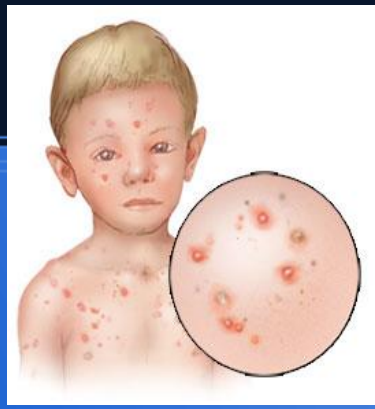


HUMAN HERPES VIRUSES

Herpes Viridae

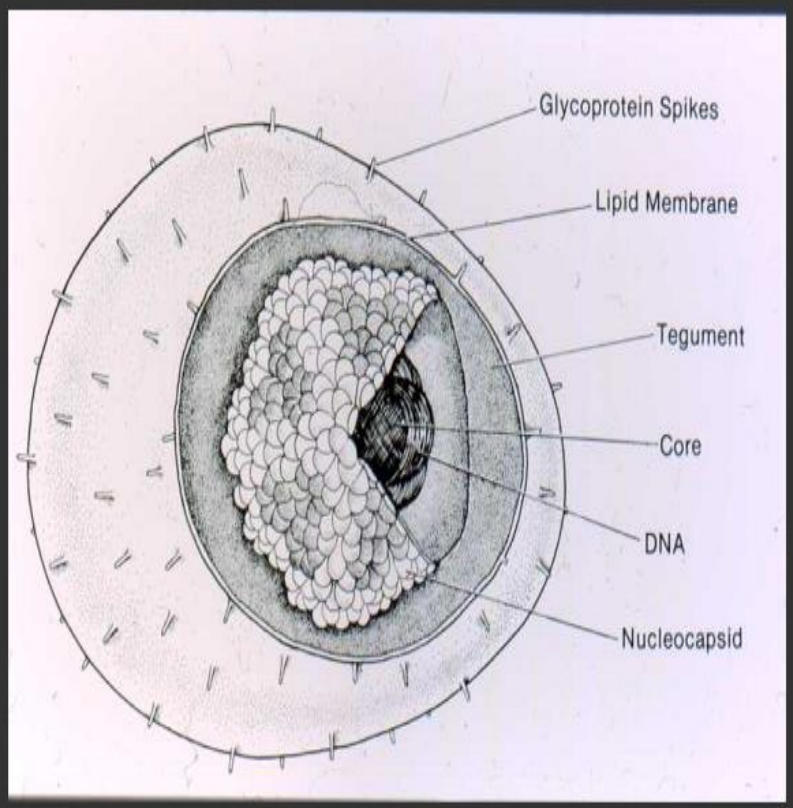
The family of herpesviruses is very large, and its members infect most animal species. There are 7 herpesviruses which are known to infect humans:

1. **HSV I** — **Herpes Simplex Virus Type I: Oral (genital) Coldsores**
2. **HSV II** — **Herpes Simplex Virus Type II: Genital Herpes**
3. **VZV** — **Varicella Zoster: Chicken Pox, Shingles**
4. **CMV** — **Cytomegalovirus: Virus like illness and Immunosuppressed visceral disease**
5. **EBV** — **Epstein-Barr Virus: Glandular Fever**
6. **HHV 6** — **Human Herpes Virus Type 6:**
7. **HHV 7** — **Human Herpes Virus Type 7:**
8. **HHV 8** — **Human Herpes Virus Type 8:**

Properties of herpesviruses

- Enveloped double stranded DNA viruses.
- Three subfamilies:
  - Alphaherpesviruses - HSV-1, HSV-2, VZV
  - Betaherpesviruses - CMV, HHV-6, HHV-7
  - Gammaherpesviruses - EBV, HHV-8
- Set up latent or persistent infection following primary infection
- Reactivation are more likely to take place during periods of immunosuppression
- Both primary infection and reactivation are likely to be more serious in immunocompromised patients.

STRUCTURE OF THE VIRION



- They have a large double stranded DNA genome. The VIRION consists of an icosahedral nucleocapsid of about 100 nm in diameter, which is surrounded by a lipid bilayer envelope. Between the capsid and the envelope is an amorphous layer of proteins, termed the tegument.

HERPES SIMPLEX VIRUS HSV

Both viruses cause painful vesicles on the skin at the site of inoculation

HSV1 is usually associated with oro-facial lesions.

HSV2 is usually associated with genital lesions.

HSV EPIDEMIOLOGY

Mode of Transmission

- direct contact with the rash
- Airborne respiratory droplets
- vertical transmission (mother to baby) during pregnancy

Period of communicability

- can transmit the virus for up to 48 hours before rash appears and remains contagious until all spots crust over

Reservoir

- MAN -the only reservoir

Susceptible host- early childhood, more in winter and spring, more severe in immuno-suppressed and pregnant women

HSV PATHOGENESIS

- The virus entry via the respiratory tract and spreads shortly after to the lymphoid system.
- After an incubation period of 14 days, the virus arrives at its main target organ, the skin.
- Following the primary infection, the virus remains latent in the cerebral or posterior root ganglia. In 10 - 20% of individuals, a single recurrent infection occurs after several decades.
- The virus reactivates in the ganglion and tracks down the sensory nerve to the area of the skin innervated by the nerve, producing a varicellaform rash in the distribution of a dermatome.

CLINICAL FEATURES

There are 2 clinical patterns of disease:

a) Primary Infection

b) Recurrent disease

HSV
Primary Infection

- Most primary infections are silent.
- In clinically apparent cases, vesicles usually develop at between 1-3 days post exposure and remain localized to the site of inoculation.
- In immunocompromised individuals the virus may disseminate.
- The nature of the disease is determined by the site of inoculation:

HSV
Primary Infections

1. Acute gingivostomatitis
2. Herpes Labialis (cold sore)
3. Ocular Herpes
4. Herpes Genitalis
5. Meningitis
6. Encephalitis
7. Neonatal herpes
8. Other cutaneous manifestation

HSV
Oral-facial Herpes

- Acute Gingivostomatitis
  - Acute gingivostomatitis is the commonest manifestation of primary herpetic infection.
  - The patient experiences pain and bleeding of the gums. 1 - 8 mm ulcers with necrotic bases are present. Neck ganglia are commonly enlarged accompanied by fever.
  - Usually a self limiting disease which lasts around 13 days.
- Herpes labialis (cold sore)
  - Herpes labialis (cold sore) is a recurrence of oral HSV.
  - A prodrome of tingling, warmth or itching at the site usually heralds the recurrence. About 12 hours later, redness appears followed by papules and then vesicles.

Gingivostomatitis

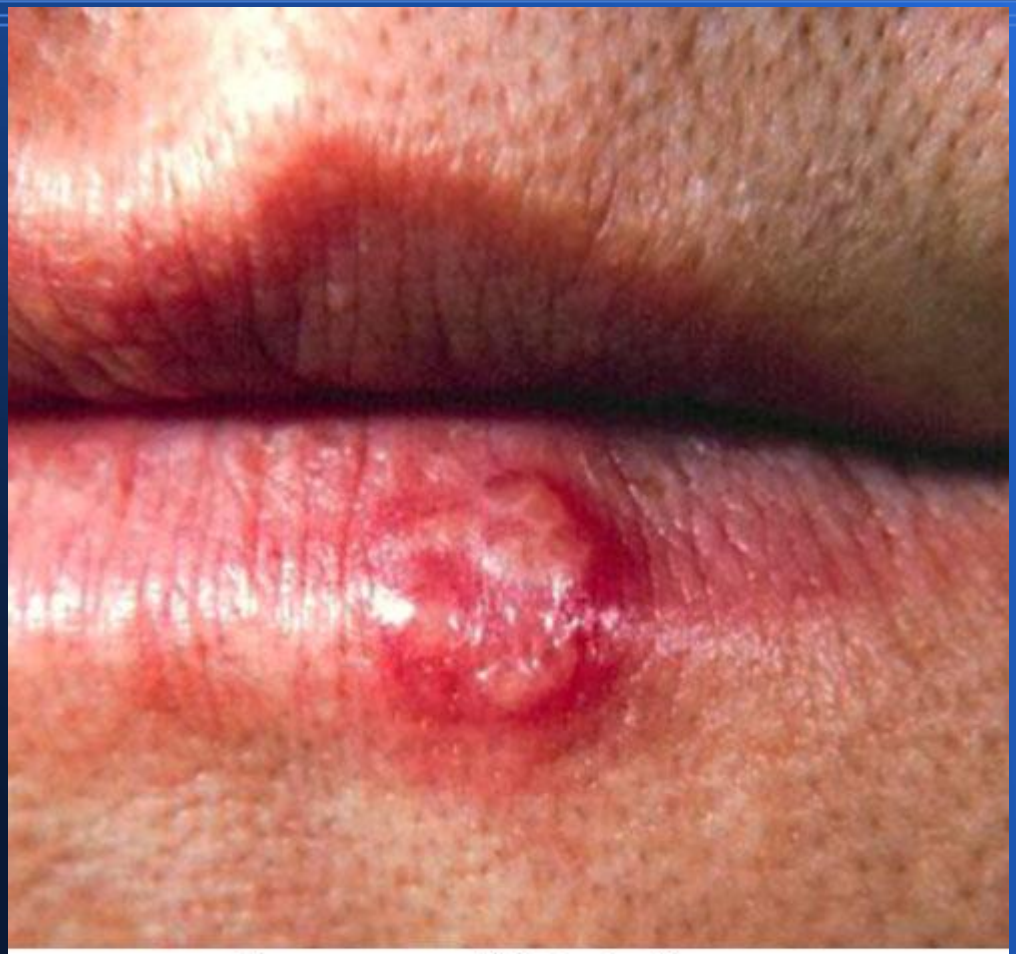
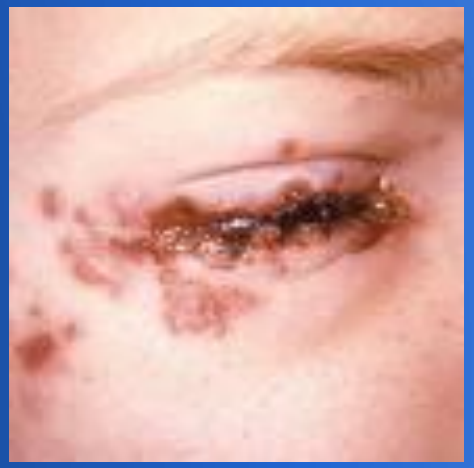


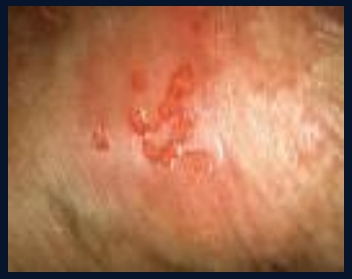
Photo courtesy of CDC - Dr. Herrmann

HSV
Ocular Herpes

HSV causes a broad spectrum of ocular disease, ranging from mild superficial lesions involving the external eye, to severe sight-threatening diseases of the inner eye. Diseases caused include the following:

- Primary HSV keratitis – dendritic ulcers
- Recurrent HSV keratitis
- HSV conjunctivitis
- Iridocyclitis, chorioretinitis and cataract





HSV
Genital Herpes

- Genital lesions may be primary, recurrent or initial.
- Many sites can be involved which includes the penis, vagina, cervix, anus, vulva, bladder, the sacral nerve routes, the spinal and the meninges. The lesions of genital herpes are particularly prone to secondary bacterial infection eg. S.aureus, Streptococcus, Trichomonas and Candida Albicans.
- Dysuria is a common complaint, in severe cases, there may be urinary retention.
- Local sensory nerves may be involved leading to the development of a radiculitis. A mild meningitis may be present.
- 60% of patients with genital herpes will experience recurrences.

Herpes Simplex Encephalitis

- Herpes Simplex encephalitis is one of the most serious complications of herpes simplex disease. There are two forms:
- Neonatal – there is global involvement and the brain is almost liquefied. The mortality rate approaches 100%.
- Focal disease – the temporal lobe is most commonly affected. This form of the disease appears in children and adults. It is possible that many of these cases arise from reactivation of virus. The mortality rate is high (70%) without treatment.
- It is of utmost importance to make a diagnosis of HSE early. It is general practice that IV acyclovir is given in all cases of suspected HSE before laboratory results are available.

Neonatal Herpes Simplex (1)

- The baby is usually infected perinatally during passage through the birth canal.
- Premature rupturing of the membranes is a well recognized risk factor.
- The risk of perinatal transmission is greatest when there is a florid primary infection in the mother.
- There is an appreciably smaller risk from recurrent lesions in the mother, probably because of the lower viral load and the presence of specific antibody

Neonatal Herpes Simplex (2)

- The spectrum of neonatal HSV infection varies from a mild disease localized to the skin to a fatal disseminated infection.
- Particularly dangerous in premature infants.
- Dissemination - most commonly involved organs are the liver, adrenals and the brain.
- Survivors of neonatal HSV infection have residual disabilities.
- Acyclovir should be promptly given in all suspected cases of neonatal HSV infection.
- The only means of prevention is to offer caesarean section to mothers with florid genital HSV lesions.

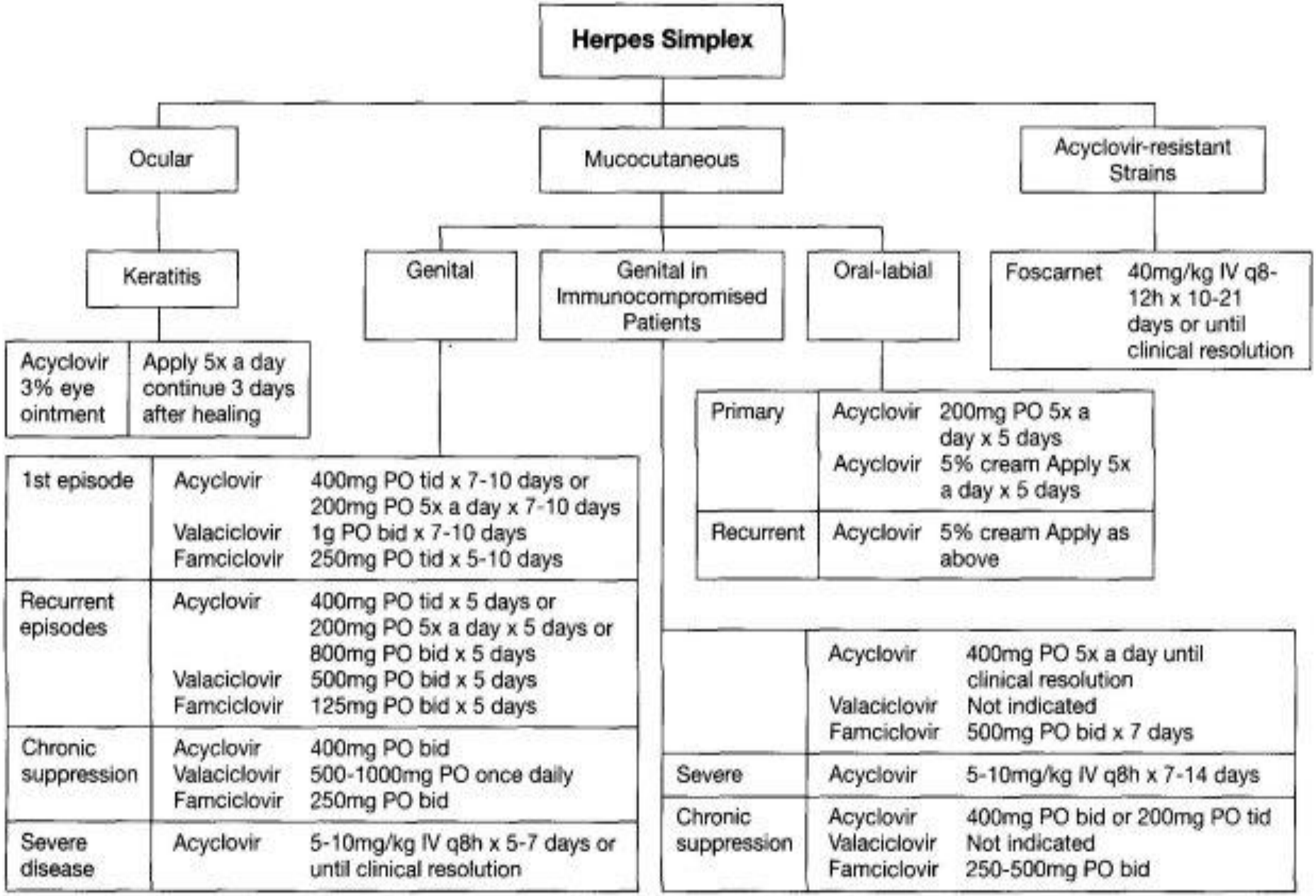
Other Manifestations

- Disseminated herpes simplex are much more likely to occur in immunocompromised individuals. The widespread vesicular resembles that of chickenpox. Many organs other than the skin may be involved e.g. liver, spleen, lungs, and CNS.
- Other cutaneous manifestations include
  - eczema herpeticum which is potentially a serious disease that occurs in patients with eczema.
  - Herpetic whitlow which arise from implantation of the virus into the skin and typically affect the fingers.
  - “zosteriform herpes simplex". This is a rare presentation of herpes simplex where HSV lesions appear in a dermatomal distribution similar to herpes zoster.

Herpes skin infections

- Localised or disseminated
- herpes gladatorium
  - sumo wrestlers
  - rugby players

Table 1 Treatment of Herpes Simplex Virus



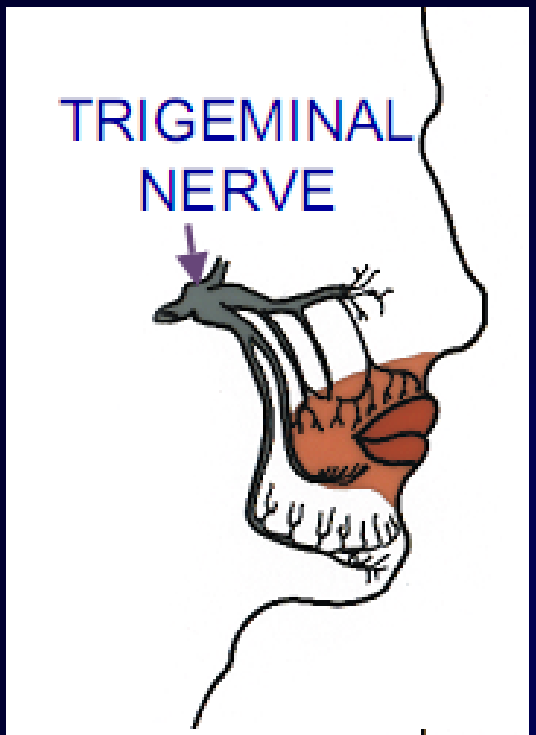
HSV
Latency and Recurrent disease

HSV1 and HSV2 can establish a latent infection in the ganglia of the nerves that supply the site of the primary infection

Genital area - sacral ganglia Oro-facial - trigeminal ganglion

Reactivation may be provoked by a number of stimuli including:

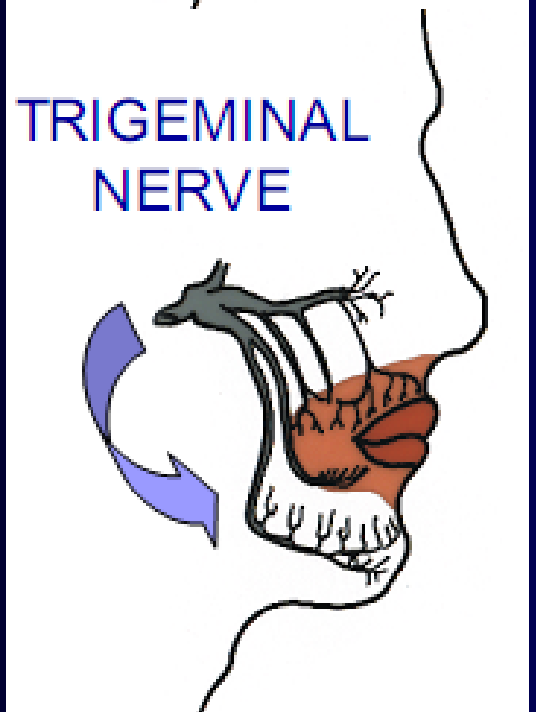
- Sunlight
- Stress
- Febrile illnesses
- Menstruation
- Immunosuppression



Latent Infection

1. **Asymptomatic - No virus or virion proteins produced**

2. **Viral DNA resides in sensory cells of Trigeminal nerve ganglion**



Recurrent Infection

1. **Virus replicates and travels down sensory nerve fiber to infect epithelial cells around the nose and mouth**

2. **Symptoms are usually a milder form of primary infection**

Clinical manifestations of HSV reactivation

- 1. Cold sores (follows gingivo-stomatitis): - vesicles erupt on the muco-cutaneous junctions of the nose or mouth. These are more localized than the primary infection and heal more rapidly (7-10 days). The eruption is often preceeded by paraesthesia of the involved area.
- 2. Recurrent genital herpes:Recurrence with HSV 2 infections is more common than with HSV 1. Lesions are less extensive and heal more rapidly than the primary infection.
- 3. Keratitis:The virus reaches the cornea via the ophthalmic branch of the trigeminal nerve; the clinical lesion is termed a dendritic ulcer. It heals more rapidly than the primary infection.

Clinical disease recognised in two forms

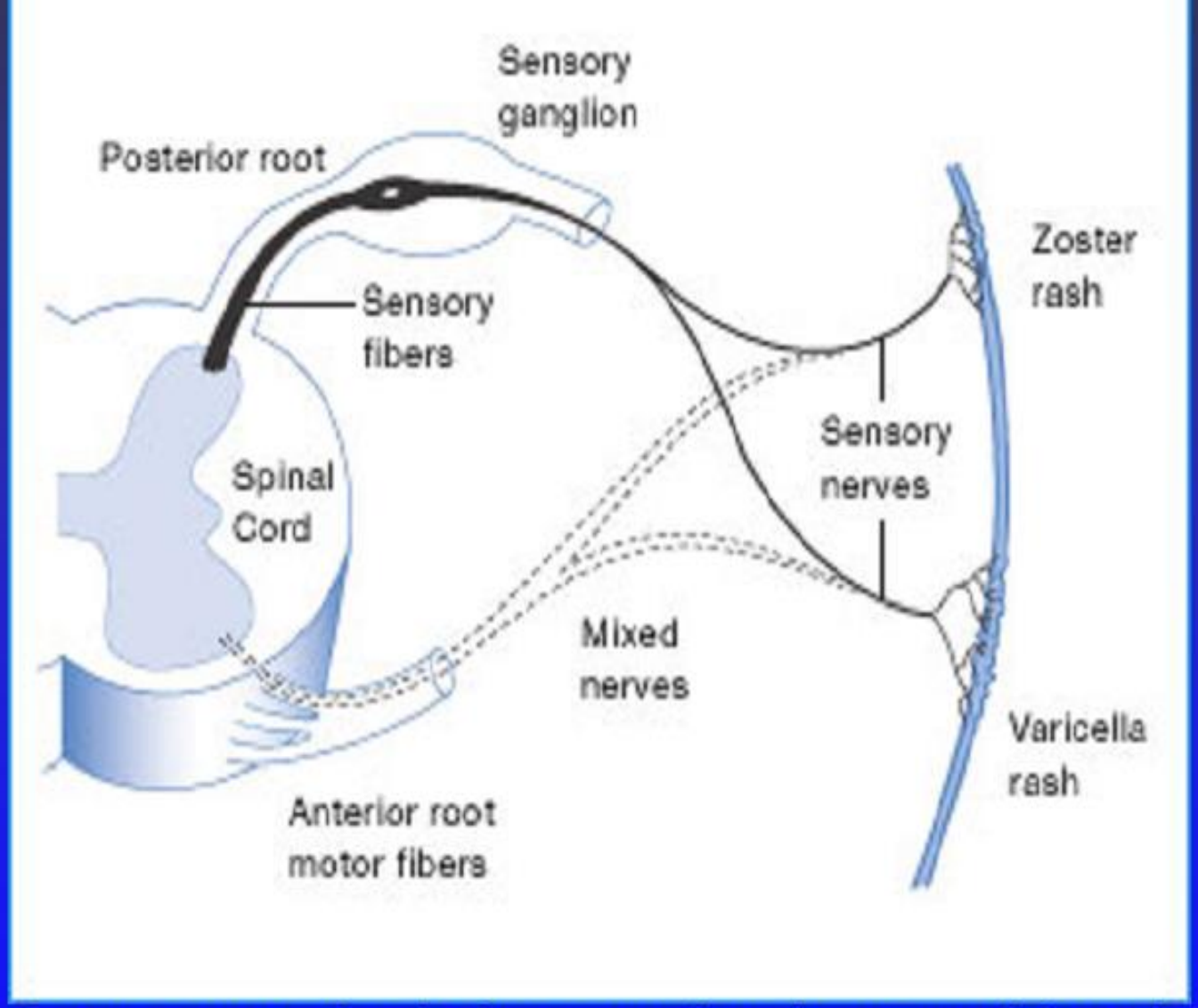
Primary infection - Varicella (Chicken Pox)

Reactivation - Zoster

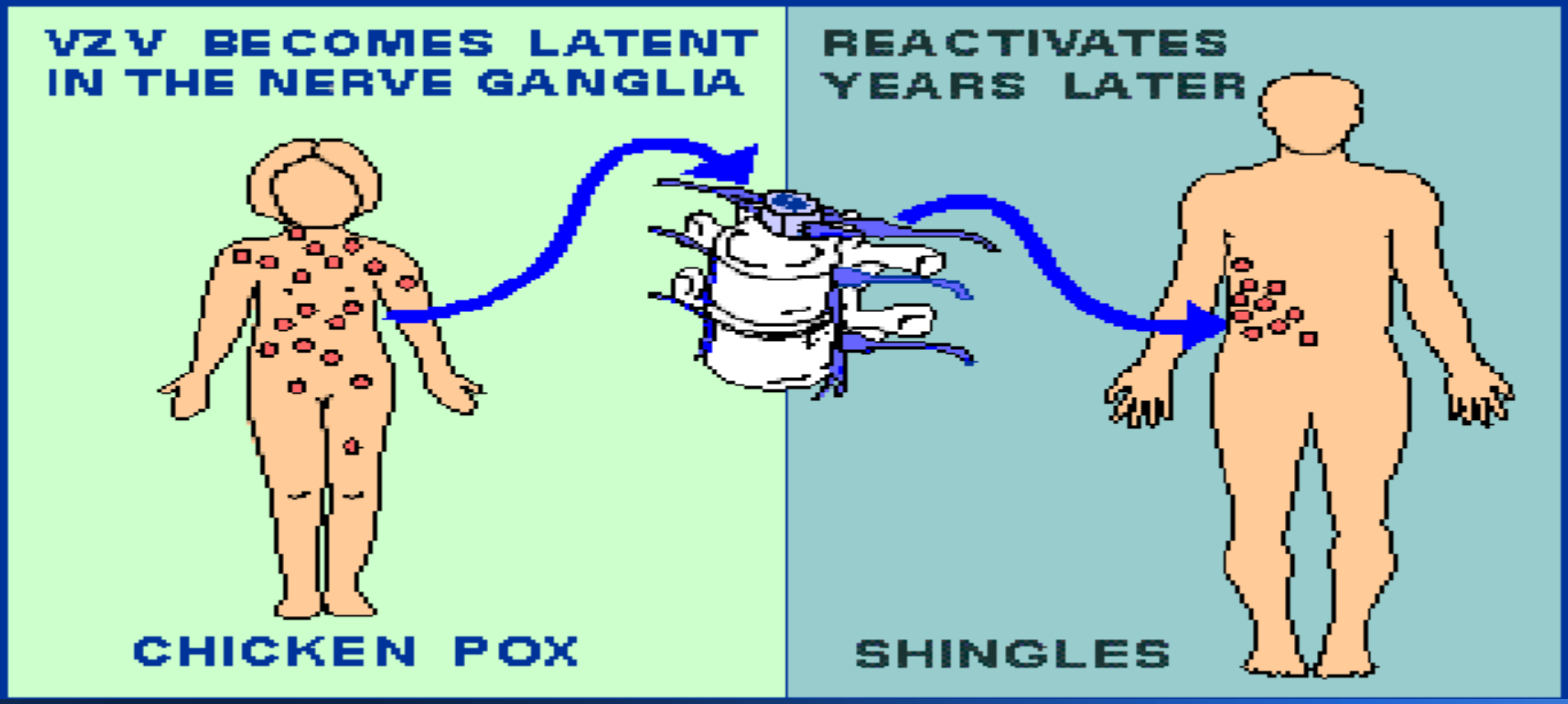
Varicella- Zoster Virus VZV

VZV Epidemiology

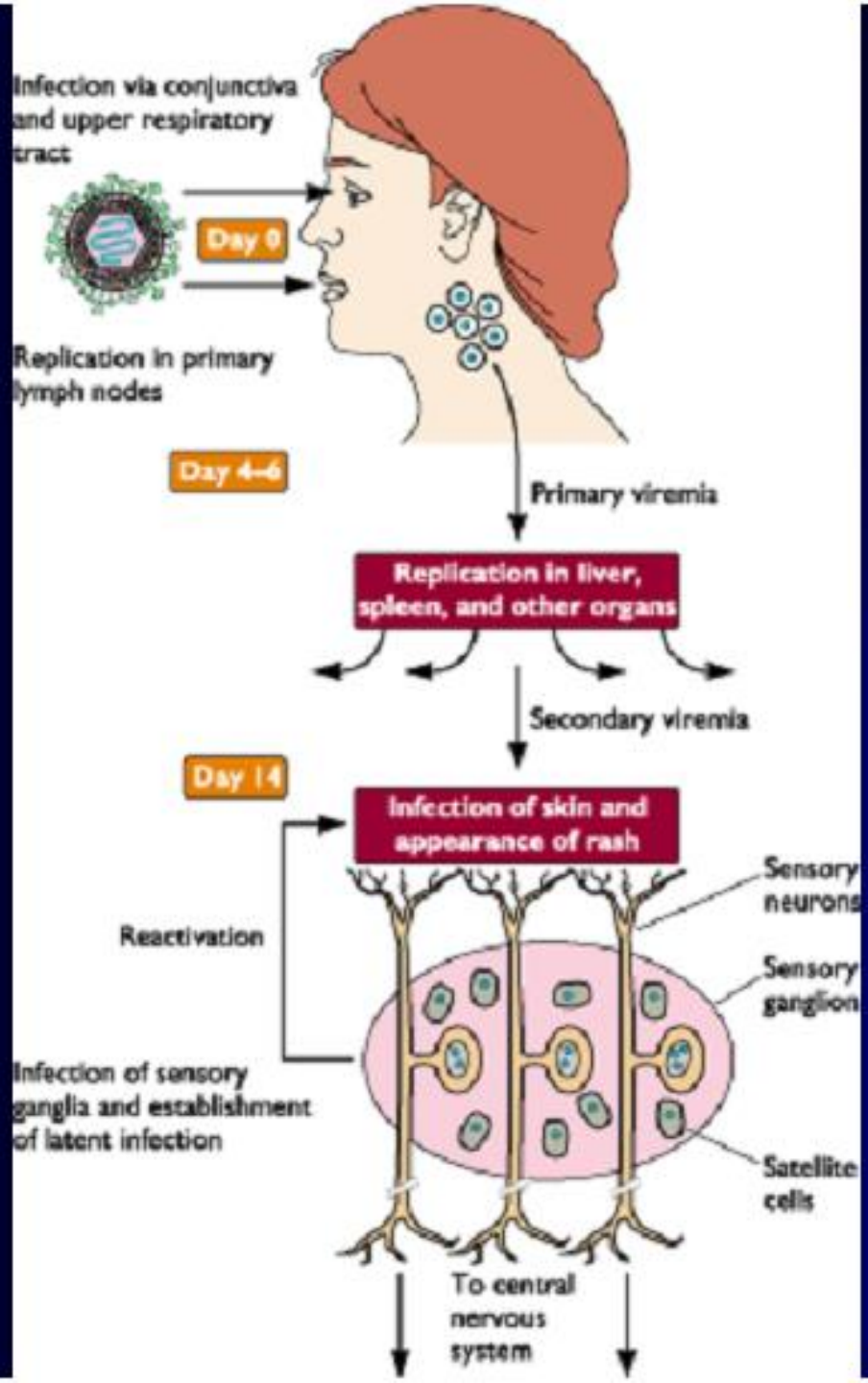
- Primary varicella is an endemic disease with the highest prevalence occurring in the 4 - 10 years old age group.
- Varicella is highly communicable, with an attack rate of 90% in close contacts.
- Most people become infected before adulthood, but 10% of young adults remain susceptible.
- Herpes zoster, in contrast, occurs sporadically and evenly throughout the year.



The enveloped virus creates the chickenpox rash and can travel from the skin to sensory nerves. Once in the sensory nerves, the virus moves to the sensory ganglia where it becomes latent. If reactivated, the virus travels from the sensory ganglia back to the skin where it creates the shingles rash.

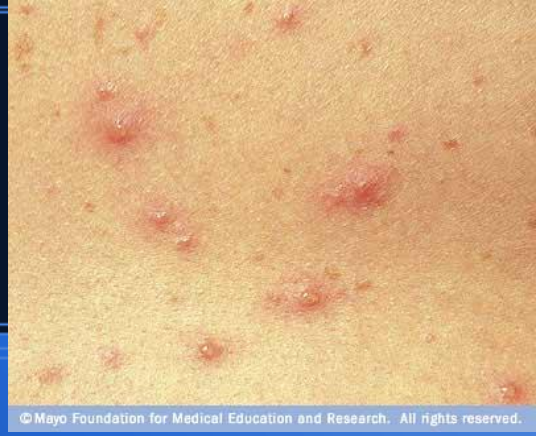


The VZV infectious cycle is cell-type specific in that infection of epidermal cells produces lytic infection, while infection of the sensory ganglia leads to latency.



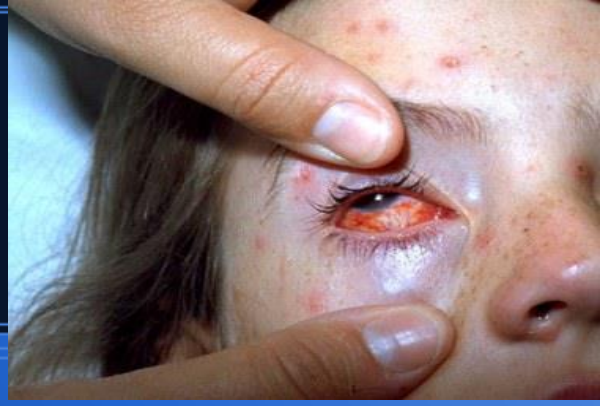
- Secondary viremia is associated with prodromal symptoms followed by cutaneous and mucosal lesions
- Viremia is usually terminated after 3 days by humoral and cell-mediated factors
- Prodromic symptoms first appear 14-15 days post-infection involving fever and rash
- Eruption into maculopapular rash forming lesions over 2-4 days. May appear on scalp, trunk, extremities and mucosal surfaces.
- Vesicles dry over 1-3 weeks. Infectious virus found in vesicular fluid.

Clinical picture



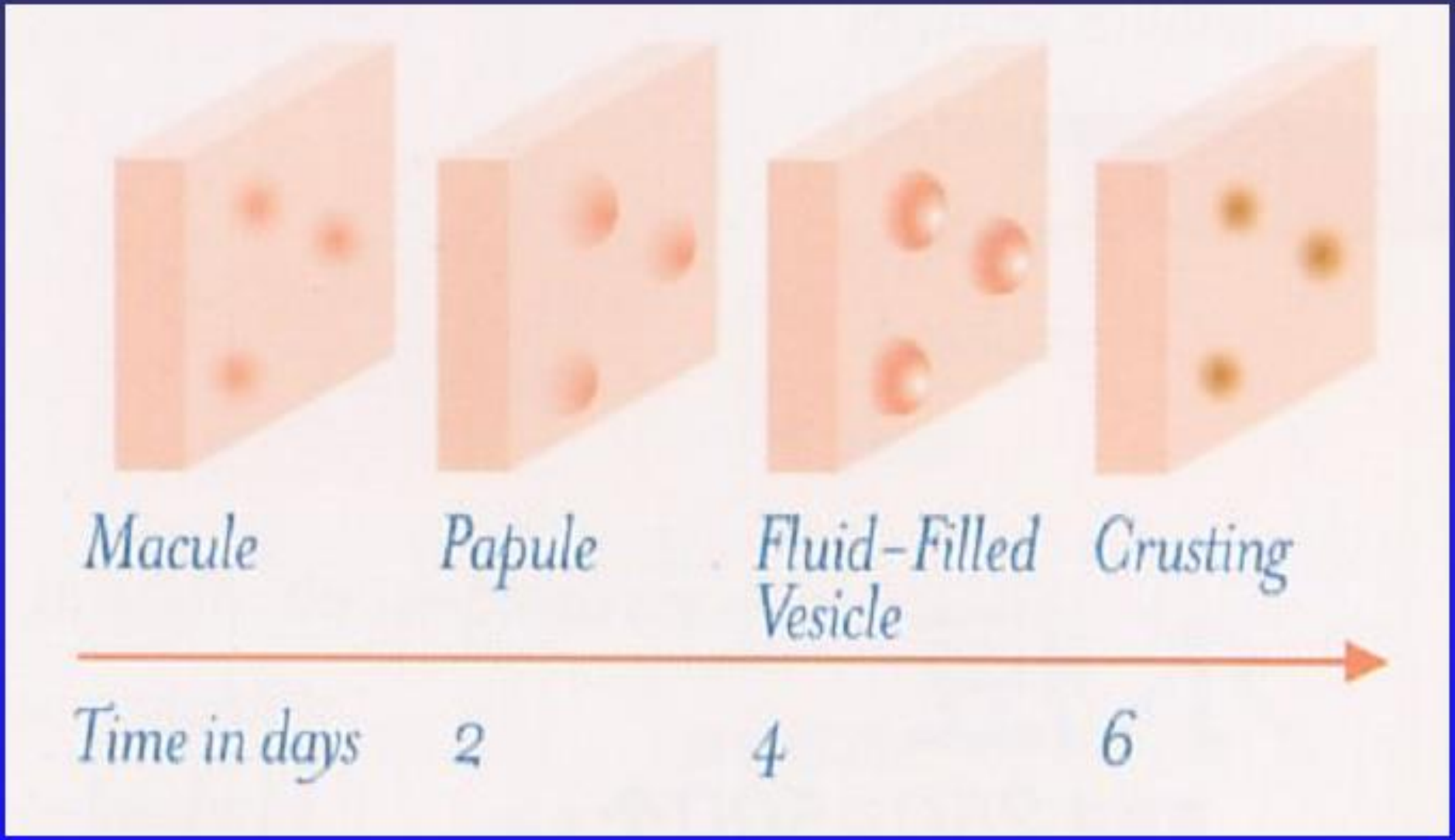
- Incubation period 10-21 days (2-3 weeks)
- Prodromal symptoms : particularly in older children
  - Low-grade fever preceding skin manifestations by 1-2D
  - 24-48 hr before rash
    - Mild abdominal pain
    - Mild cough and runny nose
  - mild headache
  - malaise or irritability

Varicella rash

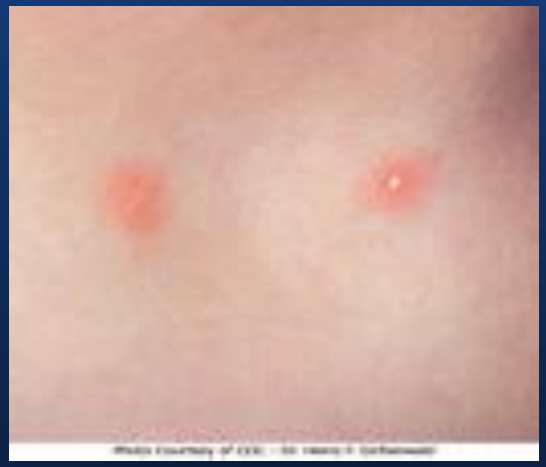


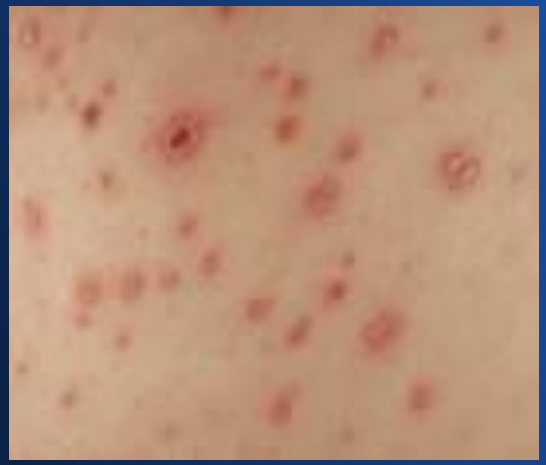
- red, itchy rash appear first on the scalp, face, trunk
- quickly turn into clear fluid-filled vesicles
- 24-48 hr later, clouding and umbilication of lesions
- initial lesions are crusting, new crops form on trunk and then the extremities
- characteristics : various stages of evolution
- the average number of varicella lesion is about 300 lesions
  - <10 to >1,500 lesions
- itching may range from mild to intense

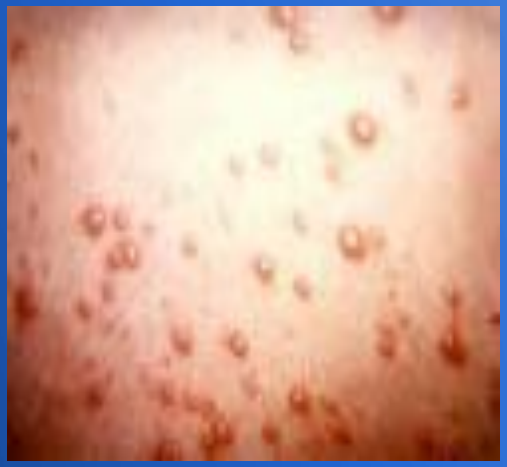
Stages of chickenpox rash



Rash of Chickenpox







Laboratory Diagnosis

UNNECESSARY FOR DIAGNOSIS ***OBVIOUS CLINICALLY***

Virus Isolation - rarely carried out as it requires 2-3 weeks for a results.

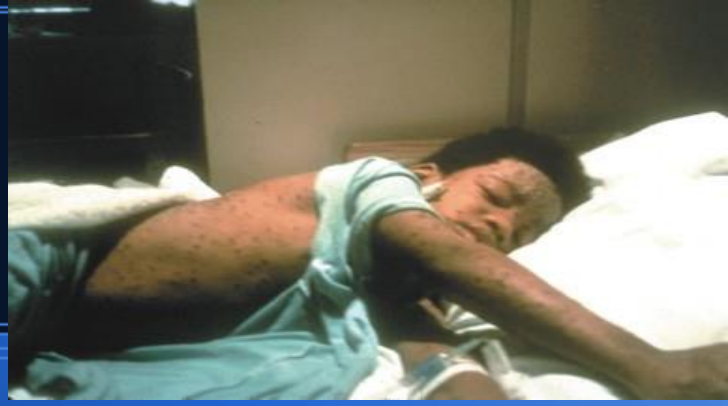
Direct detection

- electron microscopy may be used for vesicle fluids but cannot distinguish between HSV and VZV
- immunofluorescense on skin scrappings can distinguish between the two.- Tzanck smear : multinucleated giant cells

Serology - VZV IgG is indicative of past infection and immunity.
VZV IgM ----------> recent primary infection.

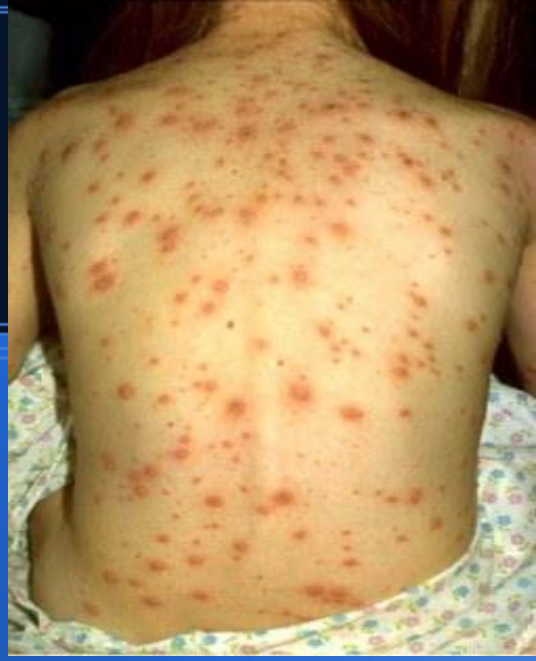
Not that useful in the acute phase because it takes 1-2 weeks for before antibodies appear after infection

VZV
Immune response



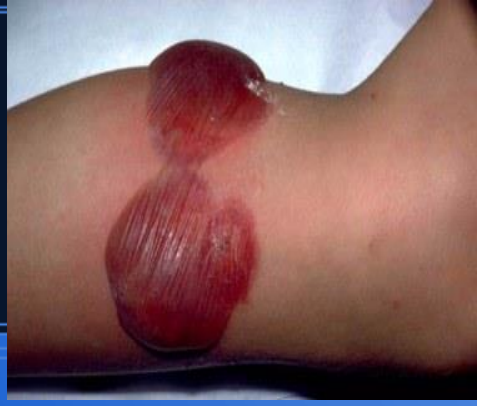
- Natural infection induces lifelong immunity to clinical varicella in almost all immunocompetent persons
- Newborn babies of immune mothers are protected by passively acquired antibodies during their first months of life
- Temporary protection of non-immune individuals can be obtained by injection of varicella-zoster immune globulin within 3 days of exposure
- The immunity acquired in the course of varicella prevents neither the establishment of a latent VZV infection, nor the possibility of subsequent reactivation as zoster.

Varicella
High-risk groups



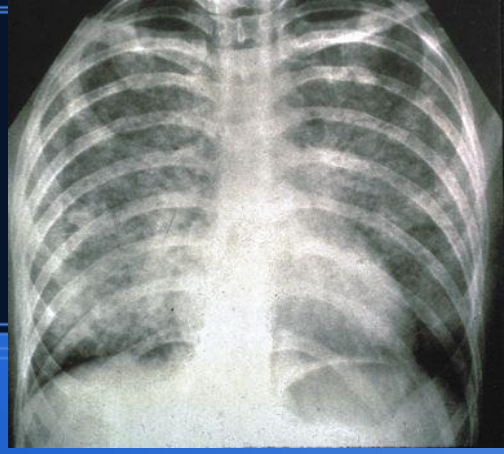
- High risks of complications
  - Newborns and infants whose mothers never had chickenpox or the vaccine
  - Teenagers
  - Adults
  - Pregnant women
  - People whose immune systems are impaired by another disease or condition
  - People who are taking steroid medications for another disease or condition, such as asthma
  - People with the skin inflammation eczema

Complications of Varicella



- herpes zoster (shingles)
  - lifetime risk 15%-20%
  - mainly affecting the elderly and immunocompromised persons
- secondary bacterial skin and soft tissue infections
- otitis media
- bacteremia, pneumonitis
- osteomyelitis
- septic arthritis
- endocarditis
- necrotizing fasciitis
- toxic shock-like syndrome
- hepatitis
- thrombocytopenia hemorrhegic varicella
- cerebellar ataxia
- encephalitis
- severe invasive group A streptococcal infection increases the risk 40-60 fold*

Complications of Varicella



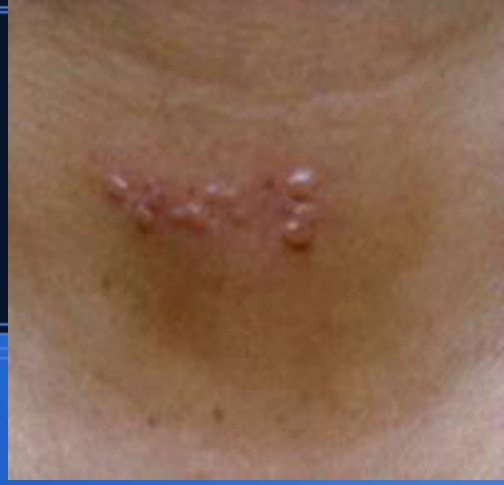
- When compared with children, adults are
  - higher risk : admitted to hospital for varicella
  - higher rates of complications such as pneumonia and Encephalitis

- The risk factors identified in adults for varicella pneumonia
  - underlying chronic lung disease
  - smoking

Herpes Zoster (Shingles)
Reactivation lesion of VZV

- Like HSV, the virus (VZV) establishes a latent infection in sensory ganglia. Reactivation usually occurs many years after primary infection and is often associated with immunosuppresion of the host.
- Herpes Zoster mainly affect a single dermatome of the skin.
- It may occur at any age but the vast majority of patients are more than 50 years of age.
- There is a characteristic eruption of vesicles in the dermatome which is often accompanied by intensive pain which may last for months (postherpetic neuralgia)
- Herpes zoster affecting the eye and face may pose great problems.
- Complications are rare and include encephalitis and disseminated herpes zoster.

Complications of Herpes Zoster



- Postherpetic neuralgia
- Ocular involvement with facial zoster
- Meningoencephalitis
- Cutaneous dissemination
- Superinfection of skin lesions
- Hepatitis/pneumonitis
- Peripheral motor weakness/segmental myelitis
- Cranial nerve syndromes, particularly ophthalmic and facial (Ramsay Hunt syndrome)
- Corneal ulceration
- Guillain-Barré syndrome

VZV
Treatment

- Uncomplicated VARICELLA - a self limited disease and requires no specific treatment.

Acyclovir

- immunocompromised individuals with varicella infection
- normal individuals with serious complications such as pneumonia and encephalitis.

- HERPES ZOSTER in a healthy individual is not normally a cause for concern. The main problem is the management of the postherpetic neuralgia.
- Three drugs can be used for the treatment of herpes zoster: acyclovir, valaciclovir, and famciclovir.

Table 2 Treatment of Herpes Zoster in Adults

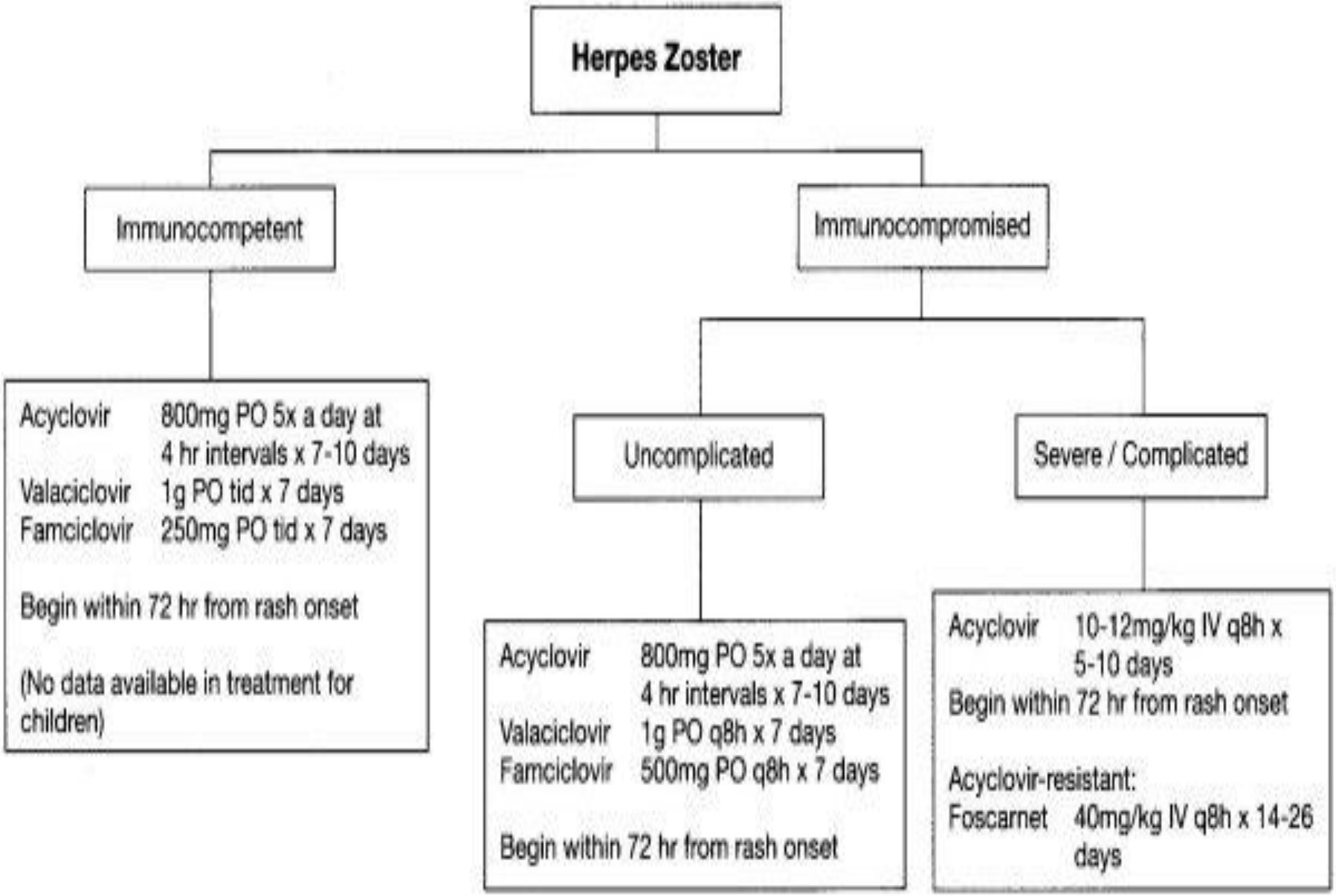
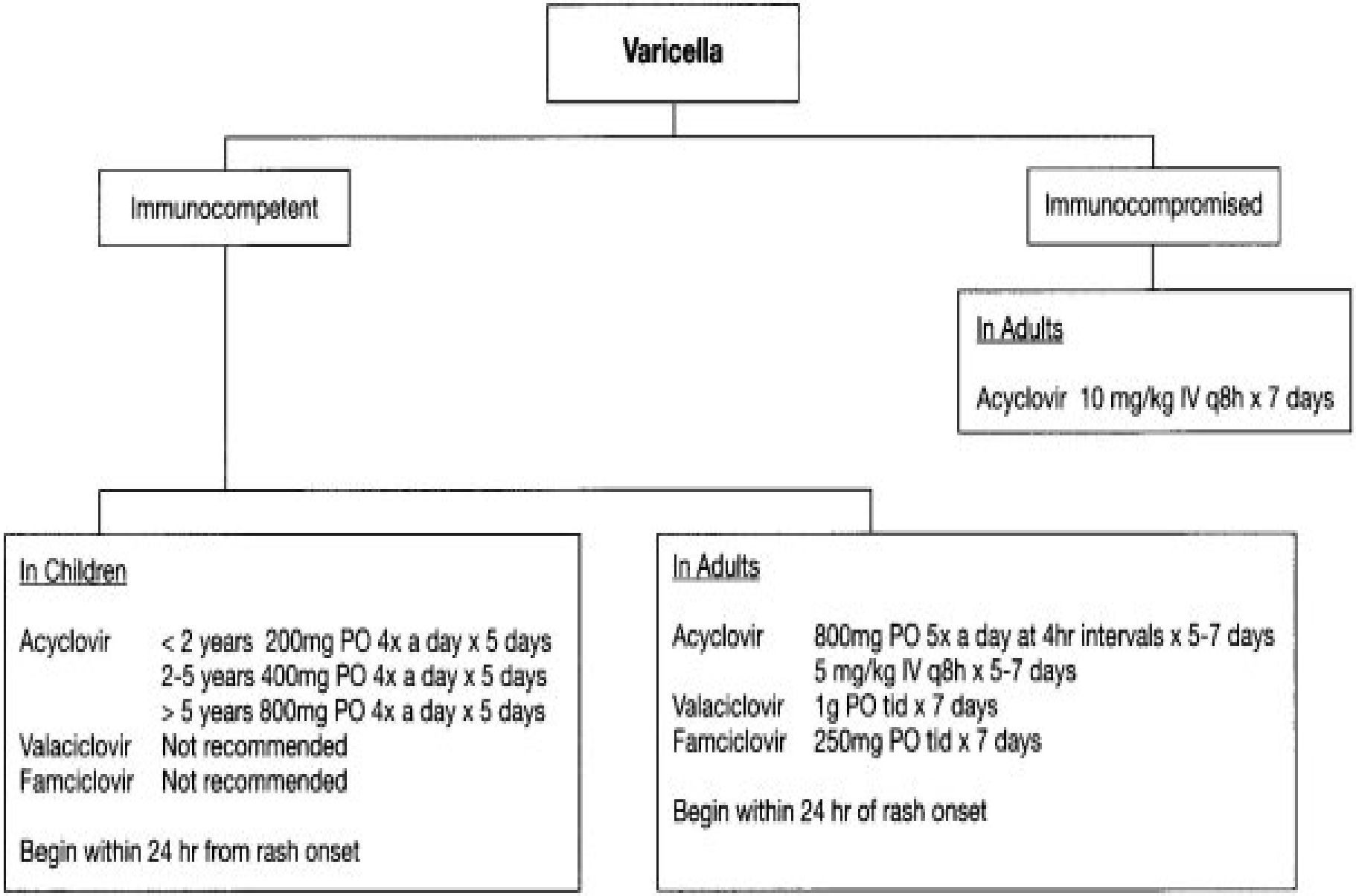
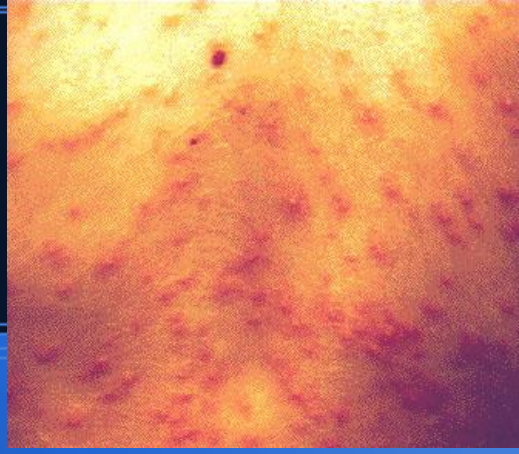


Table 3 Treatment of Varicella

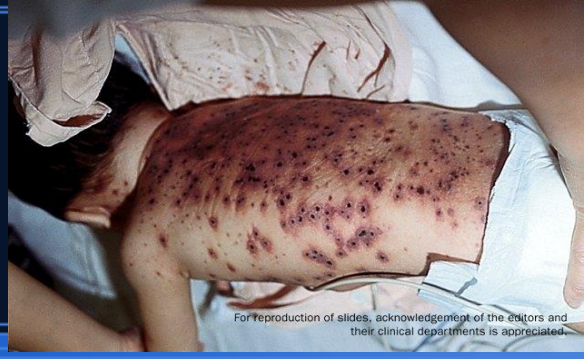


Postexposure Immunization



- Varicella vaccine
  - Susceptible people ≥ 12 mo of age, including adults
  - As soon as possible within 72 hr and possibly up to 120 hr after varicella exposure

VZV
Passive immunoprophylaxis



- VariZIG should be administered as soon as possible, but no later than 96 hours after exposure
  - Newborns whose mothers have chicken pox five days prior to two days after delivery
  - Children with leukemia or lymphoma who have not been vaccinated
  - Persons with cellular immunodeficiencies or other immune problems
  - Persons receiving drugs, including steroids, that suppress the immune system

Congenital VZV Infection

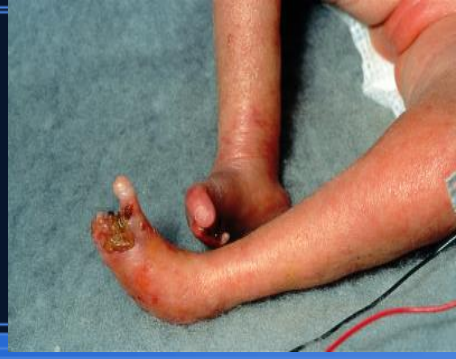
- 90% of pregnant women already immune, therefore primary infection is rare during pregnancy.
- Primary infection during pregnancy carries a greater risk of severe disease, in particular pneumonia.

First 20 weeks of Pregnancy

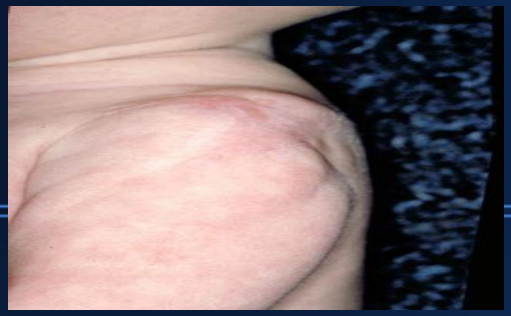
congenital varicella syndrome;

- Scarring of skin
- Hypoplasia of limbs
- CNS and eye defects
- Death in infancy normal

Stigmata of Varicella-Zoster Virus Fetopathy



- ***Damage to Sensory Nerves***
  - Cicatricial skin lesions
  - Hypopigmentation
- ***Damage to Optic Stalk and Lens Vesicle***
  - Microphthalmia
  - Cataracts
  - Chorioretinitis
  - Optic atrophy



- ***Damage to Brain/Encephalitis***
  - Microcephaly
  - Hydrocephaly
  - Calcifications
  - Aplasia of brain
- ***Damage to Cervical or Lumbosacral Cord***
  - Hypoplasia of an extremity
  - Motor and sensory deficits
  - Absent deep tendon reflexes
  - Anisocoria
  - Horner’s syndrome
  - Anal/urinary sphincter dysfunction

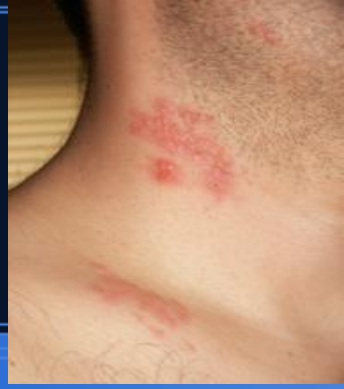
Neonatal Varicella

- VZV can cross the placenta in the late stages of pregnancy to infect the fetus congenitally.
- If rash in mother occurs more than 1 week before delivery, then sufficient immunity would have been transferred to the fetus.
- Zoster immunoglobulin
  - to susceptible pregnant women who had contact with suspected cases of varicella.
  - to infants whose mothers develop varicella during the last 7 days of pregnancy or the first 14 days after delivery.

Neonatal varicella

- can be a serious illness, depending upon the timing of maternal varicella and delivery
- If the mother develops varicella within 5 days before or 2 days after delivery
  - acquires the virus transplacentally
  - no protective antibodies
  - Prophylaxis or treatment is required with varicella-zoster immune globulin (VZIG) and acyclovir
  - Without these drugs, mortality rates 20% - 30%*
  - The primary causes of death are severe pneumonia and fulminant hepatitis

Isolation of the hospitalized patient



- Immunocompromised patient who have zoster (localized or disseminated) and immunocompetent patients with disseminated zoster
  - Airborne and contact precautions for the duration of illness
- For immunocompetent patients with localized zoster
  - Contact precautions until all lesions are crusted

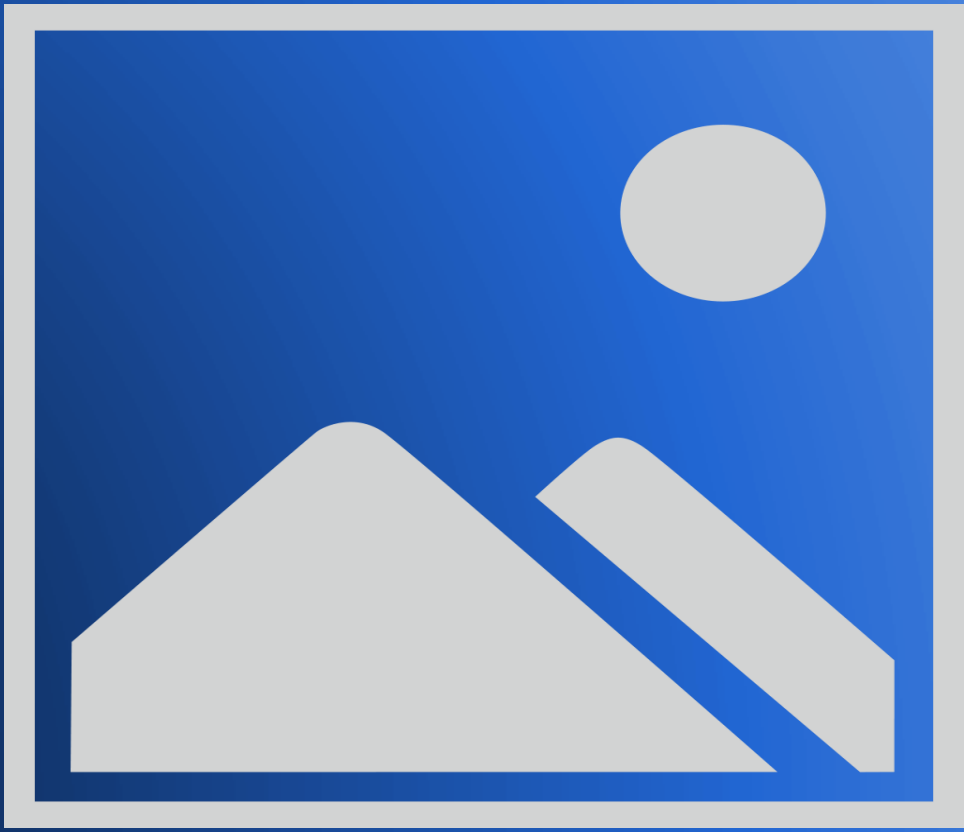
THANK YOU

MUMPS

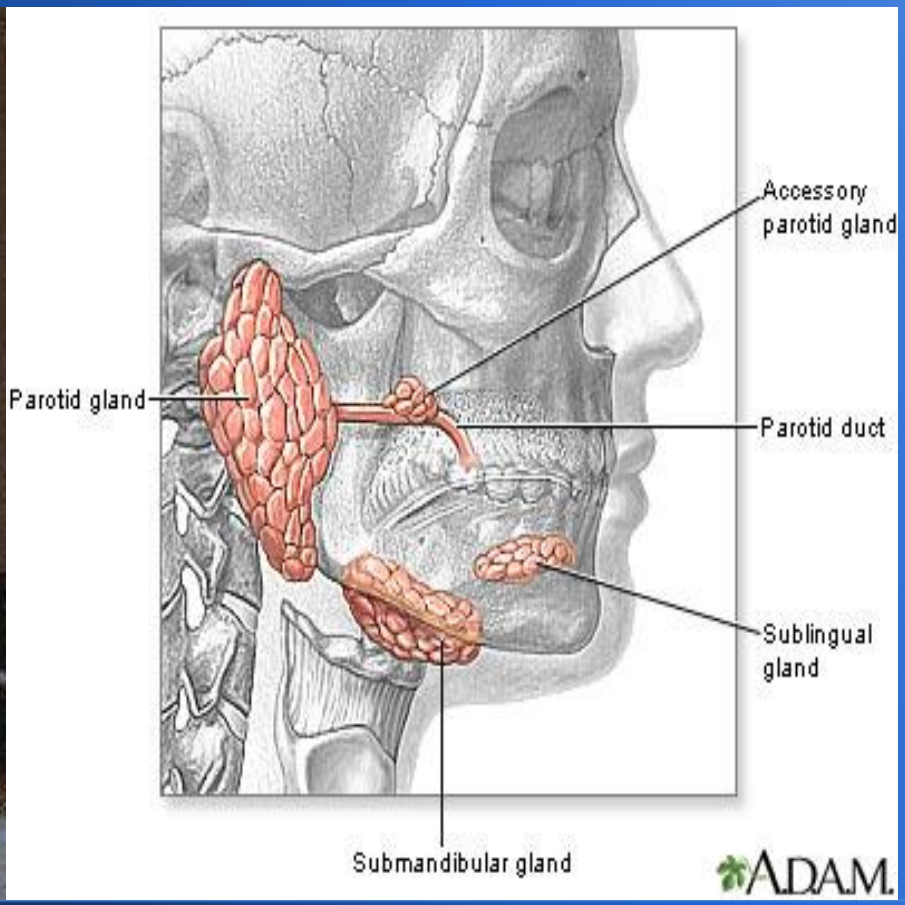
To MUMP= to grimase appearance due to parotid gland swelling

PARAMYXOVIRUSES
MUMPS

- Mumps virions- pleomorphic enveloped particles 120-200 nm
- single-stranded, negative-sense RNA surrounded by an envelope.



MUMPS


Accessory parotid gland
Parotid gland
Parotid duct
Sublingual gland
Submandibular gland
A.D.A.M.

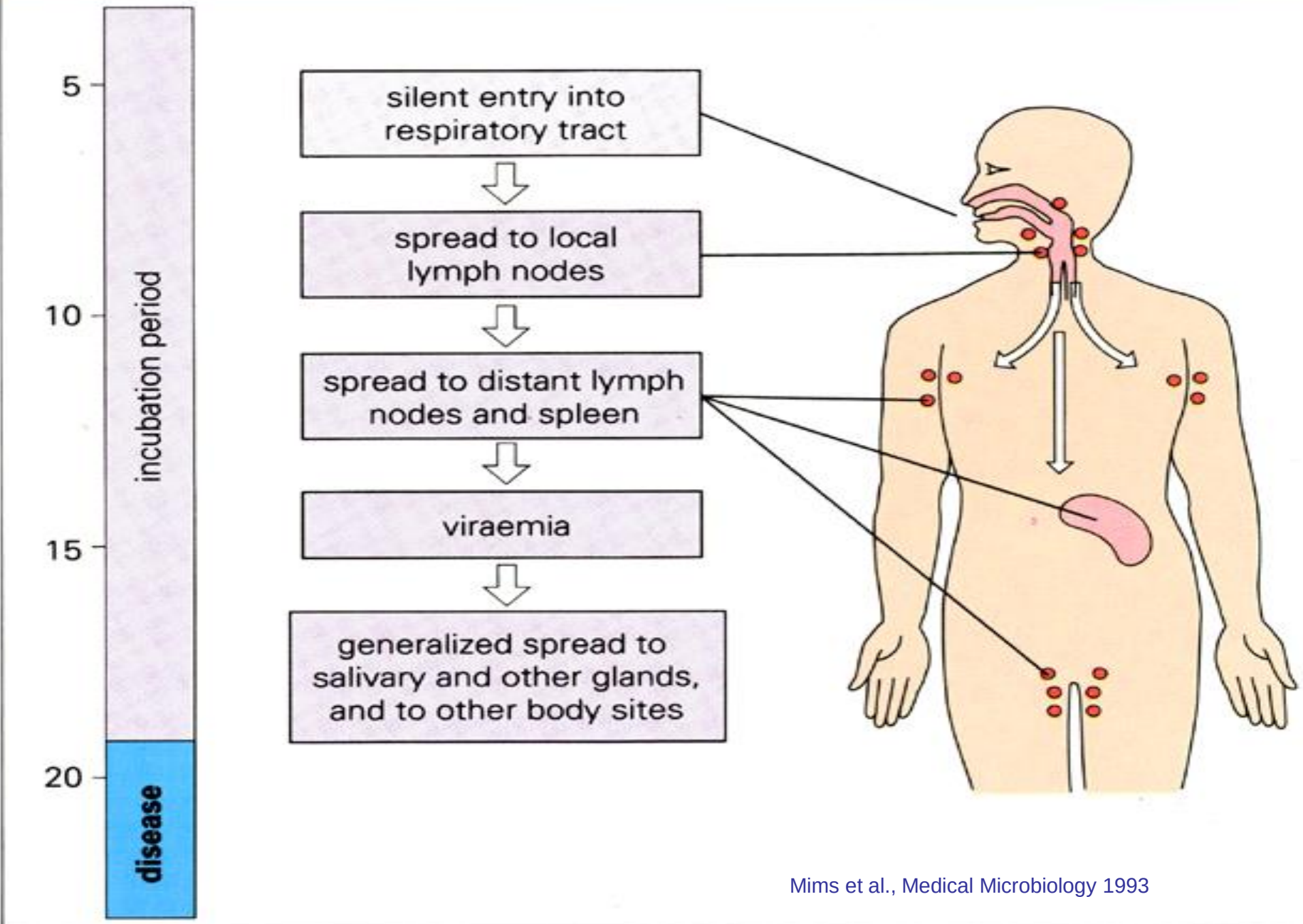
Epidemiology

- MAN ONLY HOST
- transmitted by contact with infected respiratory secretions
- most common in late winter and early spring
- the period of communicability is usually from 9 days prior to the onset of parotid edema lasting 7 days after onset of swelling
- immunity - lifelong

Pathogenesis

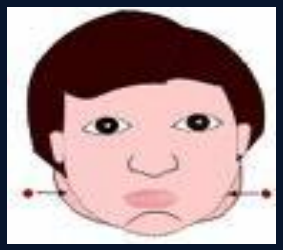
- After the initial entry into the respiratory system, the virus replicates locally, then follows with a viremic dissemination to target tissues, such as the central nervous system (CNS) and salivary glands, particularly the parotid glands
- A secondary phase of viremia, found before the immune response, is the result of replication of the virus at the target organs CNS, testis, epididymis, pancreas, ovary

PATHOGENESIS OF MUMPS



Mims et al., Medical Microbiology 1993

CLINICAL STAGES of Mumps



- Asymptomatic incubation period 12-25 days
- Prodromal stage- 2 days

  - constitutional symptoms: low grade fever, malaise, headache, myalgia
- Parotitis - generally within 1 day, unilateral parotid swelling will be evident , in 75% followed 1-5 days later by enlargement of the contralateral gland

  - the swollen gland may lift the adjacent ear upward and outward and will obscure the mandibular angle.

  - complaint of earache on the affected side and disconfort on ingesting acidic foods or liquids

- Resolution – of systemic illness occurs within 3-5 days and parotitis within 7-10 days

Mumps
Epididymo-orchitis

Epididymo-orchitis is the second most common manifestation of adult mumps, which is usually preceded by parotitis. Unilateral involvement is found in 20-30% of the patients, whereas bilateral involvement occurs in fewer than 2% of cases.

* Orchitis presents acutely with fever, chills, nausea, vomiting, and lower abdominal pain. After the fever, the testes begin to rapidly swell. The size increase could be slight or as much as 4 times normal size. As the fever decreases, the pain and edema subside. Absolute sterility sequela is rare- impairment of fertility 13%

Oophoritis is associated with pelvic pain and tenderness- impairment of fertility is not evident.

Mumps Meningoencephalitis

Meningoencephalitis is 1;6000 cases complication in childhood

The pathogenesis is described as a primary infection of the neurons and/or postinfection encephalitis with demyelination.

Parotitis may appear simultaneously with the primary neuron infection, or it may appear 10 days after the parotitis in the postinfection type.

The illness presents with fever, headache, nausea, vomiting, nuchal rigidity, and change of sensorium. Mumps is a common cause of aseptic meningitis, which usually is indistinguishable from other causes, such as enteroviruses and herpes or pox viruses. The cerebrospinal fluid (CSF) has less than 500 cells/mm3, mostly lymphocytes. Mumps virus can be isolated in the CSF.

Mumps
Clinical

Pancreatitis- is a rare manifestation

sudden onset of epigastric pain and tenderness occurs accompanied by fever, chills, nausea, and vomiting.

Elevated amylase level

Lipase is a more specific indicator of pancreatic involvement

After 1 week- completely recovery

Thyroiditis may occur about 1 week after parotitis, with the development of antithyroid antibodies.

Myocarditis is a serious and extremely rare manifestation.

Differential diagnosis

- Suppurative or recurrent parotitis
- Parotid calculus
- Coxsackievirus infection
- Parainfluenza type 3 infection
- Mixed tumors, hemangiomas, lymphangiomas of the parotid gland
- Human immunodeficiency virus (HIV) infection
- Meningoencephalitis
- Allergic reaction, rare

Laboratory diagnosis

Mumps virus can be isolated in a cell culture inoculated with throat washings, urine, or spinal fluid.

Serum amylase level is elevated in mumps parotitis and pancreatitis. Serum lipase level is elevated in pancreatitis.

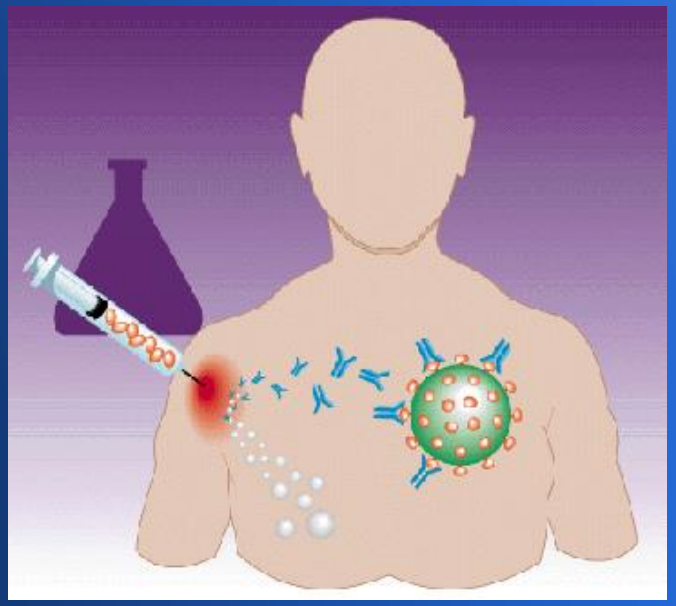
The complete blood count (CBC) may be elevated with a predominance of lymphocytes.

The complement fixation (CF), neutralization, or hemagglutination inhibition (HAI) test or an enzyme immunoassay (EIA) can be used to serologically confirm infection or vaccination.

If considering meningoencephalitis, perform a lumbar puncture to eliminate causes other than mumps

PREVENTION

- live attenuated vaccine MMR vaccine
- Contradindicated in
  - immune-suppressed
  - pregnant women



MUMPS

I had a feeling in my neck,
And on the sides were two big bumps;
I couldn't swallow anything
At all because I had the mumps.

And Mother tied it with a piece,
And then she tied up Will and John,
And no one else but Dick was left
That didn't have a mump rag on.

He teased at us and laughed at us,
And said, whenever he went by,
"It's vinegar and lemon drops
And pickles!" just to make us cry.

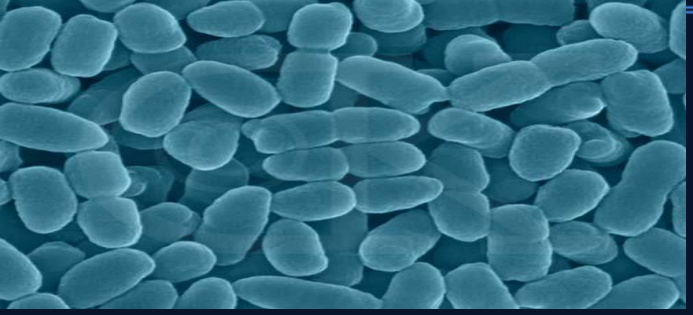
But Tuesday Dick was very sad
And cried because his neck was sore,
And not a one said sour things
To anybody any more.

ELIZABETH MADOX ROBERTS

Bordetella pertussis
Whooping cough

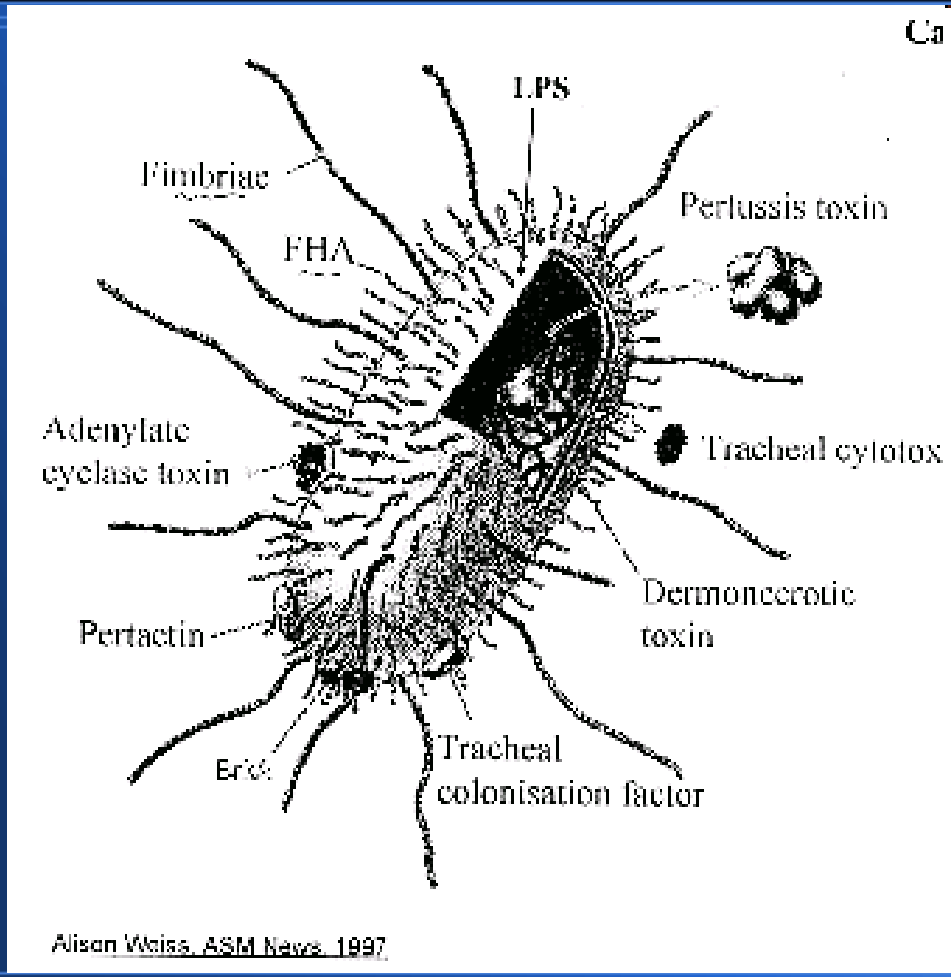
Donkey cough

- a peculiar whooping noise made as the person breathes in after coughing



Bordetella pertussis

- Belongs to Alcaligenaceae Family
- A very small Gram-negative aerobic coccobacillus that appears singly or in pairs.
- Lengh is 0.5 microns
- Non motile, Non sporing
- Capsulated – loose on repeated culturing



Bordetella pertussis
Epidemiology

B.pertussis - 95 % B.parapertussis – 5% B.brochoseptica-occasionally

- Humans are the only reservoir
- The bacteria spread from person to person through tiny drops of fluid from an infected person's nose or mouth.
- These may become airborne when the person sneezes, coughs, or laughs.
- Other people then can become infected by inhaling the drops or getting the drops on their hands and then touching their mouths or noses.
- Pertussis is most infectious when patients are in the catarrhal phase, but pertussis may remain communicable for 3 or more weeks after the onset of cough.

Bordetella pertussis
Immunity

Pertussis is highly contagious.

- Most severe in unimmunized children and in infants under 1 year of age
- Maternal antibodies are not protective
- Non immune rarely escape infection
- Chronic carriers are not known
- After an attack of pertussis, lifelong immunity
- The second attacks may have been parapertussis, viruses (adenoviruses) or chlamydia

Components of B. pertussis

adhesion

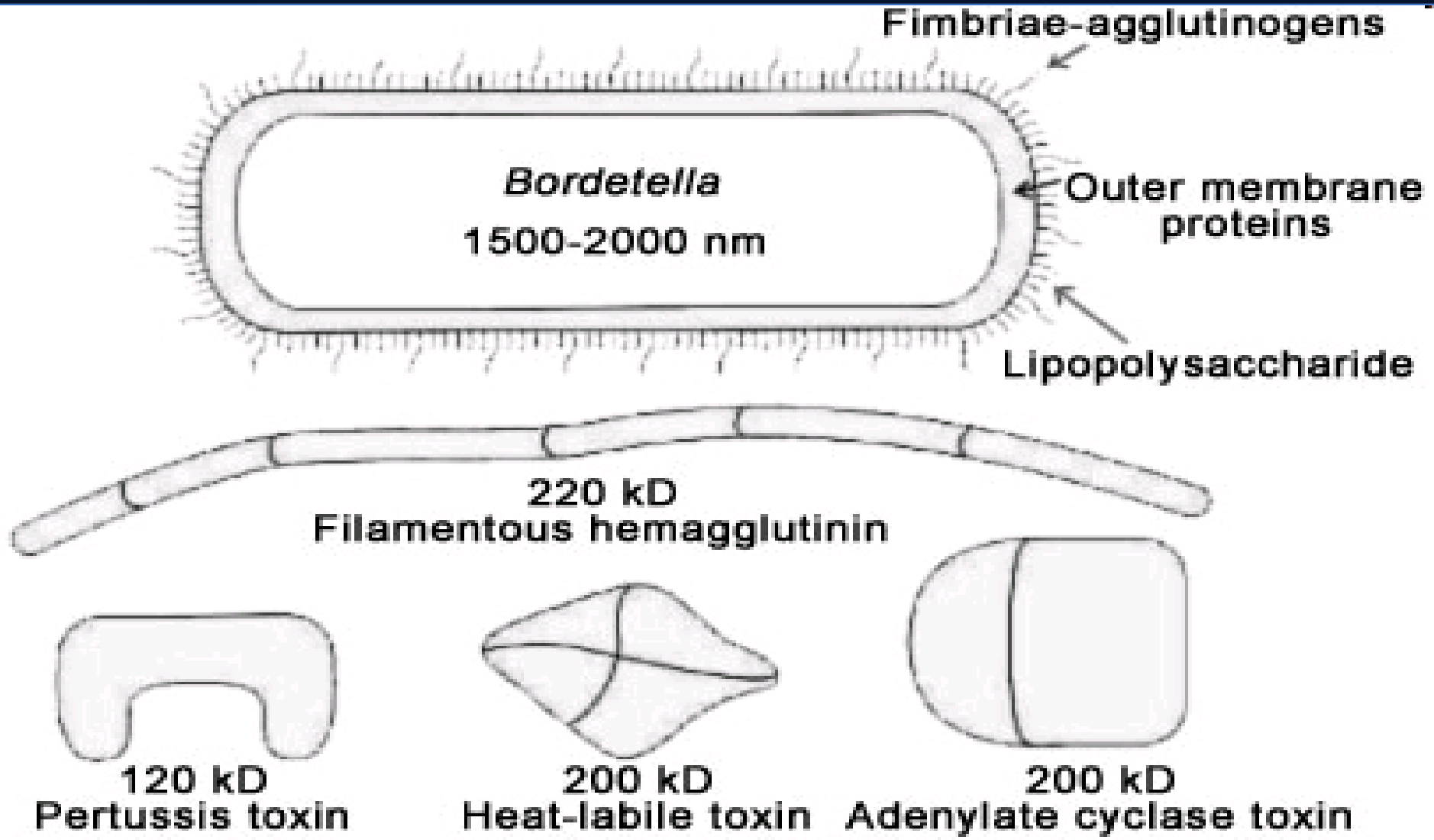
- Pertussis toxin- bacterial A-B toxin, affects host immune function
- Filamentous hemagglutinin- agglutinates RBC,forms filaments, and attaches to ciliated cells
- Pertactin –attaches to protein receptors
- Fimbriae - antibody to fimbriae - agglutination of the organisms
- Lipooligosaccharide – envelope toxin similar to endotoxin of G- bacteria aid colonization by agglutinating human cells

Adenylate cyclase toxin - cell ability to phagocytose bacteria, inhibits chemotaxis and the superoxide burst of neutrophils

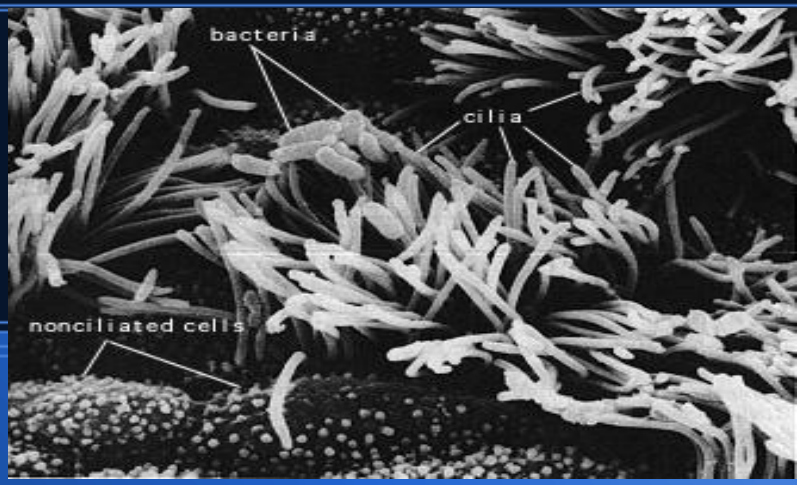
Heat labile toxin, Tracheal cytotoxin → contribute to local tissue damage in the respiratory tract

Tracheal cytotoxin cell wall fragment that kills ciliated cells

Virulent Molecules



Pertussis Toxin



- Causes pathogenesis
- Present only in B.pertussis
- Pertussis toxin is expressed on the surface, secreted into the surrounding medium

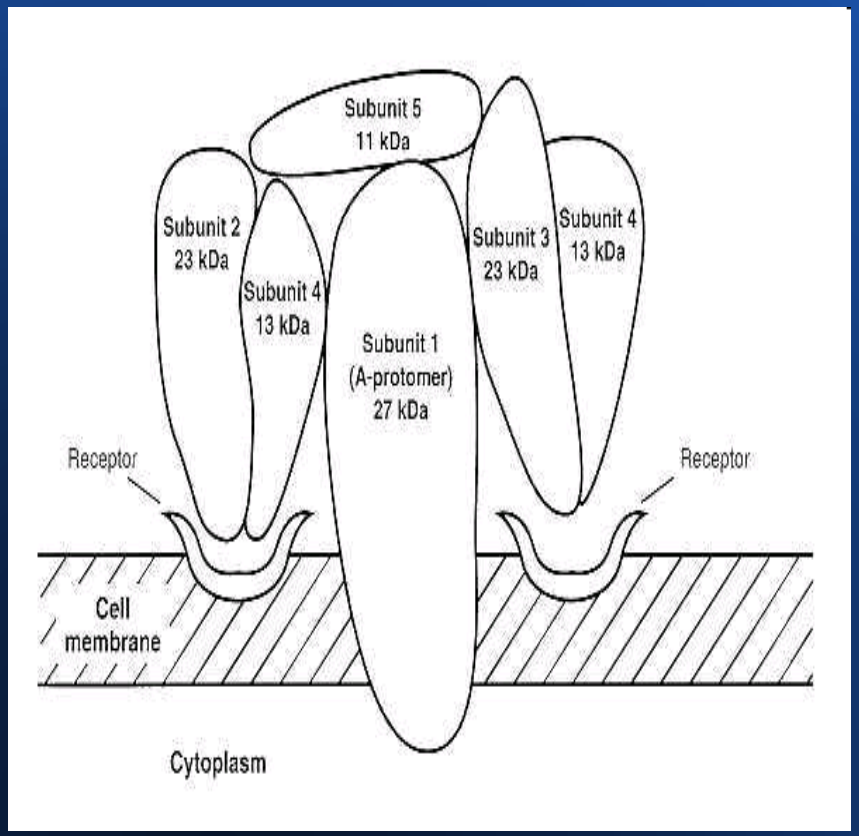
- producing lymphocytosis producing factor ----> Lymphocytosis

-acts as Histamine sensitizing factor

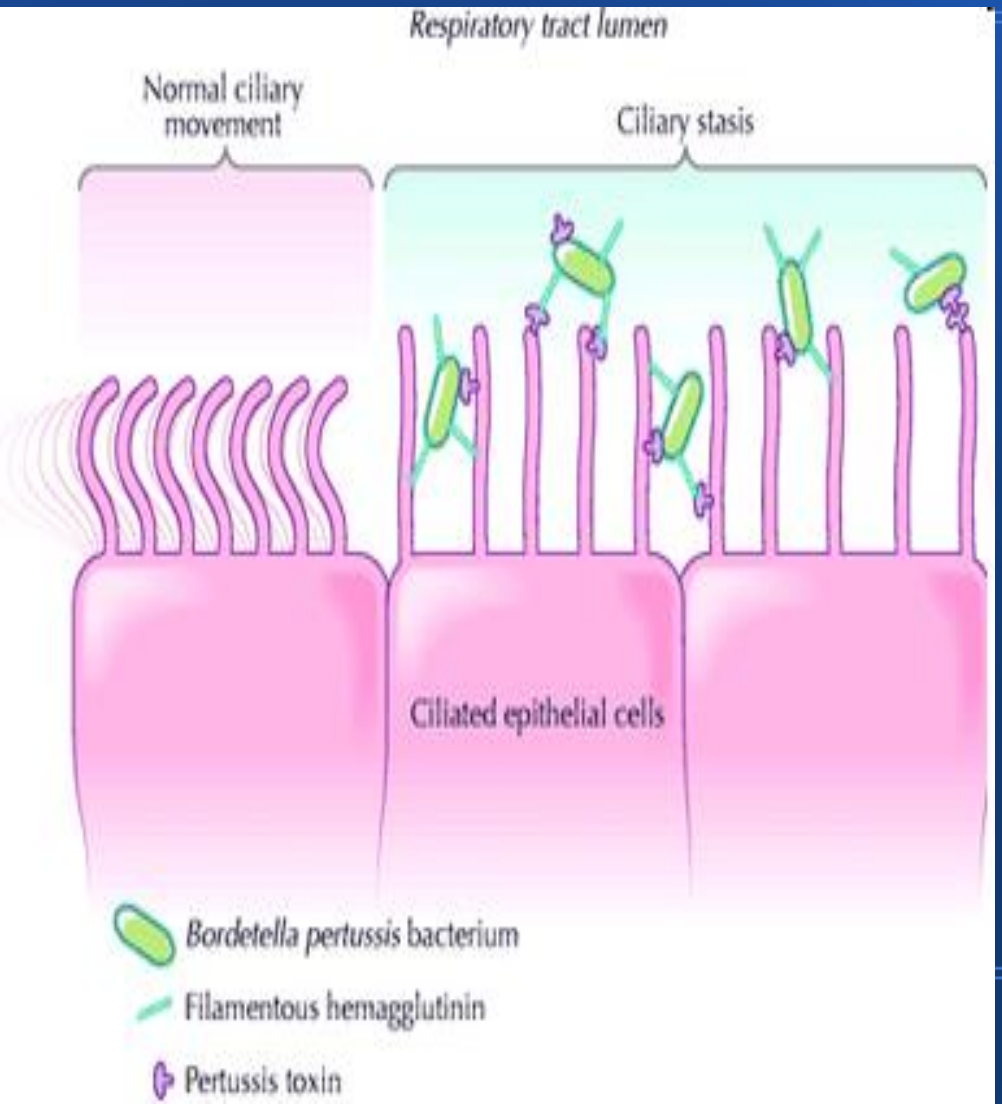
-islet activating function – causes excessive Insulin secretion

Pertussis toxin is the major component of Acellular Pertussis vaccine..

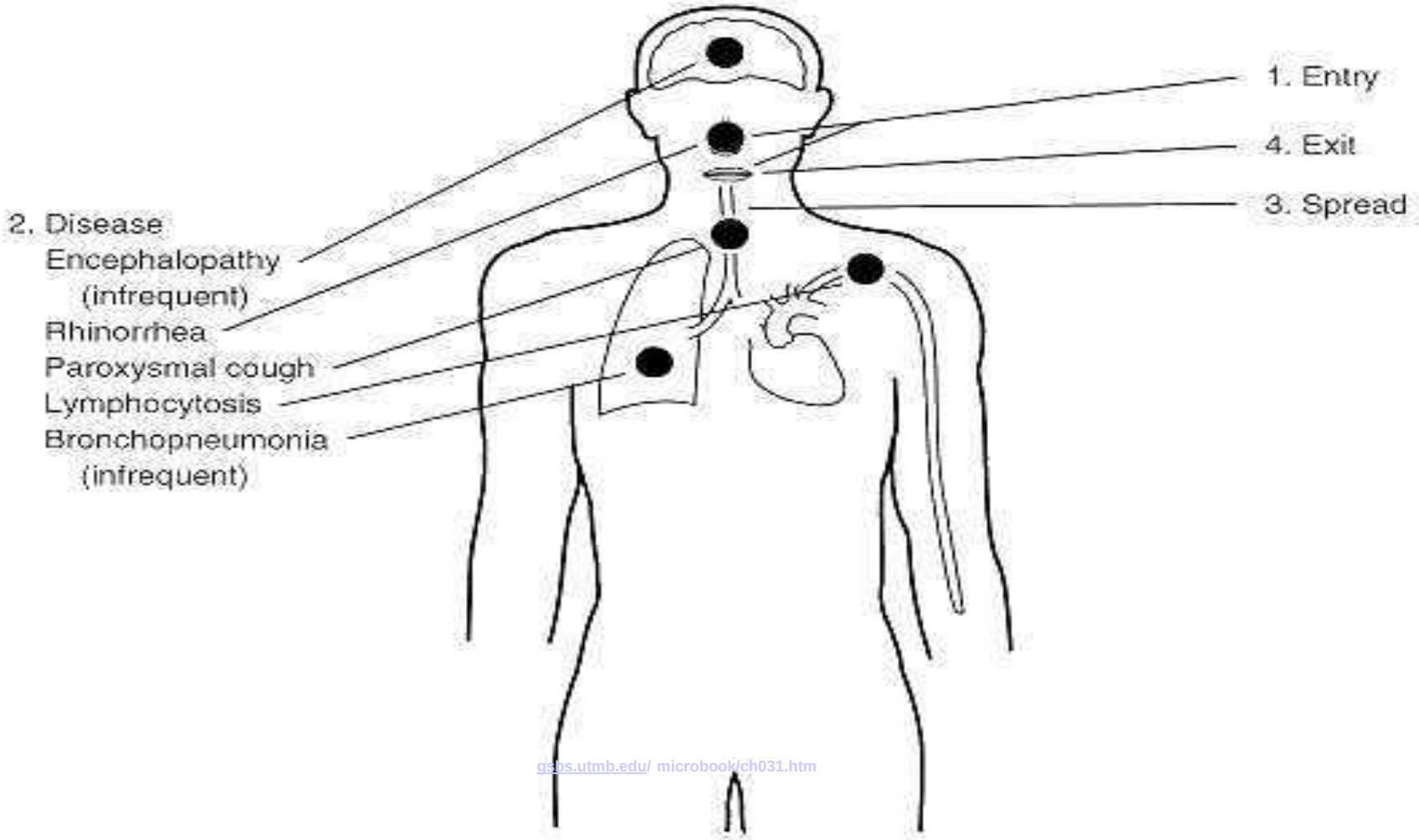
Bordetella pertussis toxin



Bordetella pertussis virulence



Pertussis Infection



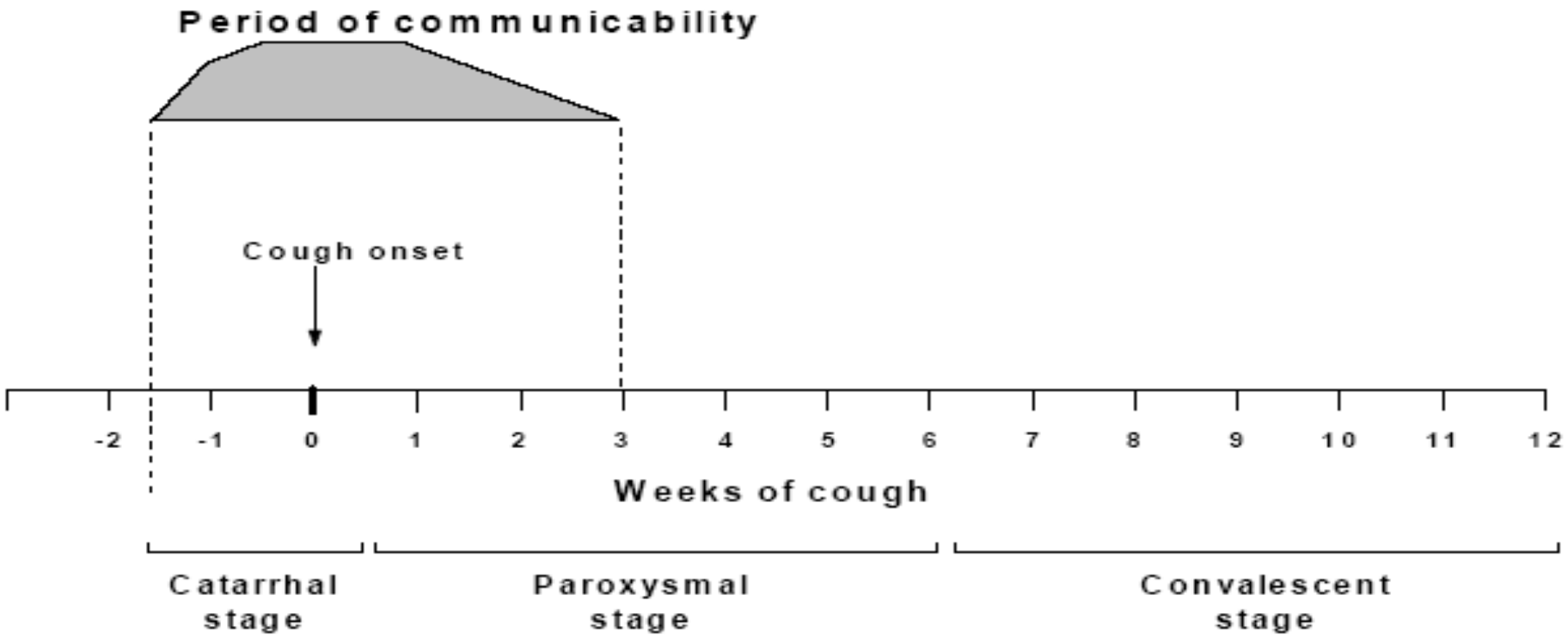
Clinical Features

- Incubation period 4-21 days
- 3 Stages
  - 1st Stage- Catarrhal Stage 1-2 weeks
    Maximal infective
  - 2nd Stage- Paroxysmal Stage 1-6 weeks
  - 3rd Stage- Covalescent Stage weeks-months

Clinical

Bordetella pertussis

1st Stage- Catarrhal Stage indistinguishable from common upper respiratory infections with nasal congestion, rhinorrhea, and sneezing, low-grade fever, tearing, and conjunctival suffusion.



Clinical

Bordetella pertussis

2nd Stage- Paroxysmal Stage- paroxysms of intense coughing lasting up to several minutes. In older infants and toddlers, the paroxysms of coughing occasionally are followed by a loud whoop as inspired air goes through a still partially closed airway. Infants younger than 6 months do not have the characteristic whoop but may have apneic episodes and are at risk for exhaustion. Posttussive vomiting and turning red with coughing are common in affected children.

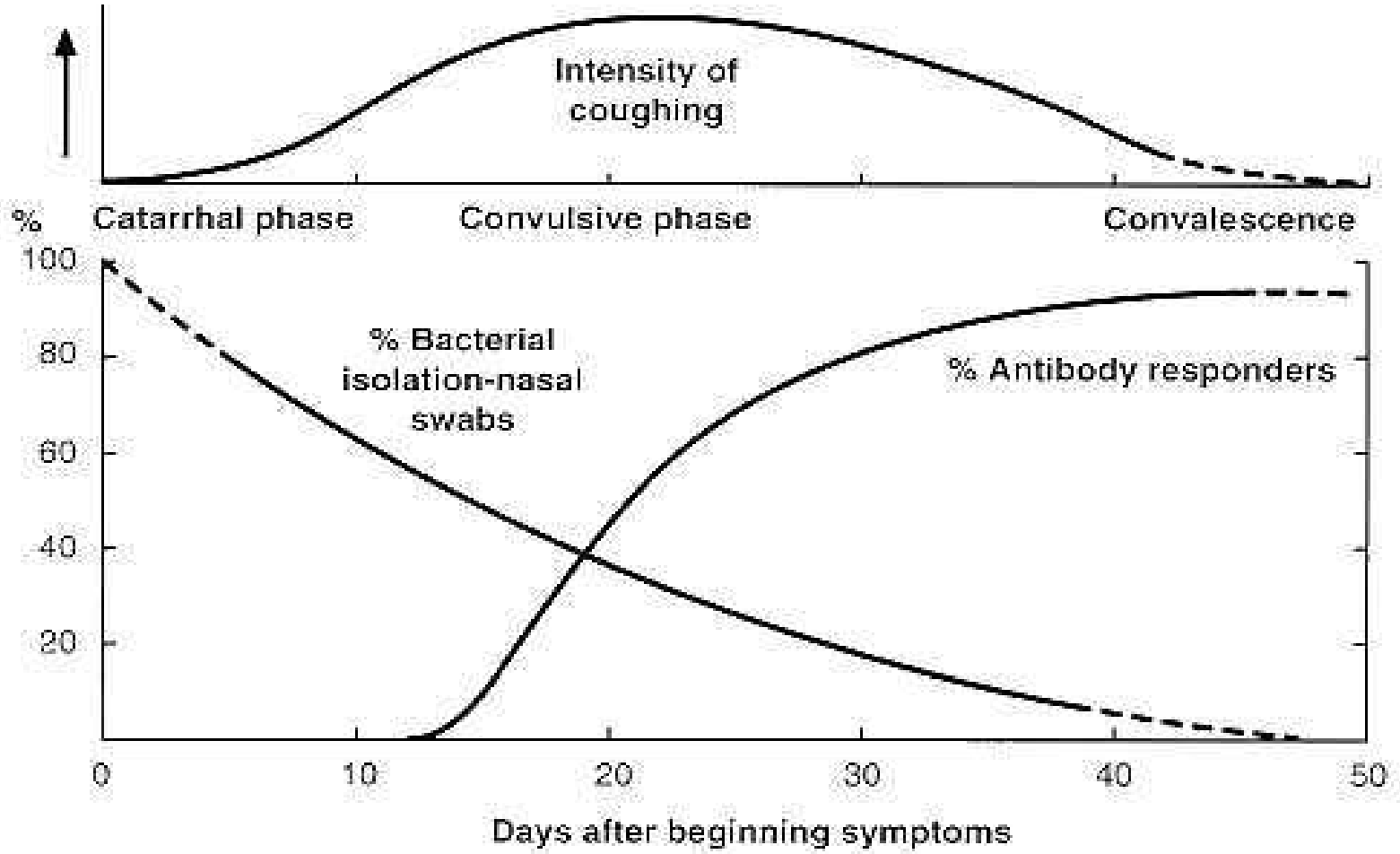
3rd Stage- Covalescent Stage a chronic cough, which may last for weeks. Older children, adolescents, and adults may not exhibit distinct stages. Symptoms in these patients include uninterrupted coughing, feelings of suffocation or st

Physical

- In all patients with pertussis, fever is typically absent.
- In patients with uncomplicated pertussis, physical examination findings contribute little to the diagnosis.
- Most patients do not have signs of lower respiratory tract disease.
- Conjunctival hemorrhages and facial petechiae are common and result from intense coughing

Subconjunctival Hemorrhage

Relationship of B pertussis to the developing antibody response during whooping cough



Differential diagnosis

Some times Adenovirus, Mycoplasma pneumonia may mimics whooping cough.

* Adenoviral respiratory infection: Children present with fever, sore throat, and conjunctivitis.

* Mycoplasmal pneumonia: Patients with mycoplasmal infections have more pronounced systemic symptoms, fever and headache may occur, and rales may be appreciated on chest auscultation.

* Chlamydial pneumonia: Young infants with chlamydial infections present with staccato cough, purulent conjunctival discharge, tachypnea, rales, and wheezing.

* Respiratory syncytial virus infection: Patients present with predominantly lower respiratory tract signs (eg, wheezing, rales).

Diagnosis

A clinical case of pertussis is defined as one of the following:

* An acute coughing illness that lasts at least 14 days in a person with at least one characteristic pertussis symptom (ie, paroxysmal cough, posttussive vomiting, or inspiratory whoop)
* A cough that lasts at least 14 days in an outbreak setting

A confirmed case is defined as one of the following:

* Any cough illness in which B pertussis is isolated and cultured
* A case consistent with the clinical case definition confirmed by polymerase chain reaction (PCR) findings or epidemiologic linkage to a laboratory-confirmed case

Complications

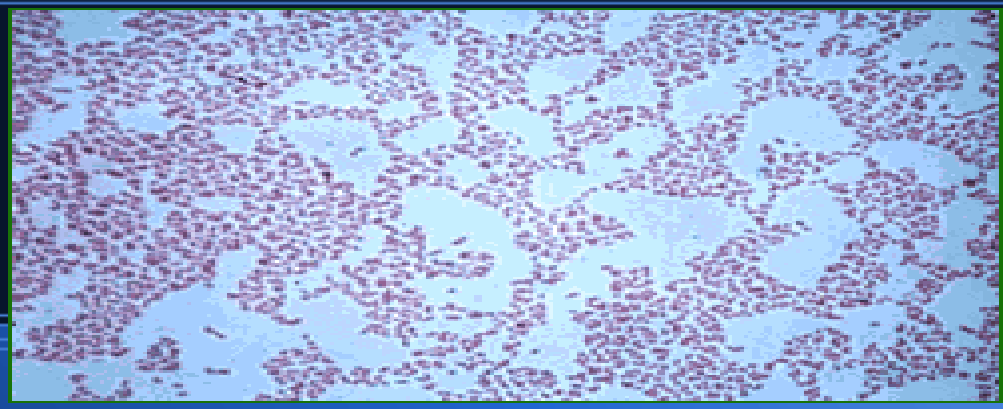
The violent bouts of cough leads to

- Subconjuctival hemorrhage
- Subcutaneous emphysema
- Bronchopneumonia
- Lung collapse

Neurological complications

- Epilepsy, paralysis, mental retardation, blindness, deafness.

Lab diagnosis



Gold standard: Culture
- less sensitive after 2 weeks - preferred media include Regan-Lowe or Bordet-Gengou B

Culture can be negative in patients who

- were previously immunized
- have received antimicrobial therapy
- or have been coughing for more than 3 weeks
- not exclude the diagnosis of pertussis

- Polymerase Chain Reaction (PCR) - Rapid/Sensitive/Specific
- Direct Fluorescent Antibody (DFA) - Low sensitivity, variable specificity

- Leukocytosis (15,000-50,000 103/µL) with absolute lymphocytosis occurs during the late catarrhal and paroxysmal phases. It is a nonspecific finding but correlates with severity of the disease.

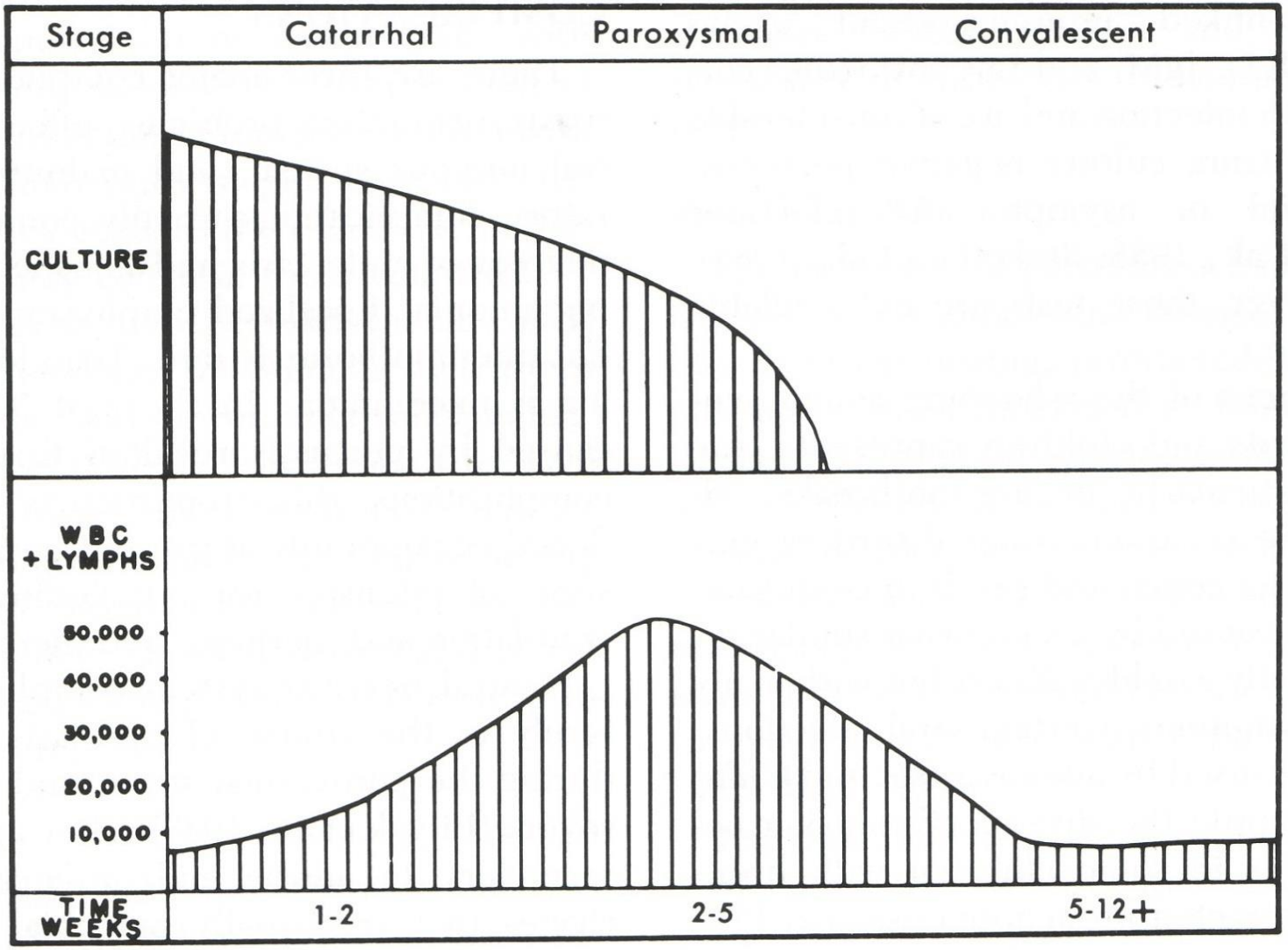


Fig. 19-1. Diagram illustrating diagnostic laboratory findings in pertussis. *Bordetella pertussis* may be recovered, usually during catarrhal and early paroxysmal stages (first 4 weeks of illness). The white blood cell count usually is elevated during the paroxysmal stage (second to fifth weeks). Lymphocytes predominate.

Mercury Drop colonies on Bordet-Gengou Medium

- Growth takes longer up to 48 – 72 hours
- On blood agar

Resembles bisected pearly or mercury drops

Cough Plate Method

- Culture plate held at 10-15 cm in front of the mouth when the patient is coughing spontaneously or induced cough
- Droplets of respiratory exhaled impinge on the media.
- Helpful as bed side investigation

Cough Plate Method

Treatment

- B Perstussis is naturally RESISTANT to Peniciline
- Antibiotic therapy

Erythromycin 40-50 mg/kgc/day 4 doses 14 days

Azithromycin 10 mg/kgc/day single dose 5 days

Clarithromycin 15 mg/kgc/day 2 doses 7 days

TMP-SMX 8 mg/kgc/day 2 doses 7 days

- Supportive : adequate nutrition and hydration
- Cough suppressants in low doses
- Family members : a full course of erythromycin to prevent further disease and subsequent spread

TABLE 4. Recommended antimicrobial treatment and postexposure prophylaxis for pertussis, by age group

Age group	Primary agents			Alternate agent*
	Azithromycin	Erythromycin	Clarithromycin	TMP-SMZ
<1 month	Recommended agent. 10 mg/kg per day in a single dose for 5 days (only limited safety data available.)	Not preferred. Erythromycin is associated with infantile hypertrophic pyloric stenosis. Use if azithromycin is unavailable; 40–50 mg/kg per day in 4 divided doses for 14 days	Not recommended (safety data unavailable)	Contraindicated for infants aged <2 months (risk for kernicterus)
1–5 months	10 mg/kg per day in a single dose for 5 days	40–50 mg/kg per day in 4 divided doses for 14 days	15 mg/kg per day in 2 divided doses for 7 days	Contraindicated at age <2 months. For infants aged ≥2 months, TMP 8 mg/kg per day, SMZ 40 mg/kg per day in 2 divided doses for 14 days
Infants (aged ≥6 months) and children	10 mg/kg in a single dose on day 1 then 5 mg/kg per day (maximum: 500 mg) on days 2–5	40–50 mg/kg per day (maximum: 2 g per day) in 4 divided doses for 14 days	15 mg/kg per day in 2 divided doses (maximum: 1 g per day) for 7 days	TMP 8 mg/kg per day, SMZ 40 mg/kg per day in 2 divided doses for 14 days
Adults	500 mg in a single dose on day 1 then 250 mg per day on days 2–5	2 g per day in 4 divided doses for 14 days	1 g per day in 2 divided doses for 7 days	TMP 320 mg per day, SMZ 1,600 mg per day in 2 divided doses for 14 days

* Trimethoprim sulfamethoxazole (TMP–SMZ) can be used as an alternative agent to macrolides in patients aged ≥2 months who are allergic to macrolides, who cannot tolerate macrolides, or who are infected with a rare macrolide-resistant strain of *Bordetella pertussis*.

Pertussis Duration

- Pertussis can cause prolonged symptoms
- The child usually has 1 to 2 weeks of common cold symptoms first
- This is followed by approximately 2 to 4 weeks of severe coughing, though the coughing spells can sometimes last even longer
- The last stage consists of another several weeks of recovery with gradual resolution of symptoms
- In some children, the recovery period may last for months

Early Immunization is best solution to prevent the Pertussis

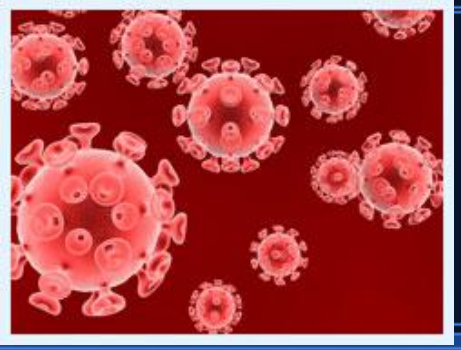
Routine DTaP Primary Vaccination Schedule

Dose	Age	Minimum Interval
Dose 1	2 months	---
Dose 2	4 months	4 wks
Dose 3	6 months	4 wks
Dose 4	15-18 months	6 months
Dose 5	Prior to school	

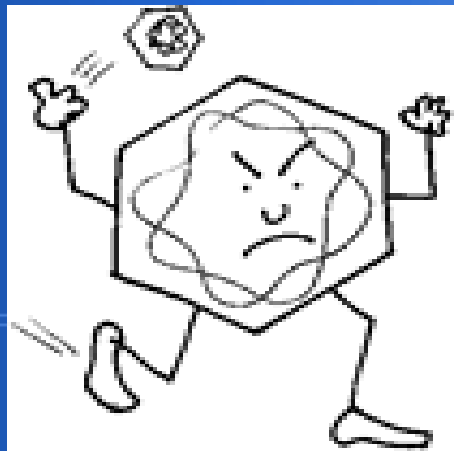
Acellular Pertussis Vaccines

- DTaP (diphtheria, tetanus, acellular pertussis) - has greatly reduced the incidence of neurological adverse effects observed with the earlier "whole-cell" pertussis vaccine : seizures and hypotonic episodes immunization.
- DTaP immunizations are routinely given in five doses before a child's sixth birthday
- Immunity from the childhood vaccination series lasts for about ten years
- In general, pertussis vaccine is not given to persons 7 years of age or older, since reactions to the vaccine may be increased in older children and adults.

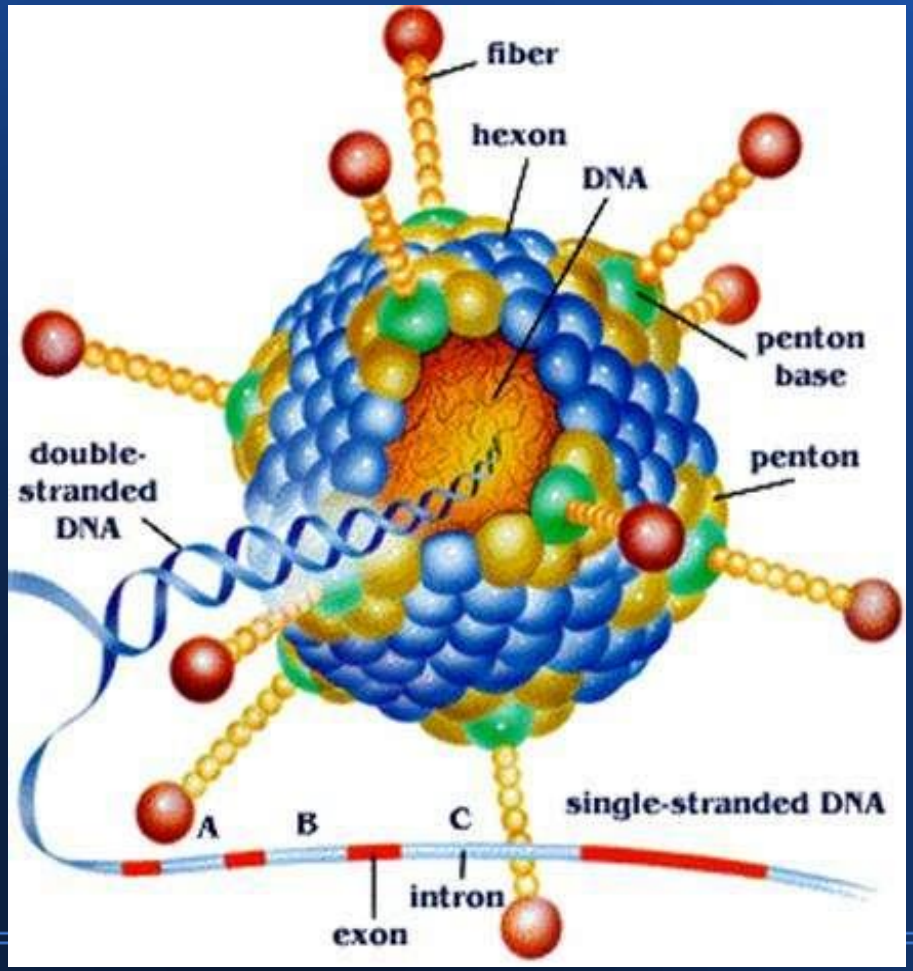

Thank you!



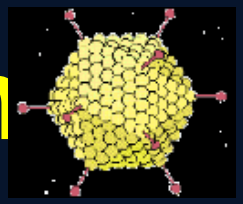
ADENOVIRUSES



Adenovirus


fiber
hexon
DNA
penton base
penton
double-stranded DNA
single-stranded DNA
A
B
C
intron
exon

Adenovirus introduction



- **Adenovirus was first isolated in the 1950's in adenoid tissue–derived cell cultures**
- two genera:

  Mastodenovirus affect mammals

  Aviadenovirus affect birds

cause wide range of diseases:

- bind same glycoprotein Ig family receptor as Coxsackie B virus named CAR (coxsackie-adenovirus receptor).
- mild URI to conjunctivitis, gastroenteritis, hemorrhagic cystitis
- used as vector for gene therapy - low pathogenic potential

ADENOVIRUS AND HUMAN DISEASE

Grup A- enteral asymptomatic infections

Grup B and C- respiratory infections

Grup D- keratoconjunctivitis

Grup E -conjunctivitis and respiratory infections

Grup F- infantile diahorrea

-80% of current isolates remain serotypes 4 and 7

ADENOVIRUS AND HUMAN DISEASE

- Mild pediatric respiratory disease type 1, 2 & 5 (prevalent 0-6 yrs.)
- Acute respiratory disease of recruits 4, 7, 14, 21
- Pneumonia 1, 2, 3, 7
- Follicular conjunctivitis 3, 4, 11
- Epidemic keratoconjunctivitis **“shipyard eye”,** 8, 19, 37
- Pertussis-like syndrome 5 ,8
- Acute haemorrhaghic cystitis 11, 21
- Acute infantile gastroenteritis 40, 41
- Intussusception 1, 2, 5
- Immunocompromized patients 5, 34, 35
- Meningitis 3, 7

GENERAL ADENO PROPERTIES

- In humans, they infect cells in tissues at the portal of entry. Many serotypes commonly infect local lymphoid tissue (adenoids, tonsils, Peyer's patches) in persistent or latent fashion, perhaps for life.

- Adenoviruses also replicate in the intestine, where they may persist for months and are usually not pathogenic.

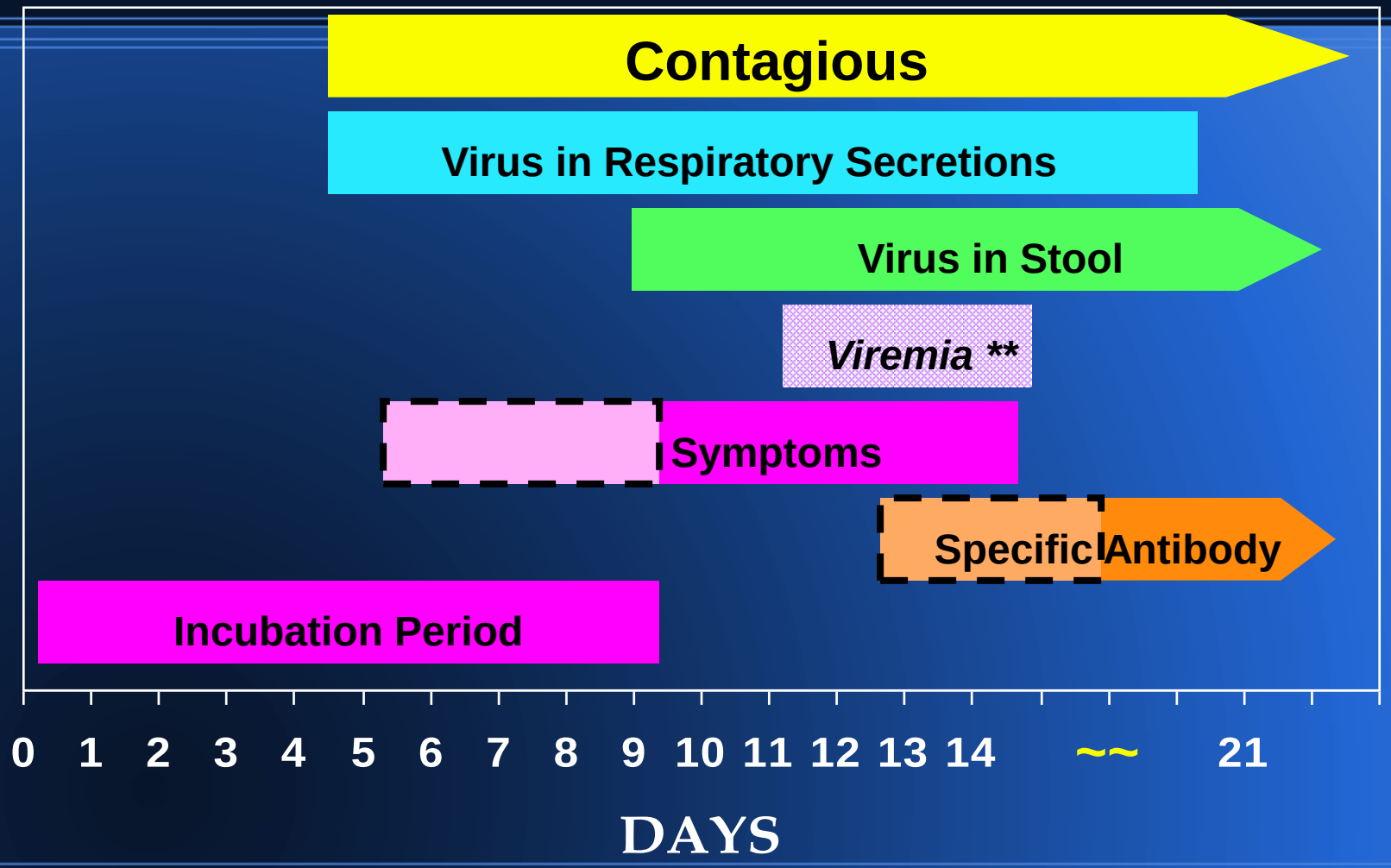
- NO viremia or disseminated diseases occurs except in immuncompromised patients.

- As a general rule all DNA viruses replicate in the nucleus, except the Pox viruses which replicate in the cytoplasm.

Adenovirus epidemiology

- ***Localised**: nasopharyngeal secretions, urine, feces*
- ***> 60% of school- age children have specific respiratory serotype antibodies***
- **Spread via:**
  fecal- oral*, fingers, fomites, *poorly chlorinated swimming pools
- ***Only human** to human spread* **-no animal vectors**
- ***Most infections are asymptomatic***
  - increase spread by shedding from pharnyx and feces
- **Increased risk with close contact**
  - army barracks, classrooms, day care etc.

Time Course of Adenovirus Respiratory Infections

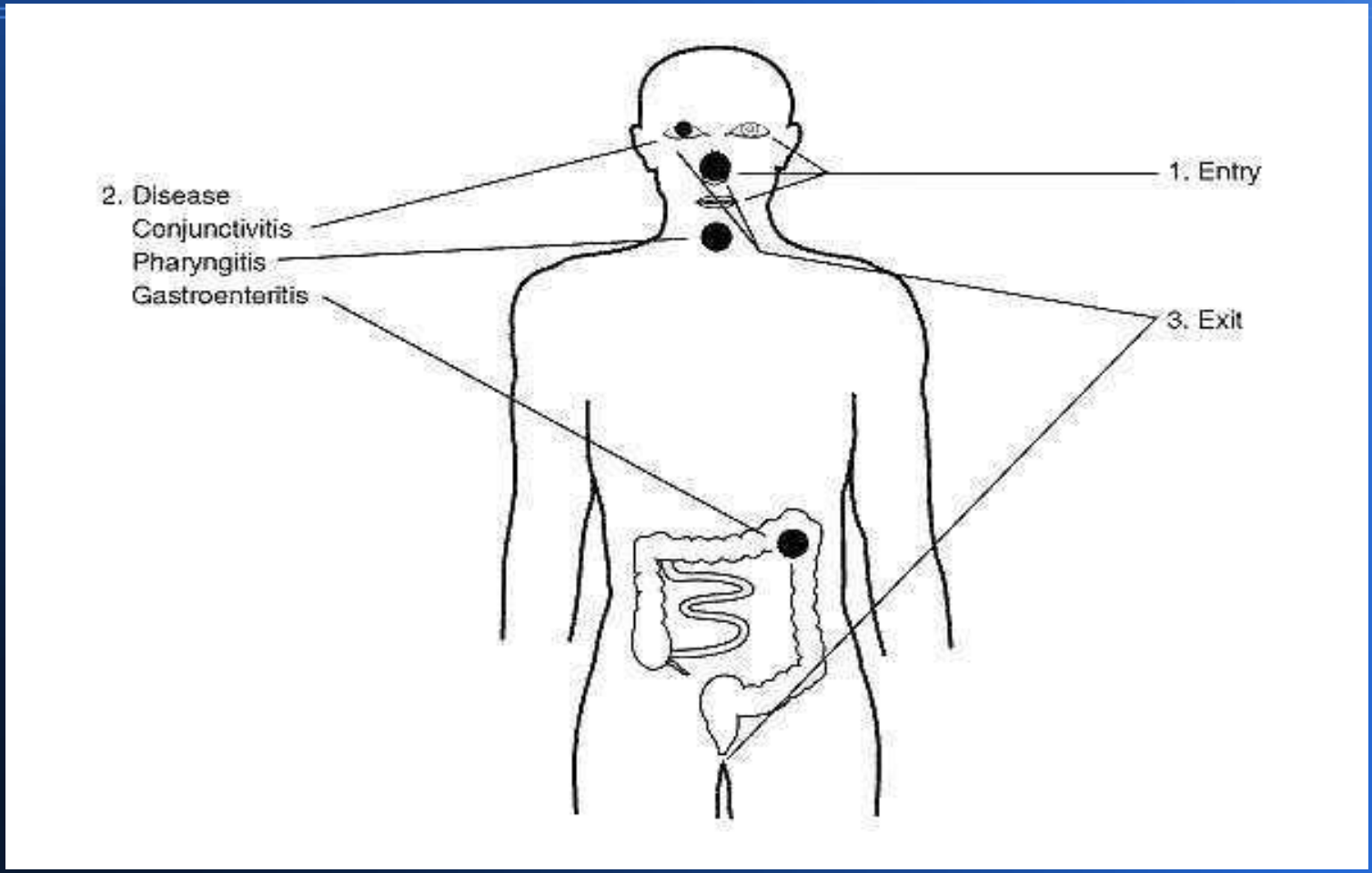


** in the immunosuppressed

Adenovirus pathogenesis

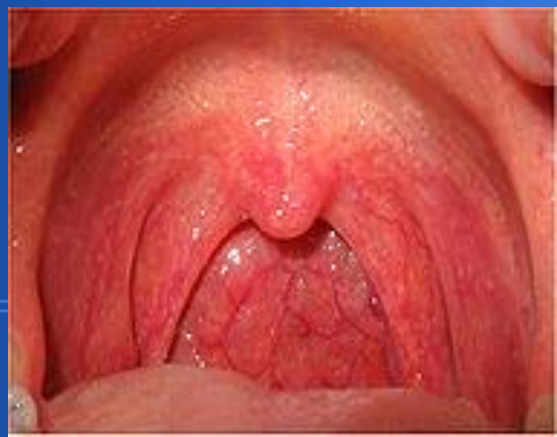
- Infect epithelial cells lining respiratory and enteric organs
- Different serotypes have different targets. Adenovirus immunity protect from re-infection by the same serotype only
- Cause:
  - *lytic infections* in mucoepithelial cells
  - *latent infections* in lymphoid/ adenoid cells, tonsils, Peyer's patches
    - reactivate iff immunosuppressed or co-infection
  - *oncogenic transformation may occur* in rodent/ hamster cells only
    - NOT in humans

ADENO TARGETS



Acute febrile pharyngitis

- Pharyngitis and conjunctivitis - mostly in older children -mild URI with fever, rhinorrhea, exudative pharyngitis and cough
- Adenovirus-induced respiratory illness may mimic other diseases, such as pertussis (whooping cough).
- Adenovirus may be isolated from children with whooping cough syndrome in the presence or absence of Bordetella pertussis infection



Pharyngo-conjunctival fever
predominantly serotypes 3, 4, and 7

- Affects school-aged children, especially summer camps in the setting of an inadequately chlorinated water source such as a pool or lake.
- The classic presentation after incubation period of 5 days is characterized by fever, sore throat, coryza, exudative pharyngitis and red eyes. Upper respiratory tract symptoms may precede ocular findings or may be absent.
- Conjunctivitis (typically mild granular appearance) usually begins with one eye then spreads to the other, although both eyes may be affected simultaneously with mild pain or discomfort, tearing and pruritus.
- The hallmark is preauricular lymphadenopathy This finding is not common; however, its presence in the setting of a viral conjunctivitis is very suggestive of adenovirus infection.

It usually is self-limited to 5 days

- Uncommonly, an exanthem –harsh congestive maculo-papular rash, appears in the same time on the face, trunk and abdomen predominanty on extension areas .
- also diarrhea may occur.

Epidemic keratoconjunctivitis

predominantly serotypes 8, 19, and 37

- Highly contagious, with transmission in household contacts via hands and fomites, associated with instrumentation, industrial trauma (shipyard workers , airborne particles), contaminated ophthalmic solutions, and the hands of health care workers. Corneal trauma facilitates infection.
- After an 8-day incubation period, an insidious onset of unilateral red eye occurs, which spreads to involve both eyes. Patients have photophobia, tearing, and pain (indicating corneal involvement). Children may have fever and lymphadenopathy.

Palpebral conjunctiva may be granular

- Inflammation may persist for weeks, and residu

scarring and visual impairment may occur.

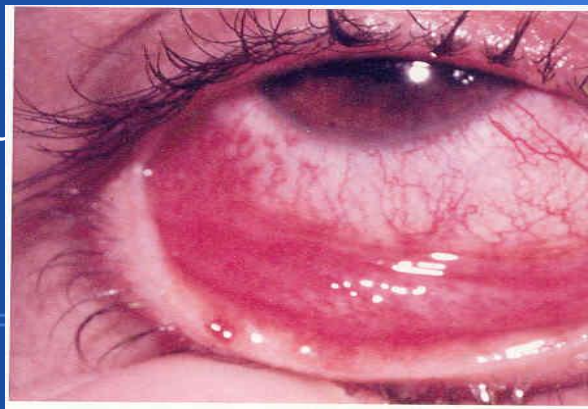


FIGURE 50–6. Conjunctivitis caused by adenoviru

Acute hemorrhagic cystitis

(serotypes 11 and 21)/nephritis

- Acute hemorrhagic cystitis usually affects children aged 5-15 years but may also affect immunosuppressed adults (eg, from kidney or bone marrow transplantation, AIDS). Boys are affected more often than girls.
- Dysuria, Hematuria is self-limited to 3 days, and other symptoms resolve later. Symptoms may be more prolonged in recipients of hematopoietic stem cell transplants.
- Nephritis has occurred in recipients of hematopoietic stem cell transplants and is associated with fever, hematuria, and flank pain.

Adenoviral infections in immunocompromised hosts

(multiple serotypes)

- Adenovirus cause disease during the posttransplantation period in patients who have received hematopoietic stem cell transplants.
- Prolonged neutropenia or immunosuppression also enhances the risk of developing adenoviral infections.
- Manifestations may vary but include hemorrhagic cystitis/nephritis, pneumonitis, hepatitis/liver failure, and gastroenteritis, particularly during the acute posttransplantation period prior to engraftment.
- Adenovirus should be considered in patients with a fever, hematuria, flank pain, and worsening renal function.
- A prior history of adenoviral infection in a patient with recovered immunocompetence may herald recurrence when the patient again becomes immunosuppressed.

Gastroenteritis

(serotypes 40 and 41)

Enteric adenovirus infection is a common cause of infantile diarrhea in the daycare setting

1) Rotavirus
2) Astrovirus
3) Adenovirus

- infectious diarrheal syndromes in recipients of hematopoietic stem cell transplants.
- Nonenteric adenovirus serotypes (ie, 1, 2, 3, 5, 6) has been associated with intussusception.
- Fever , emesis, watery diarrhea (without blood or fecal leukocytes) are usually limited to 1-2 weeks (can last longer than other types of viral gastroenteritis)
- Persistent lactose intolerance has been reported.

Differential diagnosis

- Allergic conjunctivitis
- Bronchiolitis
- Glaucoma
- Measles
- Respiratory Syncytial Virus Infection
- Scleritis
- Tracheobronchitis
- Uveitis
- Whooping cough

Adenovirus lab diagnosis

- Sample must be taken from site (eg. Throat swab) or secretion relevant to disease (eg. Sputum, feces)
- Culture:
  - characteristic CPE (Cytopathic effect) after 1-3 weeks
- Microscopy:
  - dark, dense, intranuclear inclusion bodies in infected epithelial cells
  - rare, and similar to Owl's eye inclusion body in CMV
  - electron microscopy of stool sample
- Lab: leukocytosis
  - increased CRP (unique to viruses similar to bacteria)

Inclusion bodies- Adenovirus vs CMV

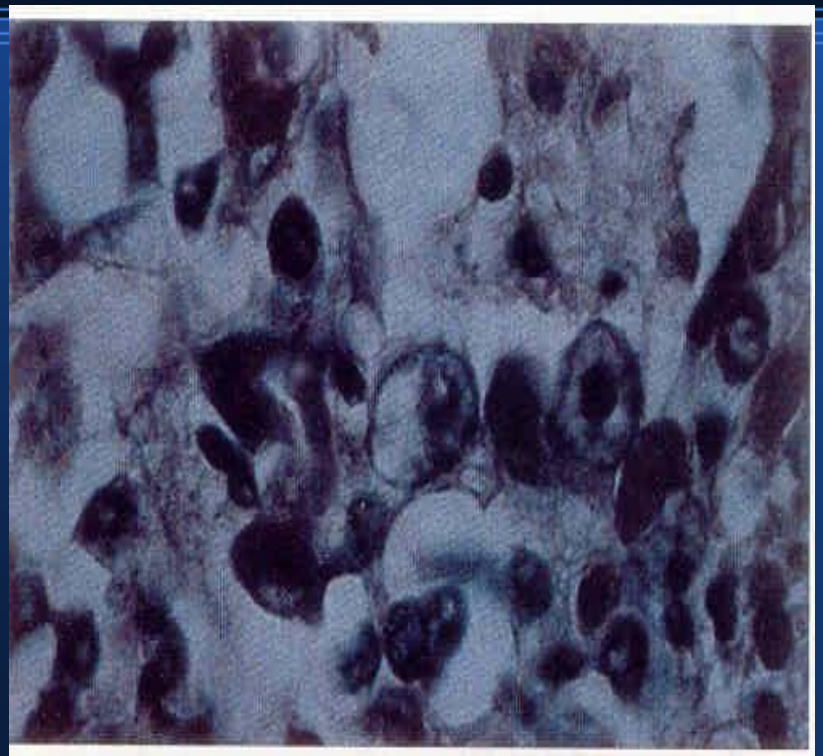


FIGURE 50–5. Histologic appearance of adenovirus-infected cells. Inefficient assembly of virions yields dark basophilic nuclear inclusion bodies containing DNA, proteins, and capsids.

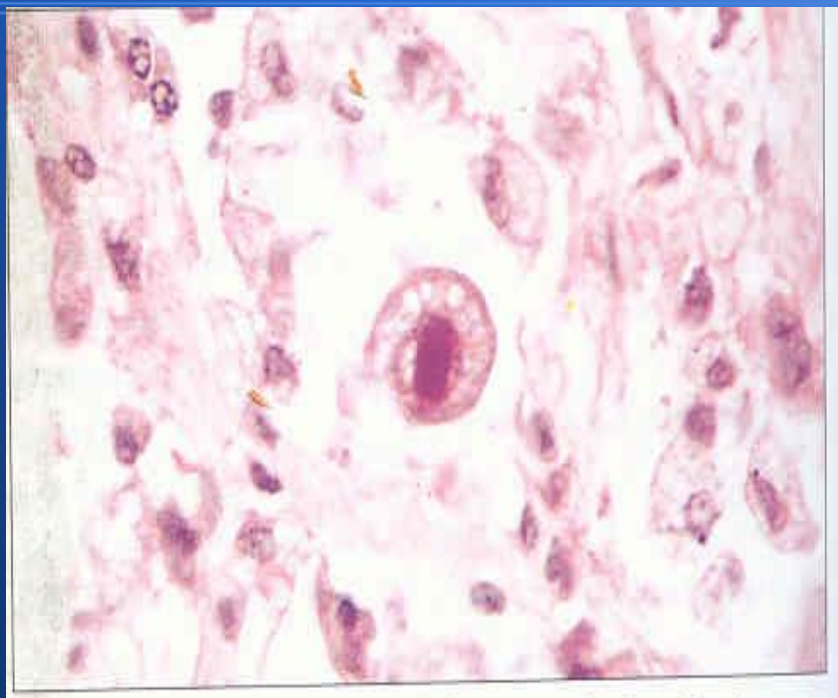


Fig. 17.19 Owl's eye inclusion body in cytomegalovirus infection. Large numbers of virus particles accumulate in the nucleus of the enlarged infected cell to produce a single dense inclusion. (Hematoxylin and eosin stain) (Courtesy of ID Starke and ME Hodson.)

Adenovirus control and gene therapy

Gene replacement therapy:

-low pathogenic potential

- Use as vectors for treating disease like CF, lysosomal storage disease etc
- The virus can be engineered to remove its replicative capacity by removing essential genes.
- Specific genes can be inserted into the virus that then can repair defective metabolic, enzymatic, or synthetic pathways in the host. Suicide gene systems that convert nontoxic systemically delivered prodrugs to active chemotherapeutic agents have been delivered via adenoviral vectors directly into cancer cells

Treatment and Prevention

Treatment:

- supportive only
- Ribavirin and cidofovir - in immunosuppressed hosts

Control:

- good hygiene
- Vaccines□ live oral vaccines.

A vaccine is available against Adult Respiratory Distress Syndrome. It consists live adenovirus 4, 7, and 21 in enterically coated capsules. It is given to new recruits into various arm forces around the world.

THANK YOU