American Canine Hepatozoonosis

Douglass K. MacIntire, DVM, MS, DACVIM, DACVECC
Professor
Department of Clinical Sciences
College of Veterinary Medicine
Auburn University
Auburn, Alabama

American canine hepatozoonosis (ACH) is a tickborne disease that has been reported in domestic dogs in Texas, Louisiana, Alabama, Georgia, Mississippi, Oklahoma, Tennessee, and Florida. It is considered to be an emerging disease in the southcentral and southeastern United States that is highly pathogenic and causes a debilitating clinical syndrome in affected dogs. The clinical signs associated with ACH can mimic other diseases, and veterinarians must be familiar with both the life cycle of the parasite and the clinical syndrome of the disease in order to successfully diagnose and treat infected dogs.

Hepatozoon americanum, the causative agent of ACH, is a protozoal organism transmitted to dogs (the intermediate host) through the definitive host, Amblyomma maculatum (the Gulf Coast tick). A dog must ingest an infected tick for transmission to occur. After the tick reaches the dog’s intestines, sporozoites are released in the presence of bile, and the organisms then invade canine host cells, where asexual reproduction and multiplication occur through merogony (also called schizigony).

Merogony most commonly takes place in skeletal muscle inside a cystic structure that protects the developing organisms from cidal drugs. When the meront (or schizont) is mature, numerous merozoites are released, causing pyogranulomatous inflammation, pain, and fever. Some merozoites are phagocytized by white blood cells and enter the circulation as gamonts (the sexual stages). If these gamonts are ingested by a Gulf Coast tick, fertilization and oocyst production occur within the tick followed by sporogony (development of sporocytes and sporozoites).

As a result of the oocyst production and sporulation process, a single tick can contain over 1,000 infective sporozoites. Once infected, dogs usually exhibit a waxing and waning course of recurrent fever spikes, muscle pain, and progressive debilitation over a period of several months. In the later stages of the disease, most affected dogs develop proteinuria and renal failure secondary to immunoproliferative glomerulonephritis. Without treatment, death usually occurs within 12 months following ingestion of the infected tick. Extreme cachexia and muscle wasting are common.

Diagnostic Criteria

Historical Information
Gender Predisposition: None.

Age: Dogs of any age can be infected following ingestion of an infected tick.

Breed Predisposition: Most affected dogs are large-breed, outdoor dogs. Infection with ACH has also been documented in coyotes, foxes, bobcats, and ocelots in endemic areas.

Owner Observations:
- Most owners notice depression, reluctance to move, stiff gait, mucopurulent ocular discharge, progressive weight loss, and muscle wasting.
- Clinical signs have a waxing and waning course with recurrent episodes of hyperesthesia and fever.
- Dogs usually maintain their appetite despite progressive weight loss.
- Many dogs live near wooded areas and have a history of tick infestation.
- Some dogs have a history of ingesting a deer carcass 3 to 4 weeks before developing clinical signs of disease.
- Some infected dogs develop transient bloody diarrhea 3 to 4 weeks after ingesting an infected tick.

Other Historical Considerations/Predispositions: Coyotes often live in endemic areas and may be an important intermediate host reservoir for local tick populations.

Physical Examination Findings
- Fever (102.7°F–105.6°F).
- Mucopurulent ocular discharge (due to pyogranulomatous inflammation of extraocular muscles).
- Hyperesthesia: Neck-guarding is common.
- Gait abnormalities: Stiffness, weakness, ataxia, rear limb paresis, inability or unwillingness to rise.
- Extreme cachexia, muscle wasting with chronic disease (especially evident in head muscles).
- Polyuria, polydipsia, nausea, and vomiting may be present in dogs with renal involvement.
Muscle biopsy of the limbs or lumbar skeletal muscle preserved in formalin usually reveals the “onion-skin cyst” stage (Figure 1) of the meront or pyogranulomatous myositis.

Gametocytes may be present on a blood smear or buffy coat smear, although they are often hard to find, as usually less than 0.1% of the leukocytes are infected.

Lymph node aspirates reveal lymphoid hyperplasia.

Electromyography is consistent with generalized polymyopathy.

Results of joint aspiration are consistent with non-septic inflammation.

Bone marrow aspiration reveals granulocytic hyperplasia and erythroid hypoplasia.

**Laboratory Findings**

- Extreme leukocytosis (20,000 to 200,000 cells/µl; normal: 6,000 to 17,000/µl).
- Mature neutrophilia, occasionally with a mild left shift.
- Mild normocytic, normochromic nonregenerative anemia (28% to 35%; normal: 37% to 55%).
- Normal to elevated platelet count (normal: 200,000 to 400,000/µl). Thrombocytopenia may indicate concurrent infection with other tickborne disease; check tick titers.
- Mild to moderate elevation in serum alkaline phosphatase (SAP) activity (normal: 10 to 150 IU/L).
- Hypoglycemia (40 to 60 mg/dl; normal: 80 to 120 mg/dl; may be a spurious artifact due to extreme leukocytosis).
- Hypoalbuminemia (normal: 2.6 to 4.3 g/dl).
- Low blood urea nitrogen (BUN) level (<15 mg/dl) due to negative nitrogen balance and production of inflammatory proteins (normal: 15 to 27 mg/dl).
- With chronic disease, increased urine protein:creatinine ratio from glomerulonephritis or renal amyloidosis (normal: <1.0).
- Serum bile acids are usually normal. Despite its name, ACH does not cause primary hepatic disease (normal: <25 /µmol/L).
- Despite muscle inflammation, creatinine kinase activity is usually normal (normal: 10 to 200 IU/L).

**Other Diagnostic Findings**

- Radiographs often reveal periosteal proliferation at the site of muscle attachments (more common in young, growing dogs).
- Pelvic or long bone radiographs can be used as a screening test to look for periosteal exostoses or smooth lamellar thickening of long bones, although not all infected dogs exhibit bony lesions.

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**Summary of Diagnostic Criteria**

- History of waxing and waning fever that is not responsive to antibiotics.
- Hyperesthesia, stiffness, reluctance to ambulate.
- Mucopurulent ocular discharge.
- Marked leukocytosis.
- Elevated SAP level; decreased BUN, glucose, and albumin levels.
- Radiographic evidence of periosteal proliferation of long bones.
- Meront cysts or pyogranulomatous myositis with phagocytized merozoites on muscle biopsy.
- Identification of gamonts in white cells on blood smear (Figure 2).

**Differential Diagnosis**

- Diskospondylitis: No spondylitis on radiographs of spinal vertebrae.
- Meningitis: Normal cerebrospinal fluid tap.
• Canine distemper: Negative conjunctival scraping, negative IgM titer.
• Insulinoma: No elevation of serum insulin level.
• Pyometritis: No evidence of uterine horn enlargement with radiographic or ultrasonographic examination.
• Polyarthritis: Joints not swollen.
• Lymphosarcoma: Lymphoid hyperplasia on cytologic examination of aspirate.
• Other tickborne disease: Titers should be checked to rule out bartonellosis, babesiosis, Rocky Mountain spotted fever, ehrlichiosis, and borreliosis.

TREATMENT RECOMMENDATIONS

Initial Treatment $$
- Antiprotozoal therapy ("combination therapy"); all three drugs are administered concurrently for 2 weeks:
  - Trimethoprim–sulfadiazine (15 mg/kg PO q12h)
  - Clindamycin (10 mg/kg PO q8h)
  - Pyrimethamine (0.25 mg/kg PO q24h)
- Long-term treatment to prevent relapses as merozoites are released from tissue cysts: decoquinate (Deccox 22.7 g/lb Premix, Alpharma, Fort Lee, NJ) at a dosage of 10 to 20 mg/kg or 0.5 to 1 tsp/10 kg mixed in food q12h for 2 years.
- Antiinflammatory therapy for muscle pain: standard doses of NSAIDS.
- Intravenous fluids as needed for dehydration and hypoglycemia.

Alternative/Optional Treatments/Therapy $$
- Doxycycline may be needed if there is concurrent infection with other tickborne diseases.
- Imidocarb (5 mg/kg SC repeated every 14 days until parasitemia is gone) has been used effectively to treat Hepatozoon canis, but its efficacy against H. americanum is questionable.

CHECKPOINT
- ACH was first reported in dogs from Texas in 1978. Initially the causative agent was mistakenly thought to be H. canis, but in 1997 H. americanum was recognized as a new, emerging, and more pathogenic species.

Supportive Treatment $
- Clean matted eyes with a warm, moist towel.
- Provide soft bedding.
- Institute an effective program to control ticks.
- Do not allow the dog to ingest dead animals that may harbor ticks (e.g., deer carcasses).
- Bring food and water to dogs that are unwilling to ambulate.

Patient Monitoring
- Repeat complete blood count and physical examination in 2 weeks. If fever, muscle pain, or marked leukocytosis is present, continue combination therapy for 2 more weeks.
- After completing combination therapy, initiate long-term treatment with decoquinate.
- Relapses may occur even though the dog is receiving decoquinate because it is a static rather than cidal agent. If necessary, the combination therapy can be repeated while the dog is receiving decoquinate. Subsequent relapses are usually mild.
- Relapses are characterized by fever, mucopurulent ocular discharge, hyperesthesia, and leukocytosis.

Home Management
- Long-term decoquinate therapy.
- Tick control.

Milestones/Recovery Time Frames
- Without treatment, hepatozoonosis is usually fatal within several months.
- With antiprotozoal combination therapy alone, relapses occur requiring repeated therapy. Relapses become more frequent and refractory to treatment. Death usually occurs within 1 year of the initial diagnosis.
- Long-term cure (>5 years) has been achieved with combination therapy followed by long-term decoquinate therapy.

ON THE NEWS FRONT
- Researchers at Oklahoma State University have developed an ELISA test for H. americanum, but it is not yet commercially available. At the present time, muscle biopsy is the only way to definitively diagnose H. americanum. An immunofluorescence assay is available in Israel for testing dogs with H. canis, but it is not useful for diagnosing H. americanum.
Treatment Contraindications
Corticosteroids might provide temporary benefit because of their antiinflammatory effects, but they are contraindicated because immunosuppression can lead to exacerbation of the disease.

PROGNOSIS

Favorable Criteria
- Normal white blood cell count following 2 weeks of treatment.
- Weight gain; reversal of cachexia.
- Resolution of lameness, pain, and stiffness.
- Disappearance of ocular discharge.

Unfavorable Criteria
- Severe proteinuria with elevated urine protein:creatinine ratio.
- Frequent, severe relapses.
- No improvement with combination therapy.
- Renal failure.

RECOMMENDED READING