

Tick-borne zoonoses

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Ixodidae (hard-ticks)

- *Ixodes ricinus* (Euroasia)
- *Ixodes persulcatus* (Asia)
- *Ixodes pacificus* (West-cost of N. America)
- *Ixodes scapularis* (East-cost of N. America)

- transstadial transmission

Ticks

- Cover a wide geographic region (woodland and mixed forest)
- Can survive under various environmental conditions (requiring a relative humidity of at least 80% and are restricted to areas of moderate to high rainfall with good vegetation)

Life stages

- Egg – larva – nympha – adult
- Ixodidae – small ticks, females being larger than males
- Larvae have three pairs of leggs
- Nymphs and adults have four pairs of leggs
- The lifecycle is completed within three years
- An engorged female can produce up to 2000 eggs

Tick as a vector: viruses

- *Flaviviridae:*
 - **TBEV (CEEV, NEEV, FEV)**
Tick-borne encephalitis virus
- *Reoviridae: (Coltivirus: Eyach virus)*
Colorado tick fever virus
- *Bunyaviridae: (Nairovirus)*
Crimean- Congo hemorrhagic fever virus

Tick as a vector: bacteriae

- *Spirochetes: Borrelia burgdorferi sensu lato*
- *Bartonella:*
 - *B. hensellae*
- *Francisella:*
 - *F.tularensis*
- *Rickettsiae:*
 - *R. rickettsii*
 - *R. sibirica, australis, canada*
 - *R. conorii*
 - *R. slovaca*
 - *Coxiella burneti*
 - *Ehrlichia chaffeensis*
 - *Anaplasma phagocytophilum*

Tick as a vector: parasites

- *Babesia*:

- *B. microti*

- *B. divergens*

- *Filariae*:

- *Wuchereria bancrofti*

- *Brugia malayi*

- *Brugia timori*

Tick-borne encephalitis

- Tick-borne infection
- Biphasic course
- Severity according to the age
- Neurologic disease accompanied by pareses
→ permanent involvement
- Prevention: vaccination

Etiology

- Flavivirus
- TBEV:
- **3 antigenic variants:**
- Central-European subtype I (CEEV)
- Siberian (Near-east) subtype II (NEEV)
- Far-east subtype III (FEEV)

Flaviviridae

- **Arboviruses causing encephalitis:**
- **Mosquito-borne:**
- West-Nile fever
- St. Louis encephalitis
- Japanese encephalitis
- Murray Valley encephalitis
- **Tick-borne:**
- Louping ill
- Powassan encephalitis

Flaviviridae

- **Arboviridae causing hemorrhagic fever:**
- **Mosquito-borne:**
- Dengue hemorrhagic fever
- Yellow fever

- **Tick-borne:**
- Omsk hemorrhagic fever
- Kyasanur forest disease

TBE: the routes of transmission

- 1) Tick-borne (*Ixodes ricinus*)
 - Seasonal incidence (spring-summer)
- 2) Drinking of non-pasteurized milk containing the virus (family epidemics)
- 3) Breast-feeding (newborns of mothers with viremia – rare!)

Clinical course of TBE

- IP: 3 to 14 days
- I. phase: fever, myalgia, arthralgia
- ↓
- Asymptomatic interval (4-10 days)
- ↓
- II. phase: headache, fever, vomiting, meningeal signs, ataxia, disturbances of consciousness, focal neurologic signs

Clinical forms of TBE

- Inapparent
- Abortive
- Meningitis (in children, less in adults)
- Encephalitis (75% adults, 25% children)
- Encephalomyelitis (>60 y)
- Bulbar (rare)

Diagnosis and therapy

- Direct – virus isolation from the blood in the viremic phase
- Indirect – serology (IgM, IgG)
CSF antibodies (IgM)

Therapy: symptomatic

Prevention: vaccination

Vaccines

- FSME (Pfizer) = 2.4 μg TBEV
- Encepur (GSK Vaccines) = 1.5 μg TBEV
- 1. 0 d
- 2. after 1 to 3 months (protective titer)
- 3. after 6 to 12 months
- Booster every 3 to 5 years

Lyme borreliosis

- Lyme disease, tick-borne borreliosis
- Endemic in North America, Europe, Asia
- The most frequent tick-borne infection in Europe and USA
- Involvement of the skin, nervous and musculoskeletal system

Epidemiology

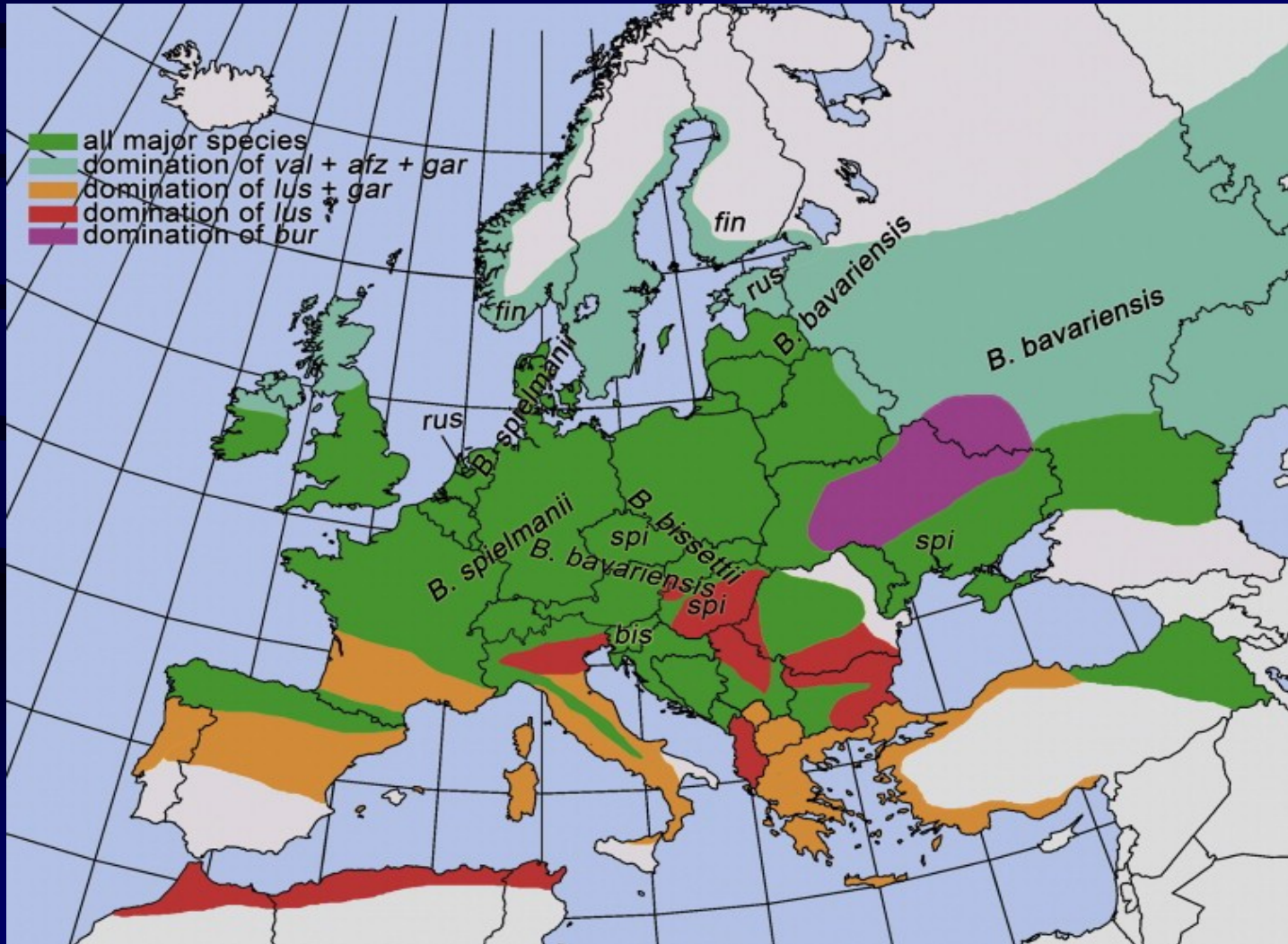
- Reservoirs: vertebrates (small mammals, rodents, birds)
- All stages of ticks play role in the transmission (larvae, nymphae, adults)
- Transstadial transmission in ticks
- Seasonal zoonosis (spring to autumn)

Patogenic borreliae in Europe

Borrelia burgdorferi sensu lato:

- *B. afzelii*
- *B. garinii*
- *B. burgdorferi sensu stricto*
- *B. bavariensis*
- *B. valaisiana*
- *B. lusitaniae*
- *B. spielmanii*

Distribution of borreliae



Clinical course in LB

- **80-95 % abortive (self-limited disease)**
- **5-20 % symptomatic**
- Cutaneous manifestation: 70-75 % (mostly EM)
- Nervous manifestations: 15-20 %
- Joint manifestations: 5 %
- Cardiac manifestations: 1 %
- Chronic course: 1-2 %

Clinical stages of LB

Early localized	Erythema migrans
Early disseminated	Erythema migrans multiple Borrelial lymphocytoma Nervous and joint manifestations
Late disseminated	Acrodermatitis chronica atrophicans Chronic nervous and joint manifestations

Erythema migrans

- IP = one to several weeks
- In Europe: *B.afzelii* (88,7 %), *B.garinii*, *B.burgdorferi s.s.*
- **Expanding red or bluish-red patch with central clearing, advancing edge intensely coloured, not markedly elevated, around the tick bite**
- Laboratory evidence: none
- Clinical findings are sufficient for the diagnosis of EM















Erythema migrans multiple

- **Multiple lesions of EM, not only at the site of the tick bite**
- Secondary lesions are similar to primary EM
- Non-specific symptoms: fatigue, fever, headache, arthralgia, myalgia
- Laboratory evidence: antiborrelial antibodies positive



Borrelial lymphocytoma

- IP: several weeks to months
- Causative agent: *B. afzelii*
- **Painless bluish-red nodule, usually on ear lobe, ear helix, nipple or scrotum**
- More frequent in children
- Laboratory evidence: 1) **essential**: significant change in levels of specific antibodies
2) **supporting**: histology, culture from skin biopsy











Acrodermatitis chronica atrophicans

- IP = several months to years
- **Long-lasting red or bluish-red lesions, usually on the extensor surfaces of extremities. Initial doughy swelling. Lesions become atrophic. Possible skin induration over bony prominences.**
- Laboratory evidence: high level of specific serum IgG antibodies





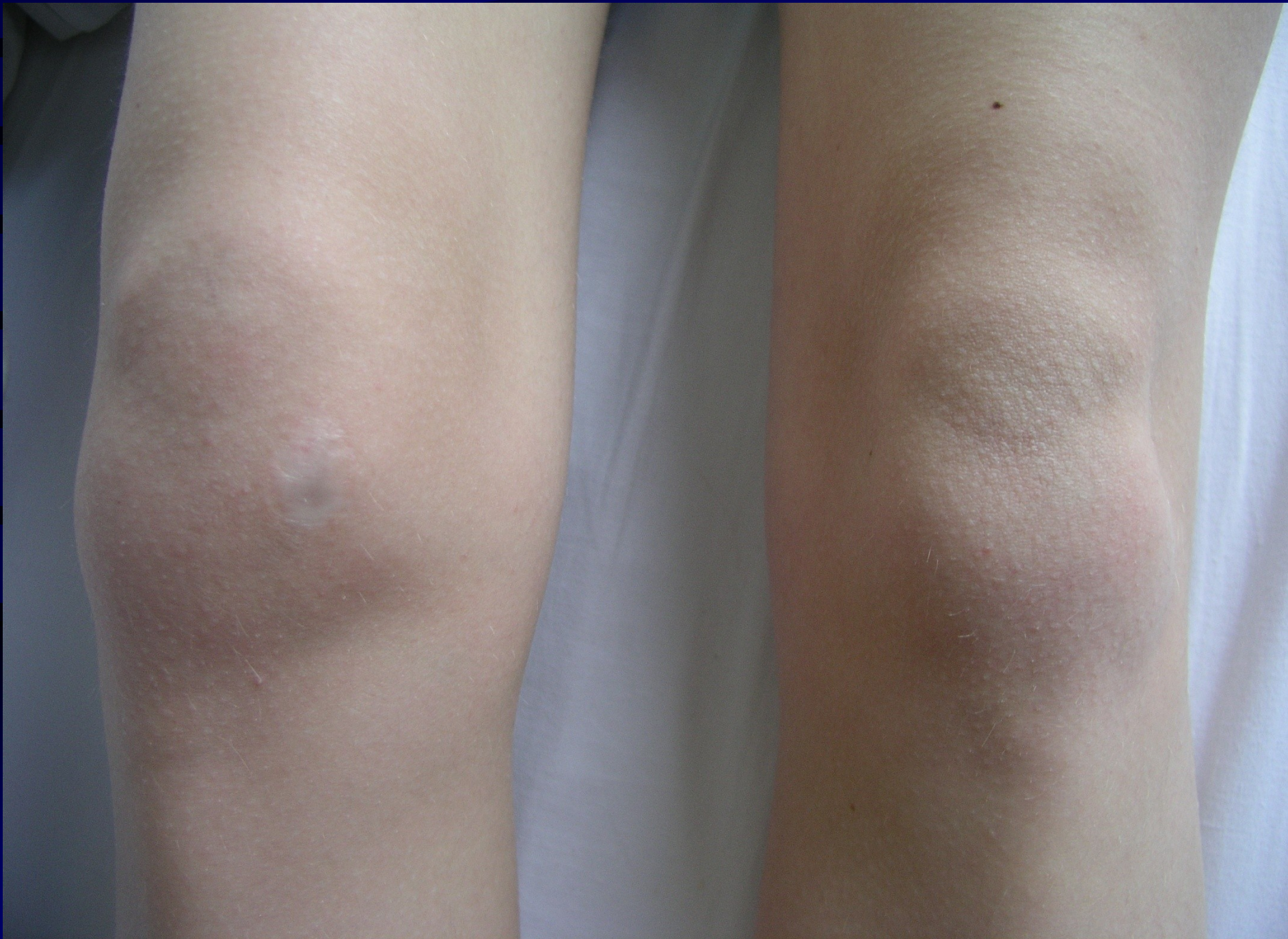
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Lyme arthritis

- **Recurrent brief attacks of objective swelling in one or a few of large joints, occasionally progressing to chronic arthritis**
- Antibiotic-refractory Lyme arthritis (LFA-1, ECGF, HLA-DRB1*0401 a 0101), 10% in USA, less in EU
- Laboratory evidence: 1) **essential**: high level of specific serum (or/and synovial) IgG antibodies
2) **supporting**: culture from synovial fluid and/or tissue





Lyme carditis

- Rare
- Causative agent: *B. burgdorferi s.s.*
- **Acute onset of atrio-ventricular (I-III) conduction disturbances, rhythm disturbances, sometimes myocarditis or pancarditis**
- Laboratory evidence: significant change in levels of specific IgG antibodies

Neuroborreliosis

- IP = one to twelve weeks
- Causative agent: *B.garinii*, *B. bavariensis*
- Neurologic involvement: primary meningitis
- **Minimal clinical signs can lead to dramatic inflammatory changes in subarachnoidal space !!!**

Clinical features in LNB

- **Nonspecific:** mild (transitory) headache, mild fever, fatigue, arthralgia, myalgia
- lack of meningeal signs !!! (vs TBE)
- **Erythema migrans** (history of untreated EM, missed or present) = high positive predictive value

Clinical features in LNB

- **Specific:**
- Radiculitic pain (severe in adults)
dermatomal sensory, motor, and reflex changes
- Cranial neuritis (VII, VI, III, IV) uni-,
bilateral

Clinical syndromes in LNB

- **Garin-Bujadoux-Bannwarth syndrome** (=meningopolyradiculoneuritis) in adults
- Aseptic meningitis
- Cranial neuritis (facial palsy): isolated or with meningitis (90 % of all cases with NB)
- (Poly)radiculitis
- Disseminated encephalomyelitis (rare)
- Radiculoneuropathies



Diagnosis

- **Direct:**
 - Cultivation (skin biopsy, synovial tissue, CSF, synovial fluid)
 - PCR – detection of borrelial DNA

Serology

Indirect:

- Two-tier testing:
 - 1) ELISA – screening test
 - 2) Western blot – confirmation if the result of ELISA is positive

ELISA and WB

- Recombinant antigens from several genospecies
 - Borrelia b.s.l. IgG EIA 5,122 **Pozitivní**
 - Borrelia b.s.l. IgM EIA 1,963 **Pozitivní**
 -
 - Borrelia b.s.lato IgG WB ... **Pozitivní**
 - Borrelia b.s.lato IgM WB ... **Negativní**
 - Antibodies against following specific borrelial antigens:
p19 H,p20,p21 H,p58,OspC,p39,p41,p83,VlsE-Bg,VlsE-Bb,VlsE-Ba

Diagnostic criteria for LNB

- 1) Meningitis/radiculitis/neuritis
- 2) Lymphocytic pleocytosis (x absence of meningeal signs)
- 3) Intrathecal synthesis of antiborrelial antibodies!

Intrathecal synthesis

- **Estimation of intrathecal synthesis of specific antibodies in CSF**
- Serum + CSF samples obtained simultaneously = determine the specific CSF/serum AI
- IgG/IgM, albumin in CSF/serum = calculation of Qalb (dysruption of HEB)
- AI = antibody index, positive ≥ 1.5

CSF finding in LNB

- CSF-mono 240.0 /1ul (0 - 3) VH
- CSF-poly 5.0 /1ul (0 - 0.3) H
- CSF-CB 1.54 g/l (0.15 - 0.45) VH

- 70 % lymphocytes

- HEB: Qalb 21.1 (≥ 5.0)
- CSF – 12 OB
- **Lymphocytic pleocytosis**

Intrathecal synthesis in LNB

- Intratekální syntéza IgG ... Pozitivní
- Intratekální syntéza IgM ... Pozitivní
- **AI IgG = 6,1 (B.garinii)**
- **AI IgM = 8,3 (B.garinii)**
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-

Obsahuje IgM protilátky v testu EU na BG proti: p30

Obsahuje IgG protilátky v testu EU na BG proti:

- p21 H,p29,p30,p39,p41,p50 H,p57,p62,p83

European guidelines for therapy of LB

- Penicillins
- Aminopenicillins
- Cephalosporins
(II.+III. generation)
- Tetracyclines
- Macrolides
- **Cutaneous clinical findings**
- **Extracutaneous manifestations + diagnostic testing performed in quality-control laboratories**

Cutaneous manifestations

- Adults: tetracyclines, penicillins, second-generation cephalosporins, macrolides
- Children < 8 years: penicillins, aminopenicillins, second-generation cephalosporins, macrolides
- 10 to 14 days p.o.

Extracutaneous manifestations

- **Arthritis, carditis:** amoxicillin, tetracyclines, third-generation cephalosporins - 14 to 28 days i.v. or p.o.
- **Neuroborreliosis:**
- **CNS:** third-generation cephalosporins, penicillin G - 14 to 21 days i.v.
- **PNS:** phenoxymethylpenicillin, amoxicillin, doxycycline - 14 to 21 days p.o.

Ehrlichiosis

Anaplasmosis

- **Seasonal tick-borne zoonosis with the tropism of etiologic agent to white blood cells**
- **Ehrlichia spp.** – intracellular bacteriae (Rickettsiae, Coxiellae, Chlamydiae)
- 1986 – first infection by Ehrlichia in Fort Chaffee, Arkansas
- 1991 – isolation and classification of the agent = *E.chaffeensis*

HME

(human monocytic ehrlichiosis)

- Emerging human pathogen
- Transmission: tick *Amblyoma americanum*, only in the USA
- Etiologic agent: *Ehrlichia chaffeensis*
(Rickettsiaceae)
- Infection of ticks: in the USA 32,5 %
- Reservoirs: deer

HGA

(human granulocytic anaplasmosis)

- Formerly known as HGE
- Transmission: *I. scapularis* - USA
I. ricinus - Europe
- Etiological agent: *Anaplasma phagocytophilum*
(*Rickettsiaceae*), intracellular pathogen
- Infectivity rate of ticks: USA 50 %,
Europe: Switzerland - 26 %, CZ – 16 %

Clinical symptoms (similar in HME and HGA)

- IP = 7 to 14 days (3 – 10 days)
- Fever $\geq 38,5$ st. C (100 % of patients)
- Myalgia (100 %)
- Headache (100 %)
- Chills (100 %)
- Hepatomegaly
- Rash (petechial, maculopapular)
- Erythema

Laboratory findings

- Leukopenia - neutropenia, lymphopenia
- Trombocytopenia
- Anemia
- Liver enzymes elevation
- High sedimentation rate and CRP

Complications

- Respiratory abnormalities (ARDS)
 - Renal failure (anuria)
 - Gastrointestinal bleeding
 - Hepatocellular necrosis
 - Aseptic meningitis
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- **fatal course in 2 % of cases (ehrlichiae in lungs, liver, spleen)**

Diagnosis

- Cultivation
- Intragranulocytic morulae (smear)
- PCR
- Antibody detection: IFA – 1:80, Western blot

Therapy

- Tetracyklines
- Rifampicin
- Ciprofloxacin

- Betalaktams (used in the therapy of LB) are ineffective !!!

TIBOLA tick-borne lymphadenopathy

DEBONEL dermacentor-borne necrosis erythema lymphadenopathy

SENLAT scalp eschar necrosis lymphadenopathy after a tick bite

- Etiologic agent: *Rickettsia slovaca*, *R. raoulti*
- Transmission: *Dermacentor marginatus*, *D. reticulatus*, *I. ricinus*
- Lesions (eschar) on the scalp (90%)
- More frequent in children

Clinical symptoms

- IP = several days to 2 months
- Fever, fatigue, headache, myalgia, arthralgia,
- Typical signs:
- **Vesiculo-ulcer skin reaction at the site of the tick-bite (eschar)**
- Painfull regional lymphadenopathy

Diagnosis and therapy

- Lymph node biopsy - PCR
- Serology

- Therapy: doxycykline, rifampicin, ciprofloxacin







Differential diagnosis after a tick bite

- **Lyme borreliosis**
- **Tick-borne encephalitis**
- **HGA (granulocytic anaplasmosis)**
- **Tularemia**
- **Q Fever**
- **Bartonellosis (cat scratch fever)**
- **TIBOLA (tick-borne lymphadenopathy)**
- **Meditarranean (Boutonneuse) spotted fever**
- **Babesiosis**
- **Rocky Mountain spotted fever (USA)**
- **Colorado tick fever (USA)**