Infections of the central nervous system

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Clinical spectrum

1. Meningitis
   - Viral
   - Bacterial
   - Of other origin
2. Encephalitis
3. Inflammatory diseases of the peripherial nerves

Meningitis

- Meningitis is a disease caused by the inflammation of the protective membranes covering the brain and spinal cord known as the meninges.
- The inflammation is usually caused by an infection of the fluid surrounding the brain and spinal cord.
- Meningitis is also referred to as spinal meningitis.
- Meningitis may develop in response to a number of causes, usually bacteria or viruses, but meningitis can also be caused by physical injury, cancer or certain drugs.

Pathogens producing meningitis

- Bacteria

  Haemophylus influenzae,, Streptococcus pneumoniae, Listeria monocytogenes,

  Streptococcus.agalactiae, Propionebacterium acne., Staphylococcus.aureus, Staphylococcus epidermidis Enterococcus fecalis, E.coli, Klebsiella pneumoniae, Pseudomonas aeruginosa,Salmonella sp., Nocardia sp.

  Mycobacterium tuberculosa

- Spirochets(leptospira,borrelia,treponema)
- Rickettsiae
- Protozoons and helminths
- Viruses
- Fungi
- Non-infectious agents

Meningitis

- Meningitis infection is characterized by a sudden onset of fever, headache, and stiff neck. It is often accompanied by other symptoms, such as
  - Nausea
  - Vomiting
  - Photophobia (sensitivity to light)
  - Altered mental status
  - Nuchal rigidity
  - Pozitive „meningeal" signs (Kernig, Brudzinski signs)

Viral meningitis

- Viral meningitis is an infection of the meninges (the covering of the brain and spinal cord) that is caused by a virus.
- Enteroviruses, the most common cause of viral meningitis, appear most often during the summer and fall in temperate climates.

Viral meningitis /meningitis serosa/

- Major characteristics:
  - The symptoms are generally mild, the patient is not unconscious
  - No leukocytosis in the blood (in case of viral origin)
  - The pleocytosis in the liquor is not high (few hundred leukocytes, mostly lymphocytes)
  - Meningitis serosa can be present in many viral diseases (parotitis, measles, etc.) and in certain bacterial infections: Lyme disease, leptospirosis, syphilis also

Viral meningitis

- The diagnosis is based on the clinical signs and symptoms
- The etiology of the viral meningitis many times remain unknown.
- Treatment is symptomatic, supportive

Differences in the liquor findings between viral and bacterial meningitis

Liquor findings	Bacterial meningitis	Viral meningitis
No. of leukocytes (µl)	1000-10000 Range: <100 - >10000	< 300 Range: <100 - > 1000
Rate of neutrophils	> 80%	< 20%
Protein levele	Elevated	Normal
Glucose level in liquor	Strongly reduced	Normal

Bacterial meningitis

- Bacterial meningitis is usually more severe than viral meningitis.
- Bacterial meningitis can have serious after-effects, such as brain damage, hearing loss, limb amputation, or learning disabilities.
- One of the leading causes of bacterial meningitis in children and young adults is the bacterium *Neisseria meningitidis*.
- Meningitis caused by this bacterium is known as meningococcal disease.

Bacterial meningitis (causative agents)

Age Group	Causes
Newborn	Group B Streptococci, *Escherichia coli, Listeria monocytogenes*
Infants	*Neisseria meningitidis, Haemophilus influenzae, Streptococcus pneumoniae*
Children	*N. meningitidis, S. pneumoniae*
Adult	*S. pneumoniae, N. meningitidis*, Mycobacteria

Bacterial meningitis (spreading)

- Bacterial meningitis is contagious.
- The bacteria are spread through the exchange of respiratory and throat secretions (i.e., coughing, kissing).
- Fortunately, none of the bacteria that cause meningitis are as contagious as things like the common cold or the flu.
- Also, the bacteria are not spread by casual contact or by simply breathing the air where a person with meningitis has been.

Bacterial meningitis (spreading)

- Sometimes the bacteria that cause meningitis have spread to other people who have had close or prolonged contact with a patient with meningitis caused by *N. meningitidis* (also called meningococcal meningitis) or *H. influenzae* serotype b (also called Hib meningitis).
- People in the same household or daycare center or anyone with direct contact with a patient's oral secretions (such as a boyfriend or girlfriend) would be considered at increased risk of getting the infection.
- People who qualify as close contacts of a person with meningitis caused by *N. meningitidis* should receive antibiotics to prevent them from getting the disease.

Bacterial meningitis (epidemiology)

- The estimated incidence of bacterial meningitis per year is 0·6–4 per 100 000 adults in developed countries, and might be up to ten times higher in other parts of the world.
- Meningitis caused by *Haemophilus influenzae* type b has nearly been eliminated in many developed countries since routine childhood vaccination was initiated
- The introduction of conjugate vaccines against seven serotypes of *Streptococcus pneumoniae has* reduced the burden of childhood pneumococcal meningitis substantially.
- With community-acquired bacterial meningitis, the most common aetiologic agents now are *S. pneumoniae and N. meningitidis, which cause 80–85% of all cases*

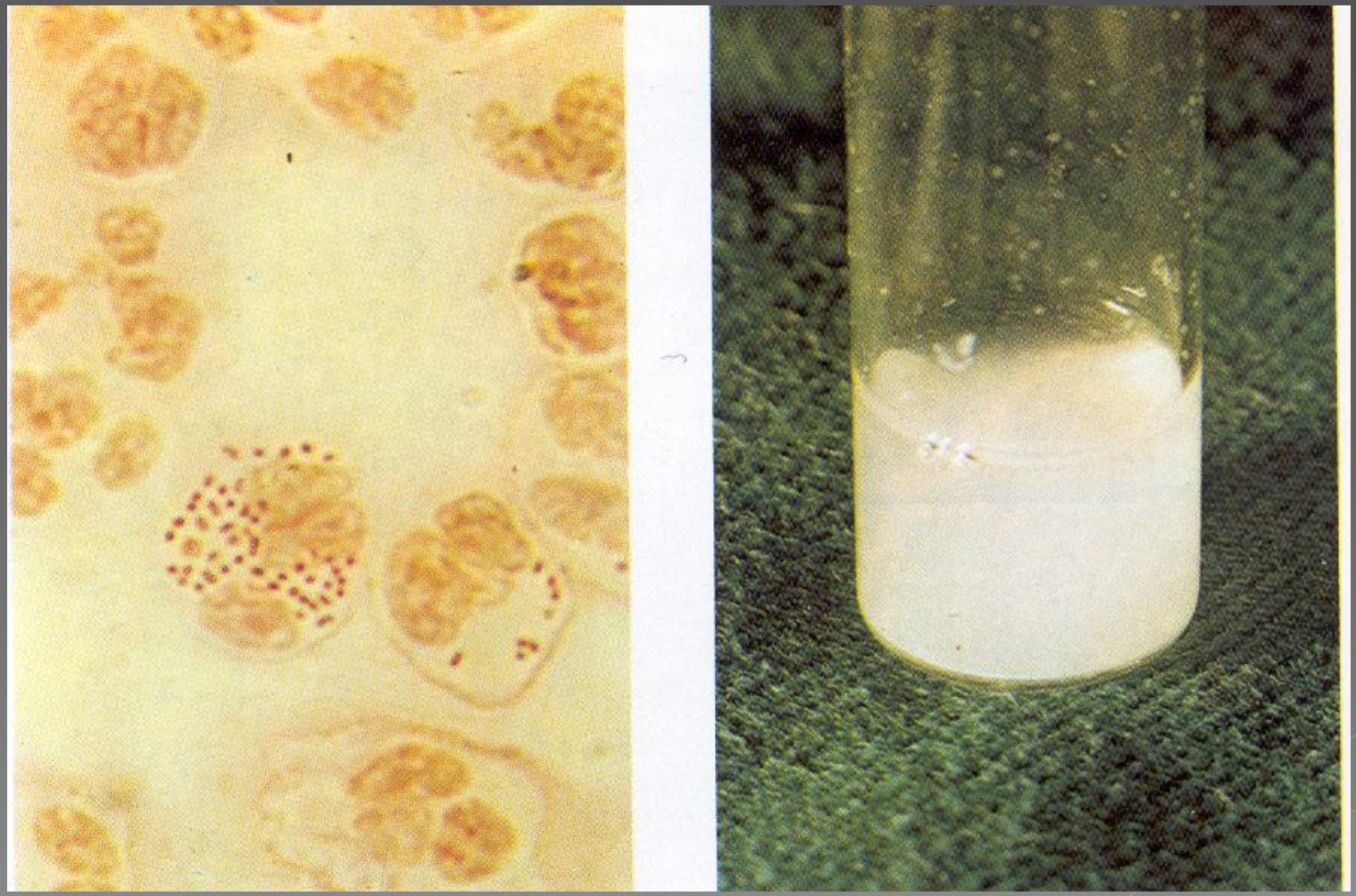
Bacterial meningitis (signs, symptoms)

- The symptoms of bacterial meningitis can appear quickly or over several days.
- Typically they develop within 3-7 days after exposure.
- Infants younger than one month old are at a higher risk for severe infection.
- In newborns and infants, the classic symptoms of fever, headache, and neck stiffness may be absent or difficult to notice.
- The infant may appear to be slow or inactive, irritable, vomiting or feeding poorly.

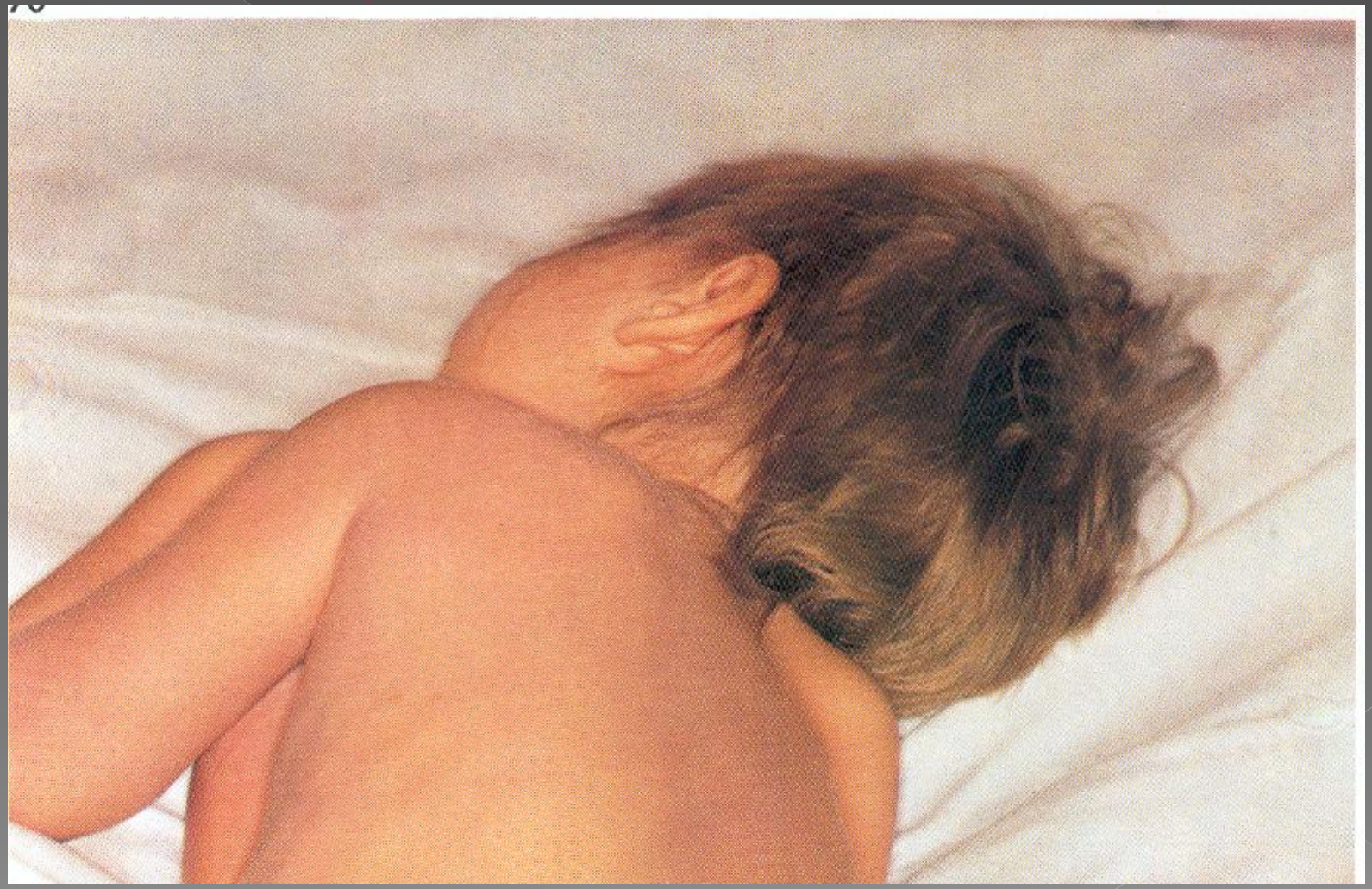
Bacterial meningitis (signs, symptoms)

- Although the traditionally described purpuric rash of meningococcal disease would influence a clinician's suspicion for meningitis caused by this pathogen, the presence, particularly in children is @ 10-20%.
- The presence or absence of meningeal signs such as Kernig's sign, Brudzinski's sign, and nuchal rigidity are physical examination findings often documented when evaluating a patient for possible meningitis.

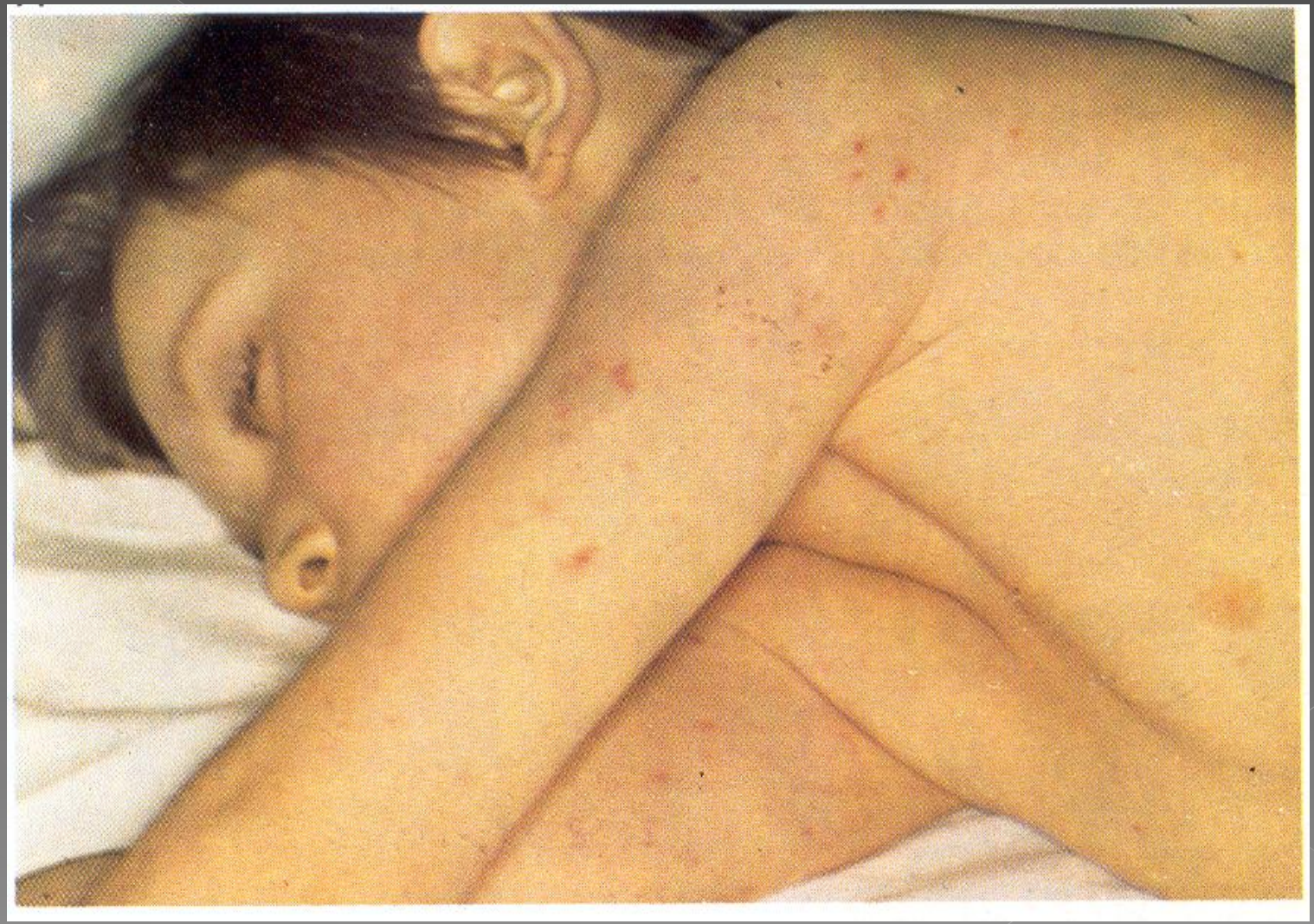
Intracellular diplococci (*N. meningitidis*) in the granulocytes from the liquor



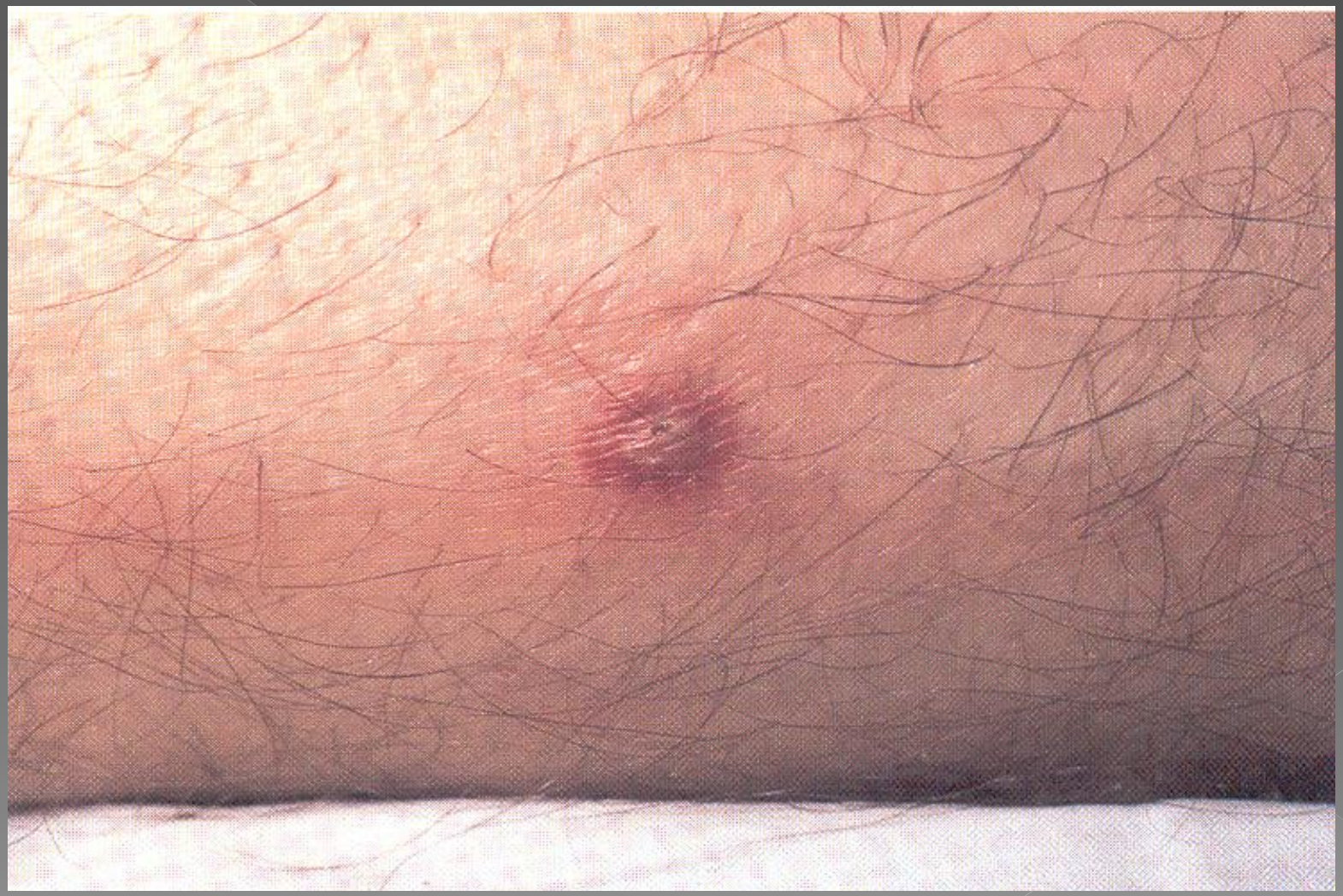
„Haund”-dog position in meningitis



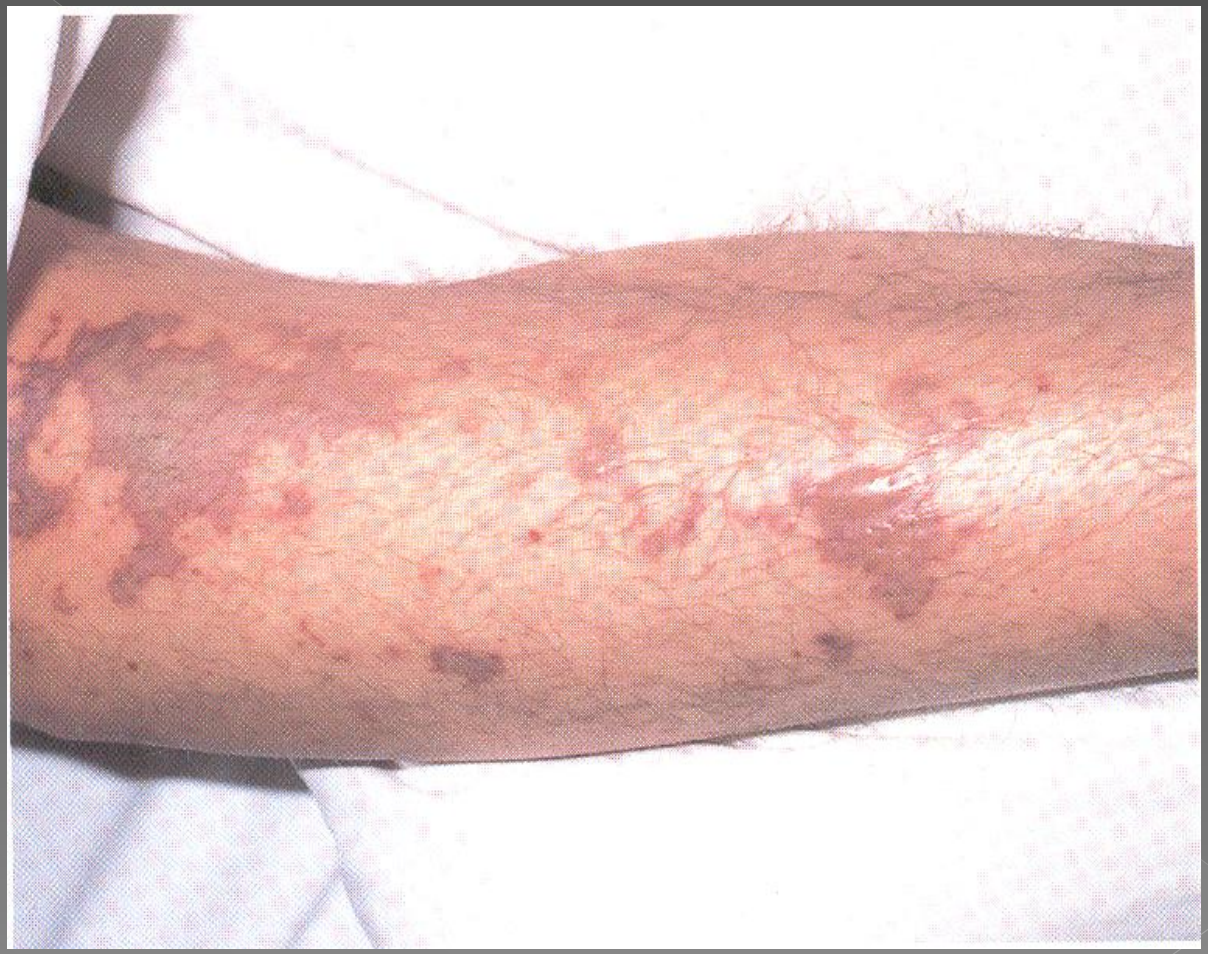
„Haund”-dog position with petehial rash



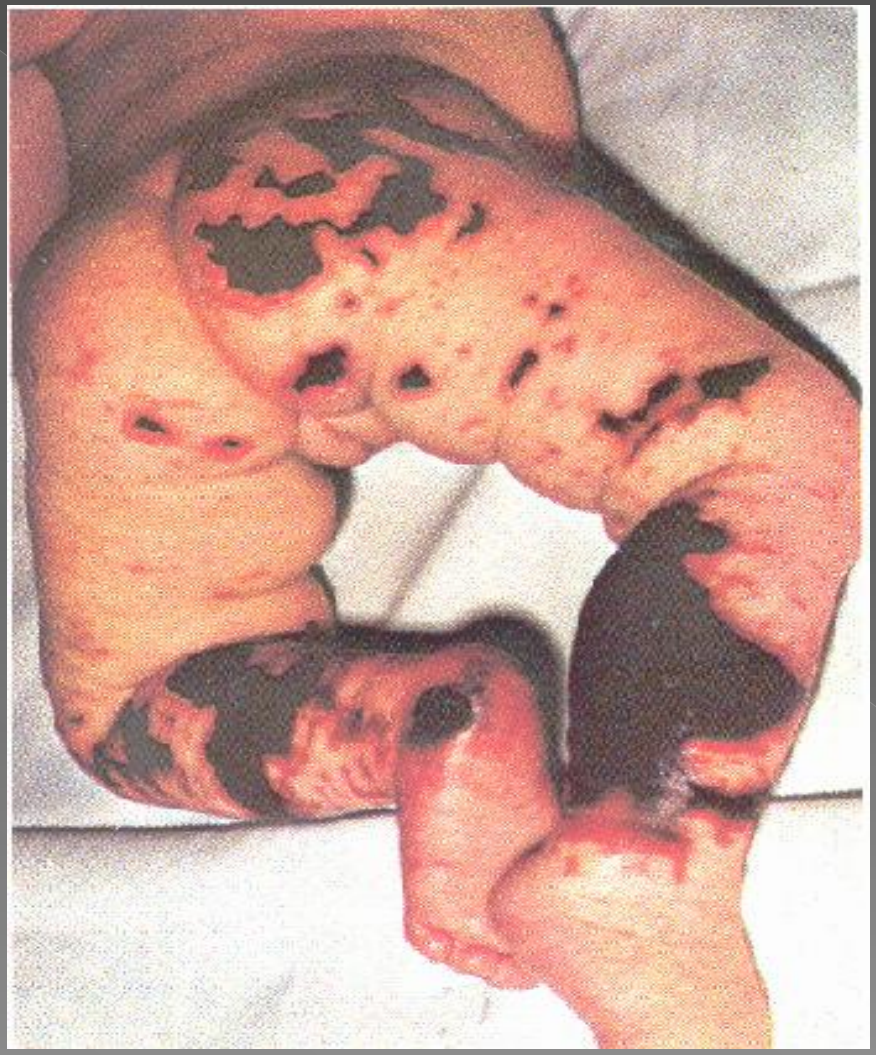
N. meningitidis bacteraemia with vesiculopapular skin lesions



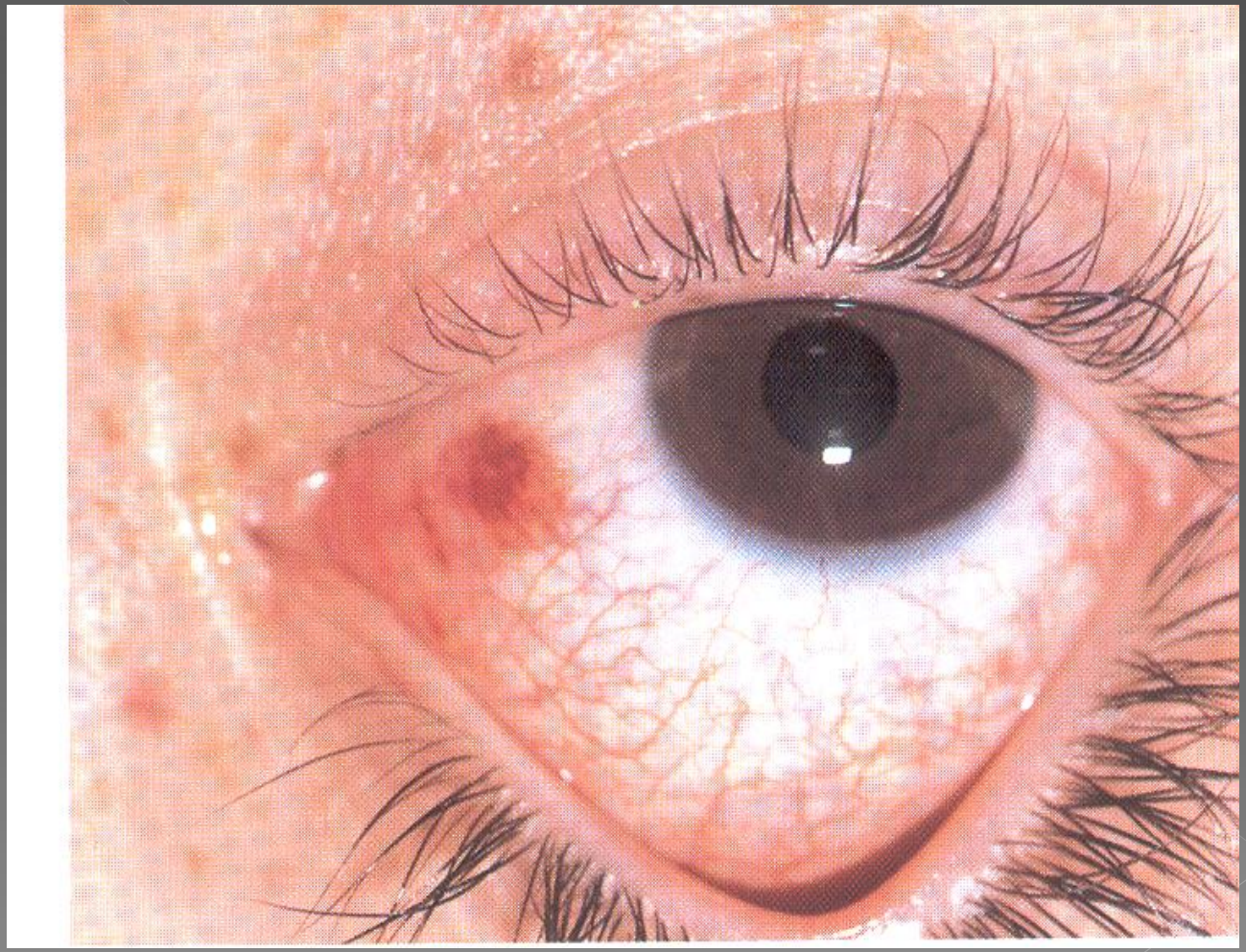
Skin haemorrhagies



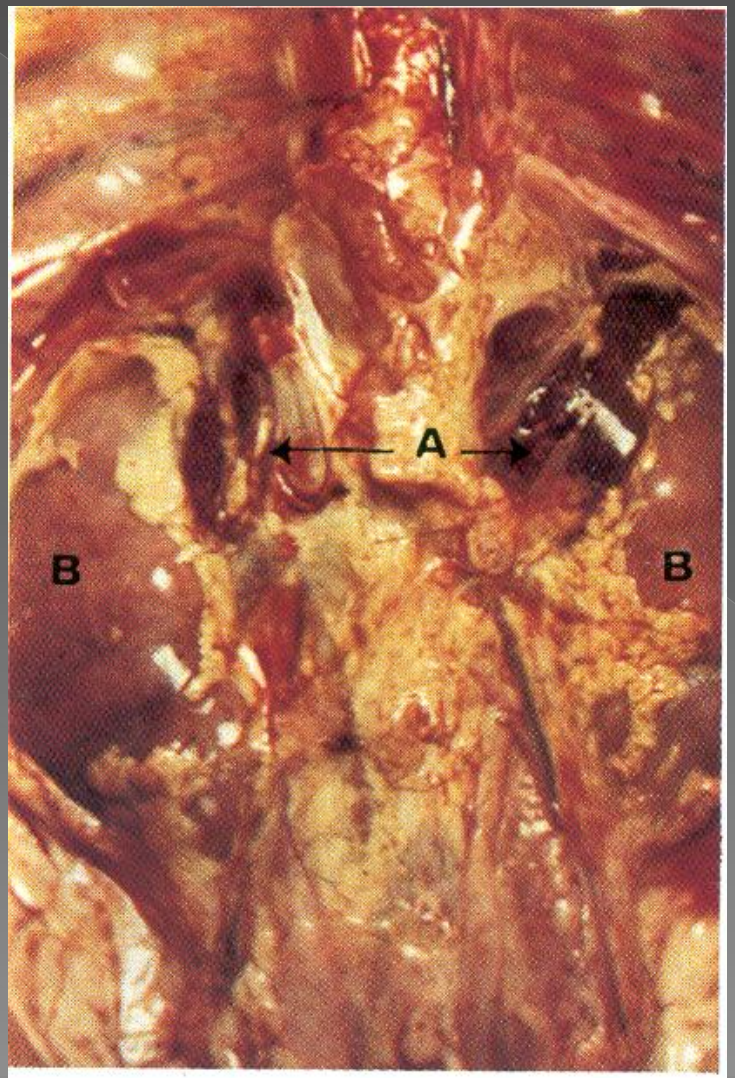
Extensive skin haemorrhagies

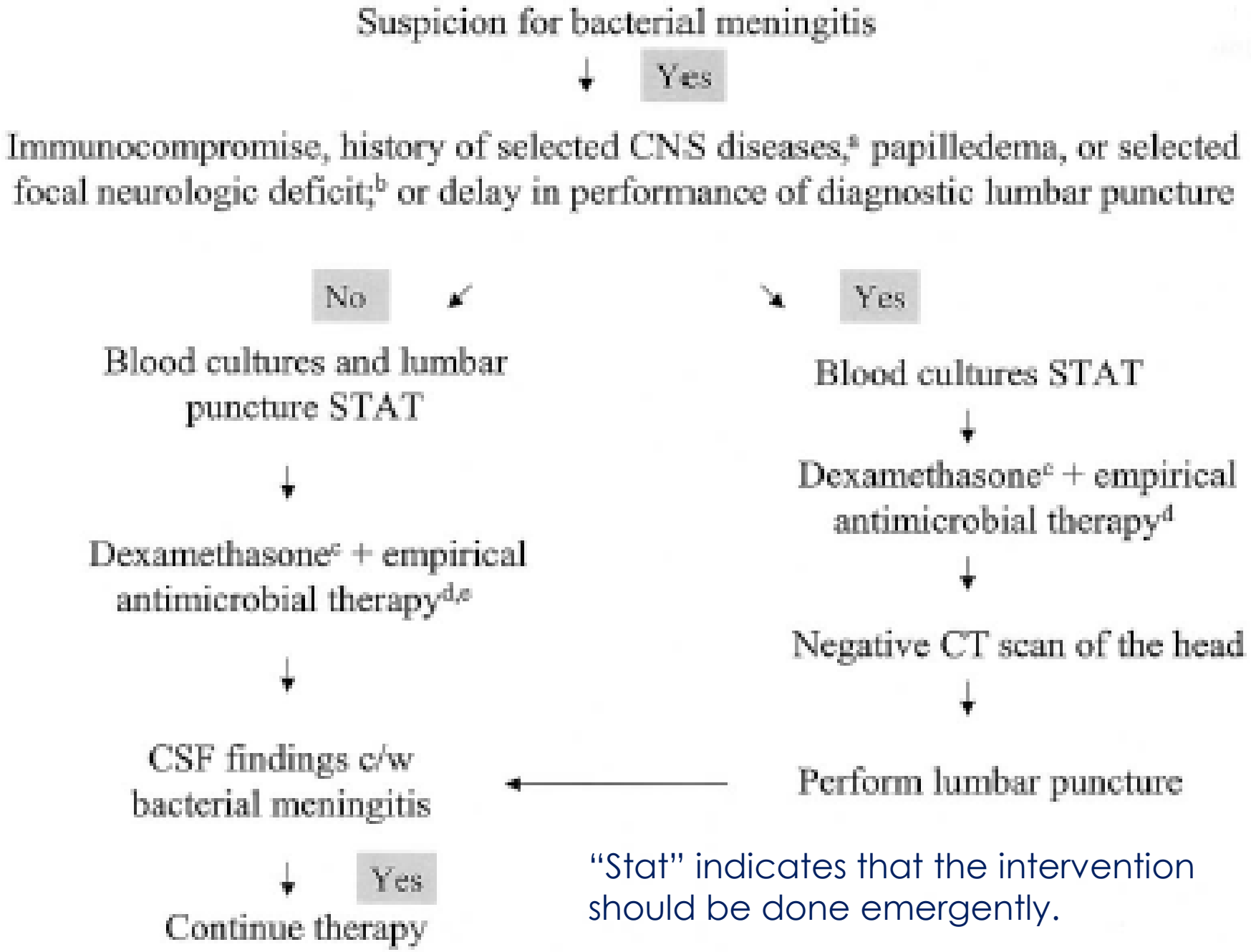


Petechia on the conjunctiva



Waterhouse-Friderichsen syndroma





"Stat" indicates that the intervention should be done emergently.

Antibiotic treatment in the case of identified pathogens (0,015 mg/kg/ dexamethasone should be added to the antibiotic treatment for four days)

Pathogen	First selection of antibiotics	Second choice
Streptococcus pneumoniae	Vancomycin + 3. generációs cephalosporin (ceftriaxon, **or** cefotaxim)	Meropenem, **or** fluoroquinolon (moxifloxacin, gatifloxacin)
Neisseria meningitidis	3. generációs cephalosporin	Penicillin G, ampicillin, fluoroquinolon (chloramphenicol, aztreonam)
Listeria monocytogenes	Ampicillin, **or** penicillin G	Trimethoprim-sulfamethoxazol, meropenem
Streptococus agalactiae	Ampicillin, **or** penicillin G	3. gen. cephalosporin
Haemophilus influenzae	3. generációs cephalosporin	Cefepim, meropenem, fluoroquinolon, chloramphenicol
Escherichia coli	3. generációs cephalosporin	Cefepim, meropenem, fluoroquinolon,

Empirical treatment

TABLE 71–13 Empirical Therapy for Purulent Meningitis*

Predisposing Factor	Antimicrobial Therapy
Age	
0–4 wk	Ampicillin plus cefotaxime; or ampicillin plus an aminoglycoside
4–12 wk	Ampicillin plus a third-generation cephalosporin†
3 mo to 18 yr	Third-generation cephalosporin†; or ampicillin plus chloramphenicol
18–50 yr	Third-generation cephalosporin†‡
>50 yr	Ampicillin plus a third-generation cephalosporin†
Immunocompromised state	Vancomycin plus ampicillin plus ceftazidime
Basilar skull fracture	Third-generation cephalosporin†
Head trauma; postneurosurgery	Vancomycin plus ceftazidime
Cerebrospinal fluid shunt	Vancomycin plus ceftazidime

*Vancomycin should be added to empirical therapeutic regimens when highly penicillin- or cephalosporin-resistant strains of *Streptococcus pneumoniae* are suspected; see the text for details.
†Cefotaxime or ceftriaxone.
‡Add ampicillin if meningitis caused by *Listeria monocytogenes* is suspected.

TABLE 3. Common Bacterial Pathogens Based on Predisposing Factor in Patients with Meningitis

Predisposing Factor	*Common Bacterial Pathogens*
Age	
0–4 weeks	*Streptococcus agalactiae, Escherichia coli, Listeria monocytogenes, Klebsiella pneumoniae, Enterococcus* spp., *Salmonella* spp.
4–12 weeks	*Streptococcus agalactiae, Escherichia coli, Listeria monocytogenes, Haemophilus influenzae, Streptococcus pneumoniae, Neisseria meningitidis*
3 months to 18 years	*Haemophilus influenzae, Neisseria meningitidis, Streptococcus pneumoniae*
18–50 years	*Streptococcus pneumoniae, Neisseria meningitidis*
>50 years	*Streptococcus pneumoniae, Neisseria meningitidis, Listeria monocytogenes,* aerobic gram-negative bacilli
Immunocompromised state	*Streptococcus pneumoniae, Neisseria meningitidis, Listeria monocytogenes,* aerobic gram-negative bacilli (including *Pseudomonas aeruginosa*)
Basilar skull fracture	*Streptococcus pneumoniae, Haemophilus influenzae,* group A β-hemolytic streptococci
Head trauma; postneurosurgery	*Staphylococcus aureus, Staphylococcus epidermidis,* aerobic gram-negative bacilli (including *Pseudomonas aeruginosa*)
Cerebrospinal fluid shunt	*Staphylococcus epidermidis, Staphylococccus aureus,* aerobic gram-negative bacilli (including *Pseudomonas aeruginosa*), *Propionibacterium acnes*

Prevention

- Vaccine: against A, C, Y és a W-135 serotypes, but we do not have vaccine against serotype B
- Contact prophylaxis:

Age	Doses	Duration	Effectivity
Rifampin: Under 1 month Above 1 month	5 mg/kg, po., two times daily 10 mg/kg (maximum 600 mg), po., two times daily	2 days 2 days	90-95%
Ceftriaxon Under 15 years Above 15 years	125 mg, im. 250 mg im.	Single dose	90-95%
Ciprofloxacin From 18 years	500 mg tabl.	Single dose	90-95%

Tick-borne encephalitis

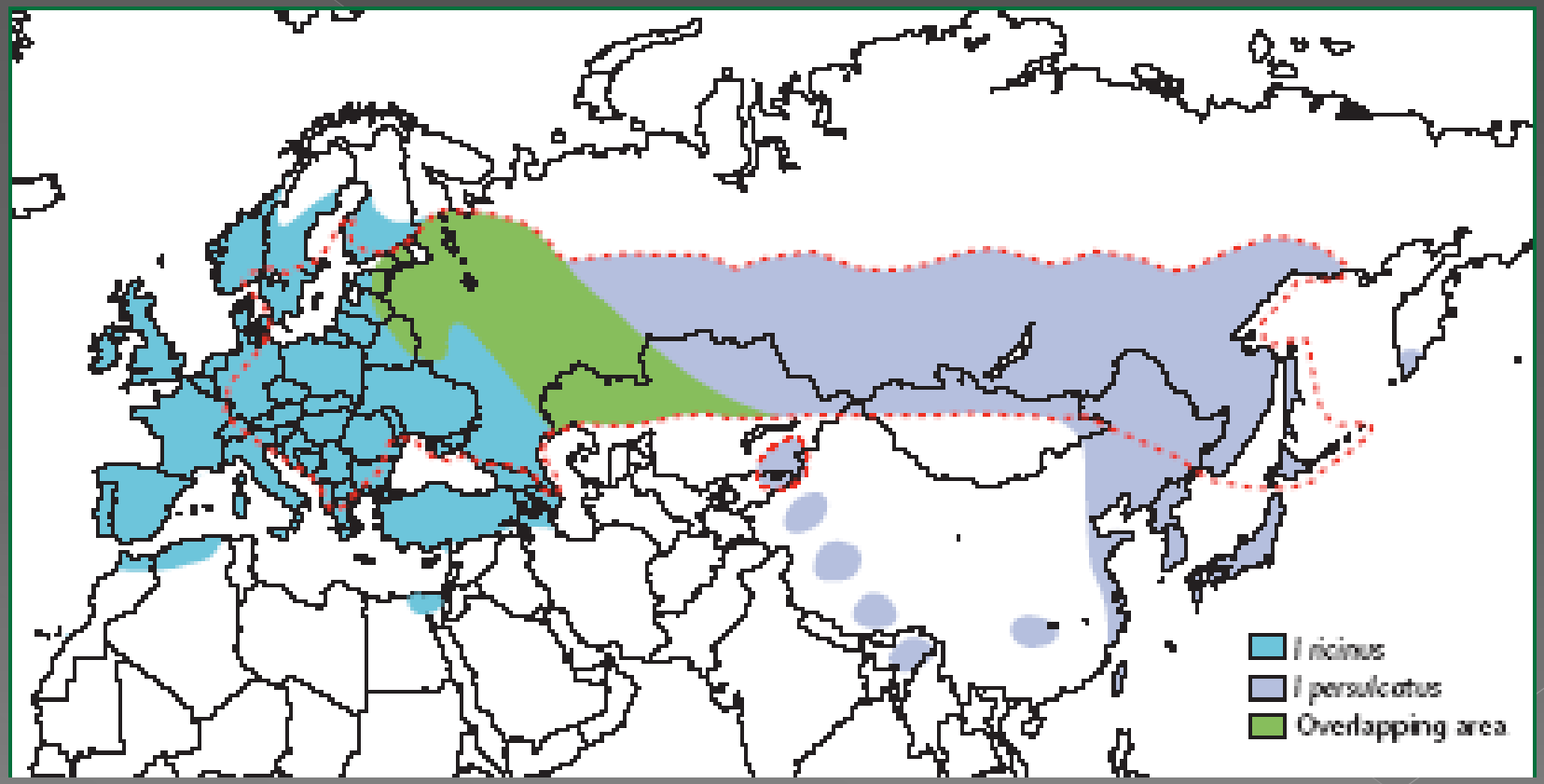
Discovery

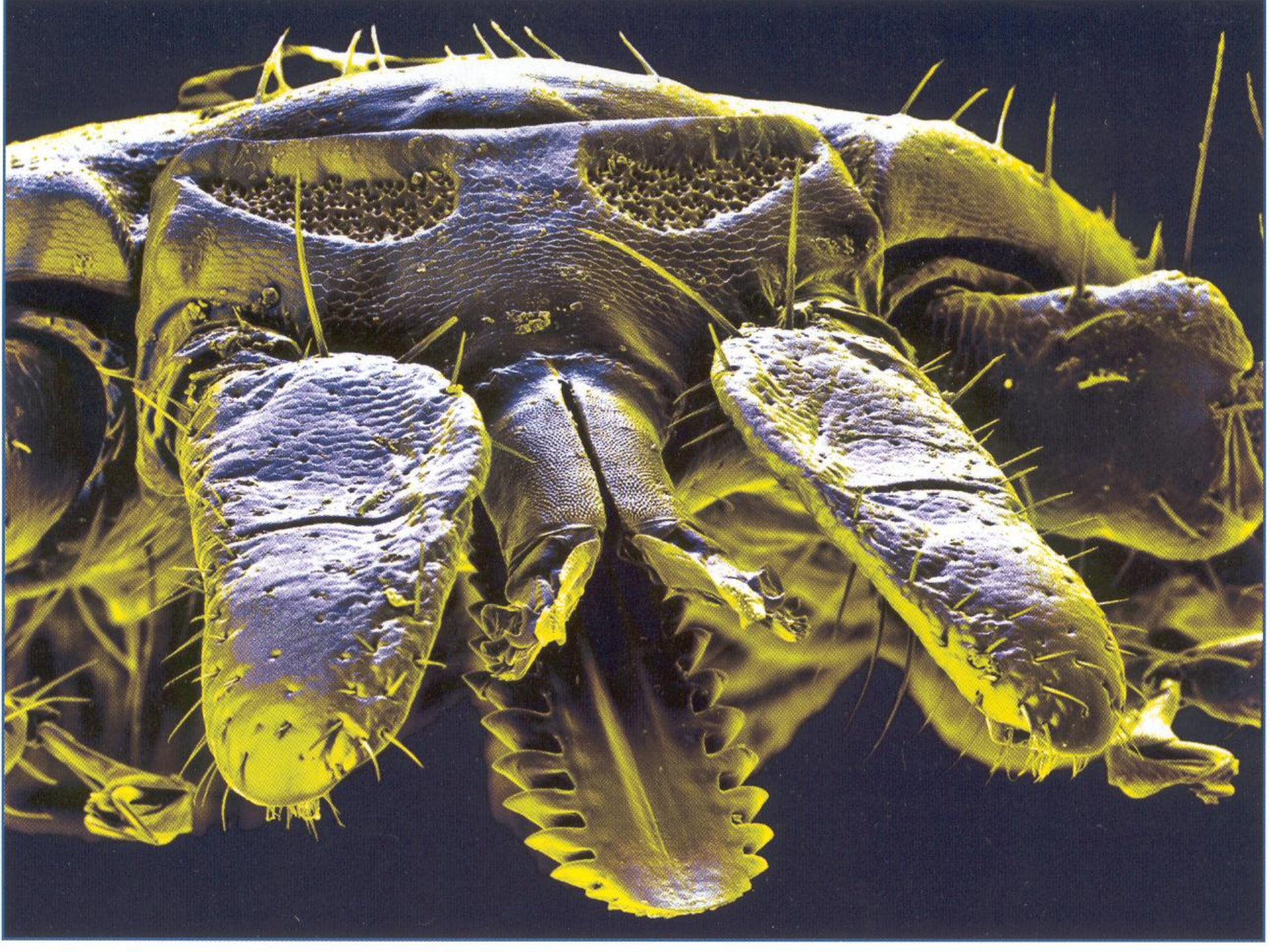
- The first description of a tick-borne encephalitis-like disease dates back to Scandinavian church records from the 18th century.
- The disease was described as a clinical entity in Austria in 1931 and its causative agent was isolated in the eastern region of Russia in 1937.
- More than 10 000 cases of the disease arise every year, and in terms of morbidity, this frequency is second only to Japanese encephalitis among neurotropic flaviviruses.

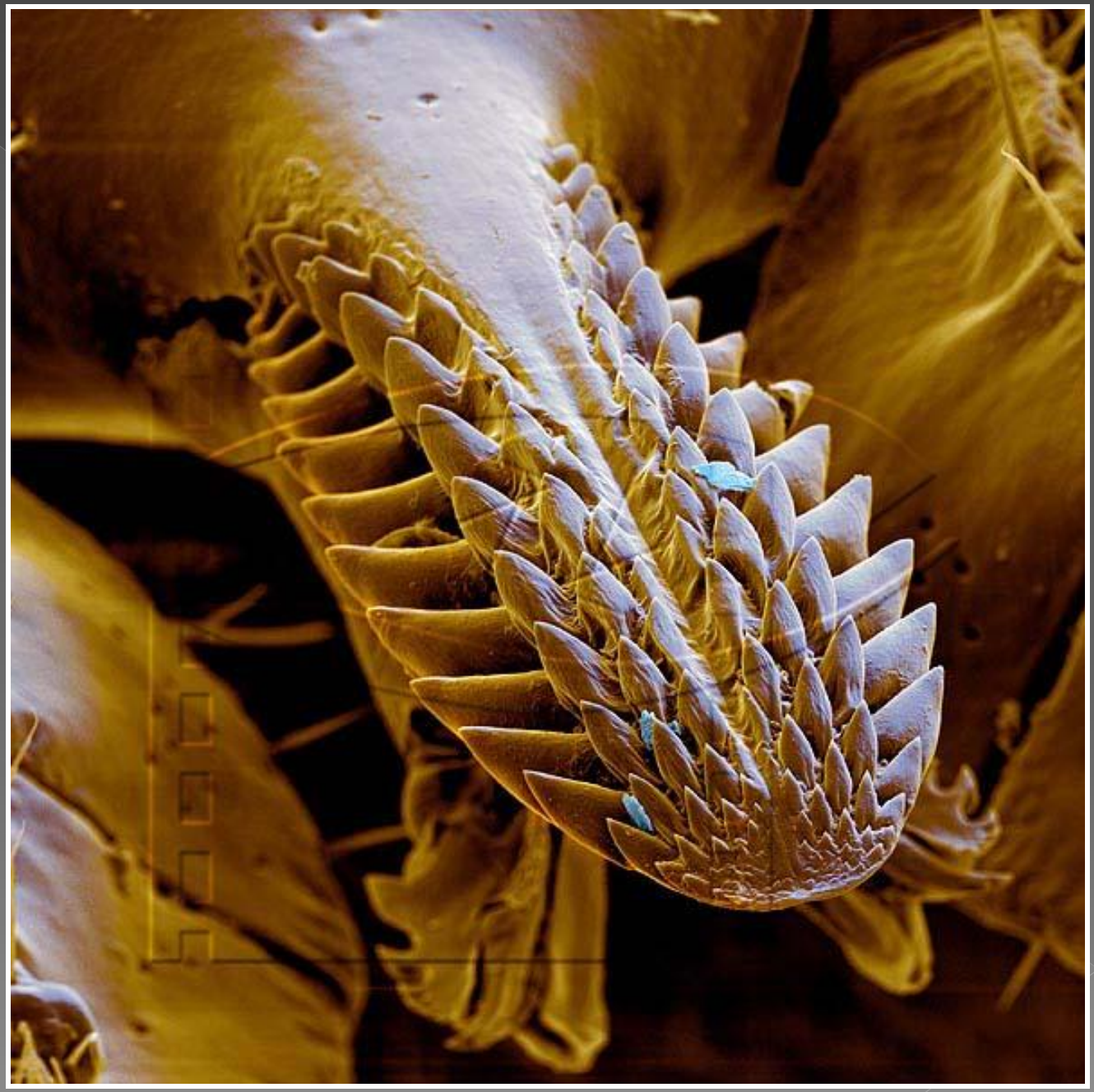
The virus

- Tick-borne encephalitis virus (TBEV) is a member of the genus flavivirus, family Flaviviridae.
- Flaviviruses are icosahedral enveloped 50 nm viruses with an RNA genome of about 11 kb.
- The C (capsid) protein, along with the viral RNA, form the spherical 30 nm capsid structure of the virus, which is covered by a lipid bilayer with two surface proteins, prM (precursor M) and E (envelope) that have double membrane anchors.

Distribution of the vectors







The TBE-Belt

Maps of Distribution of the TBE in Eurasia

subtype 1: CEE

Central European Encephalitis

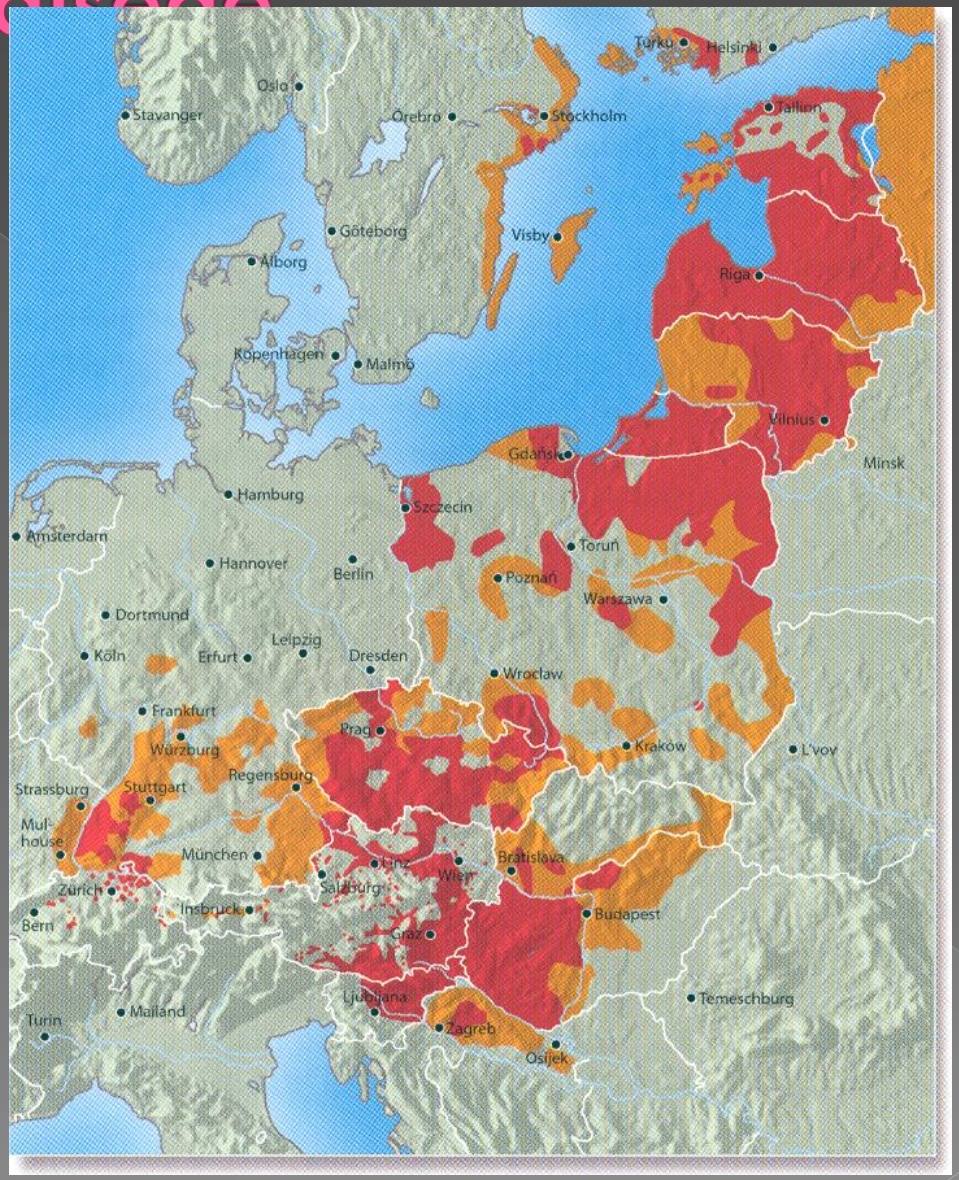
occurrence of all types

subtypes 2: RSSE

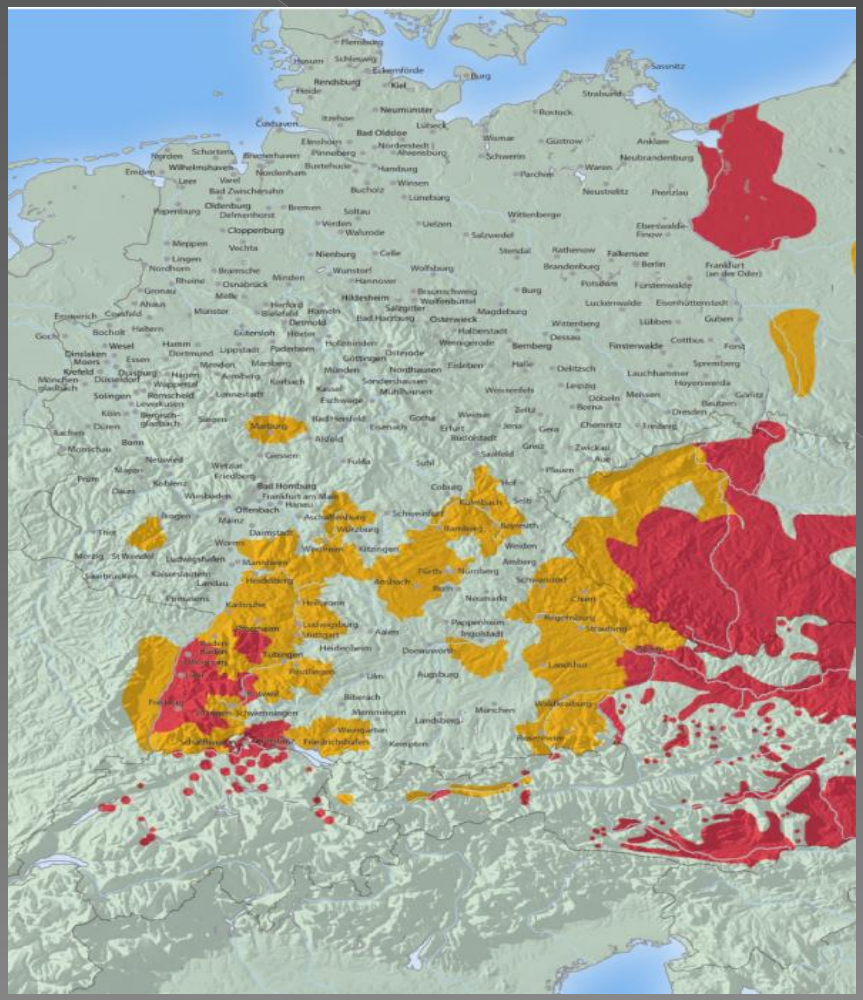
Russian-Spring-Summer Encephalitis

(eastern subtypes)

A kullancs encephalitis elterjedtsége



Endemic TBE Regions in Germany



high-risk regions

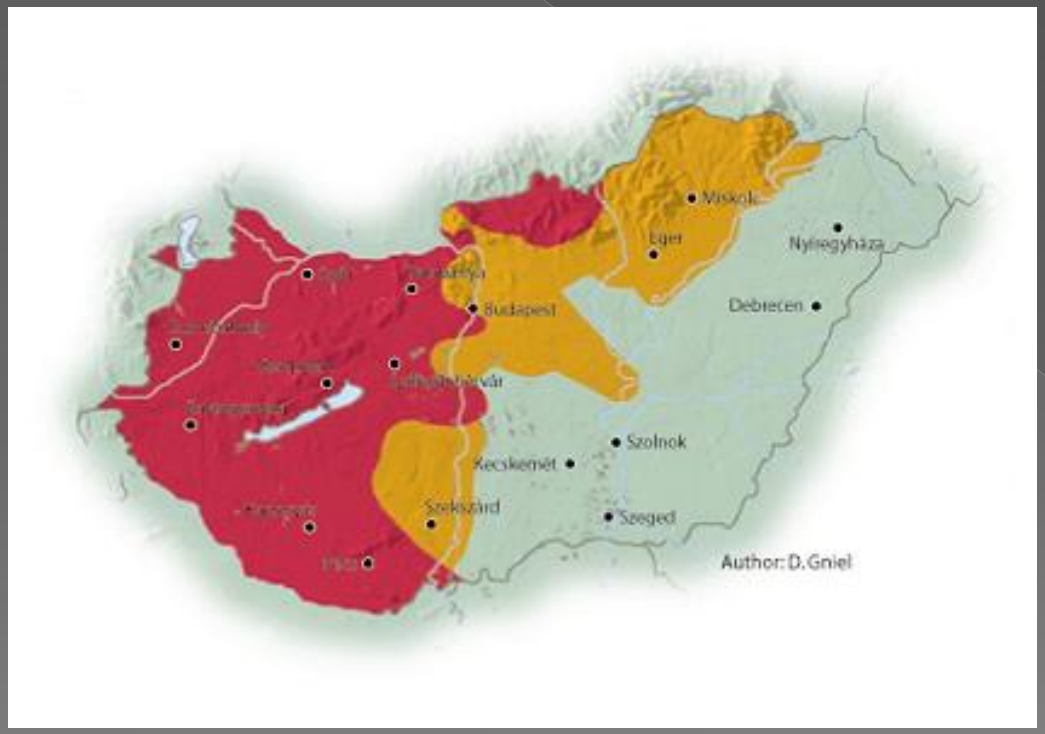
high risk of developing the disease

several or many cases of TBE in the last few years

low risk of developing the disease

few or no cases of TBE in the last few years

Endemic TBE Regions in Hungary



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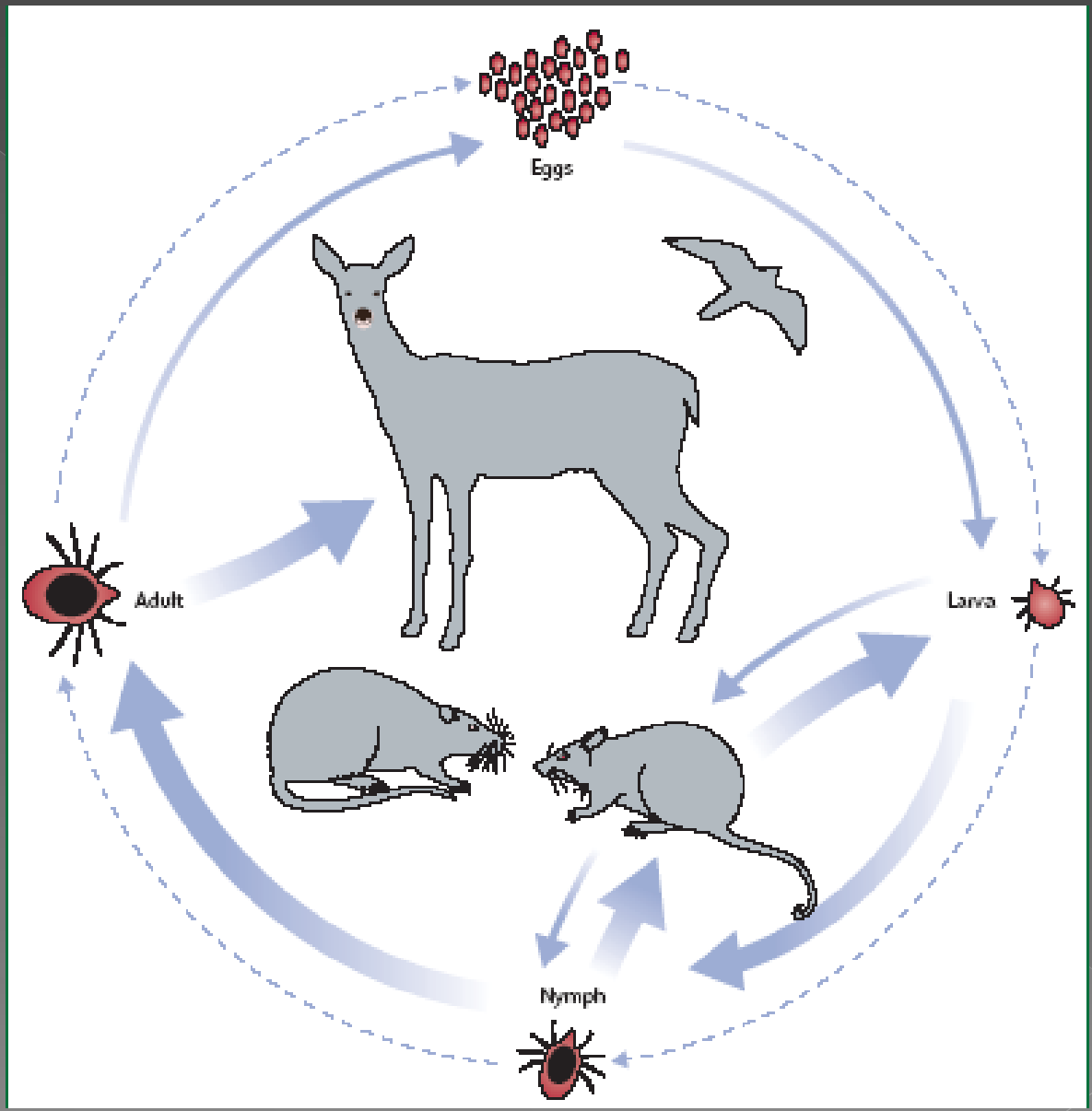
Eggs
Adult
Larva
Nymph

Clinical presentation and pathogenesis

- Tick-borne encephalitis follows an incubation period of a median of 8 days (range 4–28) after tick bite, which is unnoticed in about a third of patients.
- Typically, the disease is biphasic in 72–87% of patients.
- The median duration of the first stage of illness is 5 days (range 2–10) with a 7 day (range 1–21) symptom-free interval to the second phase.

Clinical presentation and pathogenesis

- In the first viraemic stage, the dominant symptoms are fever (99%), fatigue (63%), general malaise (62%), and headache and body pain (54%).
- Leucopenia and thrombocytopenia and slightly raised serum transaminases can be seen in this first stage, although leucocytosis is frequent in the second stage.
- Seroconversion without prominent morbidity is common.

Clinical presentation and pathogenesis

- In the second stage, the clinical spectrum ranges from mild meningitis to severe encephalitis with or without myelitis and spinal paralysis.
- Neurological symptoms at this stage do not, in principle, differ from other forms of acute viral meningoencephalitis .
- Seizures are infrequent but altered consciousness is seen in a third of patients.

Clinical presentation and pathogenesis

- Cerebrospinal fl uid (CSF) analyses reveal moderate pleocytosis, with two-thirds of patients having 100 leucocytes per µL or less.
- An initial predominance of polymorphonuclear cells is later changed to an almost 100% mononuclear cell dominance.
- Two-thirds have a moderate increased CSF albumin, peaking at a median day 9.
- Objective meningeal signs could be absent in about 10%, despite CSF pleocytosis.

Clinical presentation and pathogenesis

- As a result of a preference for the anterior horn of the cervical spinal cord, a flaccid poliomyelitis-like paralysis arises that, unlike poliomyelitis, usually aff ects the arms, shoulders, and levator muscles of the head.
- In about 5–10% of cases, monoparesis, paraparesis, and tetraparesis can develop, as well as paralysis of respiratory muscles, requiring ventilatory support

Clinical presentation and pathogenesis

- Cranial nerve involvement is mainly associated with ocular, facial, and pharyngeal motor function, but vestibular and hearing defects are also encountered.
- In severe cases, brainstem involvement can lead to substantial respiratory and circulatory failure.

Clinical presentation and pathogenesis

- Apart from myelitis, tick-borne encephalitis can develop into a myeloradiculitic form, typically presenting a few days after defervescence, and could be accompanied by severe pain in the back and limbs, weak muscle reflexes, and sensory disturbances.
- Paralyses could develop that, compared with myelitis, have a more favourable prognosis.

Treatment and prophylaxis

- No specific treatment for tick-borne encephalitis exists.
- In a large German study, 12% of patients needed intensive care and 5% assisted ventilation.
- The use of corticosteroids is not supported by any controlled study or uncontrolled
- studies.
- No established treatment exists for chronic progressive forms.

Treatment and prophylaxis

- Tick-borne encephalitis can be prevented by active immunisation.
- Apart from the Russian vaccines based on TBEV-FE, two vaccines based on almost identical TBEV-Eu strains (strain Neudoerfl , FSME-IMMUN by Baxter Vaccines, Vienna, Austria; strain K23, Encepur by Novartis, Basel, Switzerland) are licensed in Europe.
- In animals, cross-protection between major subtypes of TBEV are induced.