heterophil antibody test

Is useful for the early diagnosis of infectious mononucleosis because it is usually positive by week 2 of illness.

However, because the antibody titer declines after recovery, it is not useful for detection of prior infection.

The Monospot test is often used to detect the heterophil antibody; it is more sensitive, more specific, & less expensive than the tube agglutination test.

EBV Laboratory Diagnosis

immunologic approach

b) The EBV-specific antibody tests

Are used primarily in diagnostically difficult cases.

IgM VCA antibody response can be used to detect early illness;

IgG VCA antibody response can be used to detect prior infection.

In certain instances, antibodies to EA & EBNA can be useful diagnostically.

VCA: Viral capsid antigen

EA: Early antigens

EBNA: Nuclear antigen

EBV Treatment

No antiviral therapy is necessary for uncomplicated infectious mononucleosis.

Acyclovir has little activity against EBV, but administration of high doses may be useful in life-threatening EBV infections.

EBV prevention

There is no EBV vaccine.

Human herpes virus 6

Roseola infantum

Roseola infantum is a common childhood disease. The cause is primary infection with **human herpesvirus 6 (HHV-6)** .

The classic presentation of roseola infantum is a 9- to the 12-month-old infant who acutely develops a high fever and often a febrile seizure. After 3 days, a rapid defervescence occurs, and a morbilliform rash appears (see the image below).



HHV 6

Like other herpes viruses, HHV-6 then remains latent in most patients who are immunocompetent. Although the clinical disease is uncommon in patients who are immunocompetent,

HHV-6 is a major cause of morbidity & mortality in patients who are immunosuppressed, particularly in patients with AIDS & in those who are transplant recipients (eg, liver transplantation

Human Herpesvirus 7

HHV-7 primary infection occurs early in life & manifests as exanthema subitum, or other febrile illnesses mimicking measles & rubella.

HHV-7 has to be considered as a causative agent in a variety of macular- papular rashes in children.

HHV-7 was found in some cases of other inflammatory skin disorders, such as psoriasis.

Human Herpesvirus 7

There are controversial data on the detection of HHV-7 in pityriasis rosea, but so far there is not enough evidence for a pathogenetic association of HHV-7 with this exanthematic skin disease.

Although HHV-7 can be found in some cases of Hodgkin's disease, there are no data supporting a direct causative role in this lymphoma type nor in other nodal or primary cutaneous lymphomas.

Human Herpesvirus 7

In various epidemiologic forms of Kaposi's sarcoma, infection of monocytic cells with HHV-7 was demonstrated, which may indirectly influence tumor biology.

In the context of immunosuppression, HHV-7 has recently been identified as an emerging pathogen in transplant recipients & may exacerbate graft rejection in renal transplant recipients.

The ability of HHV-7 to induce cytokine production in infected cells could make HHV-7 an important pathogenetic co-factor in inflammatory and neoplastic disorders .

Human Herpesvirus 8

(Kaposi's Sarcoma–Associated Herpesvirus)



Human Herpesvirus 8

Transmission

Transmission of HHV-8 is primarily sexually

It is also transmitted in transplanted organs such as kidneys & appears to be the cause of transplantation-associated KS.

DNA of HHV-8 is found in the cells of transplantation-associated KS but not in the cells of other transplantation-associated cancers.

Human Herpesvirus 8

In 1994, it was reported that a new herpesvirus, now known as HHV-8, or Kaposi's sarcoma–associated herpesvirus (KSHV), may be the cause of Kaposi's sarcoma (KS), the most common cancer in patients with AIDS.

The idea that a virus other than HIV is the cause of KS arose from epidemiologic data that showed:

- KS was common in patients who acquired HIV sexually but

- Rare in patients who acquired HIV via blood transfusion.

- A second virus transmitted sexually appeared likely to be the cause.

Human Herpesvirus 8

Laboratory diagnosis

Diagnosis of KS is often made by biopsy of the skin lesions.

HHV-8 DNA & RNA are present in most spindle cells, but that analysis is not usually done.

Virus is not grown in culture.

Human Herpesvirus 8

treatment

Surgical excision

Radiation

Systemic drugs, such as alpha interferon or vinblastine, can be used.

No specific antiviral therapy

No vaccine against HHV-8.