CHRONIC BABESIOSIS

CAUSED BY *BABESIA ODOCOILEI*

PATHOPHYSIOLOGY, DIAGNOSIS AND TREATMENT

WITH CASE PRESENTATION

HENRY H. LINDNER, MD

ILADS 2021

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Disclosures

- ❑ I have no relevant financial or non-financial relationships to disclose.
- ❑ All references to off-label or non-FDA approved usage in this presentation will be noted and disclosed.

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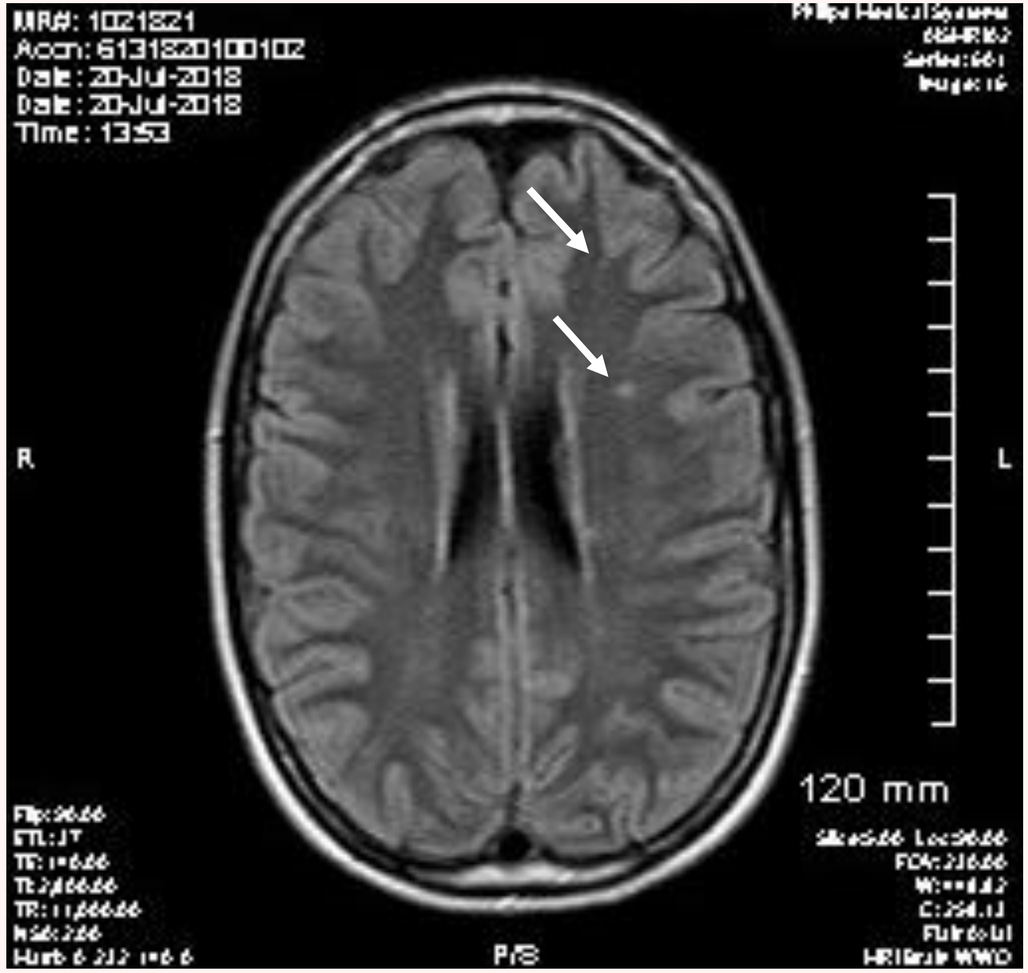
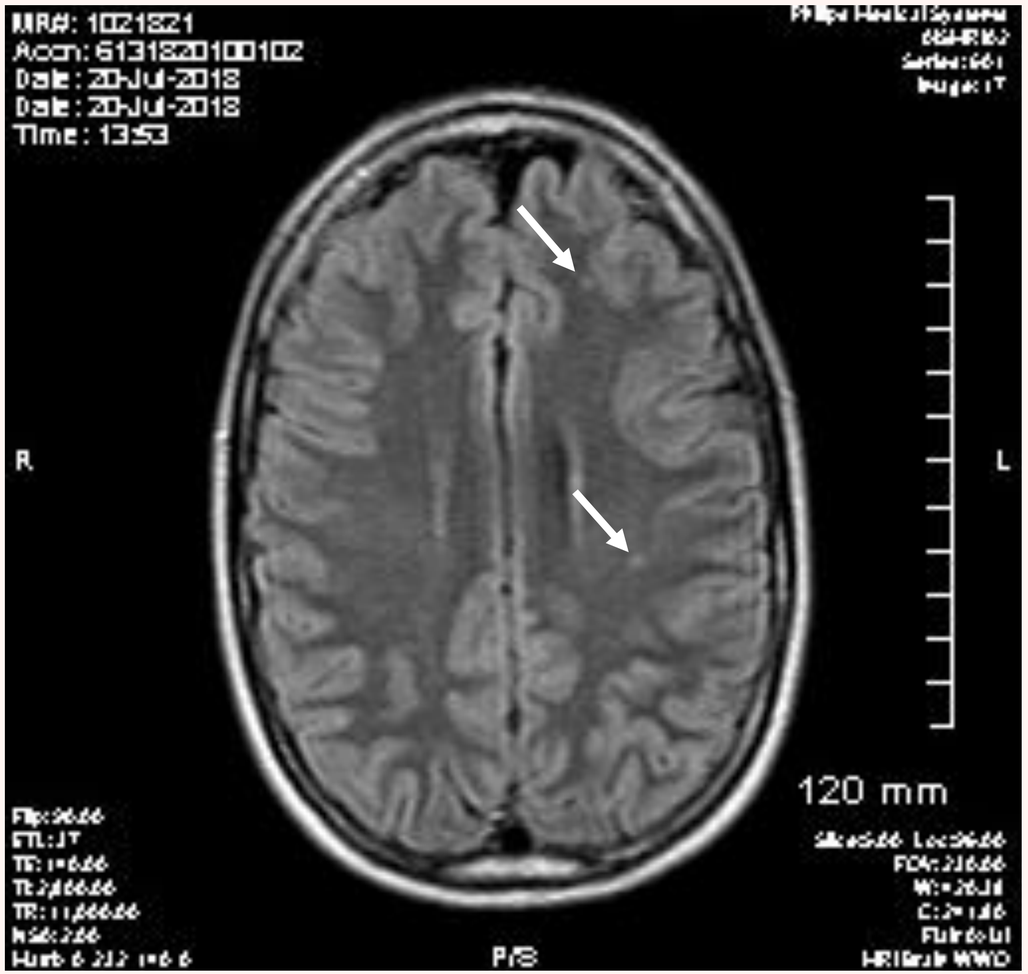
CASE: 27 Y.O. FEMALE IN PENNSYLVANIA

- ❑ Childhood: anhedonia, violent thoughts; needed distraction
- ❑ Age 10: Engorged deer ticks. No prophylaxis. No rash or fever.
- ❑ Gradual onset of fatigue, depression, frustration; couldn't draw, contact friends
- ❑ Intact intellect/memory but low brain energy/function, ↑violent/suicidal ideation
- ❑ Strange "hunger"—had to eat frequently/excessively to function, reduce malaise
- ❑ NO signs/symptoms of Lyme, Babesia, Bartonella; Worsened throughout college
- ❑ Age 25: Neurologist: Brain MRI: WMHs. Mayo Auto. Enceph. panel Neg., Dx: MS?
- ❑ LabCorp: Lyme WB Neg., IGeneX: Lyme and coinfections panel Neg.

AGE 25: WHITE MATTER HYPERINTENSITIES





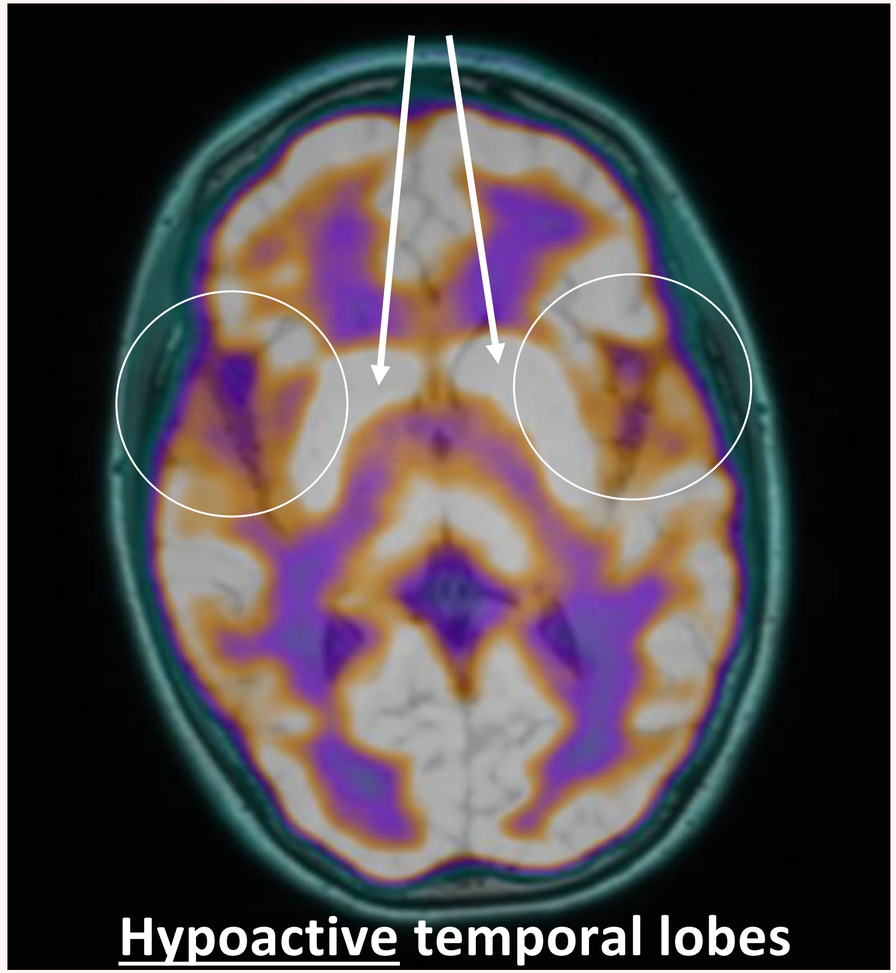
EMPIRIC TICKBORNE DISEASE TREATMENT

- ❑ Doxycycline 600mgs/day for Lyme→mental/physical "herxing", no improvement
- ❑ Mepron, hydroxychloroquine→unbearable mental pain, ↑violent/suicidal ideation
- ❑ "Shock Effect": Initial improvement on new or ↑'d antimicrobial, then herxing
- ❑ ↑Herxing after mental or physical activity, especially leg exercises
- ❑ Galaxy Diagnostics: +*Bartonella henselae/quintana* abs; TLab: +*B. henselae* FISH
- ❑ Clarithromycin/rifabutin x 9 mos→mental/physical herxing, no improvement
- ❑ Cunningham panel: +anti-D1, anti-tubulin abs; Dx: PANS* (Bartonella in childhood?)
- ❑ Brain SPECT and PET/MRI abnormal; Neurologist: Autoimmune encephalitis (AE)

*Pediatric acute-onset neuropsychiatric syndrome; Better name: Autoimmune basal ganglia encephalitis (ABGE)

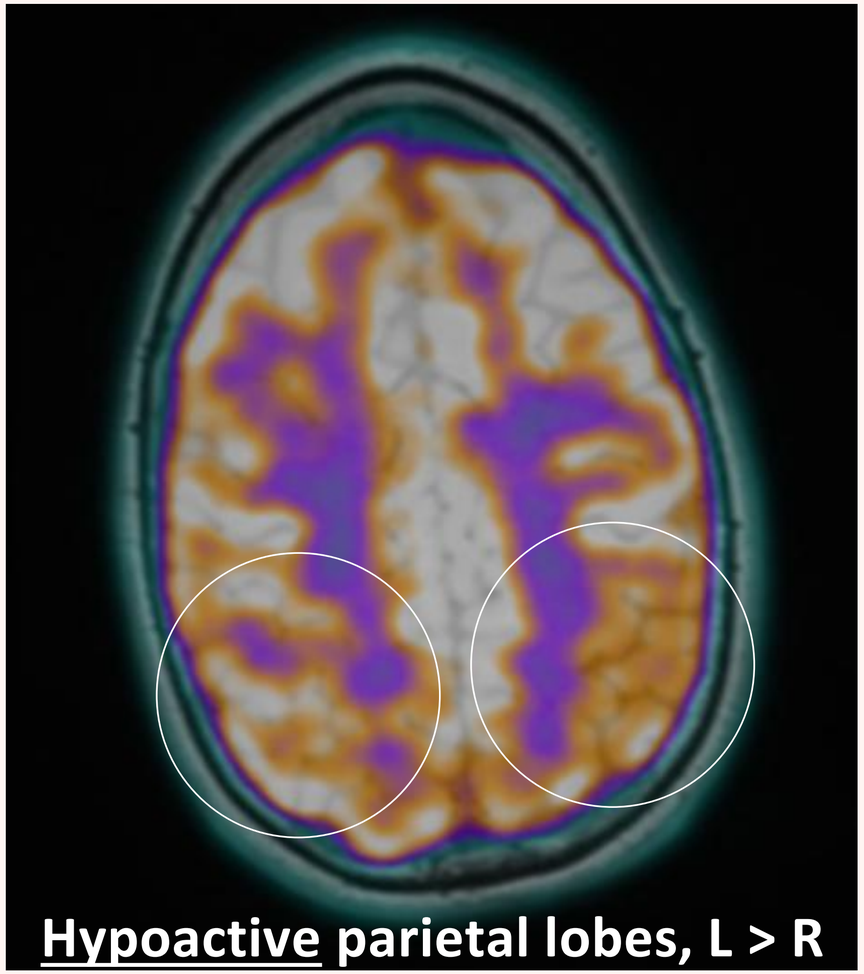
AGE 26: PET-MRI

Hyperactive basal ganglia



Hypoactive temporal lobes

Lighter color = Higher metabolic activity



Hypoactive parietal lobes, L > R

Radiologist: c/w autoimmune/inflammatory encephalitis

BABESIA DETECTED: DEFINITIVE TREATMENT

- ❑ For suspected PANS: Dexamethasone taper, IVIG x2—No benefit
- ❑ Repeat IGeneX: +Babesia FISH, +*B.duncani* IgM; Blood smears negative
- ❑ Mepron, Allicin→intolerable mental herxing, remained worse; Could not Treat!
- ❑ Low-dose immunotherapy→Flaring: Bart—agitation/anger, Bab—delirium, flu-like
- ❑ IV Solumedrol for AE: No help, much worse with withdrawal, needed prednisone
- ❑ Greatly worsened by treatments! Unable to walk outside, exercise, read, watch videos. Mental pain. Self-dosed prednisone 400mgs/day to get up, eat, sleep!
- ❑ Oct. 2020: Immunosuppressed with prednisone+plasmapheresis, started high-dose artesunate, atovaquone, azithromycin, and tafenoquine

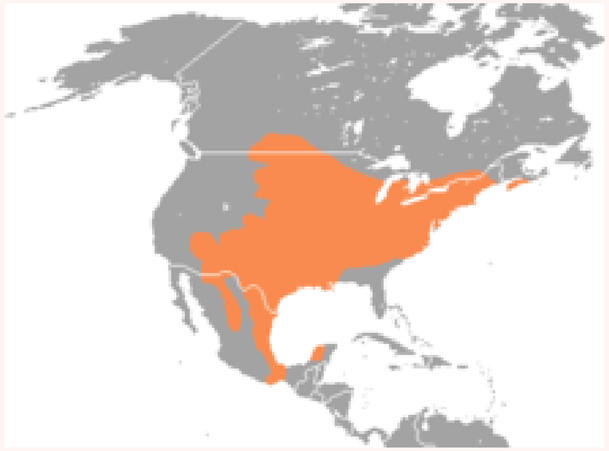
BABESIA SPECIES

- ❑ Intraerythrocytic unicellular protozoa, related to malaria (phylum: *Apicomplexa*)
- ❑ Eukaryotes—nucleus, mitochrondria, apicoplast (incorporated cyanobacterium)
- ❑ Consume hemoglobin, must detoxify/isolate iron
- ❑ >100 species, most wild animals infected from early age
- ❑ Transmitted by ticks; reside in ticks' salivary glands, activated by feeding
- ❑ Ubiquitous: Infected ticks carried by migrating birds

Schnittger L et al. Babesia: a world emerging. *Infect Genet Evol*. 2012;12(8):1788-809. PMID: 22871652
Jalovecka M et al. Babesia Life Cycle - When Phylogeny Meets Biology. *Trends Parasitol*. 2019;35(5):356-368. PMID: 30733093
Hasle G. Transport of ixodid ticks and tick-borne pathogens by migratory birds. *Front Cell Infect Microbiol*. 2013;3:48. PMID: 24058903
Tahir D et al. Interrupted Blood Feeding in Ticks: Causes and Consequences. *Microorganisms*. 2020;8(6):910. PMID: 32560202

BABESIA MICROTI ?

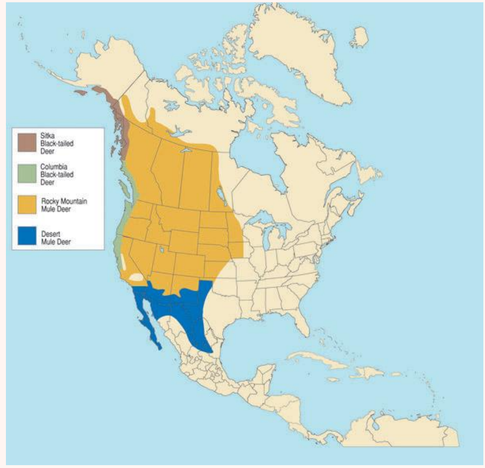
- ❑ Not a *Babesia sp.*! Different genus, 20% smaller genome
- ❑ Rare: 3% of deer ticks; Host: white-footed mouse
- ❑ Acute babesiosis only: Spontaneously cleared by immunocompetent host
- ❑ Centers for Disease Control (CDC) and Infectious Diseases Society of America (IDSA) claim that almost all babesiosis in U.S. is caused by *B. microti*; and cured by 7-10 days of atovaquone-azithromycin (speeds resolution)
- ❑ Patient repeatedly negative for *B. microti* antibodies



White-footed mouse range
Wikipedia

Cornillot E et al. Sequencing of the smallest Apicomplexan genome from the human pathogen *Babesia microti*. *Nucleic Acids Res*. 2012;40(18):9102-14. PMID: 22833609
Krause PJ et al. 2020 IDSA Guideline on Diagnosis and Management of Babesiosis. *Clin Infect Dis*. 2021;72(2):185-189. PMID: 33501959

BABESIA DUNCANI ?



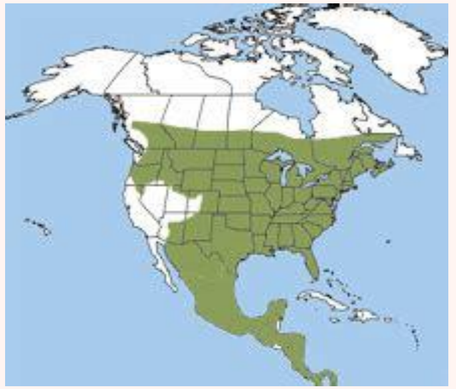
Mule deer range
Deerfriendly.com

- ❑ *Babesia* sensu lato (s.l. = broader sense)
- ❑ Not found in Eastern US deer ticks, Host: Mule deer
- ❑ Few reported cases in Western US, immunocompromised hosts
- ❑ But *B. duncani* antibodies prevalent across US and Canada: 2% of blood donors, 27% of patient samples (5x > *B. microti*!)*
- ❑ Conclusion: Immunoassay cross-reaction with antibodies to another babesia sp.

What species?

Persing DH et al. Infection with a babesia-like organism in northern California. *N Engl J Med*. 1995;332(5):298-303. PMID: 7816065
*Prince HE et al. Comparison of the *Babesia duncani* (WA1) IgG detection rates among clinical sera submitted to a reference laboratory…*Clin Vaccine Immunol*. 2010;17(11):1729-33. PMID: 20861326
Scott JD et al. Human Babesiosis Caused by *Babesia duncani* Has Widespread Distribution across Canada. *Healthcare (Basel)*. 2018;6(2):49. PMID: 29772759
Horowitz RI et al. Precision medicine: retrospective chart review and data analysis of 200 patients on dapsone combination therapy for chronic Lyme…*Int J Gen Med*. 2019;12:101-119. PMID: 30863136

BABESIA ODOCOILEI !



White-tailed deer range

http://www.nhptv.org

- ❑ ***Babesia*** **sensu stricto (s.s.), small size**
- ❑ **Host: white-tailed deer (*Odocoileus virginianus*)**
- ❑ **Common: 7 to 35% of deer ticks in US, 20% in PA (c/w Lyme 30%)***
- ❑ **Detected (2021) in 2 persons with chronic, treatment-resistant babesiosis****
- ❑ **Problem: Deer population has doubled since 1950! (Deer tick, deer babesia!)**
- ❑ **To understand: Veterinary babesia and human Falciparum malaria literature**

Why was it not discovered in humans until now?

Livengood J et al. Detection of *Babesia, Borrelia, Anaplasma*, and *Rickettsia* spp. in Adult Black-Legged Ticks from Pennsylvania…*Vector Borne Zoonotic Dis*. 2020;20(6):406-411. PMID: 31976829

*Chinnici N, Pennsylvania Tick Research Lab, personal communication (*B.* odoc*oilei,* stats not listed at tick lab website)

Scott JD et al. Detection of *Babesia odocoilei* in *Ixodes scapularis* Ticks Collected in Southern Ontario, Canada. *Pathogens*. 2021;10(3):327. PMID: 33802071

Milnes EL et al. Babesia odocoilei and zoonotic pathogens identified from Ixodes scapularis ticks in southern Ontario, Canada. *Ticks Tick Borne Dis*. 2019;10(3):670-676. PMID: 30833200

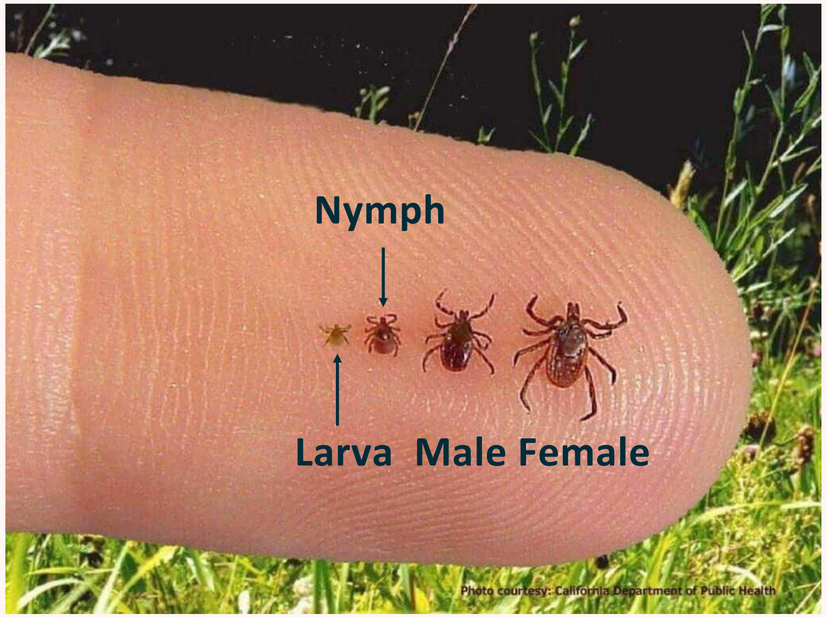
**Scott JD et al, Detection of *Babesia odocoilei* in Humans with Babesiosis Symptoms. *Diagnostics (Basel)*. 2021;11(6):947. PMID: 34070625

BABESIA S.S.: HIGHLY EVOLVED PARASITES

- 7.5x larger genome than Lyme-*Borrelia sp.* (9.7Mbp vs. 1.3Mbp) NCBI

- Adept at immune evasion and suppression
  - Modulation of immune system
  - Antigenic variation
  - Cytoadherence and sequestration

- Transovarial transmission: Larvae infected (not Lyme)



- Age-related host response in animals:
  - Young—no acute illness; strong innate but no adaptive immunity; lifelong infestation
  - Adults—acute illness; adaptive immunity; death or lifelong infestation

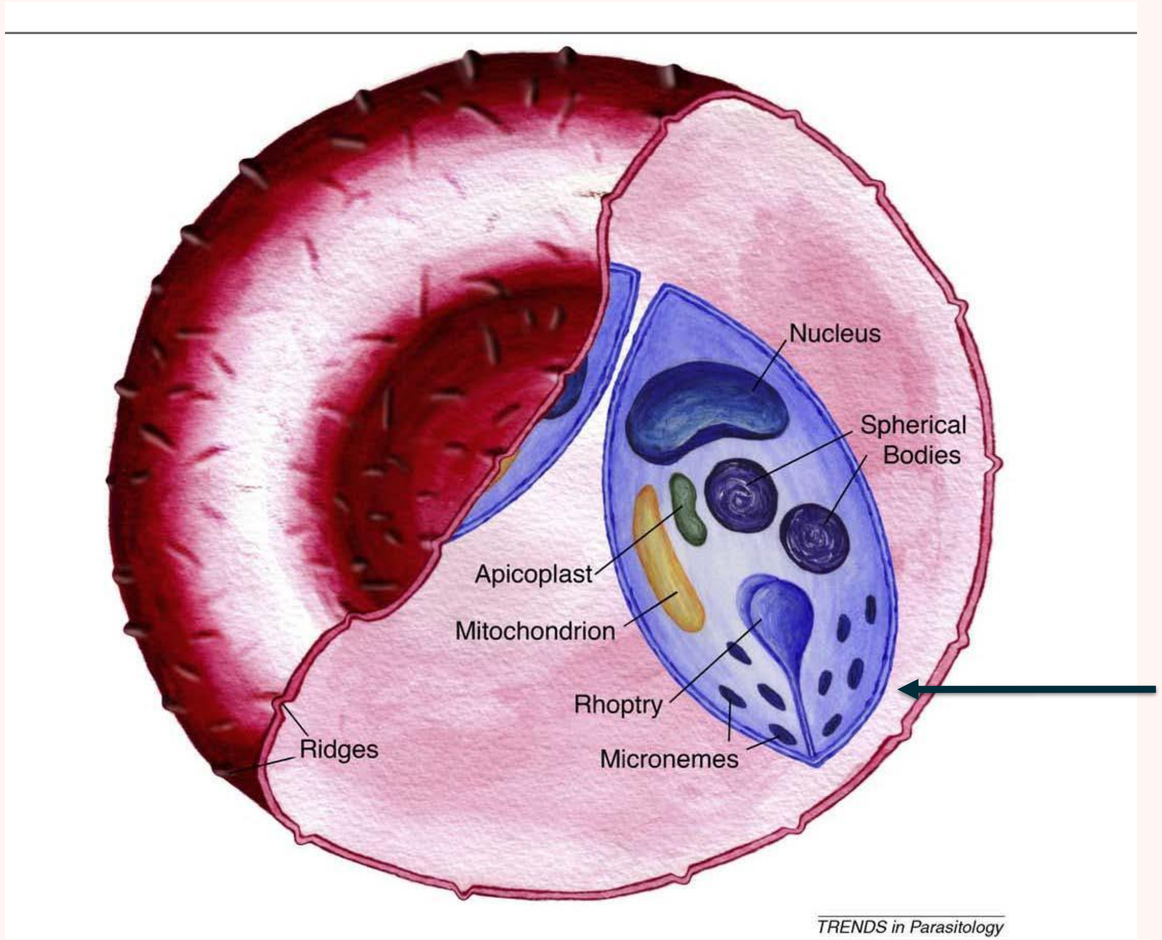
Chauvin A et al. Babesia and its hosts: adaptation to long-lasting interactions as a way to achieve efficient transmission. *Vet Res*. 2009;40(2):37. PMID: 19379662
Allred DR. Antigenic variation in babesiosis: is there more than one 'why'? *Microbes Infect*. 2001;3(6):481-91. PMID: 11377210
Suarez CE et al. Unravelling the cellular and molecular pathogenesis of bovine babesiosis: is the sky the limit? *Int J Parasitol*. 2019;49(2):183-197. PMID: 30690089
Zintl A et al. Possible mechanisms underlying age-related resistance to bovine babesiosis. *Parasite Immunol*. 2005;27(4):115-20. PMID: 15910419

CYTOADHERENCE AND SEQUESTRATION

- ❑ Babesia alter surface of infected erythocytes (IEs)→“stickiness”
- ❑ Cytoadherence: IEs adhere to endothelium of capillaries and venules (slow flow)
- ❑ Rosetting: Uninfected erythrocytes (UEs) adhere to IEs
- ❑ Sequestration: Masses of IEs and UEs occlude capillaries and venules, damage endothelium
- ❑ Local proliferation: In the vascular nests, esp. brain, intestines, lungs
- ❑ Chronic infestation: Evasion of spleen, immune system, and antimicrobials

Allred DR et al, Antigenic variation and cytoadhesion in *Babesia bovis* and *Plasmodium falciparum*: different logics achieve the same goal. *Mol Biochem Parasitol*. 2004;134(1):27-35. PMID: 14747140
Allred DR. Babesiosis: persistence in the face of adversity. *Trends Parasitol*. 2003;19(2):51-5. PMID: 12586467
Wright IG. An electron microscopic study of intravascular agglutination in the cerebral cortex due to *Babesia argentina* infection. *Int J Parasitol*. 1972;2(2):209-15. PMID: 4652608

B. BOVIS: ADHERENT RIDGES



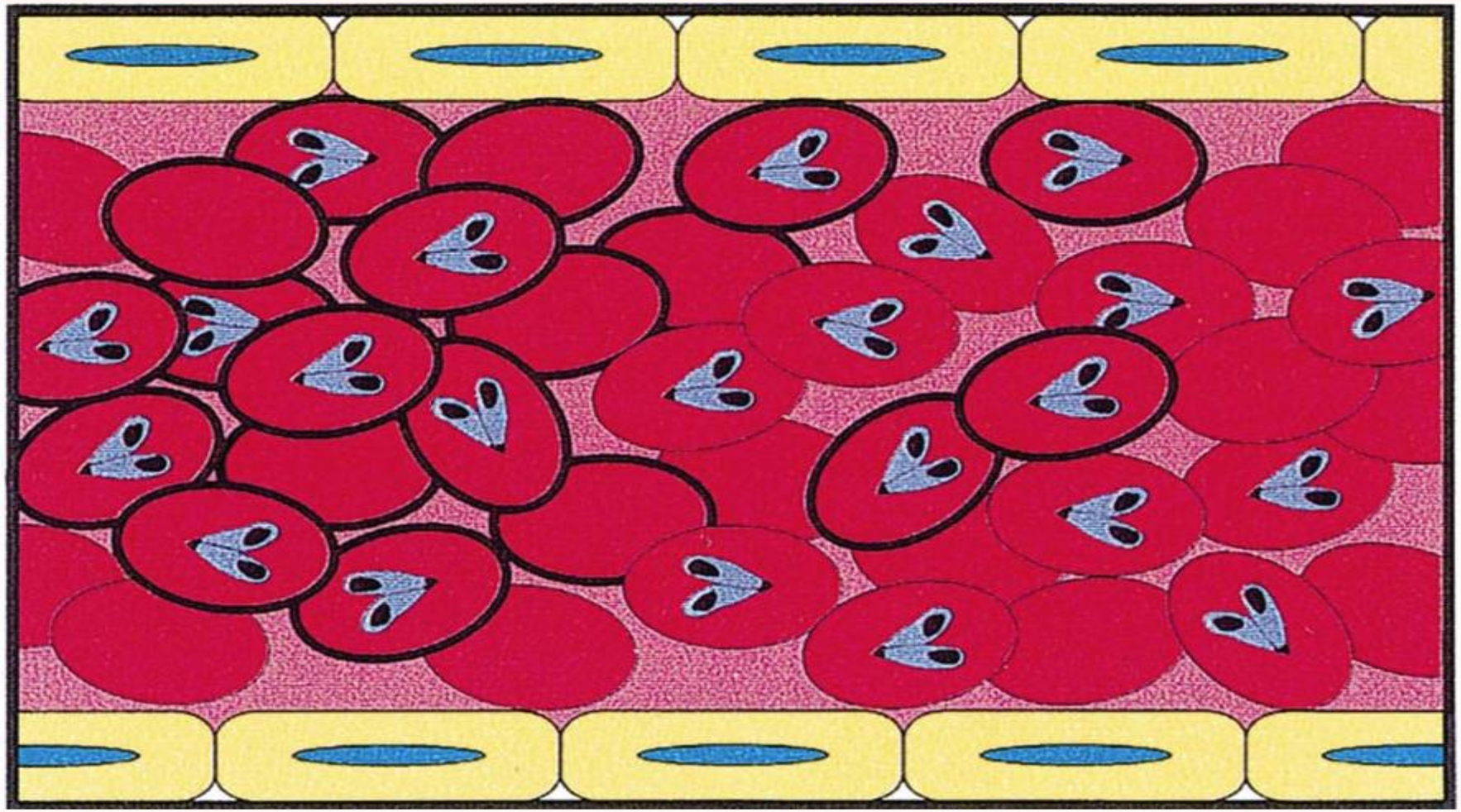
Merozoite

Apical complex for invading erythrocytes

Gohil S et al. Recent insights into alteration of red blood cells by *Babesia bovis*: moovin' forward. *Trends Parasitol*. 2010;26(12):591-9. PMID: 20598944

BABESIA NEST IN VENULE

IEs and UEs



The ultimate "biofilm"

Nests must contain Bartonella, possibly Borrelia

Schetters TP et al. Can Babesia infections be used as a model for cerebral malaria? *Parasitol Today*. 1999;15(12):492-7. PMID: 10557150

B. CANIS IN DOGS: MODEL FOR *B. ODOCOILEI* IN HUMANS

pathogens

MDPI

Review

Mechanisms Involved in the Persistence of *Babesia canis* Infection in Dogs

Theo Schetters [1,2]

1 ProtActivity R&D, 5431 Cuijk, The Netherlands; th.schetters@protactivity.com or theo.schetters@up.ac.za; Tel.: +31-615006839

2 Department of Veterinary Tropical Diseases, University of Pretoria, Onderstepoort 0110, South Africa

Received: 31 May 2019; Accepted: 27 June 2019; Published: 29 June 2019

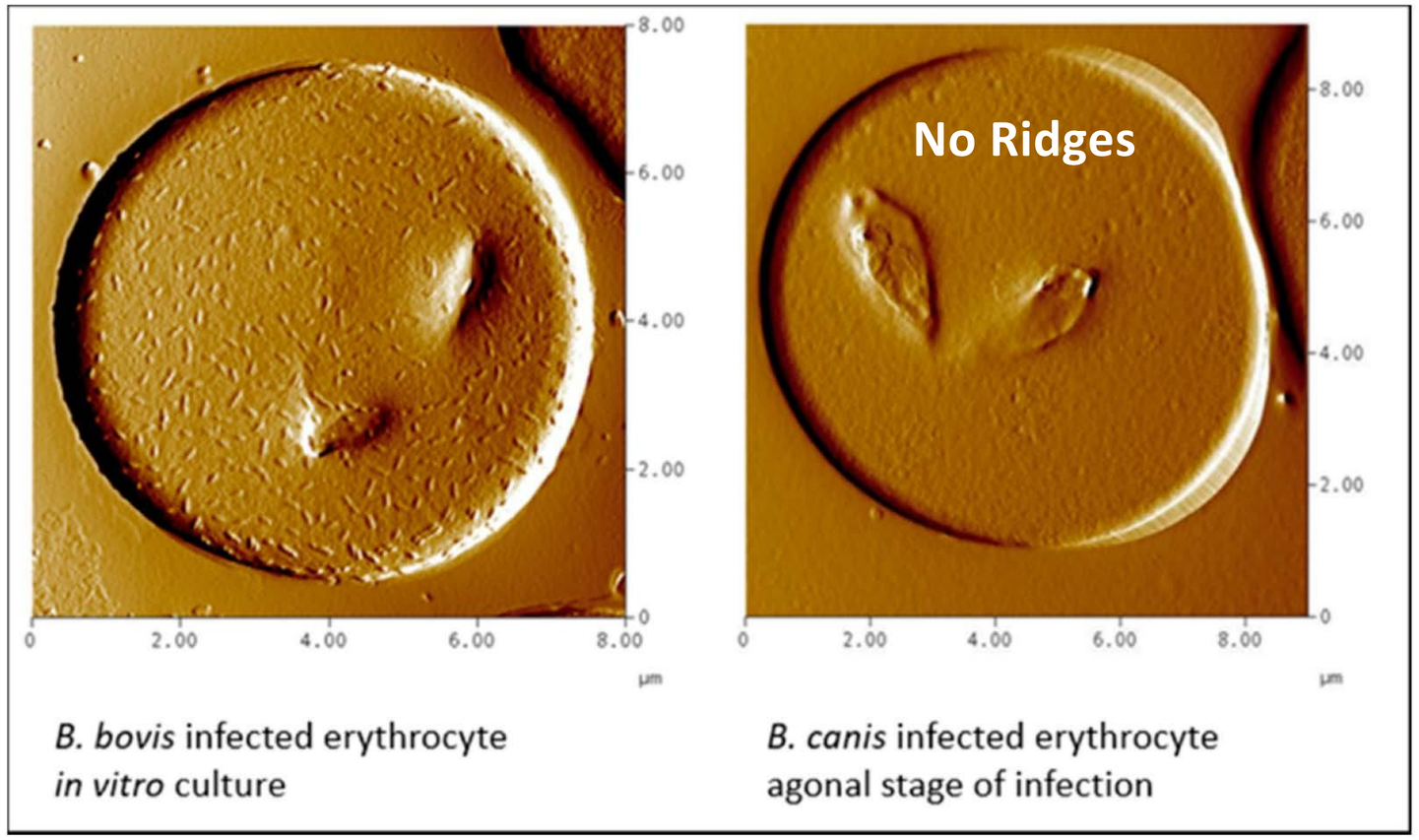
check for updates

Abstract: Dogs that are infected with *Babesia canis* parasites usually show severe clinical signs, yet often very few parasites are detectable in the blood circulation. The results showed that large numbers of *B. canis*-infected red blood cells accumulate in the microvasculature of infected subjects. The initial process leading to the attachment of infected erythrocytes to the endothelial cells of small capillaries (sequestration) appears to involve the interaction of parasite molecules at the erythrocyte surface with ligands on the endothelial cells. Since parasites continue to develop in the sequestered erythrocyte, it would be expected that the infected erythrocyte is destroyed when the mature parasites escape the host cell, which would make it hard to explain accumulation of infected erythrocytes at the initial site of attachment. Apparently, additional processes are triggered that lead to consolidation of parasite sequestration. One possible explanation is that after initial attachment of an infected erythrocyte to the wall of a blood capillary, the coagulation system is involved in the trapping of infected and uninfected erythrocytes. The data further suggest that newly formed parasites subsequently infect normal red blood cells that are also trapped in the capillary, which finally leads to capillaries that appear to be loaded with infected erythrocytes.

Keywords: Babesia canis; sequestration; blocked capillaries; shock; coagulation; inflammation

Schetters T. Mechanisms Involved in the Persistence of *Babesia canis* Infection in Dogs. *Pathogens*. 2019;8(3):94. PMID: 31261942

B. CANIS: CYTOADHERENCE BY FIBRIN BONDING



Alteration of IE surface with negatively-charged molecules can cause fibrin deposition*

***B. argentina* (cattle) employs fibrin bonding**

***B. odocoilei*: IEs have no ridges**

Schetters T. Mechanisms Involved in the Persistence of *Babesia canis* Infection in Dogs. *Pathogens*. 2019;8(3):94. PMID: 31261942

*Berends ET et al. Bacteria under stress by complement and coagulation. *FEMS Microbiol Rev*. 2014;38(6):1146-71. PMID: 25065463

Wright IG. An electron microscopic study of intravascular agglutination in the cerebral cortex due to *Babesia argentina* infection. *Int J Parasitol*. 1972;2(2):209-15. PMID: 4652608

B. CANIS: HEPARIN INJECTIONS MOBILIZE IEs

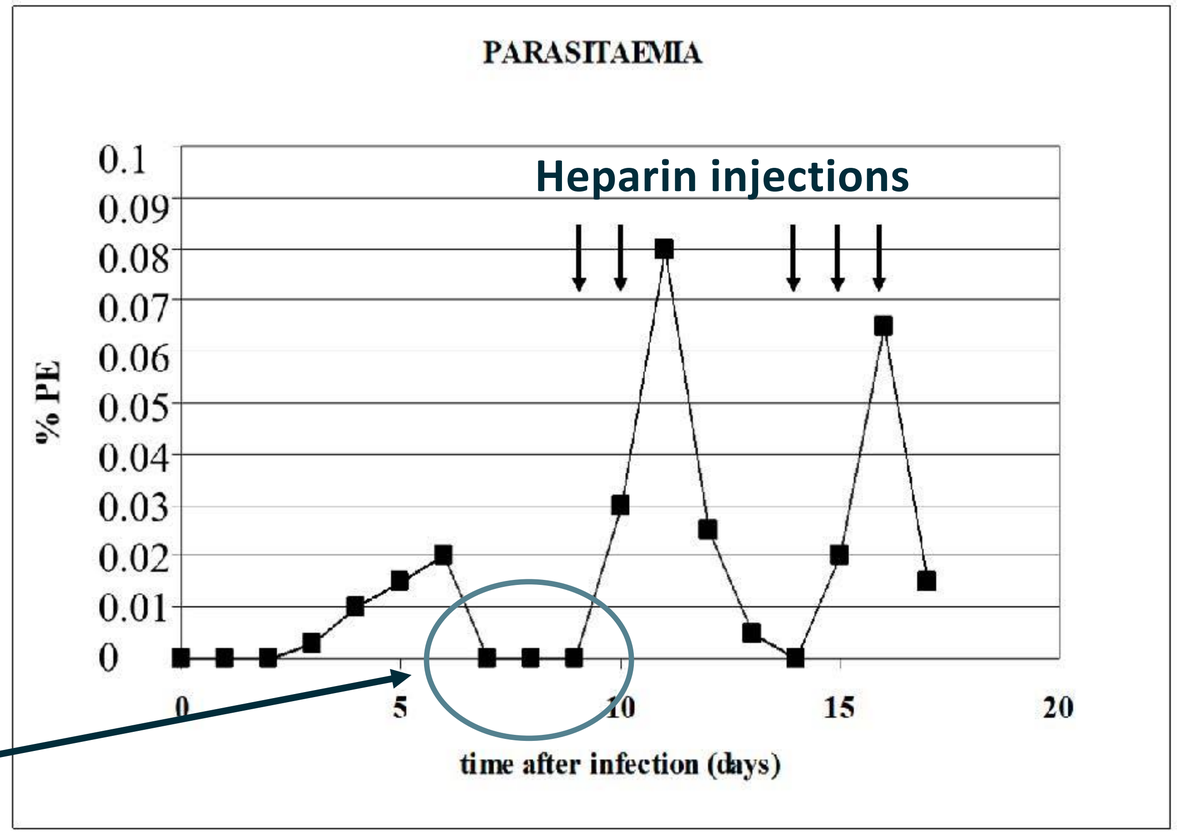


Figure 10. The effect of a heparin injection on the parasitaemia of a *B. canis*-infected dog. The time points of heparin administration are indicated with arrows [23].

Not detectable in venous blood

Heparin promotes fibrinolysis

***B. odocoilei*: lumbrokinase (fibrinolytic) causes herxing and ↑hemolysis**

Schetters T. Mechanisms Involved in the Persistence of *Babesia canis* Infection in Dogs. *Pathogens*. 2019;8(3):94. PMID: 31261942

Upchurch GR et al. Effect of heparin on fibrinolytic activity and platelet function in vivo. *Am J Physiol*. 1996;271(2 Pt 2):H528-34. PMID: 8770093

DOG BRAIN: *B. CANIS* CAPILLARY NEST

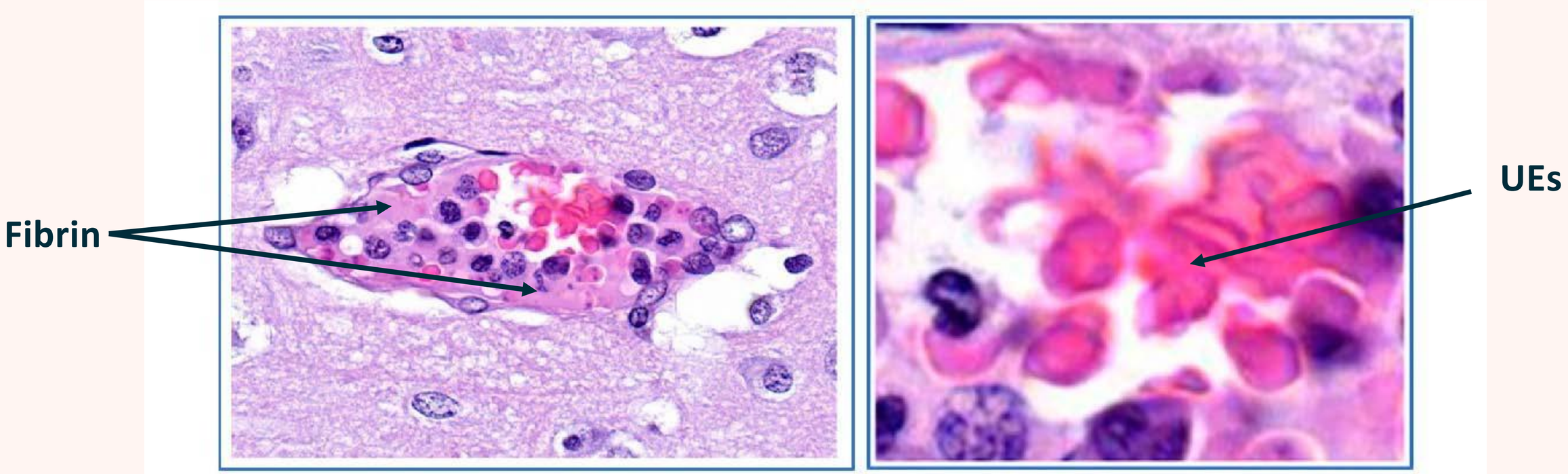


Figure 9. Histological section of brain tissue of a dog that developed severe clinical signs upon infection with *B. canis*-infected erythrocytes. The deposits of fibrin (amorphous pink staining material) with leukocytes are found at the margin of the capillary (**left panel**). In the central part of the capillary, normal red blood cells are found (**right panel**). HE stain.

Schetters T. Mechanisms Involved in the Persistence of *Babesia canis* Infection in Dogs. *Pathogens*. 2019;8(3):94. PMID: 31261942

DOG HEART: FEW CAPILLARIES PLUGGED→NO INFARCTION

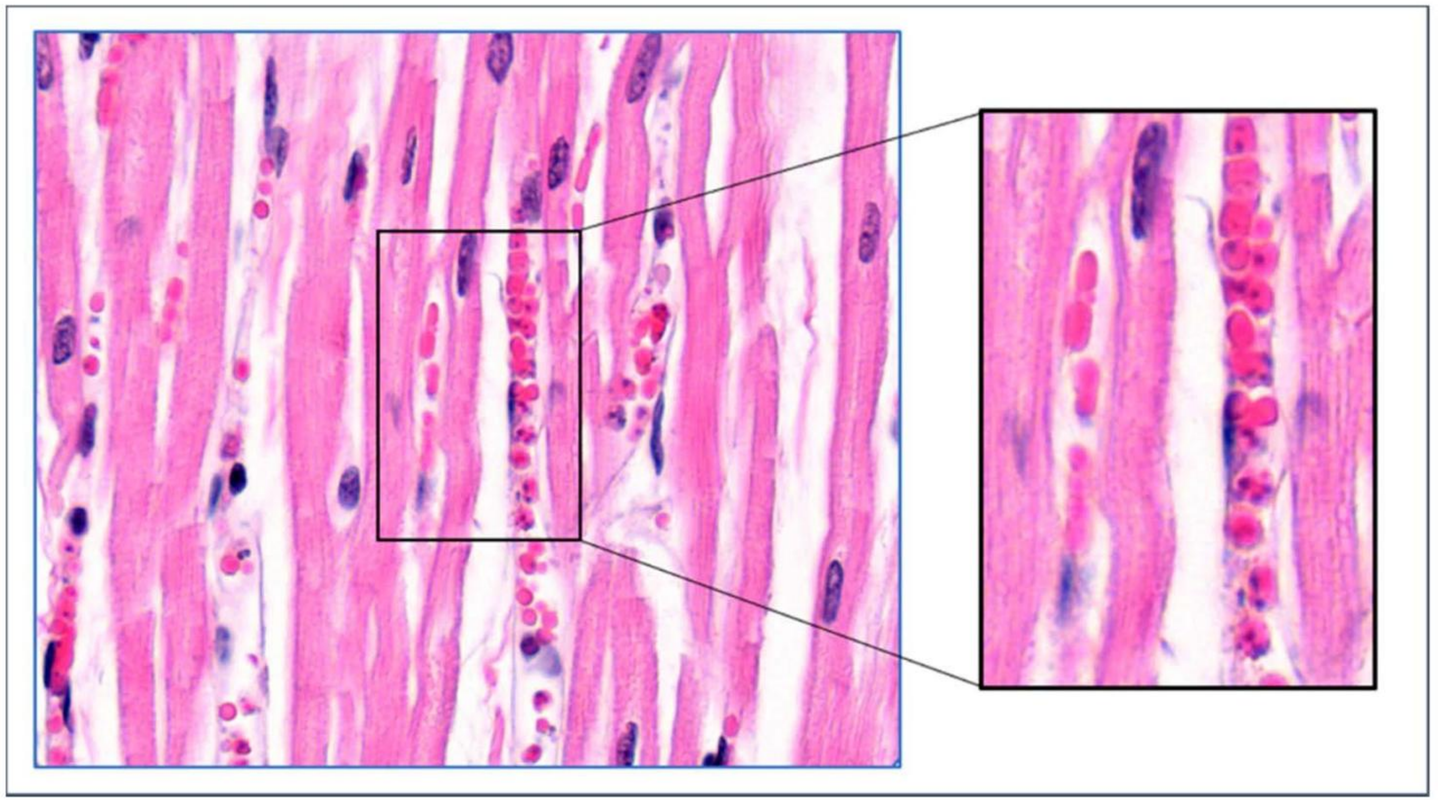


Figure 3. Obstructed capillary filled with *B. canis*-infected erythrocytes. The capillary in the right part of this section of heart tissue of a *B. canis*-infected dog is completely filled with infected erythrocytes. The adjacent capillary at the left appears not affected. HE stain.

Schetters T. Mechanisms Involved in the Persistence of *Babesia canis* Infection in Dogs. *Pathogens*. 2019;8(3):94. PMID: 31261942

BABESIA NESTS DISABLE THE HOST

- **Localized ischemia and inflammation in all tissues/organs (direct effects—not just a host immune-response disease)**
- **Inflammation→↑nitric oxide (NO)→capillary leakage→edema and hypotension**
- **↑NO→ATP depletion: NO+superoxide→peroxynitrite →DNA nicks→PARP1 activation→ATP consumption→impaired Na^+/K^+ pump→tissue/organ anergy/dysfunction**
- **ATP accumulates during sleep, rapidly exhausted with activity. Patient must rest to reaccumulate ATP.**

B. canis infection

Schetters T…*Pathogens.* 2019;8:94

Clark IA et al. The pathophysiology of falciparum malaria. *Pharmacol Ther*. 2003;99(2):221-60. PMID: 12888113

Clark IA et al. Do babesiosis and malaria share a common disease process? *Ann Trop Med Parasitol*. 1998;92(4):483-8. PMID: 9683899

CEREBRAL BABESIOSIS

- ❑ Brain is favored site for sequestration (small capillaries, no motion or pressure)
- ❑ Brain ischemia, inflammation and ATP depletion
- ❑ Rupture of blood-brain barrier (BBB)→entry of proteins, antigens, leukocytes
- ❑ White matter most affected: watershed areas→WMHs, “disconnect syndrome”
- ❑ Neurotransmission distorted by ↑NO, cytokines, quinolinic acid
- ❑ Low brain energy, slow cognitive processing, neuropsychiatric disorders

Clark IA et al. Proposed link between cytokines, nitric oxide and human cerebral malaria. *Parasitol Today*. 1991;7(8):205-7. PMID: 15463497

Nonaka H at al. The microvasculature of the cerebral white matter: arteries of the subcortical white matter. *J Neuropathol Exp Neurol*. 2003;62(2):154-61. PMID: 12578225

Lin J et al. Multiple Factors Involved in the Pathogenesis of White Matter Lesions. *Biomed Res Int*. 2017;2017:9372050. PMID: 28316994

Annals of Tropical Medicine & Parasitology, Vol. 92, No. 4, 483–488 (1998)

Do babesiosis and malaria share a common disease process?

BY I. A. CLARK* AND L. S. JACOBSON

Division of Molecular Biology and Biochemistry, School of Biological Sciences, Australian National University, Canberra, ACT 0200, Australia

Received and accepted 2 October 1997

Clinical confusion between human babesiosis and malaria is often reported in the literature. Headache, fever, chills, nausea, vomiting, myalgia, altered mental status, disseminated intravascular coagulation, anaemia with dyserythropoiesis, hypotension, respiratory distress, and renal insufficiency are common to both diseases. This remarkable similarity is not restricted to the human host. In the mouse, for example, the histological changes wrought by fatal malaria (*Plasmodium vinckei*) and babesiosis (*Babesia rhodaini*) are identical, and parasites of both genera cross-protect. Malarial disease pathogenesis is now generally associated with excessive production of pro-inflammatory cytokines, such as tumour necrosis factor. While this concept has not yet been examined in babesiosis, indirect evidence arises from noting the parasite density at which illness occurs in primary infections caused by either organism. Naive mice tolerate high loads of malarial or babesial parasites before they become ill, and are also tolerant to endotoxicity, which is mediated by these same cytokines. In contrast, humans require very much smaller loads of *Plasmodium* or *Babesia* spp. before becoming ill, and likewise are very sensitive to endotoxin, the harmful effects of which are mediated by the pro-inflammatory cytokines. For these reasons, as discussed in this review, the diseases caused by these two genera of intra-erythrocytic protozoan parasites will probably prove to be conceptually identical.

Clark IA et al. Do babesiosis and malaria share a common disease process? *Ann Trop Med Parasitol*. 1998;92(4):483-8. PMID: 9683899

Review TRENDS in Parasitology Vol.23 No.12

Shared features in the pathobiology of babesiosis and malaria

Peter J. Krause[1], Johanna Daily[2], Sam R. Telford[3], Edouard Vannier[4], Paul Lantos[2] and Andrew Spielman[2*]

[1] University of Connecticut School of Medicine, 263 Farmington Avenue, Farmington, CT 06030, USA
[2] Harvard School of Public Health, 677 Huntington Avenue, Boston, MA 02115, USA
[3] Tufts University School of Veterinary Medicine, 200 Westboro Road, North Grafton, MA 01519, USA
[4] Tufts-New England Medical Center, 750 Washington Street, Boston, MA 02111, USA

The pathobiology of malaria has been extensively studied in humans but many questions remain, especially regarding fulminant disease associated with *Plasmodium falciparum* infection. Babesiosis, recognized since biblical times as an important disease of livestock and more recently as an emerging health problem in humans, is caused by related intraerythrocytic protozoa with a similar pathogenesis and clinical course. Recent studies of cytokine activation and erythrocyte cytoadherence in babesiosis and malaria have exploited these similarities to provide new insights into malaria pathobiology. Continued investigation of similarities and differences in the pathogenesis of babesiosis and malaria should lead to additional fundamental insights for both conditions.

A tale of two diseases

Malaria is a significant cause of morbidity and mortality in humans. Although the pathobiology of this group of disease[illegible] changes that begin immediately after pathogen transmission. We shall focus on two fundamental pathogenic mechanisms thought to be of central importance in the pathobiology of these infections: (i) erythrocyte cytoadherence; and (ii) the host proinflammatory cytokine response to infection.

Asymptomatic infection

During the first few weeks following infection by *Babesia* or *Plasmodia* spp. in humans, no symptoms are apparent. The parasites initially undergo silent development, the burden within the vasculature has not yet become heavy and the host inflammatory response has not yet developed. Chronic infection tends to be asymptomatic when endogenous mechanisms limit the pathogen load and the immunopathologic response [4]. Asymptomatic *Plasmodium* infection is common in highly endemic areas where reinfection is frequent and people remain persistently infected. Human babesiosis, a zoonotic infection owing mainly to [illegible]

Krause PJ et al. Shared features in the pathobiology of babesiosis and malaria. *Trends Parasitol*. 2007;23(12):605-10. PMID: 17988944

Can *Babesia* Infections be used as a Model for Cerebral Malaria?

T.P.M. Schetters and W.M.C. Eling

Infections with certain species of Plasmodium *and* Babesia *induce, among other symptoms, cerebral pathology. The finding of heavily parasitized cerebral capillaries upon post-mortem examination has led to the assumption that blockage of capillaries with infected red blood cells caused the cerebral symptoms and subsequent death. As this type of cerebrovascular pathology is found both in humans dying from malaria and in cattle dying from babesiosis, the latter could possibly be used as an animal model for the study of human cerebral malaria. However, before such a model system is adopted, the experimental data concerning cerebral pathology of babesiosis needs critical evaluation. Here, Theo Schetters and Wijnand Eling review the pathological mechanisms in cerebral babesiosis and relate these to cerebral malaria. Finally, they discuss the use of animal model systems for specific aspects of the pathological picture.*

Malaria and babesiosis are diseases caused by blood protozoans that proliferate in the red blood cells of the host. The parasites are transmitted by arthropod vectors: malaria parasites by mosquitos, *Babesia* parasites by ticks. There appear to be many similarities between the manifestations of these diseases, which vary from uncomplicated to severe disease that is sometimes accompanied by symptoms suggestive of involvement of the brain – cerebral malaria (CM) and the infected animals. Exact figures are not available, but less than 0.1% of 1200 African dogs assessed for rabies over a period of three years (that had died with cerebral pathology) showed massive accumulation of infected erythrocytes in the brain[7], which is suggestive of a low incidence. In a study of cerebral pathology in cattle, only 8% of the animals had babesiosis, of which only 10% exhibited heavily parasitized capillaries[8]. However, because of this low incidence and the fact that few studies have analysed CB, one should be careful in concluding that other *Babesia* species do not cause CB. Some *Babesia* species also parasitize humans. These include *B. microti*, *B. divergens*[9], the recently described strain WA1 from the USA[10], and possibly *B. bovis*[9]. None of the ensuing infections developed into cerebral disease; infected subjects suffered from high parasitaemias and eventually developed multiple organ failure[11]. However, only when relatively large numbers of cases have been studied will it become clear whether CB can occur in humans.

Disturbance of brain function

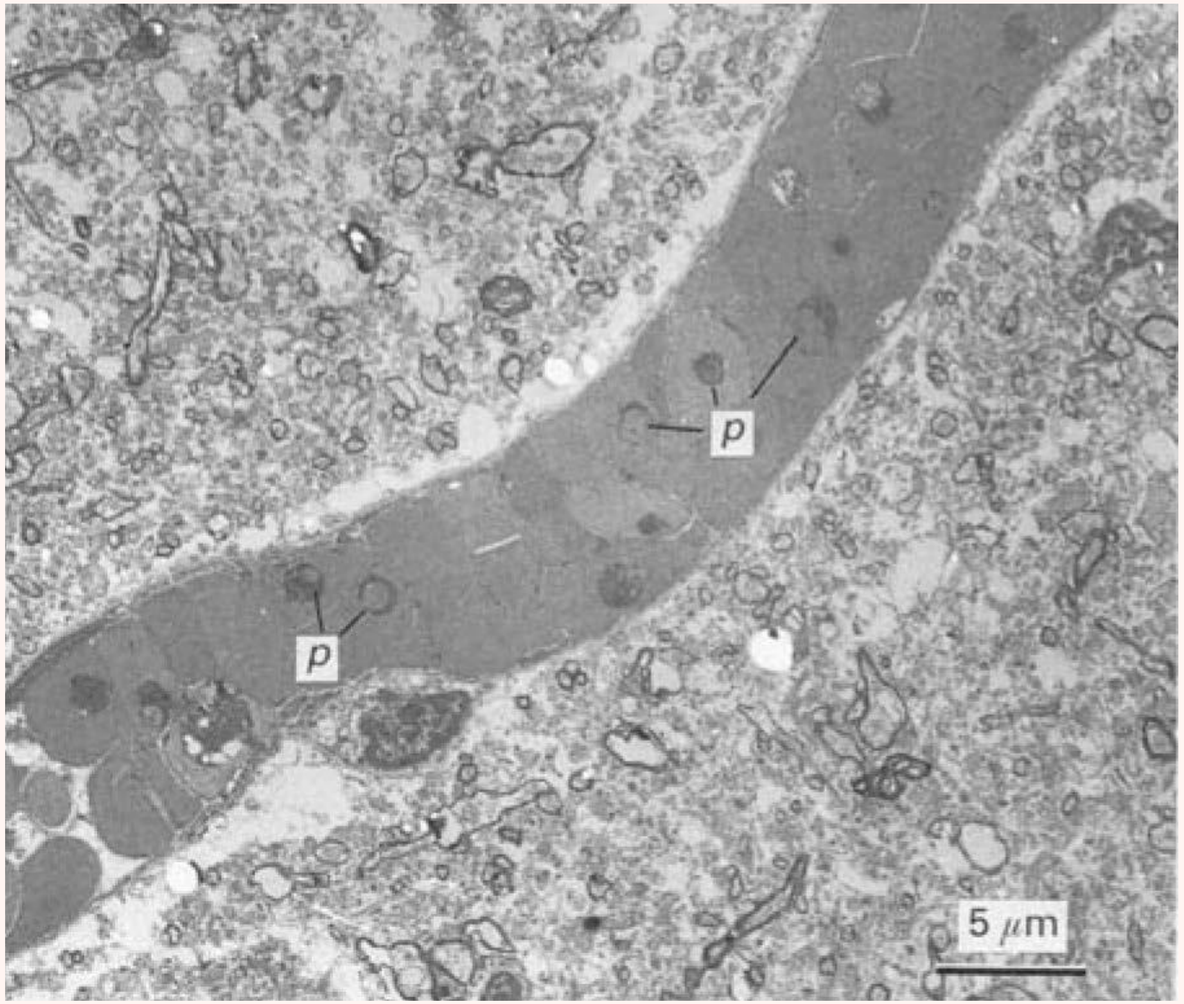
The criteria for diagnosing CM and for estimating the severity of the disease are generally accepted[1]. This is not the case for CB. Nervous symptoms that are reported vary from odd behaviour to paralysis and

Schetters TP et al. Can *Babesia* infections be used as a model for cerebral malaria? *Parasitol Today*. 1999;15(12):492-7. PMID: 10557150

PLASMODIUM FALCIPARUM ALSO SEQUESTERS

Brain biopsy: patient died from cerebral malaria

Extensive brain sequestration→coma



Venule packed with IEs(p) and UEs

Berendt AR et al. Molecular mechanisms of sequestration in malaria. *Parasitology*. 1994;108 Suppl:S19-28. PMID: 8084651

P. FALCIPARUM ALSO CAUSES CHRONIC DISEASE

P. Falciparum **also produces chronic infestation.**

Kenya and Uganda: 30 to 50% of school children have chronic malaria→↓'d sustained attention and abstract reasoning: chronic cerebral malaria

Treatment improves school performance and reduces absenteeism.

POLICY FORUM

"Asymptomatic" Malaria: A Chronic and Debilitating Infection That Should Be Treated

Ingrid Chen[1], Siân E. Clarke[2], Roly Gosling[1]*, Busiku Hamainza[3], Gerry Killeen[4,5], Alan Magill[6], Wendy O'Meara[7], Ric N. Price[8,9], Eleanor M. Riley[10]

Summary Points

- Are afebrile malaria infections truly asymptomatic, benign, or even beneficial to the individual? The evidence suggests the contrary.
- So-called "asymptomatic" malaria infections are associated with recurrent episodes of symptomatic parasitemia, chronic anemia, maternal and neonatal mortality, co-infection with invasive bacterial disease, cognitive impairment, and ongoing transmission of the parasite.
- "Asymptomatic" malaria infections have significant health and societal consequences, and we propose that they should be renamed "chronic" malaria infections.
- Targeting chronic malaria infections poses major scientific, operational, and ethical challenges.
- We call for the malaria community to work with malaria control and elimination programs to target all malaria infections, irrespective of their density or presentation. The operational challenges to detect and treat chronic infections are significant, but accomplishing this is likely to result in substantial gains to both the individual and society.

Chen I et al. "Asymptomatic" Malaria: A Chronic and Debilitating Infection That Should Be Treated. *PLoS Med*. 2016;13(1):e1001942. PMID: 26783752
Nankabirwa J et al. Asymptomatic Plasmodium infection and cognition among primary schoolchildren in a high malaria transmission setting in Uganda. *Am J Trop Med Hyg*. 2013;88(6):1102-8. PMID: 23589533

CHRONIC MALARIA

A CLINICAL CONSIDERATION

GEORGE H. FONDÉ, M.D.
AND
EDGAR C. FONDÉ, M.D.
MOBILE, ALA.

Malaria is a chronic disease, not alone an infection of the blood stream characterized by chills and fever. Failure to comprehend or detect its insidious course and its strong tendency to relapse, even after months or years, accounts for the fact that it still ranks as one of the serious social and economic problems. Some authors [1] have recognized the persistent and prolonged course of malaria; nearly all acknowledge it to be the most widespread and destructive of tropical diseases. Because in its chronic form it is generally disguised, the problem of control is doubly hard to master.

We are not concerned here with early "classic" forms of malaria. These conditions constitute the minority and are largely limited to well known regions; they offer little or no difficulty in diagnosis and are easily controlled, temporarily at least, by specific treatment. Moreover, in these early infections plasmodia can usually be demonstrated (except in hyperpyrexial, cerebral and "blackwater" forms).[2]

On the other hand, in dealing with chronic malaria the physician is confronted with a complex problem. In this stage the disease is not easy to recognize, and it is difficult to demonstrate the parasite. The chronic infection is generally masked under syndromes closely resembling a number of common local and systemic diseases. In all cases it tends to become asymptomatic, whether treated or not, during some phase of its course.

INCIDENCE

First, it should be pointed out that there are no geographic limitations to the chronic forms of malaria, as contrasted to early typical infections, which are largely confined to endemic zones. From a study of 10,000 malarial patients in the dispensaries of Odessa, U. S. S. R., Korovitskiy [3] concluded that chronic malaria does exist in temperate

From 1939: Best description of the clinical presentation, diagnosis and treatment of chronic malaria including use of diagnostic/therapeutic trial of antimalarial medication

Perfectly applicable to chronic babesiosis!

Fondé, GH, Fondé EC. Chronic Malaria: A Clinical consideration. *Arch Intern Med (Chic)*. 1939; 64(6):1156-1169. doi:10.1001/archinte.1939.00190060025002

A TALE OF TWO DISEASES

- **Acute Babesiosis: known to CDC/IDSA**
  - **Easy to diagnose: Fever, hemolysis, high parasitemia→positive blood smear**
  - **Easy to treat: Antimicrobials speed resolution of parasitemia, acute illness**
  - **Rare: Adults—often asplenic, immunocompromised**
  - **Resolves: with elimination of parasites (*B. microti*) or chronic infection (*B. odocoilei*)**
- **Chronic Babesiosis: unknown to CDC/IDSA**
  - **Hard to diagnose: Negative blood smears, FISH; No *B. odocoilei* antibody or PCR test**
  - **Hard to treat: Isolated from antimicrobials in capillary/venule nests**
  - **Common: Immunocompetent hosts, transmitted by larvae (5% or more the human population)**
  - **Chronic symptoms/disability determined by 1. Babesia load, 2. Host immune reaction**

SIGNS AND SYMPTOMS OF CHRONIC BABESIOSIS

DIRECT EFFECTS OF NESTS

FATIGUE: Energy in AM only (ATP depletion)

Poor stamina/recovery—mental/physical

Slow/impaired cognition: memory/intellect intact

Gastrointestinal anergy—bloating, nausea, constip.

Hypotension/edema—POTS, heart racing

Appetite—reduced or excessive

Hypothermia, cold intolerance

IMMUNE-MEDIATED EFFECTS

Night sweats, low-grade fever

Shortness of breath, air hunger

Psychiatric: Anxiety, anhedonia, depression, anger, tearfulness, nightmares, hallucinations

Neurological: delirium, numbness, weakness, headache (pressure), pains, insomnia, visual sxs.

Mast cell activation: flushing, hives, etc.

In children presentation often psychiatric*
Immune-mediated symptoms may appear only with treatment (herxing)

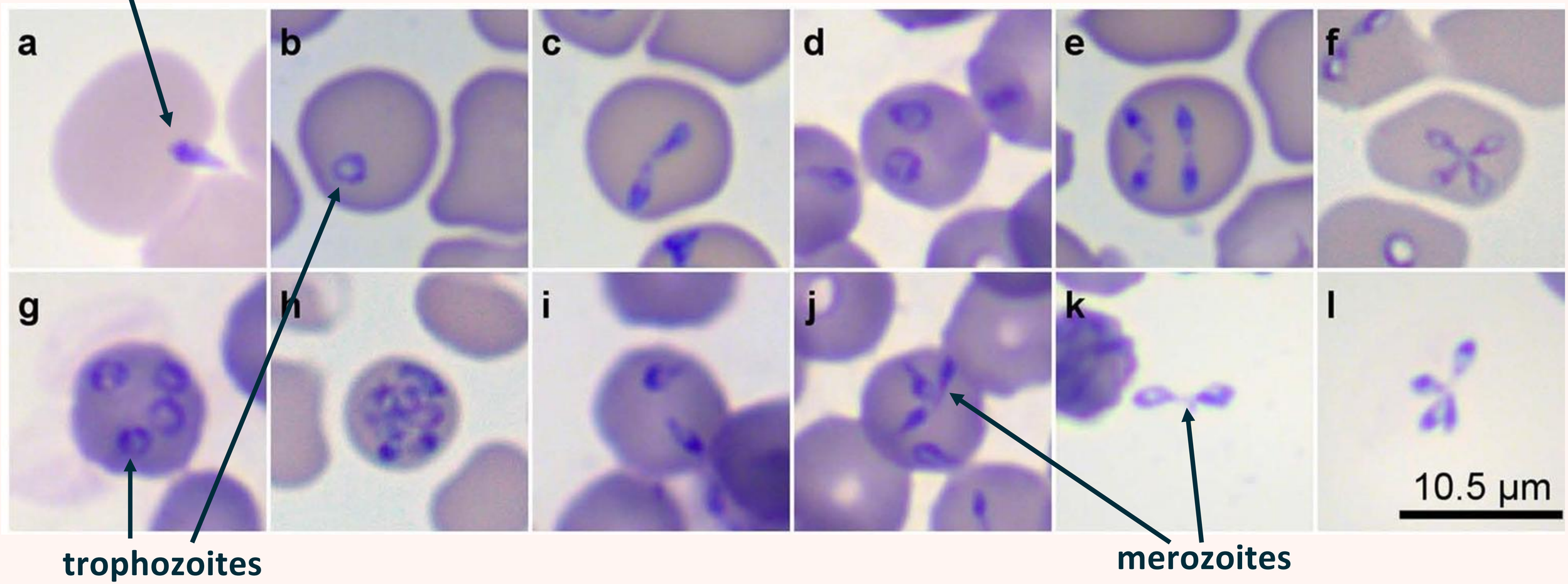
*Greenberg R. Infections and Childhood Psychiatric Disorders: Tick-Borne Illness and Bipolar Disorder in Youth. *Bipolar Disord.* 2017; 3: 113. doi: 10.4172/2472-1077.1000113

TESTING FOR CHRONIC BABESIOSIS

- ❑ CBC, CMP, ESR, CRP usually normal, may have ↓CD57 (NK cells), ↑C4a
- ❑ Hard to find in venous blood by microscopy or non-specific FISH. NO PCR available.
- ❑ IGeneX: +FISH or *B. duncani* antibodies; false negatives the rule
- ❑ TLab: Research-only *B.odocoilei* 18s rRNA FISH, sensitivity unclear

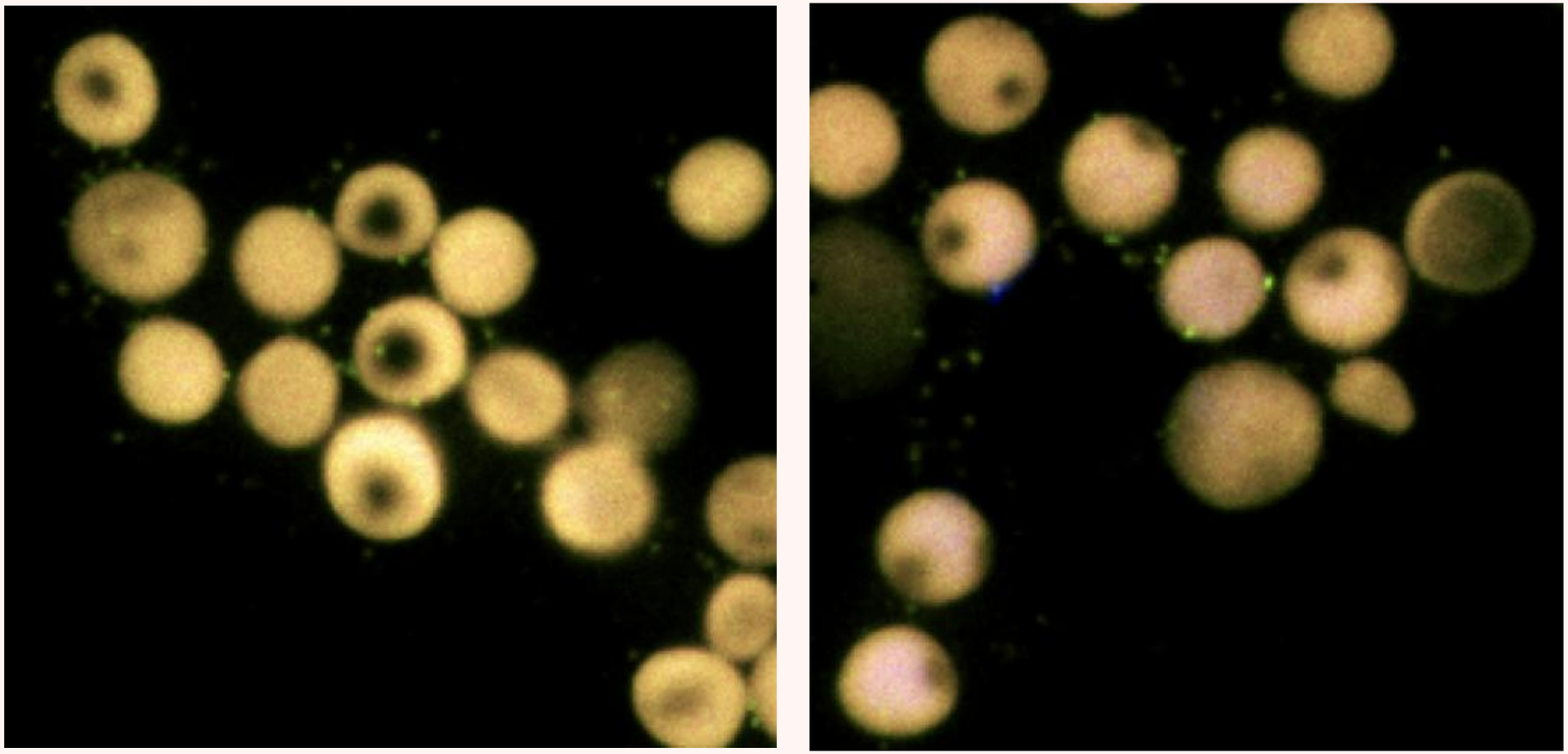
Thomford JW et al. Isolation and in vitro cultivation of Babesia parasites from free-ranging desert bighorn sheep and mule deer in California. *J Parasitol.* 1993;79(1):77-84. PMID: 8437062
Bock R et al. Babesiosis of cattle. *Parasitology*. 2004;129 Suppl:S247-69. PMID: 15938514

MICROSCOPY: *BABESIA DIVERGENS* IN VITRO



Sevilla E et al. Kinetics of the invasion and egress processes of *Babesia divergens*, observed by time-lapse video microscopy. *Sci Rep*. 2018;8(1):14116. PMID: 30237573

PATIENT: *B. ODOCOILEI* 18s rRNA FISH



***Confirmed*: *B. odocoilei* ribosomes in patient's serum after 7 months of Rx**

DIAGNOSIS OF CHRONIC BABESIOSIS

- Clinical judgment: best theory to explain Hx, Sxs, tests
- Exam: hypotension, subcut. edema, splenomegaly (with treatment)
- Historical Clues:
  - Hx of tick bite, tick-borne illness, or exposure to deer ticks (everyone!)
  - Flu-like syndrome after camping/hiking in wooded area; ill ever since
  - Improvement or worsening with NDT/T3, steroids, many medications, herbs, supplements
  - Herxing with herbs, supplements, antibiotics, antimalarials (Affect immune system or babesia)
  - Interminable herxing with Rx for Lyme, Bartonella; No improvement or permanently worse
- Ultimate Criterion: Diagnostic trial of atovaquone, artemisinin/artesunate and/or tafenoquine→improvement followed by herxing

TREATMENT OF CHRONIC BABESIOSIS

- ❑ Small babesia spp. are highly resistant to antimalarials: 1000x > malaria*
- ❑ Need Synergy: atovaquone, azithromycin, artesunate and tafenoquine
- ❑ Ramp up: Add meds at low doses q1-2 weeks or as tolerated, then lumbrokinase
- ❑ Erode/eradicate nests with lumbrokinase, also exercise, shaking, massage
- ❑ Retreat, but don't Stop: in vitro, babesia double every 24hrs if no antimicrobials
- ❑ Gradually increase antimicrobials+lumbrokinase until patient is well, does not herx
- ❑ One to Two years to clear all nests, eradicate all organisms

*Abraham A et al. …*in vitro* culture of *Babesia duncani* in human erythrocytes reveals unusually high tolerance to recommended therapies. *J Biol Chem*. 2018;293(52):19974-19981. PMID: 30463941
Cursino-Santos JR et al. *Babesia divergens* builds a complex population structure composed of specific ratios of infected cells… *Cell Microbiol*. 2016;18(6):859-74. PMID: 26663747

ATOVAQUONE (MEPRON®)

- ❑ Babesiostatic—inhibits protozoal mitochondrial function
- ❑ Babesia-malaria specific: No antibacterial activity. Non-toxic to humans
- ❑ No effect on human mitochondria; “Mepron blues”, “Mepron psychosis” are mental herxing. Patients can take CoQ10.
- ❑ Half-life: 3 days, enterohepatic circulation, excreted unchanged
- ❑ Expensive: $300 for 21 day supply at 1 tsp bid (GoodRx.com)
- ❑ Dose: ½ to 1 tsp bid, increase up to 2 tsps bid if necessary with combination Rx

FDA-approved only for the prevention and treatment of *Pneumocystis jirovecii* pneumonia at 1500mgs/day

Nixon GL et al. Antimalarial pharmacology and therapeutics of atovaquone. *J Antimicrob Chemother*. 2013;68(5):977-85. PMID: 23292347

Srivastava IK et al. Resistance mutations reveal the atovaquone-binding domain of cytochrome b in malaria parasites. *Mol Microbiol*. 1999;33(4):704-11. PMID: 10447880

Fiorillo M et al. Repurposing atovaquone: targeting mitochondrial complex III and OXPHOS to eradicate cancer stem cells. *Oncotarget*. 2016;7(23):34084-99. PMID: 27136895

AZITHROMYCIN (ZITHROMAX®)

- ❑ Babesiostatic: Delayed mode of action—affects progeny
- ❑ Most antibiotics disable the apicoplast→Herxing with doxycycline, ceftriaxone...
- ❑ Prolongs Q-T interval: If risk factors, check EKG before/during treatment. Avoid other Q-T prolonging drugs. Advise magnesium 400mgs/day
- ❑ Causes tinnitus: duration and dose-dependent, use lowest dose necessary
- ❑ Kills gut bacteria: Advise high-dose probiotic mix and *Saccharomyces boulardii*
- ❑ Dose: 250mgs/day, increase to 500 mgs daily if necessary with combination Rx

FDA-approved only for 1-to-5 day courses for infections caused by susceptible bacteria

Peters DH et al. Azithromycin. A review of its antimicrobial activity, pharmacokinetic properties and clinical efficacy. *Drugs*. 1992;44(5):750-99. PMID: 1280567
Goodman CD et al. The effects of anti-bacterials on the malaria parasite *Plasmodium falciparum*. *Mol Biochem Parasitol*. 2007;152(2):181-91. PMID: 17289168
Vanoverschelde A et al. Macrolide-associated ototoxicity:…association of macrolide use with tinnitus and hearing loss. *J Antimicrob Chemother*. 2021:dkab232. PMID: 34312676

ARTESUNATE (ARTE-M®)

- ❑ Babesiocidal: Reacts with iron in RBCs to produce carbon-centered iron radicals
- ❑ Rapid action—kills babesia 1 to 4 hrs after dose, More potent than atov. or azith.
- ❑ Dr. Zhang's 50mg artesunate (Arte-M) caps: $141/mo.@1 tid, $282/mo.@2 tid
- ❑ Artemisinin less expensive, less effective—need up to 400mgs tid
- ❑ Take antioxidants to prevent neurotoxicity, ototoxicity, neutropenia
- ❑ Dose: 1 cap po tid, increase to 2 caps tid if neccessary

FDA-approved for severe malaria by intravenous injection

Karunajeewa HA. Artemisinins: Artemisinin, Dihydroartemisinin, Artemether and Artesunate. *Milestones in Drug Therapy*. 2012;41:157-190 doi: 10.1007/978-3-0346-0480-2_9
Carvalho LJM et al. Activities of artesunate-based combinations and tafenoquine against *Babesia bovis* in vitro and *Babesia microti* in vivo. *Parasit Vectors*. 2020;13(1):362. PMID: 32690081

TAFENOQUINE (KRINTAFEL®)

- ❑ **Babesiostatic/cidal: Most potent antibabesial agent*; similar to mefloquine**
- ❑ **R/O G6PD deficiency to avoid tafenoquine-induced hemolysis**
- ❑ **Methemoglobinemia—asymptomatic at usual doses, causes shortness of breath**
- ❑ **Long-acting: half-life 2 weeks, accumulates for 3 mos with weekly dosing**
- ❑ **Expensive: often not covered; $40 for 300mgs @GoodRx.com**
- ❑ **Dose: Start 150mgs/wk, ↑to 300mgs/wk; if > 80kgs: 450mgs/wk**

FDA-approved for the treatment of *Plasmodium vivax* malaria in patients aged 16 years and older who are receiving chloroquine therapy

*Mordue DG, Wormser GP. Could the Drug Tafenoquine Revolutionize Treatment of *Babesia microti* Infection? *J Infect Dis*. 2019;220(3):442-447. PMID: 31099380

Walsh DS et al. Randomized trial of 3-dose regimens of tafenoquine (WR238605)…for preventing *Plasmodium vivax* malaria relapse. *Clin Infect Dis*. 2004;39(8):1095-103. PMID: 15486831

Youngster I et al. Medications and glucose-6-phosphate dehydrogenase deficiency: an evidence-based review. *Drug Saf.* 2010;33(9):713-26. PMID: 20701405

OTHER ANTI-BABESIAL DRUGS AND HERBS

- **Clindamycin+Quinine: Not more effective than Mepron/Zithro, ↑adverse effects**
  FDA approved for susceptible anaerobic bacterial infections and for Plasmodium falciparum malaria, respectively
- **Malarone® (atovaquone 250mgs+proguanil 100mgs) Weak, more side effects**
  1 tab bid for insurance-covered suppression FDA approved for 3 day-course for *Plasmodium falciparum* malaria
- **Coartem® (artemether 20mgs+lumefantrine 120mgs*)** FDA approved for 3 day-course for *Plasmodium falciparum*
- **Dapsone: Anti-malarial, SE's—hemolysis, methemoglobinemia, rash, fever Can't combine with tafenoquine.** FDA-approved for dermatitis herpetiformis and leprosy
- **Disulfiram: Anti-malarial, clinically effective, neuro SEs** FDA-approved for alcoholism
- **Allicin (garlic-allitridi): safe, Dr. Zhang's Allicin up to 2 caps tid, Allimed 1 cap tid**
- **Herbals: Cryptolepis, ECGC, Berberine, Chinese Skullcap, Japanese Knotweed**

Krause PJ et al. Atovaquone and azithromycin for the treatment of babesiosis. *N Engl J Med*. 2000;343(20):1454-8. PMID: 11078770
Scheibel LW et al. Tetraethylthiuram disulfide (Antabuse) inhibits the human malaria parasite *Plasmodium falciparum*. *Proc Natl Acad Sci U S A*. 1979;76(10):5303-7. PMID: 388434
Liegner KB. Disulfiram (Tetraethylthiuram Disulfide) in the Treatment of Lyme Disease and Babesiosis: Report of Experience in Three Cases. *Antibiotics (Basel)*. 2019;8(2):72. PMID: 31151194
Salama AA et al. Inhibitory effect of allicin on the growth of *Babesia* and *Theileria equi* parasites. *Parasitol Res*. 2014;113(1):275-83. PMID: 24173810
Zhang Y et al. Botanical Medicines…Demonstrate Inhibitory Activity Against *Babesia duncani*. *Front Cell Infect Microbiol*. 2021;11:624745.PMID: 33763384

LUMBROKINASE

- ❑ Worm-derived enzymes that lyse fibrin
- ❑ Required to break up *B. odocoilei* nests; allow antibabesials to enter nests
- ❑ Extensively studied—especially Boluoke®
  - ❑ Orally active, 10% absorption with delayed-release caps, must take on empty stomach
  - ❑ Does not alter hemostasis
- ❑ 30x stronger than nattokinase, 300x > than serropeptidase (t-PA activity per mg)
- ❑ Expensive: $200/mo. for Boluoke® or ARG @ 2 caps tid, can try cheap brands, ↑dose
- ❑ Dose: 1 cap po tid, increase as tolerated to 2 caps tid or more (4 caps tid reported)

No FDA approved form—an over-the-counter supplement.

Cooper EL et al. Earthworms: sources of antimicrobial and anticancer molecules. *Adv Exp Med Biol*. 2004;546:359-89. PMID: 15584386

Verma MK et al. Lumbrokinase – A Potent and Stable Fibrin–Specific Plasminogen Activator. *IJBSBT*. 2011;3(2):57-70. https://www.researchgate.net/publication/236264109

Hemostasis Ref. Lab. Inc., Ontario Canada, 2011, cited by Kwok M. *Townsend Letter*, May 2018

Tjandrawinata RR et al. The Safety and Tolerability of Lumbrokinase DLBS1033 in Healthy Adult Subjects. *Drug Res (Stuttg)*. 2016;66(6):293-9. PMID: 27011386

THE PATHOPHYSIOLOGY OF BABESIA HERXING

- ❑ Jarisch-Herxheimer reaction seen with Rx of syphilis—exposure of hidden bacteria
- ❑ Classic J-H: Brief immune reaction (TNF-α, IL-2…) to death of all organisms
- ❑ Chronic babesiosis: Large number of parasites isolated in nests; few killed at a time
- ❑ Immune reaction increases whenever babesia are exposed or killed.
- ❑ Amount and duration of herxing depend upon babesia load, aggressiveness of Rx
- ❑ Severity of Herxing = Pt's immune reactivity X No. of exposed organisms

Butler T. The Jarisch-Herxheimer Reaction After Antibiotic Treatment of Spirochetal Infections… *Am J Trop Med Hyg*. 2017;96(1):46-52. PMID: 28077740

Akel T, Mobarakai N. Hematologic manifestations of babesiosis. *Ann Clin Microbiol Antimicrob.* 2017;16(1):6. PMID: 28202022

Ramos-Casals M et al. Adult haemophagocytic syndrome. *Lancet*. 2014;383(9927):1503-1516. PMID: 24290661

HERXING EVERYWHERE

- Babesia are everywhere→herxing symptoms/dysfunction in every tissue and organ
- Typical babesia signs/symptoms either worsen or appear for first time
- Especially with treatment: Dysgeusia—food tastes terrible, petechiae, acneiform eruption, meningeal and icepick headaches, nightmares, perceptual distortions
- Psychiatric Herxing: anger, irritability, violent/suicidal ideation, anxiety, mental pain, hallucinations, etc. (Autoimmune? Bartonella-related?)
- Not side effects of antibabesials! Proof: Different agents cause same symptoms

THERAPEUTIC PROCESS: HERXING AND IMPROVEMENT

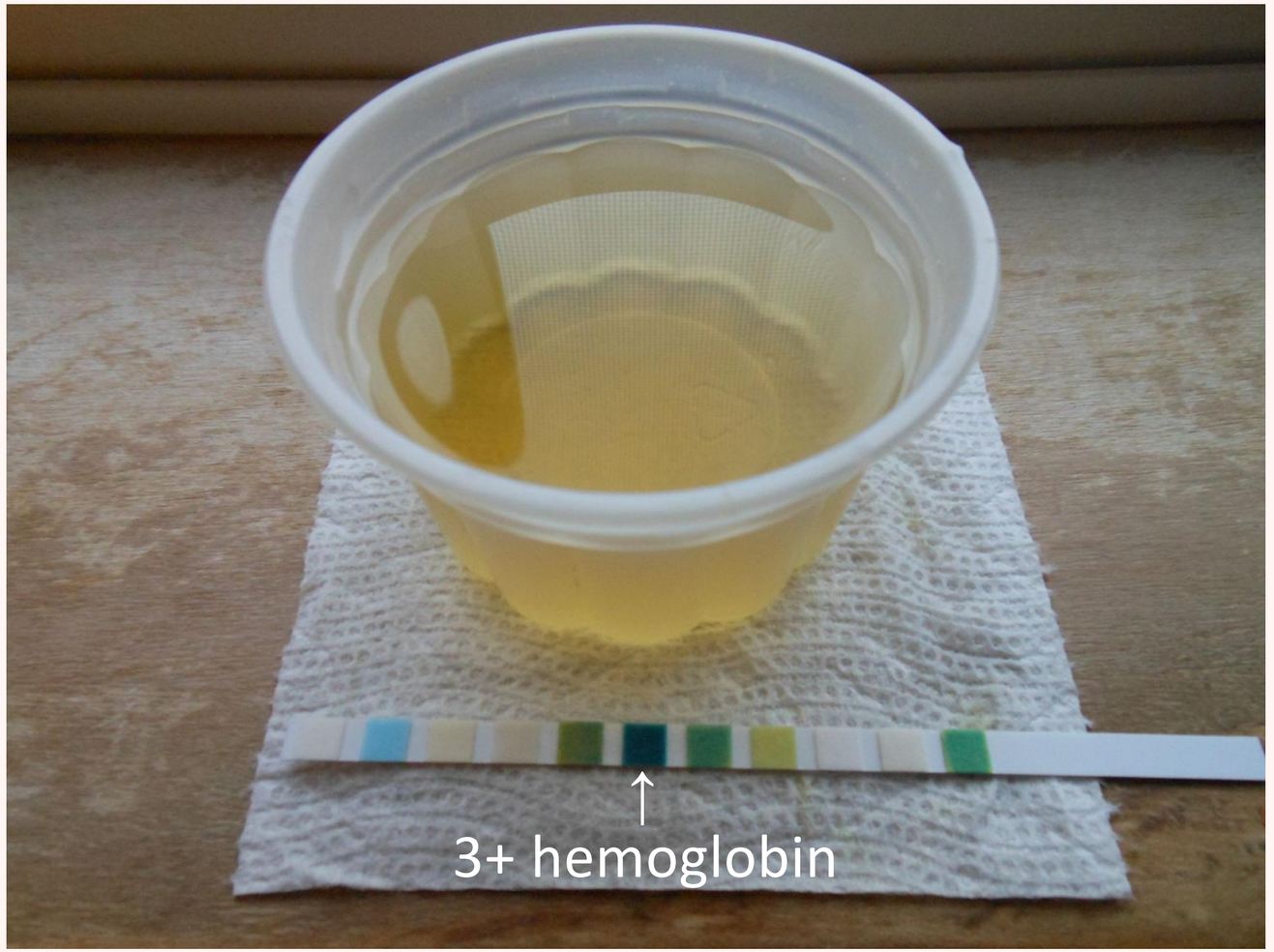
- ❑ Patients often worse for weeks/months before improving. Stamina improves first.
- ❑ Some symptoms disappear even as patient continues to suffer from herxing.
- ❑ Effective treatment lowers babesia load; Ineffective treatment→herxing forever
- ❑ Persistent herxing: Increase/add agents→↑'d herxing short term, ↓'d long term
- ❑ Clearing nests with lumbrokinase: ↑↑babesia die-off, ↑↑immune reaction (herxing), ↑↑inflammation, ↑↑hemolysis→→IMPROVEMENTS!!
- ❑ Ascending saw-tooth pattern: More aggressive treatment→more herxing→more improvements and less herxing, allowing more aggressive treatment...

HEMOLYSIS, HEMOGLOBINURIA, PIGMENTURIA

- ❑ Killing Babesia→lysis of IEs, also many more UEs (bystander phenomenon)
- ❑ High Babesia load→↑'d hemolysis, hemolytic anemia
- ❑ Clearing nests→↑↑hemoglobinuria, proteinuria and pigmenturia (nest detritus)
- ❑ For severe hemolysis: Stop lumbrokinase, lower antibabesials
- ❑ Free hemoglobin is oxidative, depletes NO→painful smooth muscle spasms in esophagus, intestines. Rx: oral citrulline 3gms bid or tid
- ❑ No kidney injury with sufficient hydration and antioxidants

Rother RP et al. The clinical sequelae of intravascular hemolysis and extracellular plasma hemoglobin: a novel mechanism of human disease. *JAMA*. 2005;293(13):1653-62. PMID: 15811985
Zager RA. Rhabdomyolysis and myohemoglobinuric acute renal failure. *Kidney Int*. 1996;49(2):314-26. PMID: 8821813

PATIENT: HEMOGLOBINURIA



-Pigment, -Protein

AMBER PIGMENT FROM YOUNG NESTS

After 1 week on lumbrokinase

Acidic pH, red color suggests iron; detritus from younger capillary/venule nests

2+Heme, 1+Protein

GREEN-BLACK PIGMENT FROM OLD NESTS

After 4 weeks on lumbrokinase

Rancid odor—like old blood, alkaline pH

4+Heme, 2+Protein

NEUROPSYCHIATRIC CHANGES WITH TREATMENT

- Heavy infestation of brain in some patients
- Brain adapts to chronic ischemia, inflammation and altered neurotransmission
- Die off in brain→inflammation, BBB leakage→confusion, transient neurological sxs
- Reduction in load→improved blood flow and connectivity, reduced inflammation
- Brain configuration changes→derealization, perceptual distortions
- Slow rewiring/adaptation: Eventually functions better in healthier configuration

BABESIA TREATMENT CAUTIONS

- ❑ High Babesia loads in patients treated with corticosteroids for Dxs: AE, MS, RA, etc.
- ❑ Aggressive RX→large/rapid die off→severe acute babesiosis (fever, hemolytic anemia, inflammation), possible hemophagocytic syndrome
- ❑ If Babesia- or Bartonella-related autoimmunity—Rx will worsen it until Babesia or Bartonella load is much reduced
- ❑ If autoimmune encephalitis or myelitis (anti-myelin antibodies)—Hx of "MS"—aggressive Rx can cause acute disseminated encephalomyelitis (ADEM)

Auerbach M et al. Systemic babesiosis. Another cause of the hemophagocytic syndrome. *Am J Med*. 1986;80(2):301-3. PMID: 3946448
Schwarz S et al. Acute disseminated encephalomyelitis: a follow-up study of 40 adult patients. *Neurology*. 2001;56(10):1313-8. PMID: 11376180

SUPPORTIVE MEASURES

- ❑ **Antioxidants to protect liver and kidneys, reduce inflammation: Vitamins C, D & E; N-acetylcysteine, astaxanthin, alpha-lipoic acid**
- ❑ **Alka-Seltzer Gold to correct acidosis**
- ❑ **Hydrocortisone/prednisone for very ill and/or autoimmune patients:**
  - ❑ **Correct relative hypocortisolism (prostration, malaise, nausea, etc),**
  - ❑ **Control inflammation—reduce cytokines, tissue damage**
  - ❑ **Tolerate Treatment: Some may require very high steroid doses temporarily!**
  - ❑ **Patient-controlled: Dose rises with die-offs, drops with load reduction by antimicrobials.**
  - ❑ **Include DHEA (sublingually), mitigates steroid harms, may cause ↑herxing**
  - ❑ **Does not prevent eradication: Sufficient antimicrobials kill organisms***

Padayatty SJ et al. Vitamin C as an antioxidant: evaluation of its role in disease prevention. *J Am Coll Nutr*. 2003;22(1):18-35. PMID: 12569111
*Mordue DG et al. Could the Drug Tafenoquine Revolutionize Treatment of *Babesia microti* Infection? *J Infect Dis*. 2019;220(3):442-447. PMID: 31099380

SUPPRESSION VS. ERADICATION

- ❑ Eradication requires artemisinin/artesunate, tafenoquine and lumbrokinase.
- ❑ Eradication is a major medical intervention if high load, reactivity, autoimmunity
- ❑ Atovaquone/azithromycin or Malarone® reduce load, suppress proliferation; Cannot cure
- ❑ Consider indefinite/intermittent suppression or non-treatment if patient:
  - ❑ Is sufficiently functional
  - ❑ Cannot afford to herx—must work, care for children
  - ❑ Is too ill to tolerate eradication, has severe infection-related autoimmunity
  - ❑ Cannot afford eradication ($$)

MONITORING TREATMENT

- ❑ Regular Report from patient: Current doses, change in sxs, overall status
- ❑ Patient monitors urine with multistix for pigment, hemoglobin, protein, bilirubin
- ❑ Safety labs: CBC, CMP, others as indicated.
- ❑ Hemolysis Labs: ↑LDH, ↓haptoglobin, ↑reticulocyte count. ↑Ferritin and AST from lysed RBCs. Brisk bone marrow response →↑WBCs, platelets, NRBCs
- ❑ Tafenoquine: assess methemoglobinemia with pulse oximeter; Hold if SpO2 <85%, Restart when ≥95%. Rx: Vit. C (4 to 10gms/d) or methylene blue (50-200mgs po qd)

PATIENT: BARTONELLA ENCEPHALITIS COMPLICATED BY BABESIOSIS

- ❑ @11 days Rx: Marked hemolysis, improved mental/physical stamina, derealization
- ❑ 1 year: Atovaquone, azithromycin, artesunate, and tafenoquine (as tolerated)
- ❑ Addition of lumbrokinase@6mos→↑hemolysis, pigmenturia, more improvements!
- ❑ Needed prednisone at up to 1000mgs/day to tolerate clearing nests with lumbro.
- ❑ Continuous mental/physical herxing, biggest improvements after nest clearing
- ❑ Complications: Hemolytic anemia x5, Transfusion x2, steroid myopathy, osteoporosis
- ❑ @1 year: Lower load, better stamina and cognition, still clearing nests!

NEW APPROACH TO TICKBORNE DISEASE

- ❑ *B. odocoilei* infection is common and very hard to eradicate; probable cause of much "chronic Lyme disease", MSIDS, chronic fatigue, brain fog, anxiety, etc.
- ❑ Larvae transmit only *B. odocoilei*, 40% of adult ticks carry just one organism*
- ❑ WRONG: "Lyme and coinfections", "Lyme+"; Patients need precision Dx/Rx!
- ❑ Tick bite prophylaxis must include antibabesial agent! (e.g., atovaquone)
- ❑ If TBD suspected: Trial of atovaquone: Herxing = Chronic Babesiosis
- ❑ Treat Babesia First: Eliminate nests that harbor Bartonella, Lyme(?)
- ❑ 4-drug regimen kills Bartonella, add doxycycline if Lyme present

Suggestion: Rename "ILADS" as "North American Vector-Borne Zoonoses Society" (NAVZS)

*Livengood J et al. Detection of *Babesia, Borrelia, Anaplasma*, and *Rickettsia* spp. in Adult *Ixodes scapularis* Ticks from Pennsylvania…*Vector Borne Zoonotic Dis*. 2020;20(6):406-411. PMID: 31976829