Medical Virology for 2nd Year M.D. Students

Herpesviruses
Part II

University of Jordan
School of Medicine
Section of Microbiology & Immunology
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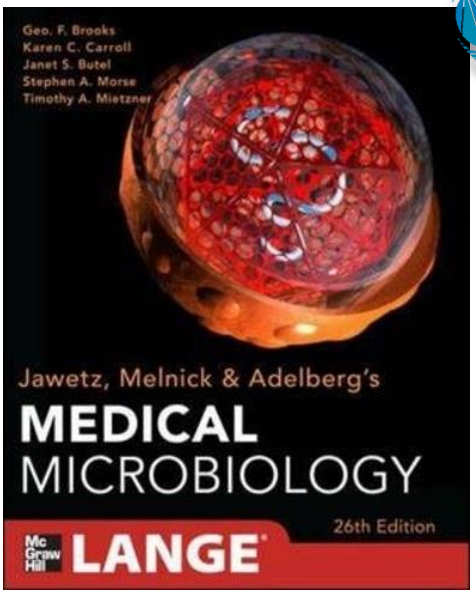
Important Note:

The Required Material for the Exams:

Section IV (Virology) in the provided textbook: Jawetz Medical Microbiology

References

- Jawetz, Melnick & Adelberg's Medical Microbiology. 26th edition. New York : London: McGraw-Hill Medical ; McGraw-Hill, 2013.
- Recent original and review articles in high impact and well renowned scientific journals



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Varicella Zoster Virus (VZV)

- Varicella (chickenpox) is a mild, highly contagious disease, characterized clinically by a generalized vesicular eruption of the skin and mucous membranes.
- The disease may be severe in adults and in immunocompromised individuals.
- Zoster (shingles) is a sporadic, incapacitating disease of elderly or immunocompromised individuals that is characterized by pain and a rash limited in distribution to the skin innervated by a single sensory ganglion.
- The lesions are similar to those of varicella. zoster is the response of the partially immune host to reactivation of varicella virus present in latent form in neurons in sensory ganglia.

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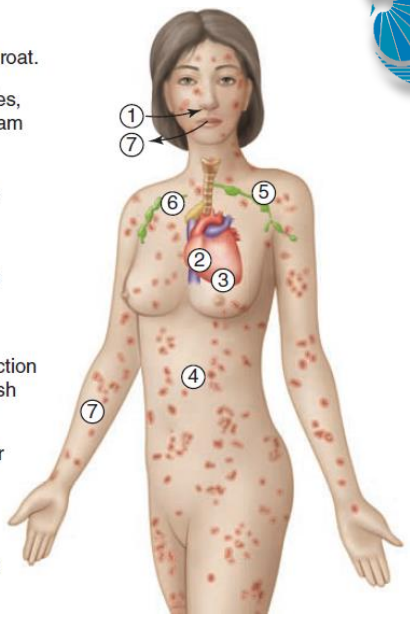
The pathogenesis of primary infection with VZV

1. Varicella-zoster virus is inhaled; infects mucosal cells in nose and throat.
2. The virus infects nearby lymph nodes, replicates, and enters the bloodstream (primary viremia).
3. Infection of other body cells occurs, with replication in liver and spleen, resulting in secondary viremia.
4. The virus causes successive crops of skin lesions, which evolve into blisters and crusts.
5. Immune system eliminates the infection except for some virions that establish latent infections inside nerve cells.
6. If immunity wanes with age or other reason, the virus persisting in the nerve ganglia can infect the skin, causing herpes zoster.
7. Transmission to others occurs from respiratory secretions and skin.



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The pathogenesis of primary infection with VZV

- The route of infection is the mucosa of the upper respiratory tract or the conjunctiva
- Local replication in the LNs is followed by primary and secondary viremia
- Infected mononuclear cells transports virus to the skin, where the typical rash develops
- VZV replication and spread are limited by host humoral and cellular immune responses. IFN is likely involved also.
- It has been shown that a VZV-encoded protein, **ORF61**, antagonizes the β-interferon pathway. This presumably contributes to the pathogenesis of viral infection.

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0022-538X/11/$12.00 doi:10.1128/JVI.05098-11

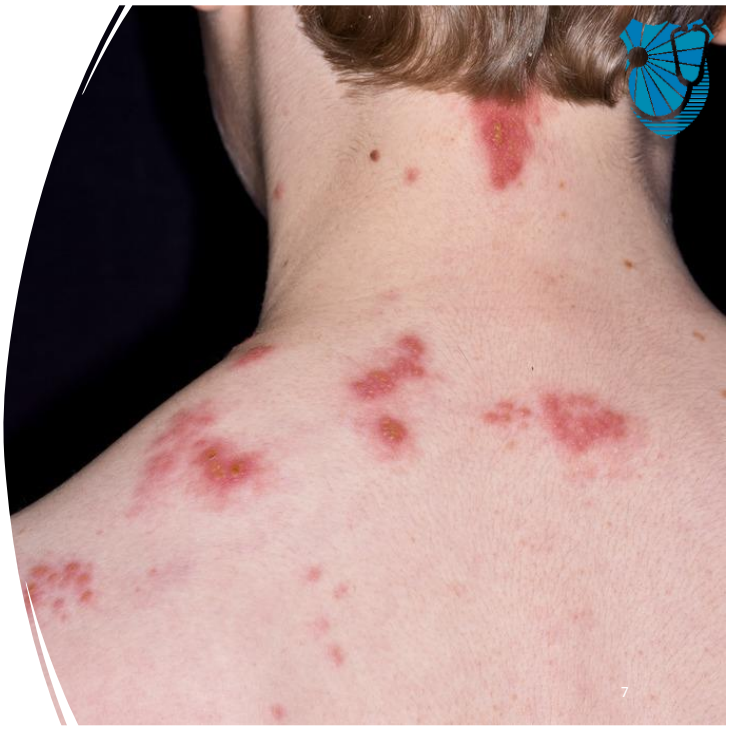
Varicella-Zoster Virus Immediate-Early Protein ORF61 Abrogates the IRF3-Mediated Innate Immune Response through Degradation of Activated IRF3[▽]

Huifang Zhu,[1]# Chunfu Zheng,[1]#* Junji Xing,[1] Shuai Wang,[1] Shuping Li,[2] Rongtuan Lin,[3] and Karen L. Mossman[4]

The pathogenesis of primary infection with VZV

The pathogenesis of zoster

- The skin lesions of zoster are histopathologically identical to those of varicella.
- There is also an acute inflammation of the sensory nerves and ganglia.
- Often only a single ganglion may be involved.
- As a rule, the distribution of lesions in the skin corresponds closely to the areas of innervation from an individual dorsal root ganglion.



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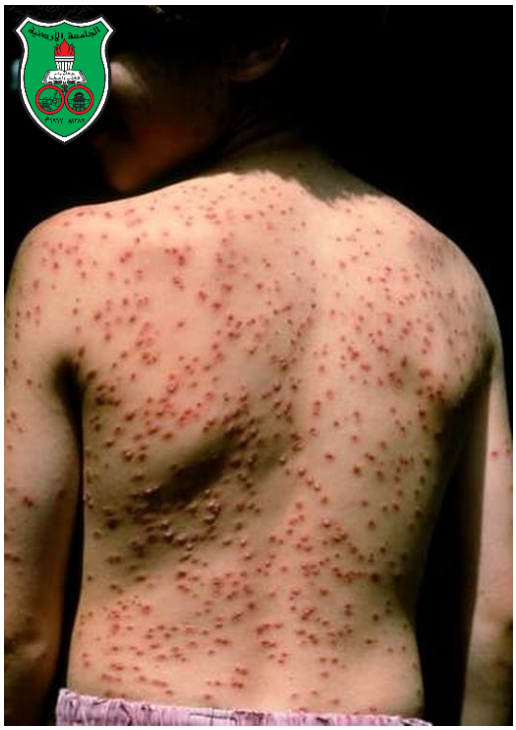

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Varicella – Clinical Findings

- Subclinical varicella is unusual.
- The incubation period of typical disease is 10–21 days. Malaise and fever are the earliest symptoms, soon followed by the rash, first on the trunk and then on the face, the limbs, and the buccal and pharyngeal mucosa in the mouth. Successive fresh vesicles appear in crops, so that all stages of macules, papules, vesicles and crusts may be seen at one time.
- The rash lasts 5 days, and most children develop several hundred skin lesions.

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Varicella – Clinical Findings

- Complications are rare in normal children, and the mortality rate is very low (1 per 100,000 cases among children age 1 through 14 years, 6 per 100,000 cases among persons age 15 through 19 years, and 21 per 100,000 cases among adults).
- Encephalitis does occur in rare cases (1 per 50,000 cases of varicella in unvaccinated children) and can be life threatening. Survivors of varicella encephalitis may be left with permanent sequelae.
- In neonatal varicella, the infection is contracted from the mother just before or after birth but without sufficient immune response to modify the disease. Virus is often widely disseminated and may prove fatal.

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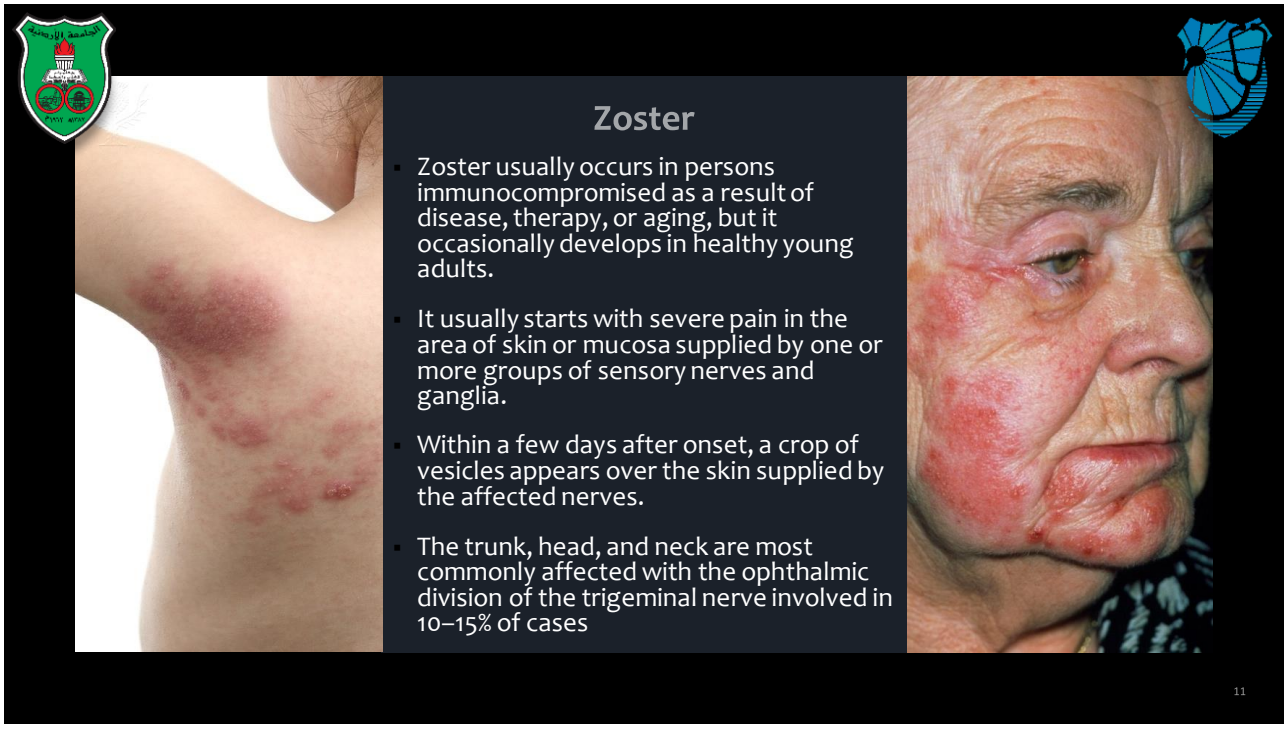
Varicella – Clinical Findings

- Varicella pneumonia is rare in healthy children but is the most common complication in neonates, adults, and immunocompromised patients. It is responsible for many varicella-related deaths.
- Immunocompromised patients are at increased risk of complications of varicella.
- DIC may occur that is rapidly fatal.
- Children with leukemia are especially prone to developing severe, disseminated varicella-zoster virus disease.


Zoster
Zoster usually occurs in persons immunocompromised as a result of disease, therapy, or aging, but it occasionally develops in healthy young adults.
It usually starts with severe pain in the area of skin or mucosa supplied by one or more groups of sensory nerves and ganglia.
Within a few days after onset, a crop of vesicles appears over the skin supplied by the affected nerves.
The trunk, head, and neck are most commonly affected with the ophthalmic division of the trigeminal nerve involved in 10–15% of cases
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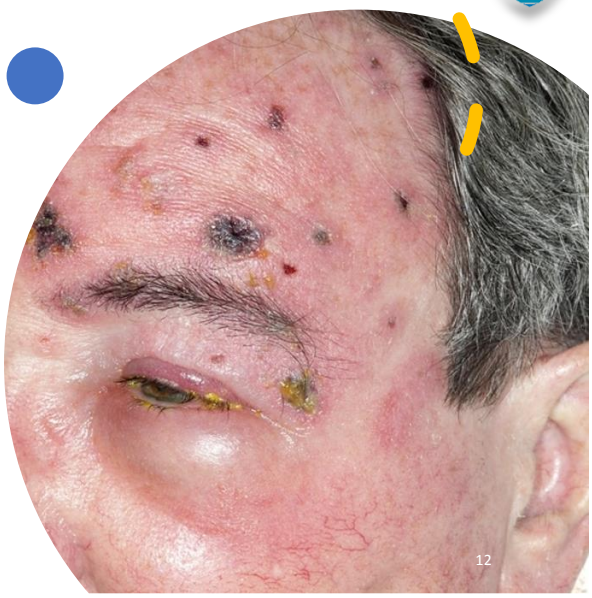
Zoster – Clinical Findings

- The most common complication of zoster in elderly adults is postherpetic neuralgia—protracted pain that may continue for months.
- It is especially common after ophthalmic zoster.
- Visceral disease, especially pneumonia, is responsible for deaths that occur in immunosuppressed patients with zoster (<1% of patients).
- Varicella zoster central nervous system disease, most frequently meningitis, often presents without a typical zoster rash.



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VZV – Immunity

- Previous infection with varicella is believed to confer lifelong immunity to varicella.
- Antibodies induced by varicella vaccine persist for at least 20 years. Zoster occurs in the presence of neutralizing antibody to varicella.
- Increases in varicella antibody titer may occur in persons with HSV infections.
- The development of VZV-specific cell-mediated immunity is important in recovery from both varicella and zoster.
- Appearance of local interferon may also contribute to recovery. VZV encodes means of evading host immune responses (e.g. it downregulates MHC class I and II antigen expression and the β-interferon pathway).

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0022-538X/01/$04.00+0 DOI: 10.1128/JVI.75.10.4878–4888.2001

Varicella-Zoster Virus Retains Major Histocompatibility Complex Class I Proteins in the Golgi Compartment of Infected Cells

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Centre for Virus Research, Westmead Millennium Institute of Health Research, University of Sydney, Sydney, New South Wales, Australia[1]; Departments of Pediatrics and Microbiology & Immunology, Stanford University School of Medicine, Stanford, California[2]; and Department of Pathology, Harvard Medical School, Boston, Massachusetts[3]

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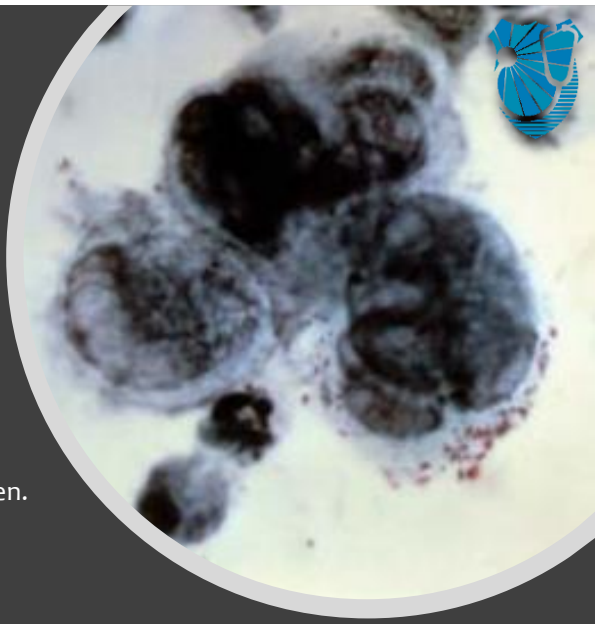
VZV – Laboratory Diagnosis

- Rapid diagnostic procedures are clinically useful for VZV.
- PCR assays are preferred for sensitivity, specificity, and rapidity. VZV DNA can be detected in saliva in many patients, including those with zoster without rash.
- Viral DNA can be detected in vesicle fluid, skin scrapings, and biopsy material.
- In stained smears of scrapings or swabs of the base of vesicles (Tzanck smear), multinucleated giant cells are seen.
- Intracellular viral antigens can be demonstrated by IF staining of similar smears. Herpesviruses can be differentiated from poxviruses by the morphologic appearance of particles in vesicular fluids examined by EM.



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VZV – Laboratory Diagnosis

- Virus can be isolated from vesicle fluid early in the course of illness using cultures of human cells in 3–7 days.
- VZV in vesicle fluid is very labile, and cell cultures should be inoculated promptly.
- A rise in specific antibody titer can be detected in the patient's serum by various tests, including fluorescent antibody and enzyme immunoassay.
- The choice of assay to use depends on the purpose of the test and the laboratory facilities available.
- Cell-mediated immunity is important but is difficult to demonstrate.

VZV – Epidemiology

- Varicella and zoster occur worldwide.
- Varicella is a common epidemic disease of childhood. Adult cases do occur.
- It is much more common in winter and spring than in summer in temperate climates.
- Zoster occurs sporadically, chiefly in adults and without seasonal prevalence. About 10–20% of adults will experience at least one zoster attack during their lifetime, usually after the age of 50 years.
- A live attenuated varicella vaccine is available; however, varicella outbreaks continue to occur among school children because some children are unvaccinated and a single dose of the vaccine is 80–85% effective in vaccinated persons.

SHINGRIX
(HERPES ZOSTER VACCINE RECOMBINANT, ADJUVANTED)

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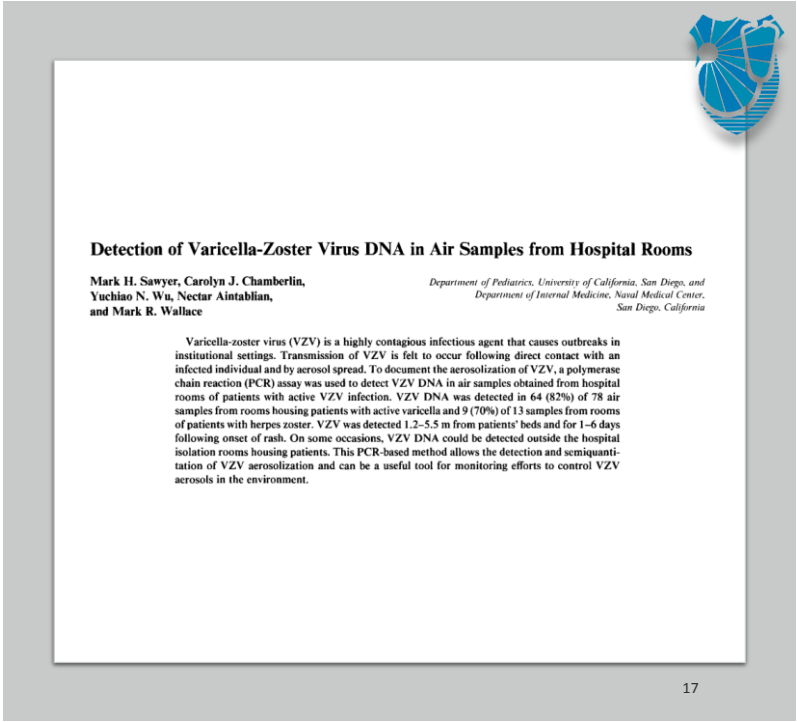
VZV – Epidemiology

- Varicella spreads readily by airborne droplets and by direct contact.
- A varicella patient is infectious from shortly before the appearance of rash to the first few days of rash.
- Contact infection is less common in zoster.
- Zoster patients can be the source of varicella in susceptible children.
- VZV DNA has been detected using a PCR amplification method in air samples from hospital rooms of patients with active varicella (82%) and zoster (70%) infections.



Detection of Varicella-Zoster Virus DNA in Air Samples from Hospital Rooms

Mark H. Sawyer, Carolyn J. Chamberlin, Yuchiao N. Wu, Nectar Aintablian, and Mark R. Wallace

Department of Pediatrics, University of California, San Diego, and Department of Internal Medicine, Naval Medical Center, San Diego, California

Varicella-zoster virus (VZV) is a highly contagious infectious agent that causes outbreaks in institutional settings. Transmission of VZV is felt to occur following direct contact with an infected individual and by aerosol spread. To document the aerosolization of VZV, a polymerase chain reaction (PCR) assay was used to detect VZV DNA in air samples obtained from hospital rooms of patients with active VZV infection. VZV DNA was detected in 64 (82%) of 78 air samples from rooms housing patients with active varicella and 9 (70%) of 13 samples from rooms of patients with herpes zoster. VZV was detected 1.2–5.5 m from patients' beds and for 1–6 days following onset of rash. On some occasions, VZV DNA could be detected outside the hospital isolation rooms housing patients. This PCR-based method allows the detection and semiquantitation of VZV aerosolization and can be a useful tool for monitoring efforts to control VZV aerosols in the environment.

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VZV – Treatment

- Varicella in normal children is a mild disease and requires no treatment.
- Neonates and immunocompromised patients with severe infections should be treated.
- VZV Ig can be used to prevent the development of the illness in patients exposed to varicella. It has no therapeutic value after varicella has started.

- Standard Ig is without value because of its low titer of varicella antibodies.
- Effective antivirals for varicella, include acyclovir, valacyclovir, famciclovir, and foscarnet.
- Acyclovir can prevent the development of systemic disease in varicella-infected immunosuppressed patients and can halt the progression of zoster in adults.
- Acyclovir does not appear to prevent postherpetic neuralgia.

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VZV – Prevention and Control

Vaccine-related varicella-zoster rash in a hospitalized immunocompetent patient

Paul Bernstein, RN, BSN,[a] Yoko Furuya, MD,[b] Sharon Steinberg,[c] Brian Scully, MB,[b] Philip LaRussa, MD,[c] and Anne A. Gershon, MD[c]
New York, New York

- A live attenuated varicella vaccine was approved in 1995 for general use in the US.
- A similar vaccine has been used successfully in Japan for about 30 years.
- A single dose of the vaccine is highly effective at inducing protection from varicella in children (80–85% effective) but less so in adults (70%).
- The vaccine is about 95% effective in preventing severe disease.
- About 5% of individuals develop a mild vaccine-associated rash 1 month after immunization.

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VZV – Prevention and Control

- In 2006, two doses of the vaccine were recommended for children, and that schedule is reportedly more than 98% effective in preventing varicella disease.
- Transmission of the vaccine virus is rare but can occur when the vaccinee has a rash.
- The duration of protective immunity induced by the vaccine is unknown but is probably long term.
- Varicella infections can occur in vaccinated persons, but they are usually mild illnesses.
- A zoster (shingles) vaccine was licensed in 2006. It has been shown to be effective in older adults at reducing both the frequency of outbreaks of zoster and the severity of disease that does occur.
- The zoster vaccine is recommended for those with chronic medical conditions and for persons older than 60 years of age.

Cytomegalovirus (CMV)

- CMVs are the agents of the most common congenital infection.
- Cytomegalic inclusion disease is a generalized infection of infants caused by intrauterine or early postnatal infection with the CMVs. The name for the classic cytomegalic inclusion disease derives from the propensity for massive enlargement of CMV-infected cells.
- CMV poses an important public health problem because of its high frequency of congenital infections, which may lead to severe congenital anomalies.
- Inapparent infection is common during childhood and adolescence.
- Severe CMV infections are frequently found in adults who are immunosuppressed.

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Properties of CMV

- CMV has the largest genetic content of the human herpesviruses. Its DNA genome (240 kbp).
- Many proteins are encoded by the virus (~200). One, a cell surface glycoprotein, acts as an Fc receptor that can non-specifically bind the Fc portion of immunoglobulins. This may help infected cells evade immune elimination by providing a protective coating of irrelevant host immunoglobulins.
- The major immediate-early promoter-enhancer of CMV is one of the strongest known enhancers because of the concentration of binding sites for cellular transcription factors.

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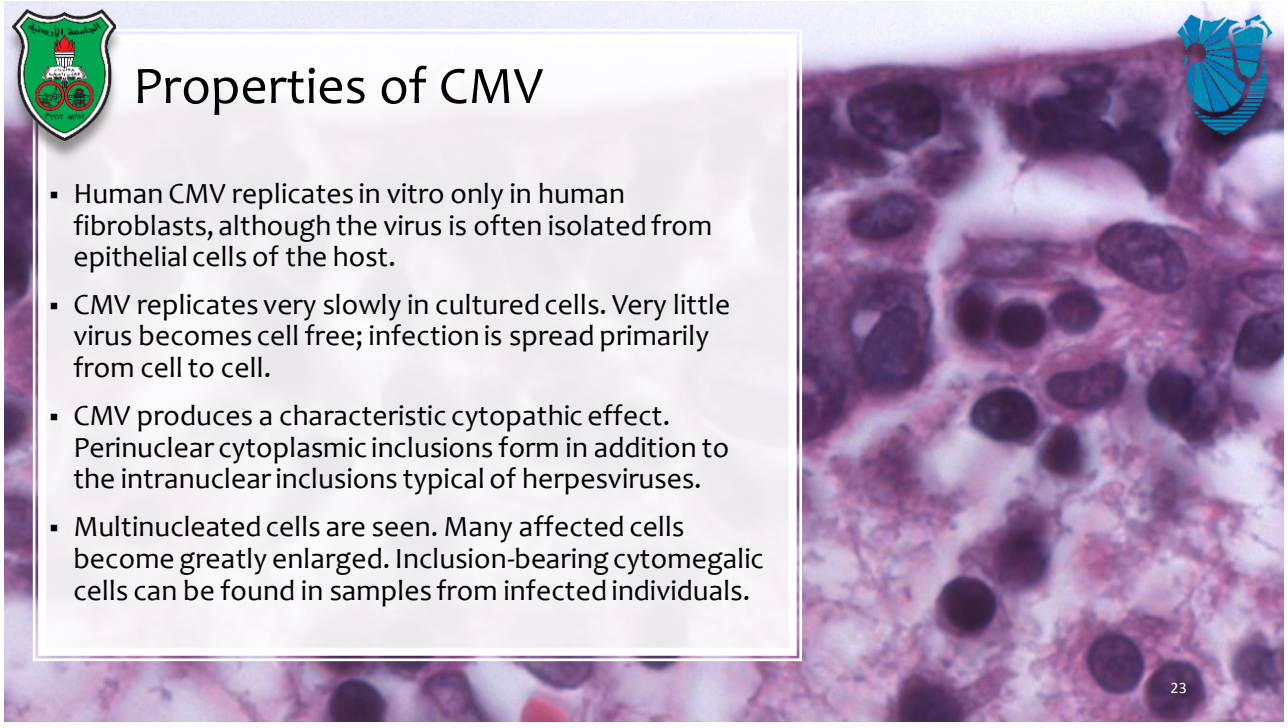
Properties of CMV
▪ Human CMV replicates in vitro only in human fibroblasts, although the virus is often isolated from epithelial cells of the host.
▪ CMV replicates very slowly in cultured cells. Very little virus becomes cell free; infection is spread primarily from cell to cell.
▪ CMV produces a characteristic cytopathic effect. Perinuclear cytoplasmic inclusions form in addition to the intranuclear inclusions typical of herpesviruses.
▪ Multinucleated cells are seen. Many affected cells become greatly enlarged. Inclusion-bearing cytomegalic cells can be found in samples from infected individuals.
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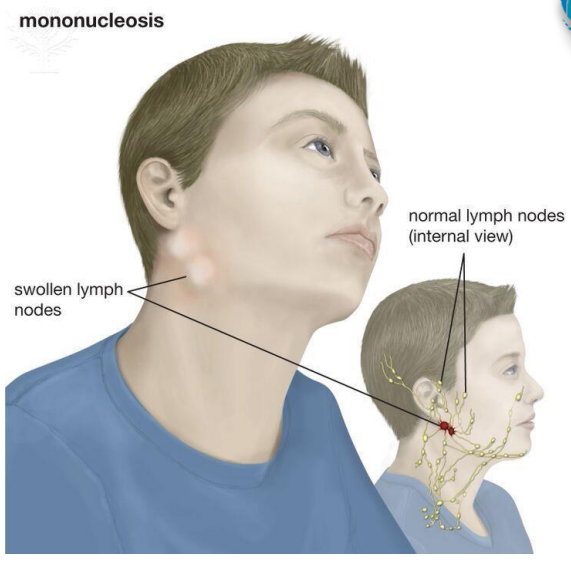
CMV - Pathogenesis and Pathology in Normal Host

- CMV is transmitted by close contact.
- There is a 4- to 8-week incubation period in normal older children and adults after viral exposure.
- The virus causes a systemic infection; it has been isolated from lung, liver, esophagus, colon, kidneys, monocytes, and T and B lymphocytes.
- The disease is IM-like syndrome, although most CMV infections are subclinical.
- CMV establishes lifelong latent infections. Virus can be shed intermittently from the pharynx and in the urine for months to years after primary infection.



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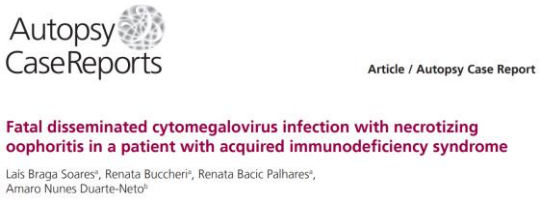
CMV - Pathogenesis and Pathology in Normal Host, Immunocompromised Host

- Prolonged CMV infection of the kidney and salivary glands is common and probably chronic.
- Cell-mediated immunity is depressed with primary infections, and this may contribute to the persistence of viral infection. It may take several months for cellular responses to recover.
- Primary CMV infections in immunosuppressed hosts are much more severe than in normal hosts. Viral excretion is increased and prolonged, and the infection is more likely to become disseminated.
- Pneumonia is the most common complication.
- Although usually less severe, reactivated infections may be as virulent as primary infections.


Autopsy Case Reports

Article / Autopsy Case Report

Fatal disseminated cytomegalovirus infection with necrotizing oophoritis in a patient with acquired immunodeficiency syndrome

Laís Braga Soares[a], Renata Buccheri[a], Renata Bacic Palhares[a], Amaro Nunes Duarte-Neto[b]

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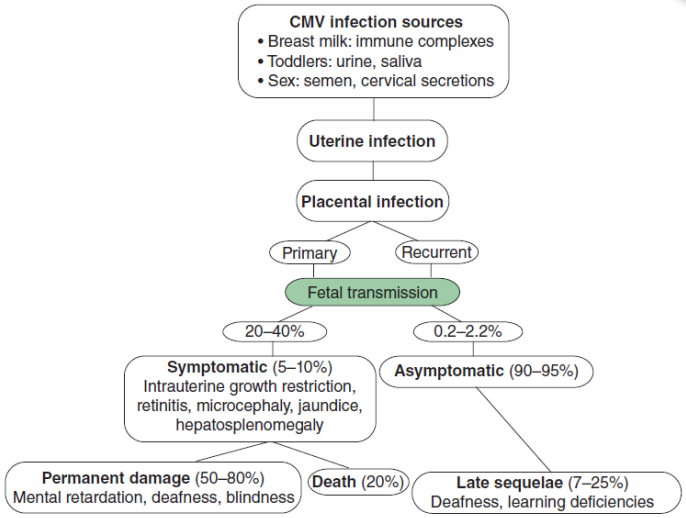
CMV - Pathogenesis and Pathology – Congenital CMV Infection

- Fetal and newborn infections with CMV may be severe.
- About 1% of live births annually in the US have congenital CMV infections, and about 5–10% of those will develop cytomegalic inclusion disease.



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CMV - Pathogenesis and Pathology – Congenital Infection

- CMV can also be acquired by the infant from exposure to virus in the mother's genital tract during delivery and from maternal breast milk. In these cases, the infants usually have received some maternal antibody, and the perinatally acquired CMV infections tend to be subclinical.
- Transfusion-acquired CMV infections in newborns vary, depending on the amount of virus received and the serologic status of the blood donor. Whether CMV is acquired in utero or perinatally, a more chronic infection results—with respect to viral excretion—than when the virus is acquired later in life.

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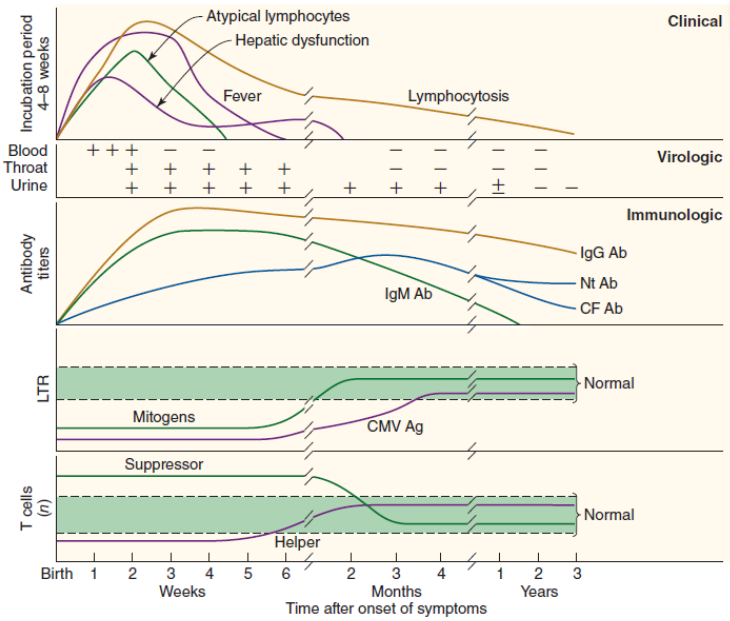
Clinical, virologic, and immunologic features of cytomegalovirus infection in normal individuals



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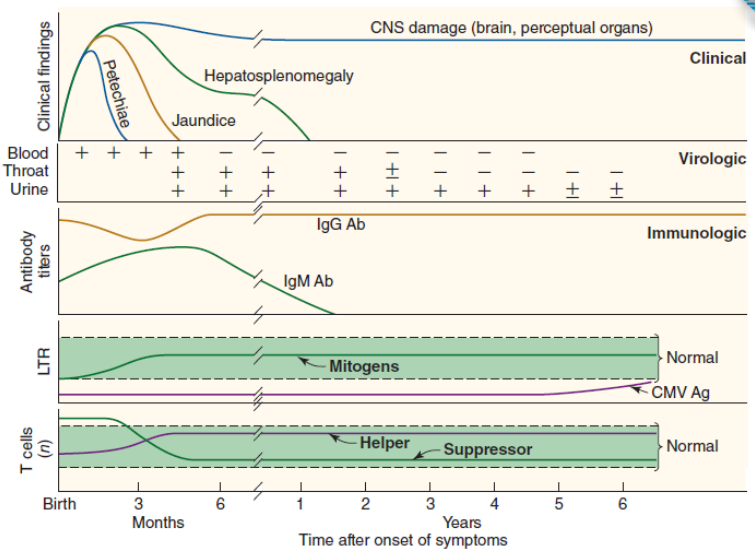
Clinical, virologic, and immunologic features of cytomegalovirus infection in congenitally infected infants



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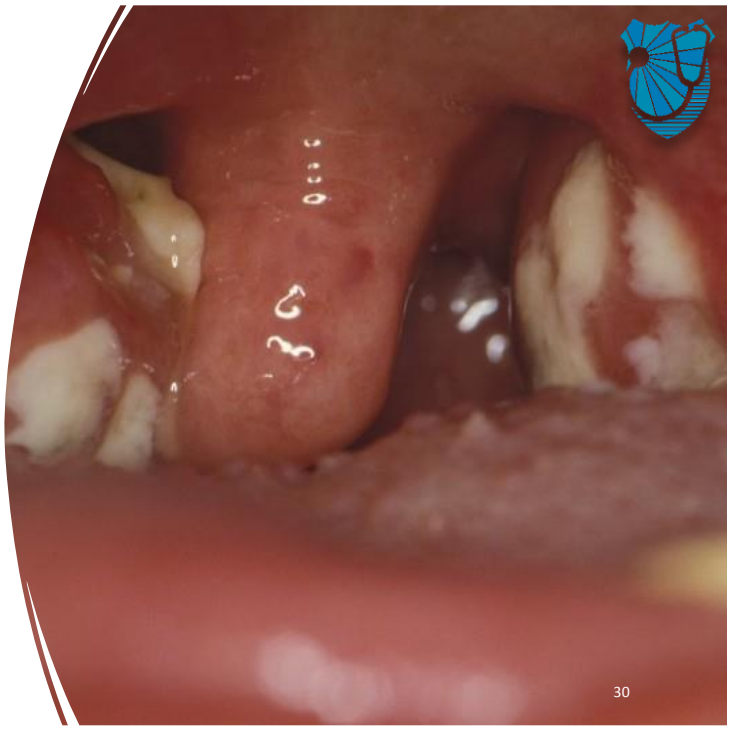
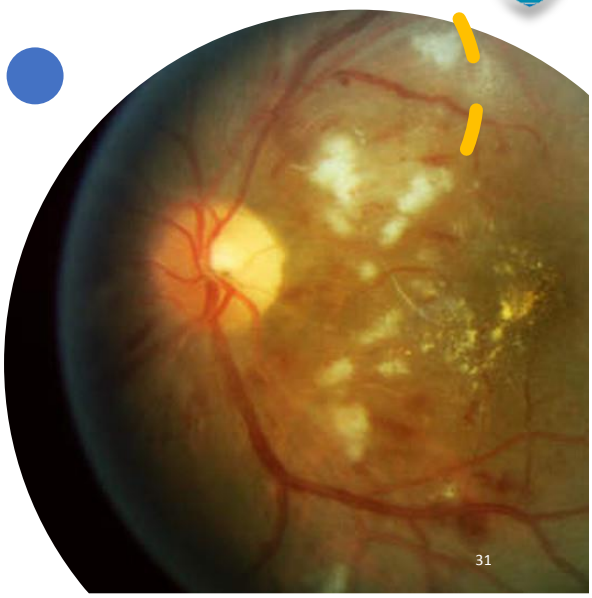
CMV – Clinical Findings

- Primary CMV infection of older children and adults is usually asymptomatic but occasionally causes a spontaneous infectious mononucleosis syndrome.
- CMV is estimated to cause 20–50% of heterophil-negative (non-EBV) mononucleosis cases.
- CMV mononucleosis is a mild disease, and complications are rare. Subclinical hepatitis is common. In children younger than 7 years old, hepatosplenomegaly is frequently observed.



CMV – Clinical Findings

- Both morbidity and mortality rates are increased with primary and recurrent CMV infections in immunocompromised individuals.
- Pneumonia is a frequent complication.
- Interstitial pneumonitis caused by CMV occurs in 10–20% of bone marrow transplant recipients.
- CMV often causes disseminated disease in untreated AIDS patients; gastroenteritis and chorioretinitis are common problems, the latter often leading to progressive blindness.



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CMV – Clinical Findings – Congenital Infections

Congenital infection involve intrauterine growth retardation, jaundice, hepatosplenomegaly, thrombocytopenia, microcephaly, and retinitis.

Mortality rates are about 20%.

The majority of survivors develop significant CNS defects within 2 years; severe hearing loss, ocular abnormalities, and mental retardation are common.

About 10% of infants with subclinical congenital CMV infection develop deafness.

It has been estimated that one in every 1000 infants born in the US is seriously retarded as a result of congenital CMV infection.

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CMV – Immunity

- Abs to CMV in human sera in the US increase with age, from about 40% in teenagers to more than 80% in those more than 60 years old.
- Reactivation of latent infection occurs in the presence of humoral immunity.
- The presence of Ab in breast milk does not prevent transmission of infection to breastfeeding infants.
- Maternal antibody protects more against development of serious disease in the infant than viral transmission.

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CMV – Laboratory Diagnosis

- PCR assays have replaced virus isolation for routine detection of CMV infections.
- The PCR assays are designed to detect replicating virus, not latent viral genomes. Blood and urine are most commonly tested.
- PCR assays can provide viral load data, which appears to be important in predicting CMV disease.
- Human fibroblasts are used for virus isolation attempts. The virus can be recovered most readily from throat washings and urine.
- In cultures, 2–3 weeks are usually needed for the appearance of cytologic changes, consisting of small foci of swollen, translucent cells with large intranuclear inclusions.
- Detection of viral IgM antibodies suggests a current infection.

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CMV – Epidemiology

CMV is endemic in all parts of the world, with no seasonal variation seen in infection rates.

Ab prevalence may be moderate (40–70%) in adults in high socioeconomic groups in developed countries—in contrast to a prevalence of 90% in children and adults in developing nations and in low socioeconomic groups in developed countries.

New infections are almost always asymptomatic. After infection, virus is shed from multiple sites. Viral shedding may continue for years, often intermittently, as latent virus becomes reactivated. Thus, exposures to CMV are widespread and common.

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CMV – Epidemiology

- Humans are the only known host for CMV.
- Transmission requires close person-to-person contact. Virus may be shed in urine, saliva, semen, breast milk, and cervical secretions and is carried in circulating white blood cells. Oral and respiratory spread are probably the dominant routes of CMV transmission.
- CMV can be transmitted by blood transfusion.
- Estimated risk varies widely but is about 1–5% per unit of whole blood. Sero-negative solid organ transplantation recipients are at risk because a sero-positive organ transmits the virus in 60–80% of cases.

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CMV – Treatment and Control

- Ganciclovir is used to treat life-threatening CMV infections in immunosuppressed patients. The severity of CMV retinitis, esophagitis, and colitis is reduced by ganciclovir.
- Early treatment with ganciclovir reduces the incidence of CMV pneumonia in BM allograft recipients. Ganciclovir also controls progressive hearing loss in neonates with congenital infections.
- Foscarnet, an analog of inorganic pyrophosphate, is recommended for treatment of CMV retinitis.
- Acyclovir and valacyclovir have shown some benefits in bone marrow and renal transplant patients.

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CMV – Treatment and Control

- Screening of transplant donors and recipients for CMV antibody may prevent some transmissions of primary CMV.
- The CMV-seronegative transplant recipient population represents a high-risk group for CMV infections.
- The use of blood from seronegative donors has been recommended when infants will require multiple transfusions. This approach would eliminate transfusion-acquired CMV infections, but it is difficult to implement.
- Both live and recombinant CMV vaccines are under development.

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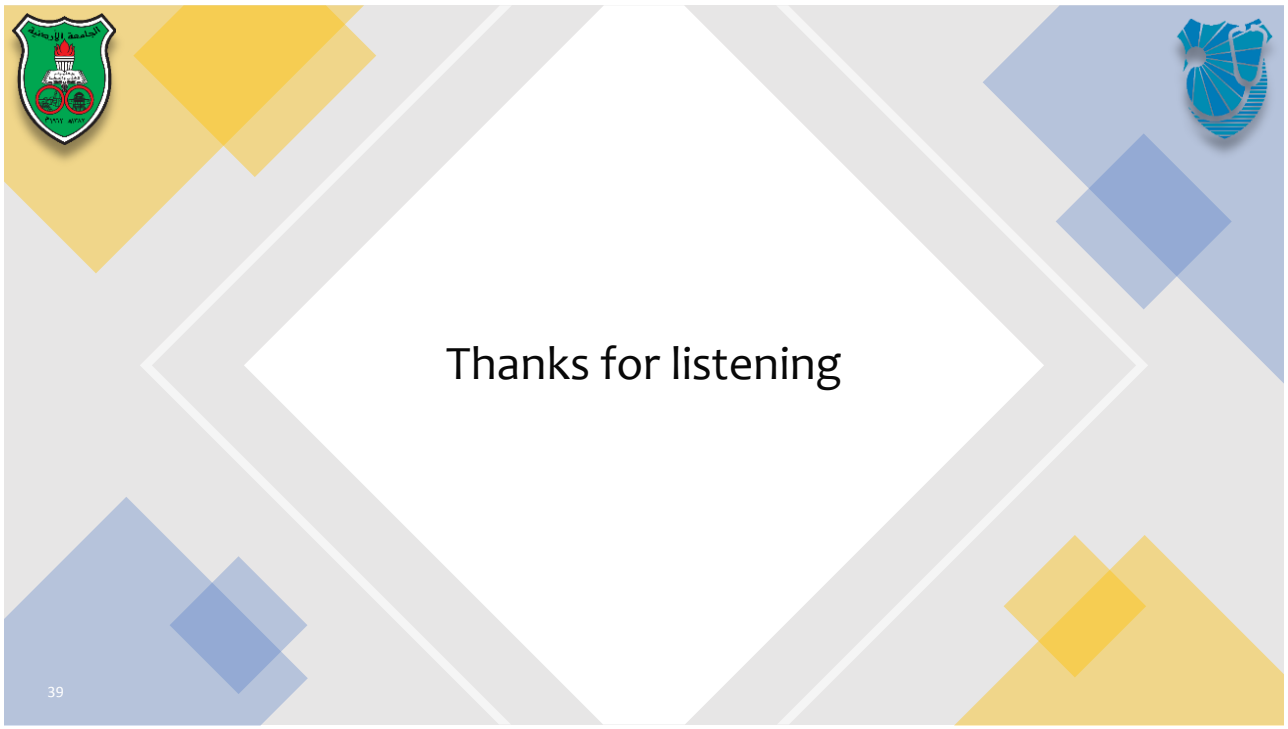
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