

Update on Equine Tick-borne Illnesses in the Eastern U.S.

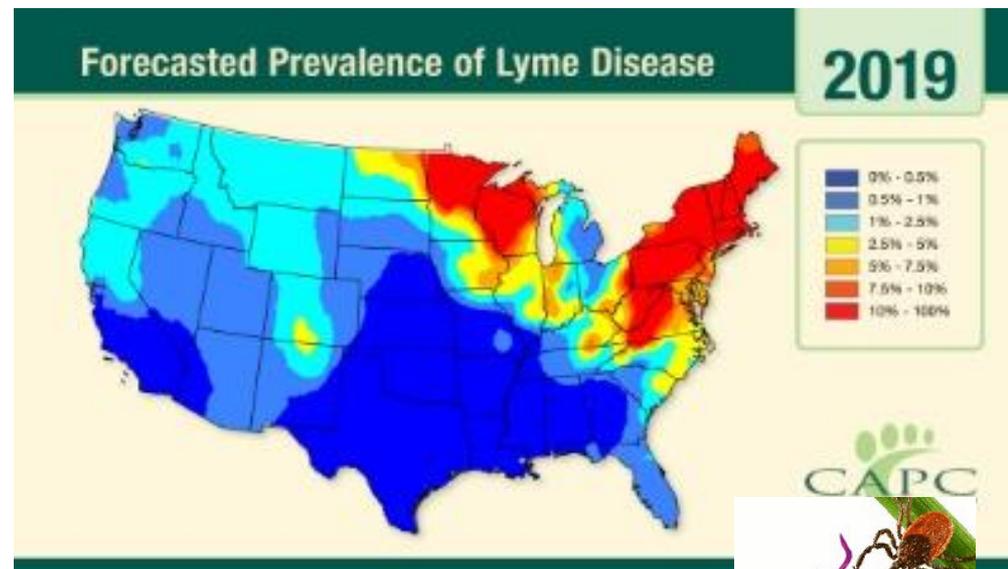
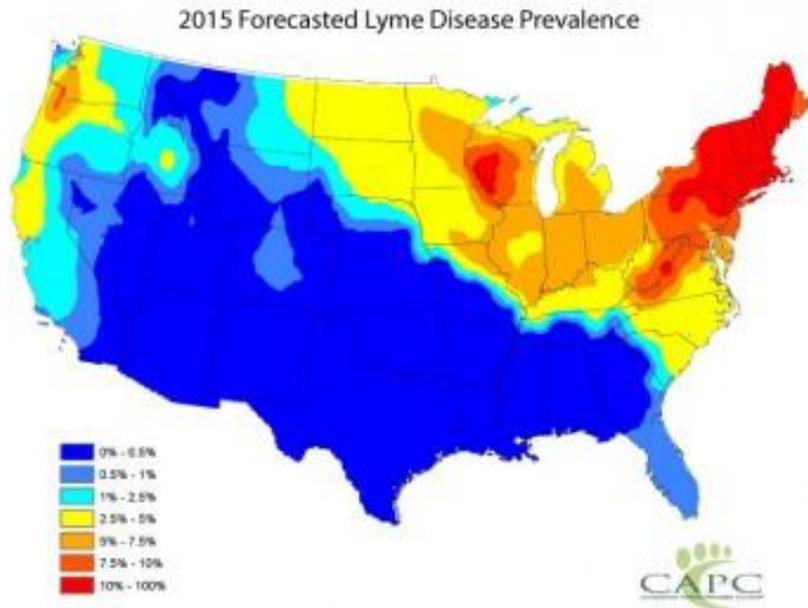


Ixodes scapularis

Lyme Disease
Anaplasmosis
Other Potential TB Pathogens

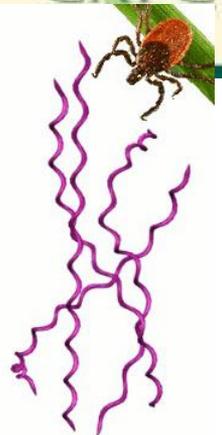


Ixodes Ticks and *B. burgdorferi* infections are Spreading!



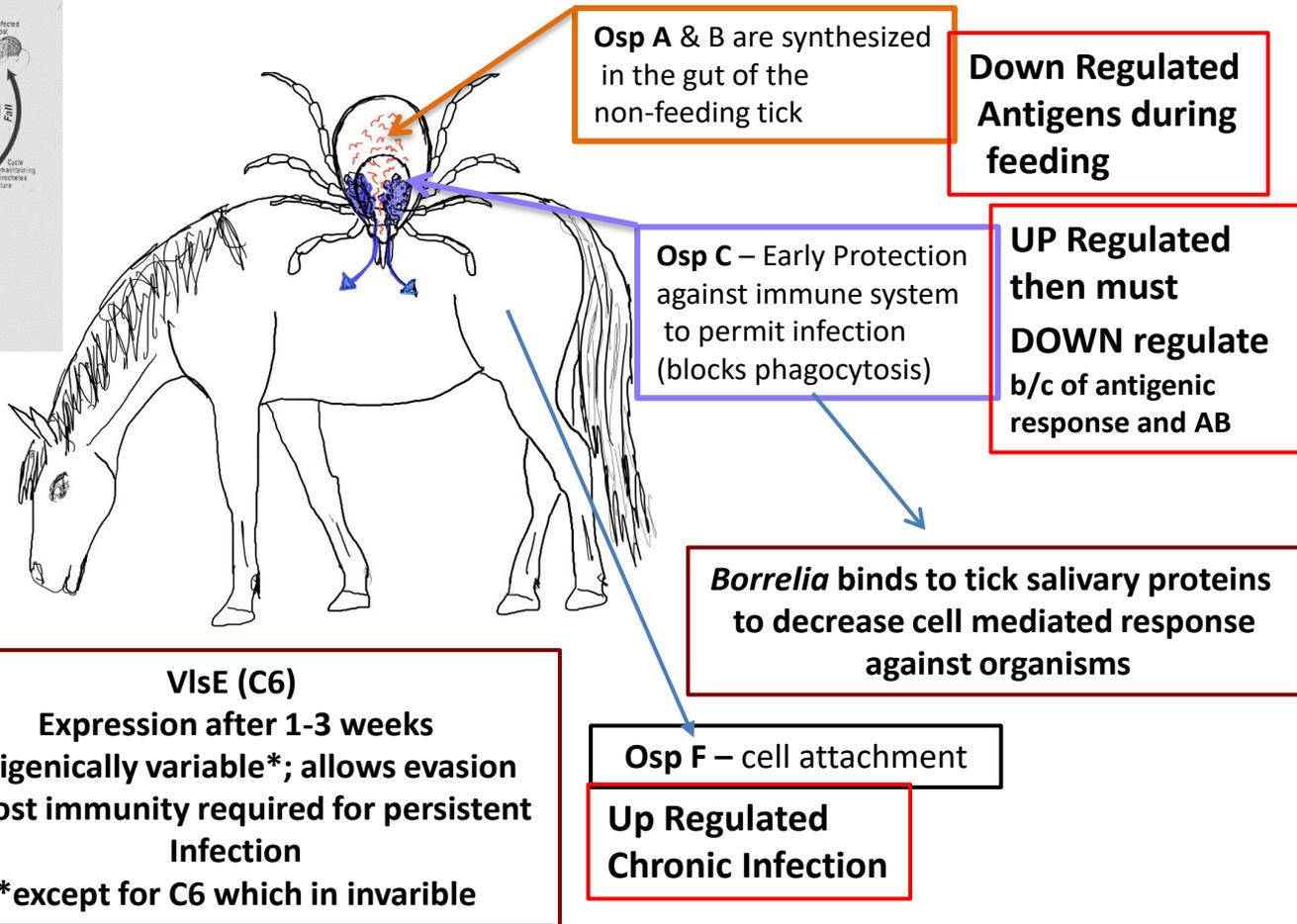
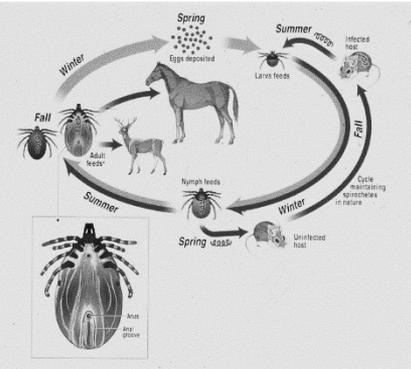
Clinically normal horses living in endemic areas often have detectable antibody levels against *B. burgdorferi*.

Southwest VA – 33% Funk et al. 2016



Borrelia burgdorferi
Lyme disease

Borrelia Infection – Biology of Infection



Clinical Disease

- The best-documented, naturally occurring syndromes attributed to *B. burgdorferi* infection include **neuroborreliosis**, **uveitis**, and **cutaneous pseudolymphoma**.
- A plethora of undocumented clinical signs have been associated with Lyme disease in horses: ***stiffness, behavioral changes, shifting leg or intermittent lameness, muscle wasting and hyperesthesia***
 - *These and other clinical signs often associated with Lyme disease are in need of further experimental and epidemiological evaluation!*

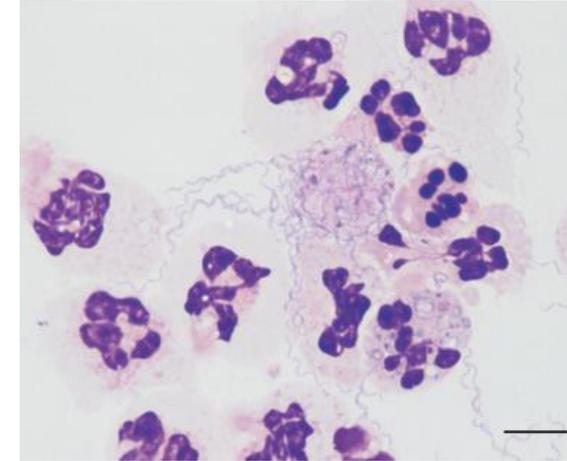


(Nuchal bursitis) Photo courtesy of Dr. Amy Johnson

Not Laminitis!

Lyme Uveitis

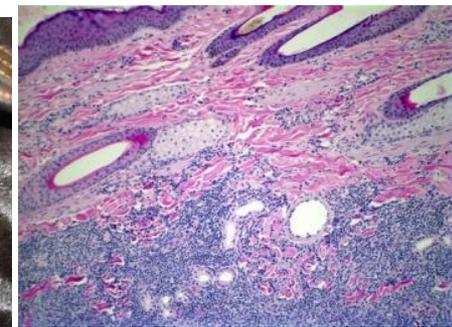
- Generally rapidly progressive with bilateral involvement
- Organism found predominantly in vitreous fluid
- May precede onset of CNS signs



Vet Ophthalmol. 2012

Pseudolymphoma

- Well described
- Site of tick attachment



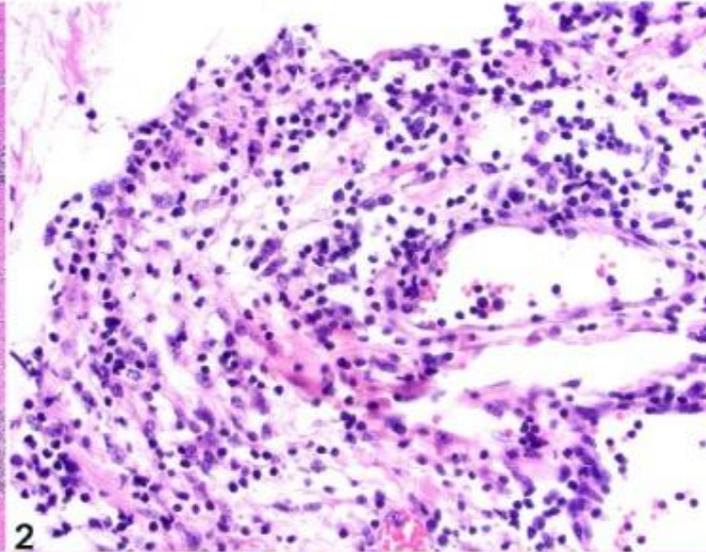
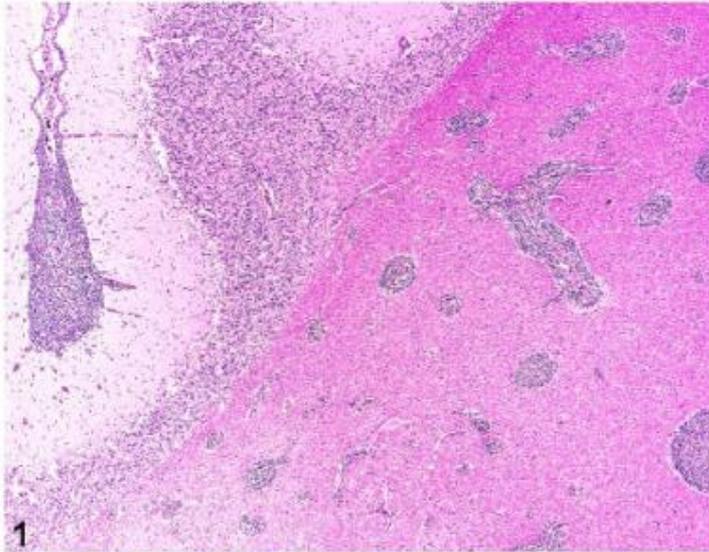
Vet Dermatol. 2011

Clinical Signs Reported with Neuroborreliosis-

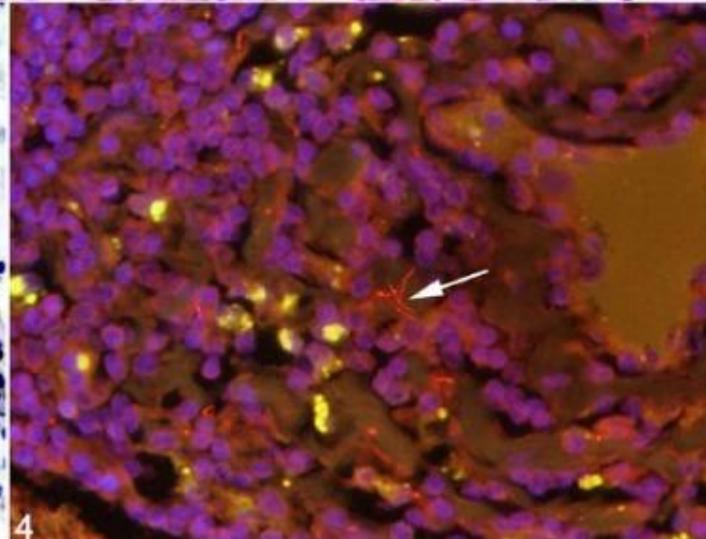
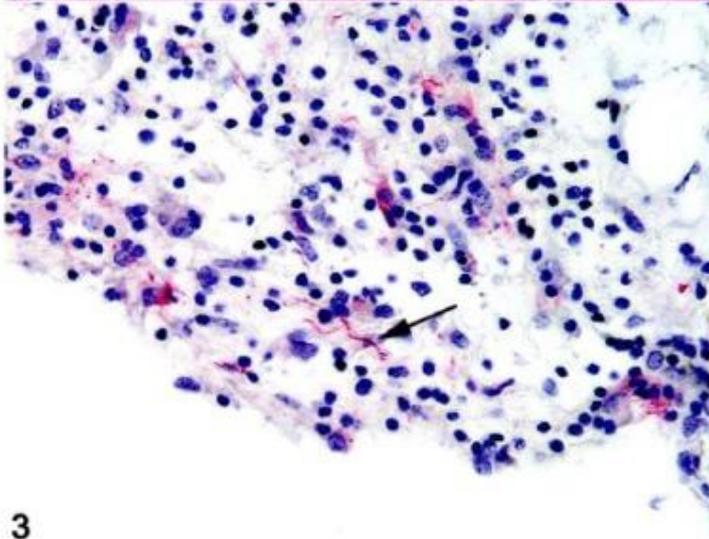
- Muscle atrophy (most commonly spinous muscles)
- Weight loss
- Cranial nerve deficits (VII, IX, X, XII) causing dysphagia, laryngeal dysfunction resulting in respiratory distress, facial paresis, tongue paresis
- Ataxia and paresis
- Change in behavior, including narcolepsy
- Hyperesthesia
- Fasciculations
- Neck* and back stiffness with pain
- Concurrent uveitis

**Some horses are unwilling to lift their head above a horizontal plane.*

Neuroborreliosis in a horse with *common variable immunodeficiency* JVDLI 2019



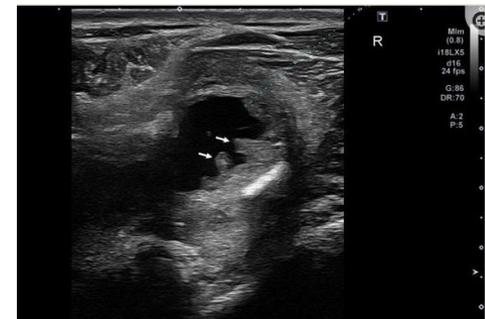
Uveitis
Lymphadenopathy
Narcolepsy



OspA (18), OspC
(15), and OspF (9)
titers

Borrelia Infection and Nuchal Bursitis

- Examined for low head carriage, dull demeanor, and resistance to haltering
- Lyme multiplex assay- OspC and OspF were negative
- **OspA** (24,204 median fluorescent intensity (MFI); RI <2,000 MFI)- horse not vaccinated
- PCR positive bursal fluid



[Case Report: Nuchal Bursitis Associated With *Borrelia burgdorferi* Infection in a Horse.](#)

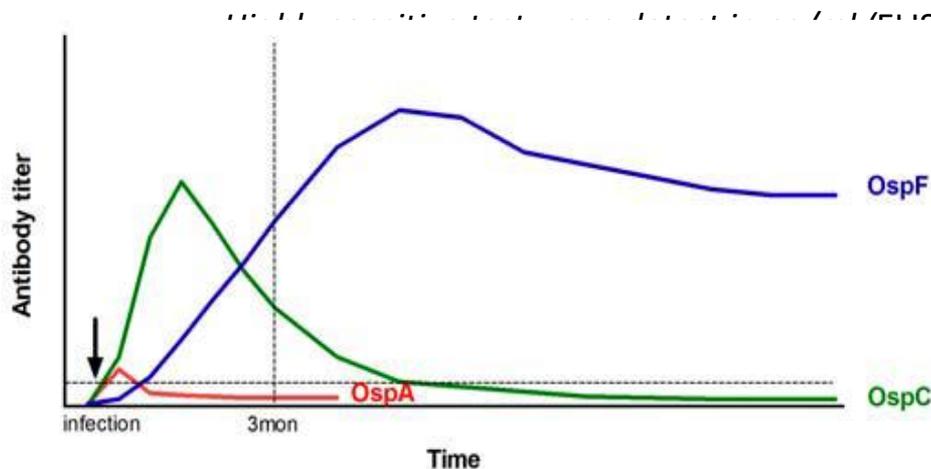
Guarino C, Pinn-Woodcock T, Levine DG, Miller J, Johnson AL. Front Vet Sci. 2021 Sep 23;8:743067

Diagnosis of Lyme Disease: General Remarks

- Definitive diagnosis of clinical Lyme disease in horses is challenging!
- Positive serology merely confirms past exposure or present infection but does not confirm clinical disease.
- Other equine diseases may share similar clinical signs with Lyme disease, making the diagnosis difficult and “*making it likely that Lyme disease is over-diagnosed*” in areas with a high seroprevalence.

Diagnosis of Exposure or Infection- Antibody Testing:

- **Luminex assay** -Development of a multiplex assay for the detection of antibodies to *Borrelia burgdorferi* in horses and its validation using Bayesian and conventional statistical methods. *Wagner B Vet Immunol Immunopathol. 2011*



From: Wagner, EVJ 2013

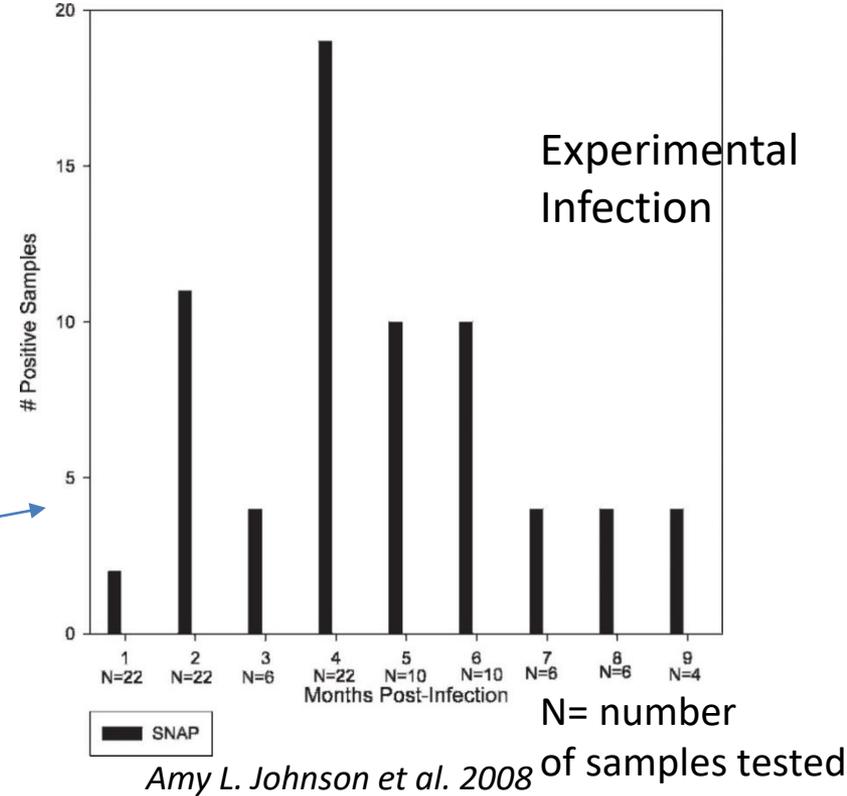
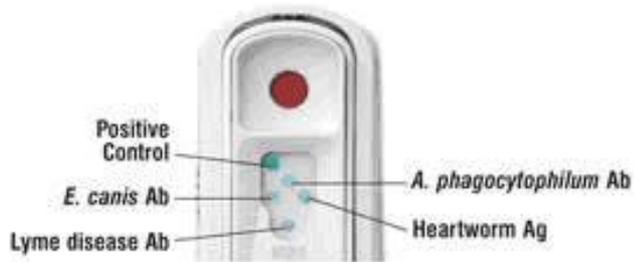
Positive / OspA (>2000
Positive / OspC (>1000
Positive / OspF (>1250
MFI- mean fluorescent intensities

Questions:

1. Are horses with chronically elevated OspF chronically infected?
2. Significance of unvaccinated horses with Elevated OspA?
3. Can horses have Lyme Disease and be serologically negative?

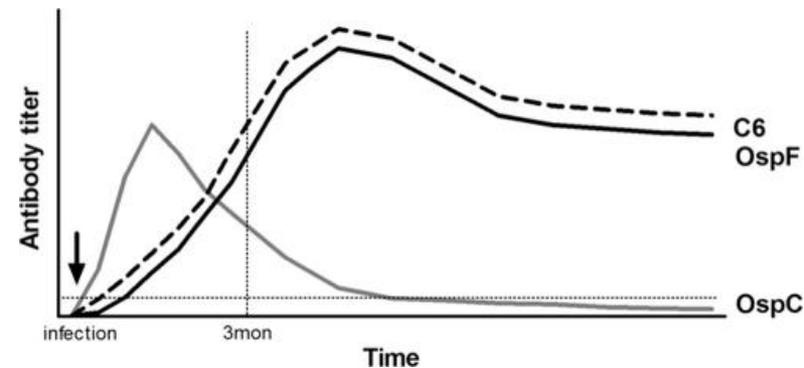
Also C6, whole cell ELISA assays and Western blot

Other Serologic Testing- C-6 Snap Test- it works in horses



Comparison of multiplex analysis and SNAP 4Dx® test results in horse serum (n = 90) B. Wagner et al. 2013

Snap		Multiplex	
		Negative	Positive
Snap	Negative	43	3
	Positive	2	42



Whole Cell ELISA and Western Blot are also common antibody test

Antemortem Diagnosis of Equine Lyme Disease

1. Possibility of exposure to *Borrelia* -infected ticks.

Serology may be negative with neuroborreliosis, uveitis, immune deficiency or early infection

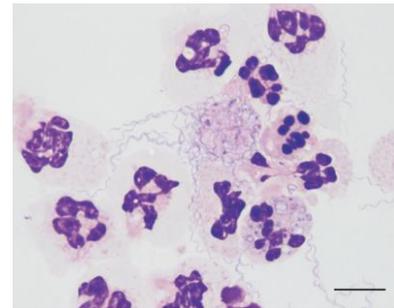
2. Clinical signs compatible with Lyme disease in horses or other species.

“Ruling out other diseases that cause similar clinical signs is likely the most important aspect of working towards a diagnosis of Lyme disease!”

3. Cytology, histopathology and ideally *B. burgdorferi* detection!

- Ocular fluid often positive on cytology and PCR
- **CSF usually neg.** PCR; Joint fluid limited data

4. Response to treatment not a specific diagnostic modality for confirmation of most Lyme disease syndromes.



Improved method for *B. burgdorferi* detection in CSF

11 YO mare – acute onset neurologic signs

Negative for EPM, well vaccinated for EEE, WNV

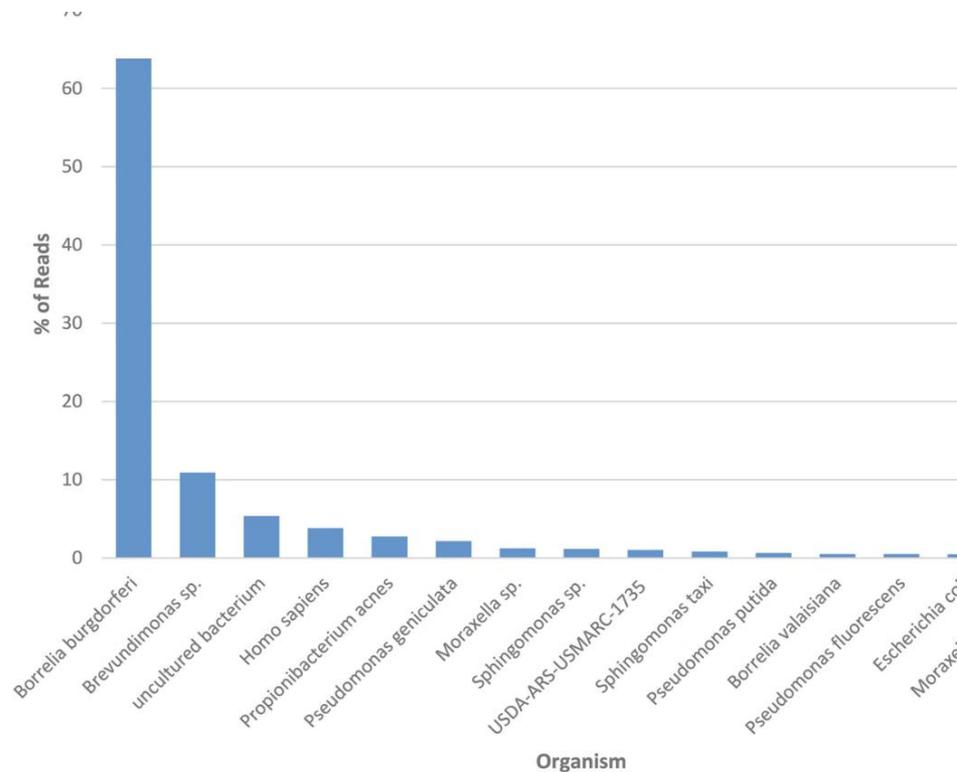
Neutrophilic CSF with very high protein in fluid

PCR *B. burgdorferi* – negative

SEROLOGY

	OspA MFI	OspC MFI	OspF MFI
Initial Serum and CSF Results			
Serum	459	60	757
CSF	15,021	2,789	19,040

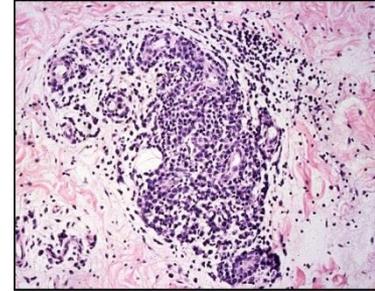
Hybrid capture enhancement and metagenomics testing of CSF



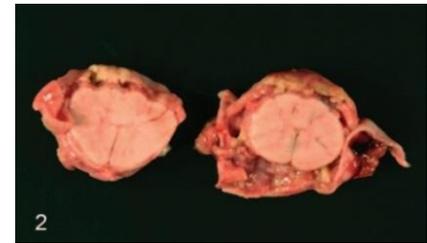
A. Targeted (hybrid capture enrichment) metagenomics findings on cerebrospinal fluid from Horse 1 diagnosed with Lyme neuroborreliosis.

Pathology of Equine Lyme Disease

- *The most common histopathologic lesion of Lyme disease in horses is a lymphohistiocytic and plasmacytic infiltrate.*



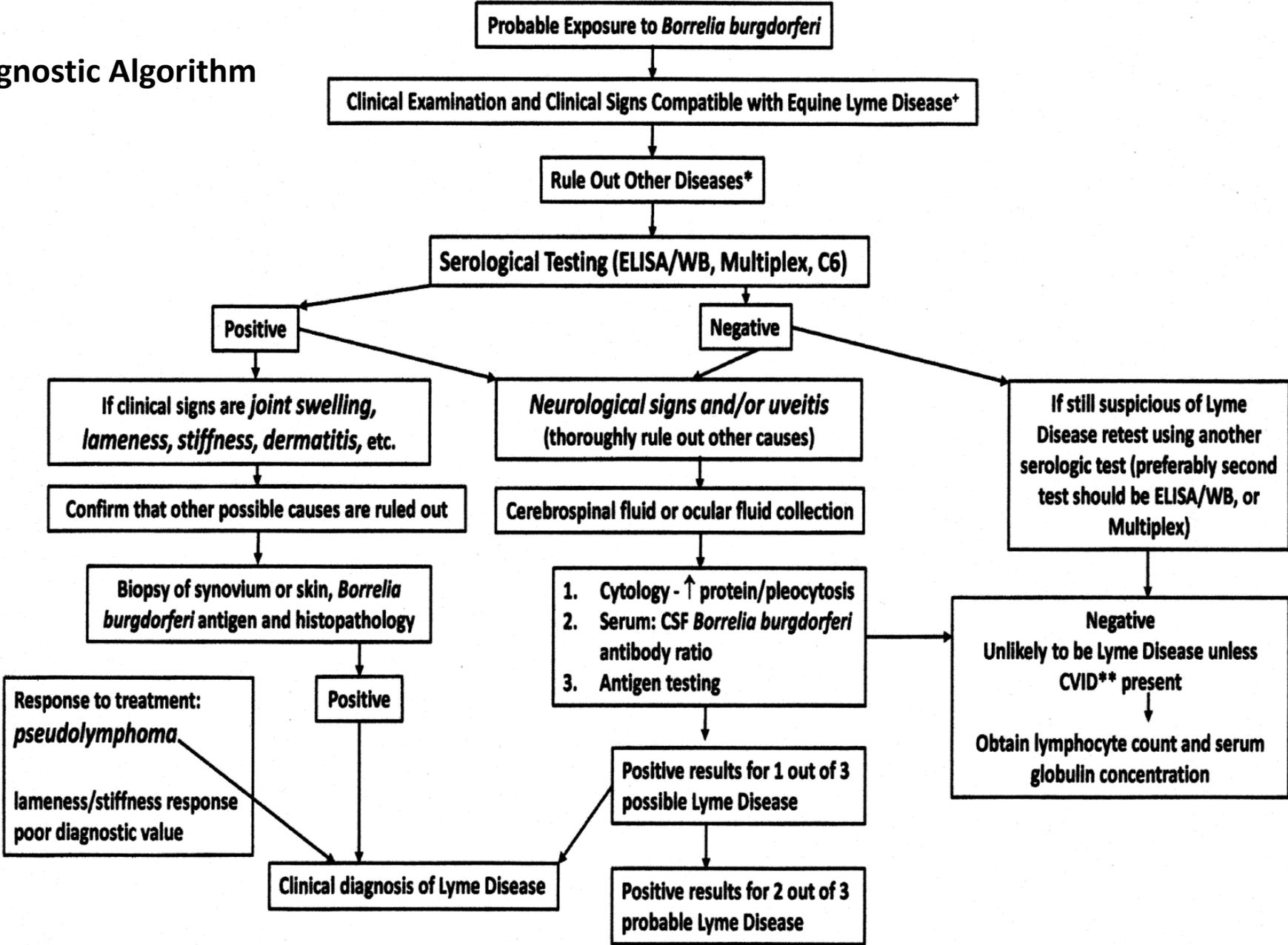
- *Gross thickening of the dura may be observed with equine neuroborreliosis.*



Imai DM Vet Pathol 2011

- *When these lesions are found in horses with clinical signs compatible with Lyme Disease, testing for the organism should be performed.*

Diagnostic Algorithm



Which horses should we treat?

- *“Treatment of asymptomatic seropositive horses will result in treatment of many horses when there is no indication for such, unnecessary expense, increased risk of adverse events and inappropriate use of antimicrobials”.*
 - Repeat titers over 5-36 months in presumably healthy, untreated horses did not change nor were clinical signs reported to develop, further supporting the low positive predictive value of serologic testing for clinical Lyme disease. (Funk et al 2016; Divers et al 2009)
- An ACVIM consensus statement recommended that horses with clinical signs consistent with Lyme disease, for which other potential causes have been excluded, be the only seropositive animals selected for antimicrobial treatment.
- Does it make sense to treat non-clinical horses with elevated OspC?

Treatment of Equine Lyme Disease

Treatment recommendations for equine Lyme have been based on:

- *in vitro* *B. burgdorferi* susceptibility studies
- extrapolation from human treatment guidelines
- available antibiotic pharmacokinetic data, safety and cost in horses
- a single treatment trial in experimentally infected ponies.

Chang et al. 2005

There is no consensus on a preferred drug for treating Equine Lyme disease.

Penicillin, Ceftiofur, Tetracyclines recommended

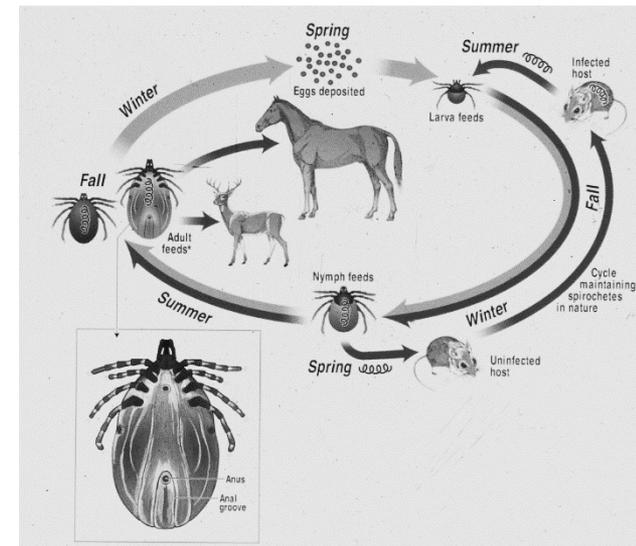
Ceftriaxone, Metronidazole, Enrofloxacin not recommended

Treatment Duration

- Although a “standard of care” treatment duration is published for human Lyme disease, the same can not be applied to horses due to:
 - likely differences between duration of disease prior to beginning treatment
 - marked species differences in bioavailability of tetracycline or β lactam drugs between species and increased potential G.I. or renal toxicity in horses.
- A continual decline in antibody to negative range following antibiotic treatment suggests successful elimination of the organism but *treatment decisions, either initiation or duration of, should not be based solely on a quantitative antibody test!*
- Complementary medicine may be helpful for some cases

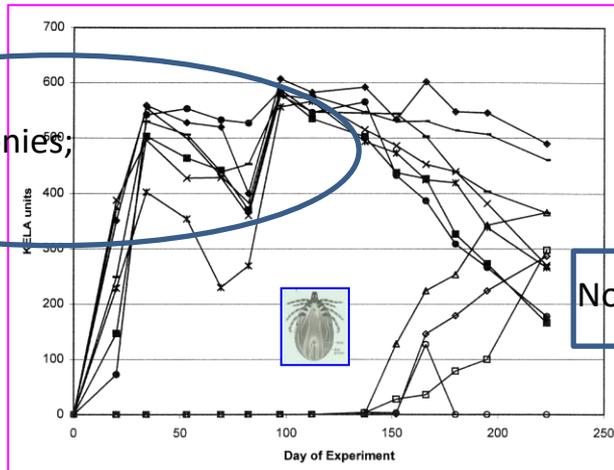
Tick Control and Vaccination

- Adult female *Ixodes* ticks are thought to be responsible for the highest percentage of *B. burgdorferi* horse infections. Butler et al. 2016
- The adult females predominantly feed in early spring or in fall and these are the times that horses are likely at greatest risk for infection.
- There is a need for better tick control in horses!



Vaccination

- Protection against infection using an OspA/adjuvant vaccine has been demonstrated in ponies. (Chang 2000)

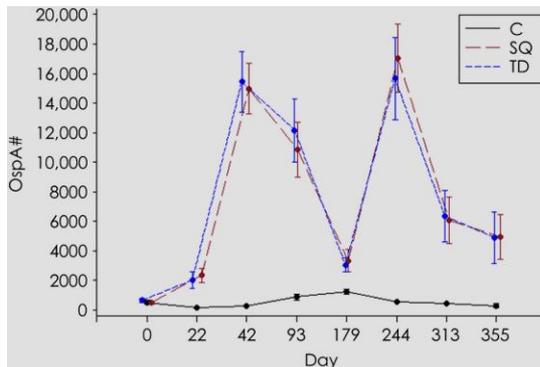


Vaccinated ponies;
No infection

Tick challenge all ponies 112 day after starting 3 dose vaccine protocol (days 1,20 and 82)

Non-vaccinated ponies got infected

- Humoral antibody response and basic safety have been reported in horses using a canine approved OspA vaccine (Slaughter 2016)



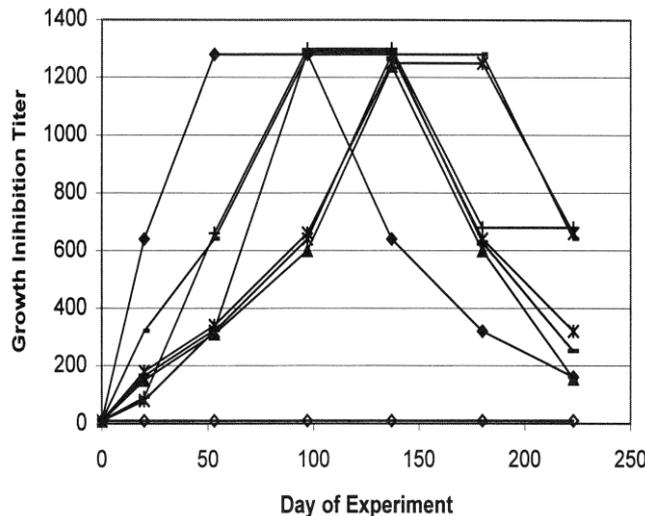
*- Practitioners have not always found this consistent vaccination response in OSP A titer !

Vaccination of horses with Lyme vaccines for dogs induces short-lasting antibody responses

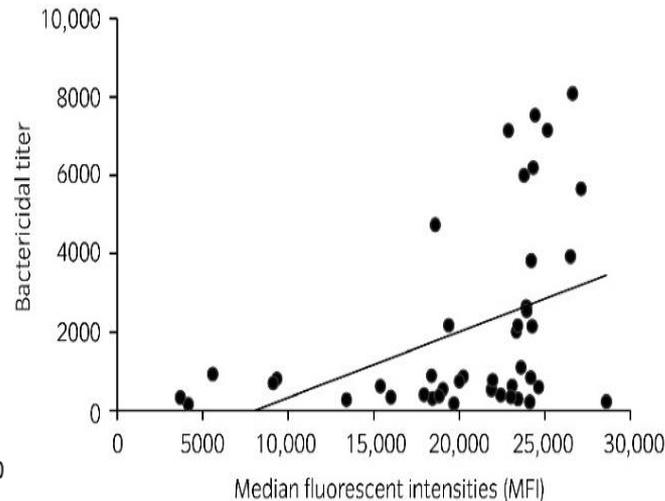
Guarino C. et al Vaccine 2017

- Lyme vaccines for dogs induce OspA antibodies in horses only transiently and inconsistently.
- Increasing the vaccination dose for horses can enhance the OspA antibody response, and adding another booster vaccination can extend the duration of the OspA antibody response.
- Route of Vaccination (IM vs SC) made no difference in OspA antibody response.

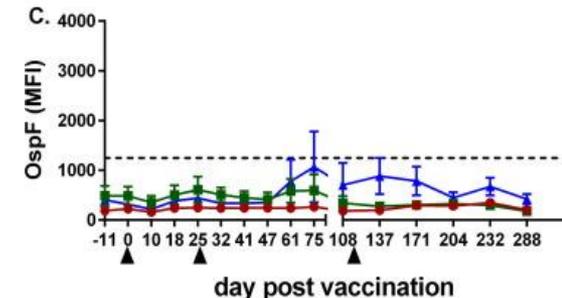
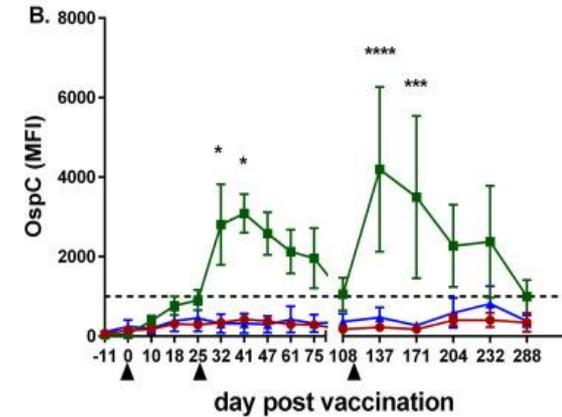
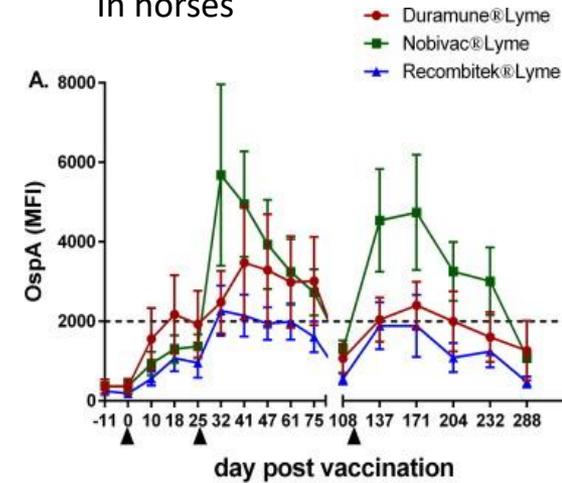
B. Burgdorferi growth inhibition following 3 dose OspA vaccine



Correlation OspA titer and bactericidal effect



No published data on LymeVax
In horses



Serologic Testing of Healthy Horses

- Serologic testing should, in general, not be recommended in healthy horses in high seroprevalence areas.
- recommendations for serologic testing of horses at select examinations* (e.g., purchase exams or wellness exams) in the absence of compelling clinical signs compatible with Lyme disease is not supported by current literature or research data.
- *analogy of EPM testing to support these recommendations.*
- ** there might be occasional exceptions?*

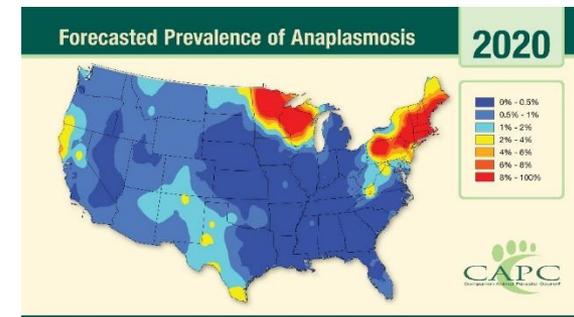
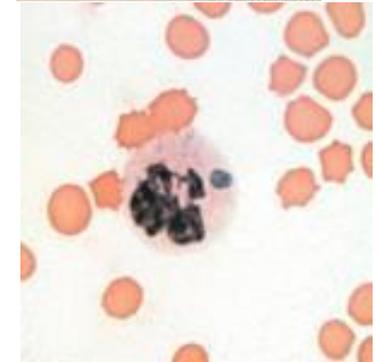
- **Other *Borrelia spp.* organisms that are known to be present in North American *Ixodes* ticks.**
 - *B. mayonii*- transmitted by *Ixodes* ticks and causes bacteremia with signs similar to Lyme along with G.I. signs; X-react with *B. burgdorferi*.
 - *B. miyamotoi*- transmitted by *ixodes* ticks and causes relapsing fever in humans; does not X-react serologically with *B. burgdorferi*
 - *Anaplasma Phagocytophilium*-

- **Other tick-borne infections that occur in humans in the eastern U.S**
 - *B. microti*- human babesiosis- fever, hemolytic anemia
 - *Powassan virus* is a *Flavivirus* that can cause encephalitis
 - *Rickettsia rickettsia*

Theileria equi, and *Babesia caballi* are all rare in the region

Equine Granulocytic Ehrlichiosis- Anaplasmosis

- *Anaplasma phagocytophilum*
- Bacteremia develops 5-7 days after Ixodes tick bite- attached 2hrs.
- Up to 30% of all granulocytes can be infected
- Clinical signs occur mostly in adult horses- Stiffness, limb edema, anorexia, icterus
- Fever accompanies bacteremia
 - Can last for several days
 - High as 41° C (105.8 F)



Anaplasma Infection and Disease

- Within hours after an infected tick bite the organism is present in the skin and within 5 or more days infects neutrophil and spreads to multiple organs
- Anaplasma phagocytophilia infection can cause a TH1 immune response with cytokine related inflammation in small vessels (vasculitis) affecting subcutaneous tissue, muscle, liver, lungs, heart, kidneys and spleen.

-Gribble, D.H. (1969) Equine ehrlichiosis. *J. Am. Vet. Med. Assoc.* **155**, 462-469.

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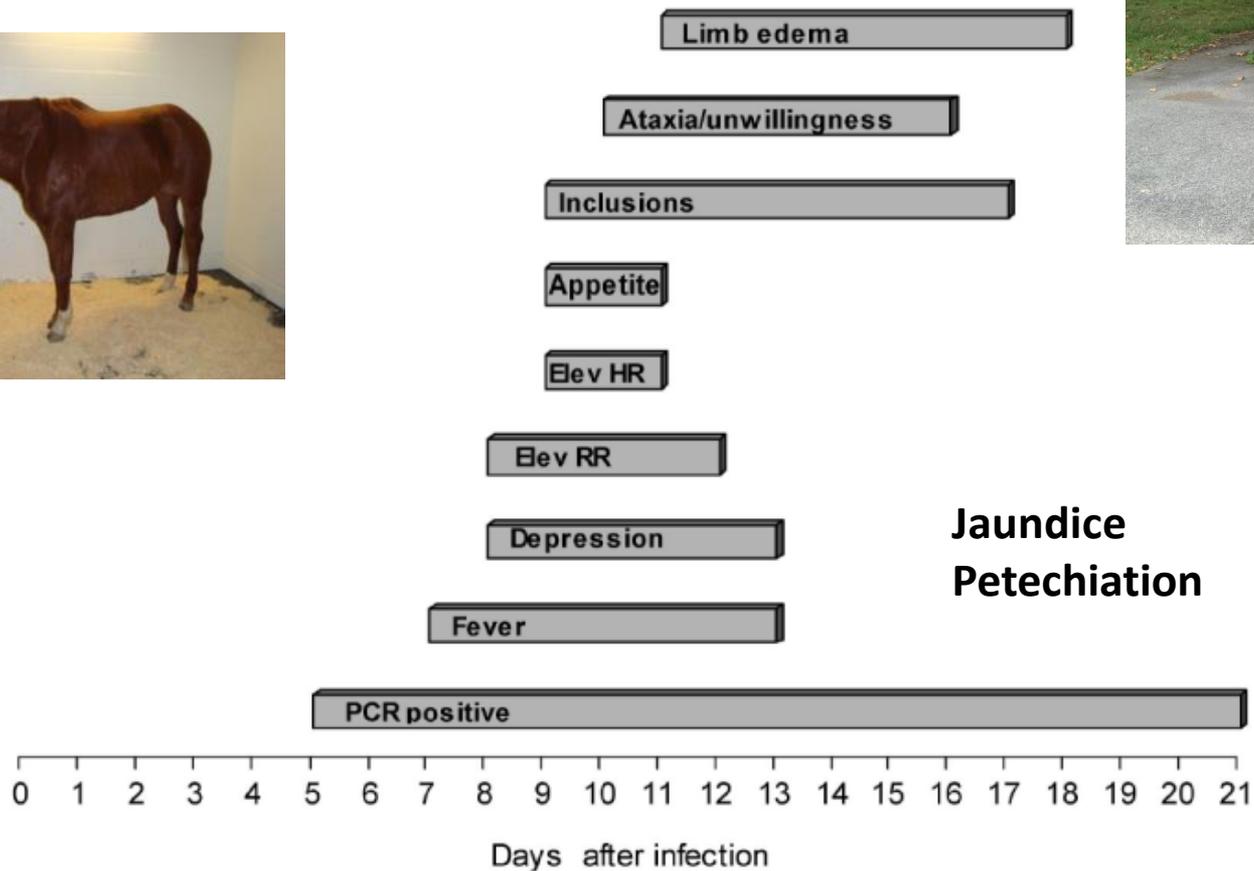


Fig 2. Days of onset and duration of clinical signs, compared to inclusion presence and polymerase chain reaction–positive signal in 5 horses experimentally infected with a European (Swedish)-derived *Anaplasma phagocytophilum* strain. Elev HR, heart rate increase; Elev RR, respiratory rate increase; Ataxia/unwillingness, ataxia and unwillingness to move or stumbling.

Other less common syndromes associated with equine anaplasmosis

- **Myopathy**

- 11 YO Hanoverian-Cross acute onset of fever, ataxia, recumbency Rose-Walton et al. JAVMA 2004
- Rhabdomyolysis associated with *Anaplasma phagocytophilum* infection in a QH. Hilton H et al. JVIM 2008
- may trigger non-exertional rhabdomyolysis in QHs!!



- **Cavitary Effusion**

- Cavitary Effusion Associated with *Anaplasma phagocytophilum* Infection in 2 Equids M.M. Restifo et al. J Vet Intern med 2015



- **DIC/acute death-**

- Franzen P, et al. Death of a horse infected experimentally with *Anaplasma phagocytophilum* Vet Rec 2007;

- **Myelitis/Encephalitis-**

- **Hepatitis, Pulmonary distress**

Upper respiratory signs associated with *Anaplasma phagocytophilum* infection in two horses

E. L. Deane, C. L. Fielding, D. M. Rhodes, E. J. Howardal. Equine Veterinary Education, 33, (3): e58-e61 2021

- Respiratory distress occurred in both horses with 1 requiring a tracheostomy. The other horse also had severe dysphagia.
- Both horses were PCR positive for *A. phagocytophilum* and recovered fully within 14 days following tetracycline/minocycline treatments



***A. Phagocytophilium* associated Pulmonary and Hepatic Disease**

- Pulmonary lesions varied from only mild perivascular lymphohistiocytic infiltrates to patchy, alveolar wall edema and infiltrates of mostly lymphocytes and macrophages. However, 1 horse demonstrated more significant pathologic injury with focal alveolar wall necrosis, intra-alveolar fibrin and inflammatory cell exudates, and interstitial pneumonitis
- Some affected horses have increased liver enzymes with GGT having a marked increase in a small number of cases.
- nuclear cell infiltrates to slight lobular hepatitis with intra-sinusoidal aggregates of macrophages and occasional neutrophils, and focal apoptotic cells occasionally associated with small inflammatory lesions

Clinical Pathology

- Severe leukopenia during early clinical signs
 - Lymphopenia
 - Neutropenia variable- may have bands
- **Thrombocytopenia**
 - More pronounced in horses than other species
- Mild anemia
- Lymphoid depletion in spleen but little effect on bone marrow
 - Bands don't have inclusions



Diagnosis

- Clinical Signs!
- Tick Exposure
- Thrombocytopenia, Neutropenia
- PCR on whole blood during febrile stage
 - Will often be PCR positive for 1-2 days after treatment-
- Giemsa, Romanowsky or Diff-Quik exam of blood
 - buffy coat smears during febrile stage+/-
- IFA on serum after febrile stage
 - may not be positive for up to 3 weeks or may remain negative.
 - Many horses are positive w/o history of illness
- SNAP 4DX has only 50% sensitivity in early clinical cases.

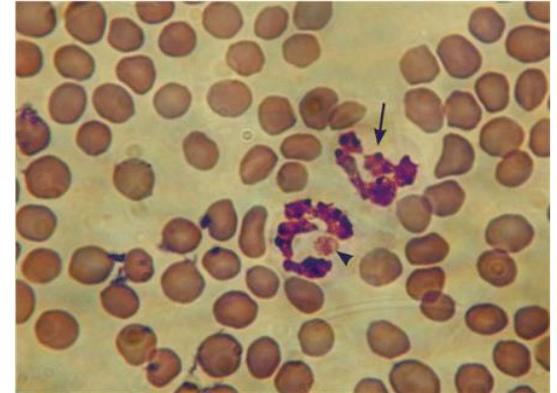


TABLE 2: Clinical signs, haematology and PCR-reverse line blot (RLB) results for horses infected *Anaplasma phagocytophilum*

Horse	Age (years)	Breed	PCV (l/l)	Platelet (x 10 ⁹ /l)	Lethargy	Temperature (°C)	Oedema	Ataxia	Anorexia	Blood smear result	PCR-RLB for <i>A. phagocytophilum</i>
1	10	Dutch warmblood	29	100	Yes	40.4	None	No	Partial	-	+
2	4	Friesian	28	344	Yes	41.1	All legs	Yes	Total	+	+
3	14	Dutch warmblood	23	22	Yes	38.7	Hindlegs	No	Partial	+	+
4	15	Dutch warmblood	24	26	Yes	40.6	Hindlegs	No	Partial	+	+
5	15	Dutch warmblood	25	23	Yes	41.0	Hindlegs	No	Partial	+	+
6	10	Dutch warmblood	29	22	Yes	41.0	Hindlegs	No	Partial	+	+

PCV Packed-cell volume, - Negative, + Positive

Treatment Options

- Oxytetracycline IV- SID or BID
- Doxycycline/Minocycline-
- Documented resistance to penicillin, ampicillin, chloramphenicol, streptomycin
- Immunity is approximately 1 year
- Tick Control-
 - Environmental
 - Insecticides- Coumaphos spray or powder; pyrethrins; synthetic pyrethroids applied as a wipe, spray, or spot-on; and zeta-cypermethrin dusting powders are the most commonly used repellents which should be applied to the horse's main, tail head, chest, and underbelly.
(Recommendations from AAEP WebSite)



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