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Educational Workshop

EW05: Tick-borne diseases prevalent in Europe

Arranged with the ESCMID Study Group for Coxiella, Anaplasma, Rickettsia and Bartonella (ESCAR) and with the ESCMID Study Group for Lyme Borreliosis (ESGBOR)

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ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

Human Babesiosis in Europe

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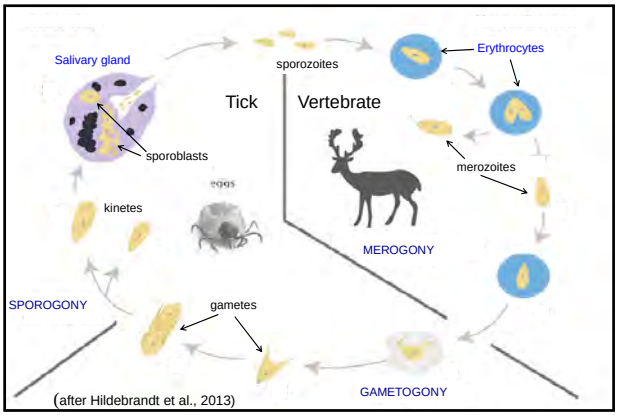
Babesiosis

- Haemolytic disease
- Acute form - sudden onset, fever, haemoglobinuria, acute anaemia, jaundice, organ failure, death
- Chronic form - slow onset, mild fever, chills, sweats, chronic anaemia, malaise, myalgia

Babesiosis – the pathogens

- Intracellular parasites of erythrocytes
- Phylum *Apicomplexa* Class *Sporozoea* Subclass *Piroplasmea* Genus *Babesia*
- >100 known species
- Notable as pathogens of cattle, sheep, dogs, horses
- Humans are accidental hosts
- Transmitted by ticks (zoonotic babesias by *Ixodes* spp.)

Gray - Human babesiosis in Europe



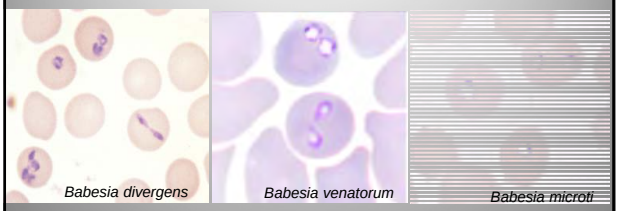
Human babesiosis - history

- **1957**: first recorded case (fatal) in splenectomised patient, Yugoslavia (Croatia), *B. bovis (divergens?),* ~ 40 cases to date
- **1970**: non-fatal, spleen-intact, east coast USA, *B.microti,* most frequent cause of human babesiosis
- **2000**: non-fatal, spleen-intact, west coast USA, eight cases in the 80s and 90s, attributed to *B. duncani*
- **2003**: two acute cases (Italy, Austria) splenectomised, EU1, 2, third in Germany 2007, EU3, now named *B. venatorum*
- **1996, 2004**: *B. divergens*-like infections in Missouri and Washington State, USA.
- Cases now reported worldwide (e.g. Japan, China, South Africa, Australia, Korea)

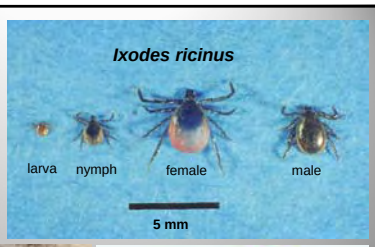
Zoonotic *Babesia* spp (European species in red)

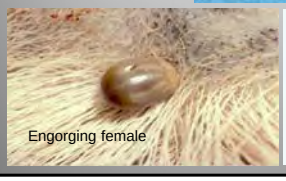
Species	Location	Animal reservoir	Cases
B. divergens	Europe, Russia	Cattle	~40
B. divergens-like	Portugal	Unknown	1
B. divergens-like MO1	USA, Missouri, Kentucky	Cottontail rabbit?	2
B. divergens-like WS	USA Washington State	Jackrabbit?	1
B. venatorum	Austria, Germany, Italy	Roe deer	3
Babesia sp. KO1	Korea	Sheep?	1
B. duncani	USA	Unknown	9
B. microti	USA (Europe), worldwide	Small rodents	Hundreds in USA, 1 in Europe

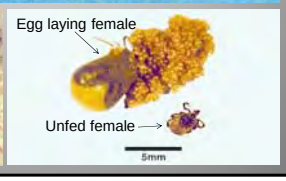
Zoonotic European *Babesia* species



The vector in Europe



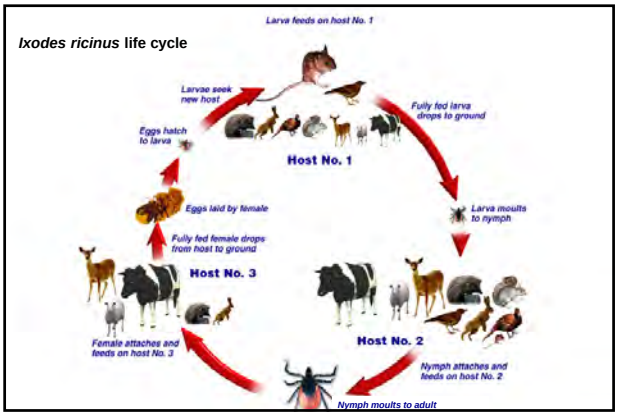


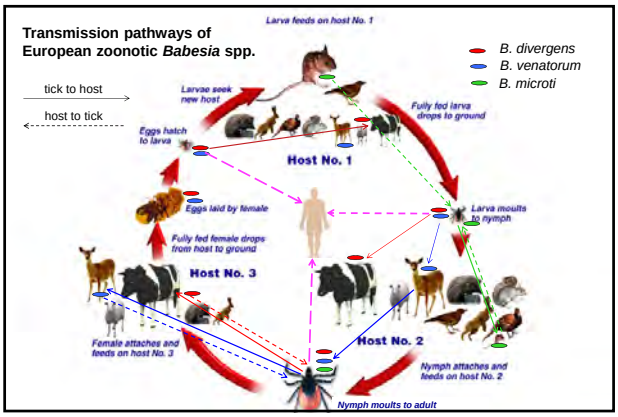


Tick habitat

- Vegetation of ground-cover must retain moisture at ground level (>80% RH) for survival of off-host stages
- Optimal habitat is deciduous forest with secondary vegetation, harbouring deer – but many variations including rough wet grazings used by livestock

Gray - Human babesiosis in Europe





Babesia divergens

- Main cause of bovine babesiosis in Europe, dramatic decline in incidence e.g. from 1.7 to 0.06% in Ireland, over the last 30 years, similar declines elsewhere
- Transovarial transmission, larva, nymph, adult female transmit, low infection prevalence (<1%)
- Human cases (~40) associated with cattle farming (rough grazing)
- Almost all cases splenectomised, often with other immunocompromising conditions, incubation period 1-2 weeks
- Medical emergency, high fever, diaphoresis, severe anaemia,, frequently haemoglobinuria, jaundice, organ failure, very high case fatality rates (~90%) in early cases, now reduced to ~40%

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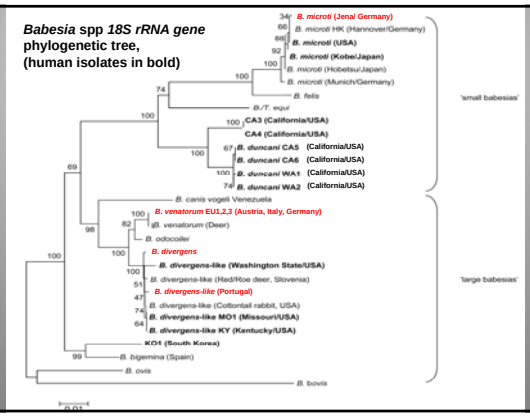
Babesia venatorum

- First cases in two splenectomised men, Hodgkin's disease, >50 yrs, Italy and Austria, hunters. Severity mild (Italy), moderate (Austria), recovered
- Third case Germany, splenectomised man, 63 yrs, Hodgkin's disease, profoundly immunosuppressed, severe, recovered
- Italian, Austrian cases designated EU1 & 2, German case EU3. Serologically indistinguishable from *B. divergens* but molecularly distinct (*18S rRNA*). Subsequently named *Babesia venatorum*
- Transmitted by *Ixodes ricinus* transovarially, roe deer (*Capreolus capreolus*) reservoir host, low prevalence in ticks (~1-2%) but most commonly encountered species in *I. riciinus*
- 8yr Chinese boy, spleen-intact, mild fever, anaemia, malaise, recovered in press (EID)



Babesia microti

- Worldwide, mainly rodent parasites
- Transmitted trans-stadially by *Ixodes* sp., infection prevalence 1-13%
- Most human cases in USA, several hundred (eastern sea-board, mid-west)
- Patients typically spleen-intact: slow onset, mild fever, malaise, myalgia, chronic course
- In asplenics acute disease may occur, similar pathology to *B. divergens* infections
- Only one authenticated endemic European case, six imported

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B. microti in Europe

- Common infection in small rodents throughout Europe
- Transmitted by rodent tick, *I. trianguliceps,* but some strains by *I. ricinus,* including an American zoonotic strain experimentally
- Seroprevalence 1-8% in Germany, Poland, Switzerland, suggests transmission to humans
- One authenticated case (Jena, Germany) occurred in a profoundly immunosuppressed patient
- Low infectivity for humans? Underlies other infections?

Do *Babesia* spp. contribute to the presentation of atypical Lyme borreliosis?

- Evidence from the USA that *B. microti* can exacerbate *Borrelia burgdorferi* sensu stricto infections. Does this occur in Europe?
- Serological indications of *B. microti* or *B. divergens* infection in febrile patients, some with possible Lyme borreliosis or TBE (unpublished, Slovenia)
- But no evidence of *Babesia* spp. infection in 86 febrile children following a tick bite (Slovenia)
- Both *B. divergens* and *Bo. burgdorferi* sensu lato infection in a severely immunosuppressed patient in Finland
- Detection of unknown *Babesia* spp. in a Lyme borreliosis patient

Babesiosis blood-transfusion transmission in Europe – cause for concern?

- Can occur when *Babesia* spp. cause asymptomatic infections
- More than 150 cases of transfusion-transmitted *B. microti* recorded in the USA since 1979, three quarters since 2000
- Single European *B. microti* case probably transfusion-transmitted
- Other risk indicators include
  - *B. divergens (B. venatorum?*) and *B. microti* antibodies in healthy individuals
  - *B. divergens*-like spp. low grade infections in immunocompetent individuals
  - Imported *B. microti* cases, mainly from the USA

Diagnosis - clinical

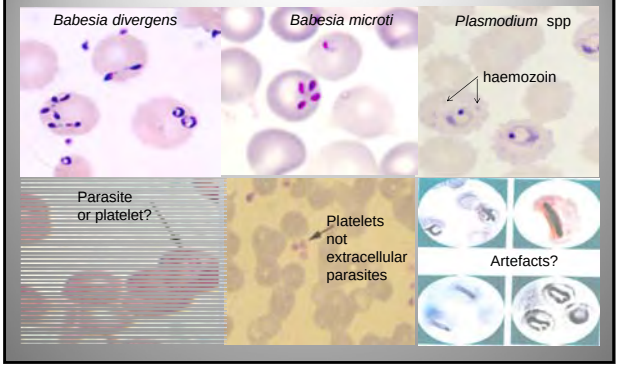
If babesiosis is suspected exposure to ticks or recent blood products is an important indicator

- Immunocompetent
  - Non-specific i.e. fever, headache, chills, sweats, myalgia
- Immunocompromised
  - high fever, diaphoresis, shortness of breath, severe anaemia, weakness, later dark urine and/or jaundice, respiratory distress syndrome, congestive heart failure, kidney failure

Diagnosis - laboratory

- Thin blood smears, usually Giema-stained (note absence of haemozoin), serial peripheral blood samples may be required
- PCR, but reference laboratory required since no standardised methodology in Europe
- Serology – of no value for acute cases because of the rapid time course. For chronic cases indirect immunofluorescence assay (IFA) (standardised in the USA for *B. microti*)
- Animal xenodiagnosis – of no value for acute cases; for *B. microti* chronic cases inoculation of hamsters or gerbils may help with detection and identification. *B. venatorum* not known to be infective for any laboratory animals

Appearance of *Babesia* spp in thin blood smears



Treatment

Acute cases – exchange transfusion in addition to antimicrobials

Drug	*Adults (70 kg)*	*Children/kg*	*Regimen*
Quinine	650 mg p.o.	8 mg max 650 mg/day	3 x daily
and			
Clindamycin	600 mg p.o. i.v.	7-10 mg max 600 mg/day	3 x daily

Chronic cases

Drug	*Adults (70kg)*	*Children/kg*	*Regimen*
Atovaquone	750 mg p.o.	10 mg max 750 mg/day	2 x daily
and			
Azithromycin	500 mg d1, then 250 mg	10 mg d1, then 5 mg	1 x daily

Is there a case for using **Atovaquone** against *B. divergens* infections?

- *B. divergens* is more susceptible to antibabesials than is *B. microti*
- Atovaquone is more effective against *Babesia divergens* than imidocarb dipropionate, the most effective veterinary antibabesial
- Unlike imidocarb, atovaquone is licensed for use in humans
- Atovaquone is much better tolerated than quinine, the current drug of choice for acute infections based on past usage
- Note atovaquone finally resorted to in order to clear *B. venatorum* in third case (EU3)

Conclusions

- Human babesiosis is a rare disease in Europe, but the majority of cases are acute, requiring emergency intervention
- Some evidence that chronic low grade infections occur, including those caused by *B. microti,* responsible for the most globally common form of human babesiosis
- The possibility that *Babesia* spp. infections could occasionally underlie Lyme borreliosis may require further investigation
- The possibility of transfusion-transmission of babesiosis in Europe and the appropriate response should be considered

Gray - Human babesiosis in Europe

Human babesiosis
Further reading

Hildebrandt A, Gray JS, Hunfeld KP. 2013. Human babesiosis in Europe: what clinicians need to know. Infection. 2013 Dec;41(6):1057-72.

Vannier E, Krause PJ. 2012. Human babesiosis. N Engl J Med. Jun 21;366(25):2397-407.

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