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Heterobilharzia americana infection in dogs: A retrospective study of 60 cases (2010-2019)

Amber M. Graham[1] | Amy Davenport[2] | Valentina S. Moshnikova[2,3] |
Lindsey J. Gilmour[1] | Michelle Fabiani[2] | Micah A. Bishop[3] | Audrey K. Cook[1]

[1]Department of Clinical Sciences, College of Veterinary Medicine, Texas A&M University, College Station, Texas

[2]Gulf Coast Veterinary Specialists, Houston, Texas

[3]WAVE Veterinary Internal Medicine, Naples, Florida

Correspondence

Audrey K. Cook, Department of Small Animal Clinical Sciences, Texas A&M University MS 4474 College Station, TX 77843.
Email: akcook@cvm.tamu.edu

Present address

Valentina S. Moshnikova, Department of Clinical Sciences, College of Veterinary Medicine, University of Minnesota, St. Paul, Minnesota,

Abstract

Background: The trematode *Heterobilharzia americana* (*HA*) causes granulomatous gastrointestinal and hepatic disease in dogs. Before 2008, diagnosis relied on saline fecal sedimentation or histopathology, and earlier reports primarily described dogs with advanced disease or cases diagnosed incidentally at necropsy. The advent of a fecal PCR test has facilitated the diagnosis of *HA* and provided insights into manifestations and response to treatment.

Objectives: Describe the clinical findings, response to treatment, and outcome for dogs infected with *HA*.

Animals: Sixty dogs diagnosed with *HA* between 2010 and 2019.

Methods: Retrospective study. Medical records were searched for dogs diagnosed with *HA* by fecal PCR testing, identification of ova in feces, or histopathology.

Results: Mean age was 7.5 (±4.1) years and weight was 23.2 (±10.18) kg. Clinical signs included diarrhea (55.8%), vomiting (46.2%), and weight loss with or without anorexia (15.4%). Laboratory abnormalities included hyperglobulinemia (42.6%) and increased liver enzyme activities (30%). More than 40% of dogs had an eosinophil count >500/μL. Hypercalcemia attributable to *HA* was identified in only 4 dogs. Pinpoint hyperechoic foci were noted in intestines, liver, or mesenteric lymph nodes during transabdominal ultrasonography in 64.4% of dogs. Survival data was available for 34 dogs, of which 73.5% (25) were alive 6 months after diagnosis.

Conclusions and Clinical Importance: Hyperglobulinemia, high eosinophil count, and ultrasonographic evidence of visceral mineralization were suggestive of infection. Hypercalcemia was uncommon. Combination treatment with praziquantel and fenbendazole was variably effective, and 17.6% of treated dogs with known outcome died as a result of *HA* infection.

KEYWORDS

enteropathy, hepatopathy, hypercalcemia, praziquantel, schistosomiasis, trematode

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1 | INTRODUCTION

Heterobilharzia americana (*HA*), the causative agent of schistosomiasis in dogs, is a trematode parasite endemic to the Gulf Coast regions of the United States which also has been reported in Kansas, North Carolina, and Indiana.[1-8] Dogs are exposed to infection when immersed in freshwater lakes or streams harboring lymnaeid snails (the intermediate host). Free swimming cercariae emerge from the infected snail, penetrate the dog's skin, and then migrate hematogenously to the lungs and liver, where sexual maturation takes place. Adult parasites subsequently travel via the portal system to the mesenteric veins to mate. Fertilized eggs are released into the mesenteric veins and use proteolytic enzymes to migrate through the intestinal walls and thereby exit the body in the feces. Upon contact with fresh water, flagellated miracidia emerge from the eggs and infect the snails, thereby completing the life cycle.

Previous reports suggest that young, large breed, hunting or herding dogs are particularly vulnerable to infection, with clinical signs including diarrhea, weight loss, hyporexia or anorexia, vomiting, hematochezia, lethargy and polyuria and polydipsia.[2-5,9] Hematologic changes associated with infection include lymphopenia, eosinophilia, anemia and thrombocytopenia.[2-4] Hyperglobulinemia, azotemia and increases in liver enzyme activities also have been described.[2-5,10] In a previous report, protein electrophoresis performed in 2 dogs identified a polyclonal gammopathy.[5] Hypercalcemia has been reported in 34% to 50% of dogs diagnosed with schistosomiasis in previous case series.[2,3,5] One report described 2 patients with subnormal serum parathyroid hormone concentrations and increased parathyroid hormone-related peptide activity,[11] but similar findings have not been confirmed in other reports.[5,9,10,12]

Radiographic findings associated with infection include mineralization of gastric and intestinal walls, hepatomegaly, and splenomegaly.[5,12-15] Transabdominal ultrasonography can be unremarkable, or may identify changes in echogenicity of the liver, lymph nodes or intestines; abdominal effusion also may be noted.[4,5,12-16]

Heterobilharzia americana ova are not reliably detected using routine fecal flotation tests, and saline sedimentation methods generally are recommended.[6] Fecal sedimentation however is not routinely performed in most practices and is not offered by large reference laboratories, although it may be performed by selected state diagnostic laboratories. In 2008, a fecal PCR test was developed, with a reported sensitivity of 1.5 eggs/g of feces.[17] Negative controls used during assay development included DNA from common parasites in the United States (roundworms, hookworms, trematodes) and fecal samples from dogs known to be free of parasites. Positive controls included feces and DNA from dogs with natural infection and 2 spiked fecal samples. During the validation phase, all fecal samples submitted to the laboratory underwent concurrent saline sedimentation testing; miracidia hatching was performed to confirm a positive PCR result. Positive samples also were sequenced and results compared to the published PUBMED sequence, and were consistently found to be *HA*. Although this test has not been independently validated, it is commonly used at the 2 hospitals contributing cases to our study, and other sources support its use and reliability.[2,5]

We believe that increased awareness of *HA* and more frequent use of the fecal PCR test has increased the likelihood of establishing a diagnosis of *HA*, and the cases described to date may not reliably reflect the true spectrum of disease seen in infected dogs. Our objectives are to provide updated information regarding clinical findings, response to treatment, and long-term outcome of dogs with schistosomiasis.

2 | MATERIALS AND METHODS

2.1 | Case selection and data collection

We carried out a multicenter, retrospective, descriptive study. A search of the electronic medical record databases at Texas A&M University Veterinary Medical Teaching Hospital and Gulf Coast Veterinary Specialists was performed for dogs diagnosed with *HA* infection using the key words *Heterobilharzia* and schistosomiasis between March 1, 2010 and December 31, 2019. Cases were included in the study population if the medical record documented either a positive result on fecal PCR testing (GI Laboratory, Texas A&M University, College Station, Texas), *HA* ova identified in feces, ova or adult trematodes reported on histopathologic examination of affected tissues, or some combination of these. Medical records subsequently were reviewed by 1 of 2 American College of Veterinary Internal Medicine Diplomates.

Patient signalment, history, body weight, and method or methods of diagnosis of schistosomiasis were required for inclusion in the study. Results of contemporaneous (ie, performed within 48 hours of diagnosis) selected clinical pathology tests and findings on transabdominal ultrasonography were recorded, when available. Complete blood count, serum biochemistry and urinalysis were performed by the Clinical Pathology Service at Texas A&M Veterinary Medical Teaching Hospital. At Gulf Coast Veterinary Specialists, laboratory diagnostic tests either were performed at a reference facility (IDEXX Laboratories, Houston, Texas) or using in-house benchtop devices (ProCyte Dx hematology analyzer and Catalyst One Dx chemistry analyzer, IDEXX, Westbrook, Maine) and a hand-held refractometer. At both hospitals, ultrasonographic images were collected by an American College of Veterinary Radiology Diplomate or radiology resident in training and interpreted by a board-certified radiologist.

Infection was considered an incidental finding if the patient's history did not include gastrointestinal signs, increased liver enzyme activities, or hypercalcemia, or if testing for *HA* apparently was performed on the basis of imaging findings alone. The treatment protocol for each patient was extracted from the medical record. All available post-treatment *HA* fecal PCR test results also were recorded. Patient outcome (defined as alive or dead at 6 months after diagnosis) was derived from the record or by follow up phone calls to the primary care veterinarian.

The hospital boards of the 2 institutions approved the collection of data from pertinent patient medical records. Because of the retrospective nature of the study, approval by Institutional Animal Care and Use Committees was not required.

2.2 | Statistical analyses

Statistical analysis was performed using a commercial software program (GraphPad Prism v 8.0, GraphPad Software, San Diego, CA). Data were tested for normality using the D'Agostino and Pearson tests; normal data were expressed as mean (±SD); data with a nonnormal distribution were expressed as median (range).

3 | RESULTS

3.1 | Study population

Sixty dogs were diagnosed with HA at the 2 hospitals over the approximately 10-year period; all were included in the study. Imaging findings for 55 of these dogs have been reported previously.[16] Thirty-five dogs were females (of which 3 were intact) and 25 were males (5 intact). Patient ages ranged from 7 months to >17 years, with a mean of 7.5 (±4.1) years. A total of 28 pure breeds were represented, including the Labrador retriever (n = 11) and the German shepherd dog (n = 6). Most dogs (85%) were >10 kg in weight; mean weight was 23.2 (±10.18) kg.

In most cases (n = 49; 81.7%), diagnosis was established on the basis of positive fecal PCR test results alone, including 1 dog with a negative fecal sedimentation test; 6 dogs were diagnosed by biopsy of either the gastrointestinal tract (n = 4) or liver (n = 2), 3 of which were also positive on contemporaneous fecal PCR testing; 3 dogs were diagnosed by direct fecal smear (n = 2) or fecal sedimentation (n = 1); and 2 were diagnosed at necropsy. Necropsy findings in 1 dog showed diffuse disease and granulomatous inflammation with intralesional HA ova in the small intestines, colon, pancreas and lungs, along with granulomas affecting both kidneys. The other dog that underwent necropsy had HA ova with mild inflammation identified in the liver; the primary diagnosis for this patient was necrotizing meningoencephalitis.

3.2 | Reasons for testing and clinical signs

Heterobilharzia americana testing was performed most commonly as part of a diagnostic evaluation for chronic enteropathy (n = 32; 53.3%) or undefined hepatopathy (n = 7; 11.7%). In 9 patients (15%), testing was prompted primarily by findings on transabdominal ultrasonography, performed during evaluation of nonspecific problems (chronic anemia, lethargy; n = 2), during investigation of hypercalcemia (n = 5, 8.3%) or for apparently unrelated issues (neoplasia, neurologic disease, oral ulceration, possible intestinal obstruction; n = 7). Infection appeared to be truly incidental (ie, apparently not causing any clinical signs) in these 7 dogs, and in the dog diagnosed at necropsy with necrotizing meningoencephalitis.

Clinical signs for patients judged to be clinically affected by HA infection (n = 52; 86.6%) were variable, but clinical signs related to gastrointestinal (GI) dysfunction were commonly noted. Diarrhea was reported in over half of these dogs (29/52; 55.8%), 8 of which had hematochezia; vomiting was reported in 24/52 (46.2%). In all, >75% of the clinically affected dogs (41/52; 78.8%) had been presented with a history of either vomiting or diarrhea. Eight dogs (15.4%) had been presented for weight loss with or without anorexia and without vomiting or diarrhea. Polyuria and polydipsia were noted in 9/52 dogs (17.3%).

3.3 | Clinicopathologic and imaging findings

Results of CBC, serum biochemical profile, urinalysis or some combination of these were available for 56/60 dogs at the time of HA diagnosis. Mean hematocrit was 39 (±10.2) %; anemia (hematocrit <30%) was noted in 9/56 dogs (17.6%). Reticulocyte counts were inconsistently available but indicated a regenerative response (ie, >125 000/μL) in 2/4 dogs. The median neutrophil count was 6295 (2560-305 910)/μL and median eosinophil count 340 (0-3069)/μL. An eosinophil count >500/μL was noted in 22/52 dogs (42.3%).

Serum total calcium concentrations were available for 54/60 dogs. Five (11.6%) were hypercalcemic (>12.2 mg/dL; median, 17.8 [16-20.7] mg/dL), 1 of which subsequently was diagnosed with primary hyperparathyroidism; hypocalcemia (<9.0 mg/dL) was noted in 9/54 dogs (16.7%). Blood urea nitrogen concentration was above the reference range in 10/54 (18.5%; median, 44 [33-131] mg/dL) dogs; serum creatinine concentration was increased in 5/54 (9.3%; median, 2.93 [2.2-5.2] mg/dL) dogs. Serum albumin concentration was <2.4 g/dL in 14/54 dogs (25.9%; median, 2 [1.1-2.2] g/dL); hyperglobulinemia (>3.7 g/dL) was noted in 23/54 (42.6%; median, 4.6 [3.8-7.7] g/dL) dogs. Liver enzyme activities were normal in 33/47 dogs (70%); when present, increases in activity for alkaline phosphatase (n = 13; median, 306 [161-1795] IU/L) and alanine aminotransferase (n = 7; median, 335 [131-1447] IU/L) were generally mild. Serum bilirubin concentration was <1.0 mg/dL in all dogs.

Urine specific gravity (USG) was recorded in 43/60 (71.6%) dogs. Median USG was 1.018 (1.012-1.037). Two of 43 dogs (4.6%) were hyposthenuric (ie, USG <1.008); 9/43 (20.9%) dogs were isosthenuric (USG 1.009-1.012); 20/43 (46.5%) dogs had USG between 1.013 and 1.030; and 12/43 (27.9%) dogs had USG >1.030. Increased serum creatinine concentration (≥2.0 mg/dL) was noted in 5/43 dogs (11.6%), all of which had USG ≤1.015. Five additional dogs had BUN concentrations ≥30 mg/dL but serum creatinine concentrations <2.0 mg/dL; USG ranged from 1.015 to 1.032. Hypercalcemia was present in 5/43 (11.6%) dogs; 4 of these had USG <1.015 and the remaining dog had a USG of 1.038. Three dogs (7%) were both hypercalcemic and azotemic (serum creatinine concentration ≥ 2.0 mg/dL; BUN concentration ≥ 30 mg/dL), with USG ranging from 1.005 to 1.015.

Transabdominal ultrasonography was performed in 59/60 dogs; abnormalities in the appearance of the GI tract, liver or both were reported in 49/59 (83%) dogs. Changes in the appearance of the small intestine (particularly the submucosal layer) were noted in 39/59 (66.1%) dogs. Pinpoint hyperechoic foci were noted in the small intestine, liver, mesenteric lymph nodes or some combination of these in 38/59 dogs (64.4%). Abdominal effusion was noted in 17/59 (28.3%) dogs and was anechoic in 14/17.

3.4 | Treatment and outcome

An antemortem diagnosis of *HA* was made in 58/60 dogs (96%). Of these, 2 were euthanized before starting treatment because of either progressive neurological disease or severe hypercalcemia. Information regarding treatment for *HA* therefore was available for 56 dogs.

Fifty-five dogs (98.2% of those treated) initially were treated with praziquantel at a median dosage of 27 (7.9-47) mg/kg PO. In all but 1 case, this dose was given q8h for 1 to 3 days (3-9 administrations); the other dog received 25 mg/kg PO once daily for 7 days. Thirty-five dogs (63.6%) also initially received fenbendazole at a median daily dosage of 50 (24-64) mg/kg PO; median duration of administration was 10 days but ranged from 4 to 14. Details regarding formulation (granules or suspension) and timing of administration (eg, with food) were inconsistently available and therefore not reported. Prednisone was administered PO concurrently to 12 dogs (21.8%); median daily dosage was 1 (0.5-1.1) mg/kg and duration ranged from 2 days to 2 weeks.

Two dogs died acutely during treatment with praziquantel and fenbendazole. An additional dog appeared to have an anaphylactoid reaction after its second dose of praziquantel; the patient recovered after being managed with crystalloid fluids and injectable dexamethasone, and subsequently was discharged from the hospital. None of these 3 dogs was prescribed prednisone.

Information regarding follow-up fecal PCR testing after initial treatment was available for 23/56 dogs. Eleven dogs (47.8%) were PCR negative 1 to 2 months after initial treatment; 1 of these dogs subsequently was positive when retested a month later. Twelve dogs (52.2%) were PCR positive 1 to 2 months after treatment. An additional 2 dogs were retreated because of persistent clinical signs without a repeat PCR. Treatment failures (both confirmed and presumed) totalled 15 (65.2%); 1/15 (0.6%) received fenbendazole alone, 3/15 (20%) received praziquantel alone, and 10/15 (67%) received combination praziquantel and fenbendazole treatment. The second treatment protocol was known for 14 dogs; 2/14 (14%) were given a second treatment of praziquantel alone and the remaining 12/14 (86%) dogs were treated with a combination of praziquantel and fenbendazole. Follow-up PCR testing 3 to 4 weeks after the second treatment was performed in 8 dogs, and was negative in all.

The variety of treatment protocols used, along with inconsistencies in follow-up testing, precluded any useful comparisons between drug regimens. Although praziquantel at 25 mg/kg PO q8h for 2 to 3 days and fenbendazole at 50 mg/kg PO q24h for 10 days was the most common approach (33/56), it was not consistently curative (4 treatment failures were documented). In 8 dogs, this treatment was repeated after 3 to 4 weeks; PCR was repeated 3 to 4 weeks after this second treatment course in 2 dogs and was negative for both.

Survival status 6 months after *HA* diagnosis was determined for 34/56 (60.7%) dogs that underwent treatment. Twenty-five dogs (73.5%) were alive 6 months after initial diagnosis; 4 had died and 5 had been euthanized. Based on the available information, it appears that 6 dogs had died or were euthanized due to complications of their infection and 3 died or were euthanized for other reasons.

4 | DISCUSSION

Previous reports of dogs with *HA* have included substantial proportions diagnosed by histopathology of affected organs, at necropsy (sometimes incidentally), or using fecal sedimentation methods.[2,3,5,11,12,14,15,18] These descriptions suggest a picture of the disease that may not appropriately reflect the true spectrum of clinical signs and laboratory findings, because many dogs were severely compromised or presented with specific abnormalities such as marked and refractory hypercalcemia.[2-4,12-15] In our case series, <5% (2/60) were diagnosed at necropsy, and most cases (81.7%) were identified noninvasively using fecal PCR. This test has effectively supplanted the traditional fecal sedimentation test at both hospitals, and is now routinely performed in dogs presented with evidence of chronic GI or hepatic disease or both. We believe this approach has facilitated earlier recognition of infected individuals, including those with less severe clinical manifestations.

Unfortunately, limited information is available about the diagnostic performance of the fecal PCR test, and it has not been directly compared to traditional saline sedimentation in a large number of naturally-infected dogs. Only 2 dogs in our series had fecal sediment tests performed; 1 of these was positive and no further testing was performed, and the other was negative. This dog subsequently was diagnosed with *HA* on the basis of a positive PCR test; its ultrasonographic findings also were strongly suggestive of infection. Similarly, fecal PCR was positive when performed in 3 dogs with histopathologic confirmation of *HA* infection. These findings suggest that fecal PCR is adequately sensitive, but do not provide any information regarding its specificity.

Similar to findings in previous reports, clinical signs associated with *HA* in the dogs in our study were often nonspecific and included vomiting, diarrhea, anorexia, and weight loss. Polyuria and polydipsia were reported in <20% of dogs; as was noted in 55% of cases in a previous case series, but just 6% had polyuria and polydipsia in another report.[2,3] Hypercalcemia in the dogs in our study commonly was associated with poorly concentrated urine but only 1 dog had evidence of concurrent clinically relevant azotemia. In all, 5 normocalcemic dogs had evidence of intrinsic renal dysfunction (ie, serum creatinine concentration ≥ 2.0 mg/dL and USG <1.015); however insufficient information was available to determine if these findings were secondary to *HA* infection or a reflection of unrelated renal disease.

Laboratory findings similarly were nonspecific in most infected dogs, and generally reflected injury or compromise of the GI tract or liver or both. Hypoalbuminemia was noted in approximately 25% of patients, likely attributable to GI or hepatic dysfunction or both, but could have indicated concurrent glomerular disease. Schistosomiasis has been reported in a dog with membranoproliferative glomerulonephritis; proteinuria resolved after treatment with fenbendazole and praziquantel.[9] Unfortunately, insufficient information was available to determine the prevalence of proteinuria in our study population. Although the life cycle of *HA* predictably involves the liver, the majority of dogs had liver enzyme activities within the reference range, and when increased, increases usually were mild to moderate and serum bilirubin concentration remained within the reference range.

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However, high eosinophil count (>500/μL in >40%) and hyper-globulinemia (>3.7 g/dL in >40%) routinely were reported; these findings therefore should prompt consideration of an HA in a dog with consistent clinical signs.

In previous reports, hypercalcemia was a prominent feature in dogs with HA,[2,3,5] and was documented in 73% (11/15) of patients presented with clinical compromise attributable to schistosomiasis in a case series.[3] In contrast, <10% of the dogs in our study were hypercalcemic. This difference may reflect a historical diagnostic bias based on the association between HA and hypercalcemia. Additionally, the lower incidence of hypercalcemia in the patient population reported here also may reflect a trend toward earlier diagnosis or the identification of dogs with lower parasite burdens. It has been suggested that HA-associated hypercalcemia is similar in pathogenesis to hypercalcemia associated with other granulomatous conditions,[3] although increased concentrations of parathyroid hormone-related protein previously were reported in 2 dogs with HA.[11] Because the mechanisms of hypercalcemia in dogs with HA are not well understood, it is unclear if the normocalcemic dogs in our study eventually would have become hypercalcemic or would have remained normocalcemic even if the disease remained undiagnosed. Hypercalcemia in dogs with HA likely is multifactorial, and may be determined primarily by the immune response of the individual rather than parasitic burden alone. Although our findings suggest that hypercalcemia is actually quite uncommon in dogs with HA, it still should be considered as a differential diagnosis for hypercalcemia even in otherwise asymptomatic dogs in endemic areas.

Changes in the liver, GI tract and other organs routinely were noted on transabdominal ultrasonography in the dogs described here. It recently was reported that abnormal small intestinal wall layering and with pinpoint hyperechoic foci in the small intestines, liver, or mesenteric lymph nodes are highly suggestive of HA infection, with a positive predictive value of 94%.[16] We believe testing for HA is appropriate if these ultrasonographic findings are noted, even when the patient history does not suggest infection. However, it is not unusual for dogs with clinically relevant schistosomiasis to have relatively unremarkable findings on ultrasonography, and failure to identify the expected changes should not exclude this possibility.[16]

Previous descriptive reports provide little information regarding treatments, cure rates, and patient outcomes. Various protocols were used in the dogs reported here, with most dogs receiving both praziquantel and fenbendazole. A lack of consistency regarding dosage, frequency, and duration of treatment limits the reliability of any conclusions that may be drawn, but currently we recommend a combination of praziquantel at 25 mg/kg PO q8h for 3 days and fenbendazole at 50 mg/kg PO q24h for 10 days. The latter should be administered with food, because food substantially enhances its bioavailability.[19] Information regarding post-treatment fecal PCR testing was inconsistently available, but the data indicate an initial treatment failure rate of approximately 50%. However, decisions regarding repeat testing may have been influenced by persistent clinical signs, resulting in a bias toward follow-up testing in refractory cases. A second course of treatment was effective in all dogs that had follow up PCR results.

One dog that tested negative by fecal PCR for HA 1 month after treatment then was positive 2 months after treatment. The initial negative result may have been a result of intermittent shedding of HA ova or treatment may have decreased ova shedding below the level of detection of fecal PCR testing. Based on this finding, we recommend follow-up testing at both 4 and 8 weeks after treatment. Continued environmental exposure to the parasite also may lead to reinfection. Previous reports describe HA infection in multiple dogs within the same household, attributable to exposure to the same contaminated environment.[5,11] We therefore recommend fecal PCR testing of all at-risk dogs.

Praziquantel is licensed for use in dogs and cats as a cestocide; dose recommendations for this purpose are made on a sliding scale and are higher for smaller dogs, but approximately 6.25 mg/kg, with a maximum of 170 mg/dog.[20] Clinical signs associated with marked overdose in dogs include vomiting, salivation and lethargy. Dosages routinely used for treatment of HA are substantially higher than those needed to treat tapeworm infections, and vomiting has been reported anecdotally during treatment for HA. Insufficient information was available to establish the likelihood of this adverse effect in the dosages used here, but clinicians might choose to preemptively prescribe an antiemetic. Praziquantel has been widely used for decades for the treatment of schistosomiasis in humans, caused by Schistosoma mansoni and haematobium. The drug is thought to target calcium ion channels in the trematode, but limited information is available regarding its mechanism of action.[21]

A recent systematic review of praziquantel use in humans with schistosomiasis reported better cure rates when a second dose of praziquantel was administered 2 to 8 weeks after the initial dose (69%-91% vs 42%-79% cure rate for S. mansoni).[22] This outcome may reflect the relative resistance of immature schistosomes to praziquantel (ie, 14-35 days after infection) compared to the more susceptible adult worms. The number of dogs in our study given a second treatment after 3 to 4 weeks is too small (n = 8) to draw any firm conclusions, but both dogs with follow-up testing were negative. This approach may be reasonable to consider, but the cost associated with a second course of treatment in a large dog may exceed the cost of follow-up fecal PCR.

Initial treatment failure in the dogs described here also may be explained by compromised uptake of praziquantel or fenbendazole because of GI tract dysfunction secondary to inflammation or fibrosis. Assuming the first treatment course ameliorated the disease, sufficient drug absorption may have occurred after the second course of treatment to effect a cure. We are unaware of any reports comparing PO vs parenteral administration of praziquantel in patients with HA, but parenteral administration may be an option to consider in individuals with evidence of substantial malabsorptive disease. One case report described unsuccessful treatment with PO praziquantel at 5 mg/kg (duration of treatment not specified) but a cure was attained after treatment with a single dose of injectable praziquantel (312 mg [approximately 11 mg/kg] SC) in combination with a high dosage of praziquantel PO (30 mg/kg; duration not specified).[4] The recommended maximum dose for SC or IM praziquantel is 3 mL (170 mg) but safety studies report that doses 5 times the labeled dosage given IM or SC at 14-day intervals are safe in healthy young dogs.[23] Additional studies are

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needed to establish the extent of GI tract dysfunction and its impact on praziquantel absorption in dogs with HA, and to determine optimal dosing protocols and routes of administration.

Two dogs died during the treatment phase; the cause of death was not established for either patient but was attributed to some form of hypersensitivity or anaphylactoid reaction in 1 dog. Concerns regarding the effect of acute and widespread worm death resulted in the short-term use of anti-inflammatory doses of prednisone by some attending clinicians. Our study was underpowered to identify a significant protective effect from concurrent glucocorticoid treatment, although 2 of us routinely use this approach.

The prognosis for treated dogs in our study generally was positive, but 6/34 (17.6%) with known outcomes died or were euthanized because of HA infection. Long-term follow-up data was limited, but indicated a 6-month survival rate of approximately 75%. When considering these results, it is important to bear in mind that both practices contributing to this case series are referral hospitals, which may have resulted in a bias toward more severely infected individuals.

Our study had several limitations, primarily related to its retrospective design. Each dog's diagnostic evaluation was determined by the attending clinician, resulting in variations in the history collected and incomplete data sets for some clinicopathologic variables. Decisions regarding clinical vs incidental infections therefore were somewhat subjective, because the absence of a comment regarding diarrhea, for example, was presumed to mean that the feces were formed. Similarly, decisions regarding treatment and follow-up were made on a case-by-case basis, thereby limiting our ability to reliably identify best practices. Prospective studies are needed to determine optimal treatment and retesting protocols.

An additional limitation was reliance on a diagnostic modality (ie, the fecal PCR test) for which limited independent validation is available. Although test sensitivity appears to be adequate (1.5 eggs/g of feces), some of the dogs included may have been false positives. Specificity is difficult to determine because of the absence of other schistosome species in dogs in the United States. However, fecal samples from military dogs stationed in Iraq and infected with S. mansoni were negative on the PCR test used here (personal communication, Micah A. Bishop). Future studies comparing findings for a large number of dogs tested using both noninvasive options (ie, fecal PCR and sediment examination) are needed.

As a consequence of increased awareness and more accessible diagnostic options, the clinical picture associated with HA infection has changed. Practitioners in endemic areas should consider the possibility of schistosomiasis in any dog with signs of chronic enteropathy or hepatopathy, particularly if high eosinophil count and hyperglobulinemia are reported. Characteristic ultrasonographic changes similarly should prompt testing for HA even in the absence of anorexia, vomiting, diarrhea, or weight loss. Prompt recognition of this infection permits timely and appropriate treatment, and is expected to improve patient outcomes.

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CONFLICT OF INTEREST DECLARATION

Audrey K. Cook serves as Associate Editor for the Journal of Veterinary Internal Medicine. She was not involved in review of this manuscript.

OFF-LABEL ANTIMICROBIAL DECLARATION

Due to the retrospective nature of the study, label usage of antibiotics could not be determined in all patients.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

ORCID

Audrey K. Cook (iD) https://orcid.org/0000-0002-2840-6497

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