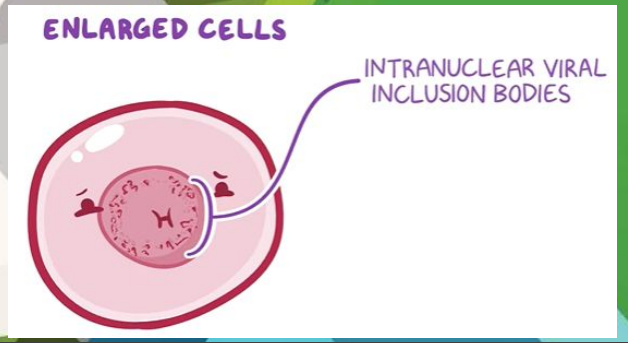
 Causes cytomegalic inclusion disease in infants



CYTOMEGALOVIRUS (CMV)

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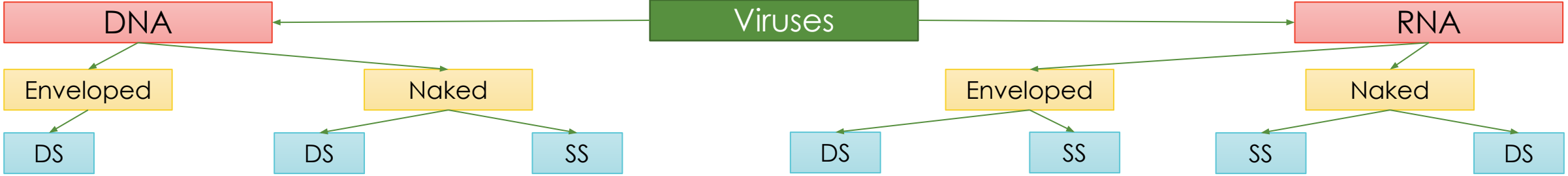
 Most common cause of congenital infections



Herpesviridae (Ic)

-Herpes simplex virus 1&2

-Varicella-zoster

-Cytomegalovirus

Adenoviridae (Ic)

Adenovirus

Parvoviridae (Ic)

Parvovirus B19

Bocaviruses

Guidelines:
SS: single stranded
DS: Double stranded
Ic: Ichosahedral capsid
He: Helical capsid
Co: Complex capsid

0- Introduction

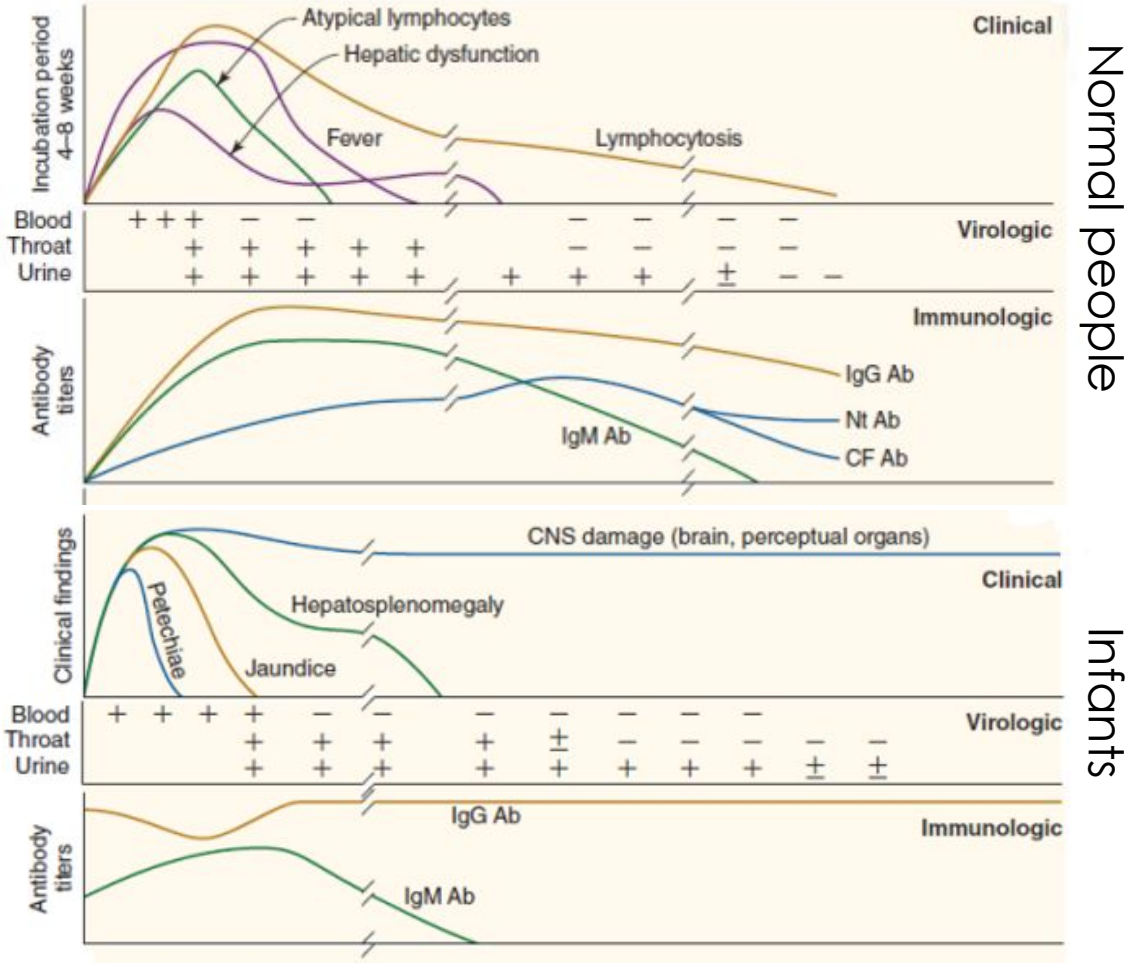
Biologic Properties				Examples	
Subfamily ("-herpesvirinae")	Growth Cycle and Cytopathology	Latent Infections	Genus ("-*virus*")	Official Name ("Human Herpesvirus")	Common Name
Alpha	Short, cytolytic	Neurons	*Simplex*	1	Herpes simplex virus type 1
				2	Herpes simplex virus type 2
			Varicello	3	Varicella-zoster virus
Beta	Long, cytomegalic	Glands, kidneys	*Cytomegalo*	5	Cytomegalovirus
	Long, lymphoproliferative	Lymphoid tissue	*Roseolo*	6	Human herpesvirus 6
				7	Human herpesvirus 7
Gamma	Variable, lymphoproliferative	Lymphoid tissue	*Lymphocrypto*	4	Epstein-Barr virus
			Rhadino	8	Kaposi sarcoma-associated herpesvirus

Cytomegalovirus

1- General information

- Have the largest genome between Herpesviridae
- Have Fc receptors
- Most common cause of congenital infection
- CMV produces a characteristic cytopathic effect. Intranuclear inclusions form in addition to damaging the cytoskeleton

2- Pathogenesis & clinical manifestations



3- Immunity

- Antibodies protect from serious infections but don't prevent infections at all

4- Laboratory diagnosis

- PCR
- Cell culture: in fibroblast / need long time (2-3 weeks)
- Serology: Detection of IgM = current infection

5- Epidemiology

- Most infections are asymptomatic
- CMV is endemic in all parts of the world, with no seasonal variation seen in infection rates.
- Humans are the only known host for CMV

6- Treatment and Control

- anciclovir is used to treat life-threatening CMV infections in immunosuppressed patients
- ganciclovir reduces the severity of disease
- Foscarnet: for retinitis
- No ready vaccines until now, but both live and recombinant CMV vaccines are under development.

1- General information

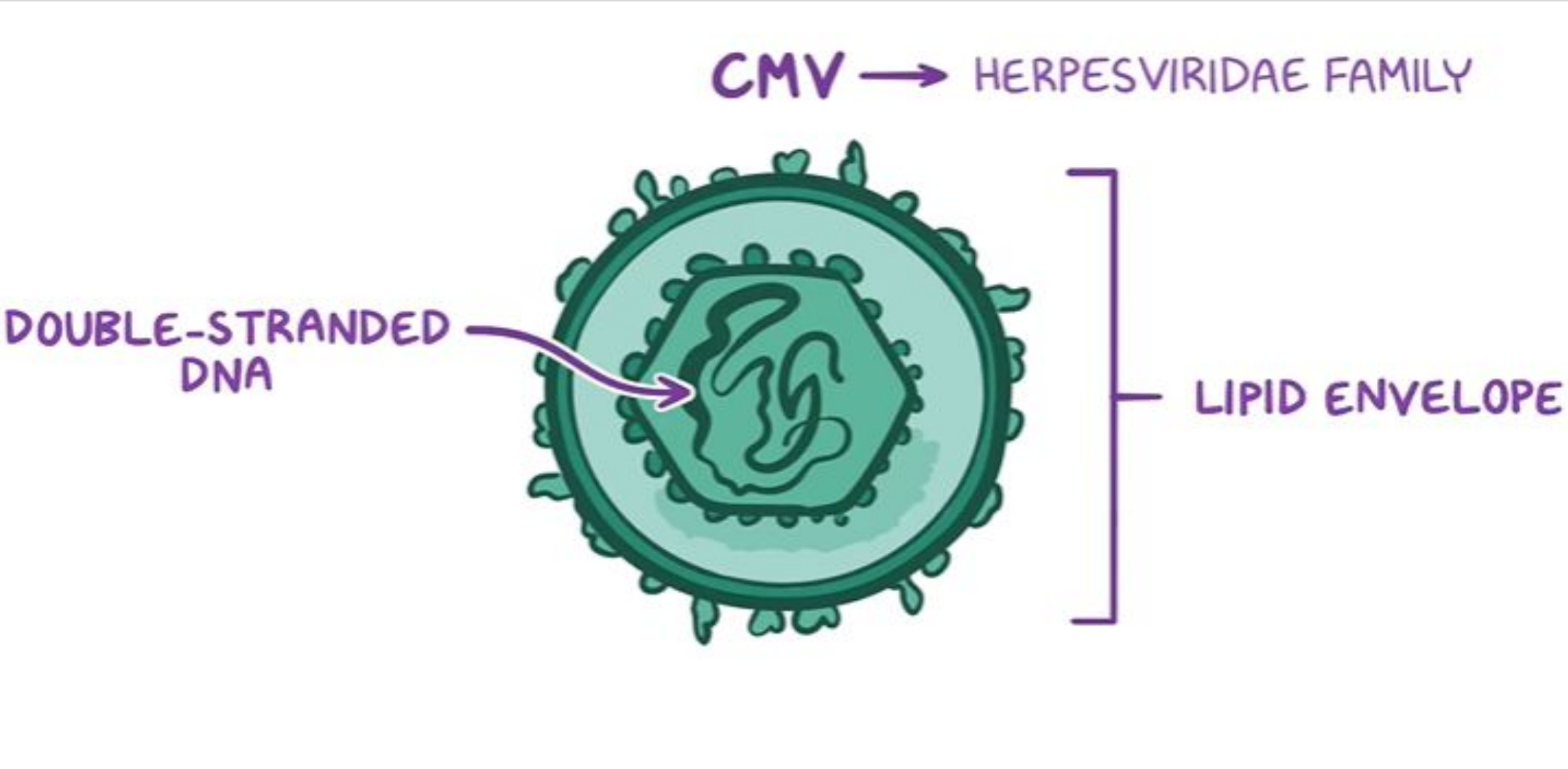
- Structure of the virus (large virus):

  Genome: CMV has the largest genetic content of the human herpesviruses. Its DNA genome (240 kbp).

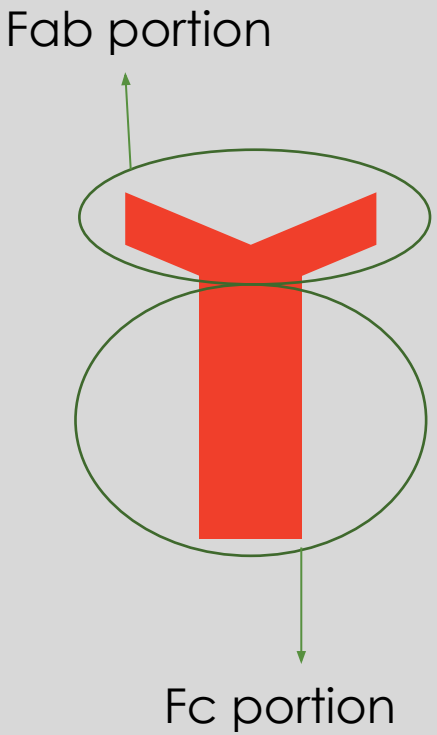
  The major immediate-early promoter-enhancer of CMV is one of the strongest known enhancers because of the concentration of binding sites for cellular transcription factors.

  Proteins: 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.

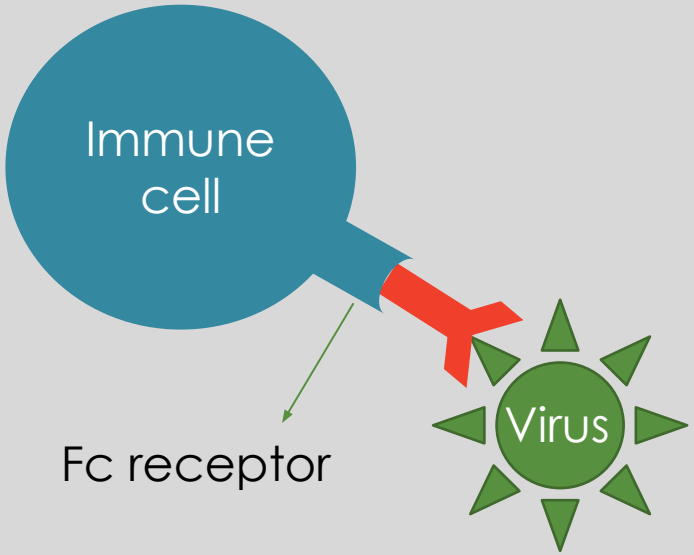
1- General information



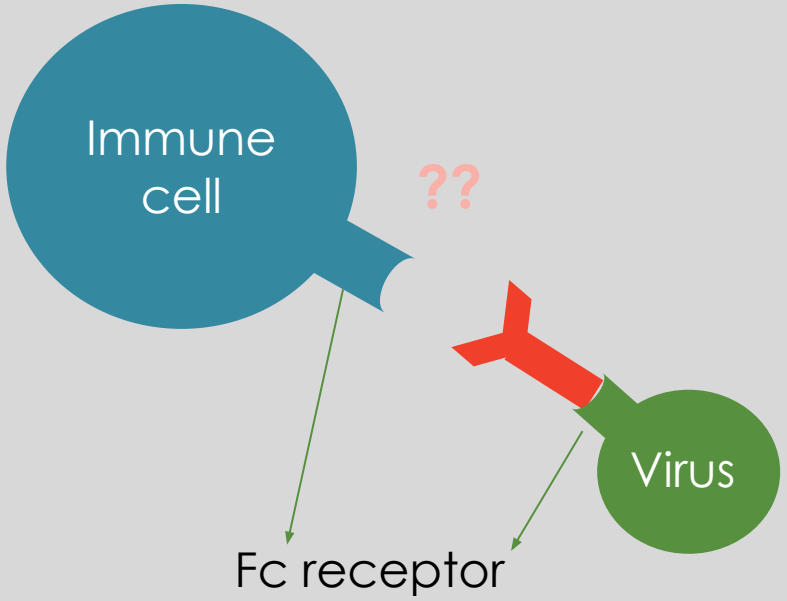
1- General information



Normal situation



Abnormal situation

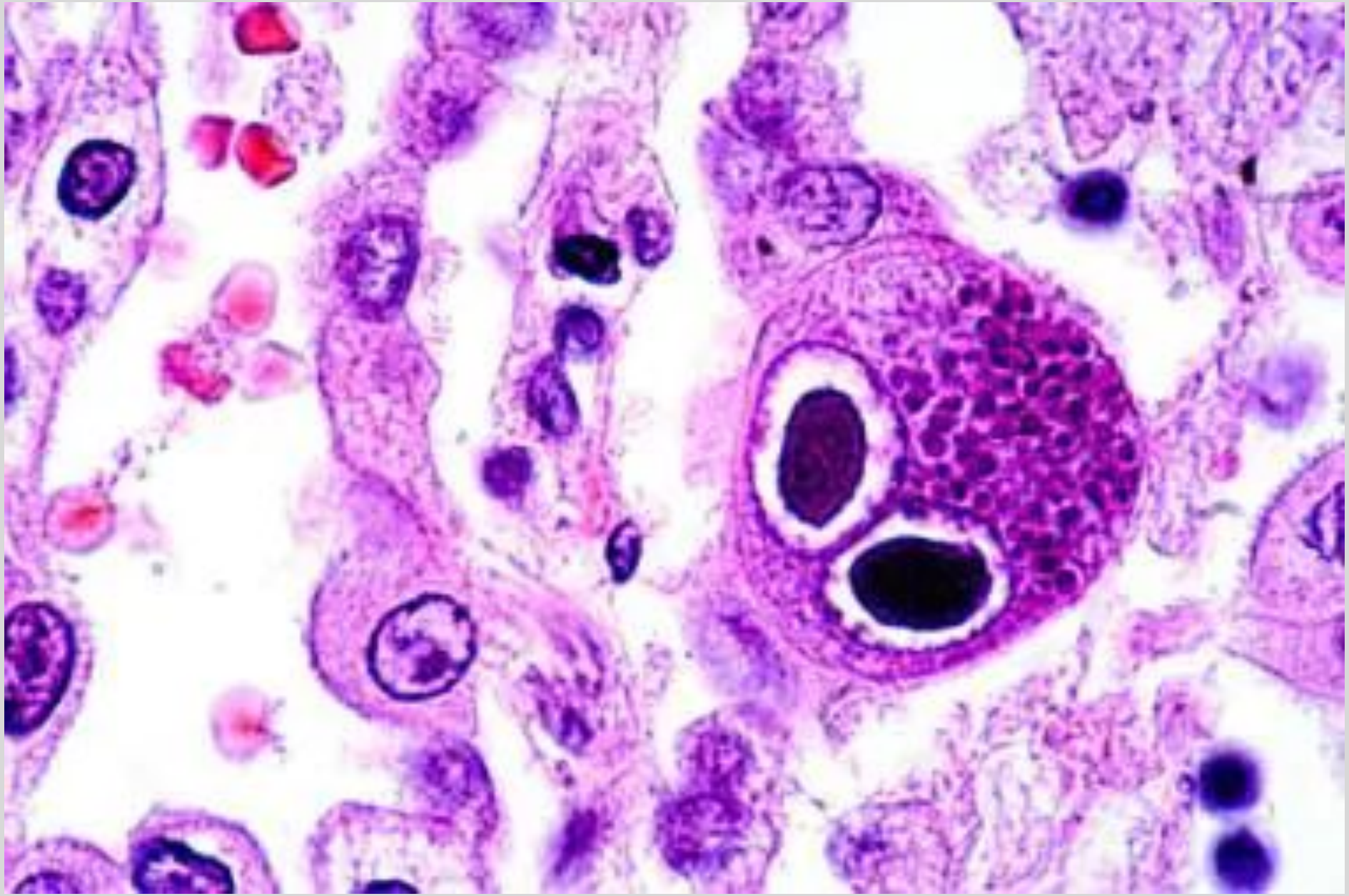


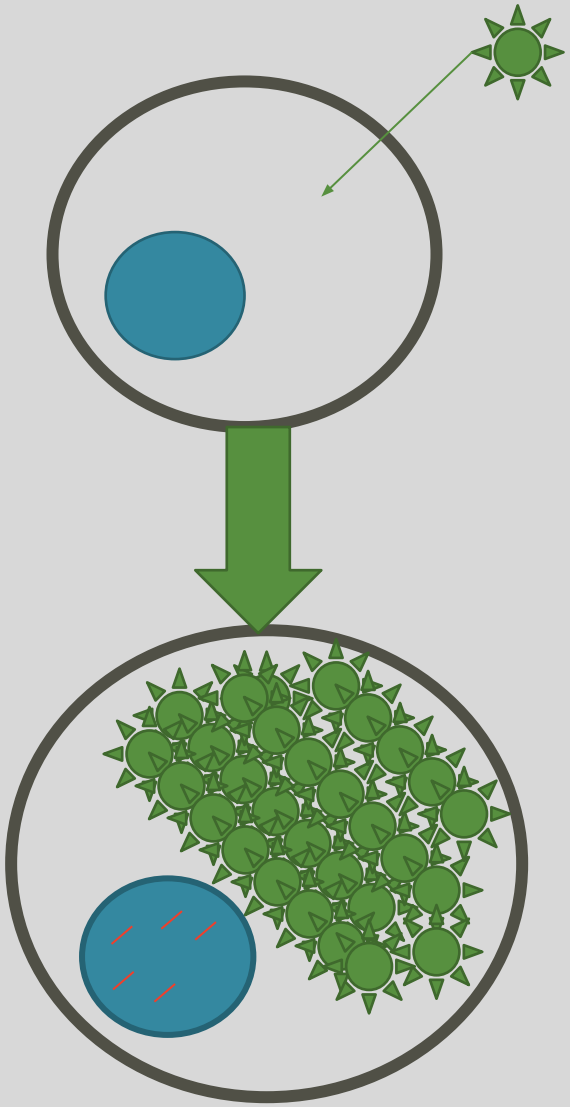
1- General information

- Cytomegalic inclusion disease is a generalized infection of infants caused by intrauterine or early postnatal infection with the CMVs.
- CMV poses an important public health problem because of its high frequency of congenital infections, which may lead to severe congenital anomalies.
- Severe CMV infections are frequently found in adults who are immunosuppressed
- Inapparent infection is common during childhood and adolescence.

1- General information

- Why the virus & the disease it cause is such called like that?
  from the propensity for massive enlargement of CMV-infected cells.
- 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 inclusion bodies are formed
- Multinucleated cells are seen. Many affected cells become greatly enlarged.
- Inclusion-bearing cytomegalic cells can be found in samples from infected individuals.

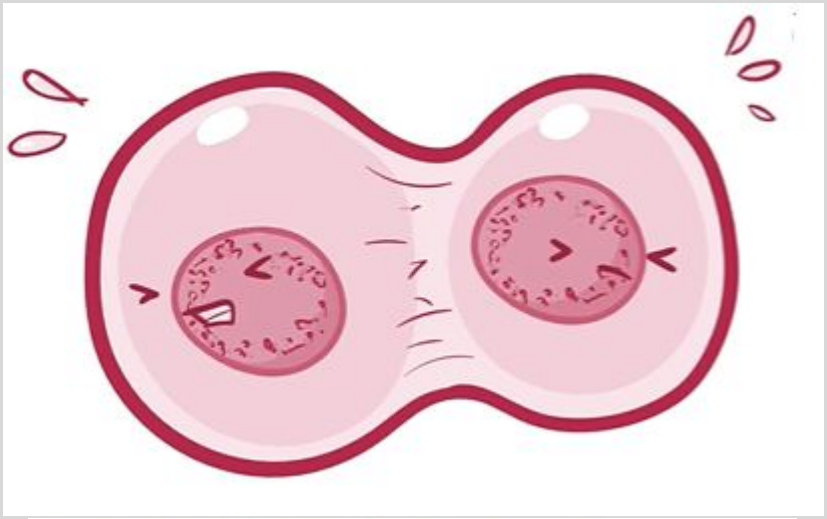




Specific Cytopathic effects are two:

1. It will destroy the cytoskeleton of the cell causing it's enlargement, and will produce intranuclear inclusions, the infected cell is called (owl cell)
2. Slow down mitosis of cells

 Remember: they are from the Herpesviridae family, so they will form multinucleated giant cells



2- Pathogenesis & clinical manifestations

- CMV first enters the body & is transmitted by close contact.
- Oral and respiratory spread are probably the dominant routes of CMV transmission.
- Virus may be shed in urine, saliva, semen, breast milk, and cervical secretions and is carried in circulating white blood cells.
- 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.

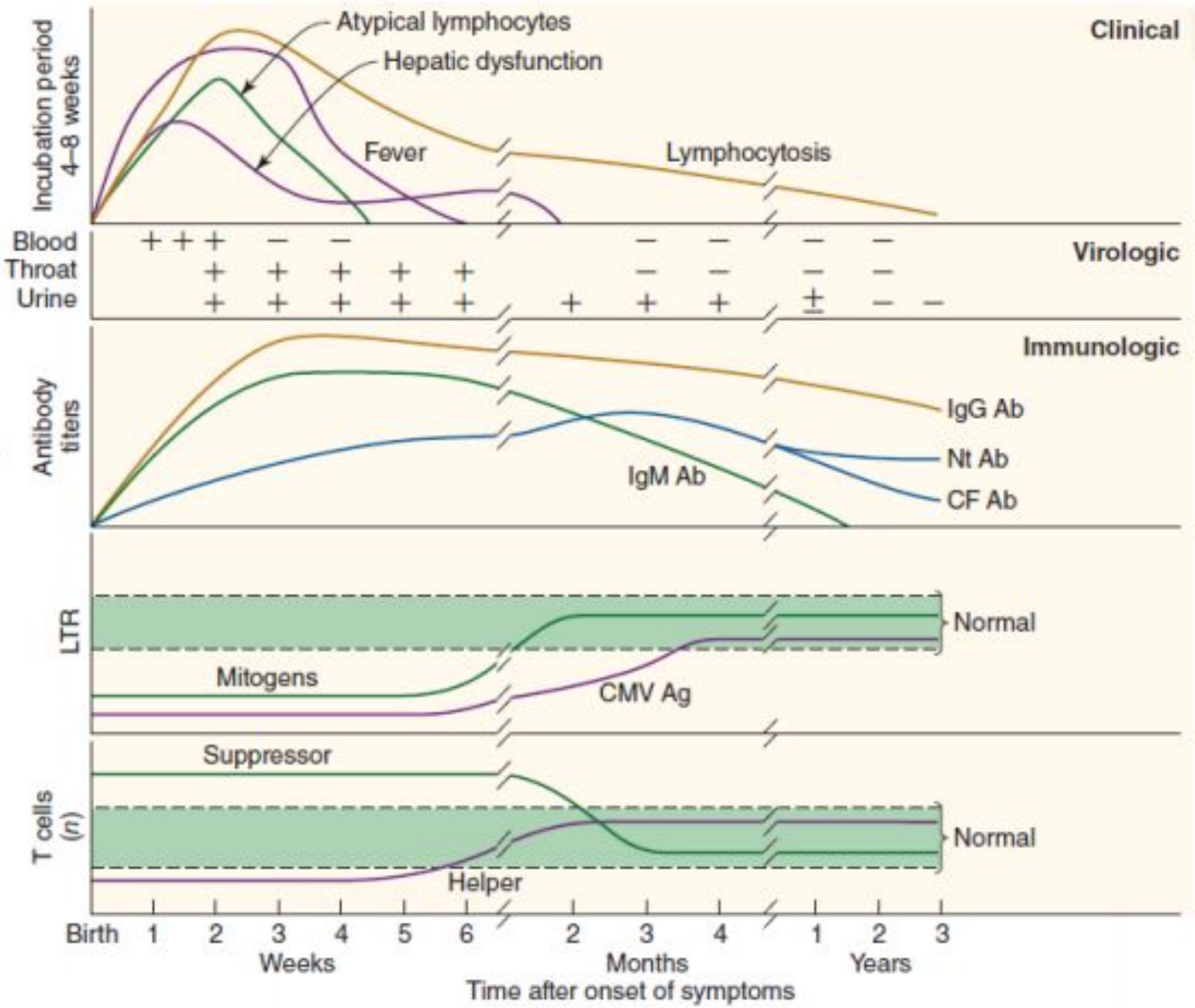
2- Pathogenesis & clinical manifestations

- Normal adults and old children:
- 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.
- 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
- The disease can take many pathways clinically:
  1) Primary CMV infection of older children and adults is usually asymptomatic
  2) causes a spontaneous infectious mononucleosis like syndrome
  3) Rarely cause some complications, such as:
  a- Pneumonia is the most common complication
  b- Prolonged CMV infection of the kidney and salivary glands is common and probably chronic
  c- Subclinical hepatitis (common)
  d- In children younger than 7 years old, hepatosplenomegaly is frequently observed.
- CMV establishes lifelong latent infections. Virus can be shed intermittently from the pharynx and in the urine for months to years after primary infection
- Although usually less severe, reactivated infections may be as virulent as primary infections.

- Mononucleosis syndrome (additional slide but extremely important for understanding):
  - symptoms of headache, fever, malaise, fatigue, and sore throat occur. Enlarged lymph nodes and spleen are characteristic.
  - The typical illness is self-limited and lasts for 2–4 weeks. During the disease, there is an increase in the number of circulating white blood cells, with a predominance of lymphocytes. Many of these are large, atypical T lymphocytes. Low-grade fever and malaise may persist for weeks to months after acute illness.

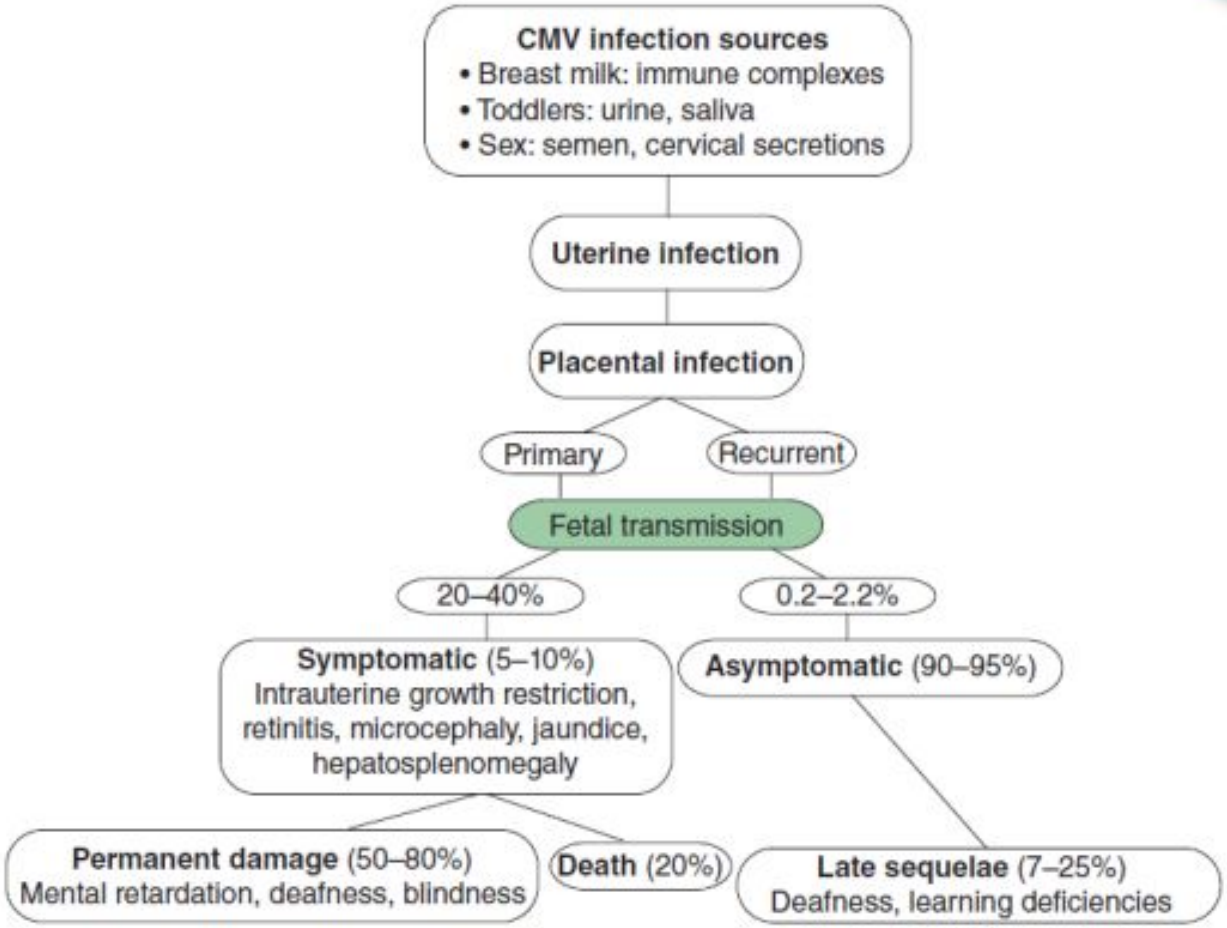
Ab: antibody
Ag: antigen
CF: complement fixing
CMV: cytomegalovirus;
CNS: central nervous system
Ig: immunoglobulin
LTR: lymphocyte transformation response
Nt: neutralizing

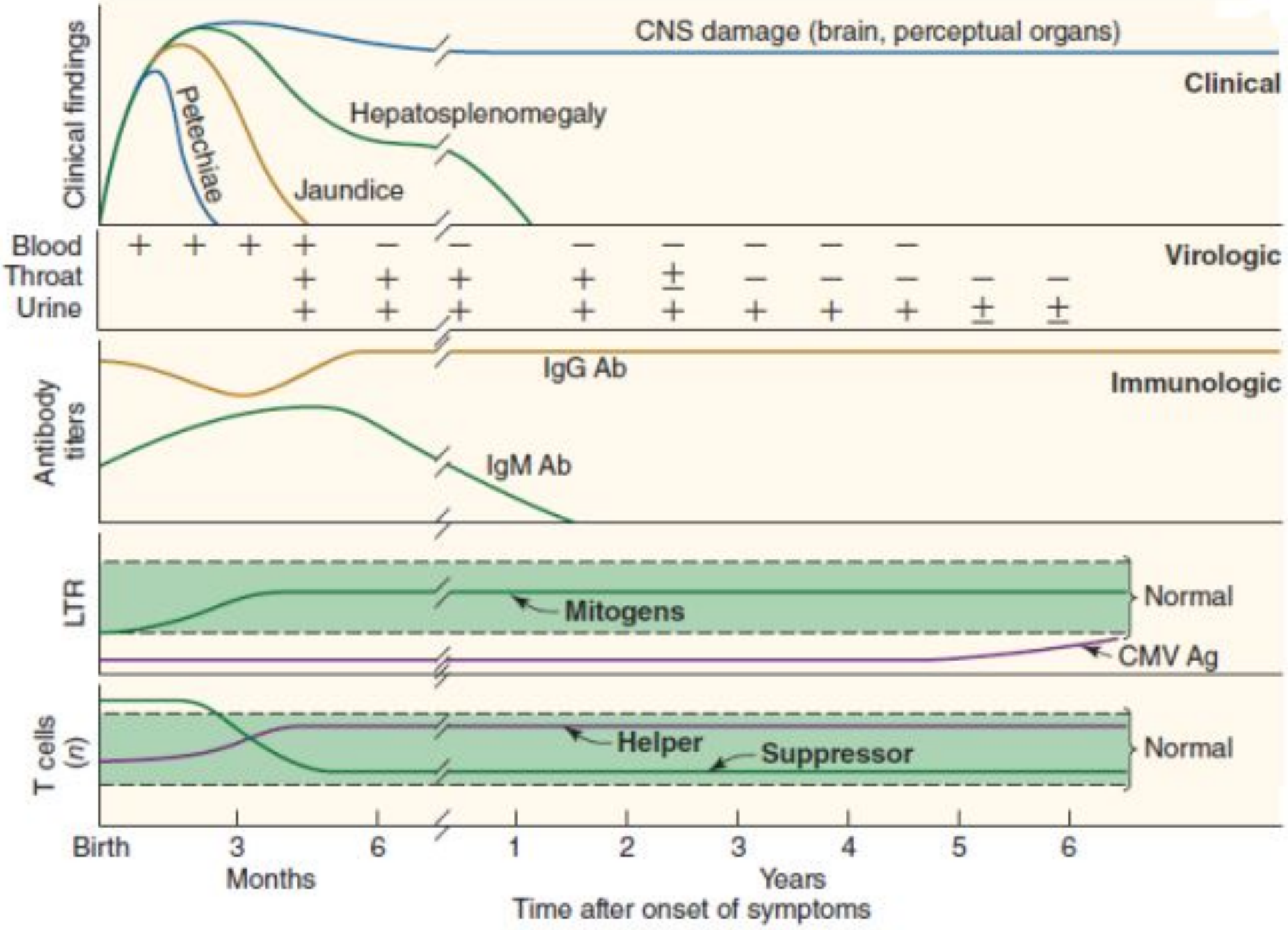
CMV is estimated to cause 20–50% of heterophil-negative (non-EBV) mononucleosis cases.



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.




Clinical findings
CNS damage (brain, perceptual organs)
Clinical
Petechiae
Hepatosplenomegaly
Jaundice
Blood
Throat
Urine
Virologic
IgG Ab
Immunologic
Antibody titers
IgM Ab
LTR
Mitogens
Normal
CMV Ag
T cells (n)
Helper
Suppressor
Normal
Birth
3
6
1
2
3
4
5
6
Months
Years
Time after onset of symptoms

2- Pathogenesis & clinical manifestations

- 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.

2- Pathogenesis & clinical manifestations

- Congenital infection:
- Disease involve intrauterine growth retardation, jaundice, hepatosplenomegaly, thrombocytopenia, microcephaly, and retinitis.
- Mortality rates are about 20%.
- Most 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.

2- Pathogenesis & clinical manifestations

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

3- 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.

4- 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 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.

5- 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.
- Note: Humans are the only known host for CMV.

6- Treatment and Control

- anciclovir 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

6- 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.