

**M**olly, a 6-year-old spayed bichon frise, was presented with a 2-month history of hematochezia and a 3-day history of inappetence and vomiting.



MAKE YOUR DIAGNOSIS

# HEMATOCHEZIA IN A DOG

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## History

Hematochezia was initially mild but had progressed in severity. At presentation, Molly was defecating mostly frank blood with little discernible fecal material. Metronidazole (10 mg/kg PO twice a day), amoxicillin (10 mg/kg PO twice a day), and sulfasalazine (20 mg/kg PO 3 times a day) were previously prescribed for treatment of diarrhea but were discontinued 10 days before presentation after no apparent improvement. Heartworm and flea and tick preventives had also been discontinued.

Molly had a previous history of acute blindness, diagnosed as bilateral retinal detachment 5 weeks before presentation (*Figure 1*, next page). Blood pressure was mildly elevated at 160 mm Hg. Tests for infectious

disease were negative. Additional testing was offered but declined. Immunosuppressive doses of prednisone (1 mg/kg PO twice a day) were prescribed for suspected steroid responsive retinal detachment. When retinal reattachment did not occur after 1 week of corticosteroid therapy, further evaluation was recommended but was declined by the owner.

## Physical Examination

Molly had a lean BCS of 4/9 and was 5% dehydrated. Frank blood was found on rectal examination, and the ophthalmic examination remained unchanged. Temperature, pulse, and respiration were normal. No additional abnormalities were identified.

BCS = body condition score



### Diagnostic Results

Serum chemistry profile revealed hyperglobulinemia (globulin, 4.1 g/dL; reference interval, 2.0-3.2 g/dL) and hypoalbuminemia (albumin, 2.7 g/dL; reference interval, 3.2-4.1 g/dL). A CBC and rectal scrape were unremarkable. Urinalysis was initially considered to be normal, with a urine specific gravity of 1.030, absence of protein, and an inactive sediment. Abdominal ultrasonography revealed moderate thickening of the intestinal wall (up to 0.41 cm thick; normal thickness, <0.3 cm), which originated at the ileocecal junction and extended the length of the colon. Numerous lymph nodes surrounding the colon were also enlarged. Ultrasound-guided fine-needle aspiration of the thickened colonic mucosa and intraabdominal lymph nodes was performed; however, cytologic evaluation was nondiagnostic because of low cellularity.

ABCD = amphotericin B colloidal dispersion

### Definitive Cytology Results

A subretinal tap was performed with the patient under general anesthesia. Cytology of the subretinal fluid (*Figure 2*)

and reevaluation of urine sediment by the clinical pathologist revealed *Prototheca* spp-like organisms. Growth of *P zop-fii* was evident on fungal culture of the urine.

### Diagnosis

Protothecosis

### ASK YOURSELF

#### QUESTION 1

What is protothecosis?

#### QUESTION 2

What are the most common ways *Prototheca* spp infection manifests clinically?

#### QUESTION 3

How is protothecosis diagnosed, and what is the appropriate treatment?

#### QUESTION 4

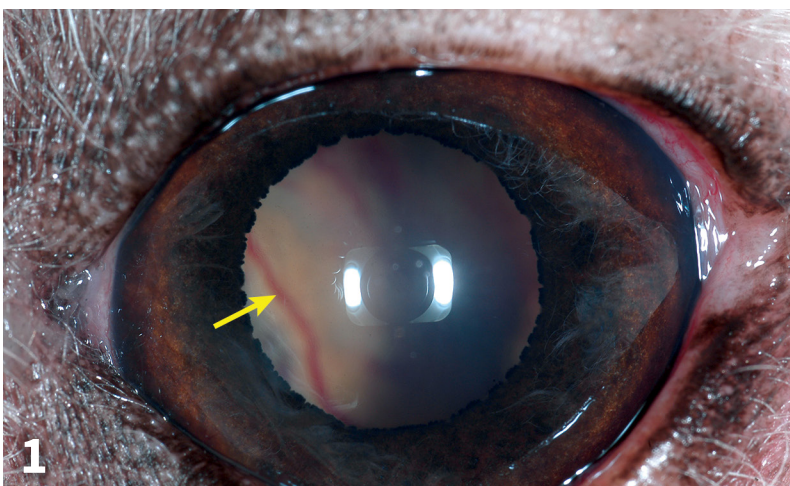
How should I monitor a patient receiving amphotericin B and itraconazole?

### Prognosis

Poor-to-grave. There is a single reported case of a dog surviving  $\geq 12$  months.<sup>1</sup> This dog had both colonic and ophthalmologic involvement; it is likely that previous immunosuppression from prednisone caused an acute worsening of the condition. Prognosis can likely worsen with neurologic and/or ophthalmic system involvement.<sup>1</sup>

### Treatment

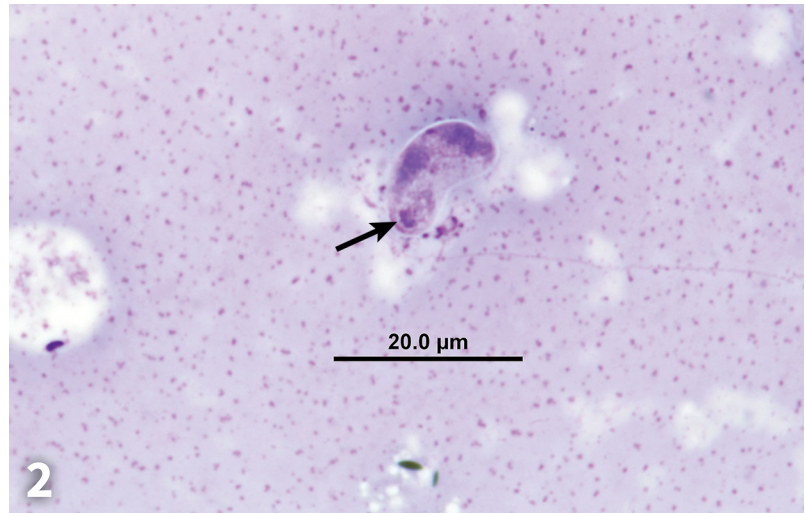
Molly was initially treated with amphotericin B colloidal dispersion (ABCD; 0.5 mg/kg IV over 4-6 hours) every 48 hours for 4 treatments. On the fourth day of treatment, Molly also received itraconazole (5 mg/kg twice a day). *Prototheca* spp infection is generally considered a progressive, terminal disease; thus, daily itraconazole was continued long-term.



▲ Molly's left eye 5 weeks before presentation. Complete bullous retinal detachment with a right subretinal exudate (arrow) can be observed.

## Outcome

Molly's hematochezia improved dramatically with ABCD and itraconazole treatment. Her stool remained soft for several weeks, but her appetite and feces returned to normal within the first month of treatment. Five months into treatment, Molly developed neurologic signs, including vocalization and ataxia; terbinafine at a low dose (10 mg/kg PO once a day; because of itraconazole continuation) was added to the treatment protocol because of suspicion of advanced disease. Neurologic signs resolved following treatment, and at the time of this publication (2 years after diagnosis), the patient is alive and being treated with itraconazole (5 mg/kg twice a day) and terbinafine (10 mg/kg PO once a day). The authors have recommended she continue this treatment for life.



▲ Single *Prototheca zopfii* organism observed in a cytologic preparation of subretinal fluid. *P. zopfii* is a round-to-oval organism with a thin, clear cell wall and granular, blue-gray-to-purple interior structures. The organism can be observed above the magnification legend. The red-to-purple round structures (**arrow**) represent endospores, which can sometimes be observed. (100× objective)

## DID YOU ANSWER?

### QUESTION 1

#### What is protothecosis?

*Prototheca* spp are achlorophyllous, saprophytic algae that are ubiquitous in the environment; however, infection is rare. *Prototheca* spp organisms are round-to-oval with a thin, clear cell wall and granular basophilic cytoplasm.<sup>2</sup> They should be differentiated from *Chlorella* spp, green algae that have much larger starch granules present in the cytoplasm.<sup>3</sup> Only 2 species, *P. zopfii* and *P. wickerhamii*, are known to be pathogenic.<sup>3</sup>

In humans, immunosuppression has been shown to predispose patients to disseminated infection,<sup>4</sup> but risk factors leading to disease development in dogs have not been identified. Dogs with protothecosis do not pose a risk to humans or other animals in the household. However, infected animals may serve as sentinels to indicate a higher prevalence in the area. *Prototheca* spp are

commonly identified in areas with raw and treated sewage, slime flux, and animal waste and can contaminate flowing and standing water.<sup>4</sup>

### QUESTION 2

#### What are the most common ways *Prototheca* spp infection manifests clinically?

The most common clinical sign associated with protothecosis in dogs is diarrhea of large-bowel origin with associated hematochezia. From there, the organism can undergo hematogenous or lymphatic spread throughout the body.<sup>5</sup> Clinical signs unrelated to the GI tract are highly variable and are associated with organ system(s) affected by ocular (eg, granulomatous chorioretinitis, retinal degeneration, exudative retinal detachment, acute blindness), neurologic (eg, head tilt, circling, ataxia, paresis), and renal (eg, polyuria, polydipsia, azotemia) involvement.<sup>6,7</sup>



Alternatively, *P wickerhamii* infection can result in cutaneous disease after traumatic inoculation of organisms; this is common in humans and cats. A combination of surgical management and systemic therapy is recommended for these patients and is sometimes curative.<sup>3</sup>

**QUESTION 3**

**How is protothecosis diagnosed, and what is the appropriate treatment?**

Protothecosis can be tentatively diagnosed based on identification of the organism on cytology and/or histopathologic examination of affected tissues. However, to definitively diagnose protothecosis, culture is necessary.<sup>1</sup>

Widely accepted treatment recommendations have not been formulated, even in humans, as the disease occurs rarely.<sup>3</sup> However, a dog that reportedly survived for ≥1 year (before being lost to follow-up) was treated successfully with a combination of amphotericin B and itraconazole,<sup>1</sup> making this a potential therapeutic consideration.

**References**

1. Stenner VJ, Mackay B, King T, et al. Protothecosis in 17 Australian dogs and a review of the canine literature. *Med Mycol*. 2007;45(3):249-266.
2. Valenciano AC, Cowell RL. *Diagnostic Cytology and Haematology of the Dog and Cat*. 4th ed. St. Louis, MO: Mosby; 2014:90.
3. Greene CE. *Infectious Disease of the Dog and Cat*. 4th ed. Philadelphia, PA: WB Saunders; 2012:696-701.
4. Shank AM, Dubielzig RD, Teixeira LB. Canine ocular protothecosis: A review of 14 cases. *Vet Ophthalmol*. 2015;18(5):437-442.
5. Hosaka S, Hosaka M. A case report of canine

**QUESTION 4**

**How should I monitor a patient receiving amphotericin B and itraconazole?**

Amphotericin B is available in many formulations. A lipid-based formulation, which is less nephrotoxic and has better tissue penetration, is recommended.<sup>8</sup> Before starting amphotericin B, a renal profile and urinalysis should be performed to evaluate for subclinical kidney disease, which can be exacerbated with treatment. During amphotericin B treatment, a urinalysis, including sediment examination, should be evaluated for casts before each treatment, as cylindruria may be the first sign of renal damage. By the time azotemia is observed, renal damage is often severe. This makes serum chemistry analysis an insensitive method of evaluating for potential toxicity.

Before starting treatment with itraconazole, liver values should be evaluated. Hepatotoxicity is a common side effect of itraconazole<sup>9</sup> and may require dose decreases or drug discontinuation. Liver values should be evaluated during the first 2 weeks of therapy and rechecked every 2 to 3 months thereafter. ■

protothecosis. *J Vet Med Sci*. 2004;66(5):593-597.

6. Strunck E, Billups L, Avgeris S. Canine protothecosis. *Compend Contin Educ Pract Vet*. 2004;26(2):96-103.
7. Pressler BM, Gookin JL, Sykes JE. Urinary tract manifestations of protothecosis in dogs. *JVIM*. 2005;19(1):115-119.
8. Bekersky J, Boswell GW, Hiles R, et al. Safety and toxicokinetics of intravenous liposomal amphotericin B (Ambisome) in beagle dogs. *Pharm Res*. 1999;16(11):1694-1701.
9. Legendre AM, Rohrbach BW, Toal RL, et al. Treatment of blastomycosis with itraconazole in 112 dogs. *JVIM*. 1996;10(6):365-371.

**Caution**

Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

**Indications**

SENTINEL<sup>®</sup> SPECTRUM<sup>®</sup> (milbemycin oxime/lufenuron/praziquantel) is indicated for the prevention of heartworm disease caused by *Dirofilaria immitis*; for the prevention and control of flea populations (*Ctenocephalides felis*); and for the treatment and control of adult roundworm (*Toxocara canis*, *Toxascaris leonina*), adult hookworm (*Ancylostoma caninum*), adult whipworm (*Trichuris vulpis*), and adult tapeworm (*Taenia pisiformis*, *Echinococcus multilocularis* and *Echinococcus granulosus*) infections in dogs and puppies two pounds of body weight or greater and six weeks of age and older.

**Dosage and Administration**

SENTINEL SPECTRUM should be administered orally, once every month, at the minimum dosage of 0.23 mg/lb (0.5 mg/kg) milbemycin oxime, 4.55 mg/lb (10 mg/kg) lufenuron, and 2.28 mg/lb (5 mg/kg) praziquantel. For heartworm prevention, give once monthly for at least 6 months after exposure to mosquitoes.

**Dosage Schedule**

Body Weight	Milbemycin Oxime per chewable	Lufenuron per chewable	Praziquantel per chewable	Number of chewables
2 to 8 lbs.	2.3 mg	46 mg	22.8 mg	One
8.1 to 25 lbs.	5.75 mg	115 mg	57 mg	One
25.1 to 50 lbs.	11.5 mg	230 mg	114 mg	One
50.1 to 100 lbs.	23.0 mg	460 mg	228 mg	One
Over 100 lbs.	Administer the appropriate combination of chewables			

To ensure adequate absorption, always administer SENTINEL SPECTRUM to dogs immediately after or in conjunction with a normal meal.

SENTINEL SPECTRUM may be offered to the dog by hand or added to a small amount of dog food. The chewables should be administered in a manner that encourages the dog to chew, rather than to swallow without chewing. Chewables may be broken into pieces and fed to dogs that normally swallow treats whole. Care should be taken that the dog consumes the complete dose, and treated animals should be observed a few minutes after administration to ensure that no part of the dose is lost or rejected. If it is suspected that any of the dose has been lost, redosing is recommended.

**Contraindications**

There are no known contraindications to the use of SENTINEL SPECTRUM.

**Warnings**

Not for use in humans. Keep this and all drugs out of the reach of children.

**Precautions**

Treatment with fewer than 6 monthly doses after the last exposure to mosquitoes may not provide complete heartworm prevention.

Prior to administration of SENTINEL SPECTRUM, dogs should be tested for existing heartworm infections. At the discretion of the veterinarian, infected dogs should be treated to remove adult heartworms. SENTINEL SPECTRUM is not effective against adult *D. immitis*.

Mild, transient hypersensitivity reactions, such as labored breathing, vomiting, hypersalivation, and lethargy, have been noted in some dogs treated with milbemycin oxime carrying a high number of circulating microfilariae. These reactions are presumably caused by release of protein from dead or dying microfilariae.

Do not use in puppies less than six weeks of age.

Do not use in dogs or puppies less than two pounds of body weight.

The safety of SENTINEL SPECTRUM has not been evaluated in dogs used for breeding or in lactating females. Studies have been performed with milbemycin oxime and lufenuron alone.

**Adverse Reactions**

The following adverse reactions have been reported in dogs after administration of milbemycin oxime, lufenuron, or praziquantel: vomiting, depression/lethargy, pruritus, urticaria, diarrhea, anorexia, skin congestion, ataxia, convulsions, salivation, and weakness.

To report suspected adverse drug events, contact Virbac at 1-800-338-3659 or the FDA at 1-888-FDA-VETS.

**Information for Owner or Person Treating Animal**

*Echinococcus multilocularis* and *Echinococcus granulosus* are tapeworms found in wild canids and domestic dogs. *E. multilocularis* and *E. granulosus* can infect humans and cause serious disease (alveolar hydatid disease and hydatid disease, respectively). Owners of dogs living in areas where *E. multilocularis* or *E. granulosus* are endemic should be instructed on how to minimize their risk of exposure to these parasites, as well as their dog's risk of exposure. Although SENTINEL SPECTRUM was 100% effective in laboratory studies in dogs against *E. multilocularis* and *E. granulosus*, no studies have been conducted to show that the use of this product will decrease the incidence of alveolar hydatid disease or hydatid disease in humans. Because the prepatent period for *E. multilocularis* may be as short as 26 days, dogs treated at the labeled monthly intervals may become reinfected and shed eggs between treatments.

Manufactured for: Virbac AH, Inc.  
P.O. Box 162059, Ft. Worth, TX 76161

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