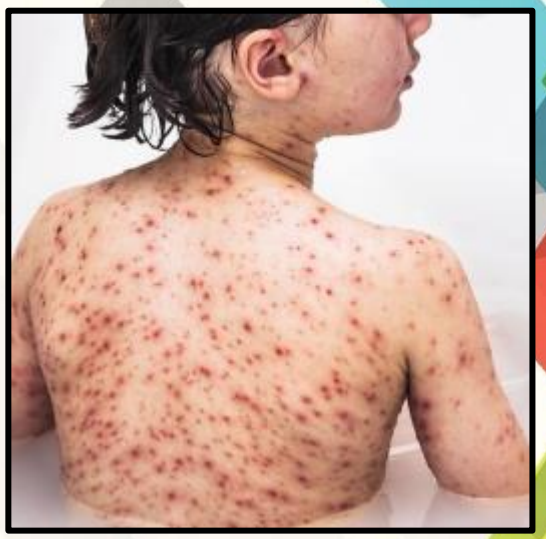
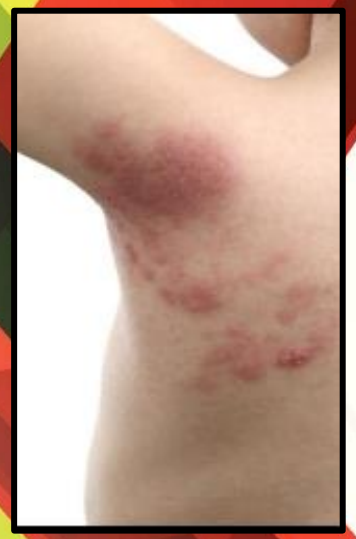


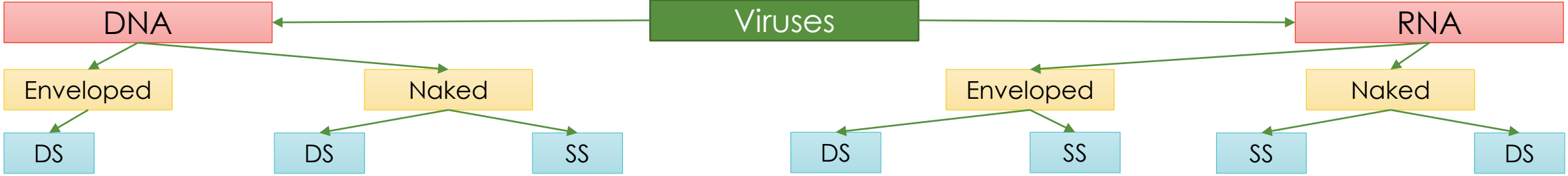


VARICELLA-ZOSTER VIRUS

Done by: Abdelhadi Okasha

Causes 2 Diseases:

1. Varicella (Chickenpox): Infects children
2. Zoster (Shingles): Infects adults



Herpesviridae (Ic)

-Herpes simplex virus 1&2

-Varicella-zoster

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

Varicella-zoster virus

1- Pathogenesis (chickenpox & shingles)

1) 1)The virus enters the host mucosal surfaces and causes a systemic infection up to reaching skin
2) The virus starts replicating in skin cells causing fever & malaise after about 10-21 days of virus entry, followed by a skin rash on the trunk and then on the face, the limbs, and the buccal and pharyngeal mucosa in the mouth, this disease is called **chickenpox**
3) Immune system kicks in and eliminate most of the viral particles, however, some of the viral particles escape to adjacent sensory neurons establish latency.
4) when immune system is compromised, virus is activated (usually in one neuron) inducing inflammation of the neuron and developing rash after several days on the skin adjacent to infected neurons, this disease is called **shingles.**
5) The most important complication related to shingles is postherpetic neuralgia.

2- Immunity

- Immune system response against VZV, such parts involved are INF, T cells (important) & B cell.
- Human body forms long-last immunity against varicella
-VZV have some evading mechanisms against immunity

3- Laboratory diagnosis

1) PCR assays are preferred for sensitivity, specificity, and rapidity
2) Detecting cytopathic effects: large multi-nucleated cell
3) Serological tests
→ Note: The choice of assay to use depends on the purpose of the test and the laboratory facilities available.

4- Treatment

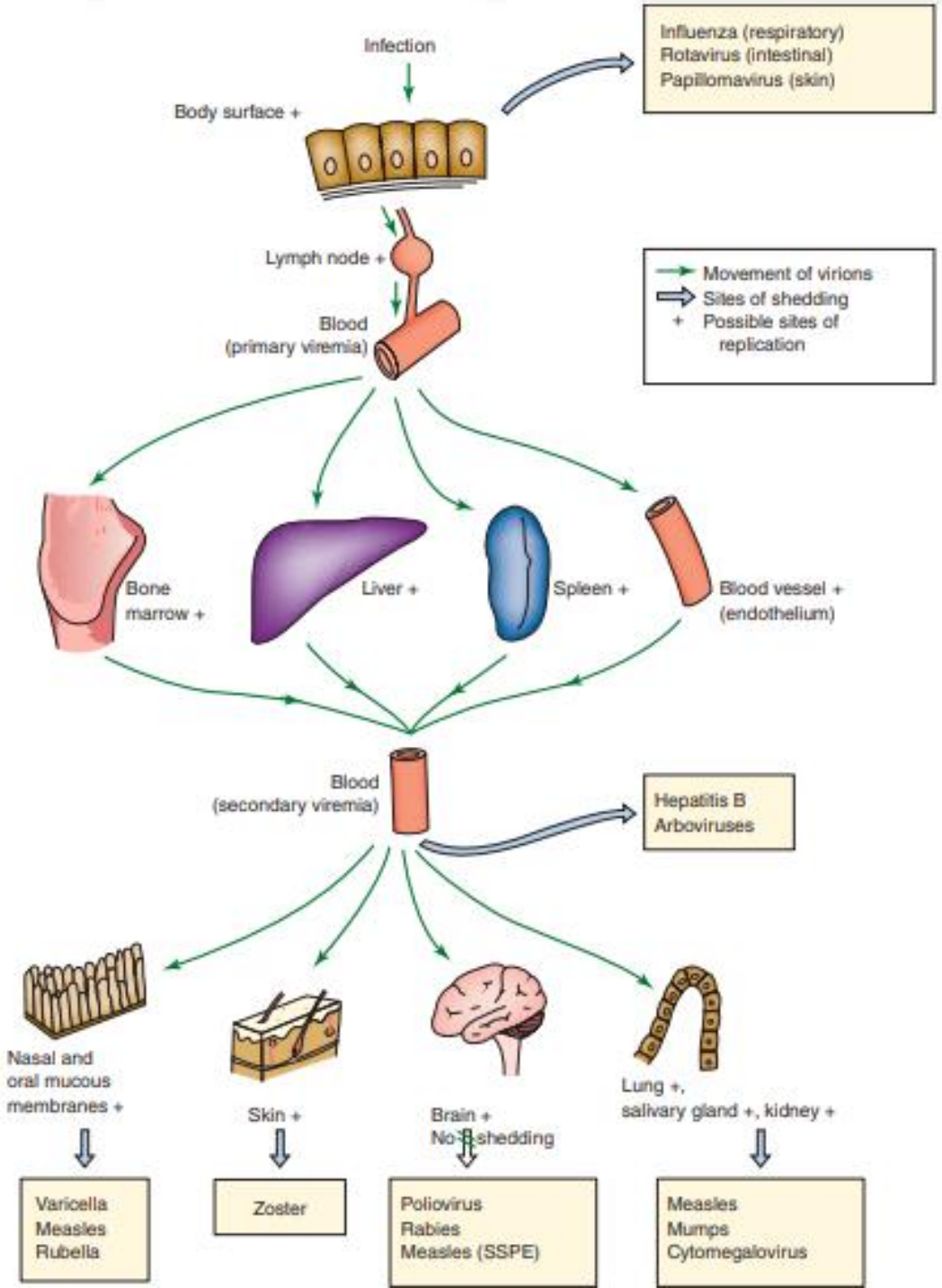
→ Usually no treatment is needed
→ Immunoglobulins vs. VZV can be given to prevent infection, but they are not benefit if infection occurs
→ Acyclovir can be used for immunocompromised patients to prevent severe infections
→ Acyclovir is not benefit for postherpetic neuralgia

5- Prevention and control

→ There are some efficient vaccines against chickenpox & shingles

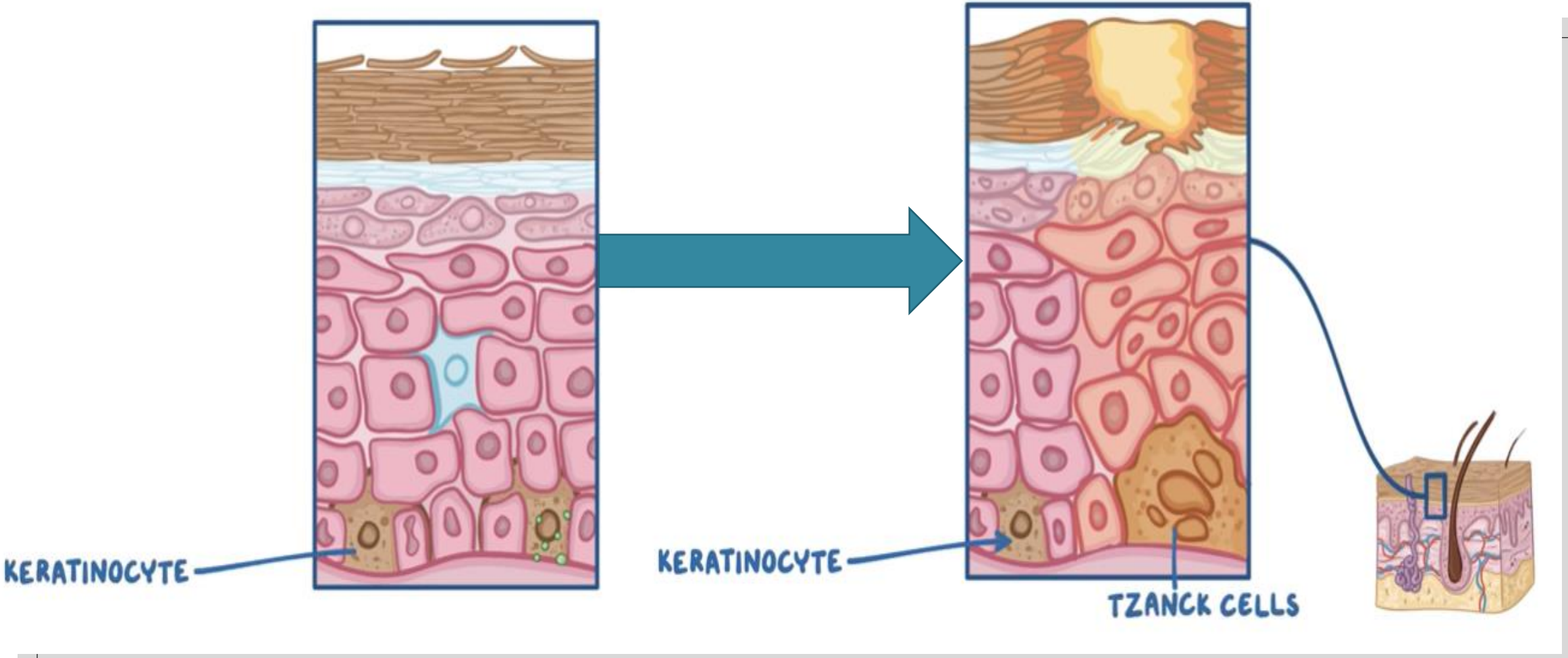
6- Epidemiology

→ Varicella is common worldwide, very contagious and transmit through airborne & direct contact
→ Zoster happens sporadically & usually less contagious



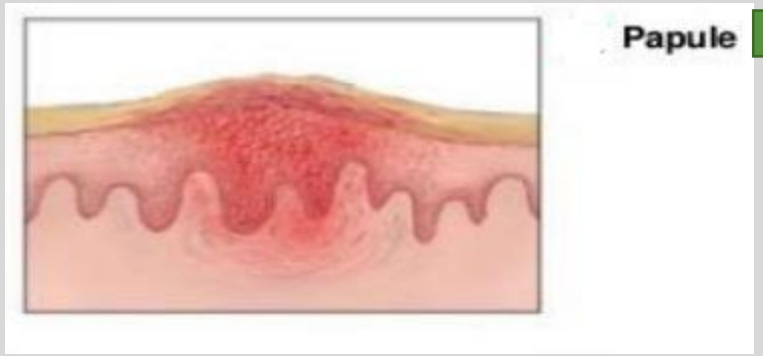
1- Pathogenesis & clinical manifestations (Chickenpox)

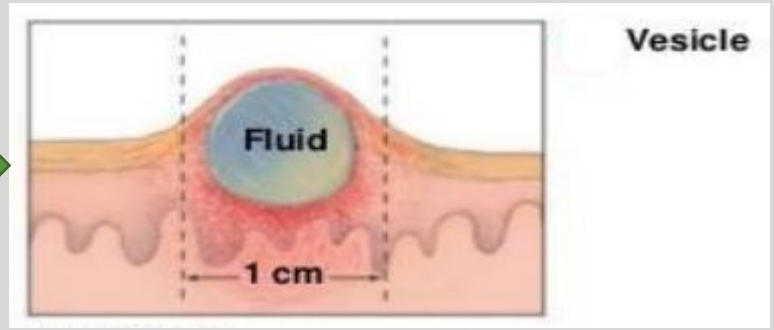
- 1)The virus enters the host through conjunctiva or by inhalation, and start to replicate in the epithelial cells at the side of entry.
- 2) Immune cells carry the virus to a nearby lymph node to eliminate it, but unfortunately, they won't be eliminated.
- 3) They enter the bloodstream causing primary viremia
- 4) Infects endothelial system (e.g. bone marrow, liver…etc)
- 5) Return to blood again causing secondary viremia
- 6) Reach the skin to replicate in a keratinocyte and neighboring cells, symptoms will start with malaise and fever after about 10-21 days of infection (incubation period) then a macule will be formed, that will transform to a papule (crop) then vesicle and lastly a crust.

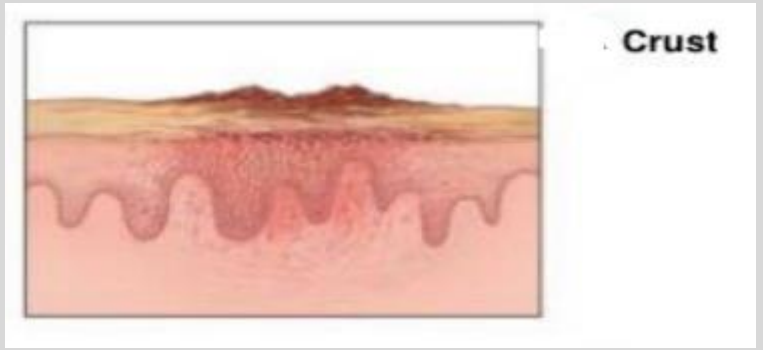


- Note: Infected keratinocytes may fuse together forming tzanck cell


Macule
Epidermis
Dermis


Papule


Fluid
1 cm
Vesicle


Crust

1- Pathogenesis & clinical manifestations (Chickenpox)

- 7) Skin cells will start to secrete Interferons, that will achieve an anti-viral state protecting them
- 8) However, Varicella-zoster virus can still infect some skin cells as it evades interferon's effect by expressing ORF61 protein, which works as an antagonist for the β–interferon pathway.
- 9) This will cause tiny lesions to appear separated by normal skin first on the trunk and then on the face, the limbs, and the buccal and pharyngeal mucosa in the mouth. This disease is called **CHIKENPOX.**

1- Pathogenesis & clinical manifestations (Chickenpox)

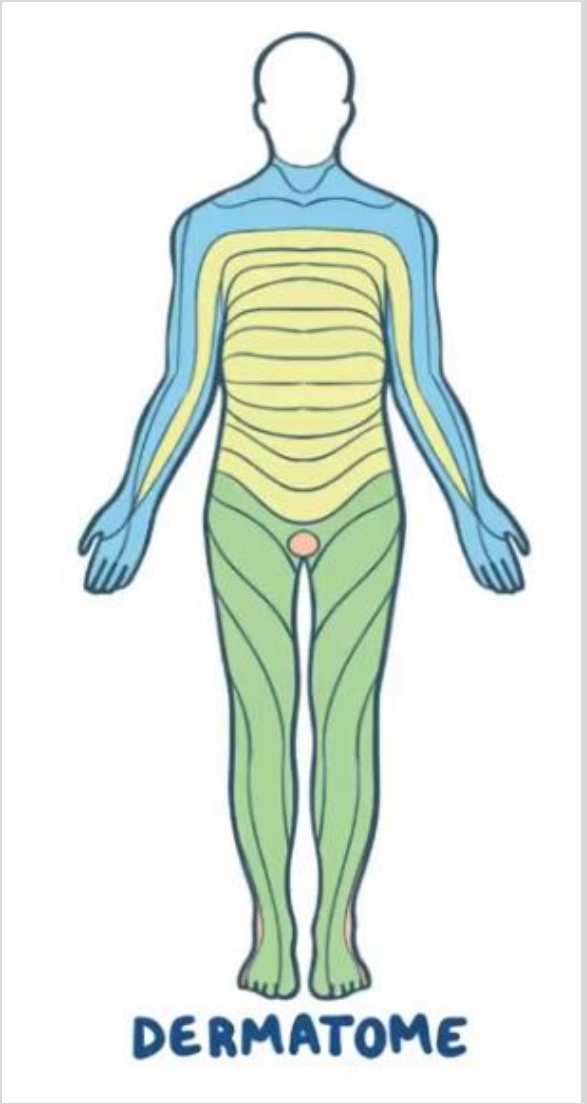
- General information's about chickenpox:
  1) The disease is highly contagious & Subclinical varicella is unusual.
  2) The disease is mild, and the mortality rate is very low (1 per 100,000 cases among children age 1 through 14 years, 6 per 100,000 cases among persons age 15 through 19 years, and 21 per 100,000 cases among adults).
  3) Complications are rare in normal children although they can occur, on the other side, immunocompromised patients are at increased risk of complications of varicella.
  4) The rashlasts 5 days, and most children develop several hundred skin lesions.

1- Pathogenesis & clinical manifestations (Chickenpox)

- There are 5 mentioned complications associated with chickenpox:
  1) Encephalitis: occurs 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
  2) Neonatal infection: 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.
  3) pneumonia: rare in healthy children but is the most common complication in neonates, adults, and immunocompromised patients. It is responsible for many varicella-related deaths.
  4) Disseminated intravascular coagulation: may occur & is rapidly fatal.
  5) Children with leukemia are especially prone to developing severe, disseminated varicella-zoster virus disease: severe, may affect Children with leukemia & immunocompromised people

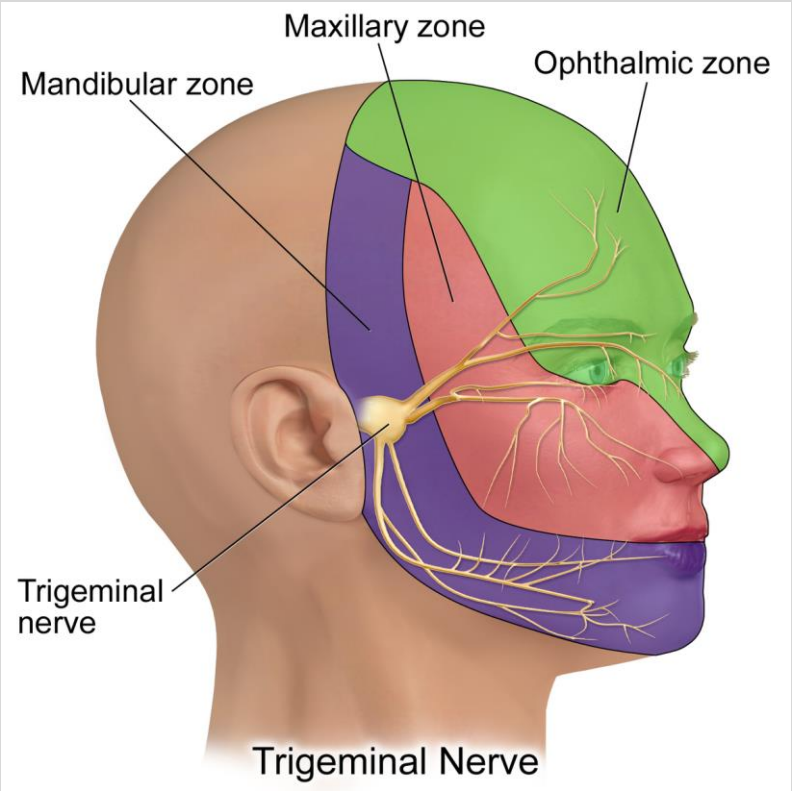
1- Pathogenesis & clinical manifestations (Shingles)

- 1) Now after the host is infected by the chickenpox, immune system will kick in and start eliminating the virus.
- 2) Some of the virus particles will escape to adjacent sensory neurons and hide there, establishing latent phase.
- 3) Once the immune system is suppressed because of a disease, therapy, or aging they will be activated (usually in one neuron only) causing severe inflammation in the sensory neuron & the ganglia (sometimes occur without immunosuppression)
- 4) after few days it travels to skin corresponds closely to the areas of innervation from an individual dorsal root ganglion causing lesions that are histopathologically identical to those of varicella.



1- Pathogenesis & clinical manifestations (Shingles)

- Note: The trunk, head, and neck are most commonly affected with the ophthalmic division of the trigeminal nerve involved in 10–15% of cases
- There are several probable complications such as:
  1) postherpetic neuralgia: most common complication in adults (specially when reactivation occurs in the trigeminal nerve), it's defined as a protracted pain that may continue for months.
  2) Visceral disease: especially pneumonia, is responsible for deaths that occur in immunosuppressed patients with zoster (less than 1% of patients)
  3) Varicella zoster central nervous system: disease, most frequently meningitis, often presents without a typical zoster rash.



2- Immunity

- Remember: immune system is divided into two parts:
  1) Innate immunity: Interferons help in the limiting of the disease & recovery
  2) Adaptive immunity: It's divided into cell mediated immunity (T cells) & humoral immunity (B cells)
  a) T cells are two subtypes: helper T cells (CD4+) & Cytotoxic T cells (CD8+)
  CD4+: Activated when antigen-presenting cells present the antigen to them on MHC II molecule
  CD8+: Usually body cells present their proteins on MHC I on their surfaces as a type of identifying, CD8+ t cells will detect these proteins to check if the cell is normal or no, if the cell is infected with a virus it will present virus proteins on MHC I, then CD8+ t cell will detect them and kill them.
  → In general: The development of VZV-specific cell-mediated immunity is important in recovery from both varicella and zoster.

2- Immunity

- B) B cells : Main function is producing antibodies
  → 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.
- In general: Previous infection with varicella is believed to confer lifelong immunity to varicella.
- Evading mechanisms of the virus: it downregulates MHC class I and II antigen expression and the β-interferon pathway

3- Diagnosis

- Diagnosis of disease is very easy as there are many rapid tests that can be done, such tests used in diagnosis are:
  1) 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, and can also be detected in vesicle fluid, skin scrapings, and biopsy material.
  2) Detecting cytopathologic effects: we can use Tzanck smear, In stained smears of scrapings or swabs of the base of vesicles, multinucleated giant cells are seen.
  Notes:
  - 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.
  - in general, 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.

3- Diagnosis

- 3) Antibodies : A rise in specific antibody titer can be detected in the patient's serum by various tests, including fluorescent antibody and enzyme immunoassay.
- 4) Detecting T cells: although cell mediated immunity is important in fighting VZV, but detecting it is difficult, so this method is not used
- Which mechanism do we choose for diagnosis?
  The choice of assay to use depends on the purpose of the test and the laboratory facilities available.

4- 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. 18
- 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.

5- prevention & control

- 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.

5- prevention & 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.

6- 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.

6- 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.

Sources of the lecture

- 1) Slides of the doctor
- 2) Osmosis microbiology
- 3) Jawatez book
- 4) Harrisons infectious diseases 2nd edition