

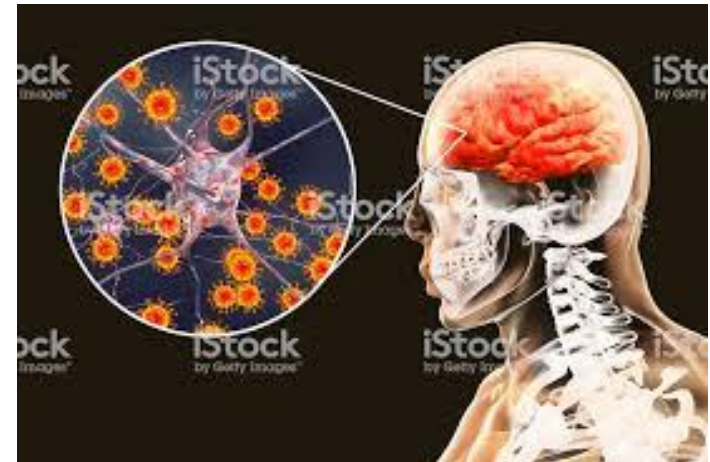
# VIRAL INFECTIONS OF THE CENTRAL NERVOUS SYSTEM

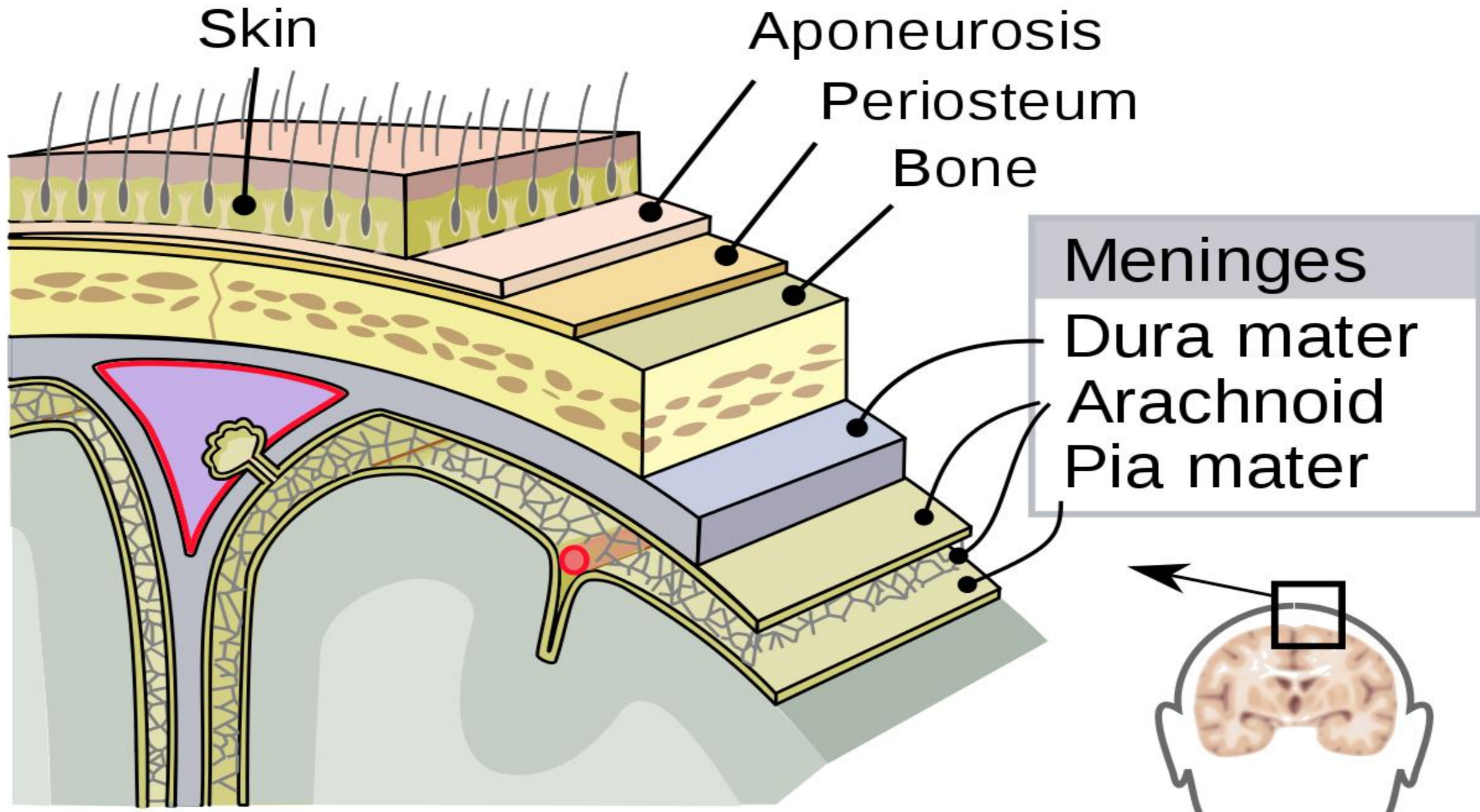
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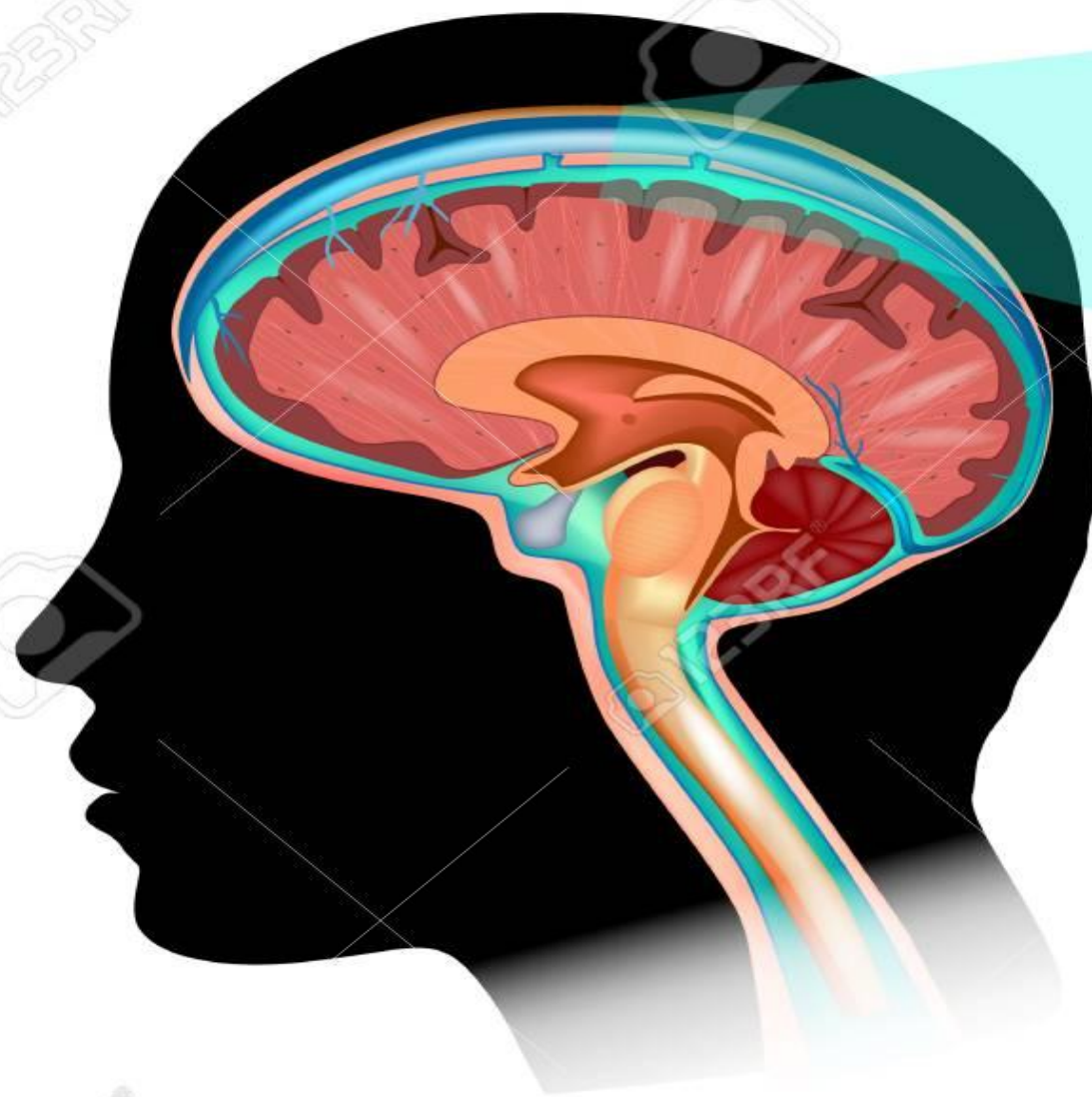
Asso. Prof Biljana Popovska Jovičić

# Viral infections of the central nervous system

- Viral infections of the CNS include several different clinical syndromes that are divided depending on the symptoms that follow them in certain anatomical structures:
- Viral meningitis
- Encephalitis
- Meningoencephalitis
- Encephalomyelitis
- Cerebellitis







Labels for the detailed view of the meninges:

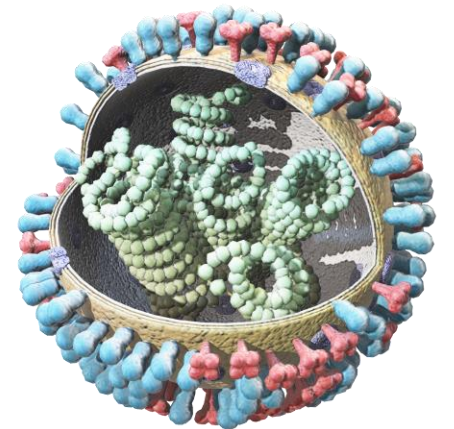
- Periosteal dura mater
- Superior sagittal sinus (venous blood)
- Meningeal dura mater
- Subarachnoid space
- Arachnoid mater
- Cerebral cortex
- Arachnoid villus





# Meningeal syndrome

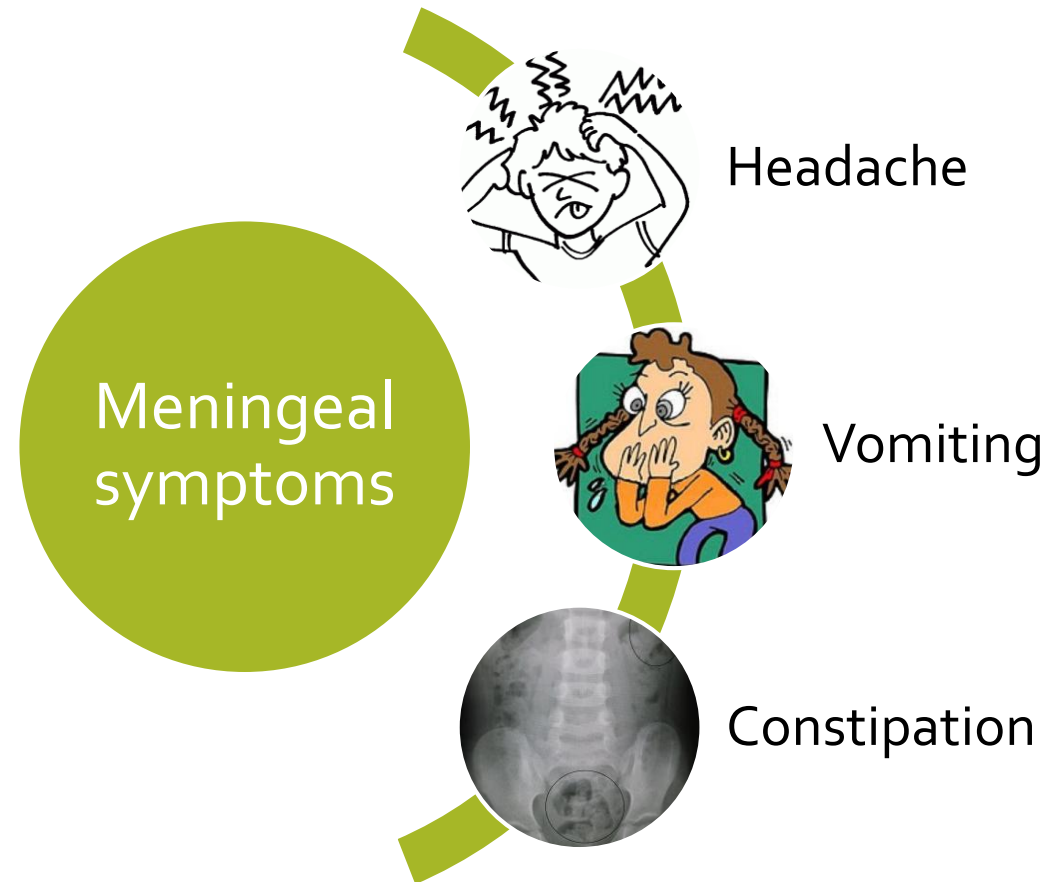
- Meningeal syndrome is a set of symptoms and signs that occur as a result of increased intracranial pressure. During a CNS infection, increased intracranial pressure occurs
- **Possible causes of increased intracranial pressure are:**
  - Disorder of cerebrospinal fluid dynamics
  - Brain edema
  - Disorder of cerebral circulation



# Meningeal syndrome

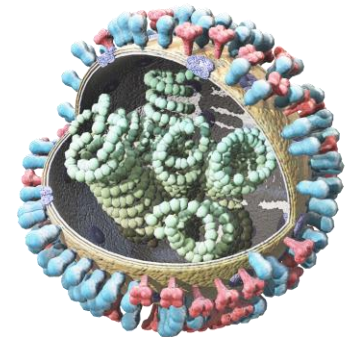
- **The consequences of increased intracranial pressure are a decrease in cerebral perfusion pressure (CPP), brain hypoxia, and neuronal damage.**
- **Meningeal symptoms and signs occur due to increased intracranial and intraspinal pressure** on the brain, anterior and posterior roots of the spinal cord (defensive reflexes to additional increased intracranial and intraspinal pressure)

# Meningeal symptoms



# Meningeal signs

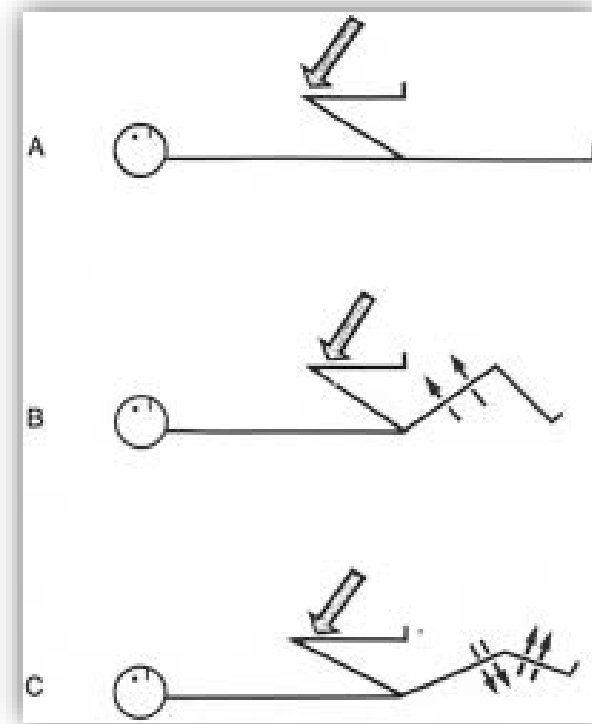
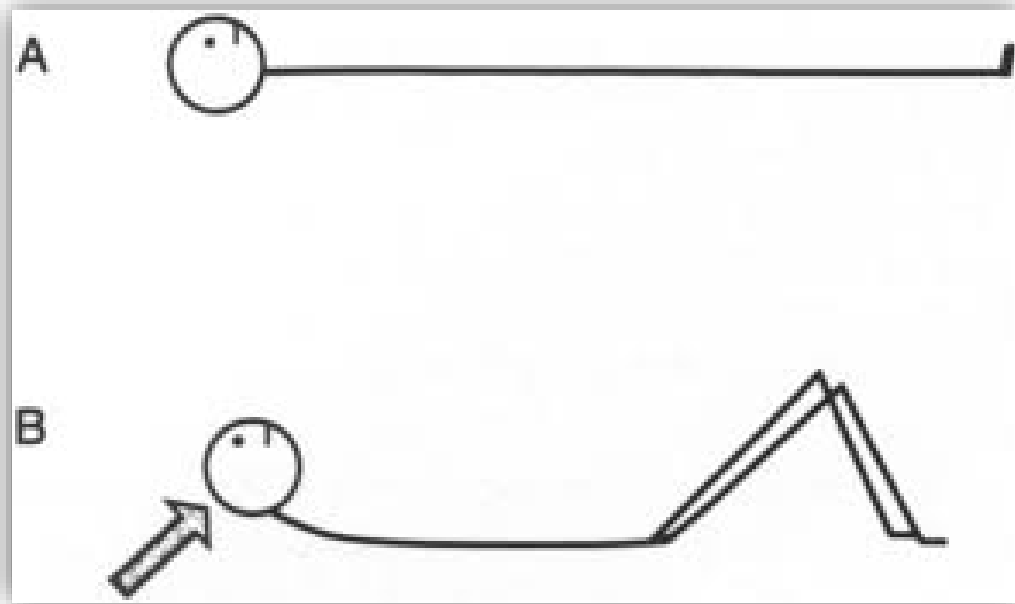
- Stiff neck
- Kernig's sign
- Bružinski (upper and lower)
- Vujić's sign
- Meningeal position
- Tense fontanelle





# Meningeal signs

Bružinski (upper and lower)

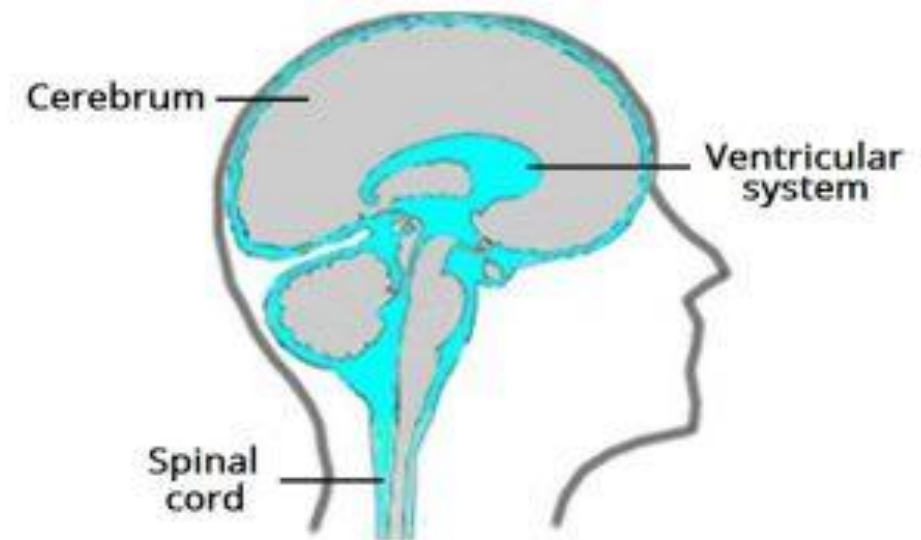


## CSF SYNDROME

- CSF pressure
- Cerebrospinal fluid appearance
- Number and type of cellular elements
- Proteins in cerebrospinal fluid
- CSF glucose or glycorrachia
- Chlorides

# NORMAL APPEARANCE OF CSF

- NORMAL PRESSURE
- CLEAR COLORLESS LIQUID CONTAINS UP TO 5 LYMPHO-MONOCYTES IN 1 mm<sup>3</sup>
- PROTEIN RATE LESS THAN 0.40 g/L
- CSF glucose –  $\frac{1}{2}$  TO  $\frac{2}{3}$  OF SERUM GLYCEMIA
- CHLORIDES DEPEND ON THE DEGREE OF DEHYDRATION



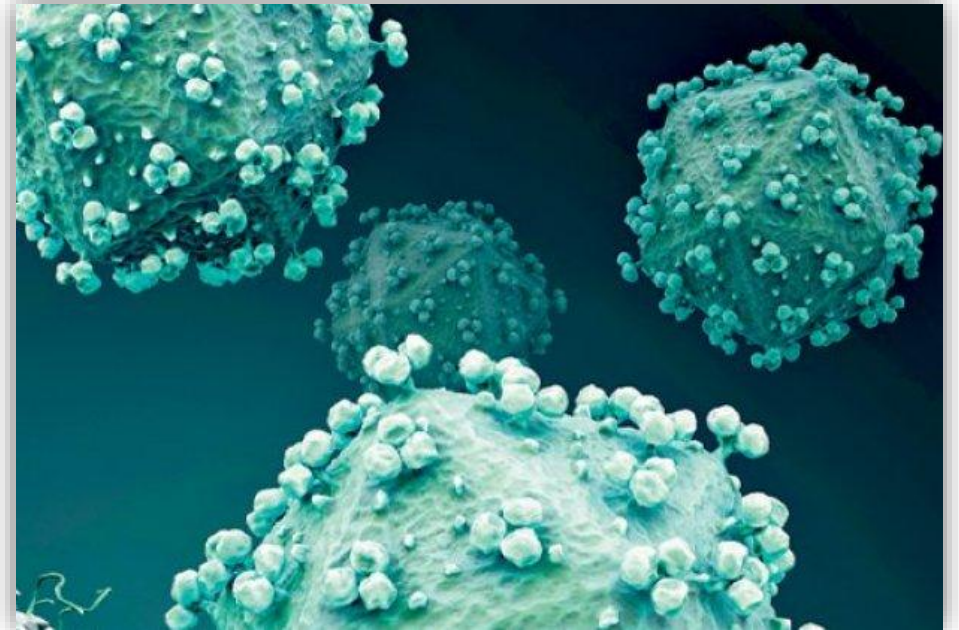
# Viral meningitis

- It represents inflammation of the soft meninges, caused by various viruses with a favorable clinical course and good prognosis
- Aseptic meningitis - lymphocyte dominance, the cause of which cannot be determined after initial clinical examinations and cerebrospinal fluid culture
- Viral meningitis can be caused by various viruses



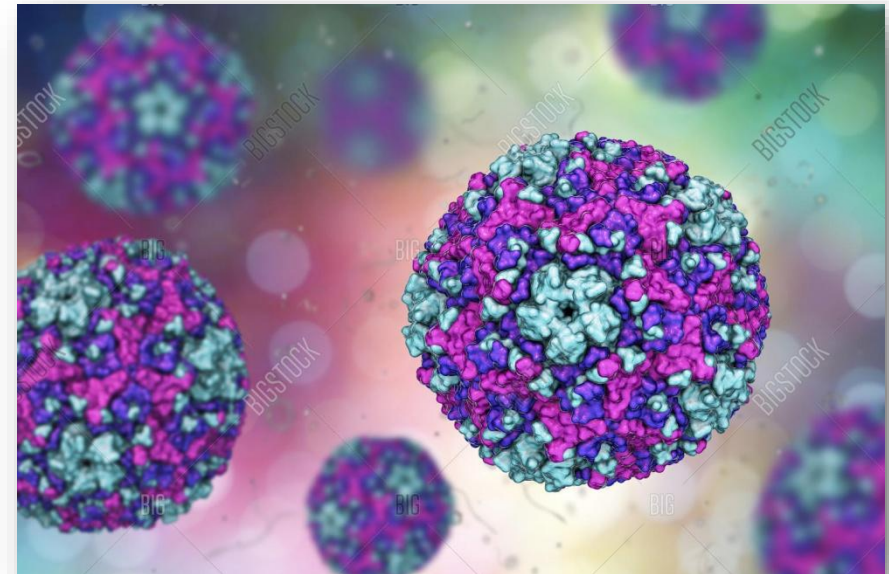
# Etiology and epidemiology of viral meningitis

- PICORNAVIRIDAE – ENTEROVIRUSES
- PARAMYXOVIRIDAE - MUMPS VIRUS
- ARBO (St. Louis)
- ARENA VIRUSES – LCM
- HERPES VIRUSES (VZV, CMV, EBV, HSV)
- HIV
- ADENOVIRUSES
- VIRUS INFLUENZAE A, B
- PARAINFLUENZA VIRUS



# Enteroviruses

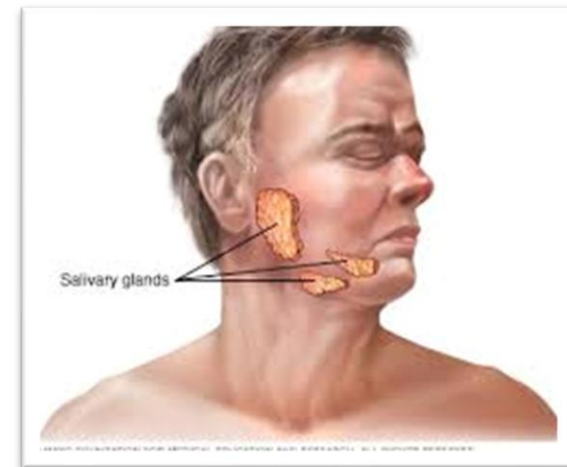
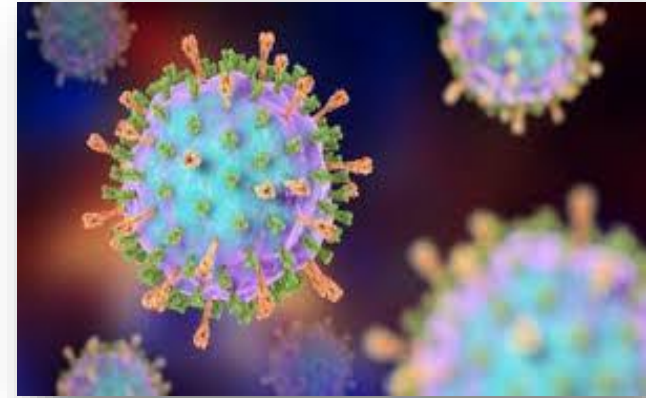
- RNA viruses
- Almost all serotypes can cause meningitis
- They are among the smallest viruses discovered
- They are transmitted feco-oral and by droplets
- Acid-resistant viruses
- They are excreted from the digestive tract for a much longer time
- Infection is prevalent during the summer months





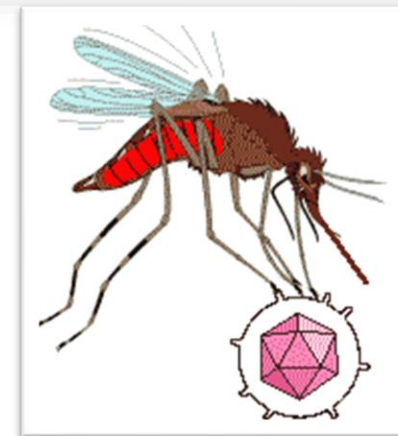
# Mumps virus

- RNA virus
- There is only one serotype of the virus
- Highly neurotropic
- 40-50% of patients do not have any manifestations of mumps
- Droplet transmission
- Winter, early spring



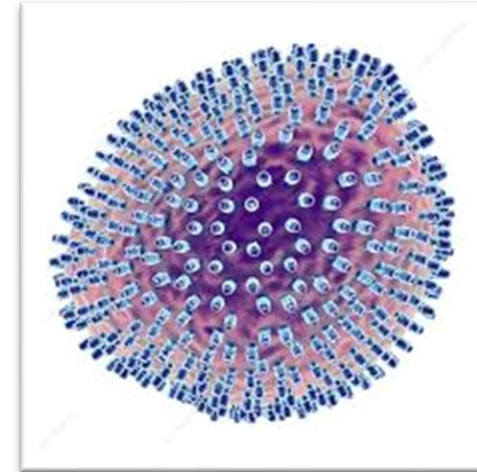
# Arboviruses

- RNA virus
- A group of over 500 viruses from different families West Nile virus, St. Louis virus, TBEV..
- Most often cause encephalitis
- Domestic animals are the reservoir of the virus
- Transmission of infection is most often through a tick or mosquito bite



# Lymphocytic choriomeningitis (LCMV virus)

- ARENA viruses
- RNA viruses
- Reservoir of infection: rodents, mainly house mice
- Aseptic meningitis, prolonged course
- Winter and early spring
- Elderly, rural environment



# Herpes viruses

- HSV<sub>1</sub>, HSV<sub>2</sub>, VZV, HHV 6, HHV 7, EBV
- DNA viruses
- HSV<sub>2</sub> more often causes meningitis
- HHV 6 in children after a three-day fever
- EBV – meningitis is rarely the only manifestation
- Other viruses: HIV, Influenza A, B, adenoviruses, measles...



# Pathogenetic mechanisms of viral meningitis

Viral entry site (skin, respiratory tract, fecooral...)

Viral colonization

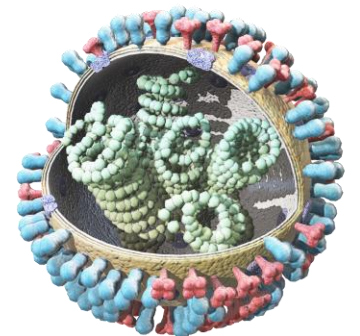
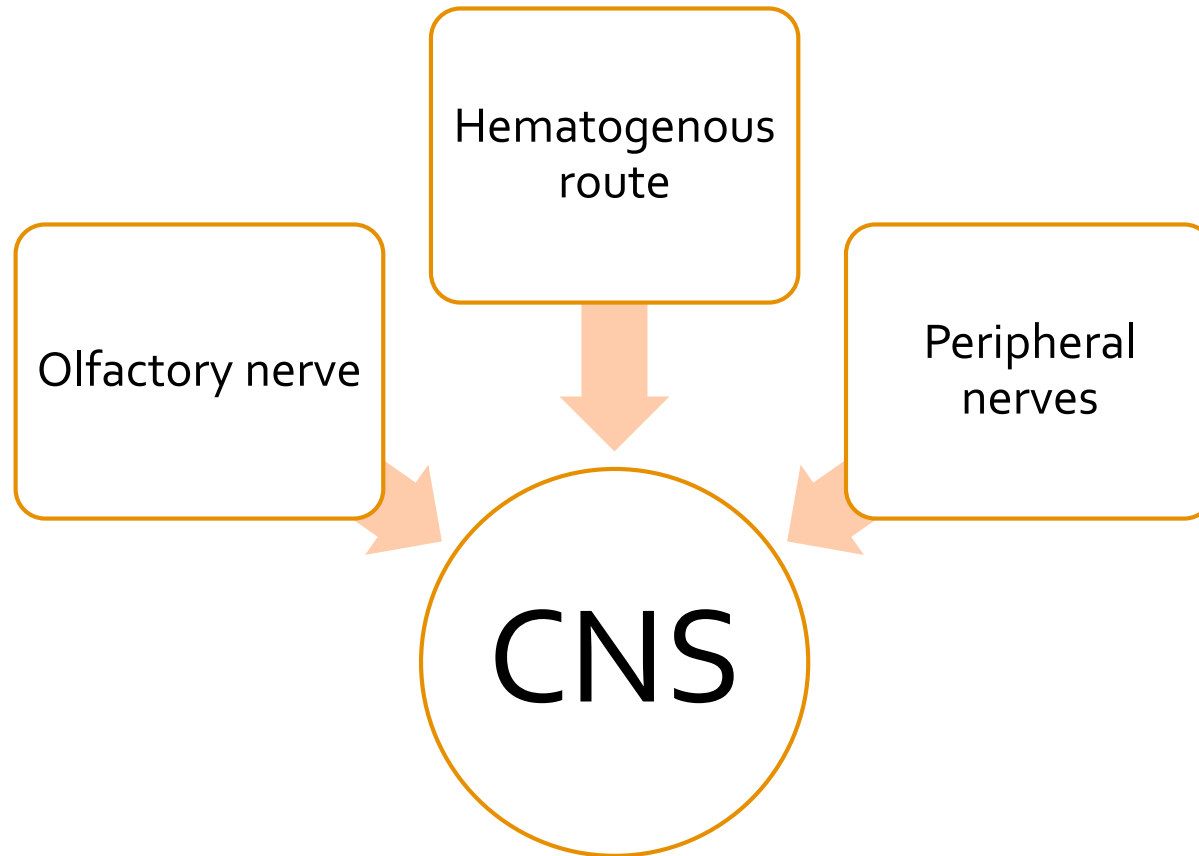
Host defense mechanisms

Secondary viremia

CNS entry

CNS inflammation

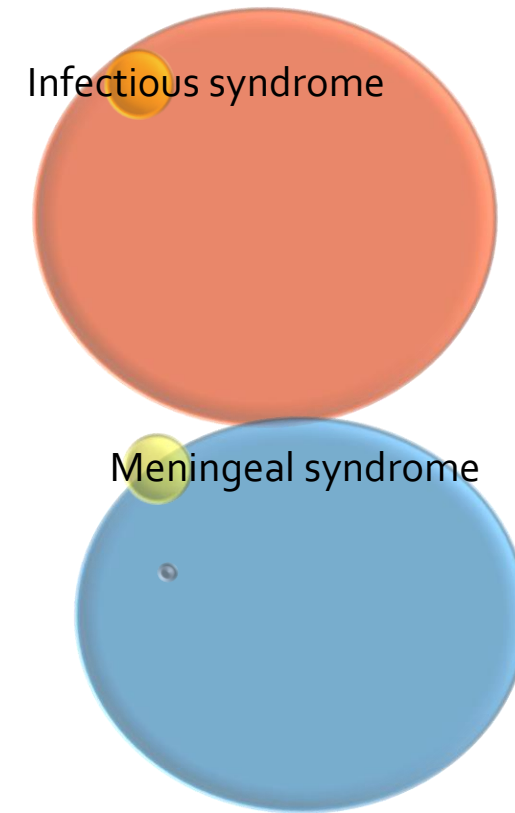
# Virus entry into the CNS





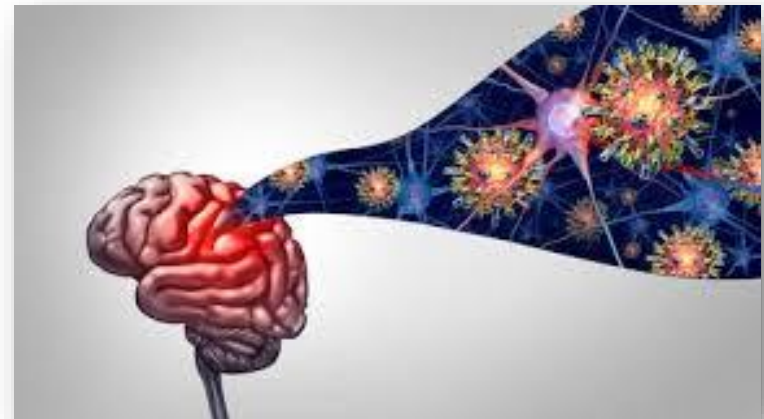
# Clinical picture of viral meningitis

- Sudden onset
- Fever
- Headache
- Photophobia
- Vomiting
- Neck stiffness
- Short clinical course
- Good prognosis



# Complications of viral meningitis

- Complications are rare because the disease has a good prognosis and resolves without sequelae
- However, they are possible depending on the age of the patient and the host's immune system
- Severe sequelae occur in the neonatal period
- Severe clinical picture in immunodeficient individuals (congenital or acquired)

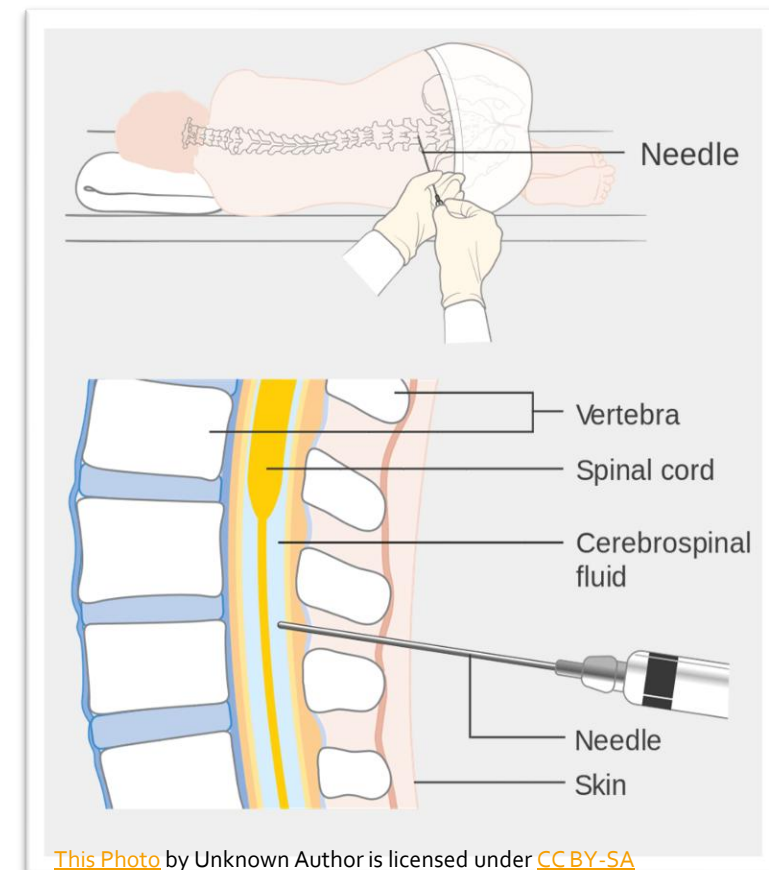


# Diagnosis of viral meningitis

- Clinical picture
- Cerebrospinal fluid examination (cytobiochemical findings)
- Etiological diagnosis:
  - ✓Molecular diagnostics (Polymerase chain reaction-PCR CSF)
  - ✓Serological diagnostics (ELISA, Ag detection)
  - ✓Viral cultivation

# Cerebrospinal fluid examination in viral meningitis

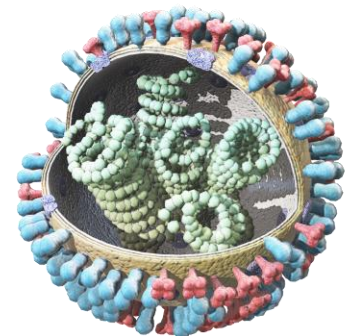
- INCREASED PRESSURE
- CLEAR COLORLESS LIQUID
- CONTAINS 10 TO 500 LYMPHOCYTES IN 1 mm<sup>3</sup>
- PROTEIN 0.40 g/L TO 1.0 g/L (SLIGHTLY INCREASED)
- CSF glucose IS NOT REDUCED (1/2 TO – 2/3 OF SERUM GLYCEMIA)



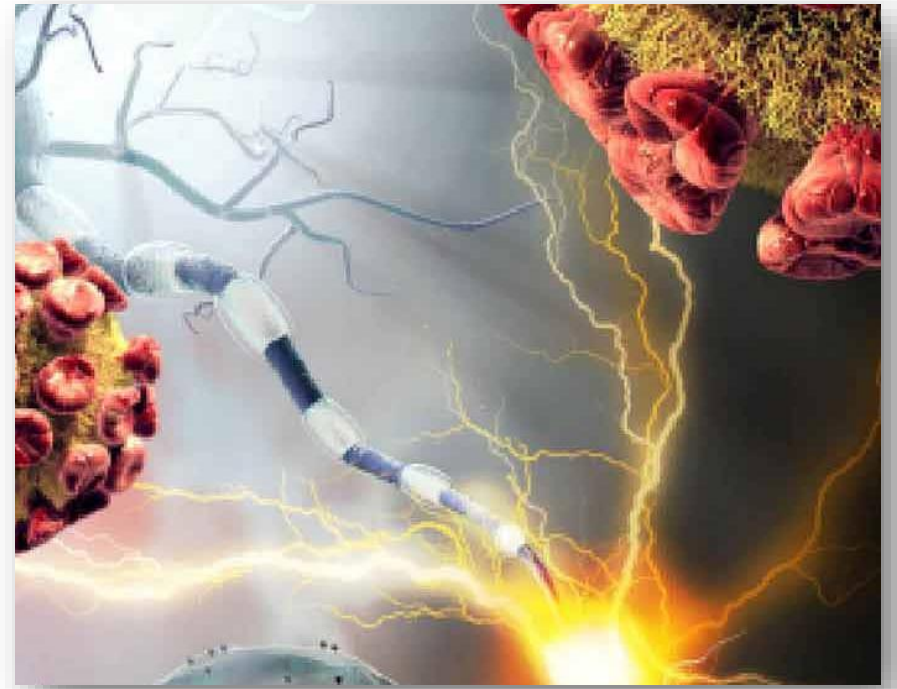
# Therapy of viral meningitis

- Therapy is **primarily** symptomatic
- Rehydration
- Analgesics
- Antipyretics
- Correction of electrolyte imbalance
- Antiedematous therapy (furosemide, mannitol)
- **Anti-inflammatory therapy (corticosteroids) rarely indicated**

❖ Specific antiviral therapy is applied in case of detection of the etiological agent (Acyclovir, Preconaril...)



# Acute viral encephalitis





# Acute viral encephalitis

- Acute viral encephalitis is an inflammatory disease of the brain parenchyma caused by viruses
- Damage to the brain parenchyma can occur directly by the virus or indirectly by immune mechanisms
- Characteristics of encephalitis are sudden onset, progressive course, high risk of disruption of vital functions and uncertain outcome with possible complications and consequences



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# Etiology of viral encephalitis

- Any virus can cause encephalitis
- However, there are viruses that have a greater tropism for the CNS than some other viruses

## The most common causative agents of acute viral encephalitis

Herpes simplex viruses type I

Herpes simplex viruses type II

Varicella zoster virus

Enteroviruses

Human immunodeficiency virus (HIV)

Influenza A and B viruses

Rubella virus

Morbilli virus

Cytomegalovirus

Lymphocytic choriomeningitis (LCM) virus

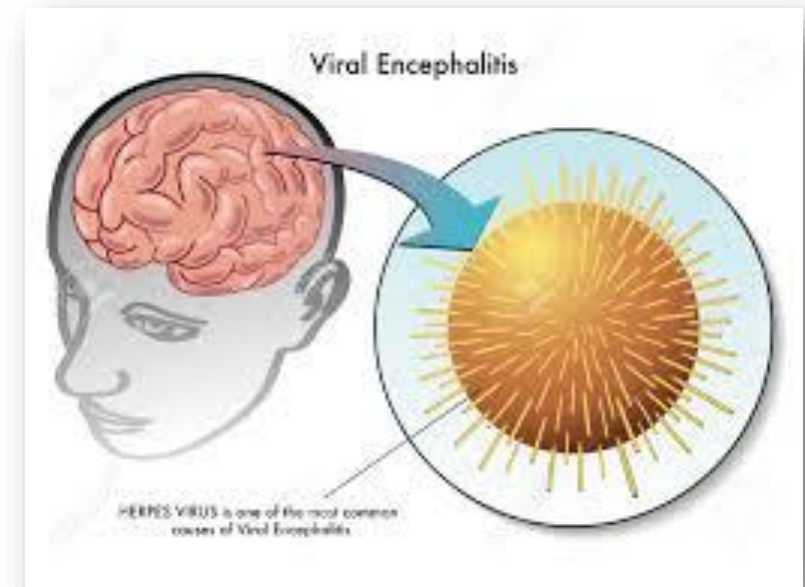
Epstein-Barr virus

Rabies virus

Arboviruses

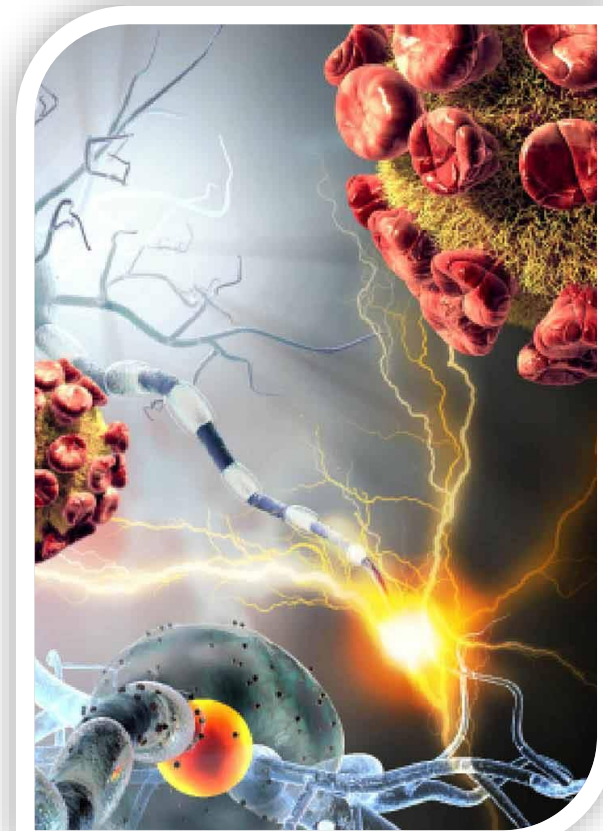
# Epidemiology of viral encephalitis

- They can occur sporadically or epidemically
- In Europe, encephalitis mostly occurs sporadically (HSV, VZV, CMV, HIV, EBV...)
- Smaller epidemic encephalitis occurs with enteroviruses
- Since 2012, West Nile virus (mosquitoes) has been occurring in Serbia in smaller epidemics
- In the world, epidemic encephalitis occurs with arbovirus infections, which is directly related to vectors



## Modes of transmission of viruses to the CNS

| Hematogenous pathway  | Neural pathway   | Olfactory pathway   |
|---|--|---|
| <ul style="list-style-type: none"><li>• Coxsackie virusi</li><li>• HIV</li><li>• CMV</li><li>• VZV</li><li>• EBV</li><li>• Arbo virusi</li><li>• LCM</li><li>• Morbilli</li></ul> | <ul style="list-style-type: none"><li>• HSV<sub>1</sub></li><li>• HSV<sub>2</sub></li><li>• VZV</li><li>• Rabies virus</li></ul> | <ul style="list-style-type: none"><li>• HSV<sub>1</sub></li></ul> |



# Pathogenetic mechanisms of viral encephalitis

## Hematogenous route of transmission



VIRUS ENTRY INTO THE HOST ORGANISM



PRIMARY REPLICATION

respiratory tract, gastrointestinal tract, skin, lymph nodes



SECONDARY REPLICATION

endothelium of blood vessels, reticuloendothelial system, muscle



VIREMIA

general infection-febrile

CHORIOID PLEXUS

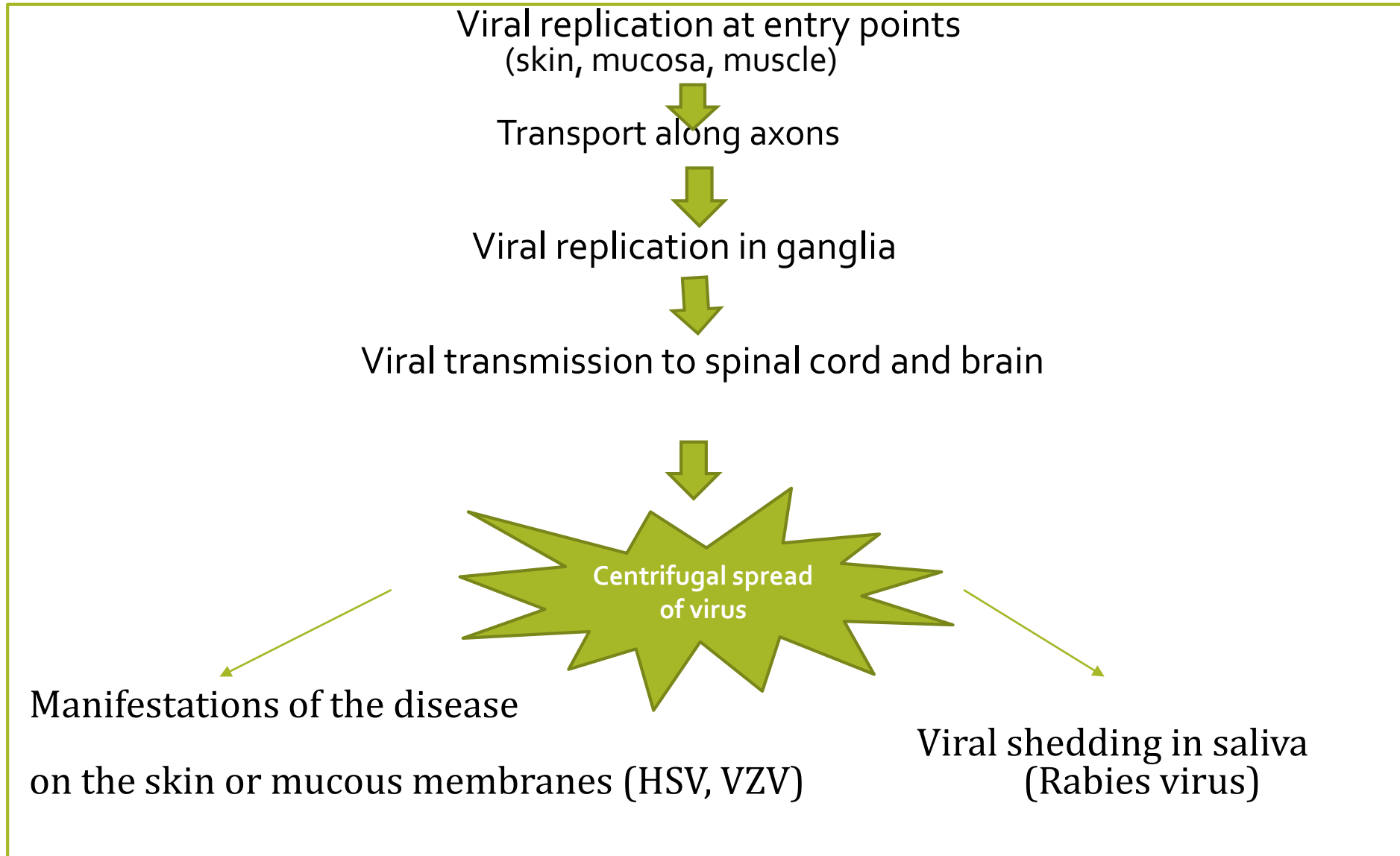


CEREBROSPINAL FLUID

Brain  
parenchyma  
(encephalitis)

# Pathogenetic mechanisms of viral encephalitis

## Neural pathway of virus transmission





# Clinical picture of acute viral encephalitis

INCUBATION - differs in etiological agents

PRODROME- gradual, difficulty concentrating, hypersensitivity to stimuli....

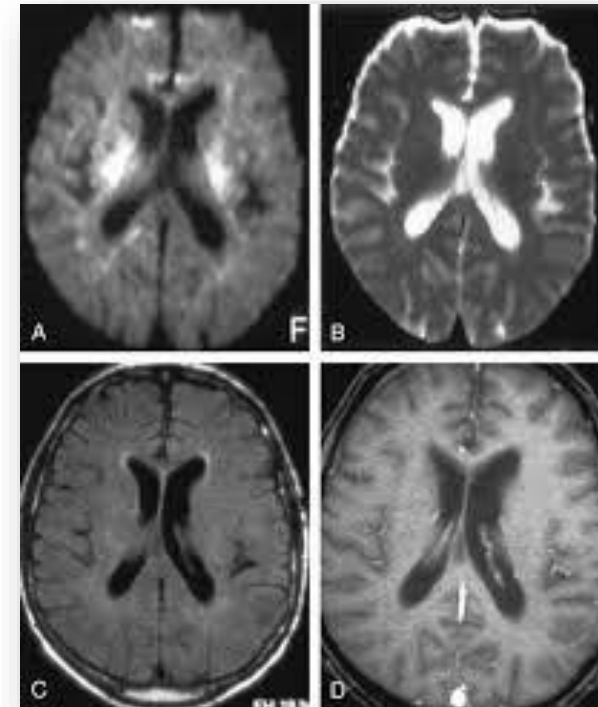
ACUTE NEUROLOGICAL DISEASE

OUTCOME

PERIOD OF STRUCTURAL AND FUNCTIONAL RECOVERY

# Acute neurological disease

- Infectious syndrome
- Headache, severe diffuse
- Vomiting and painful neck stiffness occur in up to 50% of patients
- A large number of patients have dysarthria and dysphasia
- One of the most common clinical manifestations is impaired consciousness (quantitative and qualitative)
- Confusions are very common, sometimes as an initial manifestation
- Cranial nerve lesions
- Hemiparesis and hemiplegia



- COMPLICATIONS: status epilepticus, ARI, pneumonia, hyper/hypothermia, hypo/hypertension, shock, erosive gastritis, secondary infections, sepsis, psychosis, decubitus ulcers, contractures
- OUTCOME-mortality is 3-30%, sequelae 3-70%
- Sequelae directly related to the patient's age and the severity of the neurological disorder



# DIAGNOSIS

## EPIDEMIOLOGY

## CLINICAL PICTURE

## CSF EXAMINATION

CSF is clear

9-100 lymphomonocytes in mm<sup>3</sup>

Proteins in CSF is above 0.5 gr/l

Glucose in CSF is normal or slightly elevated

## VIROLOGICAL TESTS:

polymerase chain reaction (PCR) - the most reliable method

Serological diagnostics (ELISA) - detection of intrathecally synthesized antibodies to viral antigens

Detection of viral antigens - immunofluorescence, immunoperoxidase, radioimmunoassay

Virus isolation from tissue culture - of limited importance in acute infections

OTHER TESTS: EEG, CT, MR, ECG, X-rays

# Therapy of acute viral encephalitis

Patients are treated in Intensive Care Units

## ASSESSMENT OF VITAL FUNCTIONS:

consciousness,

breathing,

heart rate and circulation,

diuresis

TREATMENT OF PSYCHOMOTOR RESTLESSNESS: **Diazepam** 0.15-0.25 mg/kg body weight, **Midazolam** i.v./i.m.

TREATMENT OF CONVULSIONS: Diazepam i.v. 0.15 mg/kg body weight, Phenobarbitone 100-200 mg i.v.

# Therapy of acute viral encephalitis

## ANTI-EDEMA THERAPY:

patient position,

oxygenation,

reduction of fluid intake, Mannitol 20% 0.5-2.0 gr/kg bw per 24h,

Furosemide 0.25 mg/kg bw, human 20% albumin 1-2 ml/kg

## ANTIVIRAL THERAPY:

Include Acyclovir in all patients with suspected viral encephalitis until etiological confirmation

In the case of an etiological diagnosis of viral encephalitis, include causal therapy, if available

Immunomodulatory therapy: corticosteroids?

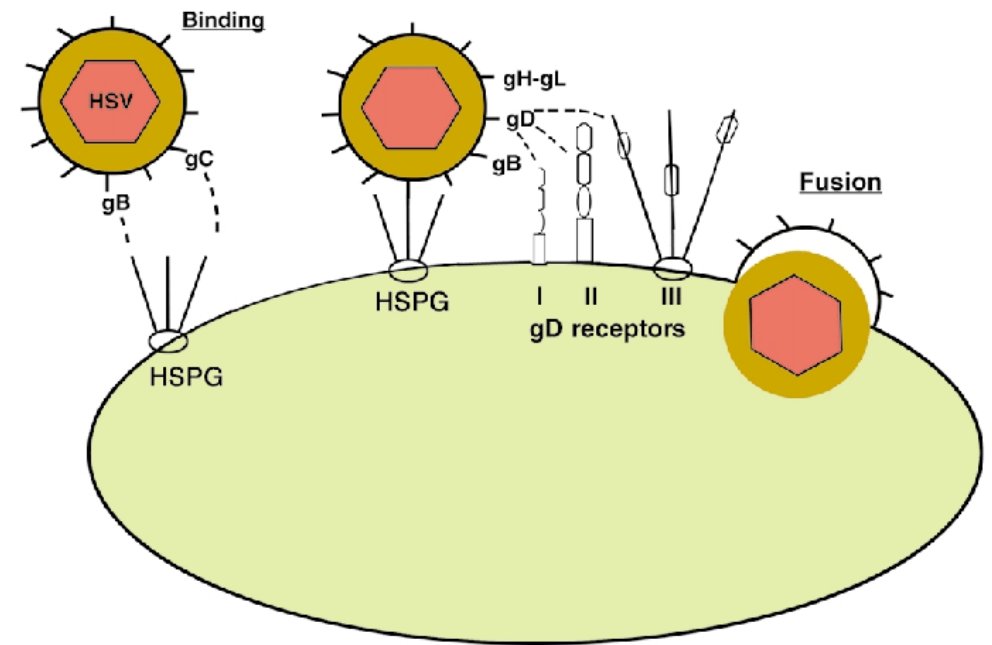
Prevention of secondary infections

Prevention of erosive gastritis

Physical therapy

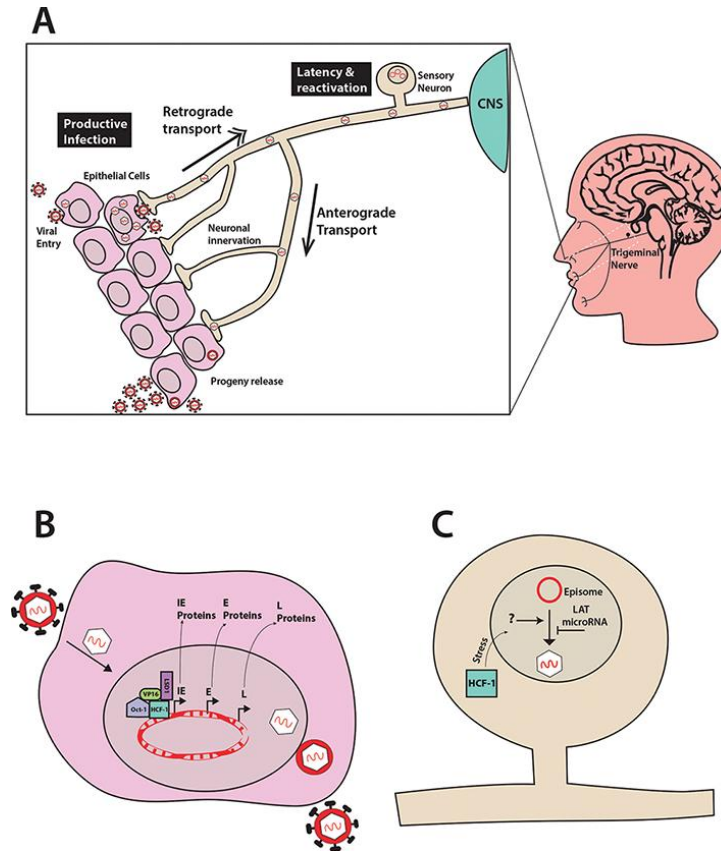
# HERPES SIMPLEX ENCEPHALITIS

- The most common sporadic form of encephalitis
- It represents acute inflammation, congestion or hemorrhage that is most often localized in the temporal lobe in adults
- The causative agent is HSV-1, and much less often HSV-2
- Double-stranded DNA
- Homology between HSV-1 and HSV-2 about 50%
- HSV binds to the host cell with the help of glycoproteins B and S, as well as glycoprotein D, which plays a role in the tropism of HSV for certain tissues



# HERPES SIMPLEX ENCEPHALITIS

- Modes of transmission of the virus to the central nervous system:
- Primary infection with HSV-1 virus
- Reactivation of HSV-1 virus from the trigeminal ganglion and autonomic ganglia
- Reinfection with another type of HSV-1 virus

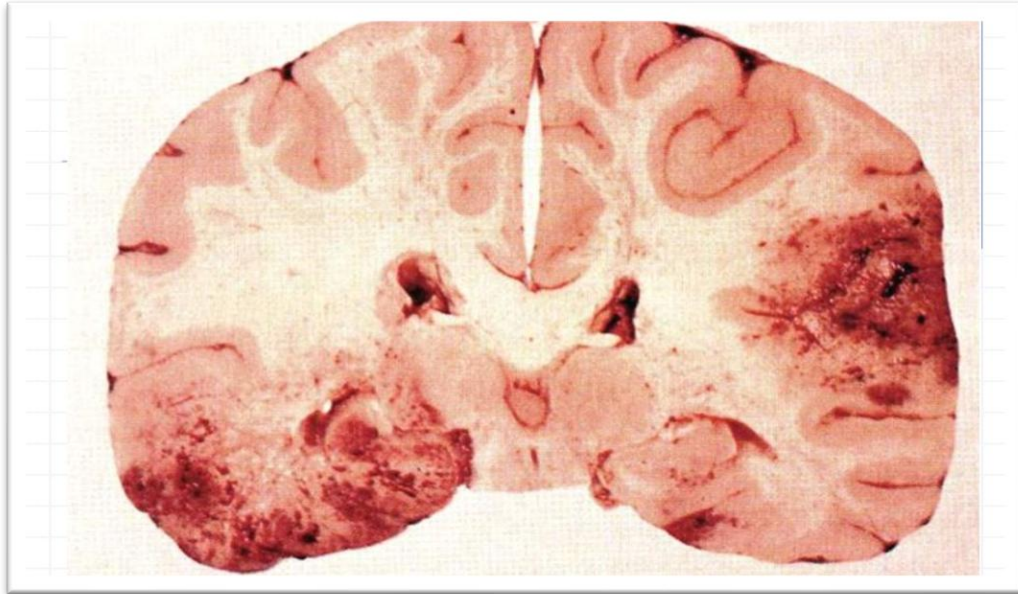




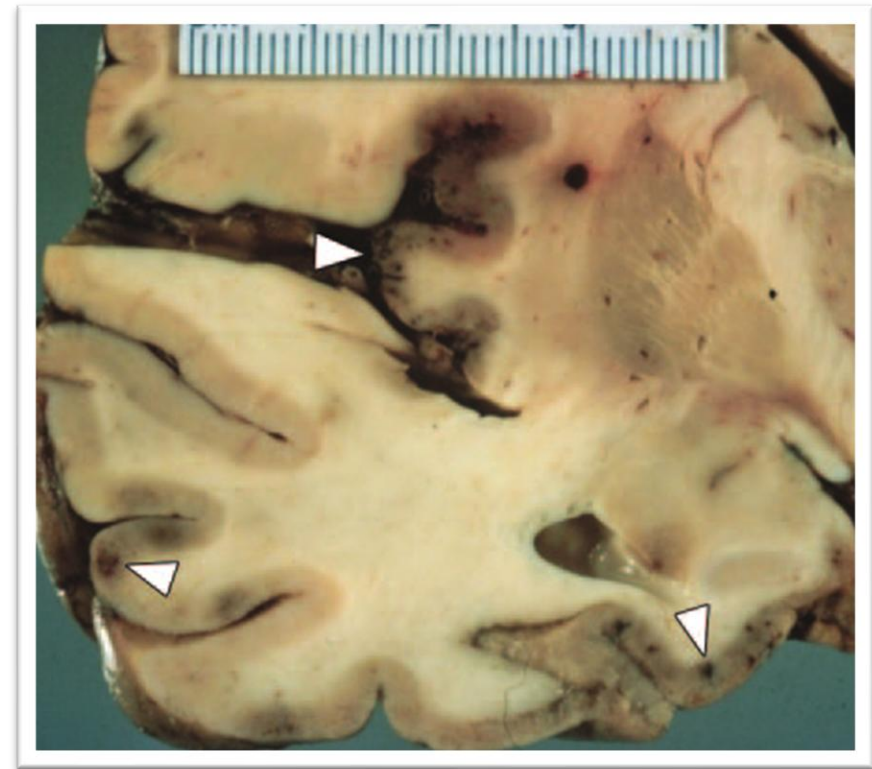
## Clinical picture of herpetic encephalitis

- Infectious syndrome
- Confusion
- Psychomotor restlessness
- Focal neurological findings
- (convulsions, cranial nerve lesions, hemiparesis, hemiplegia)
- Consciousness disturbance (somnolence, stupor, coma)

# Pathohistological findings of acute herpetic encephalitis



In the early stage of the disease, the changes are nonspecific and include capillary congestion, and petechiae are possible. Later, hemorrhagic necrosis develops, with subsequent gliosis.



Uploaded by [James George Smirniotopoulos](#)

- ✓ Multiple petechial hemorrhages and granular atrophy of the cortex and medial temporal lobe

## Diagnostic procedures

Cerebrospinal fluid examination - clear cerebrospinal fluid, mild pleocytosis (lymphocytes, rarely erythrocytes), elevated protein level, normal glycorragic values

Polymerization chain reaction (PCR), detection of HSV-1 genome in cerebrospinal fluid - the most reliable method

Serological diagnostics (ELISA) - detection of intrathecally synthesized antibodies in the IgM class

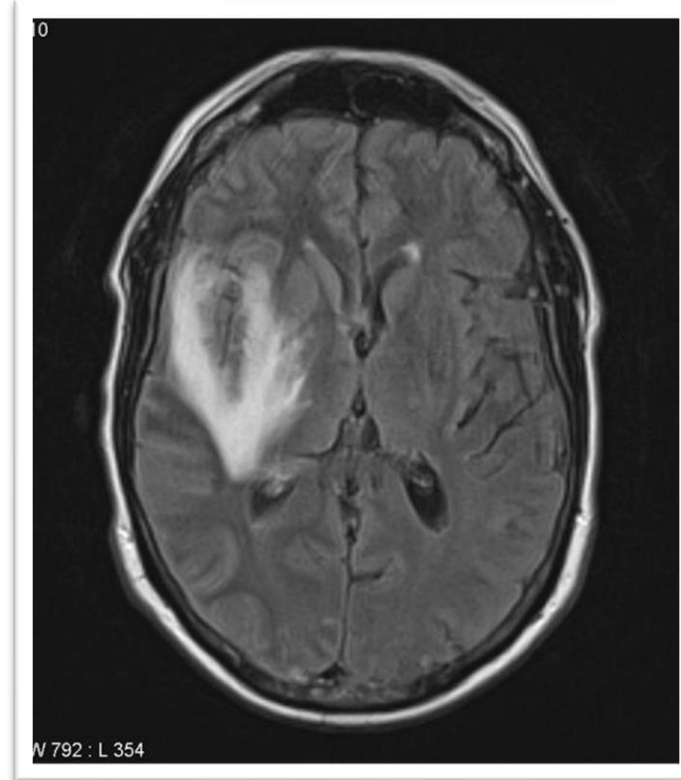
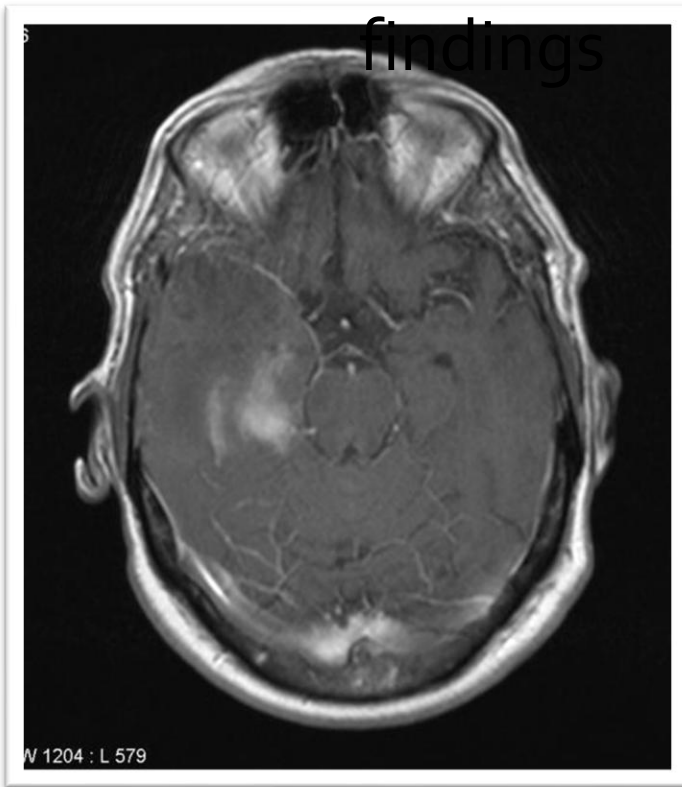
Electroencephalogram (EEG) - most often shows focal slowing and epileptic activity

Computed tomography (CT) - less sensitive than MRI, changes in the form of local ischemia, edema or necrosis can be registered after 3-4 days


Nuclear magnetic resonance imaging (MRI)

# Herpetic encephalitis - MRI

findings



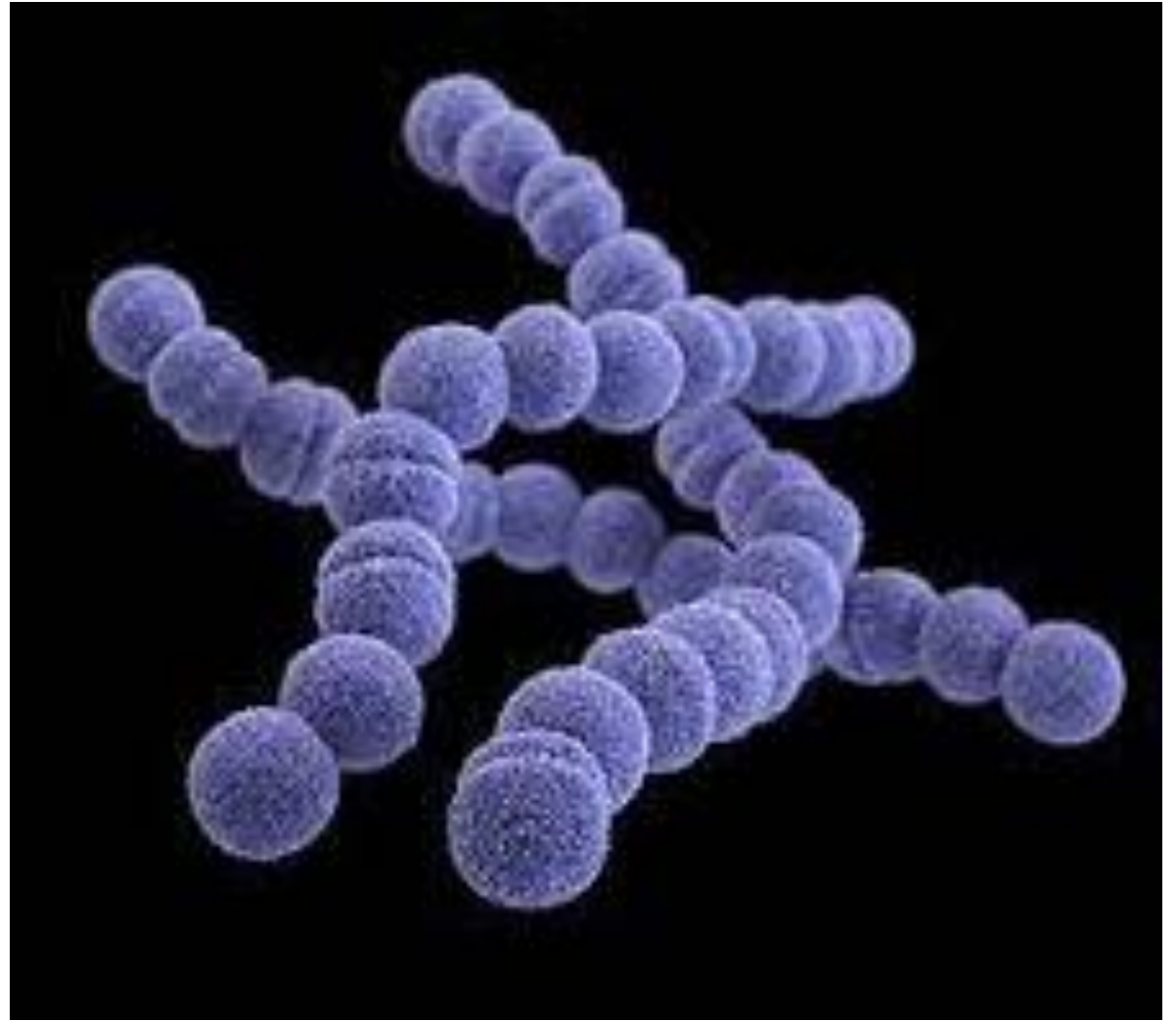
MRI is 80%-90% sensitive in detecting pathological changes in herpes simplex encephalitis. MRI is most sensitive with diffuse images and FLARE sequences. The temporal lobe is usually involved, while inferomedial changes in this lobe are seen in the cingulate gyrus. The basal ganglia are usually spared

- 
- Treatment in intensive care units
  - Patients with HSV encephalitis are treated with parenteral administration of Acyclovir at a dose of 10mg/kg every 8 hours (total daily dose 30mg/kg)
  - In newborns, it is administered at a dose of 20 mg/kg every 8 hours (total daily dose 60mg/kg)
  - The duration of antiviral therapy is at least 14 days, in children 21 days
  - In the case of resistance to Acyclovir, we can give Foscarnet or Cidofovir
  - Antiedema therapy involves the use of Mannitol and Furosemide
  - The use of corticosteroids is controversial
  - Epi seizures are treated with drugs from the benzodiazepine group





# Streptococcal infections

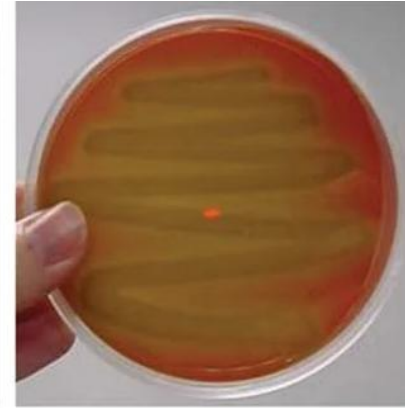


# CHARACTERISTICS OF STREPTOCOCCUS

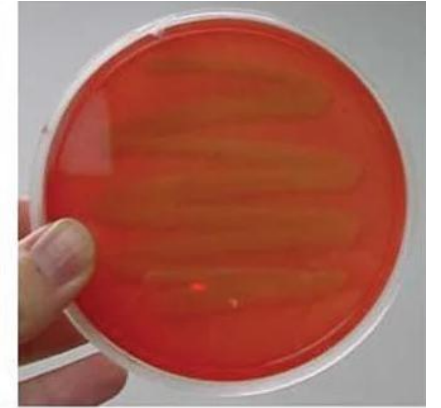
- Gram-positive bacteria of round or oval shape, connected in pairs or chains
- Complete or incomplete hemolysis ( $\alpha$ ,  $\beta$ ,  $\gamma$ )
- Lancefield classification of streptococci from A to H and from K to V
- Modern classification of streptococci: pyogenes, agalactiae, mitis, salivarius, bovis, mutans and other streptococci



**Beta Hemolysis**



**Alpha Hemolysis**



**Gamma Hemolysis**



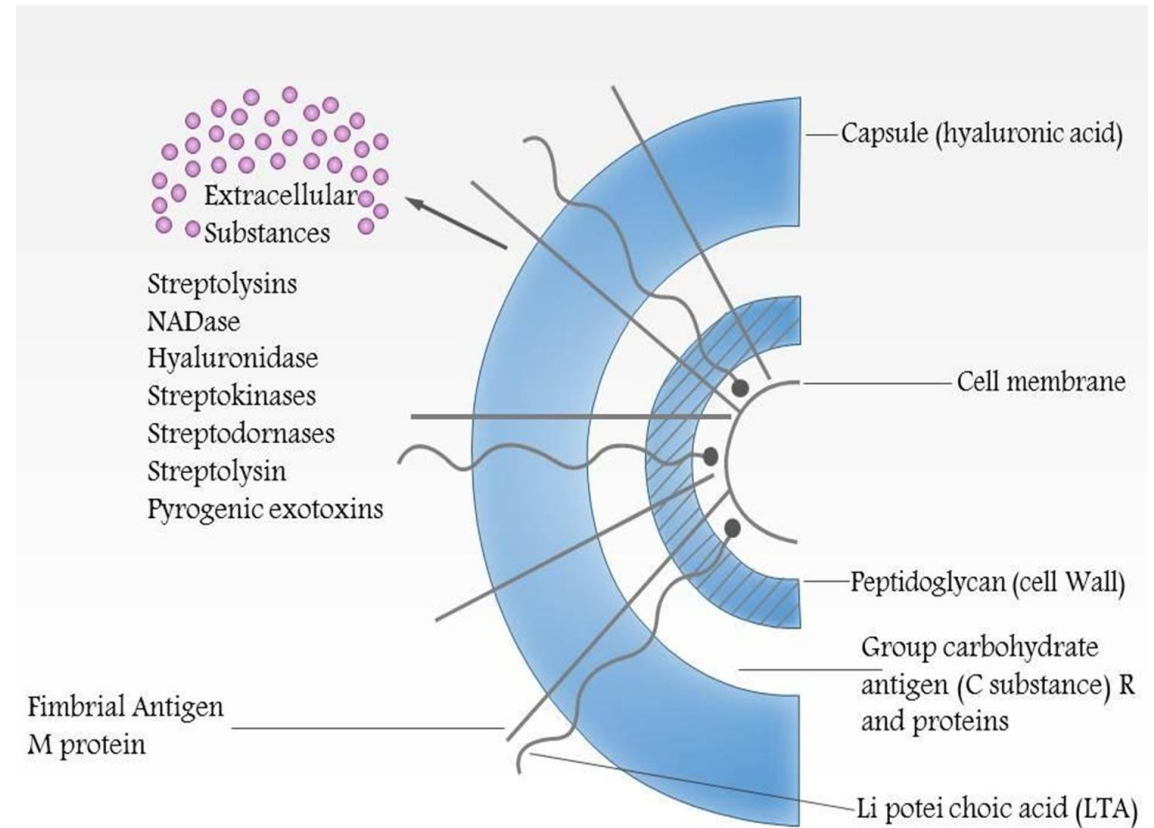
# SPECIES OF STREPTOCOCCUS AND THE CLINICAL SYNDROMES CAUSED BY THEM

| A type of streptococcus   | Clinical syndrome   |
|---|---|
| <b><i>Piogen</i></b><br><i>S. pyogenes</i>  | tonsillopharyngitis, otitis media, sinusitis, scarlet fever, pyoderma, erysipelas, cellulitis, myositis, necrotizing fascitis, bacteremia, pneumonia, endometritis, meningitis, arthritis, osteomyelitis, streptococcal shock syndrome<br>non-purulent consequences: rheumatic fever, acute glomerulonephritis, polyarthritis, erythema nodosum |
| <i>S. agalactiae</i>  | neonatal sepsis and meningitis, puerperal sepsis, cellulitis, bacteremia, urinary infection   |
| <i>S. dysgalactiae</i>  | tonsillopharyngitis, cellulitis, bacteremia, endocarditis, pneumonia, non-purulent consequences: acute glomerulonephritis   |
| <b><i>Aginosum</i></b>  | bacteremia, brain abscess, intra-abdominal abscess, periapical dental abscess   |
| <b><i>Mitis</i>*</b>  | dental plaque, endocarditis   |
| <i>Streptococcus pneumoniae</i>   | otitis, sinusitis, pneumonia, bacteremia, meningitis  |
| <b><i>Salivarius</i></b>  | endocarditis, colonization of the mucous membrane of the oral cavity  |
| <b><i>Bovis</i></b><br><i>Streptococcus gallolyticus</i><br>(ranije <i>S. Bovis</i> ) | endocarditis  |
| <b><i>Mutans</i></b>  | dental caries   |

# STREPTOCOCCUS PYOGENES

## - VIRULENCE FACTORS

- A capsular polysaccharide that prevents phagocytosis of streptococci
- M protein – the most important surface antigen and virulence factor, prevents phagocytosis and successful protection from the immune response (C3 b). It contributes to the pathogenesis of autoimmune complications (antibodies cross-react with cardiac myosin and glomeruli). It has superantigen properties and causes non-specific proliferation of a large part of the T population
- Enzymes (streptolysin O and S, hyaluronidase, streptokinase, deoxyribonuclease...)
- Toxins (pyrogenic erythrotoxic exotoxin)



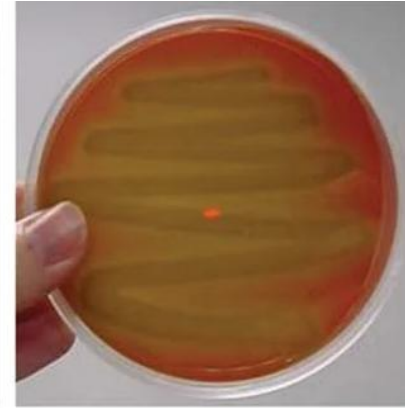
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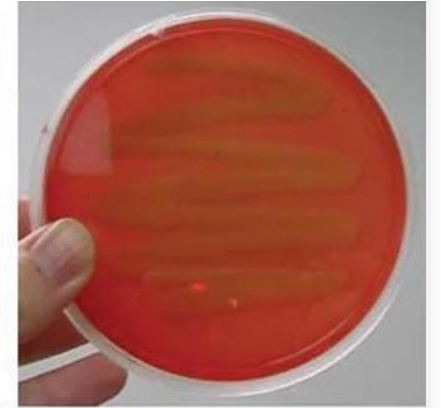
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**Beta Hemolysis**



**Alpha Hemolysis**



**Gamma Hemolysis**

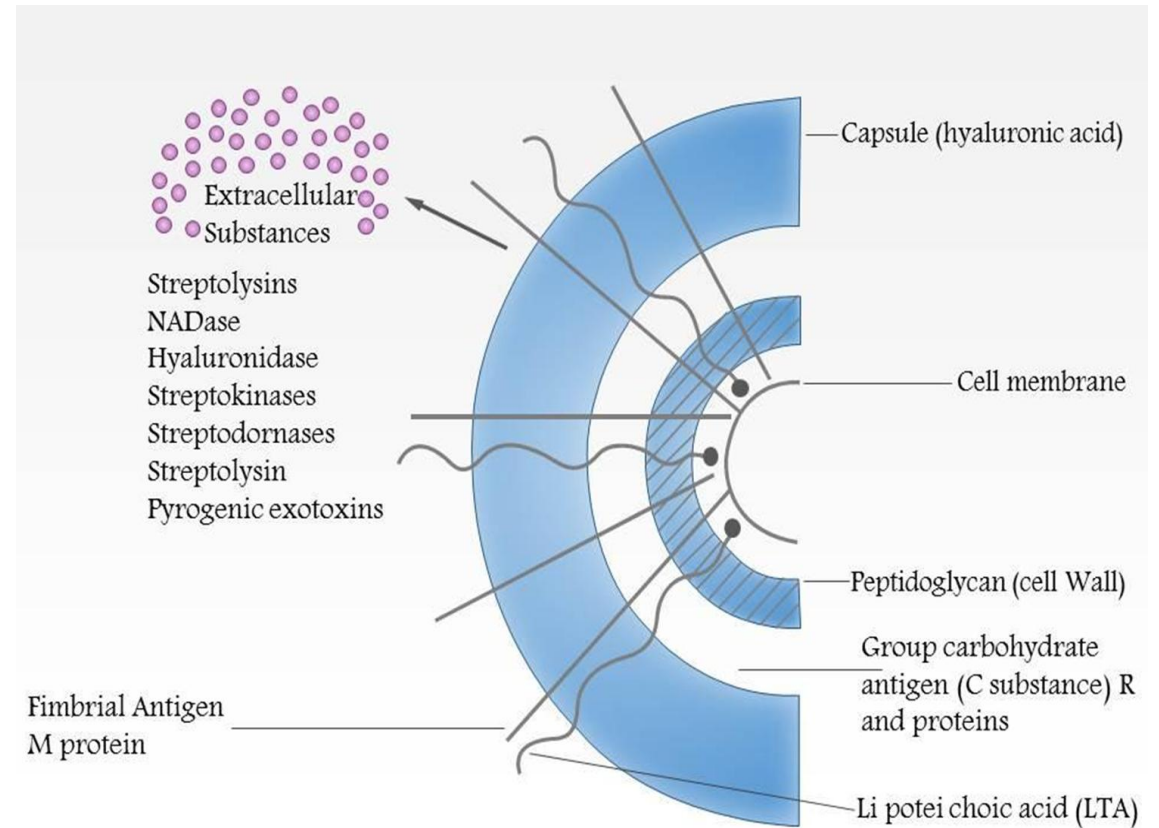
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| <b>Piogen</b><br><i>S. pyogenes</i>  | tonsillopharyngitis, otitis media, sinusitis, scarlet fever, pyoderma, erysipelas, cellulitis, myositis, necrotizing fascitis, bacteremia, pneumonia, endometritis, meningitis, arthritis, osteomyelitis, streptococcal shock syndrome<br>non-purulent consequences: rheumatic fever, acute glomerulonephritis, polyarthritis, erythema nodosum |
| <i>S. agalactiae</i>   | neonatal sepsis and meningitis, puerperal sepsis, cellulitis, bacteremia, urinary infection   |
| <i>S. dysgalactiae</i>   | tonsillopharyngitis, cellulitis, bacteremia, endocarditis, pneumonia, non-purulent consequences: acute glomerulonephritis   |
| <b>Aginosum</b>  | bacteremia, brain abscess, intra-abdominal abscess, periapical dental abscess   |
| <b>Mitis*</b>  | dental plaque, endocarditis   |
| <i>Streptococcus pneumoniae</i>  | otitis, sinusitis, pneumonia, bacteremia, meningitis  |
| <b>Salivarius</b>  | endocarditis, colonization of the mucous membrane of the oral cavity  |
| <b>Bovis</b><br><i>Streptococcus gallolyticus</i><br>(ranije <i>S. Bovis</i> ) | endocarditis  |
| <b>Mutans</b>  | dental caries   |

# STREPTOCOCCUS PYOGENES

## - VIRULENCE FACTORS

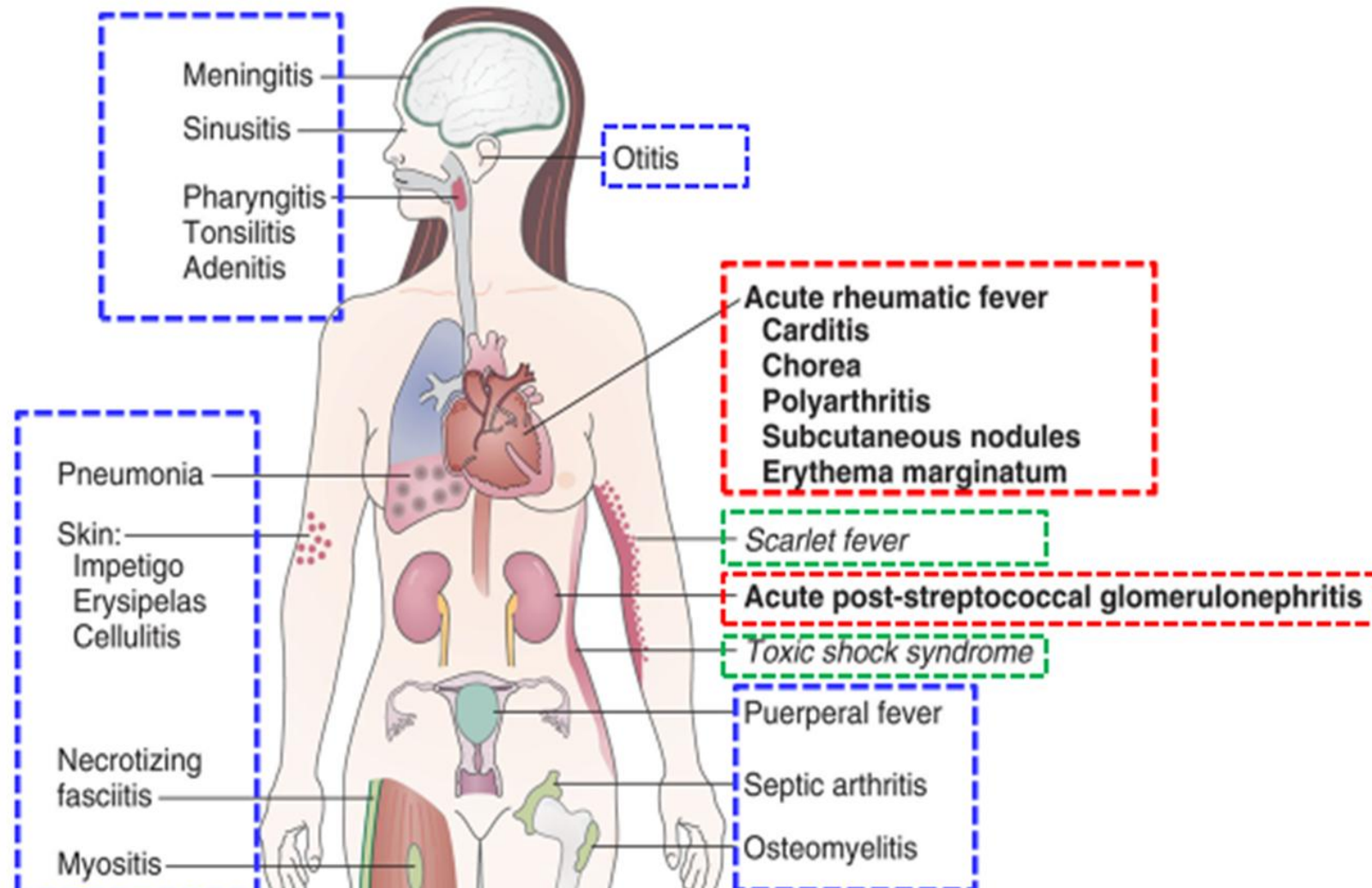
- A capsular polysaccharide that prevents phagocytosis of streptococci
- M protein – the most important surface antigen and virulence factor, prevents phagocytosis and successful protection from the immune response (C3 b). It contributes to the pathogenesis of autoimmune complications (antibodies cross-react with cardiac myosin and glomeruli). It has superantigen properties and causes non-specific proliferation of a large part of the T population
- Enzymes (streptolysin O and S, hyaluronidase, streptokinase, deoxyribonuclease...)
- Toxins (pyrogenic erythrotoxic exotoxin)



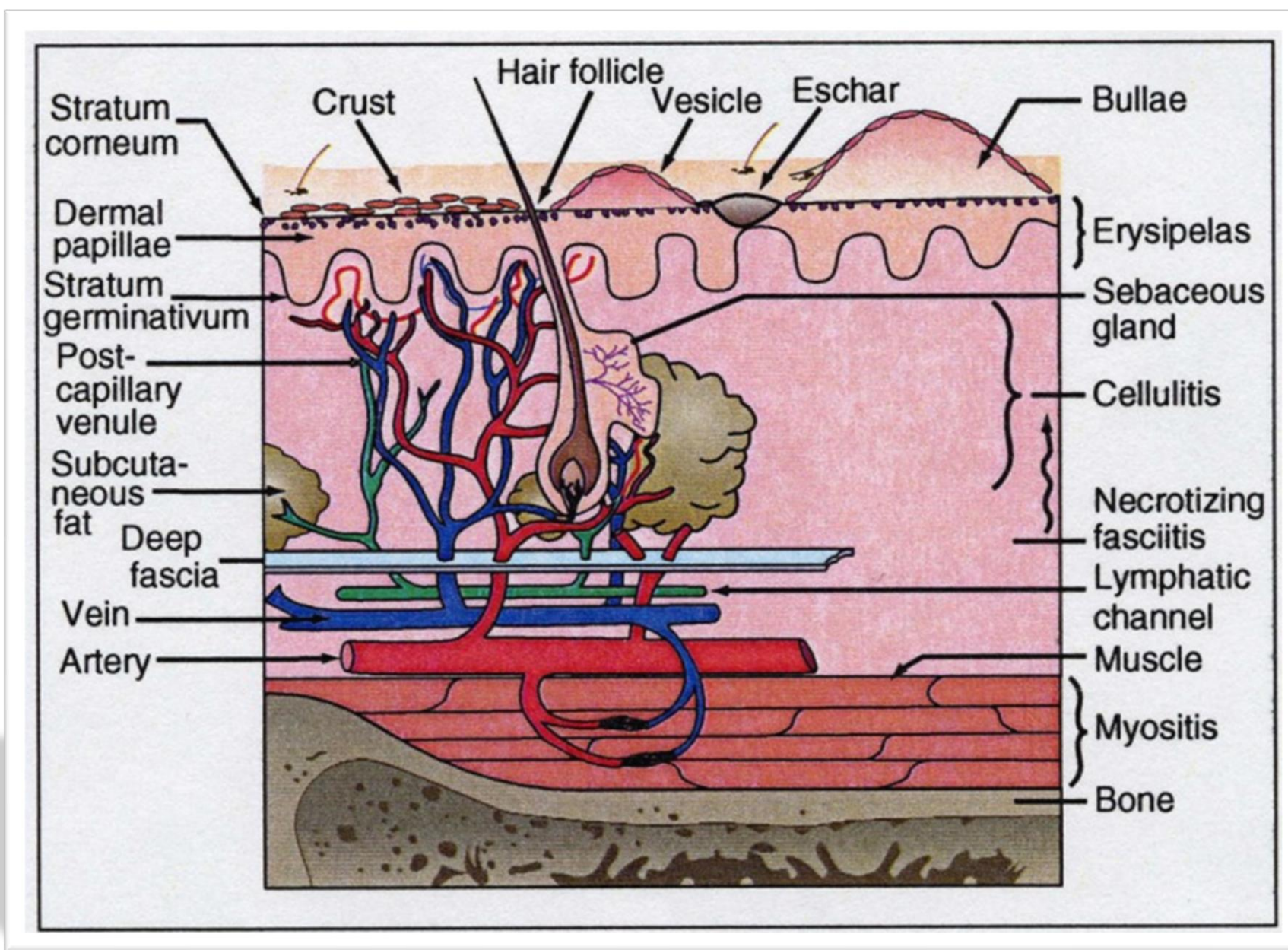
## *Diseases caused by Streptococcus pyogenes bacteria*

- Diseases of a locally invasive nature (tonsillopharyngitis, impetigo, otitis media, erysipelas, necrotic fascitis)
- Diseases of a toxemic character represent the body's systemic response to circulating bacterial toxins (scarlet fever, streptococcal toxic shock syndrome).
- Poststreptococcal sequelae (rheumatic fever and glomerulonephritis in 1-3% of untreated patients)

# DISEASES CAUSED BY STREPTOCOCCUS PYOGENES







Anatomical relationship between skin and skin structures and different *S. pyogenes* infections. From Harrison's Principles of Internal Medicine, 19th edition, and used with permission (Stevens, 2015).



# RED WIND – ERYSIPELAS

## **Definition**

Erysipelas is an acute streptococcal infection of the skin in the course of which there is a pronounced disruption of lymph flow, and it is clinically characterized by elevated temperature and local symptoms.

## **Etiopathogenesis**

- the disease is caused by group A beta hemolytic streptococcus,
- the causative agent penetrates through micro-injuries of the skin into the dermis, where it causes an inflammatory process, which quickly spreads through the lymphatic vessels,
- in addition to the causative agent and micro-injuries, it is necessary to have the sensitization of the organism to streptococcus.

## Epidemiology

- sporadic, non-contagious disease,
- predisposing factors: chronic alcoholism, surgical interventions, diabetes, lymphatic stasis, varicose veins and fungal infections on the legs, etc.

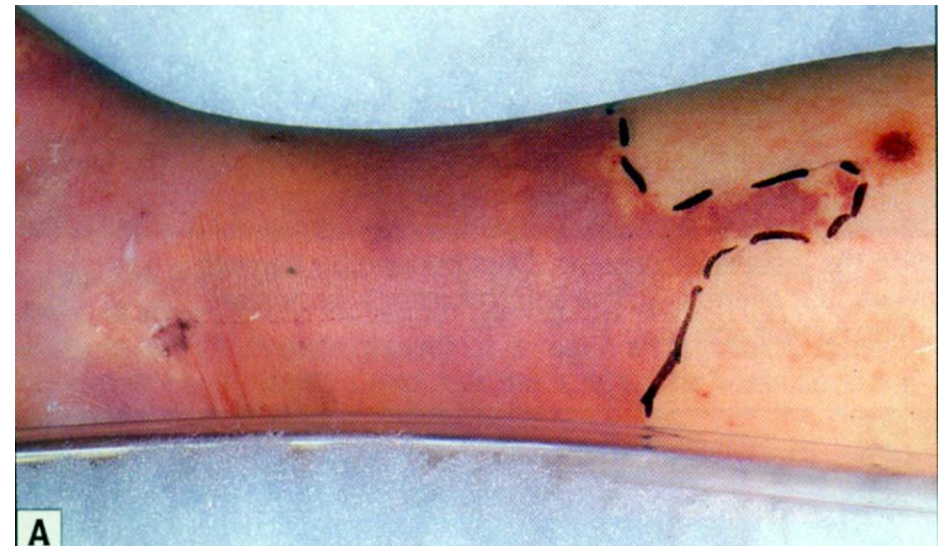
### Clinical picture

#### **Incubation:** 1-3 days

- the disease begins suddenly with general symptoms of infection: fever, chills, headache, malaise,
- after a few hours, local symptoms: redness and swelling that spread quickly ("like the wind"). The swelling is red, shiny, clearly demarcated from the surrounding tissue, warm and painful to the touch. Regional lymphadenitis is also present,
- the disease is most often localized on the face and lower legs.

# Erysipelas

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### **Complications:**

- retrobulbar phlegmon,
- sepsis.

### **Diagnosis:**

- based on the characteristic clinical picture (clinical diagnosis),
- laboratory analysis: accelerated sedimentation, leukocytosis, ↑CRP, ↑ fibrinogen, elevated AST-O titer.

### **Differential diagnosis:**

- cellulitis, phlegmon, furuncle, herpes zoster, allergic dermatitis, myositis, necrotizing fascitis, thrombophlebitis....

## **Therapy:**

- causal therapy: penicillin for 10-14 days, clindamycin,
- rest, with a slightly elevated leg,
- poultices (3% boric acid).

## **Immunity:**

- the acquired disease does not leave immunity,
- disposition is acquired for relapse.

In order to prevent recurrence, treatment of dermatomycosis and varicose veins should be carried out.

# CELULITIS

## Definition

Cellulitis is an acute streptococcal infection of the skin that affects the subcutaneous tissue.

## Epidemiology

The most common causative agents are *Streptococcus pyogenes* and *Staphylococcus aureus*, but they can also be gram-negative bacteria.



## Clinical picture

Incubation: the length of the incubation period depends on the causative agent

local symptoms: the affected skin is painful, warm, red and edematous, there is no clear border to healthy skin, local lymphadenitis and lymphangitis occur.

## Differential diagnosis

deep vein thrombosis,  
myositis,  
**necrotizing fasciitis,**  
retrobulbar abscess...

## Therapy

penicillin G 4-6 h 2 000 000 i.u. i.v.,  
cefazolin 1-2 g every 8 hours,  
clindamycin 600 mg every 6 or 8 hours,  
vancomycin 1 g every 12 hours.

# NECROTIZING FASCIITIS

## **Definition**

Necrotizing fasciitis is characterized by an inflammatory necrotic process that involves subcutaneous soft tissue, superficial and often deep fascia.

## **Etiopathogenesis**

NECROTIZING FASCIITIS TYPE I - mixed infection caused by aerobic (*Staphylococcus aureus*, *Escherichia coli*, *S. pyogenes*) and anaerobic bacteria (*Peptostreptococcus*, *Bacteroides fragilis*, ***Clostridium***),

NECROTIZING FASCIITIS TYPE II - is caused by streptococcus (*S. pyogenes*) alone or in combination with *S. aureus*. It occurs after minor trauma, stab wounds or surgical interventions, in patients with diabetes and peripheral vascular disease.

**Predisposing diseases:** diabetes mellitus, liver cirrhosis, alcoholism, corticosteroid therapy, peripheral vascular disease and drug addiction



## Clinical picture

the first sign is pain that increases,  
in the affected area, pronounced edema and erythema appear, which is vaguely limited, warm, bright, markedly tense and painful,  
very quickly the color of the skin changes from red-pink to blue-gray, with the appearance of bullae and dry skin gangrene,  
the skin is no longer tense, but anesthesia occurs due to secondary thrombosis of small blood vessels and destruction of superficial nerves,  
severe myonecrosis requiring fasciectomy,  
general intoxication, high temperature, tachycardia, hypotension.



## Diagnosis

X-ray imaging of soft tissue

Computed tomography and magnetic resonance imaging can show a gas collection

Laboratory analyses

## Therapy

Extensive surgical debridement

The combination of crystalline penicillin in a dose of 4 mil i.u./4 h and clindamycin 600-900 mg /8 h.

Piperacillin-tazobactam 4.5 g IV every 8 hours

Meropenem 1g iv every 8h if at risk of ESBL infection

Cefepime 2g iv every 8h + Metronidazole 500mg iv every 8h

Aztreonam 2g iv every 8h + Metronidazole 500mg iv every 8h

} ± **Klindamicin** 600mg iv na 8h

Vancomycin 15mg/kg

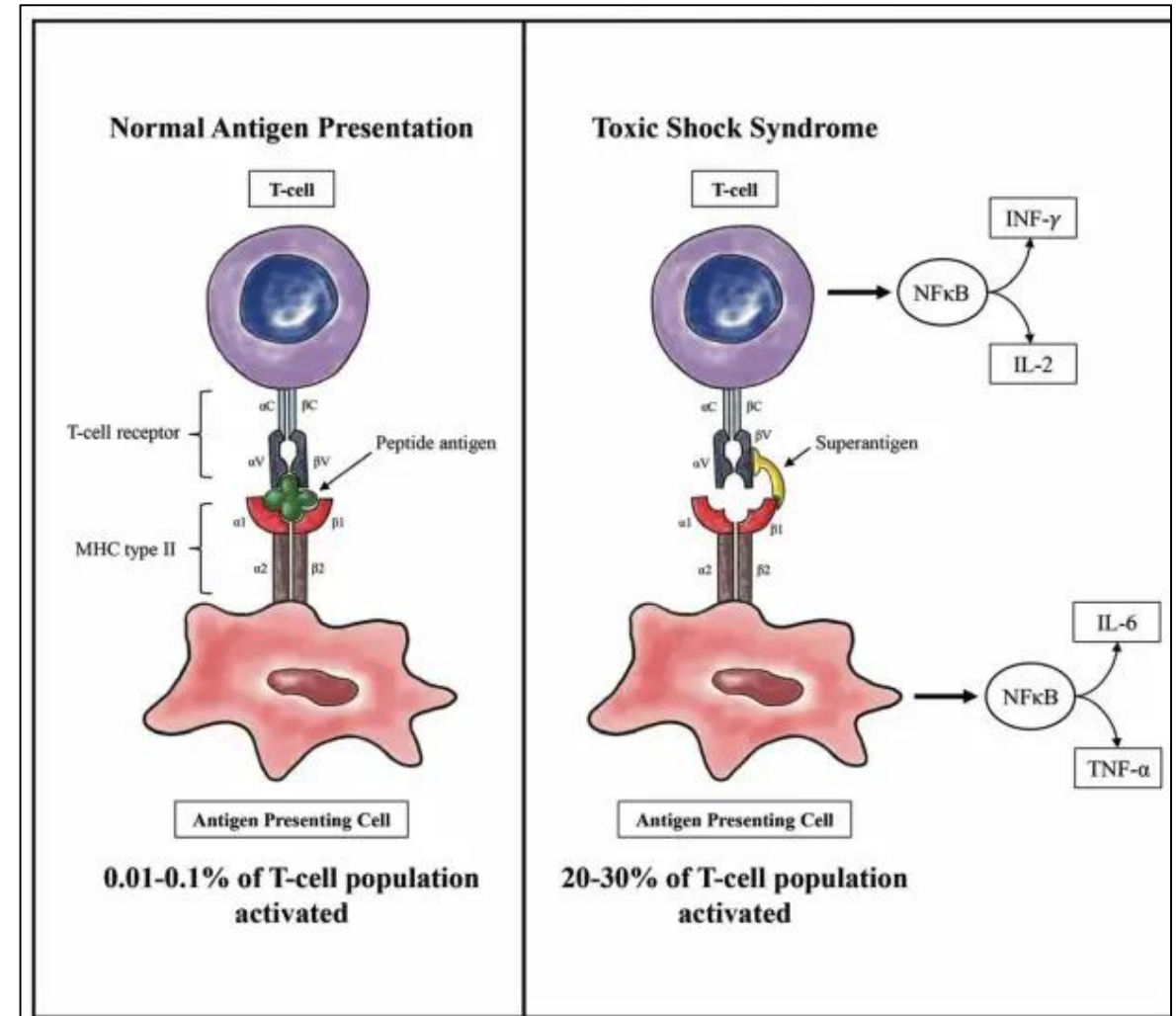
Linezolid 600mg IV every 12 hours

} ± **Klindamicin** 600mg iv na 8h

# STREPTOCOCCAL TOXIC SHOCK SYNDROME

- Streptococcal sepsis is a severe, generalized disease that occurs as a result of the spread of bacteria through the blood from the primary focus.
  - Strains of streptococci that secrete exotoxins A, B or C
  - The site of entry is usually the skin, and rarely the mucous membrane of the vagina or pharynx
  - Minor skin trauma, hematoma, scar, surgical procedures - liposuction, hysterectomy, childbirth
  - It is thought to be caused by impaired neutrophil function and increased cytokine release
-

# Pathogenesis of streptococcal shock syndrome



## CRITERIA FOR THE DIAGNOSIS OF STREPTOCOCCAL SHOCK SYNDROME

### Isolation of Streptococcus pyogenes

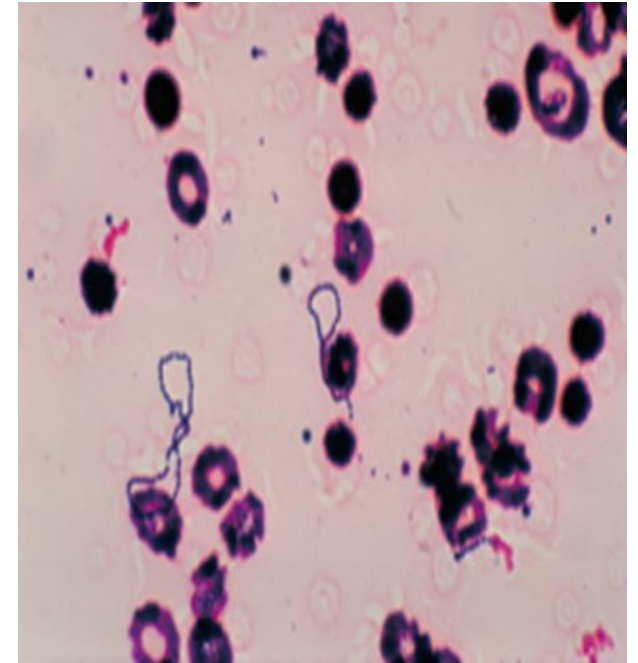
- A. from primarily sterile material (blood, cerebrospinal fluid...)
- B. B. from a non-sterile site
- C. Maculopapulose
- D. II Clinical signs of severe infection
- E. A. Hypotension: systolic pressure lower than 12 kPa in adults or 5% lower than normal values in children
- F. B. Two or more of the following characters
- G. Renal disorders - creatinine higher than 177mmol for adults or at least twice the upper limit for the appropriate age
- H. Coagulation - platelet count less than 100,000 or the presence of DIK (disseminated vascular coagulation)
- I. Liver damage - transaminase and bilirubin values at least twice the normal values
- J. a) ARSD (acute respiratory distress syndrome)
- K. b) the existence of diffuse capillary relaxation, which is manifested by the acute onset of generalized edema
- L. c) pleural or peritoneal effusions with hypoalbuminemia
- M. Generalized erythematous-macular measles that may desquamate
- N. Soft tissue necrosis, including necrotizing fascitis or myositis or gangrene

## Therapy

Crystalline penicillin 4 million IU/4 hours,  
Clindamycin 600-900 mg/8h,  
Immunoglobulins iv (2g/kg once)

## *Streptococcus viridans*

- ✓ Streptococcus viridans are alpha hemolytic species of the genus Streptococcus.
- ✓ The most commonly isolated species are: S. mutans, S. salvarius, S. mitis, S. sanguis and S. angionosus.
- ✓ 20% of cases are caused by subacute bacterial endocarditis, which usually occurs in people with damaged or artificial heart valves.
- ✓ The disease has a subacute or chronic course and symptoms can last for weeks and months.
- ✓ The diagnosis is confirmed by echosonography and evidence of the causative agent in the blood.







# Staphylococcal infections

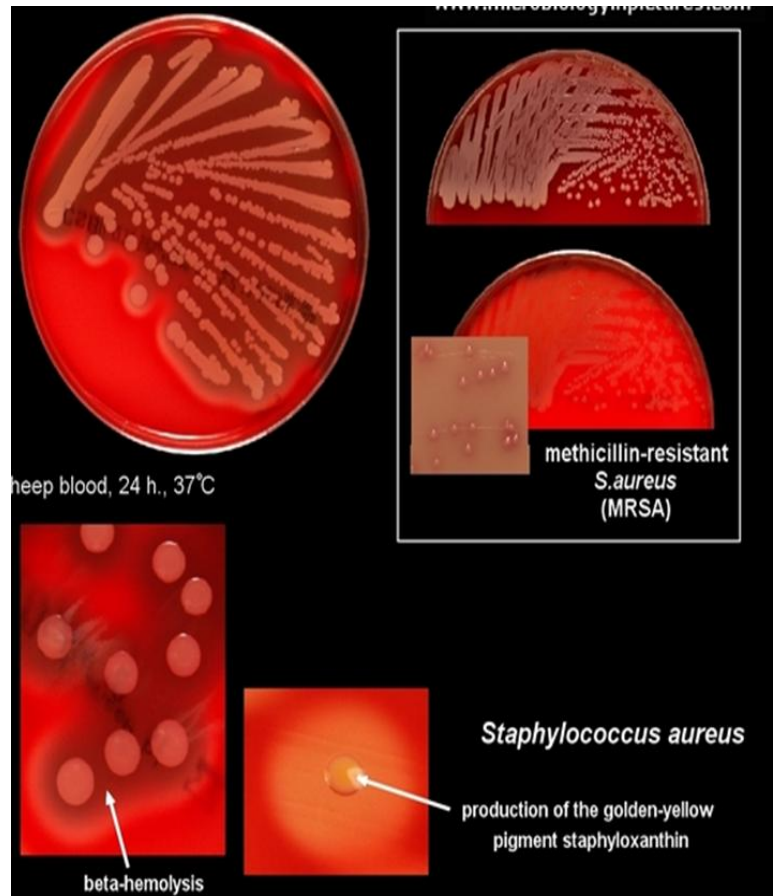


# The most important staphylococci

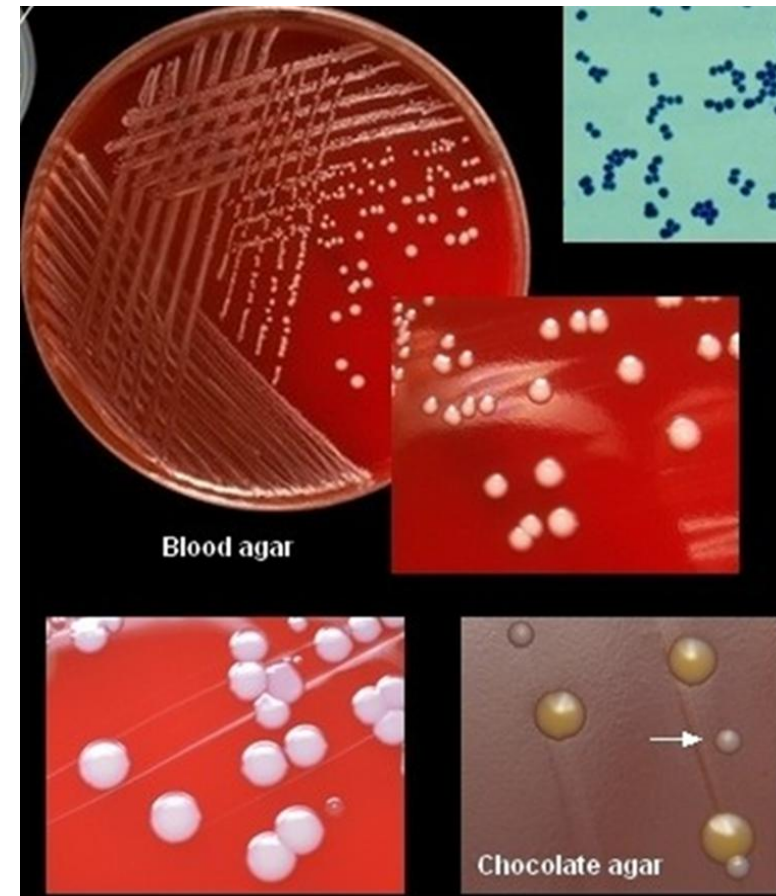
Staphylococcus  
saprophyticus

Staphylococcus aureus  
- coagulase positive  
(golden yellow  
colonies)

Staphylococcus  
epidermidis -  
coagulase-negative  
staphylococcus, which  
forms white colonies



*Staphylococcus aureus*



*Staphylococcus epidermidis*



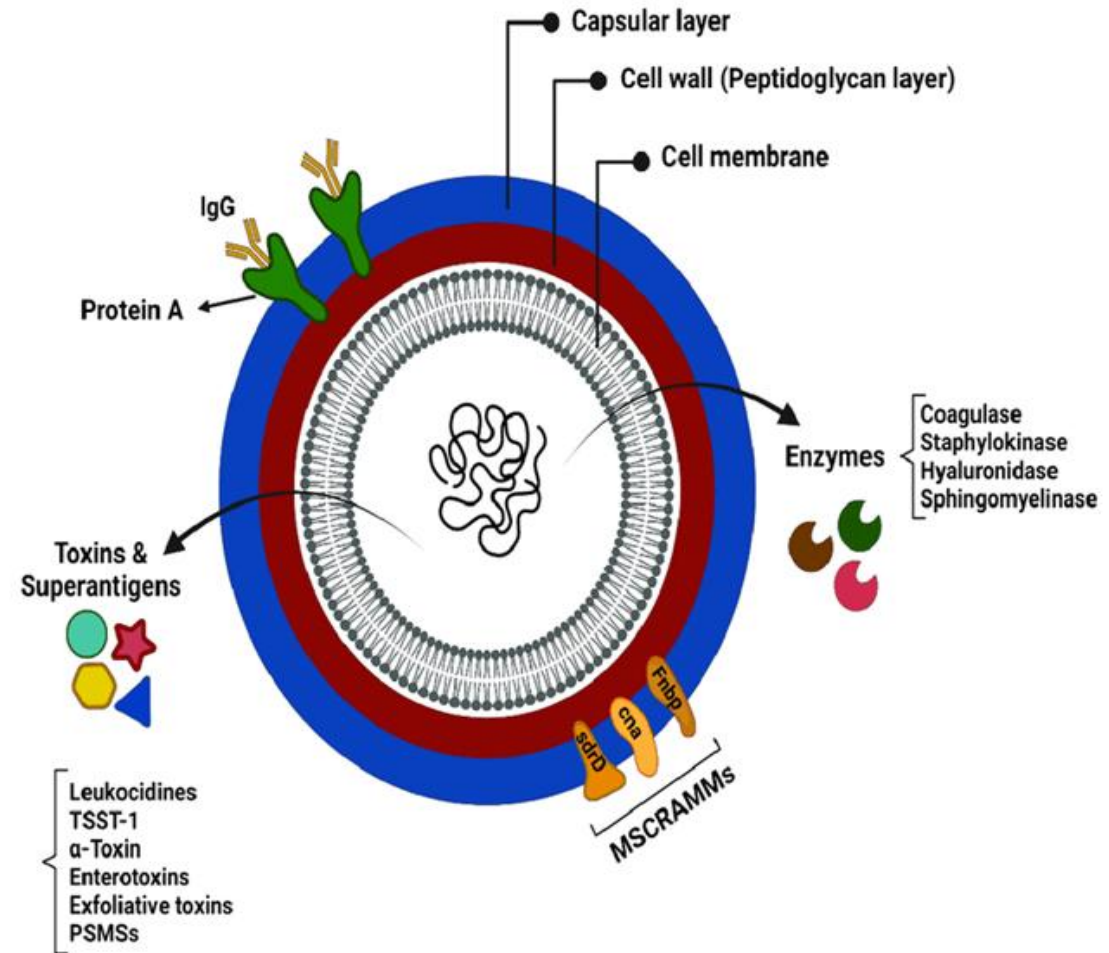
# *Staphylococcus aureus*

Epidemiology - people are the main reservoir, they colonize the skin and mucous membranes, about 20-40% of the healthy, adult population are germ carriers. Certain population groups are prone to colonization (healthcare workers, dialysis and diabetes patients, IV drug addicts, people infected with HIV, people with skin diseases)



# Virulence factors

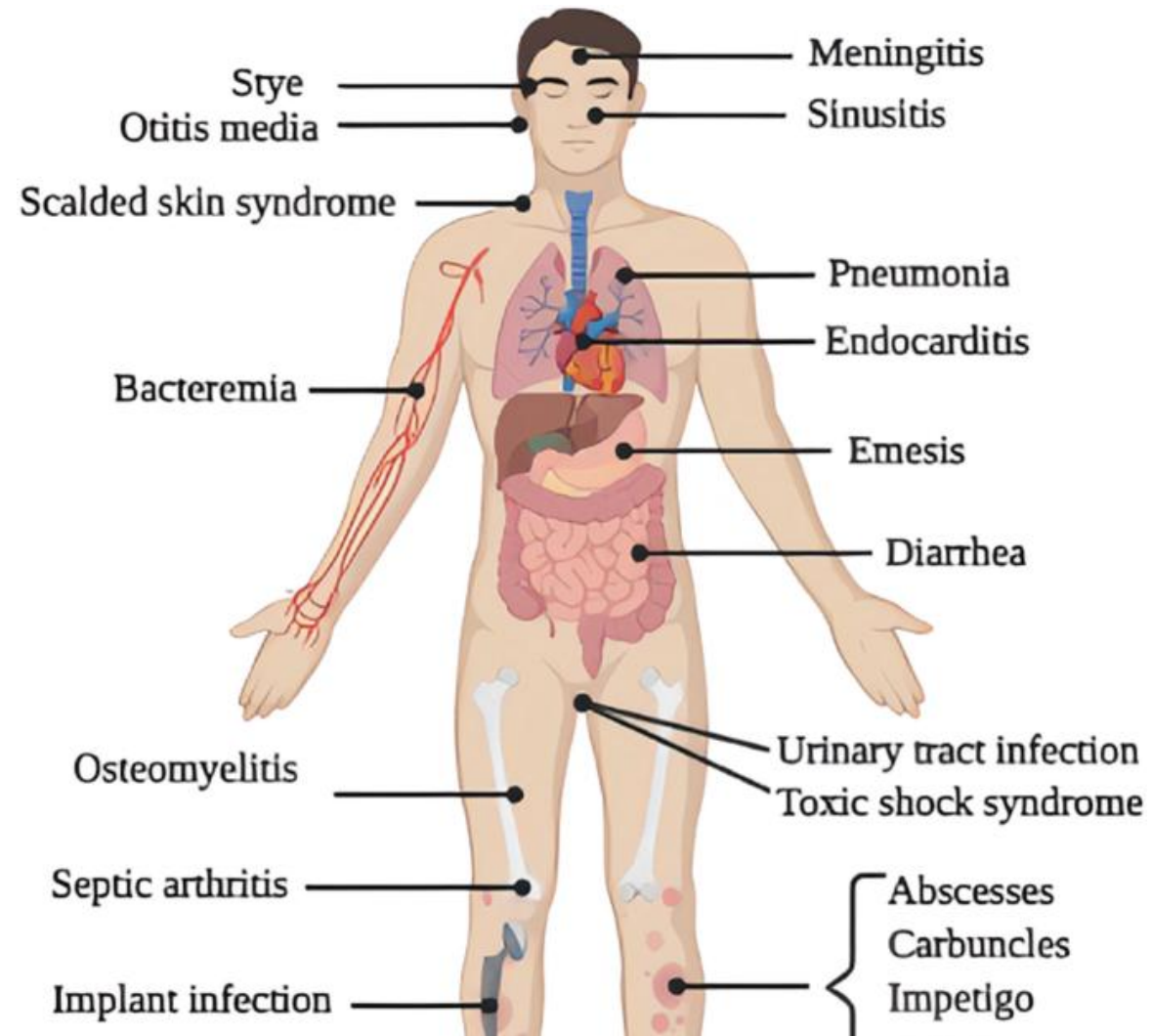
- Virulence factors
- Cell wall - teichoic acid, peptidoglycan, protein A
- Enzymes - catalase, hyaluronidase, coagulase, lipase, protease, beta-lactamase
- Toxins - enterotoxin, exfoliatin (epidermolytic toxin), toxic shock syndrome toxin 1



# Pathogenesis of staphylococcal infection

- Colonization
- Tissue invasion - penetration of bacteria through damaged skin and mucous membranes and/or direct inoculation of microorganisms into the blood
- Bacteremia occurs when bacteria reach the bloodstream via the lymphatic vessels
- Metastatic foci of infection are formed by the spread of infection





## Clinical manifestations



## Diseases caused by the bacteria *Staphylococcus aureus*

| <b>Organ system/type of disease</b>                 | <b>Clinical syndrome</b>   |
|---|--|
| infectious skin and soft tissues                    | folliculitis, carbuncle, abscess, impetigo, cellulitis, suppurative hidradenitis, surgical wound infections  |
| infections of the musculoskeletal system            | septic arthritis, osteomyelitis, pyomyositis, abscess m. psoas   |
| respiratory system infections                       | nosocomial pneumonia associated with mechanical ventilation, septic pulmonary emboli, staphylococcal pneumonia after viral infection, pleural empyema            |
| staphylococcal sepsis                               | sepsis, septic shock, septic foci (kidneys, joints, bones, lungs)  |
| infective endocarditis                              | endocarditis of natural valves, endocarditis of artificial valves, endocarditis associated with intravenous administration of narcotics, nosocomial endocarditis |
| infections associated with catheters and prostheses | sepsis, septic foci  |
| invasive infections caused by MRSA                  | necrotizing fascitis, necrotizing pneumonia,   |
| toxin-mediated diseases                             | staphylococcal toxic shock syndrome, scalded skin syndrome, staphylococcal food poisoning  |



## Malignant staphylococci of the face

- The most severe clinical manifestation is peracute septicemia with localization of the primary focus on the lip or nose (folliculitis or furuncle).
  - First, perifocal thrombophlebitis develops, which spreads into thrombophlebitis of the facial and angular veins, and then the ophthalmic veins.
  - Thus, the inflammation is transferred to the cavernous sinus, which can progress to meningitis and sepsis.
-

## **Clinical picture**

The inflammatory process on the face dominates in the form of dull red swelling that covers a large part of the face.

The entire eye socket is swollen and pushed forward due to retrobulbar inflammation.

If the infection progresses, meningeal signs, paralysis of the eyeball actuators and signs of generalized sepsis appear.

## **Therapy**

Antistaphylococcal antibiotics (cloxacillin, cefazolin, vancomycin) are given parenterally.



# Toxic shock syndrome (TSS)

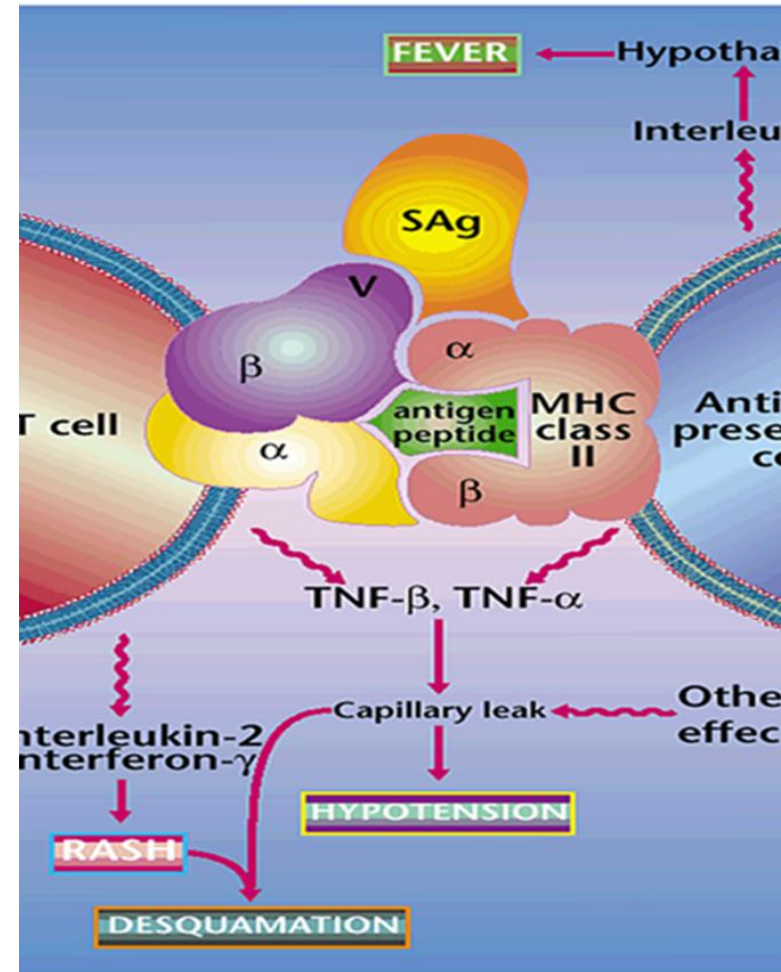
- Acute, life-threatening intoxication characterized by elevated temperature, hypotension, measles, multiorgan dysfunction and desquamation during the early convalescent period.
  - STS most often occurs during menstruation, after local application of contraceptives, as a complication of septic abortion or after surgical interventions, during superinfection of skin lesions (chemical and thermal burns, surgical wounds...).
-

## Pathogenesis of staphylococcal toxic shock syndrome

Exotoxins that are key in the development of toxic shock syndrome are TSST-1, staphylococcal enterotoxins, and especially enterotoxin of serotype B.

Bacteria release them in high concentrations, which induces the development of TSS (Toxic Shock Syndrome).

These toxins function as superantigens.



| Diagnostic criteria for staphylococcal toxic shock syndrome   |
|---|
| 1. Febrile: temperature $\geq 38.9$ C   |
| 2. Hypotension: systolic pressure $\leq 90$ mmHg, or orthostatic hypotension (orthostatic drop in diastolic pressure $\geq 15$ mmHg, orthostatic dizziness or orthostatic collapse).  |
| 3. Diffuse maculopapular measles  |
| 4. Involvement of multiple organ systems (3 or more)<br>gastrointestinal system: vomiting or diarrhea at the beginning of the disease<br>muscle: myalgias or elevated blood creatine kinase at least twice the upper limit<br>mucous membranes: hyperemia of the vagina, oropharynx or conjunctiva<br>kidneys: urea or creatinine 2 times higher than normal values, pyuria<br>liver: bilirubin and transaminase values are at least twice as high as normal<br>hematological disorders: thrombocytopenia (platelet count lower than 100,000)<br>central nervous system: disorientation or disturbance of consciousness without focal neurological signs when there is no fever and hypotension |
| 5. Desquamation: 1-2 weeks from the onset of the disease (typically on the palms and soles)   |
| 6. Negative blood cultures, throat swabs, cerebrospinal fluid cultures, negative antibodies to leptospira, rubella and rickettsia   |



## **Treatment of staphylococcal toxic shock syndrome**

- Antibiotics - semi-synthetic penicillins (nafcillin, oxacillin), first-generation cephalosporins, clindamycin as monotherapy or in combination with beta-lactam antibiotics or vancomycin.
- Intensive fluid replacement and application of vasopressors.
- Drainage of the site of infection (surgical wounds, foreign bodies must be removed).



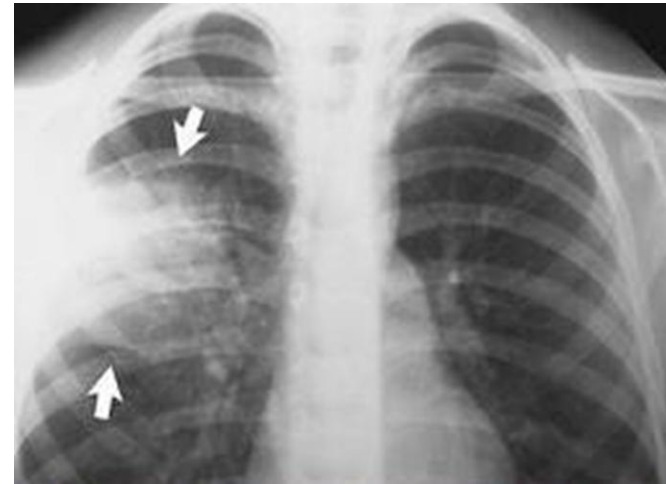
## Respiratory tract infections

Staphylococcal pneumonia (by aspiration of flora from the upper respiratory tract and hematogenous spread).

Clinical picture:

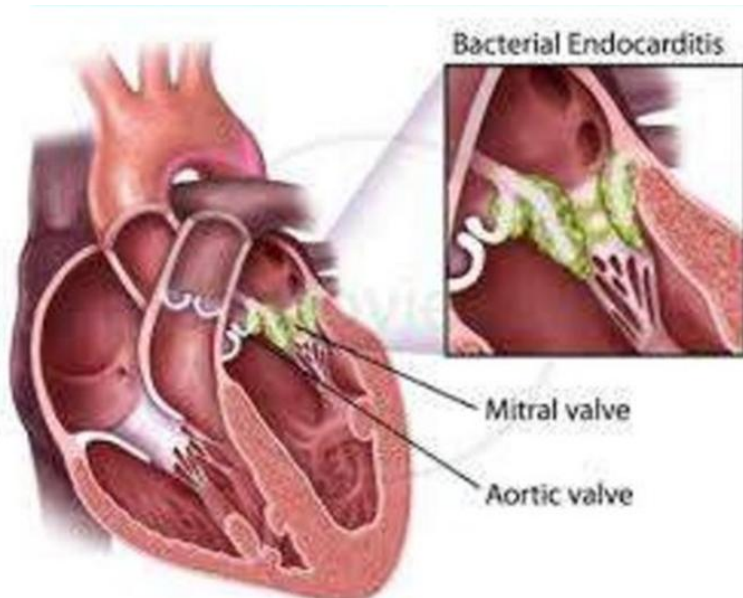
- ✓elevated body temperature,
- ✓cough,
- ✓dyspnea,
- ✓cyanosis,
- ✓pleural pain.

They tend to create pleural abscesses and empyemas.



# Intravascular infections - sepsis and endocarditis

In recent years, the number of hospital sepsis has been increasing due to the increase in treatment in intensive care units and surgical procedures (prostheses, implants).



- ✓ Bacterial endocarditis
- ✓ Septic phlebitis
- ✓ Bacteremia, sepsis (complications are brain abscess, meningitis, septic arthritis, osteomyelitis)

# Therapy of staphylococcal infections

- 5-10% of staphylococcal isolates are susceptible to penicillin
- Resistance is the result of production of beta lactamases (encoded by plasmid genes).
- Beta-lactamase-resistant semisynthetic penicillins (methicillin, oxacillin, cloxacillin, dicloxacillin, nafcillin)
- First generation cephalosporins
- Vancomycin
- Teicoplanin
- Daptomycin

# New antistaphylococcal drugs

**Oxazoline (Linezolid)** has good bioavailability, few side effects, but has a bacteriostatic effect, it is used to treat complicated skin and soft tissue infections, pneumonia.

**Daptomycin** is a parenteral bactericidal drug approved for the treatment of complicated skin infections and sepsis (including right atrial endocarditis), it is not used for the treatment of pneumonia because it is degraded by pulmonary surfactant.

**Ceftaroline** is a fifth-generation cephalosporin with a bactericidal effect on MRSA (including strains with reduced sensitivity to vancomycin and daptomycin). They are used in the treatment of hospital-acquired pneumonia, skin and soft tissue infections. The **streptogramin** antibiotic is bactericidal against all staphylococci, including those that are intermediately resistant to vancomycin (VISA from Vancomycin intermediate S. aureus).

**Telavancin**

**Dalbavancin**

**Tigecycline** (glycylcycline antibiotic) is used in the treatment of skin, soft tissue and intra-abdominal infections.

