April 2020

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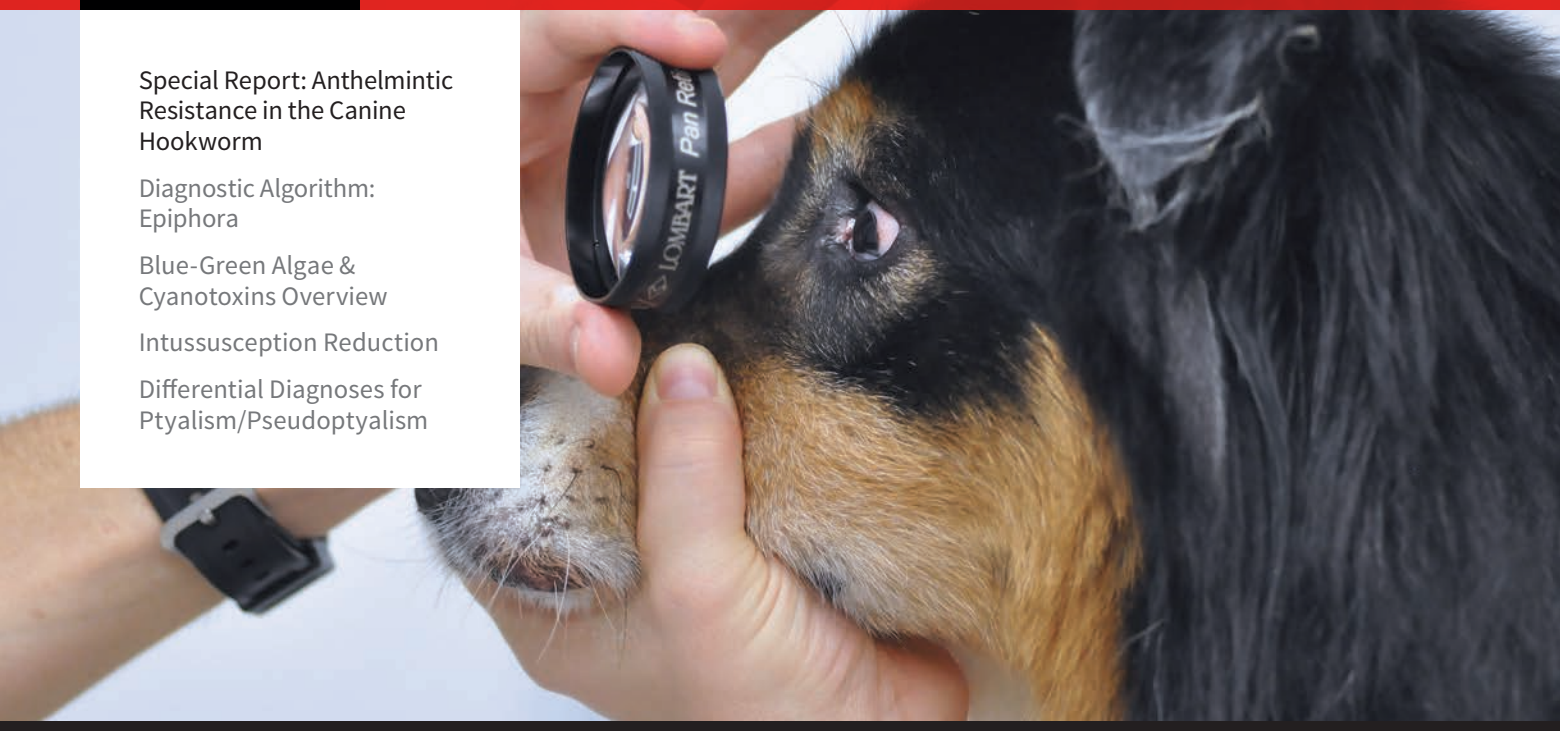
STEP-BY-STEP FUNDIC EXAMINATION

IN THIS ISSUE



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Volume 18 Number 4

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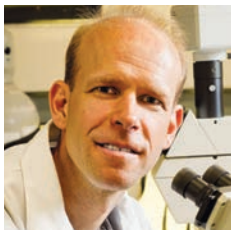

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Providing small animal practitioners and their teams with practical, relevant information on the latest topics in veterinary medicine

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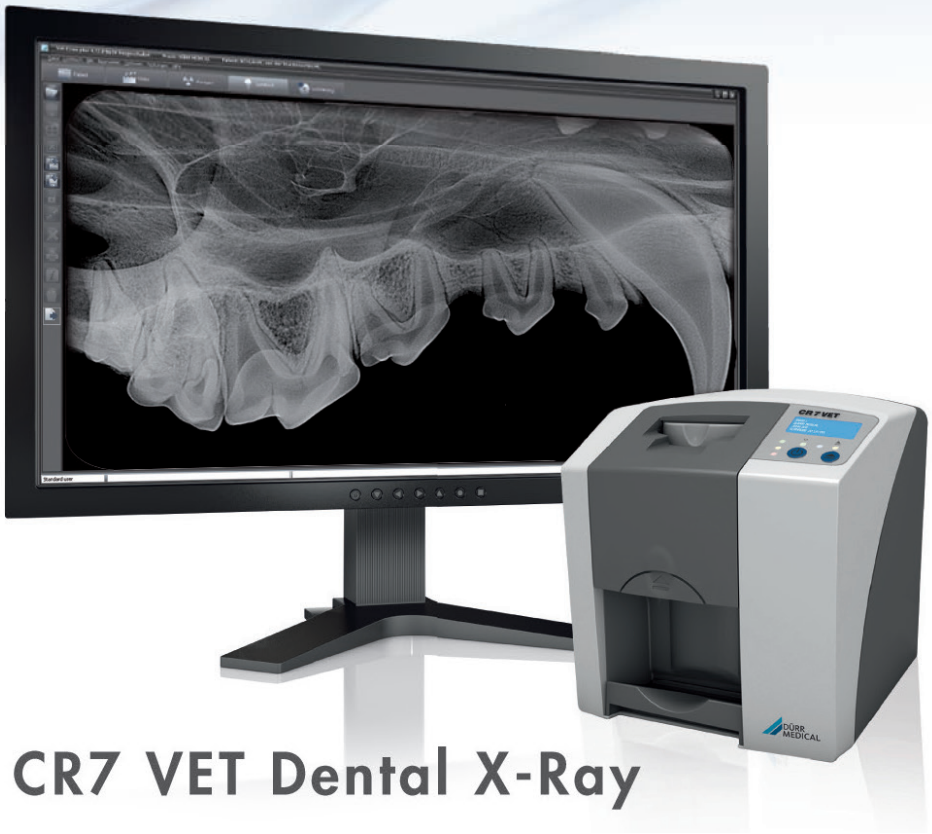

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What veterinary service industry job did you have before attending veterinary school?

"I worked as a kennel helper, veterinary assistant, dog trainer, laboratory technician, conservation educator and zookeeper in a small zoo, nail trimmer, and pet sitter! I am in veterinary school now and am a veterinary blood bank assistant, researcher, and veterinary assistant in a small and exotic animal clinic. I also volunteer at a zoo."—*Mark B*

"I have been a kennel helper, veterinary assistant, animal caretaker of research rodents, and animal caretaker at a primate research facility."—*Jackie S*

"I was a registered nurse in an emergency room, which is just like working at a zoo except the patients could talk."—*Buck B*

Have you ever said this?

"As you might be able to tell, I flunked out of art school." —*Ipsqich Animal Hospital*

"I am a far better surgeon than artist, ma'am."—*Caleb W*

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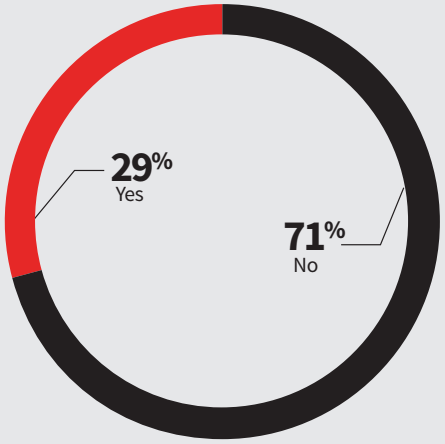
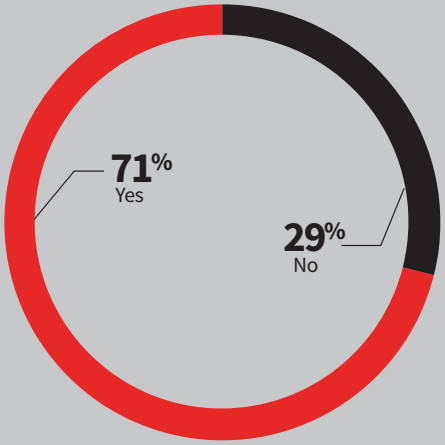


Do you send Elizabethan collars home with patients after routine spay and neuter procedures?



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DIFFERENTIAL DIAGNOSIS PAGE 13

PABLO DAVID JIMENEZ CASTRO, DVM, is currently completing his PhD in the Department of Infectious Diseases at University of Georgia. He earned his DVM from the National University of Colombia in Bogata, Columbia, in 2013 before working at Novartis Animal Health and Elanco Animal Health in regulatory affairs. Dr. Castro's research interests include clinical efficacy and safety trials, anthelmintic resistance, and the epidemiology and control of parasites of veterinary and public health importance. His work has been published in several peer-reviewed journals and has given presentations at various scientific meetings.

SPECIAL REPORT PAGE 15

STEVE ENSLEY, DVM, PhD, is a clinical professor at Kansas State University, where he also earned his DVM. He earned his MS and PhD in veterinary toxicology from Iowa State University and has published and presented extensively on applied veterinary toxicology. His interests include clinical veterinary toxicology and applied veterinary toxicology research.

CONSULT THE EXPERTS PAGE 39

SCOTT FRITZ, DVM, is a resident in toxicology at Kansas State University. Dr. Fritz earned his DVM from Iowa State University and is involved in several monitoring and mitigation programs with the goal of predicting and effectively preventing harmful algal blooms from recreational and animal drinking waters. His interests include food animal toxicology and blue-green algae.

CONSULT THE EXPERTS PAGE 39

DJ HAEUSSLER JR, DVM, MS, DACVO, is the founder and owner of The Animal Eye Institute, which has locations in Cincinnati and Dayton, Ohio, and Florence, Kentucky. Dr. Haeussler earned his DVM and MS from The Ohio State University, where he also completed a residency in comparative ophthalmology. He completed 2 internships at Garden State Veterinary Specialists in Tinton Falls, New Jersey. Dr. Haeussler has been published in many peer-reviewed publications and is the author and publisher of *Recognition of Canine Ocular Diseases*. Dr. Haeussler enjoys resident development and lecturing on ophthalmologic disease.

DIAGNOSTIC TREE PAGE 26

RAY M. KAPLAN, DVM, PhD, DEVPC, DACVM (Parasitology), is a professor at the University of Georgia College of Veterinary Medicine. He earned his DVM from Virginia-Maryland College of Veterinary Medicine and worked in a mixed-species practice before earning his PhD in veterinary parasitology at University of Florida. Dr. Kaplan's research program is focused on measuring, understanding, and solving problems of drug resistance in nematode parasites. He is past president of the American Association of Veterinary Parasitologists and has been recognized with the Pfizer Award for Research Excellence and the American Association of Veterinary Parasitologists–Boehringer Ingelheim Distinguished Veterinary Parasitologist Award.

SPECIAL REPORT PAGE 15

Continues on page 10

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ON THE COVER

PROCEDURES PRO
Fundic Examination
Brett D. Story, DVM
Caryn Plummer, DVM, DACVO

PG 70

NOTICE OF CORRECTION
In the article "Acute Pleural Effusion in a Dog" in the March 2020 issue of *Clinician's Brief*, Figure 1A and Figure 1B should have been swapped. *Clinician's Brief* regrets the error.

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*Repeat administration every 4 to 8 weeks as needed in individual patients.

References: 1. Data on file, Study Report No. C863R-US-12-018, Zoetis Inc. **2.** Gonzales AJ, Humphrey WR, Messamore JE, et al. Interleukin-31: its role in canine pruritus and naturally occurring canine atopic dermatitis. *Vet Dermatol*. 2013;24(1):48-53. doi:10.1111/j.1365-3164.2012.01098.x. **3.** Data on file, Study No. 16SORDER0101, Zoetis Inc.

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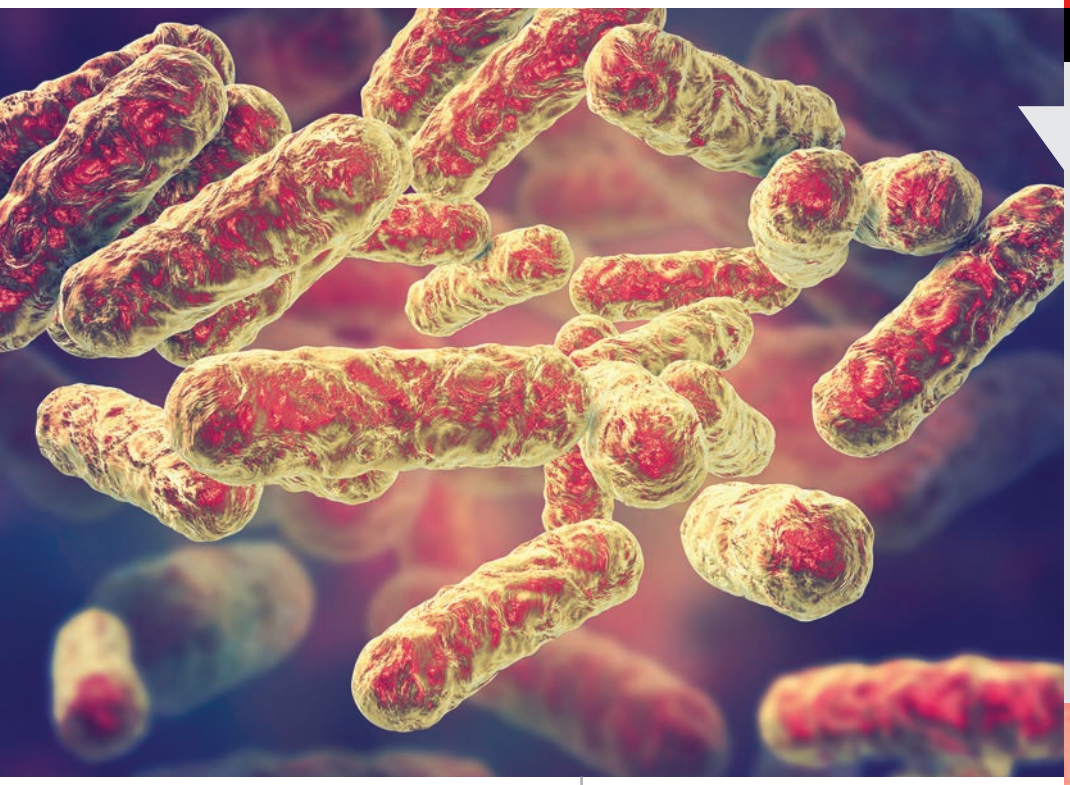

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THIS MONTH'S FEATURED CLINICAL CONTENT AVAILABLE ONLY ONLINE

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Bartonella Species of Human Significance with Dr. Davis

Radford Davis, DVM, MPH, DACVPM, discusses the risks of being exposed to *Bartonella* spp in the clinic, how to limit those risks, and how to educate pet owners without causing fear or panic.
brief.vet/bartonella

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Antibiotic Use

This lesson covers antibiotic uses ranging from GI and hepatobiliary to urinary tract and neurologic infections and includes an overview of culture and susceptibility reports.
brief.vet/antibiotic-use

Find a collection of helpful COVID-19 resources to keep your patients and practice safe by scanning the QR code or visiting brief.vet/covid

Using QR codes from your mobile device is easy and quick!

Simply focus your phone's camera on the QR code as if taking a picture (but don't click!). A notification banner will pop up at the top of your screen; tap the banner to view the linked content.

CHRISTINA KORB, DVM, is a veterinary ophthalmology resident at The Animal Eye Institute, which has locations in Cincinnati and Dayton, Ohio, and Florence, Kentucky. She earned her DVM from Purdue University before completing a small animal rotating internship at University of Missouri and a specialty ophthalmology internship at The Animal Eye Institute. Dr. Korb's interests include ocular manifestations of systemic disease and all aspects of ophthalmologic microsurgery.

DIAGNOSTIC TREE PAGE 26

CHRISTIAN LATIMER, DVM, CCRP, DACVS-SA, is a staff surgeon at Carolina Veterinary Specialists in Charlotte, North Carolina. He earned his DVM from Western University of Health Sciences and completed a small animal rotating internship and surgical residency at University of Tennessee.

PROCEDURES PRO PAGE 30

CARYN PLUMMER, DVM, DACVO, is an associate professor of small animal ophthalmology at University of Florida, where she also earned her DVM and completed a residency in comparative ophthalmology. She also completed an internship in small animal medicine and surgery at Michigan State University. Dr. Plummer has lectured extensively on many topics associated with clinical veterinary ophthalmology and animal models of ophthalmic disease, especially glaucoma, and is a charter member of and currently serves as the secretary/treasurer for the International Equine Ophthalmology Consortium. Her research interests include corneal wound healing and glaucoma.

PROCEDURES PRO PAGE 70

BRETT D. STORY, DVM, is a small animal medicine and surgery rotating intern at University of Florida with a specialty interest in veterinary ophthalmology. He previously worked as a veterinary technician and sea turtle researcher before earning his DVM from Auburn University. As a veterinary student, his research interests were in neurologic and ophthalmic pathology. His neurologic interests have involved research in gene therapy for lysosomal storage diseases.

PROCEDURES PRO PAGE 70

MIKAELA THOMASON, DVM, is a small animal surgery intern at Carolina Veterinary Specialists in Charlotte, North Carolina. She earned her DVM from Auburn University and completed a rotating internship at BluePearl Veterinary Specialist in Nashville, Tennessee. Her interests include soft tissue and orthopedic surgery with an emphasis in oncology in dogs and cats as well as diagnostic imaging and rehabilitation.

PROCEDURES PRO PAGE 30

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peace of mind.

Powerful protection can also be gentle:

- ✓ Safe for puppies as young as 8 weeks of age weighing 4 lbs or more
- ✓ Over 223 million doses of afoxolaner have been prescribed[1]
- ✓ And it's the only flea and tick control product indicated for the prevention of *Borrelia burgdorferi* infections as a direct result of killing *Ixodes scapularis* vector ticks

NexGard®
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What one little chew can do

[1]Data on file.

Boehringer Ingelheim

IMPORTANT SAFETY INFORMATION: NexGard is for use in dogs only. The most frequently reported adverse reactions include vomiting, pruritus, lethargy, diarrhea and lack of appetite. The safe use of **NexGard** in pregnant, breeding, or lactating dogs has not been evaluated. Use with caution in dogs with a history of seizures or neurologic disorders. For more information, see the full prescribing information or visit www.NexGardClinic.com.

See page 12 for product information summary.

NexGard®
(afoxolaner) Chewables

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

Description:
NexGard® (afoxolaner) is available in four sizes of beef-flavored, soft chewables for oral administration to dogs and puppies according to their weight. Each chewable is formulated to provide a minimum afoxolaner dosage of 1.14 mg/lb (2.5 mg/kg). Afoxolaner has the chemical composition 1-Naphthalenecarboxamide, 4-[5- [3-chloro-5-(trifluoromethyl)-phenyl]-4, 5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl.

Indications:
NexGard kills adult fleas and is indicated for the treatment and prevention of flea infestations *(Ctenocephalides felis),* and the treatment and control of Black-legged tick *(Ixodes scapularis),* American Dog tick *(Dermacentor variabilis),* Lone Star tick *(Amblyomma americanum),* and Brown dog tick (*Rhipicephalus sanguineus*) infestations in dogs and puppies 8 weeks of age and older, weighing 4 pounds of body weight or greater, for one month. NexGard is indicated for the prevention of *Borrelia burgdorferi* infections as a direct result of killing *Ixodes scapularis* vector ticks.

Dosage and Administration:
NexGard is given orally once a month, at the minimum dosage of 1.14 mg/lb (2.5 mg/kg).

Dosing Schedule:

Body Weight	Afoxolaner Per Chewable (mg)	Chewables Administered
4.0 to 10.0 lbs.	11.3	One
10.1 to 24.0 lbs.	28.3	One
24.1 to 60.0 lbs.	68	One
60.1 to 121.0 lbs.	136	One
Over 121.0 lbs.	Administer the appropriate combination of chewables	

NexGard can be administered with or without food. Care should be taken that the dog consumes the complete dose, and treated animals should be observed for a few minutes to ensure that part of the dose is not lost or refused. If it is suspected that any of the dose has been lost or if vomiting occurs within two hours of administration, redose with another full dose. If a dose is missed, administer NexGard and resume a monthly dosing schedule.

Flea Treatment and Prevention:
Treatment with NexGard may begin at any time of the year. In areas where fleas are common year-round, monthly treatment with NexGard should continue the entire year without interruption.

To minimize the likelihood of flea reinfestation, it is important to treat all animals within a household with an approved flea control product.

Tick Treatment and Control:
Treatment with NexGard may begin at any time of the year (see **Effectiveness**).

Contraindications:
There are no known contraindications for the use of NexGard.

Warnings:
Not for use in humans. Keep this and all drugs out of the reach of children. In case of accidental ingestion, contact a physician immediately.

Precautions:
Afoxolaner is a member of the isoxazoline class. This class has been associated with neurologic adverse reactions including tremors, ataxia, and seizures. Seizures have been reported in dogs receiving isoxazoline class drugs, even in dogs without a history of seizures. Use with caution in dogs with a history of seizures or neurologic disorders (see **Adverse Reactions** and **Post-Approval Experience**).

The safe use of NexGard in breeding, pregnant or lactating dogs has not been evaluated.

Adverse Reactions:
In a well-controlled US field study, which included a total of 333 households and 615 treated dogs (415 administered afoxolaner; 200 administered active control), no serious adverse reactions were observed with NexGard.

Over the 90-day study period, all observations of potential adverse reactions were recorded. The most frequent reactions reported at an incidence of > 1% within any of the three months of observations are presented in the following table. The most frequently reported adverse reaction was vomiting. The occurrence of vomiting was generally self-limiting and of short duration and tended to decrease with subsequent doses in both groups. Five treated dogs experienced anorexia during the study, and two of those dogs experienced anorexia with the first dose but not subsequent doses.

Table 1: Dogs With Adverse Reactions.

	Treatment Group			
	Afoxolaner		Oral active control	
	N[1]	% (n=415)	N[2]	% (n=200)
Vomiting (with and without blood)	17	4.1	25	12.5
Dry/Flaky Skin	13	3.1	2	1.0
Diarrhea (with and without blood)	13	3.1	7	3.5
Lethargy	7	1.7	4	2.0
Anorexia	5	1.2	9	4.5

[1]Number of dogs in the afoxolaner treatment group with the identified abnormality.
[2]Number of dogs in the control group with the identified abnormality.

In the US field study, one dog with a history of seizures experienced a seizure on the same day after receiving the first dose and on the same day after receiving the second dose of NexGard. This dog experienced a third seizure one week after receiving the third dose. The dog remained enrolled and completed the study. Another dog with a history of seizures had a seizure 19 days after the third dose of NexGard. The dog remained enrolled and completed the study. A third dog with a history of seizures received NexGard and experienced no seizures throughout the study.

Post-Approval Experience (July 2018):
The following adverse events are based on post-approval adverse drug experience reporting. Not all adverse events are reported to FDA/CVM. It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product exposure using these data.

The following adverse events reported for dogs are listed in decreasing order of reporting frequency for NexGard:

Vomiting, pruritus, lethargy, diarrhea (with and without blood), anorexia, seizure, hyperactivity/restlessness, panting, erythema, ataxia, dermatitis (including rash, papules), allergic reactions (including hives, swelling), and tremors.

Contact Information:
For a copy of the Safety Data Sheet (SDS) or to report suspected adverse drug events, contact Merial at 1-888-637-4251 or www.nexgardfordogs.com.

For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at http://www.fda.gov/AnimalVeterinary/SafetyHealth.

Mode of Action:
Afoxolaner is a member of the isoxazoline family, shown to bind at a binding site to inhibit insect and acarine ligand-gated chloride channels, in particular those gated by the neurotransmitter gamma-aminobutyric acid (GABA), thereby blocking pre- and post-synaptic transfer of chloride ions across cell membranes. Prolonged afoxolaner-induced hyperexcitation results in uncontrolled activity of the central nervous system and death of insects and acarines. The selective toxicity of afoxolaner between insects and acarines and mammals may be inferred by the differential sensitivity of the insects and acarines' GABA receptors versus mammalian GABA receptors.

Effectiveness:
In a well-controlled laboratory study, NexGard began to kill fleas four hours after initial administration and demonstrated >99% effectiveness at eight hours. In a separate well-controlled laboratory study, NexGard demonstrated 100% effectiveness against adult fleas 24 hours post-infestation for 35 days, and was ≥93% effective at 12 hours post-infestation through Day 21, and on Day 35. On Day 28, NexGard was 81.1% effective 12 hours post-infestation. Dogs in both the treated and control groups that were infested with fleas on Day -1 generated flea eggs at 12- and 24-hours post-treatment (0-11 eggs and 1-17 eggs in the NexGard treated dogs, and 4-90 eggs and 0-118 eggs in the control dogs, at 12- and 24-hours, respectively). At subsequent evaluations post-infestation, fleas from dogs in the treated group were essentially unable to produce any eggs (0-1 eggs) while fleas from dogs in the control group continued to produce eggs (1-141 eggs).

In a 90-day US field study conducted in households with existing flea infestations of varying severity, the effectiveness of NexGard against fleas on the Day 30, 60 and 90 visits compared with baseline was 98.0%, 99.7%, and 99.9%, respectively.

Collectively, the data from the three studies (two laboratory and one field) demonstrate that NexGard kills fleas before they can lay eggs, thus preventing subsequent flea infestations after the start of treatment of existing flea infestations.

In well-controlled laboratory studies, NexGard demonstrated >97% effectiveness against *Dermacentor variabilis*, >94% effectiveness against *Ixodes scapularis,* and >93% effectiveness against *Rhipicephalus sanguineus,* 48 hours post-infestation for 30 days. At 72 hours post-infestation, NexGard demonstrated >97% effectiveness against *Amblyomma americanum* for 30 days. In two separate, well-controlled laboratory studies, NexGard was effective at preventing *Borrelia burgdorferi* infections after dogs were infested with *Ixodes scapularis* vector ticks 28 days post-treatment.

Animal Safety:
In a margin of safety study, NexGard was administered orally to 8 to 9-week-old Beagle puppies at 1, 3, and 5 times the maximum exposure dose (6.3 mg/kg) for three treatments every 28 days, followed by three treatments every 14 days, for a total of six treatments. Dogs in the control group were sham-dosed. There were no clinically-relevant effects related to treatment on physical examination, body weight, food consumption, clinical pathology (hematology, clinical chemistries, or coagulation tests), gross pathology, histopathology or organ weights. Vomiting occurred throughout the study, with a similar incidence in the treated and control groups, including one dog in the 5x group that vomited four hours after treatment.

In a well-controlled field study, NexGard was used concomitantly with other medications, such as vaccines, anthelmintics, antibiotics (including topicals), steroids, NSAIDS, anesthetics, and antihistamines. No adverse reactions were observed from the concomitant use of NexGard with other medications.

Storage Information:
Store at or below 30°C (86°F) with excursions permitted up to 40°C (104°F).

How Supplied:
NexGard is available in four sizes of beef-flavored soft chewables: 11.3, 28.3, 68 or 136 mg afoxolaner. Each chewable size is available in color-coded packages of 1, 3 or 6 beef-flavored chewables.

NADA 141-406, Approved by FDA

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1050-4493-07
Rev. 05/2018

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Ptyalism/Pseudoptyalism

Julie Allen, BVMS, MS, MRCVS, DACVIM (SAIM), DACVP

FOR MORE
Find more Differential Diagnosis lists in upcoming issues of *Clinician's Brief* and on cliniciansbrief.com

Following are differential diagnoses for patients presented with ptyalism/pseudoptyalism.*

- GI condition
  - Abdominal pain (eg, from visceral stretching)
  - Disease associated with nausea
  - Esophageal disease (eg, reflux esophagitis, megaesophagus, foreign body, neoplasia, stricture, spirocercosis)
  - Gastric dilatation volvulus
  - Gastric ulceration
  - Hepatic failure (eg, hepatic encephalopathy), particularly in cats
  - Hiatal hernia
  - Renal failure
- Idiopathic or nonresponsive condition
- Neurologic condition
  - Facial nerve paralysis
  - Idiopathic trigeminal neuritis
  - Infectious disease (eg, rabies,† pseudorabies, tetanus, botulism)
  - Lesions of cranial nerves IX, X, or XII
  - Myasthenia gravis
  - Nausea from vestibular disease
  - Seizures
- Oral cavity or maxillofacial cause
  - Craniomandibular osteopathy
  - Faucitis
  - Foreign body
  - Immune-mediated disease (eg, masticatory muscle myositis, pemphigus)
  - Lip fold abnormalities
  - Mandibular fracture
  - Oropharyngeal neoplasia (eg, tonsillar squamous cell carcinoma)
  - Oropharyngeal trauma (eg, laceration)
  - Periodontal disease
  - Stomatitis (eg, calicivirus, herpesvirus, FeLV/FIV, caustic agent, electrical burn, ulceration secondary to systemic disease [eg, uremia])
  - Temporomandibular joint luxation or fracture
  - Tongue lesion (eg, linear foreign body), glossitis (eg, uremia, caustic agent, electrical burn), or tumor
- Physiologic reaction
  - Excitement
  - Hyperthermia
  - Purring
  - Response to feeding
- Reaction to medication
  - Anesthesia
  - Avermectins (eg, ivermectin, moxidectin/imidacloprid, selamectin) given topically or PO
  - Bitter drugs
  - Cholinergic drugs (eg, bethanechol), anticholinesterase drugs (eg, pyridostigmine), cholinesterase inhibitors (eg, organophosphates)
  - Pancreatic enzyme supplements
  - Pyrethrins/pyrethroids
- Salivary gland condition
  - Foreign body
  - Salivary gland neoplasia
  - Salivary mucocele
  - Sialadenitis or necrotizing sialometaplasia (ie, inflammation of the salivary glands)
  - Sialadenosis (idiopathic, noninflammatory salivary gland enlargement)
    –May be a form of limbic epilepsy
  - Sialolithiasis
- Sepsis
- Toxicosis
  - 5-hydroxytryptophan (ie, Griffonia seed extract)
  - Bite from a venomous animal (eg, black widow spider, scorpion, toad [*Bufo* spp], coral snake, sea hare [*Aplysia* spp])
  - Household cleaner
  - Human sleep aid (eg, zolpidem)
  - Human tricyclic antidepressant (eg, clozapine)
  - Illicit drug (eg, cocaine, amphetamine)
  - Insecticide/pesticide (eg, boric acid, aldicarb)
  - Metaldehyde
  - Mushroom (eg, *Amanita muscaria*)
  - Plant/tree (eg, Kentucky coffee tree, poinsettia)
  - Rodenticide (eg, zinc phosphide)

See page 49 for references.

*Differentiating between ptyalism and pseudoptyalism can be challenging; some conditions (eg, oropharyngeal and CNS diseases) can result in both increased salivary production and the inability to swallow.

†Rabies should always be considered in patients presented with drooling.

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Demonstrated clinical results in as little as **24 hours** in cats with diarrhea or constipation[1]

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[1]Hill's data on file. Clinical study in cats with constipation or diarrhea.

NEW RESEARCH:

Multiple-Anthelmintic Resistance in the Canine Hookworm

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Ray M. Kaplan, DVM, PhD, DEVPC, DACVM (Parasitology)
University of Georgia

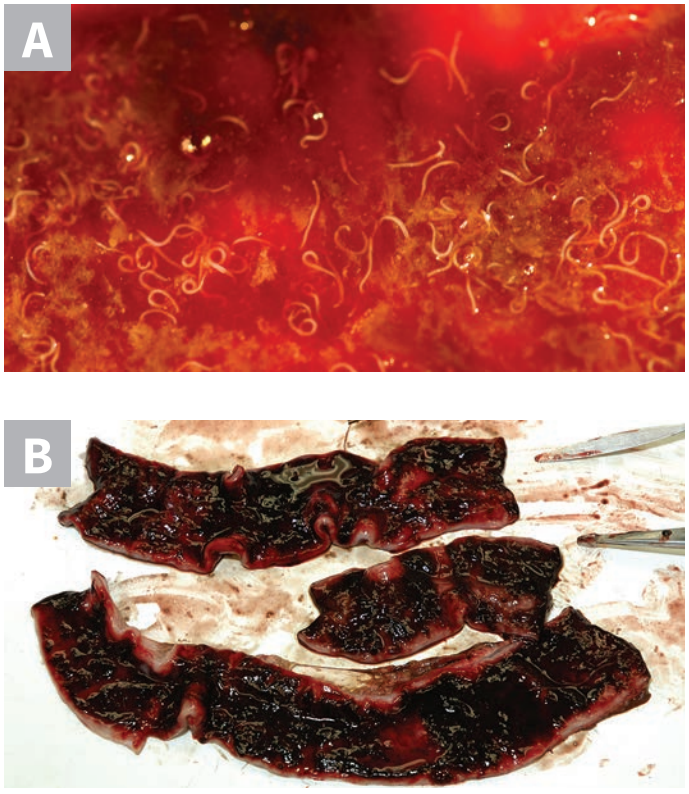
The canine hookworm (*Ancylostoma caninum*) is the most common and highly pathogenic nematode parasite in dogs.[1] This parasite uses 3 pairs of teeth to attach to the intestinal mucosa and submucosa to feed on host blood. Clinical signs of infection include hematochezia, melena, anemia, and weight loss; heavy worm burdens can cause death (***Figure 1***, next page).

Research conducted at the Kaplan Laboratory at University of Georgia has led to several key discoveries relating to anthelmintic resistance in *A caninum*:

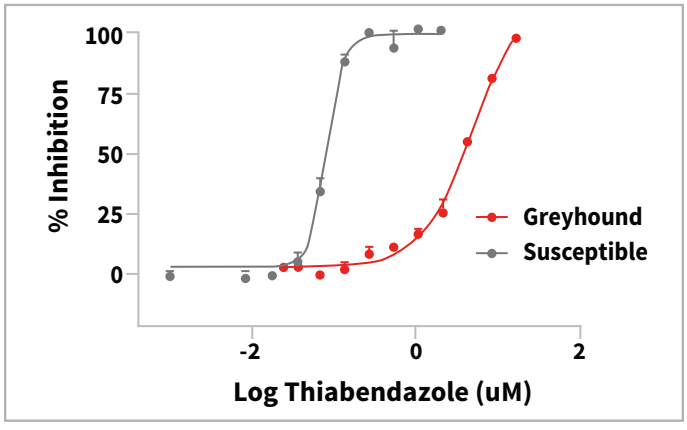
! *A CANINUM* HAS DEVELOPED MULTIPLE-ANTHELMINTIC RESISTANCE TO ALL COMMONLY USED ANTHELMINTICS.

Research conducted in the authors' laboratory over the past 2 years has confirmed that *A caninum* has developed multiple-anthelmintic resistance to the major anthelmintic classes commonly used for treatment: benzimidazoles (eg, fenbendazole, febantel), tetrahydropyrimidines (eg, pyrantel pamoate), and macrocyclic lactones (eg, milbemycin oxime, moxidectin)[2]; selected data from these studies are presented in ***Figure 2***, next page.

Anthelmintic resistance is defined as a heritable genetic change in a parasite population that enables a significantly greater proportion of individual parasites to survive treatment at a dose that was previously effective against the same species and developmental stage. Strongylid nematode parasites have extremely large effective population sizes that yield exceptionally high levels of genetic diversity that favor the development of anthelmintic resistance.[3,4] This has led to long-standing severe resistance problems in GI nematode parasites in livestock; however, few reports have documented such anthelmintic resistance in dogs. The first report of anthelmintic resistance in *A caninum* was to pyrantel pamoate in 1987 in a greyhound puppy imported from Australia.[5] Additional pyrantel pamoate resistance



▲ **FIGURE 1** Acute lethal hookworm infection showing numerous adults and immature stages of *A caninum* (***A***) and enteritis with hemorrhage seen at necropsy (***B***) in a 3-month-old greyhound that received multiple treatments with fenbendazole, pyrantel pamoate, and ivermectin. *Images courtesy of Michael Dryden, DVM, PhD*



▲ **FIGURE 2** Dose-response curves for the Egg Hatch Assay, an in vitro assay used to measure resistance to the benzimidazole drug class. The large shift to the right indicates that a much higher concentration of the drug was needed to inhibit egg hatching. In this case, the resistance ratio (ie, ratio of the drug concentration required to inhibit the resistant worms as compared with the susceptible worms) was >60-fold.

cases were subsequently diagnosed in Australia.[6,7] However, since 2008, there had been no further published reports of anthelmintic resistance in *A caninum* to any drug until 2019.

MULTIPLE-DRUG–RESISTANT HOOKWORMS EVOLVED ON GREYHOUND BREEDING FARMS & RACING KENNELS & HAVE INFECTED MOST ADOPTED GREYHOUNDS.

Evidence recently collected by the Kaplan Laboratory strongly suggests that multiple-drug–resistant (MDR) *A caninum* evolved on greyhound breeding farms and racing kennels, and most, if not all, actively racing and recently adopted greyhound dogs appear to be infected with these MDR hookworms.

The development of MDR *A caninum* is most likely the result of a combination of long-term intensive use of anthelmintics and the epidemiologic dynamics that exist on greyhound breeding farms. *A caninum* is extremely common on greyhound breeding farms, likely due to an ideal environment for larval development and transmission conferred by sand and dirt exercise runs.[8] This results in intensive anthelmintic use, which over several decades has likely resulted in heavy selection pressures for drug resistance leading to the development of MDR parasites. The adoption of thousands of retired racing greyhounds each year has likely led to the spread of these MDR parasites to the general pet population. However, to date, there are no data on the prevalence or distribution of MDR hookworms in the pet population. The authors are currently investigating the geographic distribution and the molecular epidemiology of *A caninum* drug resistance.

MDR HOOKWORMS ARE SPREADING TO THE GENERAL DOG POPULATION.

MDR hookworms are not restricted to greyhounds; the authors have observed many cases of drug-resistant hookworms in nongreyhound breeds, suggesting that MDR hookworms are spreading to the general canine population. The emergence and spread of MDR hookworms that are poorly responsive to usual anthelmintic treatments present a

serious threat to canine health and necessitate a change in how clinicians manage persistent hookworm cases. In addition, due to its zoonotic potential, the spread of MDR *A caninum* is also a threat to human health.

! CLINICIANS SHOULD DETERMINE THE CAUSE OF PERSISTENT *A CANINUM* INFECTION TO OPTIMALLY MANAGE EACH PATIENT.

Persistent cases of *A caninum* infection can be caused by either larval leak (ie, arrested larvae in somatic tissues continuously migrate to the small intestine, where they develop to the adult stage[9]) or true drug resistance; it is important to distinguish between these situations to optimally manage each patient. Dogs with larval leak typically shed hookworm eggs in small numbers, with treatment only yielding a temporary interruption in egg shedding due to newly reactivated larvae repopulating the gut. In contrast, when worms are MDR, treatments fail to interrupt egg shedding. Performing both pretreatment and 14-day post-treatment fecal egg counts is required to make this distinction.

! ALTHOUGH ALL RESISTANT *A CANINUM* ISOLATES EXAMINED TO DATE WERE MDR TO ALL 3 DRUG CLASSES, SOME MAY ONLY BE RESISTANT TO 1 OR 2 DRUG CLASSES.

All resistant *A caninum* isolates that the authors have tested to date have been MDR to all 3 drug classes mentioned previously. However, it is possible that some *A caninum* isolates are only resistant to 1 or 2 drug classes. Of note, resistance is not an "all or none" phenomenon; resistance levels differ depending on recent treatment history of the dog(s) transmitting and carrying resistant hookworms.

! ONLY 1 TEST IS CLINICALLY USEFUL FOR DIAGNOSING ANTHELMINTIC RESISTANCE IN *A CANINUM*.

The only practical method to diagnose anthelmintic resistance in *A caninum* is the fecal egg count reduction test, in which the number of worm eggs per gram of feces is measured both prior to and 2 weeks after treatment. Most large animal clinicians are familiar with this test, as testing for anthelmintic resistance on livestock farms has long been recommended. Due to the emergence of MDR hookworms in dogs, small animal clinicians should also become familiar with this test, which should be performed in any dog that has persistent hookworms.

Recommendations for performing this test and interpreting the results will be presented by the authors in a diagnostic, treatment, and management algorithm for resistant canine hookworm infections in an upcoming issue of *Clinician's Brief*. This algorithm will also provide recommendations for short- and long-term case management.

MDR = multiple-drug–resistant

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apoquel®
(oclacitinib tablet)

3.6 mg 5.4 mg 16 mg

Brief Summary of Prescribing Information

For oral use in dogs only

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

Indications: Control of pruritus associated with allergic dermatitis and control of atopic dermatitis in dogs at least 12 months of age.

Dosage and Administration: The dose of APOQUEL (oclacitinib maleate) tablets is 0.18 to 0.27 mg oclacitinib/lb (0.4 to 0.6 mg oclacitinib/kg) body weight, administered orally, twice daily for up to 14 days, and then administered once daily for maintenance therapy. APOQUEL may be administered with or without food.

Dosing Chart

Weight Range (in lb)		Weight Range (in Kg)		Number of Tablets to be Administered		
Low	High	Low	High	3.6 mg Tablets	5.4 mg Tablets	16 mg Tablets
6.6	9.9	3.0	4.4	**0.5**	-	-
10.0	14.9	4.5	5.9	-	**0.5**	-
15.0	19.9	6.0	8.9	**1**	-	-
20.0	29.9	9.0	13.4	-	**1**	-
30.0	44.9	13.5	19.9	-	-	**0.5**
45.0	59.9	20.0	26.9	-	**2**	-
60.0	89.9	27.0	39.9	-	-	**1**
90.0	129.9	40.0	54.9	-	-	**1.5**
130.0	175.9	55.0	80.0	-	-	**2**

Warnings:
APOQUEL is not for use in dogs less than 12 months of age (see **Animal Safety**).
APOQUEL is not for use in dogs with serious infections.
APOQUEL may increase susceptibility to infection, including demodicosis, and exacerbate neoplastic conditions (see **Adverse Reactions** and **Animal Safety**).

Human Warnings:
This product is not for human use. Keep this and all drugs out of reach of children. For use in dogs only. Wash hands immediately after handling the tablets. In case of accidental eye contact, flush immediately with water or saline for at least 15 minutes and then seek medical attention. In case of accidental ingestion, seek medical attention immediately.

Precautions:
APOQUEL is not for use in breeding dogs, or pregnant or lactating bitches.
The use of APOQUEL has not been evaluated in combination with glucocorticoids, cyclosporine, or other systemic immunosuppressive agents.
Dogs receiving APOQUEL should be monitored for the development of infections, including demodicosis, and neoplasia.

Adverse Reactions:
Control of Atopic Dermatitis
In a masked field study to assess the effectiveness and safety of oclacitinib for the control of atopic dermatitis in dogs, 152 dogs treated with APOQUEL and 147 dogs treated with placebo (vehicle control) were evaluated for safety. The majority of dogs in the placebo group withdrew from the 112-day study by Day 16. Adverse reactions reported (and percent of dogs affected) during Days 0-16 included diarrhea (4.6% APOQUEL, 3.4% placebo), vomiting (3.9% APOQUEL, 4.1% placebo), anorexia (2.6% APOQUEL, 0% placebo), new cutaneous or subcutaneous lump (2.6% APOQUEL, 2.7% placebo), and lethargy (2.0% APOQUEL, 1.4% placebo). In most cases, diarrhea, vomiting, anorexia, and lethargy spontaneously resolved with continued dosing. Dogs on APOQUEL had decreased leukocytes (neutrophil, eosinophil, and monocyte counts) and serum globulin, and increased cholesterol and lipase compared to the placebo group but group means remained within the normal range. Mean lymphocyte counts were transiently increased at Day 14 in the APOQUEL group.

Dogs that withdrew from the masked field study could enter an unmasked study where all dogs received APOQUEL. Between the masked and unmasked study, 283 dogs received at least one dose of APOQUEL. Of these 283 dogs, two dogs were withdrawn from study due to suspected treatment-related adverse reactions: one dog that had an intense flare-up of dermatitis and severe secondary pyoderma after 19 days of APOQUEL administration, and one dog that developed generalized demodicosis after 28 days of APOQUEL administration. Two other dogs on APOQUEL were withdrawn from study due to suspected or confirmed malignant neoplasia and subsequently euthanized, including one dog that developed signs associated with a heart base mass after 21 days of APOQUEL administration, and one dog that developed a Grade III mast cell tumor after 60 days of APOQUEL administration. One of the 147 dogs in the placebo group developed a Grade I mast cell tumor and was withdrawn from the masked study. Additional dogs receiving APOQUEL were hospitalized for diagnosis and treatment of pneumonia (one dog), transient bloody vomiting and stool (one dog), and cystitis with urolithiasis (one dog).

In the 283 dogs that received APOQUEL, the following additional clinical signs were reported after beginning APOQUEL (percentage of dogs with at least one report of the clinical sign as a non-pre-existing finding): pyoderma (12.0%), non-specified dermal lumps (12.0%), otitis (9.9%), vomiting (9.2%), diarrhea (6.0%), histiocytoma (3.9%), cystitis (3.5%), anorexia (3.2%), lethargy (2.8%), yeast skin infections (2.5%), pododermatitis (2.5%), lipoma (2.1%), polydipsia (1.4%), lymphadenopathy (1.1%), nausea (1.1%), increased appetite (1.1%), aggression (1.1%), and weight loss (0.7).

Control of Pruritus Associated with Allergic Dermatitis
In a masked field study to assess the effectiveness and safety of oclacitinib for the control of pruritus associated with allergic dermatitis in dogs, 216 dogs treated with APOQUEL and 220 dogs treated with placebo (vehicle control) were evaluated for safety. During the 30-day study, there were no fatalities and no adverse reactions requiring hospital care. Adverse reactions reported (and percent of dogs affected) during Days 0-7 included diarrhea (2.3% APOQUEL, 0.9% placebo), vomiting (2.3% APOQUEL, 1.8% placebo), lethargy (1.8% APOQUEL, 1.4% placebo), anorexia (1.4% APOQUEL, 0% placebo), and polydipsia (1.4% APOQUEL, 0% placebo). In most of these cases, signs spontaneously resolved with continued dosing. Five APOQUEL group dogs were withdrawn from study because of: darkening areas of skin and fur (1 dog); diarrhea (1 dog); fever, lethargy and cystitis (1 dog); an inflamed footpad and vomiting (1 dog); and diarrhea, vomiting, and lethargy (1 dog). Dogs in the APOQUEL group had a slight decrease in mean white blood cell counts (neutrophil, eosinophil, and monocyte counts) that remained within the normal reference range. Mean lymphocyte count for dogs in the APOQUEL group increased at Day 7, but returned to pretreatment levels by study end without a break in APOQUEL administration. Serum cholesterol increased in 25% of APOQUEL group dogs, but mean cholesterol remained within the reference range.

Continuation Field Study
After completing APOQUEL field studies, 239 dogs enrolled in an unmasked (no placebo control), continuation therapy study receiving APOQUEL for an unrestricted period of time. Mean time on this study was 372 days (range 1 to 610 days). Of these 239 dogs, one dog developed demodicosis following 273 days of APOQUEL administration. One dog developed dermal pigmented viral plaques following 266 days of APOQUEL administration. One dog developed a moderately severe bronchopneumonia after 272 days of APOQUEL administration; this infection resolved with antimicrobial treatment and temporary discontinuation of APOQUEL. One dog was euthanized after developing abdominal ascites and pleural effusion of unknown etiology after 450 days of APOQUEL administration. Six dogs were euthanized because of suspected malignant neoplasms: including thoracic metastatic, abdominal metastatic, splenic, frontal sinus, and intracranial neoplasms, and transitional cell carcinoma after 17, 120, 175, 49, 141, and 286 days of APOQUEL administration, respectively. Two dogs each developed a Grade II mast cell tumor after 52 and 91 days of APOQUEL administration, respectively. One dog developed low grade B-cell lymphoma after 392 days of APOQUEL administration. Two dogs each developed an apocrine gland adenocarcinoma (one dermal, one anal sac) after approximately 210 and 320 days of APOQUEL administration, respectively. One dog developed a low grade oral spindle cell sarcoma after 320 days of APOQUEL administration.

To report suspected adverse events, for technical assistance or to obtain a copy of the MSDS, contact Zoetis Inc. at 1-888-963-8471 or www.zoetis.com.

For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at http://www.fda.gov/AnimalVeterinary/SafetyHealth.

Storage Conditions:
APOQUEL should be stored at controlled room temperature between 20° to 25°C (68° to 77°F) with excursions between 15° to 40°C (59° to 104°F).

How Supplied:
APOQUEL tablets contain 3.6 mg, 5.4 mg, or 16 mg of oclacitinib as oclacitinib maleate per tablet. Each strength tablets are packaged in 20 and 100 count bottles. Each tablet is scored and marked with AQ and either an S, M, or L that correspond to the different tablet strengths on both sides.

NADA #141-345, Approved by FDA

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February 2013 428007800A&P

When it comes to **fast** relief from allergic itch without the common side effects of steroids*

IT WOULD BE A SHAME TO MAKE THEM WAIT

APOQUEL (oclacitinib tablet) gives dogs fast, effective allergic itch relief that **starts working within 4 hours**[1]

*Common side effects of steroids include polyuria, polydipsia and polyphagia.[4,5] Side effects of APOQUEL reported most often are vomiting and diarrhea.[6]

†Based on survey data from veterinarians (n=250) and pet owners (n=150).[2,3]

INDICATIONS

Control of pruritus associated with allergic dermatitis and control of atopic dermatitis in dogs at least 12 months of age.

IMPORTANT SAFETY INFORMATION

Do not use APOQUEL® (oclacitinib tablet) in dogs less than 12 months of age or those with serious infections. APOQUEL may increase the chances of developing serious infections, and may cause existing parasitic skin infestations or pre-existing cancers to get worse. APOQUEL has not been tested in dogs receiving some medications including some commonly used to treat skin conditions such as corticosteroids and cyclosporine. Do not use in breeding, pregnant, or lactating dogs. Most common side effects are vomiting and diarrhea. APOQUEL has been used safely with many common medications including parasiticides, antibiotics and vaccines.

For more information, please see Brief Summary of full Prescribing Information on adjacent page.

References: 1. Gadeyne C, Little P, King VL, et al. Efficacy of oclacitinib (APOQUEL®) compared with prednisolone for the control of pruritus and clinical signs associated with allergic dermatitis in client-owned dogs in Australia. *Vet Dermatol.* 2014;25(6):512-518. doi:10.1111/vde.12166. **2.** Data on file, APOQUEL/CYTOPOINT Vet Tracker, Wave 11, 2018, Zoetis Inc. **3.** Data on file, APOQUEL/CYTOPOINT Pet Tracker, Wave 6, 2019, Zoetis Inc. **4.** Edwards SH. *The Merck Veterinary Manual.* 11th ed. Kenilworth, NJ: Merck Sharp & Dohme Corp; 2014. http://merckvetmanual.com/pharmacology/anti-inflammatory-agents/corticosteroids?qt=antiinflammatoryagents&alt=sh. Accessed January 4, 2018. **5.** Sousa CA. Glucocosteroids in veterinary dermatology. In: Bonagura JD, Twedt DC, eds. *Kirk's Current Veterinary Therapy.* 14th ed. St. Louis, MO: Saunders Elsevier; 2009:400-404. **6.** Cosgrove SB, Wren JA, Cleaver DM, et al. Efficacy and safety of oclacitinib for the control of pruritus and associated skin lesions in dogs with canine allergic dermatitis. *Vet Dermatol.* 2013;24(5):479-e114. doi:10.1111/vde.12047.

ZOETIS PETCARE

BRAVECTO® PLUS

(fluralaner and moxidectin topical solution) for Cats

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

Description:
Each tube is formulated to provide a minimum dose of 18.2 mg/lb (40 mg/kg) fluralaner and 0.9 mg/lb (2 mg/kg) moxidectin. Each milliliter contains 280 mg of fluralaner and 14 mg of moxidectin.

The chemical name of fluralaner is (±)-4-[5-(3,5-dichlorophenyl)-5-(trifluoromethyl)- 4,5-dihydroisoxazol-3-yl]-2-methyl-N-[2-oxo-2-(2,2,2- trifluoroethylamino)ethyl]benzamide. The chemical name of moxidectin is (2aE,4E,5'R, 6R,6'S,8E,11R,13S,15S,17aR, 20R,20aR,20bS)-6'-[(E)-1,3-Dimethyl-1-butenyl]-5',6,6',7,10,11, 14,15,17a,20,20a,20b-dodecahydro-20,20b-dihydroxy-5',6,8,19-tetramethylspiro[11,15-methano-2H,13H,17H-furo[4,3,2-pq][2,6] benzodioxacyclooctadecin-13,2'-[2H]pyran]-4',17(3'H)-dione 4'-(E)-(O-methyloxime). Inactive ingredients: dimethylacetamide, glycofurol, diethyltoluamide, acetone, butylhydroxytoluene

Indications:
Bravecto Plus is indicated for the prevention of heartworm disease caused by *Dirofilaria immitis* and for the treatment of infections with intestinal roundworm (*Toxocara cati*; 4th stage larvae, immature adults and adults) and hookworm (*Ancylostoma tubaeforme*; 4th stage larvae, immature adults and adults). Bravecto Plus kills adult fleas and is indicated for the treatment and prevention of flea infestations (*Ctenocephalides felis*) and the treatment and control of tick infestations [*Ixodes scapularis* (black-legged tick) and *Dermacentor variabilis* (American dog tick)] for 2 months in cats and kittens 6 months of age and older and weighing 2.6 lb or greater.

Dosage and Administration:
Bravecto Plus should be administered topically as a single dose every 2 months according to the **Dosage Schedule** below to provide a minimum dose of 18.2 mg/lb (40 mg/kg) fluralaner and 0.9 mg/lb (2 mg/kg) moxidectin.

For prevention of heartworm disease, Bravecto Plus should be administered at 2-month intervals. Bravecto Plus may be administered year-round without interruption or at a minimum should be administered at 2-month intervals beginning at the cat's first seasonal exposure to mosquitoes and continuing until the cat's last seasonal exposure to mosquitoes. If a dose is missed and a 2-month interval between doses is exceeded, administer Bravecto Plus immediately and resume the dosing every 2 months.

When replacing a monthly heartworm preventative product, the first dose of Bravecto Plus should be given within one month of the last dose of the former medication.

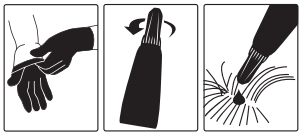
Dosing Schedule:

Body Weight Ranges (lb)	Fluralaner content (mg/tube)	Moxidectin content (mg/tube)	Tubes Administered
2.6 – 6.2	112.5	5.6	One
>6.2 – 13.8	250	12.5	One
>13.8 – 27.5*	500	25	One

* Cats over 27.5 lb should be administered the appropriate combination of tubes.

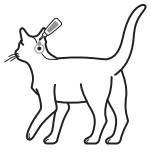
A veterinarian or veterinary technician should demonstrate or instruct the pet owner regarding the appropriate technique for applying Bravecto Plus topically to cats prior to first use.

Step 1: Immediately before use, open the pouch and remove the tube. Put on gloves. Hold the tube at the crimped end with the cap in an upright position (tip up). The cap should be rotated clockwise or counter clockwise one full turn. The cap is designed to stay on the tube for dosing and should not be removed. The tube is open and ready for application when a breaking of the seal is felt.



Step 2: The cat should be standing or lying with its back horizontal during application. Part the fur at the administration site. Place the tube tip vertically against the skin at the base of the skull of the cat.

Step 3: Squeeze the tube and gently apply the entire contents of Bravecto Plus directly to the skin at the base of the skull of the cat. Avoid applying an excessive amount of solution that could cause some of the solution to run and drip off of the cat. If a second spot is needed to avoid run off, then apply the second spot slightly behind the first spot.



Greasy, oily, or wet appearance may occur at the application site in some cats.

Contraindications:
There are no known contraindications for the use of the product.

WARNINGS:

Human Warnings:
Not for human use. Keep this and all drugs out of the reach of children.

Do not contact or allow children to contact the application site until 2 hours post application.

Keep the product in the original packaging until use in order to prevent children from getting direct access to the product. Do not eat, drink or smoke while handling the product. Avoid contact with skin and eyes. If contact with eyes occurs, then flush eyes slowly and gently with water. **If wearing contact lenses, eyes should be rinsed first, then remove contact lenses and continue rinsing, then seek medical advice immediately. Wash hands and contacted skin thoroughly with soap and water immediately after use of the product. If the product accidentally contacts skin and a sticky residue persists after washing, rubbing alcohol (70% isopropyl alcohol) can be applied to the area to remove the residue.**

The product is highly flammable. Keep away from heat, sparks, open flame or other sources of ignition.

Precautions:
For topical use only. Avoid oral ingestion (see **Animal Safety**).

Fluralaner, one of the ingredients in Bravecto Plus, is a member of the isoxazoline class. This class has been associated with neurologic adverse reactions including tremors, ataxia, and seizures. Neurologic adverse reactions have been reported in cats receiving isoxazoline class drugs, even in cats without a history of neurologic disorders. Use with caution in cats with a history of neurologic disorders.

Use with caution in cats that are heartworm positive (see **Animal Safety**).

Bravecto Plus has not been shown to be effective in kittens less than 6 months of age.

The safety of Bravecto Plus has not been established in breeding, pregnant, and lactating cats.

The effectiveness of Bravecto Plus to prevent heartworm disease after bathing or water immersion has not been evaluated.

Adverse Reactions:
In a well-controlled U.S. field study, which included a total of 176 treated cats (135 with Bravecto Plus and 41 with a monthly topical active control), there were no serious adverse reactions.

Percentage of Cats with Adverse Reactions (AR) in the Field Study

Adverse Reaction	Bravecto Plus Group: Percent of Cats with the AR During the 120-Day Study (n=135 cats)	Active Control Group: Percent of Cats with the AR During the 120-Day Study (n=41 cats)
Vomiting	5.9%	12.2%
Alopecia (not at application site)	5.2%	2.4%
Pruritus	4.4%	12.2%
Application site pruritus	4.4%	4.9%
Diarrhea	3.7%	7.3%
Lethargy	3.7%	9.8%
Dry Skin	3.0%	0.0%
Elevated alanine aminotransferase (ALT)*	3.0%	0.0%
Hypersalivation	1.5%	1.5%
Application site alopecia	0.7%	0.0%

*ALT was greater than twice the upper reference range of 100 IU/L. These cats also had mild elevations of aspartate aminotransferase (AST) (less than twice the upper reference range of 100 IU/L). No clinical signs associated with liver disease were noted in these cats.

In well-controlled laboratory effectiveness studies, the following adverse reactions were seen after application of Bravecto Plus: pyrexia, tachypnea, mydriasis, pruritus, scabbing, and bloody stool.

Foreign Market Experience: The following adverse events were reported voluntarily during post-approval use of the product in cats in foreign markets: polydipsia, swelling of chin and lips, periorbital swelling, blepharospasm, pruritus, erythema, aggression, agitation, pyrexia, mydriasis, hypersalivation, hyperactivity, alopecia, and excessive grooming. These adverse events occurred within 48 hours of administration.

In a European field study for fluralaner topical solution for cats, there were three reports of facial dermatitis in humans after close contact with the application site which occurred within 4 days of application. In foreign market experience reports for Bravecto Plus, one veterinarian experienced tingling and numbness of the fingers, hand, and arm, and swelling of the hand and arm after getting Bravecto Plus on her fingers. Additional signs, including blurred vision and disorientation, occurred after taking an antihistamine.

To report suspected adverse events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Merck Animal Health at 1-800-224-5318. Additional information can be found at www.bravecto.com. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at http://www.fda.gov/reportanimalae.

Clinical Pharmacology:
Peak fluralaner concentrations are achieved between 3 and 21 days following topical administration and the elimination half-life ranges between 11 and 18 days. Peak moxidectin concentrations are achieved between 1 and 5 days following topical administration and the elimination half-life ranges between 20 and 30 days.

Mode of Action:
Fluralaner is for systemic use and belongs to the class of isoxazoline-substituted benzamide derivatives. Fluralaner is an inhibitor of the arthropod nervous system. The mode of action of fluralaner is the antagonism of the ligand-gated chloride channels (gamma-aminobutyric acid (GABA)-receptor and glutamate-receptor).

Moxidectin is for systemic use and is a semisynthetic derivative of nemadectin, belonging to the milbemycin group of macrocyclic lactones. It binds to gamma-aminobutyric acid (GABA) and glutamate-gated chloride channels of the nerves and muscles of the parasite resulting in hyperpolarization, paralysis and death.

Effectiveness:
In two well-controlled laboratory studies, Bravecto Plus was 100% effective against induced heartworm infections when administered 2 months prior to infection. Bravecto Plus was not effective when administered more than 2 months prior to infection.

In well-controlled laboratory studies, Bravecto Plus was effective against naturally and experimentally induced adult and experimentally induced 4th stage larval and immature adult *Toxocara cati* and *Ancylostoma tubaeforme* infections in cats.

In a well-controlled laboratory study, Bravecto Plus killed 100% of fleas within 12 hours after treatment and reduced the numbers of live fleas on cats by >99% within 12 hours after treatment or infestation for 2 months. In well-controlled laboratory studies, Bravecto Plus demonstrated >90% effectiveness against *Dermacentor variabilis* 48 hours after treatment or infestation for 2 months but failed to demonstrate ≥ 90% effectiveness beyond 2 months. In well-controlled laboratory studies, Bravecto Plus demonstrated ≥ 98.1% effectiveness against *Ixodes scapularis* 48 hours after treatment or infestation for 2 months.

Animal Safety:
Margin of Safety Study: In a margin of safety study, Bravecto Plus was administered topically to 9- to 13-week-old (mean age 12 weeks) kittens at 1X, 3X, and 5X the maximum labeled dose of 93.0 mg fluralaner/kg and 4.7 mg moxidectin/kg at three, 8-week intervals (10 kittens per group). The kittens in the control group (0X) were treated with mineral oil. There were no clinically-relevant, treatment-related effects on physical examination, body weights, food consumption, clinical pathology (hematology, clinical chemistries, coagulation tests, serum amyloid A, and urinalysis), gross pathology, histopathology, or organ weights. Single incidences of self-limiting hypersalivation in three kittens (one kitten in the 1X group and two kittens in the 3X group) and pruritus at the administration site in one kitten in the 3X group were observed on the day of dose administration. Cosmetic changes at the application site included matting/clumping/spiking of hair, wetness, or a greasy appearance.

Oral Safety Studies: In an oral safety study, one dose of Bravecto Plus was administered orally to 4- to 9-month-old kittens at the maximum labeled dose of 93.0 mg fluralaner/kg and 4.7 mg moxidectin/kg. The kittens in the control group were administered saline orally. There were no clinically-relevant, treatment-related effects on physical examination, body weights, food consumption, or clinical pathology (hematology, clinical chemistries, coagulation tests, serum amyloid A, and urinalysis). Five of six treated kittens experienced hypersalivation. One treated kitten experienced vomiting 2 hours after administration and another 8 hours after treatment. Treated kittens had reduced food consumption on the day of treatment.

In an oral safety study for fluralaner topical solution for cats, four out of six cats experienced coughing immediately after oral administration of the maximum labeled dose of 93.0 mg fluralaner/kg.

In a pilot oral safety study, adult cats orally administered 0.5X or 1X the maximum labeled dose of Bravecto Plus had foaming hypersalivation for up to five minutes and reduced food consumption on the day of dosing. One cat exhibited transient lacrimation from one eye during the first 15 minutes after dosing.

Safety in cats infected with adult heartworm (Dirofilaria immitis): Bravecto Plus was administered topically to cats infected with adult heartworm at 1X or 3X the maximum labeled dose of 93.0 mg fluralaner/kg and 4.7 mg moxidectin/kg (8 cats per group). The cats in the control group (0X) received mineral oil topically. Two untreated cats were found dead prior to dosing. There were no clinically-relevant, treatment-related effects on body weights, clinical pathology (hematology, clinical chemistry, and coagulation profile), gross pathology or histopathology. Self-limiting hypersalivation due to grooming was observed on the day of treatment in both treatment groups (6/8 cats in the 1X group and 7/8 cats in the 3X group). In addition, three treated cats (2/8 cats in the 1X group and 1/8 cats in the 3X group) developed adverse neurologic signs during the study and were euthanized due to quality-of-life concerns. Clinical signs in one cat in the 1X group included vomiting, depression, vocalization, and ataxia 38 days that included ataxia, paresis, and muscle tremors 25 days after dosing. A cat in the 3X group exhibited depression, dehydration, a hunched position, and inability to stand 22 days after dosing. Heartworms were found in the epidural space in the second cat of the 1X group and the cat in the 3X group.

Field Safety Study: In a well-controlled field study, Bravecto Plus was used concurrently with other medications, such as vaccines, anthelmintics, antibiotics and steroids. No adverse reactions were observed from the concurrent use of Bravecto Plus with other medications.

Storage Conditions:
Do not store above 77°F (25°C). Store in the original package in order to protect from moisture. The pouch should only be opened immediately prior to use.

How Supplied:
Bravecto Plus is available in three tube sizes to treat cats ranging in weight from 2.6 lb – 27.5 lb (1.2 kg to 12.5 kg). Each tube is packaged individually in a pouch. Product may be supplied in 1 or 2 tubes per carton.

Approved by FDA under NADA # 141-518

Rev: 08/2019

MERCK Animal Health

2x THE DURATION OF MONTHLY PRODUCTS

Reduce her anxiety with protection that lasts twice as long.

Longer-lasting, broad-spectrum parasite protection can mean less stress on felines and better compliance.[1-3] Recommend BRAVECTO® PLUS (fluralaner and moxidectin topical solution) for Cats with **2x the duration of REVOLUTION® PLUS (selamectin and sarolaner topical solution) for Cats.**

fleas ticks heartworm roundworms hookworms

For information, visit BravoVets.com/Plus.

1 Lavan RP et al. *Parasites & Vectors*. 2017;10:284.
2 Lavan RP et al. *Parasites & Vectors*. 2018;11:581.
3 Brakke Consulting. *The US Flea Control and Heartworm Markets*. 2018:6-7.

IMPORTANT SAFETY INFORMATION: The most commonly reported adverse reactions include vomiting, hair loss, itching, diarrhea, lethargy, dry skin, elevated ALT, and hypersalivation. BRAVECTO PLUS has not been shown to be effective for 2 months duration in kittens less than 6 months of age. For topical use only. Avoid oral ingestion. The safety of BRAVECTO PLUS has not been established in breeding, pregnant and lactating cats. Fluralaner is a member of the isoxazoline class. This class has been associated with neurologic adverse reactions including tremors, ataxia, and seizures. Neurologic adverse reactions have been reported in cats receiving isoxazoline class drugs, even in cats without a history of neurologic disorders. Use with caution in cats with a history of neurologic disorders. Use with caution in cats that are heartworm positive. The effectiveness of BRAVECTO PLUS to prevent heartworm disease after bathing or water immersion has not been evaluated.

See page 20 for product information summary.

Treat Their Hyperadrenocorticism.
Help Restore Their Vitality.

Prior to treatment with VETORYL Capsules

Following 3 months of treatment with VETORYL Capsules

Following 9 months of treatment with VETORYL Capsules

VETORYL® CAPSULES
(trilostane)

VETORYL Capsules are the only FDA-approved treatment for pituitary-dependent and adrenal-dependent hyperadrenocorticism in dogs (Cushing's syndrome). They contain the active ingredient trilostane, which blocks the excessive production of cortisol.

As with all drugs, side effects may occur. In field studies and post-approval experience, the most common side effects reported were: anorexia, lethargy/depression, vomiting, diarrhea, elevated liver enzymes, elevated potassium with or without decreased sodium, elevated BUN, decreased Na/K ratio, hypoadrenocorticism, weakness, elevated creatinine, shaking, and renal insufficiency. In some cases, death has been reported as an outcome of these adverse events. VETORYL Capsules are not for use in dogs with primary hepatic or renal disease, or in pregnant dogs. Refer to the prescribing information for complete details or visit www.dechra-us.com.

To order, please contact your Dechra representative or call (866) 683-0660.
For full prescribing information please visit www.dechra-us.com.

24-hour Veterinary Technical Support available (866) 933-2472.
Nonurgent Technical Support available via email support@dechra.com.

Dechra
Veterinary Products

NADA 141-291, Approved by FDA CAUTION: Federal law restricts this drug to use by or on the order of licensed veterinarian.
Vetoryl is a registered trademark of Dechra Limited. Dechra is a registered trademark of Dechra Pharmaceuticals PLC.

01AD-VET50167-0220

See page 25 for product information summary.

2019 American Association of Veterinary Parasitologists Annual Meeting

July 7-11, 2019
Madison, Wisconsin

SAVE THE DATE

2020 American Association of Veterinary Parasitologists Annual Meeting

June 20-23, 2020
Snowbird, Utah

Dog Vaccination to Decrease Transmission of Parasitic Zoonoses: Notes from Leishmaniasis

Vaccinations are needed to prevent zoonotic transmission of *Leishmania infantum*. Dogs are the primary reservoir for this parasite, making them a crucial target for public health intervention. Vaccines should provide robust memory T cells to reactivate T-cell effector functions and mount a response at the time of parasite exposure. Development of a safe, effective, durable, and low-cost vaccine is challenging, and no vaccines are licensed for human use. Four commercial canine vaccines that provide 12 months of protection are licensed for use in Brazil and Europe. These vaccines do not block the establishment of infection; they are instead intended to reduce the risk for active infection and clinical disease. Limited information exists regarding the impact these vaccines have on preventing the spread of infection to humans. Efforts to prevent leishmaniasis should also focus on repelling sand flies and on using One Health strategies.—*Oliva G, Solano-Gallego L*

Show Us Your Ticks: A Survey of Ticks Infecting Dogs & Cats Across the United States

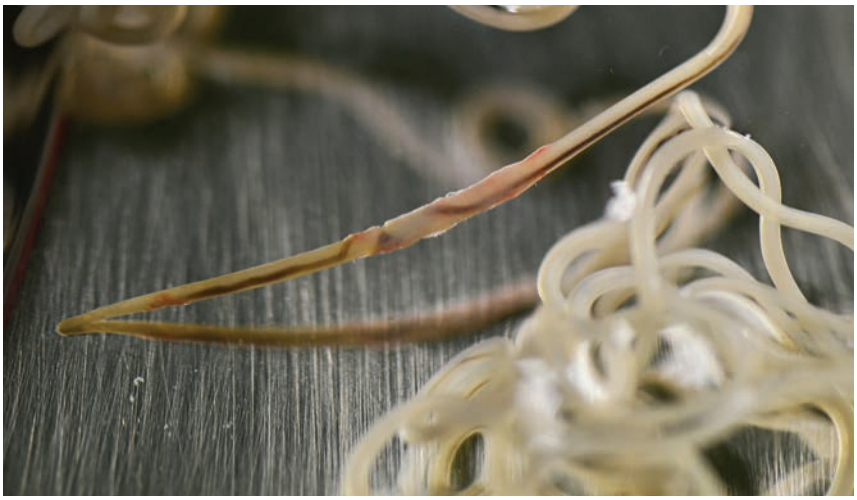
This study sought to characterize tick attachment in dogs and cats in the United States. Tick submissions from 49 states were collected over a recent 1-year period and identified for tick species and stage through morphologic or molecular analysis; attachment sites were noted. Ticks were collected every month, totaling 10,885 ticks from 1,487 dogs and 341 cats. Mean infestation intensities were 6.7 and 2.8 for dogs and cats, respectively, with a median of 1 for both dogs and cats. The dominant tick species collected from dogs were *Dermacentor variabilis*, *Ixodes scapularis*, *Amblyomma americanum*, and *Rhipicephalus sanguineus*. Cat infestations most commonly consisted of *I scapularis*, *A americanum*, and *D variabilis*. Other tick species identified included *A maculatum*, *Haemaphysalis longicornis*, *Otobius megnini*, and other (less common) *Dermacentor* spp and *Ixodes* spp. Co-infestations were noted in 14 cats and 93 dogs. In both cats and dogs, there were significant differences in reported attachment sites among tick species. In cats, *D variabilis* and *I scapularis* were most commonly found on the head and ears and *A americanum* was most commonly found on the tail and perianal region. In dogs, *D variabilis* and *I scapularis* were most commonly attached to the head and ears, *A americanum* was found most commonly on the abdomen and axillary and inguinal regions, and *R sanguineus* was most commonly attached to the head, ears, limbs, and feet.—*Saleh M, Duncan K, Lentile M, et al.*

There were significant differences in reported attachment sites among tick species.

Prevalence of *Babesia* spp and Clinical Characteristics of *Babesia microti*-like Infections in North American Dogs

This study aimed to determine the prevalence of *Babesia* spp, including *B microti*-like infection, in North American dogs. *B microti*-like infection has been rarely reported in North American domestic dogs but is seen in European dogs and North American foxes. Blood samples submitted for vector-borne disease testing at a reference laboratory over a 3-year period were evaluated for *Babesia* spp and coinfecting pathogens. *Babesia* spp were identified in 269 (2.9%) of 9376 samples through PCR. The most prevalent species were *B gibsoni* with 187 (2.0%) samples and *B microti*-like with 48 (0.51%) samples; 30 dogs were coinfected with both. In *B microti*-like infected dogs, coinfections were also found with *Mycoplasma* spp, *Dirofilaria immitis*, and *Wolbachia* spp. Seroreactivity to *Bartonella* spp, *Ehrlichia* spp, and *Rickettsia* spp was also identified in *B microti*-like infected dogs. Proteinuria, hyperglobulinemia, thrombocytopenia, anemia, and hypoalbuminemia were identified in *B microti*-like infected dogs; these findings are similar to clinicopathologic findings seen with babesiosis that is caused by other *Babesia* spp.—*Barash NR, Qurollo B, Thomas B, et al.*

Canine Heartworm Infection & Prophylaxis Use Among Pet Caretakers from the Cumberland Gap Region of Tennessee



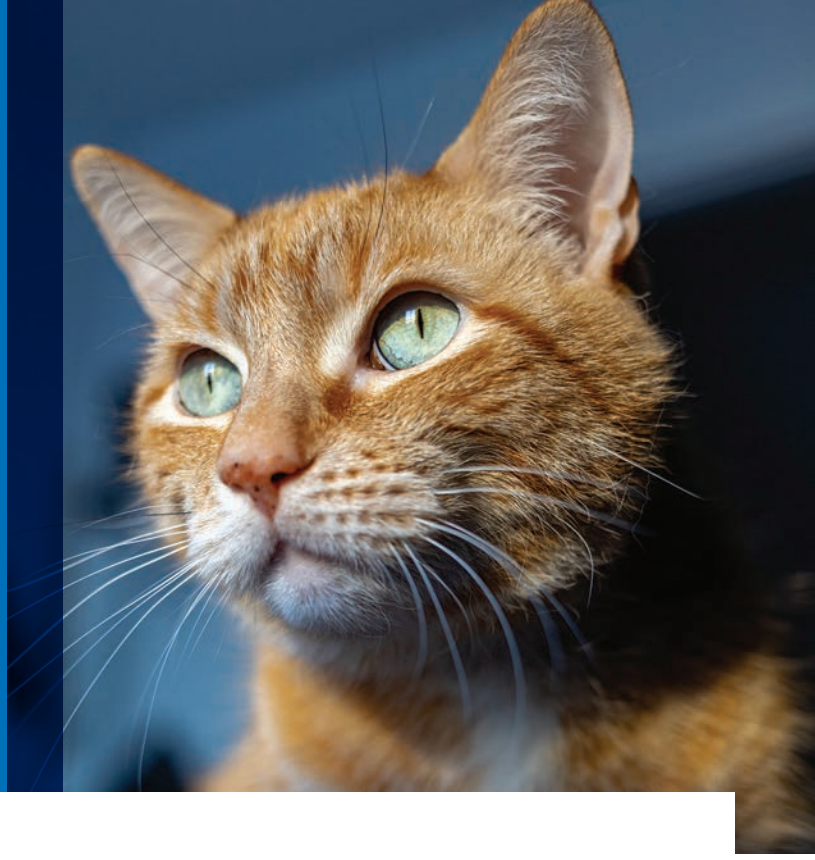
The incidence of canine heartworm (CHW) disease in the Unites States has continued to increase, despite the availability of effective preventives against *Dirofilaria immitis*. In addition, this prevalence is likely underestimated because it may not include data from dogs not receiving veterinary services or dogs in shelter facilities. This study used a pedestrian neighborhood survey in the Cumberland Gap region of Tennessee to collect blood samples and pet owner opinions on CHW disease, prophylaxis, and use of veterinary services. Of the 125 dogs tested, 2% were found to be CHW-positive and 42% were not receiving prophylaxis. Significant predictors of preventive use included household income, use of veterinary services, owner knowledge of CHW disease, spay/neuter status, and confinement outdoors. These results reinforce the importance of educating owners about heartworm disease and heartworm prevention practices.—*Cappiello B, Hudson A, Spangler D, Gruszynski K, Faulkner C*

NUTRITIONAL NOTES

Feline Chronic Kidney Disease: Aaron's Case

Rakefet Orobona, DVM

Sponsored by Hill's Pet Nutrition



Chronic kidney disease (CKD) has been estimated to affect 30% to 40% of cats older than 10 years.[1] Food is the only intervention that has been demonstrated to increase longevity and quality of life in cats with CKD[1]; however, cats are still at risk for muscle wasting during the course of disease. It is therefore critical to ensure feline CKD patients maintain a stable lean body mass (LBM) with a specially formulated kidney food. "Aaron"* was one such patient with CKD that was able to be successfully managed through a proven kidney food with palatability technology and an innovative dietary formulation.

Aaron's Case

Aaron, a 15-year-old neutered male, domestic shorthair cat, was presented to his veterinarian for a proactive senior wellness examination. He had a history of being a picky eater and vomiting on a monthly basis. On examination, Aaron weighed 12.3 lb (5.6 kg) and had a BCS of 4/5, slightly tacky mucous membranes, and stage 2 of 4 periodontal disease. Physical examination was otherwise unremarkable.

Systolic blood pressure was elevated (>150 mm Hg), and blood work revealed azotemia (creatinine, 2.7 mg/dL [range, 0.9-2.5 mg/dL]; BUN, 50 mg/dL [range, 16-37 mg/dL]) with a mildly elevated symmetric dimethylarginine (16 ug/dL [range, 0-14 ug/dL]). Urine was dilute, with a urine specific gravity of 1.016 and a quiet sediment; a urine protein:creatinine ratio was declined by the owners.

Aaron was diagnosed with International Renal Interest Society (IRIS) stage 2 CKD and was started on Hill's Prescription Diet k/d Feline. The owners were advised to slowly transition Aaron's food and to offer several Prescription Diet k/d options so that Aaron could choose his favorite. The owners were sent home with a Prescription Diet k/d starter kit containing a variety of k/d flavors and food textures (eg, dry, minced, stew).

Aaron's owners reported during a follow-up phone call 2 days later that Aaron refused the minced food but was eating both the dry and stew formulations well. A recheck examination 2 months later revealed maintenance of normal lean muscle mass and improvement in azotemia.

Maintaining LBM in Cats with CKD

Through proper feeding practices, Aaron was able to chronically maintain his weight and LBM, which are crucial components of an effective renal food. However, the ability of renal foods to maintain LBM has recently come under question.[2,3] Although renal foods have many important features (eg, reduced phosphorus and sodium; increased caloric density; supplementation with potassium, B vitamins, antioxidants, and omega-3 fatty acids),[1] their controlled level of protein is receiving attention due to its effects on LBM.[2-4]

One school of thought advocates *against* protein restriction, as it may lead to decreased LBM,[2,3,5] a concerning effect in light of

*Aaron's case is hypothetical, compiled from several cases in the records of Dr. Cynthia Courtney to demonstrate the positive effects of a therapeutic food specifically formulated for cats with CKD.

the fact that significant reduction in LBM has been associated with increased mortality in cats with CKD.[2] A second school of thought, however, advocates *for* protein restriction to reduce uremic signs caused by an accumulation of protein metabolites, which are excreted by the kidneys.[1,2,4] In addition, protein is a significant source of dietary phosphorous, and controlling intake levels of protein can help limit phosphorous intake.[2]

To promote patient comfort and longevity, effective renal foods should contain controlled but adequate levels of protein to support LBM.

Finding Innovative Solutions

Hill's Prescription Diet k/d Feline overcomes these challenges with innovative dietary solutions. The protein in Prescription Diet k/d is highly digestible and contains high levels of essential amino acids to maintain LBM. In addition, it contains high levels of L-carnitine and omega-3 fatty acids.[6] Therefore, Prescription Diet k/d Feline is not protein-restricted, as it provides adequate protein building blocks to support LBM maintenance while preserving low phosphorus levels.

In a recent, prospective clinical study, cats with IRIS stage 1 or 2 CKD were fed either Prescription Diet k/d Feline or a different therapeutic renal food for 6 months.[7] Cats fed Prescription Diet k/d experienced no change in their LBM over the course of the study and also experienced a significant increase in body weight, whereas cats fed the alternate therapeutic food lost weight and had reduced LBM. Comparatively, cats fed Prescription Diet k/d consumed 23% more calories than cats fed the alternate food.

The Importance of Adequate Food Intake

The above study demonstrates that cats fed Hill's k/d can maintain LBM and increase their body weight while on a therapeutic renal food.[7] Sufficient caloric intake is critical for cats with CKD to prevent muscle tissue from being used for energy. Specifically formulated for feline patients with CKD, Prescription Diet k/d supports optimal caloric intake through proper formulation of balanced nutrients to calories.

Prescription Diet k/d has a demonstrated track record of palatability.[7-9] Its proprietary Enhanced Appetite Trigger (EAT) Technology stimulates appetite, increasing caloric intake.[6] It has been shown that 94% of cats successfully transition to Prescription Diet k/d dry food when receiving a proper transition period.[8]

Even with appropriate transitions, however, some cats may be finicky, disliking certain flavors or textures, an effect that can be exacerbated by their disease.[1] As Aaron's case demonstrates, meeting patient preferences with regard to flavor and texture can be crucial for feeding success. To address this, Hill's offers k/d in dry, minced, and stew textures in several flavors, with all these varieties available as part of their Prescription Diet k/d starter kits.

Conclusion

CKD is a complex disease in which many nutritional factors and patient preferences must be balanced to achieve optimal management. Hill's Prescription Diet k/d Feline combines science with an understanding of feline behavior to maintain LBM, provide an ideal nutrient profile, and boost palatability, helping cats combat CKD and live longer, more comfortable lives.

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Learn more about Hill's Prescription Diet k/d at **HillsVet.com/Renal**

Effective renal foods should contain controlled but adequate levels of protein to support lean body mass.

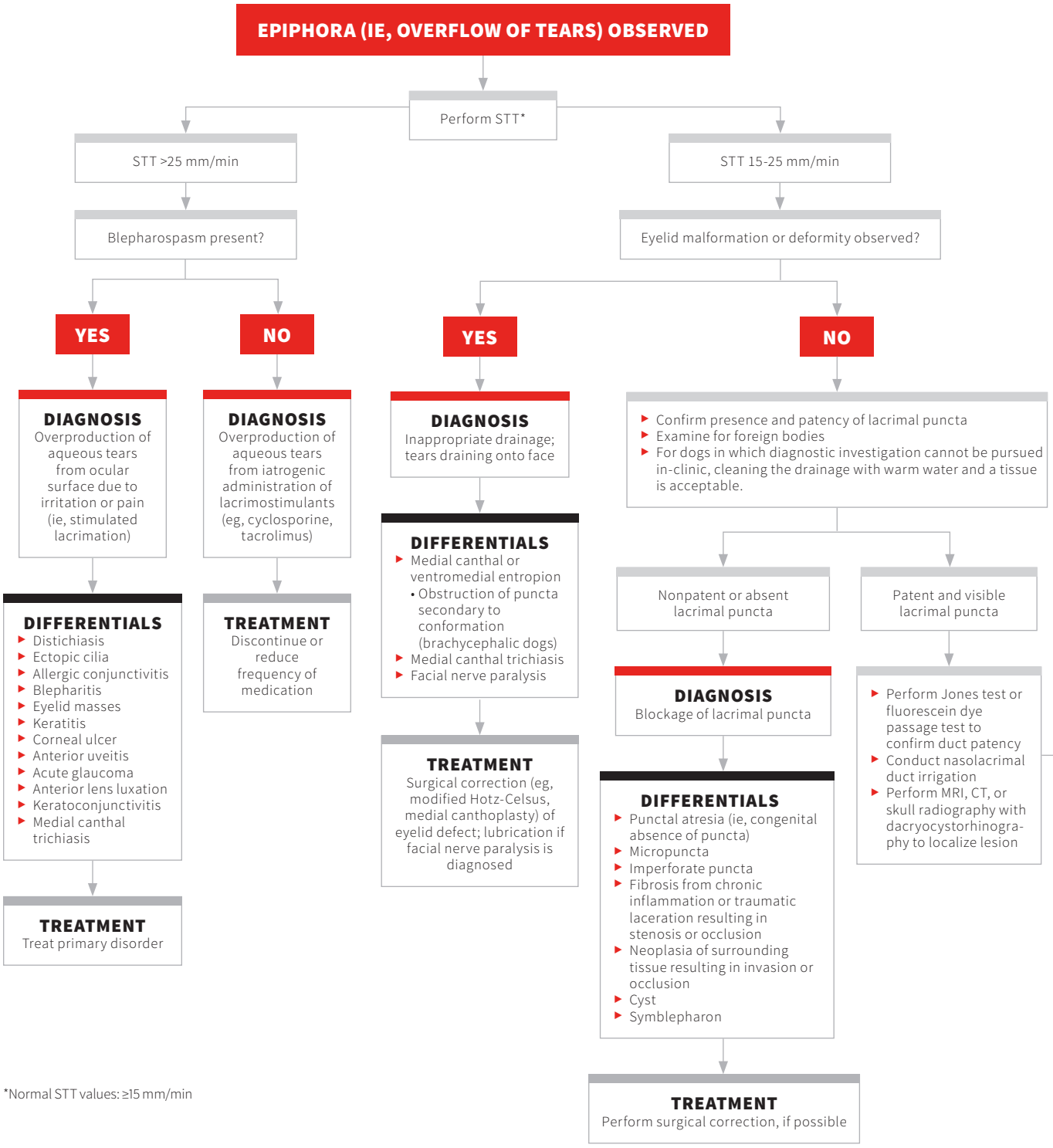
Combination Anthelmintic Treatment for Persistent *Ancylostoma caninum* Ova Shedding in Greyhounds

Drug resistant *Ancylostoma caninum* has been reported in the United States; however, because post-treatment fecal examinations can be lacking, it is unclear whether drug resistance or pet owner compliance issues are primarily at fault. In this small study, 8 greyhounds persistently positive for *A caninum* infection despite standard anthelmintic treatment were prescribed a combination protocol of topical moxidectin followed within 24 hours by pyrantel/febantel/praziquantel. Fecal examinations were performed 7 to 10 days after treatment, and treatment was continued monthly until fecal results were negative; monthly topical moxidectin was continued as a maintenance treatment. Dogs were in the study for 5 to 14 months. Three dogs resumed shedding *A caninum* ova during the study; 2 of these were attributed to owner noncompliance. Repeat treatment cleared any fecal shedding. The authors conclude that monthly treatment with pyrantel/febantel/praziquantel appears to be effective for nonresponsive or persistent *A caninum* ova shedding. Owner compliance with treatment and follow-up testing was critical. Limitations of the study included small sample size and owner compliance with fecal collection and animal care.—*Hess L, Millward L, Rudinsky A, Vincent E, Marsh A*

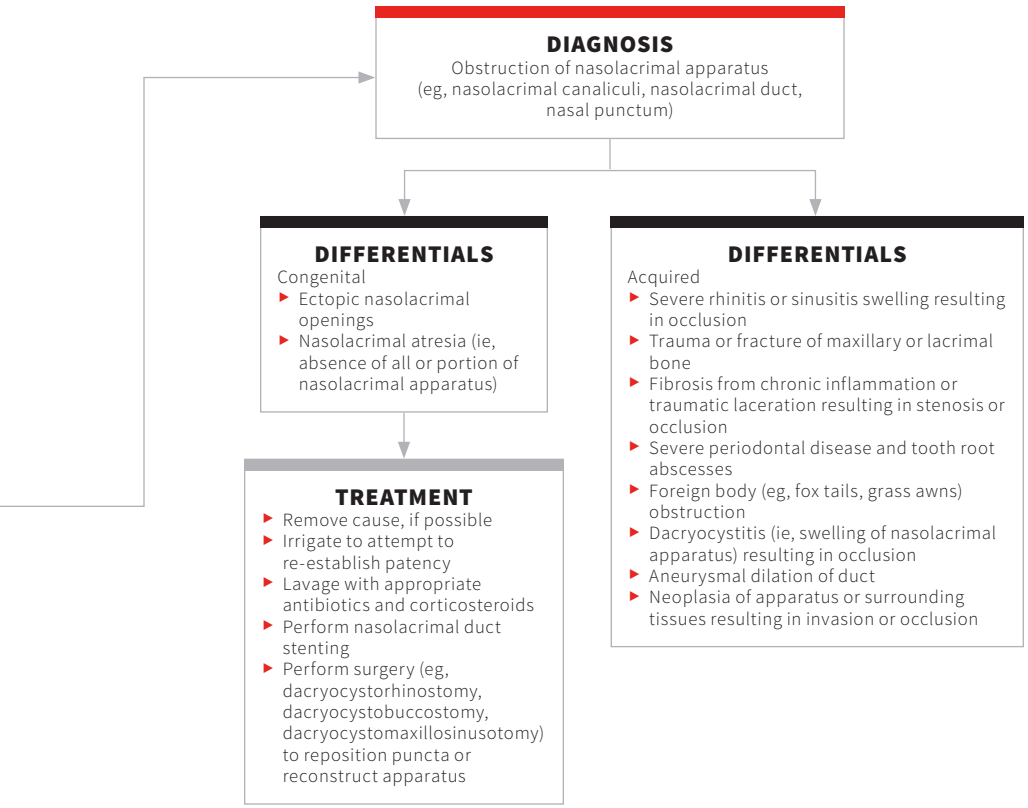
Read more about drug-resistant *A caninum* in greyhounds in the **Special Report** on page 15 of this issue.

EPIPHORA IN DOGS

Christina Korb, DVM
DJ Haeussler Jr, DVM, MS, DACVO
The Animal Eye Institute
Cincinnati, Ohio



*Normal STT values: ≥15 mm/min



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Brief Summary of Prescribing Information.

ProHeart® 12 (moxidectin)

For Extended-Release Injectable Suspension for Dogs

CAUTION
Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

INDICATIONS
ProHeart 12 is indicated for use in dogs 12 months of age and older for the prevention of heartworm disease caused by *Dirofilaria immitis* for 12 months.
ProHeart 12 is indicated for the treatment of existing larval and adult hookworm (*Ancylostoma caninum* and *Uncinaria stenocephala*) infections.

RISK MINIMIZATION ACTION PLAN
The ProHeart 12 and ProHeart 6 Risk Minimization Action Plan (RiskMAP) provides educational materials to the veterinarian, veterinary staff, and the dog owner explaining the risks and proper use of ProHeart 12 and ProHeart 6. ProHeart 12 and ProHeart 6 are the same formulation, but ProHeart 12 is three times the concentration of ProHeart 6. ProHeart 12 and ProHeart 6 are for use in dogs only and are available through a restricted distribution program to veterinarians that have completed the RiskMAP training and certification module.

The ProHeart 12 and ProHeart 6 web-based training and certification module is available at http://www.proheart12.com. This website has important information on the safe and effective use of ProHeart 12 and ProHeart 6 for veterinarians.

Only veterinarians and veterinary technicians/assistants that have completed the training and are certified can administer ProHeart 12 and ProHeart 6. Veterinarians are expected to report all adverse events that occur in animals or humans to the manufacturer. Important safety information is included below:

CONTRAINDICATIONS
ProHeart 12 is contraindicated in animals previously found to be hypersensitive to this drug or ProHeart 6.

HUMAN WARNINGS
Not for human use. Keep this and all drugs out of the reach of children.
If contact with your skin occurs, wash thoroughly with water. May be irritating to the eyes. If product accidentally gets into your eyes, flush eyes thoroughly with water. In case of accidental ingestion, or if skin or eye irritation occurs, contact a Poison Control Center or physician for treatment advice and show the package insert to the physician.

Take care to avoid accidental self-injection. In case of accidental self-injection, seek medical advice and show the package insert or the label to the physician. The Safety Data Sheet (SDS) contains more detailed occupational safety information.

WARNINGS
Anaphylactic and anaphylactoid reactions may occur in some dogs following administration of ProHeart 12 alone or with vaccines. In some cases, these reactions have resulted in death following administration of moxidectin microspheres (see **POST-APPROVAL EXPERIENCE**). Anaphylactic and anaphylactoid reactions should be treated immediately with the same measures used to treat hypersensitivity reactions to vaccines and other injectable products.

Always provide Client Information Sheet and review with owners before administering ProHeart 12. The owner should be advised to observe their dog for adverse drug events including those described on the sheet.

Do not administer ProHeart 12 to dogs who are sick, debilitated, underweight or who have a history of weight loss.

PRECAUTIONS
Prior to administration of ProHeart 12, the health of the patient should be assessed by a thorough medical history, physical examination and diagnostic testing as indicated (see **WARNINGS**).

Caution should be used when administering ProHeart 12 in dogs with pre-existing allergic disease, including food allergy, atopy, and flea allergy dermatitis. (see **WARNINGS**).

Caution should be used when administering ProHeart 12 concurrently with vaccinations. Adverse reactions, including anaphylaxis, have been reported following the concomitant use of moxidectin microspheres and vaccinations (see **WARNINGS** and **POST-APPROVAL EXPERIENCE**).

ProHeart 12 should not be used more frequently than every 12 months.

The effectiveness of ProHeart 12 has not been evaluated in dogs less than 12 months of age.

Prior to administration of ProHeart 12, dogs should be tested for existing heartworm infections. Infected dogs should be treated with an adulticide to remove adult heartworms. ProHeart 12 is not effective against adult *D. immitis*.

Caution should be used when administering ProHeart 12 to heartworm positive dogs (see **ADVERSE REACTIONS**).

ADVERSE REACTIONS
A well-controlled field study was conducted, including a total of 593 dogs (297 received two doses of ProHeart 12, 12 months apart and 296 received a monthly oral heartworm preventive as active control) ranging in age from 1 to 14 years. Over the 605-day study period, all observations of potential adverse reactions were recorded.

Table 2: Number of Dogs* with Adverse Reactions Reported During the ProHeart 12 Field Study

Adverse Reaction	ProHeart® 12 n=297 (%)	Active Control n=296 (%)
Vomiting	75 (25.3)	78 (26.4)
Lethargy	46 (15.5)	34 (11.5)
Diarrhea (with and without blood)	43 (14.5)	46 (15.5)
Anorexia	41 (13.8)	31 (10.5)
Seizures	10 (3.4)	7 (2.4)
Hepatopathy	8 (2.7)	3 (1.0)
Hypersalivation	7 (2.4)	3 (1.0)
Anaphylactoid/Hypersensitivity Reactions	6 (2.0)	4 (1.4)

*Some dogs may have experienced more than one adverse reaction or more than one occurrence of the same adverse reaction during the study.

Two ProHeart 12 (moxidectin) - treated dogs experienced anaphylactoid/hypersensitivity-related clinical signs within the first 24 hours following the initial treatment. Both dogs responded to symptomatic treatment. One dog experienced hives and facial swelling that resolved in 24 hours. The second dog experienced redness and swelling of the face and paws, followed by vomiting, polydipsia, and elevated heart rate and was treated symptomatically. Signs resolved within 4 days. One dog was pre-treated before the second injection of ProHeart 12, and neither dog had a reaction to the second dose 12 months later. One active control-treated dog experienced anaphylactoid/hypersensitivity-related clinical signs within the first 24 hours. The dog was withdrawn from the study prior to the second monthly dose.

Mild injection site reactions occurred in six ProHeart 12-treated dogs and were observed from one to seven days post dosing and included warmth, swelling and pruritus. One of these cases included mild pruritus at the injection site that resolved spontaneously within 24 hours of administration.

In a laboratory effectiveness study, dogs with 4- and 6-month-old heartworm infections administered moxidectin microspheres at a dose of 0.17 mg/kg experienced vomiting, lethargy and bloody diarrhea. These signs were more severe in the dogs with 4-month-old heartworm infections, including one dog that was recumbent and required supportive care, than in the dogs with older (6-month-old) infections.

Post-Approval Experience (2018): The following adverse events are based on post-approval adverse drug experience reporting for ProHeart 6. ProHeart 12 and ProHeart 6 are the same formulation, but ProHeart 12 is three times the concentration of ProHeart 6. Not all adverse reactions are reported to FDA/CVM. It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product exposure using these data. The following adverse events are listed in decreasing order of frequency by body system.

Immune: anaphylaxis and/or anaphylactoid reactions, urticaria, head/facial edema, pruritus, pale mucous membranes, collapse, cardiovascular shock, erythema, immune-mediated hemolytic anemia, immune-mediated thrombocytopenia (signs reflected in other system categories could be related to allergic reactions, i.e. gastrointestinal, dermatologic, and hematologic)
Gastrointestinal: vomiting (with or without blood), diarrhea with or without blood, hypersalivation
General: depression, lethargy, anorexia, fever, weight loss, weakness
Dermatological: injection site pruritus/swelling, erythema multiforme
Neurological: seizures, ataxia, trembling, hind limb paresis
Hematological: leukocytosis, anemia, thrombocytopenia
Respiratory: dyspnea, tachypnea, coughing
Hepatic: elevated liver enzymes, hypoproteinemia, hyperbilirubinemia, hepatopathy
Urinary: elevated BUN, elevated creatinine, hematuria, polydipsia, polyuria
Cardiopulmonary signs such as coughing and dyspnea may occur in heartworm positive dogs.

In some cases, death has been reported as an outcome of the adverse events listed above.

Foreign market experience with ProHeart 12 includes similar voluntarily reported adverse events, including death, following administration of ProHeart 12.

For a copy of the Safety Data Sheet (SDS) or to report suspected adverse reactions, contact Zoetis at 1-888-963-8471. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/AnimalVeterinary/SafetyHealth.

INFORMATION FOR DOG OWNERS
Always provide Client Information Sheet and review with owners before administering ProHeart 12. Owners should be advised of the potential for adverse reactions, including anaphylaxis, and be informed of the clinical signs associated with drug toxicity (see **WARNINGS, ADVERSE REACTIONS** and **POST-APPROVAL EXPERIENCE** sections.)

Owners should be advised to contact their veterinarian immediately if signs of toxicity are observed. The vast majority of patients with drug related adverse reactions have recovered when the signs are recognized and veterinary care, if appropriate, is initiated.

STORAGE INFORMATION
Store the unconstituted product at or below 25°C (77°F). Do not expose to light for extended periods of time. After constitution, the product is stable for 8 weeks stored under refrigeration at 2° to 8°C (36° to 46°F).

HOW SUPPLIED
ProHeart 12 10 mL vial product is available in the following package sizes.

1-Pack	5-Pack	10-Pack
1 - 10% moxidectin sterile microspheres- 889 mg/vial 1 - Sterile vehicle - 8 mL/vial	5 - 10% moxidectin sterile microspheres- 889 mg/vial 5 - Sterile vehicle - 8 mL/vial	10 - 10% moxidectin sterile microspheres- 889 mg/vial 10 - Sterile vehicle - 8 mL/vial

Approved by FDA under NADA # 141-519
Revised: April 2019

zoetis

Distributed by: Zoetis Inc., Kalamazoo, MI 49007

40020054A&P

ONE BITE* **can give a dog heartworm disease.†**
ONE ProHeart® 12 injection ensures
ONE FULL YEAR of constant protection.

The year-long heartworm protection of a single ProHeart 12 injection puts compliance in your control

IMPORTANT SAFETY INFORMATION: Use PROHEART 12 in dogs 12 months of age or older. Do not administer to dogs that are sick, debilitated, underweight, have a history of weight loss, or to those previously found to be hypersensitive to the drug. Hypersensitivity reactions may occur in some dogs when PROHEART 12 is administered alone or with vaccines. Anaphylactic and anaphylactoid reactions can result in death and should be treated immediately with the same measures used to treat hypersensitivity reactions to vaccines and other injectable products. The most common reported side effects in clinical trials were vomiting, lethargy, diarrhea, and anorexia. People should avoid inhalation, contact with eyes, or accidental self-injection. Certifi cation is required before veterinarians and staff administer PROHEART 12. **See Brief Summary of Prescribing Information, on page 28.**

*From an infected mosquito. †*Dirofilariaimmitis.*

ZOETIS PETCARE

ProHeart® 12 (moxidectin)

ProHeartDVM.com

Intussusception Reduction

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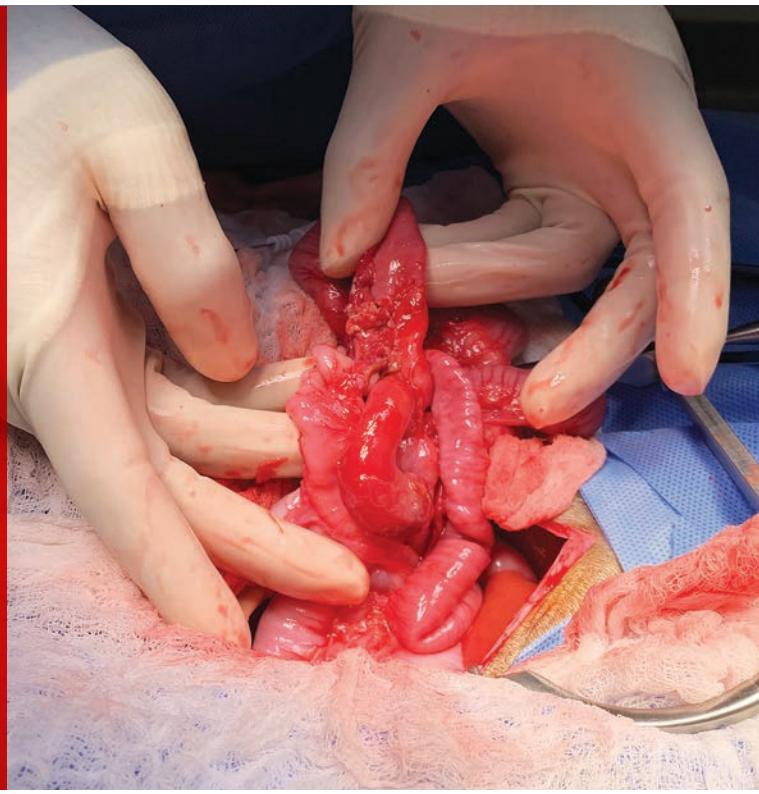
Huntersville, North Carolina



Overview

Intussusception refers to invagination of a portion of the GI tract into the lumen of an adjacent segment. It is sometimes overlooked as a potential cause of GI clinical signs in presenting patients. The 2 components of intussusception include the invaginated section (ie, the intussusceptum) and the adjoining segment that holds the intussusceptum (ie, the intussuscipiens).[1] Underlying disease processes can alter gut motility, resulting in intussusception.[2] Many cases of intussusception are idiopathic and intermittent; thus, diagnosis and treatment of the underlying cause are difficult. Causes of intussusception may include neoplasia, intestinal parasites, viral enteritis, foreign body obstruction, or cecal inversion[2,3]; previous abdominal surgery is a risk factor.

Intussusception can occur at any age but is most commonly recognized in patients younger than 1 year[1] and therefore should be included among the differential diagnoses for any juvenile patient presented with GI signs. Intussusception most commonly occurs at the ileocecocolic junction but can occur along any portion of the GI tract, including the stomach and esophagus.[1] Clinical signs at the time of presentation are typically related to the location of intussusception.

Diagnosis

Diagnostic steps include a complete physical examination, abdominal radiography, and abdominal ultrasonography (or a contrast study if ultrasonography equipment is not available). On physical examination, a thickened tubular structure may be palpated in the abdomen, which may be painful for the patient. Abdominal radiographs commonly reveal a fluid- or gas-filled bowel consistent with a mechanical obstruction.[2] Abdominal ultrasonography is often the most helpful preoperative diagnostic tool (***Figure 1***); the finding of multiple hyperechoic and hypoechoic concentric rings in transverse sections, parallel lines in longitudinal sections, or both is diagnostic of intestinal intussusception.[4] Abdominal radiography with contrast media (ie, barium) can outline the intussusceptum in the lumen of the intussuscipiens, or the contrast can appear as a ribbon-like structure in the intussusceptum.[2]

Treatment

Treatment of intestinal intussusception involves laparotomy with manual reduction if the affected segment appears potentially viable and/or resection and anastomosis of the affected intestinal segment if neoplasia is the underlying cause or if the affected segment is necrotic or cannot be reduced (***Figures 2-4***, next page).

Enteroplication

Intussusception recurrence rates are ≈6% to 27%, and recurrence is usually observed 3 days to 3 weeks postsurgery.[1] Recurrence typically affects the segment immediately proximal to the previous intussusception site.[2] Enteroplication reduces the risk for intussusception recurrence by creating permanent adhesions between adjacent loops of intestine. Enteroplication is completed by preparing the intestines using manual reduction or resection and anastomosis of compromised bowel. After the intestines have been prepared, adjoining segments should be placed side by side in a zigzag pattern with care not to create kinks or sharp bends. The adjacent loops should be sutured together with either absorbable or nonabsorbable suture and should penetrate the submucosal layer midway between the mesenteric and antimesenteric borders to ensure a secure hold. Complete plication encompasses plication of the jejunum to the ileum; the duodenum should not be included because it is rarely involved with intussusception.[3]

Enteroplication can be performed immediately after reduction if the affected segment appears viable and without obvious pathology; however, enteroplication should only be performed in select cases (eg, spontaneous reduction intussusception in young dogs, presence of hyperperistalsis during surgery, cases involving multiple or recurrent intussusception)[3] because of the risk for complications. The procedure has been associated with abdominal discomfort, vomiting/diarrhea, hyporexia, constipation, increased risk for future obstructions, bowel strangulation, and intra-abdominal abscess formation.[3]

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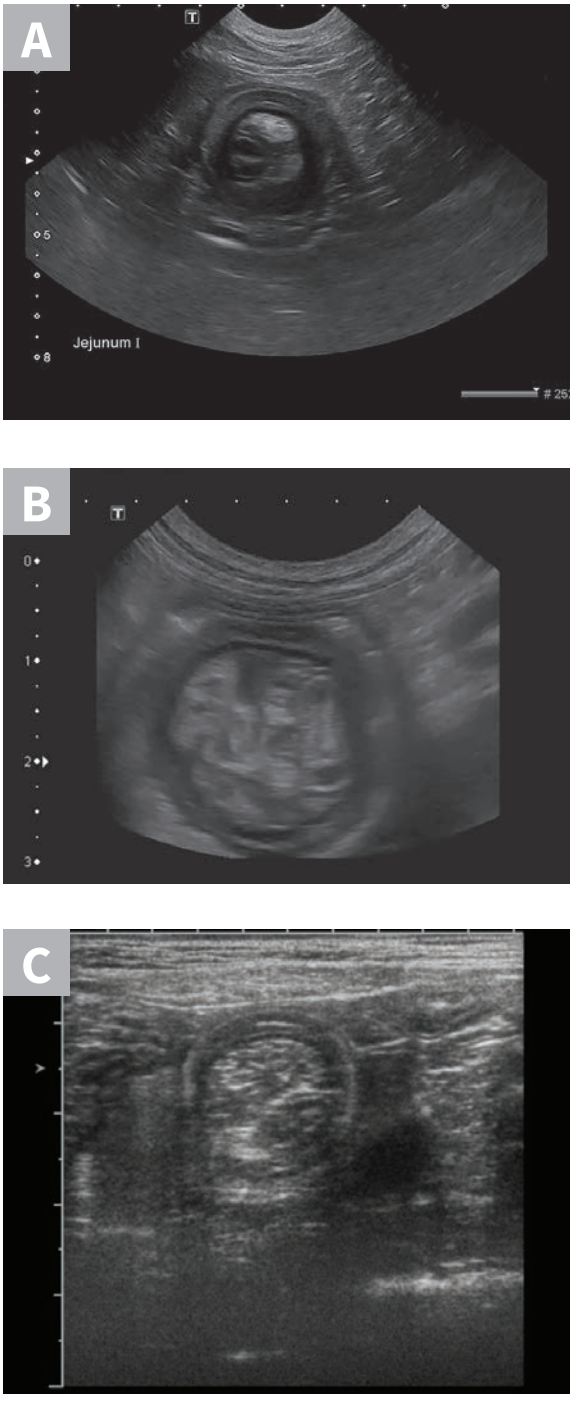
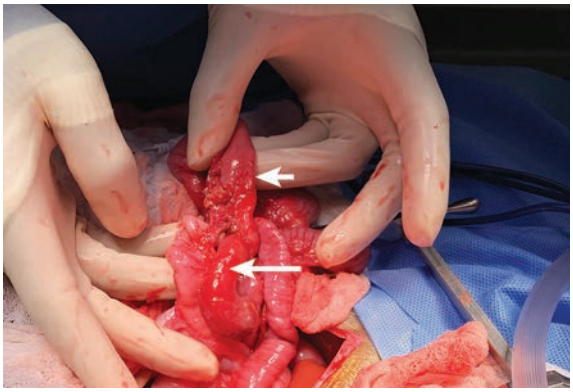
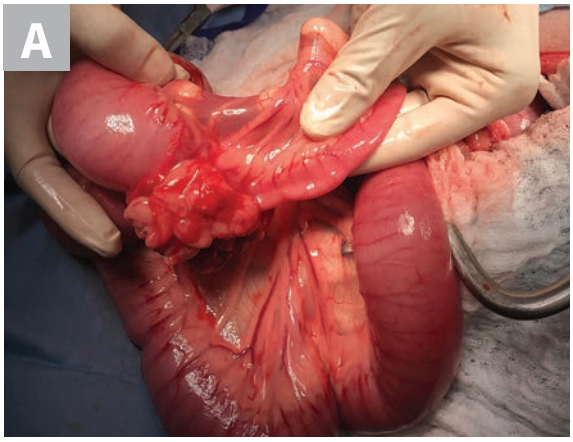
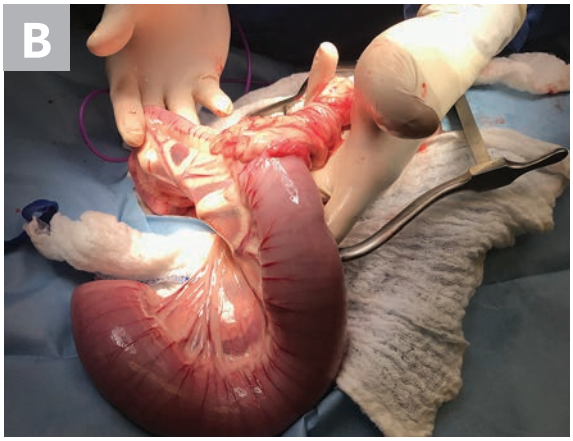


▲ **FIGURE 1** Abdominal ultrasound images of a dog with jejuno-jejunal intussusception secondary to an intestinal sarcoma (***A***), a dog with ileocolic intussusception (***B***), and a dog with jejuno-jejunal intussusception without an identifiable underlying cause (***C***)



▲ **FIGURE 2** A portion of intestine after intussusception reduction. There is serosal tearing (***short arrow***) and significant erythema (***long arrow***).





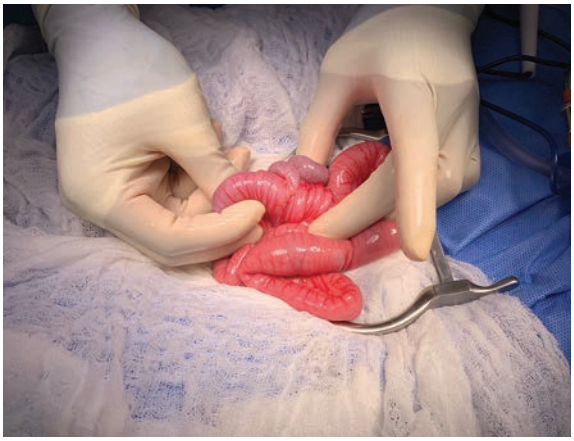
▲ **FIGURE 3** Jejuno-jejunal intussusception. A portion of the omentum is adhered to the intussusception site (***A***). Omental adhesions were removed with a bipolar vessel-sealing device (***B***).

Stomach Intussusception

Intussusception involving the stomach is rare and requires a different treatment approach. For example, patients with gastroesophageal intussusception should be treated with left (± right) incisional gastropexy and may require sutures to reduce the size of the esophageal hiatus.[5] A partial gastrectomy or Y-U pyloroplasty (ie, a procedure in which the pyloric antrum is advanced aborally) should be considered after reduction of gastroduodenal intussusception.[6]

Prognosis

For most idiopathic cases of intussusception, the long-term prognosis is good with appropriate aftercare and treatment, but prognosis ultimately depends on the specific underlying cause. In cases for which a diagnosis is not grossly apparent, samples of the area of intussusception, as well as samples of other areas of intestine, can be submitted for biopsy.[7] Because intestinal parasitism is also a potential predisposing factor for intussusception, fecal samples can also be collected preoperatively for testing and empiric deworming can be performed in case of false negatives.[2]



▲ **FIGURE 4** Intussusception involving the ileocecocolic junction immediately before reduction was attempted. An accordion-like appearance to the intestine is present at the level of intussusception.

WHAT YOU WILL NEED

- Basic surgery pack
  - Hemostats
  - DeBakey forceps
  - Scalpel handle
  - Needle drivers
  - Suture scissors
  - Metzenbaum scissors
  - Mayo scissors
  - Poole suction
  - Radiopaque gauze and laparotomy sponges
- Balfour retractor
- 3-0 or 4-0 absorbable monofilament suture
- #11 or #15 scalpel blades

Additional instruments that may be helpful:

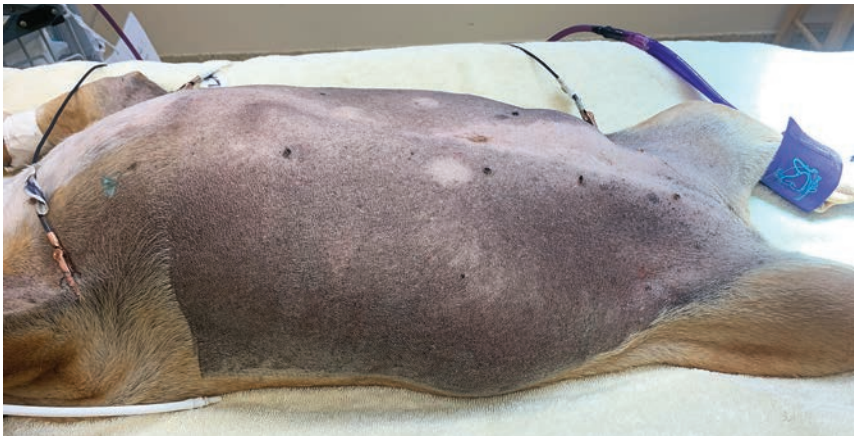
- Doyen forceps
- Vessel sealant device
- Electrocautery
- GI anastomosis stapler
- Thoracoabdominal stapler

Continues ▶

STEP-BY-STEP INTUSSUSCEPTION REDUCTION

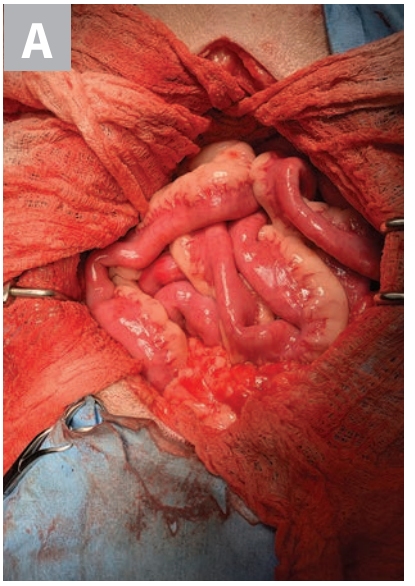
STEP 1

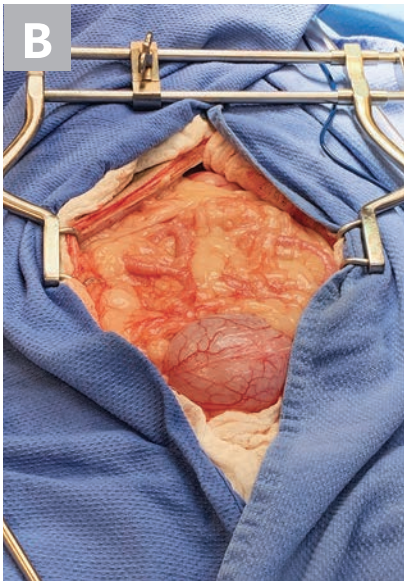
Clip, clean, and perform sterile preparation of the abdomen.



STEP 2

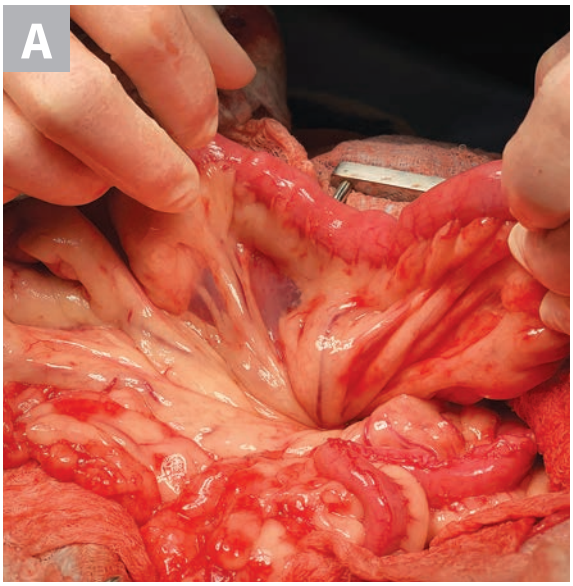
Using a standard ventral midline approach, begin abdominal exploratory surgery. Line the abdominal incision with 2 dampened laparotomy sponges along the linea alba. Place a Balfour retractor to allow appropriate visualization into the abdomen.

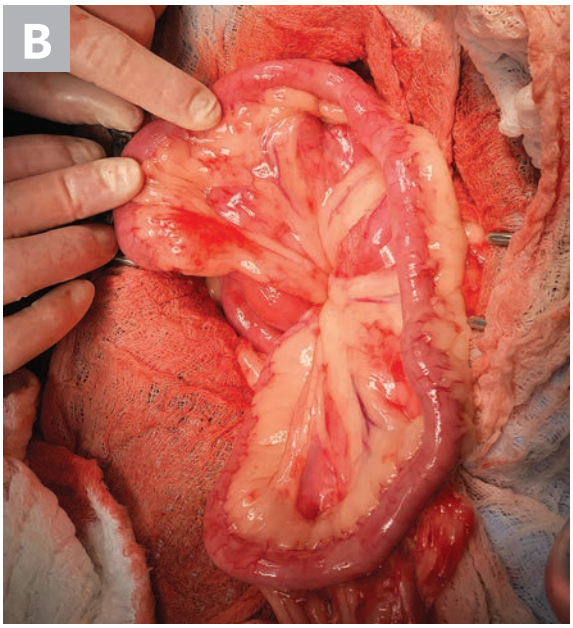




STEP 3

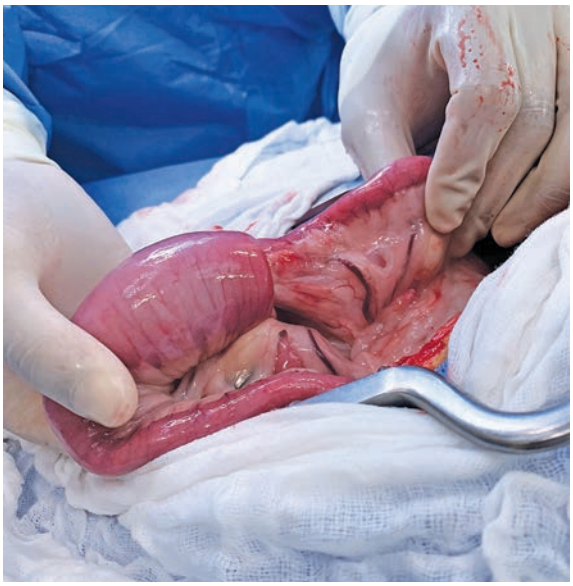
Examine the entire GI tract for abnormalities; multiple occurrences of intussusception may be present.





STEP 4

Isolate the area of intussusception and pack off the region with dampened laparotomy sponges.



VIDEOS

Reduction can often be difficult and may result in significant damage to the affected intestinal segment.

To view videos of failed intussusception reduction in a puppy and partially reduced intussusception in a 3-month-old Australian cattle dog with chronic intussusception that was later found to be necrotic, scan the QR code below.

Using QR codes from your mobile device is easy and quick!

Simply focus your phone's camera on the QR code as if taking a picture (but don't click!). A notification banner will pop up at the top of your screen; tap the banner to view the linked content.

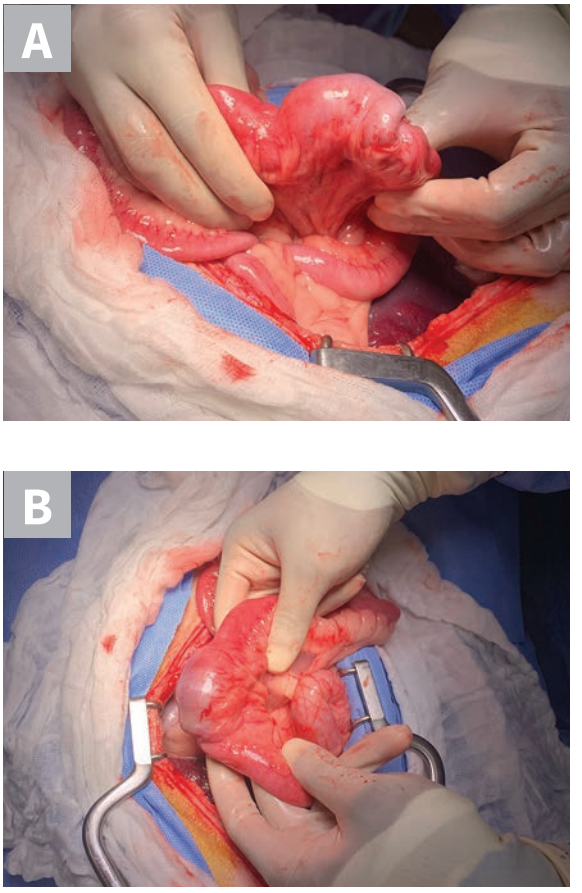
STEP 5

Attempt manual reduction via gentle manipulation. If the intussusception is easily reduced and the affected segment appears viable, complete the exploratory surgery and close the incision in a standard fashion.

If the intussusception does not easily reduce or is associated with an intestinal mass, or if the affected segment is nonviable, perform resection and anastomosis (see ***Steps 6-10***).

AUTHOR INSIGHT

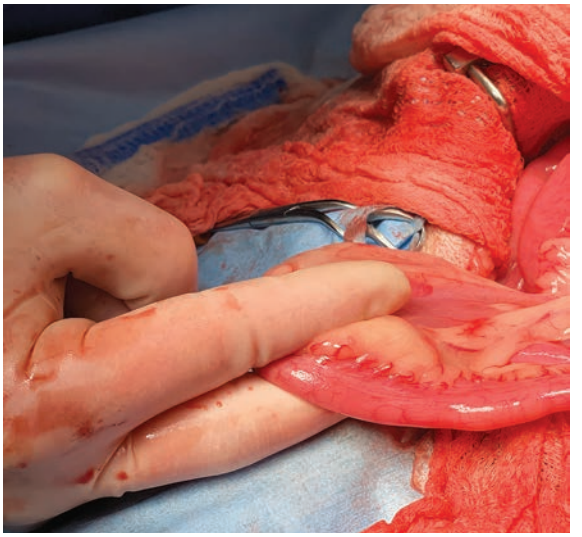
If the intussusception is recurrent, hyperperistalsis is present, or no underlying primary cause is found, consider enteroplication to prevent recurrence. Of note, however, enteroplication can lead to significant postoperative complications.



▲ **FIGURE** A portion of intestine after attempted jejuno-jejunal intussusception reduction. The intussusception could not be fully reduced.

STEP 6

Gently milk intestinal contents away from the portion of intestine that will be resected. Use digital compression or Doyen forceps to gently seal the oral and aboral portions to reduce contamination. Occlude the lumen orad and aborad to the site of resection with gloved and sterile fingers.



RELATED ARTICLE

Read more about intestinal resection & anastomosis at **brief.vet/small-intestinal-resection**

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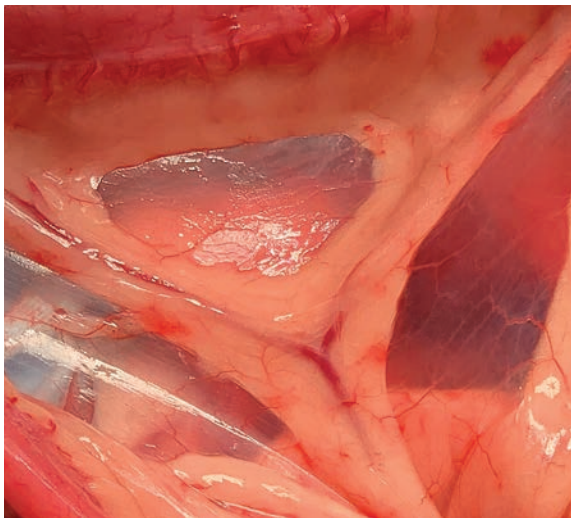
STEP 7

Isolate the blood supply of the affected bowel segment and ligate appropriately.

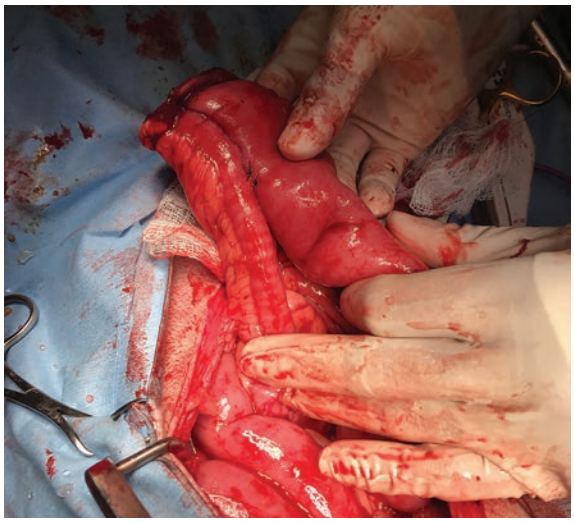


STEP 8

Sharply excise the affected intestinal tract and discard or place aside for histopathology. Be careful to avoid contamination of the surgical field.

STEP 9

Perform either end-to-end anastomosis with absorbable or nonabsorbable sutures or side-to-side anastomosis with surgical and thoracoabdominal staplers.



STEP 10

Achieve adequate intestinal closure, then lavage the peritoneal cavity with sterile saline, suture the omentum to the anastomosis site, and close the incision in a standard fashion.

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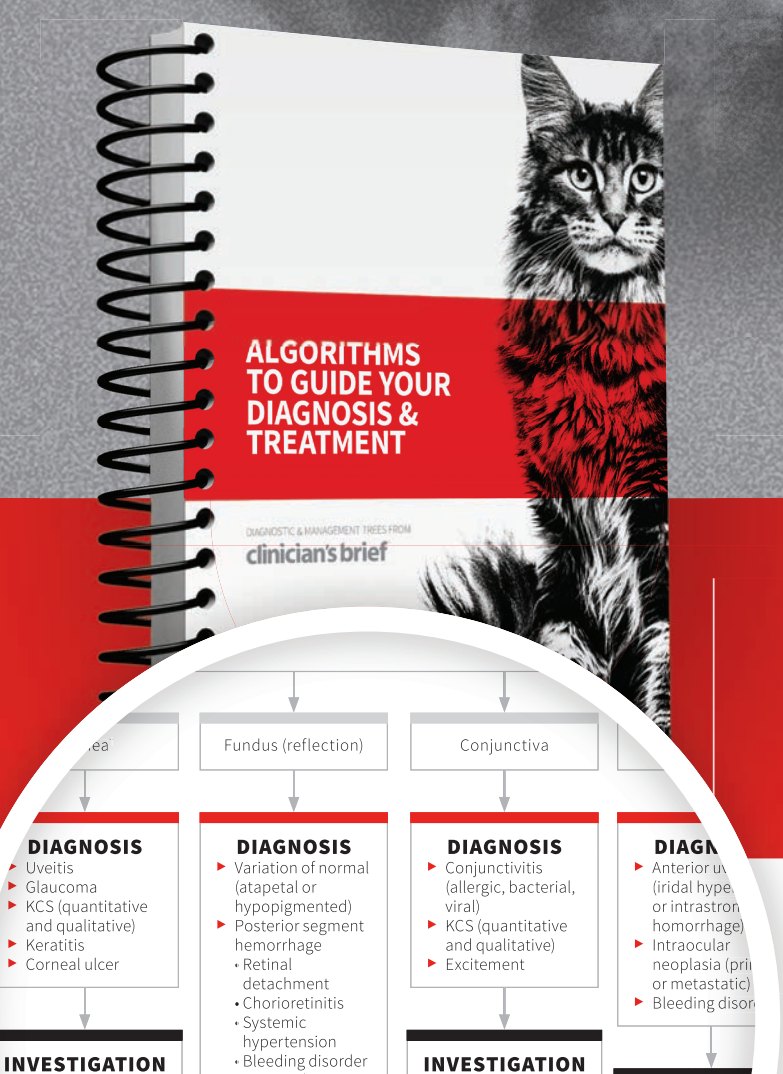
7. Levien AS, Baines SJ. Histological examination of the intestines from dogs and cats with intussusception. *J Small Anim Pract*. 2011;52(11):599-606.

clinician's brief



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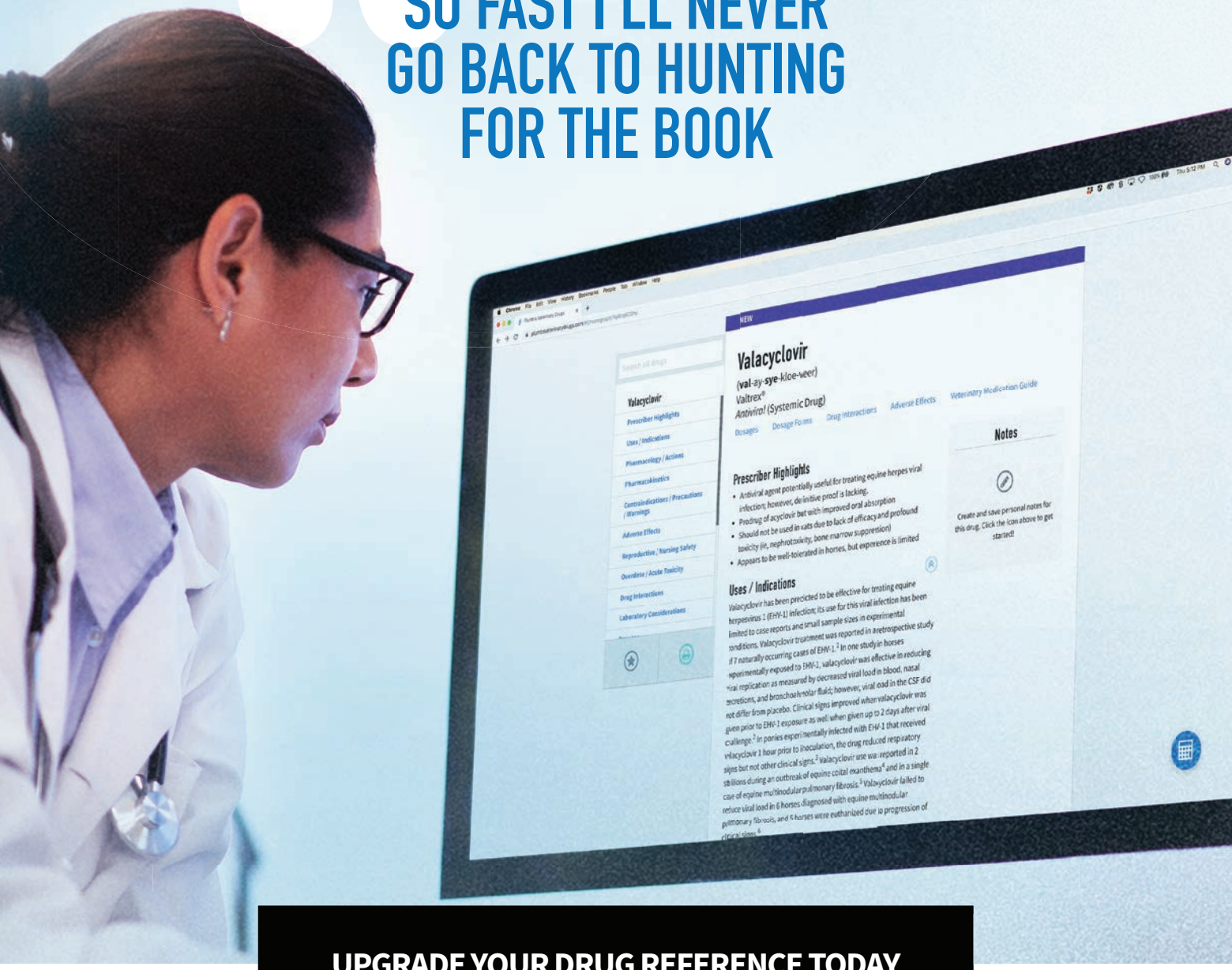

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Blue-Green Algae & Cyanotoxins

Steve Ensley, DVM, PhD
Scott Fritz, DVM
Kansas State University

Cyanotoxins are produced by cyanobacteria (ie, blue-green algae), which are harmful algal blooms, and are highly potent biotoxins that pose a risk to humans, domestic animals, and wildlife; cases of animal exposure occur worldwide and are increasingly prevalent.[1,2]

Background & Pathophysiology

Several species of blue-green algae are capable of producing toxins. Cyanotoxins commonly associated with freshwater algal blooms include microcystins/nodularins (hepatotoxic), cylindrospermopsin (hepatotoxic), anatoxin-a/anatoxin-a(s) (neurotoxic), and saxitoxins (ie, paralytic shellfish poison; neurotoxic). Microcystins and anatoxin-a/anatoxin-a(s) are the most common cyanotoxins in North America and occur across the country. Cyanotoxins can affect any species. The following discussion focuses on the effects of microcystins and anatoxin-a/anatoxin-a(s) on dogs.

Microcystins are cyclic heptapeptides that inhibit serine threonine protein phosphatases and lead to reorganization of hepatocyte infrastructure and eventual hepatocyte apoptosis.[3,4] Microcystins are transported into cells by organic anion transport proteins, which are highly expressed in hepatocytes in relation to other cell types.[5,6] Increased production of necessary transport proteins in hepatocytes can explain the propensity for microcystins to target the liver following ingestion; this could also be because the liver is the first organ exposed to ingested toxins absorbed from the GI tract. There are reports of microcystin intoxication causing lesions in the kidney.[7,8]

Anatoxin-a is a bicyclic amine alkaloid that is a potent acetylcholine-receptor agonist and exhibits greater affinity for nicotinic receptors than for muscarinic receptors.[2,9] Anatoxin-a(s) is a guanidine methyl phosphate ester that is a naturally occurring organophosphate and potent inhibitor of acetylcholinesterase.[10,11]

Although predicting the occurrence of algal blooms can be challenging, common environmental conditions exist, including warm (>70ºF [21ºC]), stagnant waters with some mechanism of nutrient accumulation. Nitrogen and phosphorus are the main nutrients implicated in eutrophication (ie, abnormal accumulation of nutrients, commonly due to surface runoff), which leads to harmful algal blooms that often appear as a thick scum, similar to paint, on the surface of a body of water.[12] Nitrogen and phosphorus can enter bodies of water from many sources (eg, fossil fuel combustion; stormwater discharge; groundwater pollution; agricultural and residential fertilizers; urban, industrial, and agricultural waste).[13] Cyanotoxin poisonings typically occur in late summer or early fall, as water temperatures rise and rainfall tapers off.

History

Patients with cyanotoxin poisoning have an acute onset of clinical signs following exposure to a suspect water source and are often in critical condition or deceased when presented to the clinic. Patients with microcystin poisoning show clinical signs within hours of exposure, and death can occur within 24 hours. Patients with anatoxin-a/anatoxin-a(s) poisoning show almost immediate clinical signs, and death can occur <1 hour after exposure. Algal blooms often produce odors attractive to dogs, leading them to play in the water and ingest the algae-created surface scum; this behavior may play a role in the susceptibility of dogs to cyanotoxin poisoning.[14]

Cyanotoxin poisoning can mimic a variety of diseases.

Clinical Signs

Clinical signs related to microcystin exposure initially reflect GI insult, particularly vomiting, abdominal pain, and bloody diarrhea. The severity of clinical signs worsens with liver damage and developing coagulopathy. Lethargy, weakness, pallor, seizures, and death can follow. Patients that do not succumb to initial GI and acute liver toxic insult may have chronically impaired liver function. The amount of microcystins ingested and the patient's ability to metabolize microcystins (via glutathione-S-transferase pathway) are the most important factors impacting the severity of clinical signs and the degree to which the patient is affected.[15]

Clinical signs associated with anatoxin-a exposure are similar to succinylcholine overdose, with muscle rigidity, tremors, seizures, paralysis, cyanosis, and death likely due to respiratory paralysis.[9] Anatoxin-a(s) inhibits acetylcholinesterase; clinical signs include SLUD (ie, salivation, lacrimation, urination, defecation) syndrome as well as signs associated with anatoxin-a exposure.

Diagnosis

Cyanotoxin poisoning can mimic a variety of diseases due to the different mechanisms of action of different toxins. Differential diagnoses for microcystin poisoning include leptospirosis, infectious canine hepatitis, aflatoxicosis, xylitol poisoning, toxoplasmosis, iron toxicosis, and hepatic neoplasia.

Differential diagnoses for anatoxin-a/anatoxin-a(s) poisoning include poisoning by organophosphate and/or carbamate insecticides, pyrethrins, and chlorinated hydrocarbons and should be considered in patients presented with acute CNS and peripheral nervous system signs, especially after being outdoors.

Diagnosis of cyanotoxin poisoning in a clinical setting should be based on clinical signs and exposure. Identification of algae in suspected ingested water or stomach contents/vomitus is suggestive of poisoning. Presence of toxins in the stomach contents is considered confirmatory. Tissue analy-

sis can be difficult; however, some laboratories possess this capability, and clinicians are urged to contact their diagnostic laboratory for a referral. Many public health departments use an ELISA kit to detect microcystins in water samples. Recent literature suggests that the most practical sample to confirm microcystin exposure in a patient is antemortem testing of urine[15]; however, improvements are needed for this method to become practical for point-of-care use. Clinical pathologic findings associated with microcystin poisoning include but are not limited to thrombocytopenia, hypoglycemia, hyperbilirubinemia, increased ALT, and increased prothrombin and partial thromboplastin times.[15] Confirmatory testing of tissue collected postmortem and histopathologic evaluation are often used for definitive diagnosis. Acute, severe, massive, hepatocellular necrosis is the main histopathologic finding associated with microcystin poisoning.[15]

Anatoxin-a poisoning is associated with rapid death, which limits pathologic assessment because often there are no lesions present or lesions are nonspecific.[16] Stomach content or vomitus samples have the greatest diagnostic value and can be analyzed via liquid chromatography/tandem mass spectrometry to confirm exposure.[16] However, this assay is not routinely offered. Anatoxin-a(s) does not cross the blood–brain barrier, so inhibition of blood acetylcholinesterase but not brain acetylcholinesterase may be supportive of anatoxin-a(s) exposure.[17]

Treatment & Management

Because there is no known antidote for cyanotoxin poisoning, treatment should be aimed at clinical signs. Cyanotoxins are rapidly absorbed from the GI tract, and decontamination is likely to have little benefit when the patient shows clinical signs. For patients with microcystin poisoning, IV fluid therapy, fresh frozen plasma, liver protectants, Vitamins E and K, gastroprotectants, antibiotics, and cholestyramine have all been used in combination with varying degrees of success. This is likely relative to the magnitude of exposure. Current therapy recommendations include cholestyramine,[18,19] IV fluids to replace volume and correct electrolyte abnormalities, glucose supplementation to address hypoglycemia, antiemetics to control vomiting, and antibiotics (if indicated by culture and susceptibility testing), to prevent secondary infections. Treatment should be aimed at combating hypovolemic shock and hemorrhage. Whole-blood transfusions may be necessary in severe cases.

Patients with anatoxin-a or anatoxin-a(s) exposure have such an acute and severe clinical presentation that treatment is often not possible prior to death. Respiratory support has been suggested but is not antidotal and likely only delays death. Anticonvulsants and methocarbamol have been used in cases of anatoxin-a poisoning, but treatment is often unsuccessful. Atropine may reduce clinical signs associated with anatoxin-a(s) poisoning, and although physostigmine and pralidoxime have been suggested for treatment, they do not appear to be of value after exposure.[10] Because cyanotoxins have clinically steep dose-response curves, once clinical signs are observed it is likely that a sufficient amount of toxin has been absorbed to cause death.

Prognosis & Prevention

Prognosis is grave for almost every patient, as morbidity and mortality are high for patients with confirmed exposure. There have been reports of successful intervention for microcystin poisoning in which exposure was relatively small and treatment was initiated quickly.[20] Even for patients with initial recovery from microcystin poisoning,

Anatoxin-a poisoning is associated with rapid death.

prognosis should remain guarded due to complications relating to hepatic insufficiency. Follow-up examination in recovered patients should include monitoring liver enzymes and, potentially, coagulation parameters. Survival after anatoxin-a or anatoxin-a(s) exposure is rare and little is known about potential long-term complications.

Prevention of exposure is the most effective means of preventing clinical illness associated with harmful algal blooms. Cyanobacteria algal blooms are increasingly prevalent and likely to continue to cause illness.[21] State agencies are aware of the risks these blooms pose and many have monitoring programs for recreational waters. There is ongoing research on preventive and mitigation techniques but there are no current effective economic solutions. More research is needed to accurately predict conditions contributing to algal bloom development.

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REVOLUTION PLUS is an easy-to-apply, quick-drying, small-volume, monthly topical solution that protects against **fleas** (*Ctenocephalides felis*), **ticks** (**Black-legged** or **deer tick** [*Ixodes scapularis*], **Gulf Coast tick** [*Amblyomma maculatum*] and **American dog tick** [*Dermacentor variabilis*]), **ear mites** (*Otodectes cynotis*), **roundworms** (*Toxocara cati*), **hookworms** (*Ancylostoma tubaeforme*), and **heartworms** (*Dirofilaria immitis*) for cats and kittens as young as eight weeks of age and weighing 2.8 pounds or greater.

*REVOLUTION PLUS broadens the scope of protection for cats and kittens against fleas, ticks, ear mites, roundworms, hookworms, and heartworms.

See page 44 for product information summary.

revolution® PLUS

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

INDICATIONS: REVOLUTION PLUS is indicated for the prevention of heartworm disease caused by *Dirofilaria immitis*. REVOLUTION PLUS kills adult fleas (*Ctenocephalides felis*) and is indicated for the treatment and prevention of flea infestations, the treatment and control of tick infestations with *Ixodes scapularis* (black-legged tick), *Amblyomma maculatum* (Gulf Coast tick) and *Dermacentor variabilis* (American dog tick), the treatment and control of ear mite (*Otodectes cynotis*) infestations, and the treatment and control of roundworm (*Toxocara cati*) and intestinal hookworm (*Ancylostoma tubaeforme*) infections for one month in cats and kittens 8 weeks and older, and weighing 2.8 pounds or greater.

CONTRAINDICATIONS: There are no known contraindications for the use of REVOLUTION PLUS.

WARNINGS: Human warnings: Not for human use. Keep this and all drugs out of the reach of children. In humans, REVOLUTION PLUS may be irritating to skin and eyes. REVOLUTION PLUS and selamectin topical solution contain isopropyl alcohol and the preservative butylated hydroxytoluene (BHT). Reactions such as hives, itching and skin redness have been reported in humans in rare instances after accidental dermal contact with selamectin topical solution. Individuals with known hypersensitivity to selamectin topical solution should use caution or consult a health care professional before applying this product on a cat. Wash hands after use and wash off any product in contact with the skin immediately with soap and water. If contact with eyes occurs, then flush eyes copiously with water; if wearing contact lenses, rinse the eyes first then remove contact lenses and continue to rinse for 5 – 10 minutes and seek medical attention. In case of ingestion by a human, contact a physician immediately. The safety data sheet (SDS) provides more detailed occupational safety information. For a copy of the SDS or to report a suspected adverse reaction, call Zoetis at 1-888-963-8471. Flammable - Keep away from heat, sparks, open flames or other sources of ignition.

PRECAUTIONS: Sarolaner, one of the ingredients in REVOLUTION PLUS, is a member of the isoxazoline class. This class has been associated with neurologic adverse reactions including tremors, ataxia, and seizures. Neurologic adverse reactions have been reported in cats receiving isoxazoline class drugs, even in cats without a history of neurologic disorders. Use with caution in cats with a history of neurologic disorders. The safe use of REVOLUTION PLUS has not been evaluated in kittens less than 8 weeks of age. The safe use of REVOLUTION PLUS has not been evaluated in breeding, pregnant, or lactating cats.

ADVERSE REACTIONS: In a field safety and effectiveness study, REVOLUTION PLUS was administered to cats with fleas. The study included a total of 430 cats (282 treated with REVOLUTION PLUS and 148 treated with imidacloprid + moxidectin once monthly for three treatments). Over the 90-day study period, all observations of potential adverse reactions were recorded. Reactions reported in the REVOLUTION PLUS group included those presented in the following table.

Adverse Reactions by Treatment Group

Adverse Reaction	REVOLUTION PLUS (*n* = 282)	Imidacloprid + moxidectin (*n* =148)
Lethargy	12 (4.3%)	1 (0.7%)
Skin lesions*	10 (3.5%)	3 (2.0%)
Anorexia	9 (3.2%)	3 (2.0%)
Pruritus	7 (2.5%)	3 (2.0%)
Conjunctivitis	7 (2.5%)	1 (0.7%)
Sneezing	6 (2.1%)	1 (0.7%)
Administration site hair changes (alopecia)	5 (1.8%)	0 (0.0%)
Administration site lesions (scabbing)	2 (0.7%)	0 (0.0%)

*Lesions not associated with application site.

In a second field safety and effectiveness study, REVOLUTION PLUS was administered to 124 cats with ear mites. Adverse reactions in cats treated with REVOLUTION PLUS included emesis, dermatitis and eczema, and pruritus. In a third field safety and effectiveness study, REVOLUTION PLUS was administered to 70 cats with hookworms. Adverse reactions in cats treated with REVOLUTION PLUS included diarrhea, anorexia, emesis, and lethargy. Foreign Market Experience: The following adverse events were reported voluntarily during post-approval use of the product in cats in foreign markets: ataxia, seizures, and tremors.

To report adverse reactions call Zoetis Inc. at 1-888-963-8471. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/AnimalVeterinary/SafetyHealth.

ANIMAL SAFETY: *Margin of Safety Studies*: One exploratory and two pivotal margin of safety studies were conducted with REVOLUTION PLUS. In the first study, REVOLUTION PLUS was applied topically to kittens eight weeks of age at doses of 12/2 (selamectin/sarolaner) mg/kg (1X), 36/6 mg/kg (3X), 45/7.5 mg/kg (3.75X), and 60/10 mg/kg (5X) every 28 days for eight consecutive doses. One female cat in the 3.75X group was found dead on study day 115. The cause was determined to be hemorrhage in multiple tissues secondary to a low platelet count. The role of the drug in contributing to this event is undetermined. No significant changes related to REVOLUTION PLUS were observed among the remaining cats for physical examination, body weight, clinical pathology (hematology, coagulation, and serum chemistry), gross pathology, histopathology or organ weights. In the second study, REVOLUTION PLUS was applied topically to cats 9 months of age at doses of 1X, 3X, and 5X every 28 days for six consecutive doses. Cosmetic changes at the application site occurred sporadically in all treatment groups and included wet appearance and dried white material. Hair loss at the dose site was also noted in two cats in the 1X group and one cat in the 5X group within 1-8 days after the fourth dose administered on day 84. No significant changes related to REVOLUTION PLUS were observed for physical examination, body weight, clinical pathology (hematology, coagulation, and serum chemistry). During an exploratory margin of safety study, one cat in the 60 mg/kg/10 mg/kg (selamectin/sarolaner) group (5X dose group) experienced piloerection, tremors, and mydriasis approximately 24 hours after receiving the third monthly dose of the combination. Signs resolved without treatment within 2 hours. This cat completed the study, receiving 3 subsequent 5X doses with no abnormal observations. *Oral safety study*: The safety of REVOLUTION PLUS administered orally to kittens was tested in case of accidental oral ingestion. Oral administration of the highest recommended topical dose of REVOLUTION PLUS to kittens resulted in transient lower food consumption and clinical findings of emesis, soft feces, and salivation. In one male, mild tremor was observed and resolved within 3 hours after dosing; the same cat demonstrated reduced activity approximately 6 hours after dosing. *Heartworm Positive Cat Safety of Selamectin*: Selamectin is the active ingredient in REVOLUTION PLUS that prevents heartworm disease in cats; it has been shown that the addition of sarolaner does not interfere with this activity. In a safety study in which selamectin topical solution was applied at 4 times the recommended dose to patent heartworm infected cats, no adverse reactions were observed. *Field safety:* In three well-controlled field studies, REVOLUTION PLUS was used concurrently with other medications, such as vaccines, cestocidal anthelmintics, antibacterials, sedatives, anesthetics, opioid analgesics, corticosteroids, and non-steroidal anti-inflammatories. No adverse reactions were associated with the concurrent use of REVOLUTION PLUS and other medications.

STORAGE CONDITIONS: Store at or below 30°C (86°F).

HOW SUPPLIED: Available in three separate dose strengths for cats of different weights (see **DOSAGE AND ADMINISTRATION**). REVOLUTION PLUS is available in cartons containing one, three, or six single dose tubes. The amount of liquid in tube varies for each weight range (2.8 - 5.5 lbs, 5.6 - 11 lbs, 11.1- 22 lbs). Tubes are never completely filled.

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FROM PAGE TO PATIENT

Designed to bridge the gap between research pages and daily practice protocol, the following pearls offer tips and techniques to grow the general practitioner's clinical excellence.

Atipamezole as a Reversal Agent in Isoflurane-Anesthetized Cats

Allison Goldberg, DVM
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Kate Cummings, DVM, DACVAA
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In the Literature

Zatroch KK, Sakai DM, Parry S, Campoy L, Martin-Flores M. Evaluation of atipamezole as a treatment for dexmedetomidine-induced cardiovascular depression in anesthetized cats. *Am J Vet Res*. 2019;80(5):455-460.

FROM THE PAGE ...

The dose-dependent cardiovascular effects of α_2 agonists have been well-characterized in numerous species and include increased systemic vascular resistance resulting in increased blood pressure, baroreceptor-mediated reflex bradycardia, decreased cardiac output, and a centrally mediated decrease in sympathetic tone.[1-3] Although not licensed for use in cats, atipamezole, an α_2-adrenoceptor antagonist, is routinely used to reverse clinical effects of the α_2 agonist dexmedetomidine. Previous research has shown that atipamezole effectively reduces dexmedetomidine-induced bradycardia in nonanesthetized cats.[1]

This randomized crossover study investigated the effects of 2 clinically relevant doses of atipamezole versus saline solution administered to anesthetized cats that received dexmedetomidine. It was hypothesized that atipamezole would increase the pulse rate to values comparable with baseline and decrease mean arterial pressure as compared with 0.9% saline. Six healthy adult cats were anesthetized 3 times with a minimal 1-week washout period. Cats were induced with isoflurane, intubated, mechanically ventilated, and maintained with isoflurane. Standard anesthetic monitoring was performed in addition to continuous pulse rate and direct blood pressure monitoring.

Following a 20-minute acclimation period, dexmedetomidine (5 µg/kg) was given IV over 5 minutes; cardiovascular variables (eg, pulse rate, mean arterial pressure, cardiac output) were measured before and 5 minutes after dexmedetomidine infusion. Either atipamezole at a low (25 µg/kg) or high dose (50 µg/kg) or saline solution was then administered IM. All variables were measured at defined intervals up to 120 minutes.

Results revealed no benefit of IM atipamezole administration following dexmedetomidine in isoflurane-anesthetized cats. Although pulse rate increased significantly over time, there were no differences between groups. A significant decrease in mean arterial pressure with no increase in pulse rate as compared with saline was observed. In addition, treatment with atipamezole resulted in a transient (ie, lasting 15 minutes) but severe hypotension in some cats in both the high- and low-dose groups. The authors proposed that the failure to increase pulse rate and blood pressure was caused by a diminished baroreceptor reflex known to occur with inhalant anesthesia. It is likely atipamezole reversed the analgesia and anesthetic-sparing effects of dexmedetomidine.

… TO YOUR PATIENTS

Key pearls to put into practice:

1. Although atipamezole was ineffective at increasing pulse rate in isoflurane-anesthetized cats following dexmedetomidine administration, the results of this study should not be extrapolated to the reversal of dexmedetomidine in nonisoflurane-anesthetized cats.
2. Administration of atipamezole to isoflurane-anesthetized cats following dexmedetomidine administration shows no clear benefit and may be detrimental, causing transient but severe hypotension with no increase in heart rate.
3. Alternative anesthetic adjuncts should be considered to provide multimodal anesthesia in isoflurane-anesthetized cats, particularly in patients that may not tolerate the hemodynamic effects of α_2 agonists or the consequences of reversal.

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Dog Restraint in Cars

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Sweetwater, Texas

In the Literature

Hazel SJ, Kogan LR, Montrose VT, Hebart ML, Oxley JA. Restraint of dogs in vehicles in the US, UK and Australia. *Prev Vet Med*. 2019;170(1):104714.

FROM THE PAGE ...

Traveling with a dog can be a significant source of distraction, and distracted driving is a major cause of vehicle accidents. In an accident, both dogs and humans are at risk from the unrestrained pet.

An online survey of dog owners in the United States, the United Kingdom, and Australia sought to determine the frequency with which restraints were used by pet owners traveling with their dog, as well as the factors involved in their decision to use or not use restraints. This study demonstrated that US owners were less likely to restrain their dog when traveling as compared with Australian or UK owners. Only ≈55% of the 706 surveyed US owners claimed that they always restrained their dog in the car; 67% of 637 Australian respondents and 72% of 692 UK respondents reported that they always restrained their dog while in the car.

Of note, only 6 US states have specific regulations limiting where or how dogs are allowed to ride in cars.[1] In the United Kingdom, however, the Highway Code has a specific statement describing suitable restraint for dogs in cars[2]; failure to comply with these regulations can lead to the driver's car insurance being invalidated. Most of Australia's regulations fall somewhere between these.[3]

Other findings regarding restraint of dogs by pet owners included:

- Small dogs were restrained more frequently than were larger dogs.
- Older owners were more likely to restrain their dog than were younger owners.
- Owners driving minivans or vans were more likely to restrain their dog than were those driving small- to medium-sized cars or SUVs.
- In the United States and United Kingdom, most dogs that were regularly restrained were restrained in crates or carriers. In Australia, a harness and tether attached to a seat buckle was most common.

Overall, the most common reasons reported for not providing restraint involved concerns for the pet's comfort or that restraint was not believed to be necessary. Most owners noted a lack of guidance in choosing the appropriate car restraint for their dog and agreed that more information is needed. Most owners agreed that restraint devices for dogs should be safety tested.

… TO YOUR PATIENTS

Key pearls to put into practice:

1. Clinicians should be prepared to remind pet owners of the importance of safe pet restraint while traveling. Distance traveled should not be a factor in whether restraint is used.
2. Confinement in crates should be encouraged when possible, and clinicians can recommend resources to owners to help determine which restraint devices have been proven safe in testing (see ***Suggested Reading***). Such resources could also be impactful for owners who believe restraint of their pet in the car is not critical.
3. Many owner misconceptions regarding the need for pet restraint can lead them to make inappropriate choices. Clinicians should help owners understand that all dogs, regardless of size, need to be safely restrained when traveling.

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Suggested Reading

Center for Pet Safety. CPS website. https://www.centerforpetsafety.org. Accessed November 2019.

DIFFERENTIAL DIAGNOSIS ▸ CONTINUED FROM PAGE 13

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Predispositions for Calcium Oxalate Urolithiasis in US Dogs

Laura Rayhel, DVM
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The Ohio State University

Risk for CaOx urolithiasis increases based on breed, increasing age, and neutered male signalment.

In the Literature

Hunprasit V, Schreiner PJ, Bender JB, Lulich JP. Epidemiologic evaluation of calcium oxalate urolithiasis in dogs in the United States: 2010–2015. *J Vet Intern Med*. 2019;33(5):2090-2095.

FROM THE PAGE ...

The prevalence of calcium oxalate (CaOx) urolithiasis is increasing, and CaOx is the most frequent urolith submitted for analysis in the United States.[1] Previous studies have identified breed predispositions for CaOx urolithiasis, but these were not conducted within the last decade and did not account for breed popularity in the United States.[1,2]

This study* sought to identify breeds at high and low risk for CaOx urolith development. Dogs that had CaOx uroliths analyzed at the University of Minnesota Veterinary Medical Center from 2010 to 2015 were compared with 3 control groups during the study period:

- Dogs that formed nonCaOx uroliths
- Dogs admitted without urinary tract disease
- A population from a breed popularity survey during a similar time period (2013-2016)

Breeds were considered to be at high or low risk if their odds ratio from all 3 control populations was >1 or <1, respectively, and statistically significant. Age and sex were also compared among the groups.

*Funded by Anadamahidol Foundation and Hill's Pet Nutrition

The following breed predispositions were identified:

High-Risk	Low-Risk
Bichon frise	American bulldog
Brussels Griffon	American Staffordshire terrier
Cairn terrier	Australian cattle dog
Chihuahua	Australian shepherd
Jack Russell terrier	Basset hound
Japanese chin	Beagle
Lhasa apso	Border collie
Maltese	Boxer
Miniature pinscher	Chow chow
Miniature schnauzer	French bulldog
Pomeranian	German shepherd dog
Yorkshire terrier	Golden retriever
	Labrador retriever
	Siberian husky

Odds ratios also increased with male dogs, neutered dogs, and older dogs, although risk may decrease after 10 years of age. The mean age at discovery of the first CaOx urolith was 8.4 ± 2.8 years, with Brussels Griffons, Yorkshire terriers, and Pomeranians forming CaOx uroliths ≈1 year earlier.

… TO YOUR PATIENTS

Key pearls to put into practice:

1. Risk for CaOx urolithiasis increases based on breed, increasing age, and neutered male signalment.
2. Based on this study's results, annual screening for CaOx uroliths in high-risk breeds should begin between 5 and 6 years of age or sooner if additional risk factors (eg, persistent CaOx urolithiasis, family CaOx urolith history, breed predisposition to CaOx urolith formation at an earlier age) exist.
3. Annual screening for CaOx uroliths in high-risk breeds may help reduce the need for surgery, allow earlier interventions that prevent urolith recurrence, and allow earlier identification of predisposing comorbidities (eg, hypercalcemia, hyperadrenocorticism).

References

1. Low WW, Uhl JM, Kass PH, Ruby AL, Westropp JL. Evaluation of trends in urolith composition and characteristics of dogs with urolithiasis: 25,499 cases (1985-2006). *J Am Vet Med Assoc*. 2010;236(2):193-200.
2. Lekcharoensuk C, Lulich JP, Osborne CA, et al. Patient and environmental factors associated with calcium oxalate urolithiasis in dogs. *J Am Vet Med Assoc*. 2000;217(4):515-519.

Research Note: A Frozen Raw Diet & Tuberculosis in Cats

Six young cats from different households in the United Kingdom were diagnosed with *Mycobacterium bovis* infection, a member of the *Mycobacterium tuberculosis* complex. All were indoor-only cats and consumed the same commercial frozen raw feline diet. Seven subclinical in-contact cats from the affected households also had evidence of *M bovis* infection. Cats were presented with clinical signs including fever, inappetence, and severe weight loss and with diagnostic findings including pyogranulomatous lesions, abdominal mass, lymphadenopathy, and/or pneumonitis. Mortality rate was 83%. *M bovis* infection is zoonotic; commercial raw meat-based diets pose a significant risk for transmitting infectious pathogens such as *M bovis* to animals and their owners.

Source

O'Halloran C, Ioannidi O, Reed N, et al. Tuberculosis due to *Mycobacterium bovis* in pet cats associated with feeding a commercial raw food diet. *J Feline Med Surg*. 2019;21(8):665-666.

Commercial raw meat-based diets pose a significant risk for transmitting infectious pathogens to animals and their owners.

Concurrent Chemoradiotherapy: What Is the Risk?

Cheryl Balkman, MS, DVM, DACVIM (Internal Medicine, Oncology)
Cornell University

In the Literature

Stibirova K, Treggiari E, Amores-Fuster I, et al. Haematologic toxicity in dogs with mast cell tumours treated with vinblastine/prednisolone chemotherapy with/without radiotherapy. *J Small Anim Pract*. 2019;60(9):534-542.

FROM THE PAGE ...

Chemoradiotherapy is considered the standard of care for certain cancers in humans and, although less common, has been used in veterinary patients. Chemoradiotherapy involves administration of chemotherapeutic agents prior to and during the course of radiation therapy as a radiation sensitizer to improve the response to local radiation, for the treatment of advanced locoregional disease, or for both local and systemic effects on tumors with a high metastatic potential.

Patients with incompletely excised high-grade or metastatic tumors require adjunctive therapy (ie, radiation and chemotherapy) to provide both adequate local and systemic control of their tumors. Although using these treatment modalities simultaneously can shorten overall treatment time, the risk for hematologic toxicity can be increased. This study aimed to determine whether dogs with microscopic mast cell tumors treated with radiation therapy and vinblastine/prednisolone demonstrated increased myelosuppression as compared with dogs treated with only vinblastine/prednisolone.

Forty-three dogs were treated with a combination of radiation therapy and vinblastine/prednisolone (RT/VBL/Pred); another 43 dogs were treated with vinblastine/prednisolone alone (VBL/Pred). Eight dogs (19%) in the RT/VBL/Pred group experienced neutropenia (6 VCOG [Veterinary Cooperative Oncology Group] grade I, 1 VCOG grade II, and 1 VCOG grade IV neutropenia) that resulted in a delay of chemotherapy, and 1 dog had a 10% dose reduction. Ten dogs (23%) in the VBL/Pred group experienced neutropenia (4 VCOG grade I, 2 VCOG grade II, and 4 VCOG grade III neutropenia), necessitating a dose delay in 10 dogs and a 10% dose reduction in 1. There was no significant difference in the frequency of neutropenia between the RT/VBL/Pred and VBL/Pred groups. The authors state that the study may have been underpowered to detect a difference.

Although no increased risk for myelosuppression was shown when radiation therapy was administered simultaneously with vinblastine and prednisolone, this may not be the case when other chemotherapy agents are used. Other factors that can influence the risk for myelosuppression when combining radiation with chemotherapy include the radiation protocol (ie, number of fractions and total radiation dose) and the amount of bone marrow in the radiation field. In humans, a major factor associated with neutropenia or thrombocytopenia during radiation therapy is the percent of marrow being irradiated.

Continues ▶

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… TO YOUR PATIENTS

Key pearls to put into practice:

1. Treating dogs concurrently with radiation and vinblastine can decrease overall treatment time without increasing the risk for myelosuppression, but different radiation protocols may not have the same result.
2. There may be an increased risk for myelosuppression associated with concurrent radiation therapy and chemotherapy when other chemotherapy agents are used and a greater amount of bone marrow is being irradiated.
3. Multimodal cancer therapy must be carefully planned and pet owners educated about the risk versus benefit for the patient.

No increased risk for myelosuppression was shown when radiation therapy was administered simultaneously with vinblastine and prednisolone.

Suggested Reading

Hume KR, Johnson JL, Williams LE. Adverse effects of concurrent carboplatin chemotherapy and radiation therapy in dogs. *J Vet Intern Med*. 2009;23(1):24-30.

Seiwert TY, Salama JK, Vokes EE. The concurrent chemoradiation paradigm—general principles. *Nat Clin Pract Oncol*. 2007;4(2):86-100.

Veterinary Cooperative Oncology Group—common terminology criteria for adverse events (VCOG-CTCAE) following chemotherapy or biological antineoplastic therapy in dogs and cats v1.1. *Vet Comp Oncol*. 2016;14(4):417-446.

Research Note:
Multidrug-Resistant Canine Hookworms

Hookworms are the most significant soil-transmitted nematodes in humans, causing debilitating iron-deficiency anemia, which can become fatal in children, pregnant women, and the elderly. This study identified a naturally occurring, multidrug-resistant strain of the canine hookworm *Ancylostoma caninum*, which harbors a fixed, single-base pair mutation at amino acid 167 of the β-tubulin isotype 1 gene; the isolate was resistant to fenbendazole. The mutation was introduced into the corresponding amino acid in the nematode *Caenorhabditis elegans* and was found to confer similar resistance to thiabendazole and ivermectin. This study highlights the importance of understanding mechanisms of resistance for the design of parasite-control strategies.

Source

Kitchen S, Ratnappan R, Han S, et al. Isolation and characterization of a naturally occurring multidrug-resistant strain of the canine hookworm, *Ancylostoma caninum*. *Int J Parasitol*. 2019;49(5):397-406.

See page 54 for product information summary.

Characteristics of GI Tract Dysfunction in Rabbits

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ZooVet Consulting, PLLC
Bothell, Washington

In the Literature

Oparil KM, Gladden JN, Babyak JM, Lambert C, Graham JE. Clinical characteristics and short-term outcomes for rabbits with signs of gastrointestinal tract dysfunction: 117 cases (2014–2016). *J Am Vet Med Assoc*. 2019;255(7):837-845.

FROM THE PAGE . . .

One of the most common presentations in exotic animal medicine is rabbit GI stasis (RGIS), which may be primary or secondary. Despite its frequency, this syndrome is not well-identified, and etiologies range widely and can include toxicosis, infections, dental disease, neoplasia (GI or nonGI), diet, and environmental conditions.

This study retrospectively examined commonalities in history, clinical, and laboratory findings in an effort to correlate them with etiologies and outcomes. Approximately 24% (n = 117) of the total rabbit caseload seen over a 2-year period was included in the study.

Ultimately, 43 rabbits were diagnosed with RGIS without mechanical obstruction; only 1 was confirmed to have a physical obstruction (impaction of the distal descending colon). Radiographs identified medical issues that were not related to the GI tract in 23 (46%) patients.

Hematologic and serum chemistry values had no statistically relevant associations with short-term outcomes. However, 4 of 7 rabbits with moderate to severe serum creatinine levels, 2 of 3 rabbits with abnormal elevations of serum ALT activity, and 4 of 6 rabbits with marked serum lactate elevations died or were euthanized, suggesting a prognostic association with outcomes despite small sample sizes.

The most significant correlation to short-term outcomes was hypothermia. Thirty-four rabbits

(29%) were hypothermic on presentation, with rectal temperatures <97.9°F (<36.6°C). These patients experienced an ≈4.6 times greater likelihood to die or be euthanized than were rabbits that were not hypothermic on presentation.

Overall, outcomes and short-term prognoses for rabbits presented and treated for RGIS are good; in this study, 72% (84/117) of rabbits survived to hospital discharge, with 15 euthanized and 18 dying prior to discharge.

… TO YOUR PATIENTS

Key pearls to put into practice:

1. GI dysfunction is common in rabbits but has a good short-term outcome.
2. Radiography is valuable but not necessary for determining GI obstruction. Mechanical obstruction causing RGIS appears to be uncommon, based on data from this study, and diagnosis is often challenging; for 18 of 50 rabbits for which abdominal radiography was performed, a boarded radiologist could not differentiate whether radiographic abnormalities noted were caused by functional ileus or mechanical obstruction.
3. Clinical pathology findings have little correlation to outcome except in cases of significant abnormalities.
4. Hypothermia at presentation is a negative prognosticator.

Suggested Reading

DiGirolamo N, Toth G, Selleri P. Prognostic value of rectal temperature at hospital admission in client-owned rabbits. *J Am Vet Med Assoc*. 2016;248(3):288-297.

Harcourt-Brown FM, Harcourt-Brown SF. Clinical value of blood glucose measurement in pet rabbits. *Vet Rec*. 2012;170(26):674.

Huynh M, Boyeaux A, Pignon C. Assessment and care of the critically ill rabbit. *Vet Clin North Am Exot Anim Pract*. 2016;19(2):379-409.

Lichtenberger M, Lennox A. Updates and advanced therapies for gastrointestinal stasis in rabbits. *Vet Clin North Am Exot Anim Pract*. 2010;13(3):525-541.

Ritzman TK. Diagnosis and clinical management of gastrointestinal conditions in exotic companion mammals (rabbits, guinea pigs, and chinchillas). *Vet Clin North Am Exot Anim Pract*. 2014;17(2):179-194.

Experience the many layers of Advantage Multi®
(imidacloprid+moxidectin)

CAUTION: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

Transdermal heartworm prevention that works all month long.

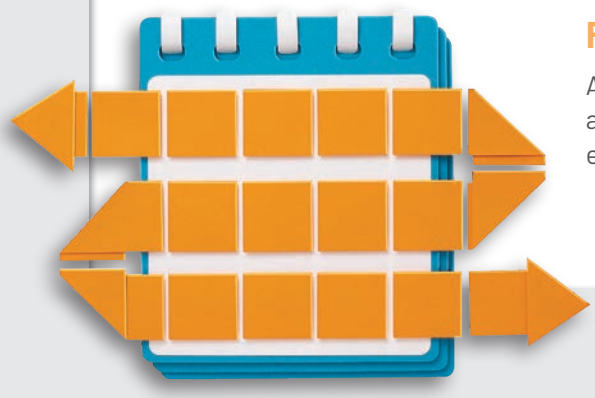
Advantage Multi® (imidacloprid + moxidectin) is a transdermal solution that delivers month-long protection from heartworm disease with one simple application.

This provides an additional layer of convenience and potentially increased compliance for pets that may not prefer oral medications.

Two kinds of heartworm coverage

Backward protection

Like all heartworm prevention products, Advantage Multi® clears tissue stages of heartworms acquired during the previous month.



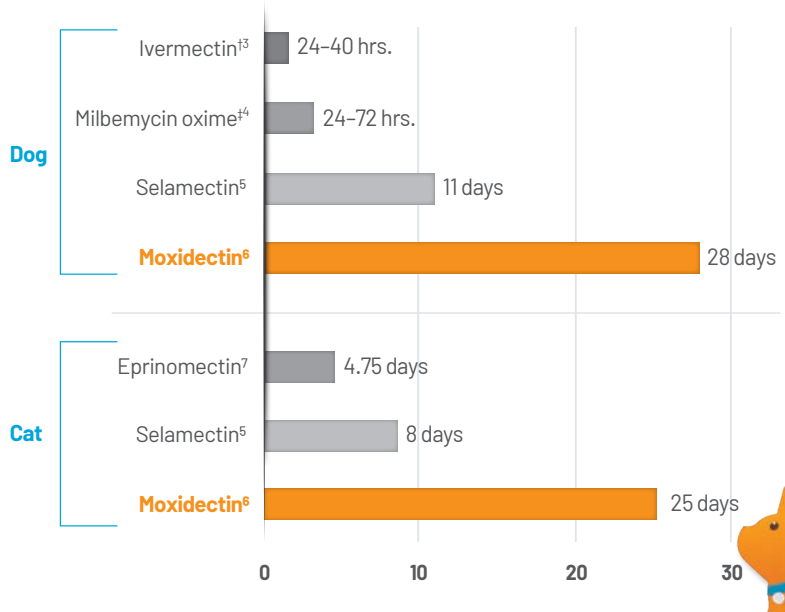
Forward protection*

Advantage Multi® keeps killing newly acquired heartworm larvae all day, every day, all month long.[1,2]

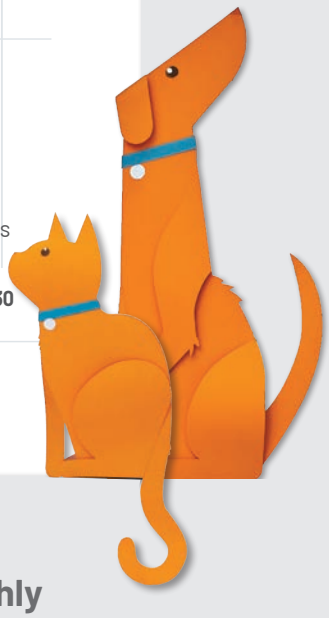
*Forward protection from heartworm infection means that after a single dose of Advantage Multi®, blood levels of moxidectin are continuously at or above the concentration required to kill newly acquired heartworm larvae and are maintained between continued monthly administration of these products.

Transdermal moxidectin has an extended half-life*

Half-life comparison chart of macrocyclic lactones



*The clinical significance of half-life data has not been demonstrated.
†Data indicates half-life of ivermectin varies between 24 and 40 hours.
‡Data indicates half-life of milbemycin oxime varies between 24-72 hours.



When your clients forget to administer the monthly dose, Advantage Multi® is ready to forgive

That's right, your clients can go more than 30 days between doses. Simply have them administer immediately and resume their regular dosing schedule, and their pet remains protected against heartworm disease.

The only FDA-approved formulation to treat circulating microfilariae in heartworm-positive dogs

In laboratory studies and field trials, Advantage Multi® for Dogs was >99% effective in reducing microfilaria counts by study day 28.[8] Eliminating microfilariae is critical in reducing heartworm transmission to other pets.

CAUTION: Advantage Multi® is only available from a licensed veterinarian.
Dogs: WARNING: **DO NOT ADMINISTER THIS PRODUCT ORALLY.** For the first 30 minutes after application, ensure that dogs cannot lick the product from application sites on themselves or other treated animals. Children should not come in contact with the application sites for two (2) hours after application. (See Contraindications, Warnings, Human Warnings and Adverse Reactions for more information.) Cats: Do not use on sick, debilitated, or underweight cats. Avoid oral ingestion.

Fleas don't have to bite to die

When Advantage Multi® (imidacloprid + moxidectin) is applied, imidacloprid spreads across the skin and coat and works through contact, paralyzing and killing these nasty parasites — no biting necessary.

This is unlike oral preventives, which work through the bloodstream, requiring fleas to bite and drink blood to die.

Prescription-only flea treatment stops biting fleas within 3-5 minutes[*9-11]

Kills fleas even after a swim or bath[†12]

*Three *in vivo* experiments were conducted to evaluate the effect of Advantage® Topical Solution (imidacloprid) on fleas (*Ctenocephalides felis*). A total of seven (7) dogs were treated with Advantage® Topical Solution. Seven (7) days after application, areas on the dogs were shaved to allow visual observation. A petri dish was attached over each spot and then infested with up to 100 fleas. In all replicates, the fleas stopped their feeding activity and started tetanic trembling movements within 3-5 minutes. In one hour, all fleas were dead.[9-11]

† A soap-free shampoo for pets is recommended with the use of Advantage Multi®.

Flea protection is just the beginning

Treat feline ear mites with one topical dose of Advantage Multi® for Cats

Plus, monthly use will control subsequent infestations of ear mites – the No. 1 cause of otitis externa in cats

Treats and controls sarcoptic mange

Advantage Multi® for Dogs was 98.7% efficacious in reducing live mite counts within 28 days[8]

Unique protection for ferrets

Advantage Multi® for Cats is the only FDA-approved product indicated for ferrets for the treatment of fleas and prevention of heartworm disease†

†Advantage Multi® for Cats (imidacloprid + moxidectin) (0.4 mL) is indicated for ferrets that weigh at least 2 lbs.

WARNING: Do not use on sick or debilitated cats or ferrets. Do not use on underweight cats. (See ADVERSE REACTIONS.) Do not use on cats less than 9 weeks of age and cats or ferrets less than 2 lbs. body weight.
WARNING: **DO NOT ADMINISTER THIS PRODUCT ORALLY.** For the first 30 minutes after application ensure that dogs cannot lick the product from application sites on themselves or other treated animals. Children should not come in contact with application sites for two (2) hours after application. (See Contraindications, Warnings, Human Warnings and Adverse Reactions for more information.)

Kill multiple parasites at multiple stages

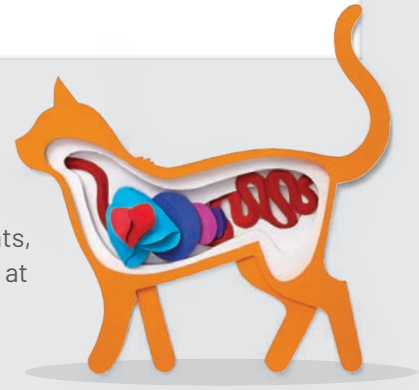
Most products only cover adult worms.* Advantage Multi® (imidacloprid + moxidectin) goes broad and deep to protect pets from multiple life stages of the most common IPs.

	advantage multi® for cats (imidacloprid + moxidectin)	Revolution®	Revolution® Plus
Hookworms			
A. tubaeforme L4	✔		
A. tubaeforme immature adults	✔		
A. tubaeforme adults	✔	✔	✔
Roundworms			
T. cati L4	✔		
T. cati adults	✔	✔	✔

Based on label comparisons for intestinal parasites.

For cats that hunt or live in high-risk areas

After five consecutive monthly administrations of Advantage Multi® for Cats, there is continuous control of hookworms, preventing cats from infection at any time between future monthly applications.[13]

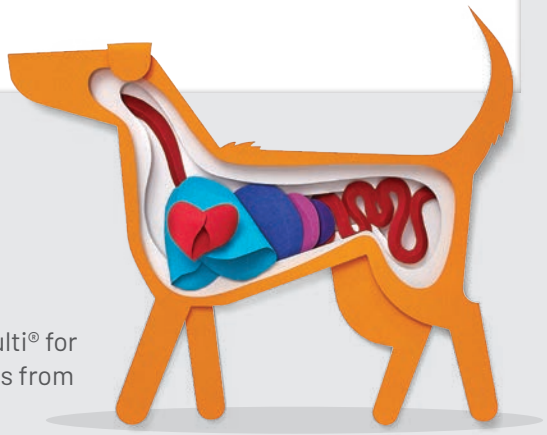


*Based on label comparisons.

PRECAUTIONS: Avoid oral ingestion. HUMAN WARNINGS: Children should not come in contact with the application site for 30 minutes following application.

	advantage multi® for dogs (imidacloprid+moxidectin)	Trifexis®	Interceptor®	Heartgard® Plus	ProHeart®6
Hookworms					
A. caninum L4	✔				✔*
A. caninum immature adults	✔				
A. caninum adults	✔	✔	✔	✔	✔*
A. braziliense				✔	
U. stenocephala L4	✔				✔*
U. stenocephala immature adults	✔				
U. stenocephala adults	✔			✔	✔*
Roundworms					
T. canis L4	✔				
T. canis adults	✔	✔	✔	✔	
T. leonina	✔	✔	✔	✔	
Whipworms					
T. vulpis	✔	✔	✔		

Based on label comparisons for intestinal parasites.



For dogs living in high-risk or heavily contaminated areas

After four consecutive monthly administrations of Advantage Multi® for Dogs, there is continuous control of hookworms, preventing dogs from infection at any time between future monthly applications.[13]

*ProHeart® 6 is indicated for the treatment of existing larval and adult hookworm (*Ancylostoma caninum* and *Uncinaria stenocephala*) infections.

CAUTION: Federal (U.S.A.) law restricts Advantage Multi® to use by or on the order of a licensed veterinarian. WARNING: **DO NOT ADMINISTER THIS PRODUCT ORALLY.** For the first 30 minutes after application ensure that dogs cannot lick the product from application sites on themselves or other treated animals. Children should not come in contact with application sites for two (2) hours after application. (See Contraindications, Warnings, Human Warnings and Adverse Reactions for more information.)

Protect your patients from heartworms, fleas and IPs with the many layers of Advantage Multi®

(imidacloprid + moxidectin)

To experience multi-layered protection, contact your Bayer sales representative or Customer Service at (800) 633-3796.

[1] Bowman DD, Ohmes CM, Hostetler JA, et al. (2017). Efficacy of 10% imidacloprid + 2.5% moxidectin topical solution (Advantage Multi® for Dogs) for the prevention of heartworm disease and infection all month long. *Parasit Vectors*. 10(2):59-64.

[2] Bowman DD, Ohmes CM, Bradford M, et al. (2018). Efficacy of Advantage Multi® for Cats for the prevention of heartworm disease and infection all month long. In: *Proceedings*. American Association of Veterinary Parasitologists. 63rd Annual Meeting. July 14-17, 2018. Denver, CO.

[3] Kojima K, Yamamoto K, Katae H, et al. (1987). Bioavailability of oral ivermectin in dogs. *Jpn J Vet Sci*. 49(5):899-900.

[4] SENTINEL® Spectrum [Summary of Product Characteristics]. Frimley, Camberley, Surrey, UK: Novartis Animal Health UK Ltd.; May 2008 revision.

[5] Sarasola P, Jernigan AD, Walker DK, et al. (2002). Pharmacokinetics of selamectin following intravenous, oral and topical administration in cats and dogs. *J Vet Pharmacol Therap.* 25(4): 265-272.

[6] Data on file. Bayer, Shawnee Mission, KS.

[7] Kvaternicka V, Kellermann M, Knaus M, et al. (2014). Pharmacokinetics and metabolism of eprinomectin in cats when administered in a novel topical combination of fipronil, (S)-methoprene, eprinomectin and praziquantel. *Vet Parasitol.* 202:2-9.

[8] Freedom of Information Summary Supplement, NADA: 141-251.

[9] Mehlhorn H, Hansen O, Mencke N. (2001). Comparative study on the effects of three insecticides (fipronil, imidacloprid, selamectin) on developmental stages of the cat flea (*Ctenocephalides felis* Bouché 1835): a light and electron microscopic analysis of *in vivo* and *in vitro* experiments. *Parasitol Res*. 87(3):198-207.

[10] Mehlhorn H. (2000). Mode of action of imidacloprid and comparison with other insecticides (i.e., fipronil and selamectin) during *in vivo* and *in vitro* experiments. *Suppl Compend Contin Educ Pract Vet*. 22(4A):4-8.

[11] Mehlhorn H, Mencke N, Hansen O. (1999). Effects of imidacloprid on adult and larval stages of the flea *Ctenocephalides felis* after *in vivo* and *in vitro* applications: a light- and electron-microscopy study. *Parasitol Res*. 85(8-9):625-637.

[12] Freedom of Information Summary, NADA: 141-251.

[13] Cruthers LR, Arther RG, Basel CL, et al. (2008). New developments in parasite prevention. In: Bayer selected proceedings, NAVC Conference. *Vet Forum Suppl.* 25(3B):15-20.

Advantage Multi® for Dogs and for Cats

(imidacloprid + moxidectin)

BRIEF SUMMARY: Before using *Advantage Multi® for Dogs* (imidacloprid+moxidectin) or *Advantage Multi® for Cats* (imidacloprid +moxidectin), please consult the product insert, a summary of which follows:

CAUTION: Federal (U.S.A.) Law restricts this drug to use by or on the order of a licensed veterinarian.

Advantage Multi for Dogs:

WARNING

- **DO NOT ADMINISTER THIS PRODUCT ORALLY.**
- **For the first 30 minutes after application ensure that dogs cannot lick the product from application sites on themselves or other treated animals.**
- **Children should not come in contact with the application sites for two (2) hours after application.**

(See Contraindications, Warnings, Human Warnings, and Adverse Reactions for more information.)

INDICATIONS:

Advantage Multi for Dogs is indicated for the prevention of heartworm disease caused by *Dirofilaria immitis* and the treatment of *Dirofilaria immitis* circulating microfilariae in heartworm-positive dogs. *Advantage Multi for Dogs* kills adult fleas and is indicated for the treatment of flea infestations *(Ctenocephalides felis). Advantage Multi for Dogs* is indicated for the treatment and control *of sarcoptic mange* caused by *Sarcoptes scabiei var.canis. Advantage Multi for Dogs* is also indicated for the treatment and control of the following intestinal parasites species: Hookworms *(Ancylostoma caninum) (Uncinaria stenocephala),* Roundworms *(Toxocara canis)* (*Toxascaris leonina) and* Whipworms (*Trichuris vulpis).*

Advantage Multi for Cats is indicated for the prevention of heartworm disease caused by *Dirofilaria immitis. Advantage Multi for Cats* kills adult fleas *(Ctenocephalides felis)* and is indicated for the treatment of flea infestations. *Advantage Multi for Cats* is also indicated for the treatment and control of ear mite *(Otodectes cynotis)* infestations and the intestinal parasites species Hookworm *(Ancylostoma tubaeforme)* and Roundworm *(Toxocara cati).* **Ferrets:** *Advantage Multi for Cats* is indicated for the prevention of heartworm disease in ferrets caused by *Dirofilaria immitis. Advantage Multi for Cats* kills adult fleas *(Ctenocephalides felis)* and is indicated for the treatment of flea infestations in ferrets.

CONTRAINDICATIONS: Do not administer this product orally. (**See WARNINGS**). **Do not use the Dog product (containing 2.5% moxidectin) on Cats.**

WARNINGS:

Advantage Multi for Dogs: **For the first 30 minutes after application: Ensure that dogs cannot lick the product from application sites on themselves or other treated dogs, and separate treated dogs from one another and from other pets to reduce the risk of accidental ingestion. Ingestion of this product by dogs may cause serious adverse reactions including depression, salivation, dilated pupils, incoordination, panting, and generalized muscle tremors. In avermectin sensitive dogs[a], the signs may be more severe and may include coma and death[b].**

[a] Some dogs are more sensitive to avermectins due to a mutation in the MDR1 gene. Dogs with this mutation may develop signs of severe avermectin toxicity if they ingest this product. The most common breeds associated with this mutation include Collies and Collie crosses.

[b] Although there is no specific antagonist for avermectin toxicity, even severely affected dogs have completely recovered from avermectin toxicity with intensive veterinary supportive care.

Advantage Multi for Cats: **Do not use on sick, debilitated, or underweight cats. Do not use on cats less than 9 weeks of age or less than 2 lbs. body weight. Do not use on sick or debilitated ferrets.**

HUMAN WARNINGS: Not for human use. Keep out of the reach of children. Dogs: Children should not come in contact with the application sites for two (2) hours after application. Cats: Children should not come in contact with the application site for 30 minutes after application.

Causes eye irritation. Harmful if swallowed. Do not get in eyes or on clothing. Avoid contact with skin. **Wash hands thoroughly with soap and warm water after handling.** If contact with eyes occurs, hold eyelids open and flush with copious amounts of water for 15 minutes. If eye irritation develops or persists, contact a physician. If swallowed, call poison control center or physician immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to do so by the poison control center or physician. People with known hypersensitivity to benzyl alcohol, imidacloprid, or moxidectin should administer the product with caution. In case of allergic reaction, contact a physician. If contact with skin or clothing occurs, take off contaminated clothing. Wash skin immediately with plenty of soap and water. Call a poison control center or physician for treatment advice. The Safety Data Sheet (SDS) provides additional occupational safety information. For a copy of the Safety Data Sheet (SDS) or to report adverse reactions call Bayer Veterinary Services at 1-800-422-9874. For consumer questions call 1-800-255-6826.

PRECAUTIONS: Do not dispense dose applicator tubes without complete safety and administration information. Use with caution in sick, debilitated or underweight animals. The safety of *Advantage Multi for Dogs* has not been established in breeding, pregnant, or lactating dogs. The safe use of *Advantage Multi for Dogs* has not been established in puppies and dogs less than 7 weeks of age or less than 3 lbs. body weight. *Advantage Multi for Dogs* has not been evaluated in heartworm-positive dogs with Class 4 heartworm disease.

Cats may experience hypersalivation, tremors, vomiting and decreased appetite if *Advantage Multi for Cats* is inadvertently administered orally or through grooming/licking of the application site. The safety of *Advantage Multi for Cats* has not been established in breeding, pregnant, or lactating cats. The effectiveness of *Advantage Multi for Cats* against heartworm infections *(D. immitis)* after bathing has not been evaluated in cats. Use of this product in geriatric cats with subclinical conditions has not been adequately studied. Ferrets: The safety of *Advantage Multi for Cats* has not been established in breeding, pregnant, and lactating ferrets. Treatment of ferrets weighing less than 2.0 lbs. (0.9kg) should be based on a risk-benefit assessment. The effectiveness of *Advantage Multi for Cats* in ferrets weighing over 4.4 lbs. (2.0 kg) has not been established.

ADVERSE REACTIONS: Heartworm Negative Dogs: The most common adverse reactions observed during field studies were pruritus, residue, medicinal odor, lethargy, inappetence and hyperactivity. **Heartworm Positive Dogs:** The most common adverse reactions observed during field studies were cough, lethargy, vomiting, diarrhea (including hemorrhagic), and inappetence. **Cats:** The most common adverse reactions observed during field studies were lethargy, behavioral changes, discomfort, hypersalivation, polydipsia and coughing and gagging. **Ferrets:** The most common adverse reactions observed during field studies were pruritus/scratching, scabbing, redness, wounds and inflammation at the treatment site; lethargy; and chemical odor.

For a copy of the Safety Data Sheet (SDS) or to report adverse reactions call Bayer Veterinary Services at 1-800-422-9874. For consumer questions call 1-800-255-6826.

Advantage Multi is protected by one or more of the following U.S. patents: 6,232,328 and 6,001,858.

NADA 141-251,141-254 Approved by FDA V-03/2016

Made in Germany.

Using Patient Established Reference Intervals to Diagnose Thyroid Disease in Cats

Lisa Singer, VMD, DACVIM
Veterinary Specialist Services
Queensland, Australia

In the Literature

Prieto JM, Carney PC, Miller ML, et al. Short-term biological variation of serum thyroid hormone concentrations in clinically healthy cats. *Domest Anim Endocrinol*. 2020;71:106389.

FROM THE PAGE ...

Hyperthyroidism is a common endocrine disease in cats, with a reported prevalence of 8.4% to 11.7% in cats >10 years of age.[1] The disease is typically diagnosed based on elevated total thyroxine (T4) values and presence of typical clinical signs (ie, weight loss in conjunction with increased appetite, polyuria, polydipsia, vomiting, diarrhea, hyperactivity). A small percentage of cats with apathetic hyperthyroidism are presented with lethargy, obtundation, and poor appetite.

Elevated total T4 values confirm a diagnosis of hyperthyroidism in 91% of cats[2]; however, the established population-based reference intervals for euthyroidism may not always be accurate, and some cats with normal values may be preclinically hyperthyroid. Many cats that have early stages of hyperthyroidism will fall in the high end of the normal reference range for T4. Free thyroxine (fT4) is the small percentage of T4 not bound to serum proteins. When elevated, fT4 has a sensitivity of 98% for diagnosis of hyperthyroidism and can be used as a second-line test in cats with high normal T4.2 Still, there is a large day-to-day biologic variation in T4 and triiodothyronine (T3) values in hyperthyroid cats, and some patients with clinical disease fall within normal reference ranges; this variation is minimal in normal cats.[3]

This study evaluated biologic variation of T4, fT4, and thyroid-stimulating hormone (TSH) values in clinically healthy cats. For each of the 10 cats in the study, biologic variation, individual reference

intervals, and index of individuality (ie, the ratio of the within-subject biologic variation to the between-subject variation) were determined for T4, fT4, and TSH values by measuring hormones weekly for 6 weeks. By comparing thyroid values over time and establishing each patient's own reference interval, clinicians may detect thyroid dysfunction earlier.

The reference change values for T4 and fT4 in this population of cats were ≈30%. Thus, a >30% increase in T4 or fT4 from the patient's previous levels may suggest early hyperthyroidism. Relying only on population-based reference intervals might be misleading and could cause the clinician to miss changes in T4 values for individual patients that indicate preclinical hyperthyroidism, even though the values may fall within the normal population-based range.

… TO YOUR PATIENTS

Key pearls to put into practice:

1. Obtaining T4, fT4, and TSH values during early mature life (ie, 5-8 years of age) might improve diagnosis of thyroid dysfunction by establishing an individual cat's normal reference range.
2. A euthyroid cat with a previously detectable TSH value that becomes undetectable should be suspected of having emerging hyperthyroidism.
3. Clinicians should not rely solely on laboratory-generated or population-generated reference intervals to diagnose thyroid disease; cats that have T4 values that are increased >30% but within normal population reference limits may still have preclinical hyperthyroidism.

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Serum Immunoglobulin E Cross-Reactivity Between Fish & Chicken Meats in Dogs

Alison Diesel, DVM, DACVD
Texas A&M University

Shared allergenic proteins may be found in seemingly unrelated food sources.

In the Literature

Bexley J, Kingswell N, Olivry T. Serum IgE cross-reactivity between fish and chicken meats in dogs. *Vet Dermatol*. 2019;30(1):25-e8.

FROM THE PAGE ...

Although they can be broken into immunologic and nonimmunologic responses, most adverse food reactions in dogs are suspected to be true immunologic food allergies involving immunoglobulin E (IgE)-mediated reactions. Cross-reactivity between seemingly unrelated food allergens has been shown to impact disease diagnosis and management in humans.

This study* aimed to evaluate whether cross-reactive canine serum IgE-binding proteins could be identified in chicken and fish. Several methods (ELISA, inhibition ELISA, sodium dodecyl sulfate–polyacrylamide gel electrophoresis, immunoblotting inhibition) were used to assess the presence of cross-reactive proteins from chicken, white fish, and salmon in a large pool ($n = 53$ dogs) of canine serum. Results indicated the presence of at least 9 different cross-reactive canine serum IgE-binding allergens in whole extracts of chicken, white fish, and salmon; proteins identified included pyruvate kinase, creatine kinase, α actin, glyceraldehyde-3-phosphate dehydrogenase, enolase, aldolase, malate dehydrogenase, lactate dehydrogenase, and triosephosphate isomerase 1. Each of these proteins has been reported as a food component allergen in humans. This identification of IgE binding in canine serum supports the finding that shared allergenic proteins may be found in seemingly unrelated food sources. Clinical implications of this, however, have not yet been evaluated in dogs with documented food allergy.

*Funded by Avacta Animal Health

Continues on page 65 ▶

clinicalapplications™

April 2020

Sponsored by an educational grant from Zoetis Petcare

KEY TAKEAWAYS

- Most (65%) dogs achieved treatment success after the first CYTOPOINT injection.
- A second and third injection at monthly intervals increased treatment success to 85% and 93% of dogs, respectively.
- For dogs that did not achieve the desired response after the first injection, 79% were treatment successes with subsequent injections of CYTOPOINT.
- Four-week postinjection progress examinations were important to determine whether additional CYTOPOINT injections were of benefit.

NEW RESEARCH

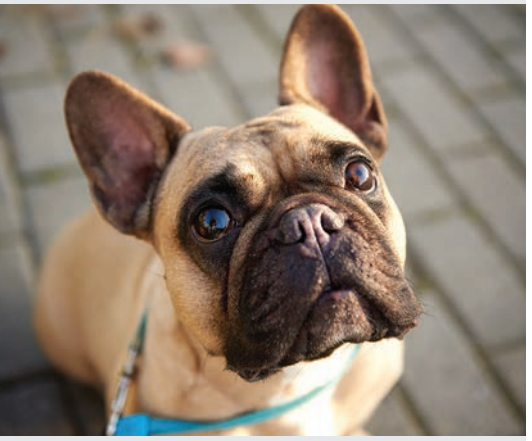
Some Dogs Benefit from Additional CYTOPOINT Injections for Maximum Response

CYTOPOINT to Treat Canine Allergic Dermatitis

Canine skin allergies—and accompanying pruritus—are the leading cause of yearly pet insurance claims.[1] However, treatment options for canine atopic dermatitis (AD) and associated pruritus are not always ideal. For example, the International Committee on Allergic Diseases of Animals considers antihistamines to be of little to no benefit in the treatment of acute flares of AD.[2,3] In addition, studies have suggested that 10% to 81% of patients receiving glucocorticoids or cyclosporine may experience adverse effects.[4] Thus, clinicians may look for other treatment options for patients with a chronic disease that can impact patient's and pet owner's quality of life.[5]

CYTOPOINT (canine allergic dermatitis immunotherapeutic) is shown to be effective for the treatment of allergic dermatitis and atopic dermatitis in dogs.[6] CYTOPOINT is a caninized monoclonal antibody that neutralizes interleukin-31,[5] a pruritus-inducing inflammatory cytokine.[7] This therapy is safe and effective for dogs of all ages and sizes, those receiving a variety of concomitant medications, and those with comorbidiites.[8-11] CYTOPOINT is labeled for administration every 4-8 weeks as needed.[12] A blinded, placebo-controlled pivotal field trial of CYTOPOINT in dogs with AD showed it was effective in reducing initial client pruritus visual analog scale (PVAS) scores by 50% or more in 57% of patients at 28 days.[10] In addition, 69% of study dogs were regarded as treatment successes (defined as a minimum 20 mm reduction in PVAS) at day 28.[12]

AD = atopic dermatitis
PVAS = pruritus visual analog scale



CYTOPOINT CHARACTERISTICS

- Starts providing itch relief within 24 hours[12]
- Lasts for 4 to 8 weeks[12]
- Effective in dogs of any size[11,16]
- Helps treat different causes of allergic itch (eg, atopic, food, flea)[11]
- Most appropriate candidates that did not completely respond to an initial injection showed treatment success after 1 to 2 subsequent injections.[15]
- Administration of CYTOPOINT should include a progress examination after 1 month.

In a retrospective study, ≈90% (87.8%) of patients with a variety of allergic dermatoses (eg, AD, adverse food reaction [AFR], allergic disease of undetermined cause [ADUC]) receiving CYTOPOINT were regarded as treatment success (defined as ≥20 mm on a PVAS).[11] Thus, CYTOPOINT has demonstrated efficacy not only in dogs with AD but also in dogs with other skin allergies, even when the specific cause of allergic dermatitis is uncertain.

A Study to Determine the Value of Additional CYTOPOINT Injections in Optimizing Patient Response[13]

During CYTOPOINT's conditional licensing period, Zoetis determined that some dogs responded incompletely to a single injection but demonstrated additional improvement after a second or third injection. A clinical study was conducted by Zoetis to assess the effect of additional CYTOPOINT injections in dogs with an initial incomplete response. The study investigators were veterinary dermatologists and the population included client-owned dogs that had confirmed AD and, at the time of entry into the study, had a PVAS score ≥50 mm and were free of ectoparasitic, bacterial, and fungal dermatitis. Candidates could also have diagnostically confirmed but actively managed flea allergic dermatitis in addition to AD.

Dogs in the study were prohibited from receiving potentially confounding medications (eg, glucocorticoids, antihistamines, cyclosporine, other anti-inflammatory or immunosuppressant drugs. Limited exceptions were made for dogs receiving long-term therapy indicated to prevent allergic flares or for the treatment of unrelated conditions (eg, carprofen, omega-3 fatty acids, allergen-specific immunotherapy) if the patient had been stable on that medication for a number of months dictated by therapy category (eg, 3 months for incidental illness, 6 weeks for hypoallergenic diet, 8 months for desensitization immunotherapy.)

Dogs that had a PVAS of ≥50mm on the first day of the study (day 0) or ≥36 mm at any subsequent visit received a CYTOPOINT injection and were asked to return 30 days later (±3 days for owner convenience) for a total of up to 4 total visits (days 0, 30, 60, and 90). At each visit, a clinician performed a physical

TABLE

SUMMARY STATISTICS FOR CUMULATIVE SUCCESS (PVAS REDUCTION OF 20 MM)[15]

PVAS <20 mm	Number of Dogs Evaluated	Number of Dogs with Treatment success	Cumulative Number of Dogs with Treatment Success	Cumulative % of Dogs with Treatment Success (Out of Total Dogs)
Day 0	110	–	–	–
Day 30	110	71	71	65%
Day 60	39	23	94	85%
Day 90	16	8	102	93%

examination and collected the pet owner's completed PVAS assessment. The PVAS assessment is a validated, easy, and repeatable method for owners to determine the severity of pruritus in their dog. A score is assigned on a sliding scale from 0 (normal dog) to 100 (extremely severe itch), with 20 mm representing very mild/occasional itching, 40 mm mild/frequent itching, and 60 mm moderate/regular episodes of itching.[14]

Of note, although patients with a 36-mm total PVAS were given a CYTOPOINT injection and returned for a repeat visit, a 20-mm reduction in PVAS from the original starting point was considered a treatment success based on initial CYTOPOINT pivotal efficacy studies and subsequent assessment studies.[11,13]

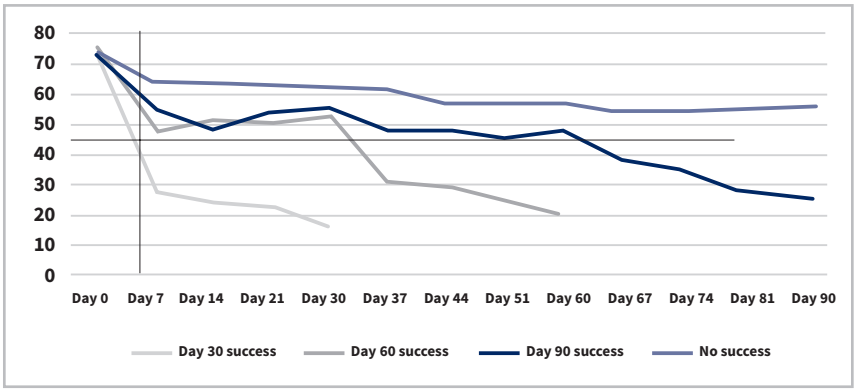
Results[15]

On day 30, most (71/110 [65%]) dogs were treatment successes and completed the study (***Table***). The remaining 39 dogs were administered a second CYTOPOINT injection according to study protocol. At the day 60 visit, 23/39 (94/110 [85%] cumulative) were treatment successes and completed the study. The remaining 16 dogs were given a third CYTOPOINT injection. At 90 days, 8/16 (102/110 [93%] cumulative) were treatment successes.

If only the 39 dogs that did not respond completely to the first injection are considered, 23/39 (59%) and 31/39 (79%) achieved treatment success after a second and third injection, respectively.

Of 147 dogs originally enrolled in the study, 37 were removed from the final study evaluation. No dogs were removed due to the need for rescue with prohibited medications; 21 were removed due to missing data points, 3 due to the owner relocating, 2 due to adverse effects (2 patients had development of masses at sites other than the injection site; in both instances, a cause and effect relationship was not suspected), and 11 due to lack of owner compliance.[13]

Of note, for the 8 dogs that never responded completely to treatment, the mean PVAS score decreased only slightly after the first injection (***Figure***). This may suggest that dogs that initially show at least some improvement in



▲ **FIGURE** Weekly Average PVAS Score by Success Group

EXPERT COMMENTARY

CYTOPOINT is an impactful therapy. In my practice, we observed pruritus reduction in 87.8% (116/132 dogs) of dogs with allergic dermatitis after a single injection.[11] The data presented here, obtained by 9 dermatologists treating 110 dogs with AD, provide even better news. Although most dogs achieved treatment success after a single injection of CYTOPOINT, some dogs required 2 or 3 injections to achieve full benefit. This information is essential for veterinarians and owners seeking long-term, steroid-free treatment for allergic dogs. I am pleased to know that by using this approach, more of my patients with chronic AD may ultimately receive relief from receiving CYTOPOINT in addition to adjunct topical, nutritional, and ectoparasiticidal therapy. Repeating injections if initial patient response is less than anticipated fits well with my recommendation for monthly assessment of patients until reliable maintenance therapy is achieved and in patient-specific flare seasons thereafter. As a clinician–scientist, I hope investigation of this information will contribute valuable knowledge of canine AD.

—***Jennifer Schissler, DVM, MS, DACVD***
Colorado State University

AD = atopic dermatitis
ADUC = allergic disease of undetermined cause
AFR - adverse food reaction
PVAS = pruritus visual analog scale

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AD = atopic dermatitis

ADUC = allergic disease of undetermined cause

AFR - adverse food reaction

the first 2 weeks—as compared with those that show no change at all—may be more likely to respond to therapy.

Discussion

This study was designed to determine a protocol to optimize treatment success for canine patients with AD. CYTOPOINT continues to appear highly effective in treating pruritus in dogs with AD. In initial pivotal studies, 69% of patients responded by day 28.[10] Similarly, in the current study, 65% of patients had responded by day 30.[15]

This study demonstrated that some dogs need additional time and CYTOPOINT injections to achieve optimal treatment success. Twenty-eight percent of total dogs in this study benefitted from a second and sometimes third injection.

The average half-life of CYTOPOINT is 16 days. Although the reason for the increased number of dogs achieving treatment success with a second and third monthly injection of CYTOPOINT is unknown, it may be due in part to increased CYTOPOINT exposure resulting from accumulation of the mAb over the first 2 to 3 doses based on pharmacokinetic modeling.

Dogs with even a partial response to an initial CYTOPOINT injection are likely to have additional beneficial responses to additional injections[11,15]; this was true for 79% of dogs in this study. The small minority of dogs (8/110 [7%]) that do not benefit from additional injections are more likely to have had no response to the initial injection.

This study did not seek to examine whether treatment beyond a third injection at monthly intervals or whether greater intervals between injections had any impact on degree or duration of effect. These may be appropriate questions for further inquiry.

In a previous retrospective clinical study, 87.8% of dogs with AD, AFR, both AD and AFR, or ADUC responded to a single injection.[11] In the current study, the successful response rate to the first injection was only 65%. Differences in study results may be related to the retrospective nature of the previous study, differences in study populations, or in expected random variation.

Implications for Practice

CYTOPOINT provides effective itch relief to most patients within 28 days. However, most dogs with only a partial response to the first injection may go on to achieve treatment success with a second or third injection. Dogs receiving CYTOPOINT should have a progress examination after 30 days and receive additional injections if necessary to optimize treatment success.

. . . TO YOUR PATIENTS

Key pearls to put into practice:

1. Of note, the findings in this study were obtained from sera samples of dogs without a diagnosis of food allergy, highlighting that these serum-based allergen tests should not be used to determine whether a patient has allergies. These tests—both for food and environmental allergies (ie, atopic dermatitis)—may be "positive" in dogs that do not have any signs of allergy. They are not diagnostic; rather, they serve as a guide when formulating allergen-specific immunotherapy for patients with atopic dermatitis and to help confirm the clinical diagnosis.

2. The gold standard for diagnosing food allergy in dogs and cats remains a strict elimination diet trial. A recent literature review evaluated current information on in vitro and in vivo tests for food allergies in veterinary species. Results identified very low repeatability and low-/high-variable accuracy for various food allergy tests, confirming the importance of elimination diet trials in diagnosing food allergies.[1]

3. Because these currently available tests use whole-allergen extracts with unknown concentrations of potentially relevant allergenic proteins, the clinical implication and accuracy of results may be impacted. Further evaluation of relevant IgE reactivity to more specific allergen components (eg, at the protein level) in food may eventually lead to more accurate diagnostic developments. At this time, an elimination diet trial is recommended.

Further evaluation of relevant IgE reactivity to more specific allergen components in food may eventually lead to more accurate diagnostic developments.

Reference

1. Mueller RS, Olivry T. Critically appraised topic on adverse food reactions of companion animals (4): can we diagnose adverse food reactions in dogs and cats with in vivo or in vitro tests? *BMC Vet Res*. 2017;13(1):275.

Suggested Reading

Mueller RS, Olivry T, Prélaud P. Critically appraised topic on adverse food reactions of companion animals (2): common food allergen sources in dogs and cats. *BMC Vet Res*. 2016;12:9.

Olivry T, Mueller RS, Prélaud P. Critically appraised topic on adverse food reactions of companion animals (1): duration of elimination diets. *BMC Vet Res*. 2015;11:225.

Brief Summary of full Prescribing Information

Simparica TRIO™

(sarolaner, moxidectin, and pyrantel chewable tablets)

FOR ORAL USE IN DOGS ONLY

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

INDICATIONS
SIMPARICA TRIO prevents heartworm disease caused by *Dirofilaria immitis*, kills adult fleas (*Ctenocephalides felis*) and is indicated for the treatment and prevention of flea infestations, the treatment and control of tick infestations with *Amblyomma americanum* (lone star tick), *Amblyomma maculatum* (Gulf Coast tick), *Dermacentor variabilis* (American dog tick), *Ixodes scapularis* (black-legged tick), and *Rhipicephalus sanguineus* (brown dog tick), and the treatment and control of roundworm (immature adult and adult *Toxocara canis* and adult *Toxascaris leonina*) and adult hookworm (*Ancylostoma caninum* and *Uncinaria stenocephala*) infections for one month in dogs and puppies 8 weeks of age and older, and weighing 2.8 pounds or greater.

DOSAGE AND ADMINISTRATION
SIMPARICA TRIO is given orally once a month, at the recommended minimum dose of 0.54 mg/lb (1.2 mg/kg) sarolaner, 0.011 mg/lb (24 µg/kg) moxidectin, and 2.27 mg/lb (5 mg/kg) pyrantel (as pamoate salt).

Dosage Schedule

Body Weight (lbs)	Sarolaner per Tablet (mg)	Moxidectin per Tablet (mg)	Pyrantel per Tablet (mg)	Number of Tablets Administered
2.8 to 5.5	3	0.06	12.5	One
5.6 to 11.0	6	0.12	25	One
11.1 to 22.0	12	0.24	50	One
22.1 to 44.0	24	0.48	100	One
44.1 to 88.0	48	0.96	200	One
88.1 to 132.0	72	1.44	300	One
>132.0	Administer the appropriate combination of tablets			

SIMPARICA TRIO can be offered to the dog with or without food.

Care should be taken to ensure that the dog consumes the complete dose and that part of the dose is not lost or refused. If a dose is missed, give SIMPARICA TRIO immediately and resume monthly dosing.

Heartworm Prevention:
SIMPARICA TRIO should be administered at monthly intervals year-round or at least within one month of the animal's first seasonal exposure to mosquitoes and continuing until at least 1 month after the dog's last seasonal exposure. If a dose is missed, give SIMPARICA TRIO immediately and resume monthly dosing. When replacing a monthly heartworm preventive product, SIMPARICA TRIO should be given within one month of the last dose of the former medication.

Flea Treatment and Prevention:
Treatment with SIMPARICA TRIO may begin at any time of the year. SIMPARICA TRIO should be administered year-round at monthly intervals or started at least one month before fleas become active.

To minimize the likelihood of flea re-infestation, it is important to treat all dogs and cats within a household with a flea control product.

Tick Treatment and Control:
Treatment with SIMPARICA TRIO can begin at any time of the year. SIMPARICA TRIO should be administered year-round at monthly intervals or started at least one month before ticks become active.

Intestinal Nematode Treatment and Control:
For the treatment of roundworm (immature adult and adult *Toxocara canis* and adult *Toxascaris leonina*) and adult hookworm (*Ancylostoma caninum* and *Uncinaria stenocephala*) infections, SIMPARICA TRIO should be administered once as a single dose. Monthly use of SIMPARICA TRIO will control any subsequent infections.

CONTRAINDICATIONS
There are no known contraindications for the use of SIMPARICA TRIO.

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

Keep SIMPARICA TRIO in a secure location out of reach of dogs, cats and other animals to prevent accidental ingestion or overdose.

PRECAUTIONS
Sarolaner, one of the ingredients in SIMPARICA TRIO, is a member of the isoxazoline class. This class has been associated with neurologic adverse reactions including tremors, ataxia, and seizures. Seizures have been reported in dogs receiving isoxazoline class drugs, even in dogs without a history of seizures. Use with caution in dogs with a history of seizures or neurologic disorders.

Prior to administration of SIMPARICA TRIO, dogs should be tested for existing heartworm infections. Infected dogs should be treated with an adulticide to remove adult heartworms. SIMPARICA TRIO is not effective against adult *D. immitis*.

The safe use of SIMPARICA TRIO has not been evaluated in breeding, pregnant, or lactating dogs.

ADVERSE REACTIONS
In a field safety and effectiveness study, SIMPARICA TRIO was administered to dogs for the prevention of heartworm disease. The study included a total of 410 dogs treated once monthly for 11 treatments (272 treated with SIMPARICA TRIO and 138 treated with an active control). Over the 330-day study period, all observations of potential adverse reactions were recorded. The most frequent reactions reported in the SIMPARICA TRIO group are presented in the following table.

Table 1. Dogs with Adverse Reactions

Clinical Sign	SIMPARICA TRIO *n* = 272	Active Control *n* = 138
Vomiting	14.3%	10.9%
Diarrhea	13.2%	8.0%
Lethargy	8.5%	6.5%
Anorexia	5.1%	5.8%
Polyuria	3.7%	3.6%
Hyperactivity	2.2%	0.7%
Polydipsia	2.2%	2.9%

In a second field safety and effectiveness study, SIMPARICA TRIO was administered to 278 dogs with fleas. Adverse reactions in dogs treated with SIMPARICA TRIO included diarrhea.

In a third field safety and effectiveness study, SIMPARICA TRIO was administered to 120 dogs with roundworms. Adverse reactions in dogs treated with SIMPARICA TRIO included diarrhea and vomiting.

For a copy of the Safety Data Sheet or to report adverse reactions, call Zoetis Inc. at 1-888-963-8471. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or www.fda.gov/reportanimalae.

STORAGE CONDITIONS
Store at or below 30°C (86°F).

HOW SUPPLIED
SIMPARICA TRIO is available in six flavored tablet sizes (see **DOSAGE AND ADMINISTRATION**). Each tablet size is available in packages of one, three, or six tablets.

Approved by FDA under NADA # 141-521

zoetis

Distributed by:
Zoetis Inc.
Kalamazoo, MI 49007

September 2019

51000400A&P

Simparica TRIO™

(sarolaner, moxidectin, and pyrantel chewable tablets)

All this coverage in just 1 monthly chewable

- **HEARTWORM DISEASE**
- **TICKS & FLEAS**
- **ROUNDWORMS & HOOKWORMS**

The TRIO Zone. It's the heart of protection.

Simparica Trio is the first monthly chewable that delivers the comprehensive protection you recommend—

- Proven protection against **HEARTWORM DISEASE**
- Kills **5 SPECIES OF TICKS*, AND FLEAS**
- Highly effective against **ROUNDWORMS & HOOKWORMS†**
- **DEMONSTRATED SAFE FOR PUPPIES & DOGS** 8 weeks and older weighing at least 2.8 lbs

Discover simple protection every best friend deserves at **SimparicaTrioDVM.com**.

IMPORTANT SAFETY INFORMATION: Use with caution in dogs with a history of seizures. Simparica Trio contains sarolaner, a member of the isoxazoline class, which has been associated with neurologic adverse reactions including tremors, ataxia, and seizures in dogs with or without a history of neurologic disorders. The safe use of Simparica Trio has not been evaluated in breeding, pregnant, or lactating dogs. The most frequently reported adverse reactions in clinical trials were vomiting and diarrhea. **See Brief Summary of full Prescribing Information on page 66.**

**Amblyomma americanum, Amblyomma maculatum, Dermacentor variabilis, Ixodes scapularis,* and *Rhipicephalus sanguineus.*
†Toxocara canis, Toxascaris leonina, Ancylostoma caninum, and *Uncinaria stenocephala.*

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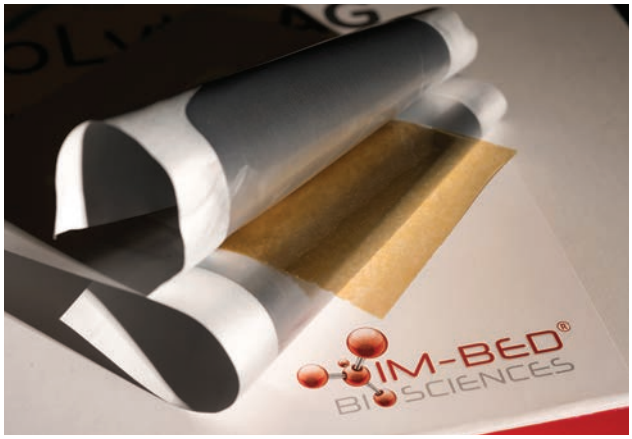

Wildlife Impacted by Australian Wildfires to Receive Wound Dressing

Imbed Biosciences (**imbedbio.com**) is providing **MicroLyte Ag VET** (**microlyteagvet.com**) wound dressing to an Australian animal rescue initiative in response to the country's recent wildfires. MicroLyte Ag VET promotes healing and fights infection in wounds, including burns, by applying a layer of antimicrobial silver that does not inhibit healing. New cells can form on top of the MicroLyte Ag VET, which completely absorbs into the body.—*Press Release 1/2020*

Online Resource for Canine Osteoarthritis

Canine Arthritis Resources and Education (**CARE**; **caninearthritis.org**) has launched PRO memberships that include up to 5 hours of RACE-approved CE credits on the topic of comprehensive care of canine osteoarthritis, as well as resources clinicians can share with pet owners. CARE also features articles and videos on topics related to osteoarthritis.—*Press Release 2/2020*

WSAVA Guidance on New Coronavirus

WSAVA (**wsava.org**) Scientific and One Health committees have prepared an advisory document confirming there is no evidence that domestic animals can be infected with the new coronavirus (SARS-Cov-2) or that animals may be a source of infection in humans. The document provides guidance for clinicians when talking with pet owners concerned about the risk for infection, including how to urge owners not to panic. Clinicians are advised against using vaccines for canine enteric coronavirus, as SARS-Cov-2 is a distinctly different coronavirus variant. The document can be accessed at **wsava.org/wp-content/uploads/2020/02/nCOV_WSAVA-Advisory-Document-final-05.02.2020.pdf**.—*Press Release 3/2020*

Test Monitors Response to Treatment for Inflammatory Bowel Disease

Antech Diagnostics has completed a final study of its new blood test for inflammatory bowel disease (IBD). This test is the first diagnostic for IBD and allows clinicians to determine whether a dog's chronic GI signs are consistent with IBD, expediting access to treatment or confirming the need for additional diagnostics. Both outcomes can increase pet owner satisfaction and increase compliance with continued diagnostics or a care plan.—*Press Release 2/2020*

New Combination Parasite Preventive for Dogs

Zoetis (**zoetis.com**) has announced FDA approval for Simparica Trio (sarolaner, moxidectin, and pyrantel), a chewable tablet that can be given once a month. Studies of Simparica Trio have shown an efficacy of 100% in preventing development of heartworm disease, 98.9% against tick infestations, >94% against adult hookworms, and >99% against adult roundworms, as well as a kill onset of fleas 4 hours after administration, with 100% efficacy achieved after 8 hours. This product is expected to be available in April 2020.—*Press Release 2/2020*

Half-Life Extension of Antibodies in Dogs

Kindred Biosciences (**kindredbio.com**) has announced development of technology that can extend canine antibody half-life by up to 3-fold. The study included 12 dogs divided into 4 groups that were given medication modifications incorporating different technologies. Half-life extension was observed in all dogs except the control group. Additional studies to further differentiate between lead molecules and expand sample size are planned. —*Press Release 1/2020*

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LOOK FOR THESE ARTICLES IN FUTURE ISSUES

- Jaw Fractures Overview
- Step-by-Step Cystocentesis
- Zinc-Responsive Dermatosis
- Image Galleries: Full-Mouth Tooth Extractions
- Feline Asthma

Clinical Report

Sponsored by Boehringer Ingelheim

The Importance of Screening to Identify Hypertension in Senior Cats

The Importance of Hypertension

Hypertension affects ≈20% of cats[1] and is often linked to other common feline diseases—most frequently chronic kidney disease[1,2] but also hyperthyroidism. Untreated, chronic, progressive hypertension has the potential to cause significant morbidity, including target organ damage (eg, eyes, brain, heart, kidneys).[3-5]

Diagnosing hypertension early is beneficial for preventing target organ damage. In one study, cats diagnosed with systemic hypertension as part of a screening protocol had improved survival as compared with those that were diagnosed after being presented with clinical signs.[1] A hypertension diagnosis may prompt further screening due to the disease's correlation with other conditions. Hypertension and renal disease are often intertwined, with up to 74% of hypertensive cats also being azotemic and up to 65% of cats with CKD found to be hypertensive.[4-9]

The AAFP, AAHA, ACVIM, and International Society of Feline Medicine (ISFM) all recommend yearly screening in older cats, though recommended starting ages vary between 7 and 11 years.[2-4,10]

Current State of Senior Cat Screening

Before senior screening can be pursued, pet owners must bring their cat to the clinic. However, 21% of cat owners report taking their senior cat to the vet *less* than they did when it was young.[11] Further, some of the most recent data suggest that only ≈35% of senior cats presented to a clinic receive senior screening.[12] Anecdotally, the percentage of clinics performing the type of screening relevant to hypertension (eg, sphygmomanometry, routine retinoscopic examination, urinalysis) is likely even lower, although published data are not readily available. It is up to the veterinary team to help get more senior cats to the clinic and recommend appropriate hypertension screening.

Overcoming Obstacles

Many owners may assume their cat is self-sufficient and in excellent health, especially if it has never been sick or lives completely indoors. In addition, cats typically hide signs of illness from their owner. Owners may perceive their cat as stressed at a veterinary appointment,[11] which can create challenges in handling and testing accuracy. In addition, some veterinary teams may have limited availability to appropriate clinic space for stress-free screening, adequate screening tools, time to thoroughly train staff, and/or time to perform accurate assessments.

Getting Senior Cats in the Door

Awareness of the need for low-stress environments and handling for cats has increased.[13] There is an increasing number cat-oriented organizations that offer programs and resources designed to increase pet owner awareness, facilitate comfortable feline visits, and reduce avoidance of future appointments.

Fundoscopy

Because up to 100% of hypertensive cats may have retinal lesions,[10] and because it is a noninvasive element of the

physical examination, fundoscopy can be a powerful hypertension screening tool. In the same way practitioners perfect auscultation or palpation skills, routine ocular screening can improve clinicians' confidence and accuracy over time. A guide to performing a reliable fundic examination is provided in the April issue of *Clinician's Brief*. Abnormal findings can encourage reluctant pet owners to agree to additional screening.

Sphygmomanometry

There are many potential benefits to making hypertension screening routine so that every senior patient receives a blood pressure (BP) measurement. Routine testing may help staff members and clinicians obtain a patient's baseline values and understand what to expect for patients with different temperaments. It may also acclimate patients to the procedure. Routine BP measurements are opportunities to empower staff members, especially veterinary nurses, and to conserve clinicians' limited time.

Doppler sphygmomanometry and/or high-definition oscillometry are commonly used for measuring BP in cats.[4] Regardless of the device used, a consistent protocol for BP measurement is essential for obtaining reliable values.[10] Detailed guidelines are available from ACVIM and ISFM (see ***References***).[4,10] Teams can adapt their approach to minimize stress to their unique patient and practice environment; for example:

The patient exits the carrier on its own and is given 5 to 10 minutes to explore a quiet room. Before the physical examination, a staff member provides the patient with a warmed blanket for comfort and measures the patient's BP.[4,10] One staff member is trained in the protocol and responsible for all measurements.[10] Either the tail or a limb is used, and the cat is kept still.[10] The average of multiple measurements is determined after discarding the first measurement.[10]

Updated Hypertension Classification & Blood Pressure Ranges with Associated Risk for Target Organ Damage[10]

Category	Risk for Target Organ Damage	Systolic Blood Pressure
Normotensive*	Minimal	<140 mm Hg*
Prehypertensive*	Low	140*-159 mm Hg
Hypertensive*	Moderate	160-179 mm Hg
Severely hypertensive*	High	≥180 mm Hg

*Category labels, some systolic reference ranges, and the exclusion of diastolic reference ranges are changes from the 2007 ACVIM Consensus Statement.[14]

Urinalysis

Key obstacles to routine urinalysis include lack of understanding by owners about its importance and their concerns about cost and urine collection. Proteinuria is significantly correlated with all-cause mortality, including mortality related to hypertension and chronic kidney disease.[10] The ACVIM recommends routine urinalysis, including dipstick protein measurements, for all senior cats as part of the annual minimum database.[3] The results of this simple test can support the need for futher hypertension and/or renal screening.

Conclusion

Increasing wellness visits for senior cats and implementing an appropriate routine minimum database, including routine fundic examination, BP screening, and urinalysis, is essential for early disease detection, prevention, and management[2-4,10] and provides a great opportunity for educating owners. Early identification and timely treatment of hypertension and/or associated conditions may increase both survival time and quality of life in senior cats.[1]

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Fundic Examination

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A fundic examination is an important component of a thorough ophthalmologic examination and a complete physical examination. Fundoscopy may seem warranted only when a patient is presented with vision loss; however, the results of a fundic examination can be helpful when determining differential diagnoses and prognosticating. For example, patients presented for potential infectious, immune-mediated, vascular, neoplastic, nutritional, or metabolic disease may exhibit ocular manifestations of systemic disease. Proper examination of the fundus is not an inherently easy skill but, once mastered with practice and patience, is an invaluable tool.

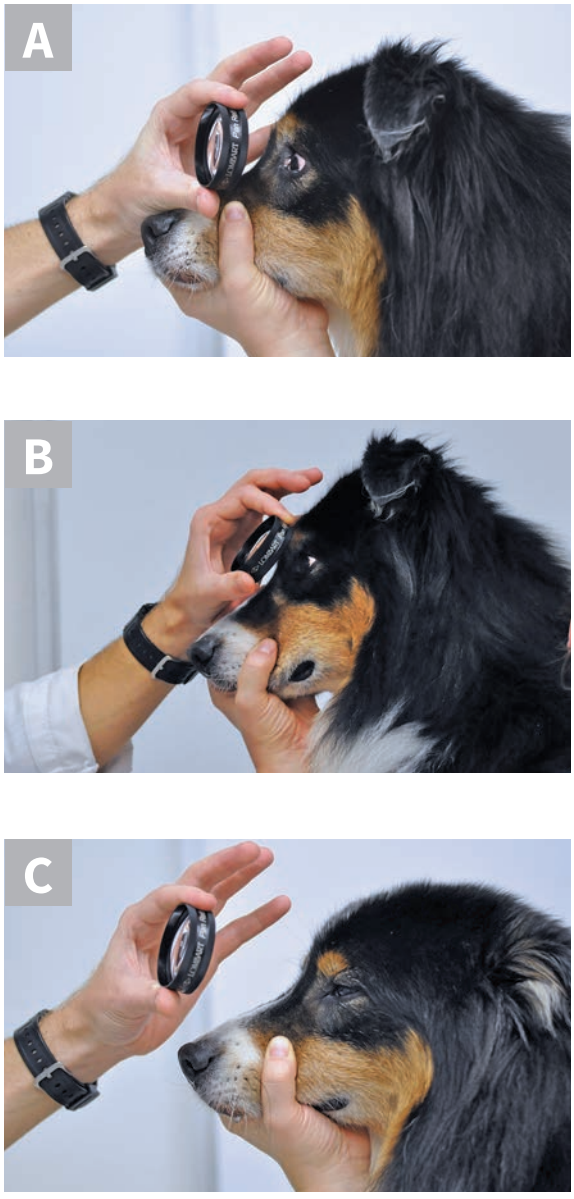
The examination should be performed in a dimly lit, quiet room with an assistant stabilizing the patient's head near the eye level of the examiner.[1,2] The patient should be in a seated position with minimal restraint. To achieve full view of the fundus, pharmacologic dilation of the pupil is necessary; otherwise, visualization of the peripheral fundus is impossible and lesions may be overlooked. The short-acting anticholinergic tropicamide (1%) is the preferred mydriatic agent for diagnostic purposes. One application typically results in mydriasis within 15 to 20 minutes that lasts 3 to 8 hours, depending on the degree of iris pigmentation.[3] Examination of the anterior segment should precede administration of mydriatic drugs, which can confound the results of other diagnostic tests or exacerbate lens luxation and intraocular pressure elevation.[4-6]

Two main techniques are used to evaluate the fundus: indirect and direct ophthalmoscopy. The most thorough examination is achieved via a survey view of the fundus with indirect ophthalmoscopy followed by examination of an identified lesion with the higher magnification used in direct ophthalmoscopy.

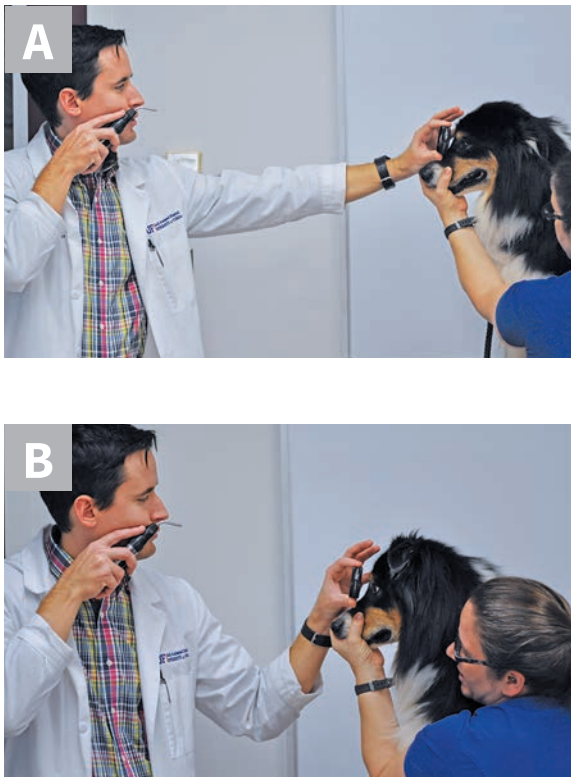
Indirect Ophthalmoscopy

Indirect ophthalmoscopy can be performed via monocular or binocular examination, the latter of which requires a head-mounted light source and permits a greater degree of stereopsis (ie, depth perception). Both methods require a handheld condensing lens to form a

magnified image of the patient's eye. The following discussion describes use of monocular indirect ophthalmoscopy using a Finoff transilluminator as a bright light source. This method provides a more thorough examination of the fundus as compared with direct techniques and is more readily available than binocular examination. When performing indirect ophthalmoscopy, the examiner's head, the light source, and the condensing lens should act as a unit, pivoting together on an axis (***Figures 1*** and ***2***); alignment is of utmost importance. Indirect ophthalmoscopy produces a reversed and inverted (ie, upside down and backward) image and allows a larger, panoramic field of view as compared with direct techniques (***Figure 3***, next page).[2] Magnification is inversely proportional to the diopter strength (ie, focal length) of the convex lens used. A lower diopter strength



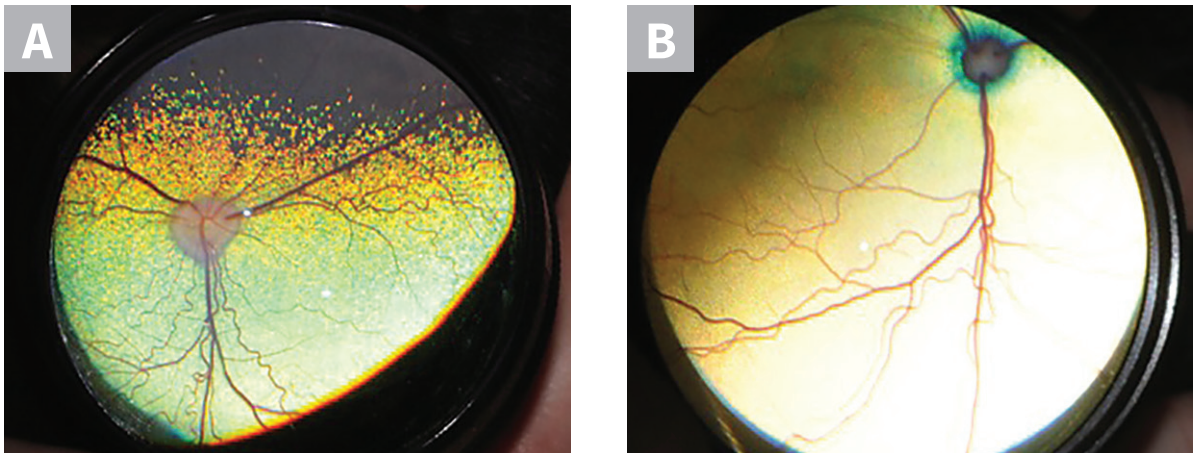
▲ **FIGURE 1** Correct (***A***) and incorrect (***B*** and ***C***) techniques for monocular indirect ophthalmoscopy. The examiner's hand should be stabilized on the patient and the lens held 2 to 4 cm away from and perpendicular to the axis of the pupil. In the images demonstrating incorrect technique, the axis of the lens is not perpendicular in alignment to the patient's eye and is less than 2 cm in distance (***B***), and the examiner's hand is floating and distanced from the patient's eye (***C***).



▲ **FIGURE 2** Correct (***A***) and incorrect (***B***) techniques for monocular indirect ophthalmoscopy. The light source should be held against the dominant eye and the examiner's elbow should be straight, permitting distance for a panoramic view of the fundus. In the image demonstrating incorrect technique, the examiner's elbow is bent and the examiner is too close to the patient to permit an image that takes up the entirety of the indirect lens.

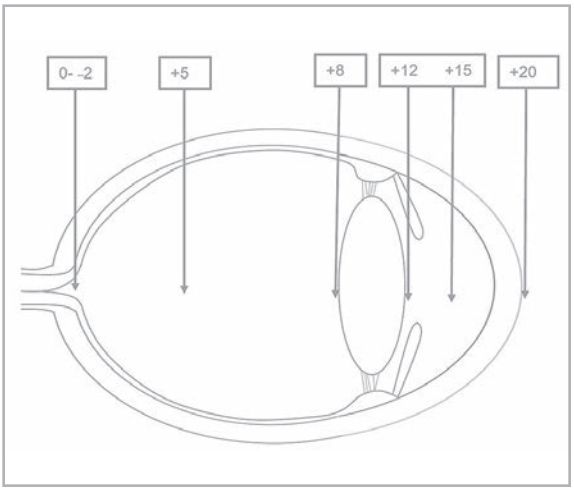
results in greater magnification with a smaller field of view, whereas a higher diopter strength results in lower magnification but a larger field of view.[2] Lenses between 20 diopter (D) and 30D are most commonly used for examining dogs and cats, although lenses can have a wider range (up to 40D). Additional advantages of indirect ophthalmoscopy include a safer working distance from the patient and increased ability to view the fundus through opacities in ocular media.

Most dogs and cats have a tapetum lucidum, the brightly colored reflective structure located in the choroid that gives the fundus its "eyeshine."



▲ **FIGURE 3** Normal canine (***A***) and feline (***B***) fundus viewed with indirect ophthalmoscopy. With indirect ophthalmoscopy, the image formed is upside down and backward.

▲ **FIGURE 4** A direct ophthalmoscope (patient side). Rotating focusing lenses (***A***), red-free filter (***B***), large circle aperture (***C***), light aperture size (***D***), and slit aperture



▲ **FIGURE 5** Cross-section of the eye. A direct ophthalmoscope can be used to view the structures of the anterior segment with magnification. To bring the anterior segment into focus, the lens wheel should be rotated through the positive (green or black) diopters. With the direct ophthalmoscope placed 2 cm from the cornea, the following structures are usually in focus at the corresponding diopters: cornea +15 to +20; anterior chamber +12 to +20; iris and pupil +12; lens +8 to +12; and vitreous 0 to +10.

Patients that do not possess a tapetum—usually those with lightly colored or blue eyes—have a red fundic reflection that originates from illumination of the choroidal vasculature. This should not be confused with posterior segment hemorrhage.

Direct Ophthalmoscopy

Direct ophthalmoscopy provides a direct, upright image of the patient's fundus. The image seen by the examiner is noninverted and magnified 15 to 17 times.[1] However, the field of view is much more restricted as compared with indirect techniques due to the higher magnification. Direct ophthalmoscopy enables description and characterization of focal fundic lesions and close examination of the optic disc. Patience is required to complete a thorough examination because a much larger series of vignettes must be acquired to piece together the entire fundus. In addition, visualization of peripheral fundic lesions with direct ophthalmoscopy is practically impossible, particularly if the eyes are not dilated.

A direct ophthalmoscope has many adjustable settings. The rheostat allows the light intensity to be controlled and should be kept low to ensure patient comfort and an accurate view for the examiner. If the pupil cannot be dilated, the patient should be examined in a darkened room and the rheostat adjusted to minimize pupillary constriction. An aperture dial and filter switch on the patient side of the ophthalmoscope allow adjustment of the size, shape, and color of the light beam. The smaller apertures should be used for nondilated eyes and the larger apertures for dilated eyes. The specific filters and apertures vary by instrument, but most include a slit beam for evaluating fundic elevations and depressions, graticule grid for size estimation, cobalt blue light for corneal fluorescein dye excitation, and red-free light for differentiation of hemorrhage (appears black) and pigment (appears brown). A series of concave and convex lenses located on the rotating diopter dial allow both depth adjustment and focus to bring structures at different levels into view (***Figure 4***). A direct ophthalmoscope may also be used to evaluate the anterior segment of the eye with magnification. The dial must be changed to the positive diopter settings to view the anterior segments (***Figure 5***). If the examiner's vision is not emmetropic (ie, ideal vision without focusing deviations or visual defects), the initial dial setting at which the normal fundus is in focus will not be 0. Each subsequent setting must be interpreted in the light of the initial setting.

Advantages of direct ophthalmoscopy include close evaluation of fundic lesions, accessory features, and lower equipment cost as compared with indirect ophthalmoscopy. Disadvantages include the lack of stereopsis, small field of view, proximity of the examiner's face to the patient, limited evaluation of the peripheral fundus, and impaired visualization of the fundus through opaque anterior ocular structures (eg, corneal edema, nuclear sclerosis).

Direct ophthalmoscopy enables description and characterization of focal fundic lesions and close examination of the optic disc.

Continues ▶

WHAT YOU WILL NEED

- Dilating agent (eg, 1% tropicamide ophthalmic solution)
- Focal light source (eg, Finoff transilluminator, high-quality pen light)
- Indirect condensing lens (between +40D and +20D)
- Direct ophthalmoscope

STEP-BY-STEP FUNDIC EXAMINATION: INDIRECT OPHTHALMOSCOPY

STEP 1

While sitting or standing an arm's length away from the patient and holding the light source next to the dominant eye so that the examiner's head and light source move as a single unit, use the opposite hand to hold and position the lens. Hold the lens between the forefinger and thumb with the flatter surface toward the patient and more convex surface toward the examiner. Position the light beam—keeping light intensity low to avoid obscuring details or disturbing the patient—until a bright reflection from the patient's fundus is observed.

Author Insights

Lenses may have one etched silver rim indicating the side to be directed toward the patient.

To facilitate examination, the examiner may rest the little finger on the patient's forehead with the condensing lens held above, ready to drop into place once the reflection has been identified.

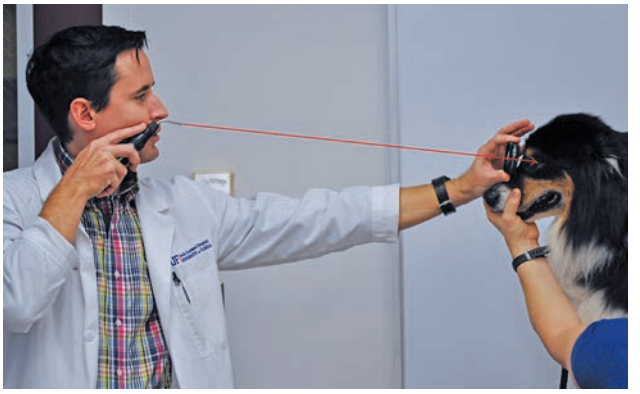
Movement of the patient's eye will frequently result in loss of the fundic image. The quickest way to regain alignment is to step back, find the tapetal reflection, and move close.

STEP 2

Locate the tapetal reflection, then place the lens 2 to 4 cm from the corneal surface and perpendicular to (ie, in the path of) the light beam while keeping the remaining fingers in contact with the patient's head.

STEP 3

Hold the condensing lens parallel to the iris with the lens axis in alignment with the pupil axis to maintain a stable fundic image. Ensure the examiner's head, light source, and condensing lens act as a unit, pivoting together on an axis. If the view of the fundus is lost, remove the indirect lens, re-establish visualization of the tapetal reflection, and replace the lens in front of the eye.



STEP 4

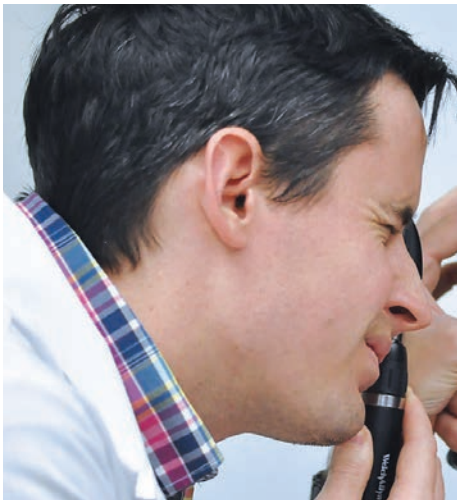
Move around, being sure to maintain a constant tapetal reflection, to observe the entire fundus, especially the periphery, and to follow the patient's eye.

Continues ▶

STEP-BY-STEP
FUNDIC EXAMINATION: DIRECT OPHTHALMOSCOPY

STEP 1

Turn on the ophthalmoscope and set the light to the correct aperture based on whether the eyes are dilated. Rest the brow on the brow rest.



STEP 2

While holding the ophthalmoscope in the dominant hand and using the opposite hand to stabilize the patient's head and keep the eyelids open, use the right eye to look through the instrument and examine the patient's right eye. Repeat using the left eye to examine to the patient's left eye.

STEP 3

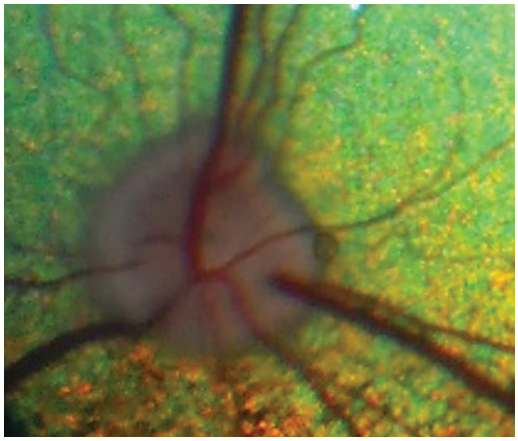
Locate the patient's fundic/tapetal reflection from approximately an arm's length distance, then move 2 to 4 cm from the patient's eye to widen the field of view. Adjust the lens settings so the fundus is in focus.

Author Insight

If the examiner has ≈20/20 corrected vision, the fundus of most dogs and cats will be in focus at the 0D setting. Deviations may indicate pathology; recessed lesions will be in focus at negative diopter settings, whereas forwardly displaced structures will be in focus at positive diopter settings.

STEP 4

Identify the optic nerve, then thoroughly examine the remainder of the fundus in quadrants.



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1 **DIAGNOSTIC TREE** **PAGE 26**

Which of the following is considered a differential for an acquired cause of nasolacrimal apparatus obstruction causing epiphora?

A Anterior lens luxation
B. Ectopic nasolacrimal openings
C. Trauma or fracture of the maxillary or lacrimal bone
D. Punctal atresia

2 **PROCEDURES PRO** **PAGE 30**

Long-term prognosis is _____ for most cases of idiopathic intussusception.

A. Poor
B. Fair
C. Good
D. Excellent

3 **CONSULT THE EXPERTS** **PAGE 39**

In patients with anatoxin-a or anatoxin-a(s) poisoning, death can occur _____.

A. <1 hour after ingestion
B. Within 48 hours of ingestion
C. Within 72 hours of ingestion
D. Within 96 hours of ingestion

4 **PROCEDURES PRO** **PAGE 70**

A diopter lens between _____ and _____ is most useful for performing indirect ophthalmologic examination in dogs and cats.

A. 5 D; 10 D
B. 20 D; 30 D
C. 40 D; 50 D
D. 55 D; 65 D

Answer Key:
1: C 2: C 3: A 4: B

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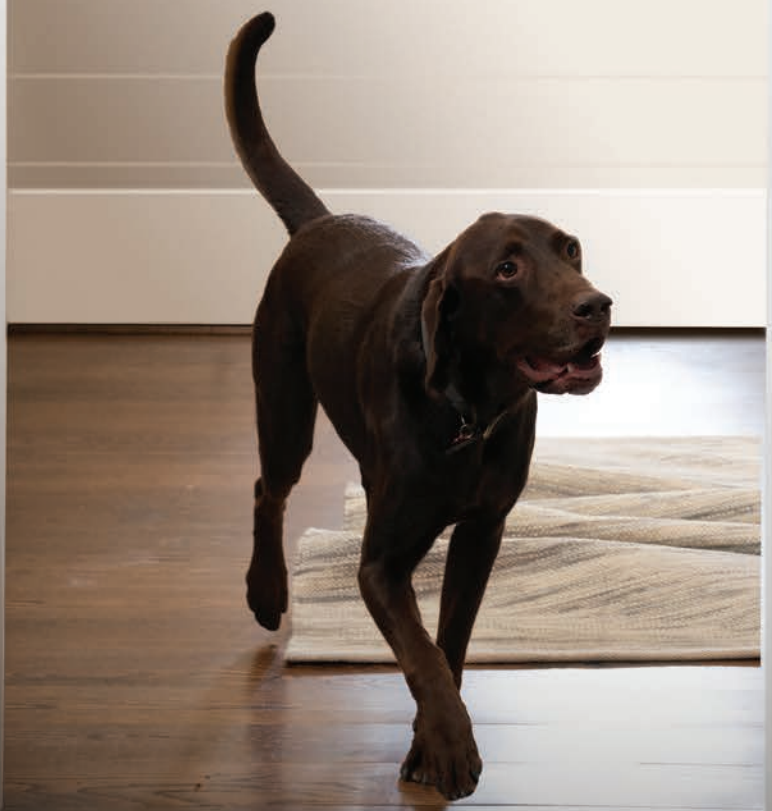

[1] Freedom of Information: NADA140-971 (January 15, 1993).

[2] Data on file at Boehringer Ingelheim.

[3] Data on file at Boehringer Ingelheim.

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See page 80 for product information summary.