March 2021

clinician's brief

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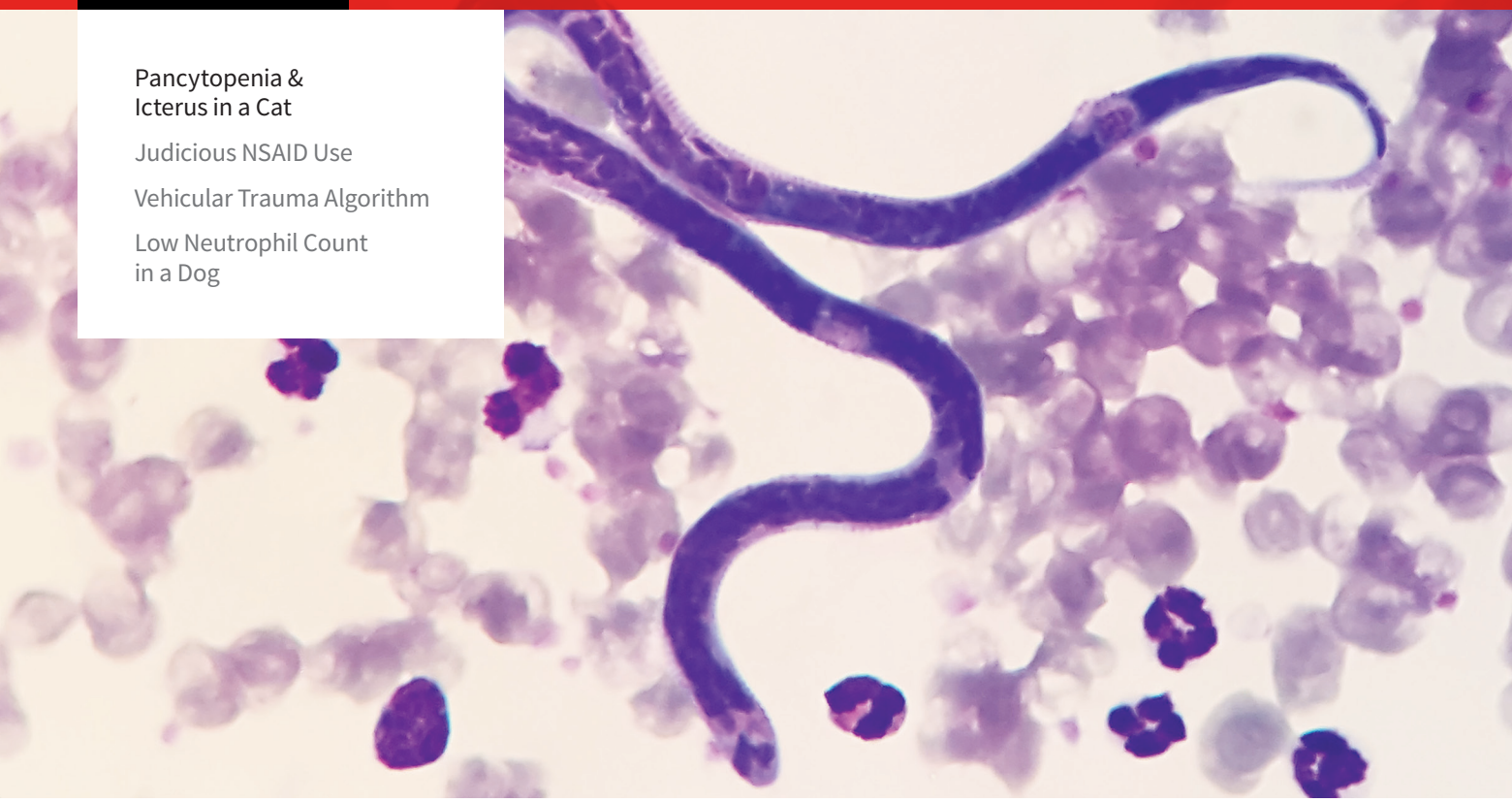
CANINE HEARTWORM

IN THIS ISSUE



Volume 19 Number 2

WSAVA Global Veterinary Community

clinician's brief
THE OFFICIAL CLINICAL PRACTICE JOURNAL OF THE WSAVA

CANADIAN VETERINARY MEDICAL ASSOCIATION
L'ASSOCIATION CANADIENNE DES MÉDECINS VÉTÉRINAIRES

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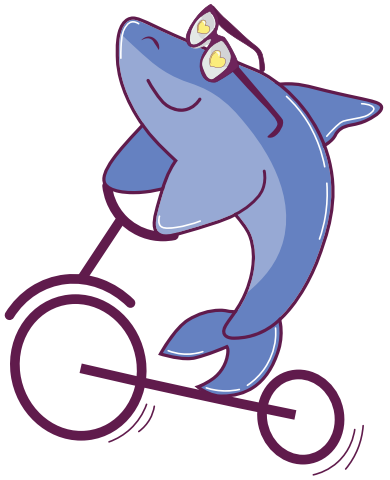

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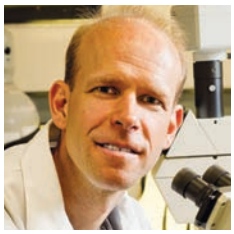

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GALLIPRANT® (grapiprant tablets)

For oral use in dogs only

20 mg, 60 mg and 100 mg flavored tablets

A prostaglandin E_2 (PGE_2) EP4 receptor antagonist; a non-cyclooxygenase inhibiting, non-steroidal anti-inflammatory drug

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

Before using Galliprant, please consult the product insert, a summary of which follows:

Indication:
GALLIPRANT (grapiprant tablets) is indicated for the control of pain and inflammation associated with osteoarthritis in dogs.

Dosage and Administration:
Always provide "Information for Dog Owners" Sheet with prescription.
Use the lowest effective dose for the shortest duration consistent with individual response.

The dose of GALLIPRANT (grapiprant tablets) is 0.9 mg/lb (2 mg/kg) once daily.

Only the 20 mg and 60 mg tablets of GALLIPRANT are scored. The dosage should be calculated in half tablet increments. Dogs less than 8 lbs. (3.6 kgs) cannot be accurately dosed.

The 100 mg tablet is not scored and should not be broken in half.

See product insert for complete dosing and administration information.

Contraindications:
GALLIPRANT should not be used in dogs that have a hypersensitivity to grapiprant.

Warnings:
Not for use in humans. Keep this and all medications out of reach of children and pets. Consult a physician in case of accidental ingestion by humans.
For use in dogs only. Store GALLIPRANT out of reach of dogs and other pets in a secured location in order to prevent accidental ingestion or overdose.

Precautions:
The safe use of GALLIPRANT has not been evaluated in dogs younger than 9 months of age and less than 8 lbs (3.6 kg), dogs used for breeding, or in pregnant or lactating dogs.

Adverse reactions in dogs receiving GALLIPRANT may include vomiting, diarrhea, decreased appetite, mucoid, watery or bloody stools, and decreases in serum albumin and total protein.

If GALLIPRANT is used long term appropriate monitoring is recommended.

Concurrent use with other anti-inflammatory drugs has not been studied. Concomitant use of GALLIPRANT with other anti-inflammatory drugs, such as COX-inhibiting NSAIDs or corticosteroids, should be avoided. If additional pain medication is needed after a daily dose of GALLIPRANT, a non-NSAID/ non-corticosteroid class of analgesic may be necessary.

The concomitant use of protein-bound drugs with GALLIPRANT has not been studied. Commonly used protein-bound drugs include cardiac, anticonvulsant and behavioral medications.

Drug compatibility should be monitored in patients requiring adjunctive therapy. Consider appropriate washout times when switching from one anti-inflammatory to another or when switching from corticosteroids or COX-inhibiting NSAIDs to GALLIPRANT use.

The use of GALLIPRANT in dogs with cardiac disease has not been studied.

It is not known whether dogs with a history of hypersensitivity to sulfonamide drugs will exhibit hypersensitivity to GALLIPRANT. GALLIPRANT is a methylbenzenesulfonamide.

Adverse Reactions:
In a controlled field study, 285 dogs were evaluated for safety when given either GALLIPRANT or a vehicle control (tablet minus grapiprant) at a dose of 2 mg/kg (0.9 mg/lb) once daily for 28 days. GALLIPRANT-treated dogs ranged in age from 2 yrs to 16.75 years. The following adverse reactions were observed:

Table 1. Adverse reactions reported in the field study.

Adverse reaction*	GALLIPRANT (grapiprant tablets) N = 141	Vehicle control (tablets minus grapiprant) N = 144
Vomiting	24	9
Diarrhea, soft stool	17	13
Anorexia, inappetence	9	7
Lethargy	6	2
Buccal ulcer	1	0
Immune mediated hemolytic anemia	1	0

*Dogs may have experienced more than one type or occurrence during the study.

GALLIPRANT was used safely during the field studies with other concurrent therapies, including antibiotics, parasiticides and vaccinations.

To report suspected adverse drug events and/or to obtain a copy of the Safety Data Sheet (SDS) or for technical assistance, call 1-888-545-5973.

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

Information for Dog Owners:
Owners should be advised of the potential for adverse reactions and be informed of the clinical signs associated with drug intolerance. Adverse reactions may include vomiting, diarrhea, decreased appetite, and decreasing albumin and total protein. Appetite and stools should be monitored and owners should be advised to consult with their veterinarian if appetite decreases or stools become abnormal.

Effectiveness:
Two hundred and eighty five (285) client-owned dogs were enrolled in the study and evaluated for field safety. GALLIPRANT-treated dogs ranging in age from 2 to 16.75 years and weighing between 4.1 and 59.6 kgs (9 – 131 lbs) with radiographic and clinical signs of osteoarthritis were enrolled in a placebo-controlled, masked field study. Dogs had a 7-day washout from NSAID or other current OA therapy. Two hundred and sixty two (262) of the 285 dogs were included in the effectiveness evaluation. Dogs were assessed for improvements in pain and function by the owners using the Canine Brief Pain Inventory (CBPI) scoring system.[7] A statistically significant difference in the proportion of treatment successes in the GALLIPRANT group (63/131 or 48.1%) was observed compared to the vehicle control group (41/131 or 31.3%). GALLIPRANT demonstrated statistically significant differences in owner assessed pain and function. The results of the field study demonstrate that GALLIPRANT, administered at 2 mg/kg (0.9 mg/pound) once daily for 28 days, was effective for the control of pain and inflammation associated with osteoarthritis.

Storage Conditions:
Store at or below 86° F (30° C)

How Supplied:
20 mg, 60 mg and 100 mg flavored tablets in 7, 30 and 90 count bottles

NADA 141-455, Approved by FDA

Manufactured for:
Elanco US Inc.
Greenfield, IN 46140

November 2018

From *Clinician's Brief* on Social Media

WE ASKED . . .

What is your favorite response to the question, "What breed do you think my dog is?"

"Even she (the dog) does not know."—*Janis A*

"Chihuahua . . . to Great Dane owners"—*Marjolein F*

"An American original; there are probably only 6 to 12 other dogs like them, and they are all brothers and sisters." —*Alice W*

"A mix of awesome and cute with a smidge of adorable" —*Brandi U*

"An exclusive model!"—*Susana C*

What is your preferred method for emesis induction in cats?

"Dexamethasone and a little spin in their carrier" —*Erica I*

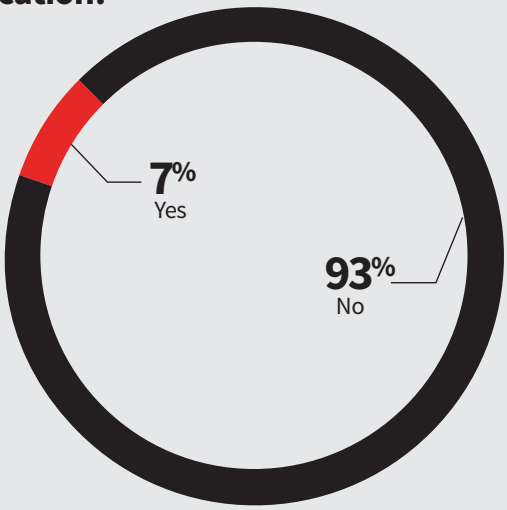
"Xylazine or medetomidine"—*Adam K*

"Xylazine is best if it is in stock. Dexmedetomidine is my second choice."—*Stan G*

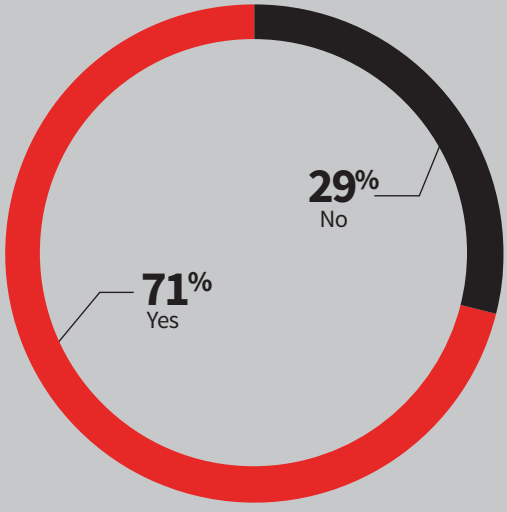
"Put them near the most expensive and difficult-to-clean area rug."—*Julie C*

"Show them my completed essay that is due the following morning—this actually happened!"—*Ailish A*

Have any of your patients developed neurogenic keratoconjunctivitis sicca after application of a long-acting topical ear medication?



Have you treated megaesophagus with sildenafil?



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Galliprant®
(grapiprant tablets)

Are your patients getting the canine osteoarthritis (OA) pain and inflammation relief they need?

Recommend Galliprant as first-line treatment

- **FIRST-IN-CLASS** non-COX inhibiting NSAID[1]
- **MODE OF ACTION TARGETS** canine OA pain and inflammation while reducing the impact on GI, kidney, and liver homeostasis[1,2‡]
- **FOR ALL STAGES** of OA from the earliest clinical signs*

*Approved for use in dogs older than 9 months of age and greater than 8 pounds.
‡Monitoring is recommended if used long-term.

Simple, once-daily chewable tablet

Go to GalliprantVet.com for more information

INDICATION
Galliprant is an NSAID that controls pain and inflammation associated with osteoarthritis in dogs.

IMPORTANT SAFETY INFORMATION
Not for use in humans. For use in dogs only. Keep this and all medications out of reach of children and pets. Store out of reach of dogs and other pets in a secured location in order to prevent accidental ingestion or overdose. Do not use in dogs that have a hypersensitivity to grapiprant. If Galliprant is used long term, appropriate monitoring is recommended. Concomitant use of Galliprant with other anti-inflammatory drugs, such as COX-inhibiting NSAIDs or corticosteroids, should be avoided. Concurrent use with other anti-inflammatory drugs or protein-bound drugs has not been studied. The safe use of Galliprant has not been evaluated in dogs younger than 9 months of age and less than 8 lbs (3.6 kg), dogs used for breeding, pregnant or lactating dogs, or dogs with cardiac disease. The most common adverse reactions were vomiting, diarrhea, decreased appetite, and lethargy. For full prescribing information see Galliprant package insert.

[1]Kirkby Shaw, K, et al. Vet Med Sci. 2016;2:3-9.
[2]Rausch-Derra L, et al. Am J Vet Intern Med. 2015;76(10):853-859.

See page 2 for product information summary.

IN THIS ISSUE

ON THE COVER

CONSULT THE EXPERT
Canine Heartworm
Andrew R. Moorhead, DVM, MS, PhD, DACVM (Parasitology)

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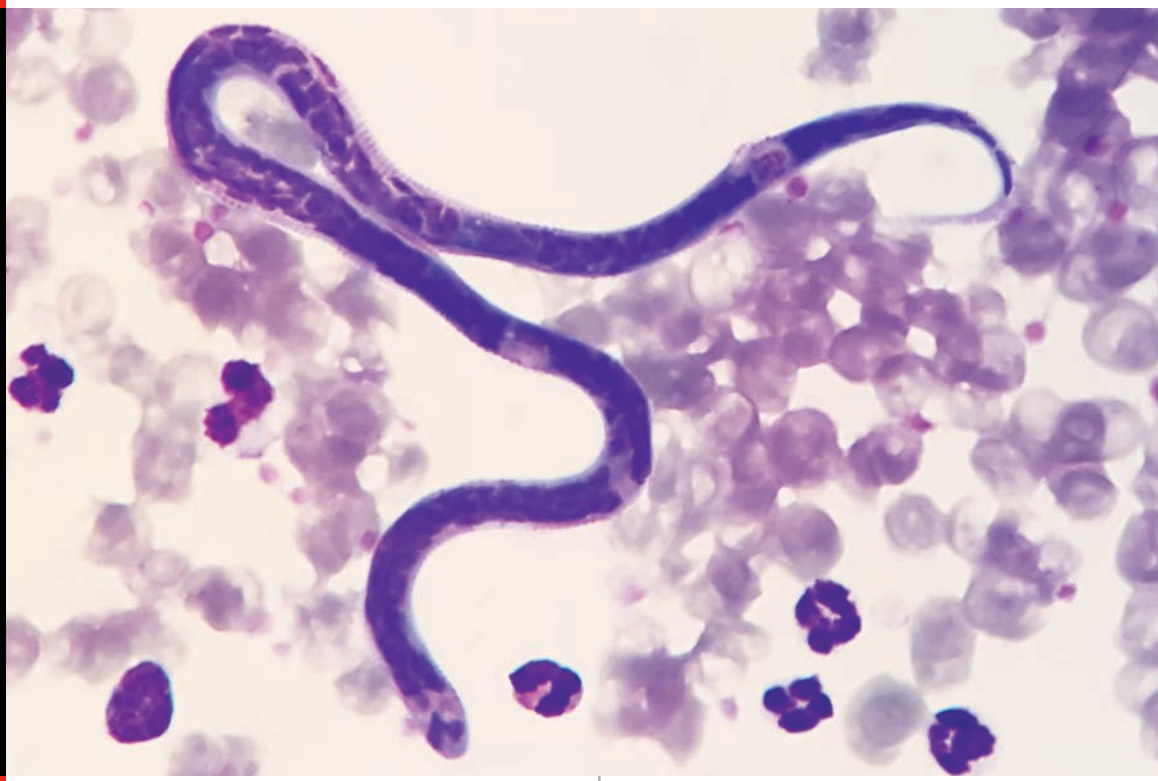

NOTICE OF CORRECTION
The article "Management Tree: Emesis Induction," published in the January/February 2021 issue of *Clinician's Brief*, contained an incorrectly placed arrow. A corrected version has been published online and can be found at **brief.vet/emesis-induction**. *Clinician's Brief* regrets the error.

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The only nutrition for both food *and* environmental allergies.

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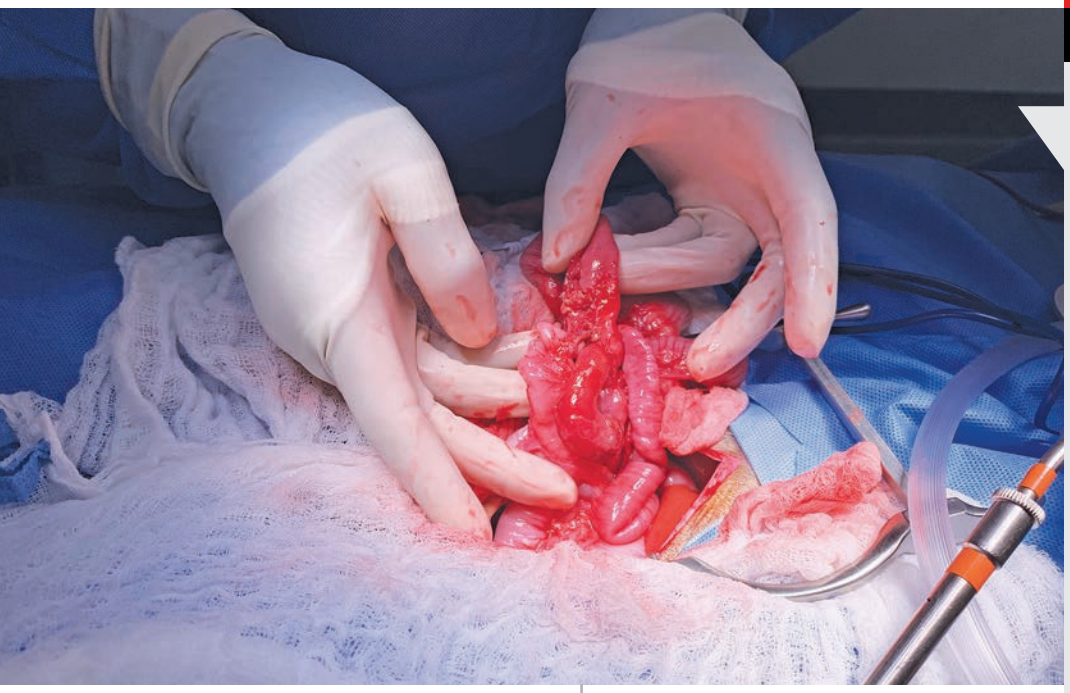
A STEP AHEAD FOR THEIR BEST LIFE



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ON THE WEB

THIS MONTH'S FEATURED CLINICAL CONTENT AVAILABLE ONLY ONLINE

CONTINUING EDUCATION

GI Surgery

This course provides step-by-step guides for performing gastropexy, small intestinal resection and anastomosis, and intussusception reduction, as well as tips to complete exploratory celiotomy and find GI obstruction on radiographs.
brief.vet/GI-surgery

PODCAST

Hypoglycemia with Dr. Schermerhorn

Tom Schermerhorn, VMD, DACVB, discusses diabetes, how hypoglycemia can be a sign of underlying disease, and the clinical challenges hypoglycemia can cause with insulin use.
brief.vet/hypoglycemia

CLEVOR®

(ropinirole ophthalmic solution)
30 mg/mL
For ophthalmic use in dogs only

Single use dropper

BRIEF SUMMARY: Before using CLEVOR® (ropinirole ophthalmic solution), please consult the product insert, a summary of which follows:

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

INDICATION:
For induction of vomiting in dogs.

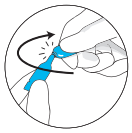
DOSAGE AND ADMINISTRATION:
This product should be administered by veterinary personnel.

Dosing Instructions:
Administer the appropriate number of eye drops topically according to Table 1. The number of eye drops administered corresponding to body weight results in a target dose of 3.75 mg/m^2 (dose band 2.7 - 5.4 mg/m^2). If the dog does not vomit within 20 minutes of the first dose, then a second dose may be administered.

Table 1. Dose Administration

Body weight in kilograms	Body weight in pounds	Total number of eye drops	Example admini-stration
1.8 - 5	4 - 11.1	1	1 drop into either left or right eye
5.1 - 10	11.2 - 22.1	2	1 drop each eye
10.1 - 20	22.2 - 44.1	3	2 drops in one eye and 1 drop in the other eye
20.1 - 35	44.2 - 77.2	4	2 drops in each eye
35.1 - 60	77.3 - 132.3	6	An initial dose of 2 drops in each eye, followed 2 minutes later by 1 drop in each eye
60.1 - 100	132.4 - 220.5	8	An initial dose of 2 drops in each eye, followed 2 minutes later by 2 drops in each eye

Dose Administration:



- Wear gloves and protective eye wear when handling or administering this product to prevent accidental exposure.
- Open the dropper by twisting off the tail.

- Keep the dog's head steady in a slightly upright position.
- Hold the dropper in an upright position without touching the eye.
- Rest your finger on the forehead of your dog to maintain the distance between the dropper and the eye.
- Squeeze the prescribed number of drops in to the eye(s).

- CLEVOR is a single use dropper and is light sensitive.
- After administration, with gloves on, return the dropper to the aluminum pouch and place in the carton.

- If the dog does not vomit, a second dose can be given 20 minutes after administration of the first dose.
- This second dose is the same number of drops as the first dose.
- Thirty minutes after opening, with gloves on, dispose of dropper, aluminum pouch, and carton.

Refer to the **Animal Safety Warnings** section for treatment of protracted vomiting.

CONTRAINDICATIONS:
Do not use in dogs with central nervous system depression or seizures.
Do not use in cases of ingestion of sharp foreign objects, corrosive agents (acids or alkalis), volatile substances or organic solvents.
Do not use in cases with corneal ulceration, ocular irritation, or ocular injury.
Do not use when there is a known sensitivity to ropinirole or the inactive ingredients.

WARNINGS:
Human Safety Warnings:
Not for use in humans. Keep out of reach of children.

Wear gloves and protective eye wear when handling or administering this product to prevent accidental exposure. In case of accidental eye, oral or skin exposure, flush with water. If wearing contact lenses, eyes should be rinsed first, then remove contact lenses and continue rinsing. Remove contaminated clothing. Ropinirole is a dopamine agonist. **Seek medical attention if accidental exposure occurs and show the package insert or label to the physician.** Exposure to this drug may cause adverse reactions such as headache, nausea, vomiting, dizziness, orthostatic hypotension, and sleepiness. Avoid contact with the product if pregnant, planning to become pregnant, or breast-feeding, as exposure has been shown to have adverse effects on embryo-fetal development based on rodent studies.

Animal Safety Warnings:
This product should be administered by veterinary personnel.
Dogs should be monitored for CLEVOR-associated clinical signs, including protracted vomiting, salivation, muscle tremors, evidence of abdominal discomfort, lethargy, transient tachycardia, transient decrease in blood pressure and signs of ocular irritation, including conjunctival hyperemia, mild blepharospasm, and protrusion of the third eyelid. These clinical signs are related to the pharmacological action of ropinirole. To stop protracted vomiting, administer metoclopramide (dopamine D2 antagonist) at a dose of 0.5 mg/kg intravenously (IV) or subcutaneously (SQ). Metoclopramide also decreases the prevalence of most CLEVOR-associated clinical signs.

PRECAUTIONS:
The safe use of CLEVOR has not been evaluated in dogs with cardiac disease or cardiovascular compromise. CLEVOR can cause transient tachycardia and transient decreased systolic blood pressure.
The safe use of CLEVOR has not been evaluated in dogs with hepatic impairment. CLEVOR is metabolized by the liver.
The safe use of CLEVOR has not been evaluated in dogs younger than 4.5 months of age and weight less than 4 pounds.
The safe use of CLEVOR has not been evaluated in dogs that are pregnant, lactating, or intended for breeding.

ADVERSE REACTIONS:
Safety was evaluated during a field study that enrolled 132 dogs (100 in the CLEVOR group and 32 in the vehicle control group). CLEVOR was administered as drops into the eyes at the dose as directed by the dosing table (see **DOSAGE AND ADMINISTRATION**). The following table shows the number of dogs exhibiting ocular, systemic, and clinical pathology adverse reactions.

Table 2: Adverse Reactions Reported During the Study (all dogs)

Organ System	Adverse Reaction	CLEVOR (N=100)	Vehicle control (N=32)
Ocular	Conjunctival hyperemia[a]	51 (51%)	6 (19%)
	Protrusion of the third eyelid[a]	38 (38%)	1 (3%)
	Conjunctival discharge[a]	30 (30%)	1 (3%)
	Blephar-ospasm[a]	19 (19%)	0
	Conjunctival swelling[a]	3 (3%)	0
	Scratching/rubbing of eyes[a]	4 (4%)	0
	Corneal ulceration	1 (1%)	0
	Corneal fluorescein uptake without corneal ulceration	1 (1%)	0
Systemic	Lethargy	41 (41%)	0
	Tachycardia (>160 beats per minute)[a,b]	14 (14%)	0
	Vomiting duration longer than one hour	8 (8%)	0
	Salivation	3 (3%)	1 (3%)
	Trembling	3 (3%)	0
	Diarrhea or soft stool	2 (2%)	1 (3%)
	Anxious	1 (1%)	0
	Borborygmi	1 (1%)	0
Clinical Pathology	Crystalluria[c]	13 (20%)	3 (15%)
	Pyuria[c]	12 (18%)	3 (15%)
	Increased liver enzymes[d]	3 (3%)	0
	Decreased blood glucose	2 (2%)	0
	Increased prothrombin time	1 (1%)	0

[a] Assessment performed 30 minutes after dose administration
[b] Tachycardia resolved for most dogs within 4 hours after dose administration
[c] Urinalysis results were reported for only 86 dogs (66 administered CLEVOR and 20 control)
[d] All three dogs had elevated alanine aminotransferase. Additionally, one of the dogs also had an elevated aspartate aminotransferase and another of the dogs also had an elevated alkaline phosphatase and total bilirubin.
Note: If any animal experienced the event more than once, only the first occurrence was tabulated.

To report suspected adverse events call 1(800) 835-9496, for technical assistance or to obtain a copy of the SDS, contact Vetoquinol USA, Inc. at 1 (800) 267-5707 or www.vetoquinolusa.com.

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

CLEVOR is a trademark of Orion Corporation

Manufactured by:
Orion Corporation

Distributed by:
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Issued 06/2020

Approved by FDA under NADA # 141-534

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THE FIRST FDA-APPROVED EYE DROP EMETIC FOR DOGS

Clevor®
(ropinirole ophthalmic solution)

When dogs eat something potentially poisonous or harmful, you need to act quickly. Clevor is a selective emetic with a fast onset of action and short duration of vomiting. A convenient, single-use dropper provides one injectionless treatment for a dog.

Clevor - a new way to induce emesis in dogs.

CLEVOR® is indicated for the induction of vomiting in dogs.

IMPORTANT SAFETY INFORMATION: Do not use in dogs with central nervous system depression or seizures. Do not use in cases of ingestion of sharp foreign objects, corrosive agents (acids or alkalis), volatile substances or organic solvents. CLEVOR® should not be administered in cases with corneal ulceration, ocular irritation, or ocular injury. Do not use when there is a known sensitivity to ropinirole or the inactive ingredients. **ADVERSE REACTIONS MAY INCLUDE:** Transient mild or moderate hyperemia of the eye, ocular discharge, protrusion of the 3rd eyelid and blepharospasm, transient mild lethargy and increased heart rate. Not recommended for use in breeding, pregnant or lactating dogs. CLEVOR® has not been evaluated in dogs with heart or liver impairments or dogs younger than 4.5 months or less than 4 pounds. Dopamine antagonists, neuroleptics and other medicines with antiemetic properties may reduce the effectiveness of ropinirole. CLEVOR® should be administered by a veterinary professional. Gloves and protective eyewear should be worn when administering. Not for use in humans. Keep out of reach of children.

For complete product safety information, see brief on the previous page or visit:
https://www.vetoquinolusa.com/clevor-info

CVR-0003-IORTRN 2/2021 v1

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OUR AUTHORS

CLAIRE L. FELLMAN, DVM, PhD, DACVIM, DACVCP, is an assistant professor of small animal internal medicine and clinical pharmacology at the Cummings School of Veterinary Medicine at Tufts University. She completed her clinical training and earned her PhD from Mississippi State University. Her interests include pharmacology, immune-mediated diseases, and antimicrobial stewardship.

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ALEX GALLAGHER, DVM, MS, DACVIM (SAIM), is a clinical assistant professor of small animal medicine at University of Florida, where he also earned his DVM. He completed a rotating internship, a residency in small animal internal medicine, and an MS in biomedical and veterinary sciences at the Virginia-Maryland College of Veterinary Medicine in Blacksburg, Virginia. His interests include gastroenterology, endocrinology, and image-guided interventions.

CASE IN POINT PAGE 73

CASSANDRA GILDAY, DVM, is a small animal rotating intern at University of Tennessee. She earned her DVM from Virginia-Maryland College of Veterinary Medicine in Blacksburg, Virginia.

DIAGNOSTIC/MANAGEMENT TREE PAGE 22

ALEX KNETSCHE, DVM candidate, is a fourth-year veterinary student (class of 2021) at Kansas State University. She plans to continue her veterinary career in Kentucky at a mixed animal practice. Her main interests are internal medicine and clinical pathology.

CASE IN POINT PAGE 57

ANDREW R. MOORHEAD, DVM, MS, PhD, DACVM (Parasitology), is a small animal parasitologist and assistant professor at University of Georgia. Dr. Moorhead earned his DVM from North Carolina State University, his MS in veterinary parasitology from Purdue University, and his PhD from Cornell University. He is also an at-large member of the executive board of the American Heartworm Society. Dr. Moorhead's main research interests are the role of host-specific cues in development of filarial worms, specifically *Dirofilaria immitis* and *Brugia malayi*.

CONSULT THE EXPERT PAGE 14

Continued on page 12

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(imidacloprid+moxidectin)

Every dog and cat deserves comprehensive, broad-spectrum protection. That's why Advantage Multi® delivers layers of protection from heartworms, fleas and intestinal parasites.

Provide the multi-layered protection of Advantage Multi® to the pets in your care.

Visit LayersofMulti.com or contact your Elanco Sales Representative.

*Treats and controls roundworms, hookworms and whipworms in dogs and roundworms and hookworms in cats.

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.

Elanco

See page 10 for product information summary.

ADESOLA ODUNAYO, DVM, MS, DACVECC, is a clinical associate professor of emergency medicine and critical care at University of Tennessee. She earned her DVM from Oklahoma State University and completed a residency in emergency medicine and critical care at University of Missouri.

DIAGNOSTIC/MANAGEMENT TREE PAGE 22

LISA M. POHLMAN, DVM, MS, DACVP, is an associate professor of clinical pathology at Kansas State University. She earned her DVM from University of Guelph and her MS in clinical pathology from Auburn University, where she also completed a residency. Dr. Pohlman serves as the president and medical director of the Riley County Humane Society in Manhattan, Kansas, and is an active teacher and mentor of veterinary interns, residents, and graduate students. She enjoys providing CE in clinical pathology through speaking engagements, online courses, and publications. Her research interests include improvement of clinical pathology laboratory methods and identification and characterization of disease in domestic species, particularly in shelter animals, as well as pets owned by individuals who cannot afford routine veterinary care.

CASE IN POINT PAGE 57

JENNA K. ROOKS, DVM, MS, is a clinical lecturer at University of Florida, where she also earned her DVM. She is certified in shelter medicine, veterinary dental education, FEMA disaster response, and Fear Free handling. Dr. Rooks earned her MS in forensics from University of Florida, which lead her to work on cruelty cases and educate students on how to handle these cases in private practice. Her interests include dentistry, forensics, and preventive medicine.

CASE IN POINT PAGE 73

NATALIE SMITH, DVM, is a small animal rotating intern at University of Wisconsin. She earned her DVM from the Cummings School of Veterinary Medicine at Tufts University. Her interests include infectious disease, endocrinology, and oncology.

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CANINE HEARTWORM

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Dirofilaria immitis **(ie, canine heartworm), a potentially deadly disease, is arguably the most important parasite that affects dogs in North America, with ≈100,000 new cases reported annually.[1] It is thus important that all clinicians (including those in historically nonendemic regions) be knowledgeable regarding the heartworm life cycle, as this will allow for better understanding of treatment and prevention strategies.**

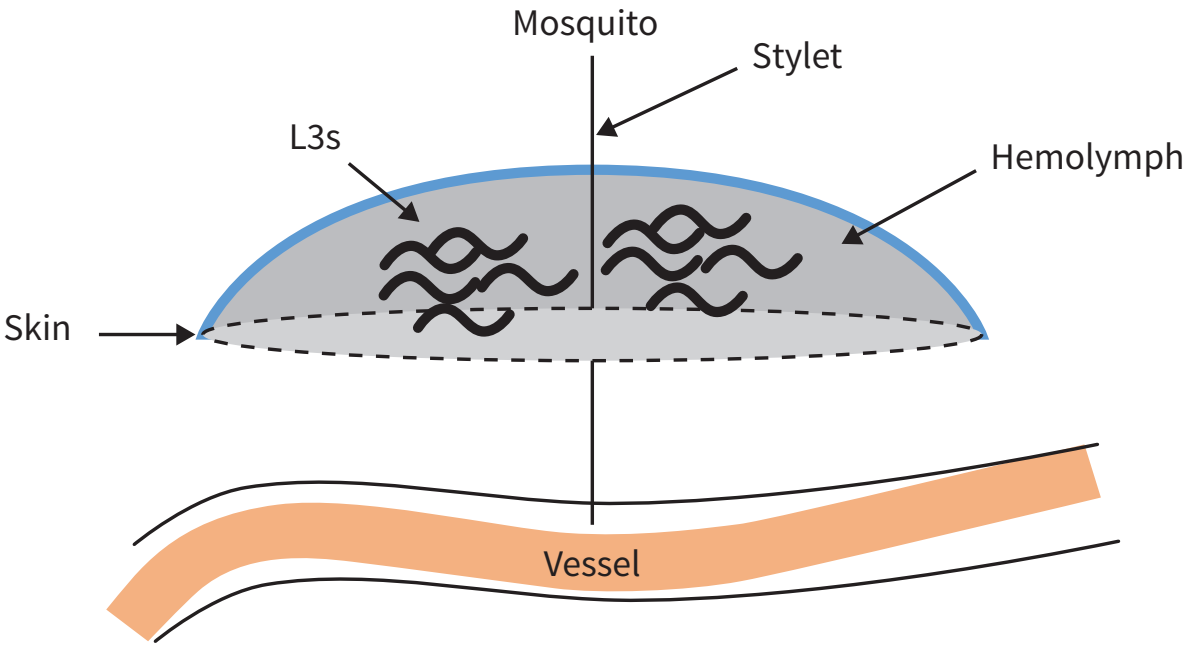
Life Cycle

Adult female heartworms can grow to a length of 10 to 12 inches; male heartworms typically reach 4 to 6 inches. Adult worms can live up to 5 to 7 years in dogs, where they mate and produce microfilariae (>300 µm in length) that circulate in the blood. Microfilariae are then ingested by an intermediate mosquito host—this is essential for heartworm development—in which they migrate for an average period of ≈14 days and develop to first-stage larvae (L1). The L1 then molt twice and become infectious third-stage larvae (L3) that are ≈1 mm in length and exist in the head of the mosquito. The ambient temperature must be >57.2°F (14°C) for larval development in the mosquito.[2] When the mosquito lands and takes a blood meal, the L3 emerge from the proboscis (ie, mosquito mouthparts) and surround the stylet (ie, piercing part of the proboscis) in a pool of mosquito hemolymph (***Figure***). When the stylet is removed, the larvae enter the host through the hole created by the stylet. This process is in contrast to the commonly held belief that larvae are injected by the mosquito into the definitive host.[3]

Once inside the definitive host, the larvae follow a complicated migration pathway. The L3 remain at the site of entrance for ≈3 to 4 days; during which time they molt to fourth-stage larvae (L4). Molting is usually completed within 4 days but may not occur until day 12.[3] L4 typically molt to the last stage (ie, juvenile adults) between day 50 to 58, then migrate through the subcutaneous tissue and musculature.[4] Worms begin arriving in the pulmonary artery (ie, the final location) by days 67 to 70[4,5]; most worms reach this location by day 120. By day 180, worms are sexually mature and begin to produce microfilariae; thus, completing the life cycle.[4] This timeline can vary.

Pathophysiology

Heartworm disease can result in death, especially in cases with a large number of worms (ie, caval syndrome). Although this acute presentation can be remarkable, pathology is most often observed secondary to the prolonged presence of worms in the pulmonary arteries, which can occur as early as day 60 to 70 of infection.[4,5] Severity of disease and extent of pathology are influenced by multiple



▲ **FIGURE** L3 in a hemolymph pool, with the mosquito stylet still inserted in the definitive host

factors (eg, number of adult worms, duration of infection, host immune response, presence of dead worms). The presence of dead worms is especially important, as they are carried by the blood flow further into the pulmonary vessels, resulting in pulmonary thromboembolism (PTE).

Heartworms are constantly pushed back and forth by the pulsing blood flow; this can cause trauma to the vessels that results in thickening of the tunica intima and inflammation of the vessel wall characterized by a pathognomonic roughened, stippled appearance.[6,7] This prolonged damage can eventually lead to vessel inelasticity, resulting in increasing pressure on the main pulmonary artery, right heart, and vena cava. In turn, this pressure can lead to chronic, passive congestion and pulmonary hypertension that results in right-sided heart enlargement and (eventually) failure.[8] Right-sided heart failure can cause liver congestion and ascites. In addition, renal lesions (eg, glomerulonephritis) can develop secondary to immune complex deposition.[9] Damage increases with the persistence of worms in the vessels.

Although worms can cause damage, data suggest that endosymbiotic *Wolbachia* spp can cause some of the inflammation associated with heartworm disease, specifically after worm death. These bacteria are endosymbionts of many filarial worms, are transmitted vertically, and live within the worm; they do not result in overt pathology.[10] When the worms die (either of a natural cause or due to drug treatment), the surface proteins of *Wolbachia* spp are exposed to the host, and the host's immune system responds.[11] It is therefore important to eliminate *Wolbachia* spp from the worms before treatment is initiated.

Clinical Signs

Dogs infected with *D immitis* may be presented with no to mild, moderate, or severe clinical signs or with caval syndrome. Although the severity of clinical signs depends on many factors, the presence or absence of clinical signs is important for staging the disease (see ***Clinical Signs of Heartworm Disease***).

Diagnostics

A 3-dose melarsomine treatment protocol is safe,[8] but complications are possible. Disease staging should thus be performed prior to treatment. Diagnostics should include physical examination, immunodiagnosis, microfilariae testing, radiography, and cardiac ultrasonography, as well as CBC, serum chemistry profile, and urinalysis. However, if diagnostic staging cannot be performed, the 3-dose protocol is recommended over other treatment protocols.

Physical Examination

Physical examination should occur first and clinical signs indicative of disease severity (see ***Clinical Signs of Heartworm Disease***) should be assessed.

Immunodiagnosis

Antigen testing is considered the gold standard for diagnosing heartworm disease. Antigen tests are highly sensitive and specific for infections of adult female worms >8 months of age because older

CLINICAL SIGNS OF HEARTWORM DISEASE

- No to mild signs: Patients are subclinical or have a mild cough but otherwise appear healthy.
- Moderate signs: Patients have a moderate cough, can have difficulty breathing, and can be slightly exercise intolerant (eg, inability to run, tire more easily than normal on walks).
- Severe signs: Patients are dyspneic and can be severely exercise intolerant (eg, difficulty walking or walking with labored breathing). Syncope and hemoptysis may be present. Signs of right-sided congestive heart failure (eg, ascites) are present.
- Caval syndrome: Patients typically have associated acute presentation of signs (eg severe dyspnea, collapse) normally related to a large numbers of worms obstructing blood flow through the tricuspid valve. Hemoglobinemia and pigmenturia are characteristic. Onset is rapid and results in death after 12 to 72 hours if not treated.[8]

PTE = pulmonary thromboembolism

worms tend to produce more antigens. However, single-sex infections of only males are undetectable using this method. Antigen tests do not routinely detect prepatent infections (worms <5 months of age) and are not quantitative. The color of any test is not correlated with worm burden. Antigen tests can also be used to determine the effectiveness of adulticidal treatment. If all worms are killed, adult antigens should be cleared from the blood by 9 months after treatment.[8]

In a subset of dogs with adult female heartworms, no detectable antigen is present. This may be due to immune complex formation between a heartworm-derived antigen and antibodies against the antigen. Therefore, it is crucial to test all dogs for microfilariae at the same time as antigen testing in case the antigen test is negative due to sequestration of the antigen by immune complex formation.[12] Immune complexes can be dissociated with heat treatment of the sample. Current recommendations for heat treatment of serum/plasma are when no antigen is directed but the patient is microfilaremic and/or has clinical signs.

Microfilariae Testing

Several methods can be used to evaluate for the presence of microfilariae, regardless of antigen status. Examination of a drop of blood or direct smear detects fewer infections than a concentration technique (eg, Knott or filter test). For the aforementioned reasons regarding the formation of immune complexes, microfilarial testing should be performed simultaneously with antigen testing. Because as many as 20% of dogs may be amicrofilaremic, this is not recommended as a stand-alone diagnostic test.[8]

In addition, *D immitis* should be differentiated from *Acanthocheilonema* (*Dipetalonema*) *reconditum*, which is a nonpathogenic worm that is transmitted by fleas, lives in the subcutaneous tissue, and does not require treatment. The easiest way to differentiate these microfilariae in a clinical setting is to observe their movement under a microscope. *A reconditum* moves progressively, whereas *D immitis* are mobile but remain in a single location.

Radiography

Radiography enables assessment of damage that has already occurred.

Cardiac Ultrasonography

ECG is not a first-line diagnostic method for heartworm disease. However, visualization of heartworms via ultrasound can confirm infection; lack of visualization does not rule out infection.

CBC, Serum Chemistry Profile, & Urinalysis

Liver and kidney function should be assessed before administration of melarsomine. Existing disease should be considered prior to treatment.[8]

Treatment

Previously, intravenous thiacetarsamide sodium was used to treat *D immitis*, but this drug had serious adverse effects.[13] Later, melarsomine dihydrochloride was introduced and considered to be a significant improvement for treatment, with early treatment protocols involving a straightforward 2-dose injection protocol and the 3-dose protocol being reserved for more complicated cases.[14] Due to advancements in knowledge about *D immitis*, treatment protocol now involves additional components, including melarsomine dihydrochloride, macrocyclic lactones, corticosteroids, and doxycycline.

It is crucial to test all dogs for microfilariae at the same time as antigen testing.

PTE = pulmonary thromboembolism

Protocol

The timing of each component of heartworm disease treatment is detailed by the AHS.[8] Macrocyclic lactone and 4-week doxycycline treatment should be initiated at the time of diagnosis. After 1 month and then monthly, a macrocyclic lactone should be administered unless a sustained-release moxidectin product was chosen as the macrocyclic lactone in the beginning of the treatment protocol. Two months after diagnosis, the first dose of melarsomine should be administered, followed 1 month later by a second and third dose given 24 hours apart. It is thought that the month in between the end of doxycycline and the start of melarsomine therapy is necessary for worm-mediated degradation of *Wolbachia* spp killed by doxycycline,[15] ensuring no immunogenic *Wolbachia* spp surface proteins are released into the bloodstream. Because *Wolbachia* spp is an endosymbiont, killing the bacteria should also weaken the worm, as *Wolbachia* spp is required for worm survival.

Macrocyclic Lactones

Macrocyclic lactone preventive treatment should be started at the time of diagnosis (ie, 2 months prior to the first melarsomine treatment). This can help prevent further infections and help eliminate developing larvae.

Doxycycline

The antibiotic doxycycline (recommended dosage, 10 mg/kg every 12 hours for 28 days) is critical in the treatment of heartworm disease because of the drug's activity against *Wolbachia* spp.[8]

Melarsomine Dihydrochloride

The labeled dosage for melarsomine is 2.5 mg/kg IM twice in the epaxial muscles 24 hours apart.[8] However, the AHS recommends an alternate or 3-dose regimen, in which 1 injection (2.5 mg/kg) is administered, then 2 doses are given 30 days later at a 24-hour interval. This regimen has increased safety and efficacy but includes an additional month of exercise restriction, increased total arsenical dose, and additional cost of a third injection.[8]

Corticosteroids

Prednisone (0.5 mg/kg every 12 hours the first week, 0.5 mg/kg every 24 hours the second week, 0.5 mg/kg every 48 hours the third and fourth weeks) can be administered.[8] It is recommended to taper the anti-inflammatory dosage concurrent with the first and third injections of melarsomine. In addition, prednisone administered concurrently with doxycycline is recommended if there are clinical signs of heartworm disease.[8]

Slow-Kill Methods

Numerous studies have evaluated the efficacy of slow-kill modalities, which consist of a prophylactic dose of ivermectin, topical moxidectin, or injectable moxidectin and concurrent administration of doxycycline as an adulticidal protocol.[15-18] These protocols have varying efficacy and require a longer time period than the 3-dose regimen of melarsomine. Although these protocols may be considered advantageous in certain settings, they are salvage procedures. The use of the slow-kill method versus the 3-dose regimen is analogous to femoral head osteotomy versus total hip replacement in a dog. The slow-kill method can be successful, but it is not ideal, as the worms remain in the vessels longer, and the time of worm death is variable as compared with melarsomine treatment.

Pulmonary Thromboembolism & Pulmonary Damage

PTE and pulmonary damage are inevitable consequences of successful adulticidal therapy. Although no current tests are predictive for PTE, the severity of clinical signs can be reduced via administration of doxycycline and corticosteroids during treatment.[8] Clinical signs of embolism include fever, cough, hemoptysis, and exacerbation of right-sided heart failure. These signs are usually seen within 7 to 10 days but may occur for up to 4 weeks posttreatment. Therefore, exercise restriction for 6 to 8 weeks posttreatment (total of 10-12 weeks) is essential.[8] This can be difficult, but cage rest (leash walk only) is as important as melarsomine injections.

Continues ▶

Compromise may be necessary to ensure adherence to exercise restriction. If the dog is anxious in a crate, confinement in a small room may be preferred to ease anxiety. Assessing the ease at which the pet owner is able to restrict the dog can help with tailoring exercise restriction recommendations. For example, the owner may be asked to rate (on a scale of 1 to 10) the ease of crate resting the dog for 10 to 12 weeks (considering this duration includes 4 weeks after the first injection of melarsomine, then 6-8 weeks after the second and third injections of melarsomine). Recommendations can be given based on the answer.

Prognosis & Prevention

Prognosis is typically good with treatment and appropriate exercise restriction. To prevent reinfection, preventives labeled for use against heartworms should be adherently administered.

Clinical Follow-Up/Monitoring

Dogs should be tested for microfilariae 30 days posttreatment. If the test is positive, a microfilaricide should be given. A test for antigen should be given 9 months post-treatment. If the test is positive, the dog should be retreated with a 2-dose protocol.

Conclusion

Treatment recommendations for heartworm disease are constantly changing. It is thus important to keep current on developments. The 3-dose treatment protocol is the recommended approach to treatment in most cases.

See page 61 for references.

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*Assessment was conducted by IDEXX® and leveraged veterinary clinic PIMS transaction level data for 2019. This analysis included data from approximately 7,000 U.S. clinics that had consistent data from 2017 to 2019. To be included, patients needed to have at least one parasiticide transaction in the baseline year (2018). The analysis was limited to loyal patients, where loyalty was defined as having one flea/tick control brand during the full three-year period. The average number of months of *NexGard* purchased per year was 6.64, compared to 6.69 for BRAVECTO. This analysis overestimates the duration of efficacy for BRAVECTO. For comparison purposes, each BRAVECTO chew was assessed as providing three months of flea & tick protection versus the labeled 12-week coverage for fleas and three species of ticks, and 8-week coverage for Lone Star ticks.

1. Data on file at Boehringer Ingelheim. 2. Data on file at IDEXX Laboratories, Inc. Westbrook, Maine USA.

Boehringer Ingelheim

See page 20 for product information summary.

VEHICULAR TRAUMA

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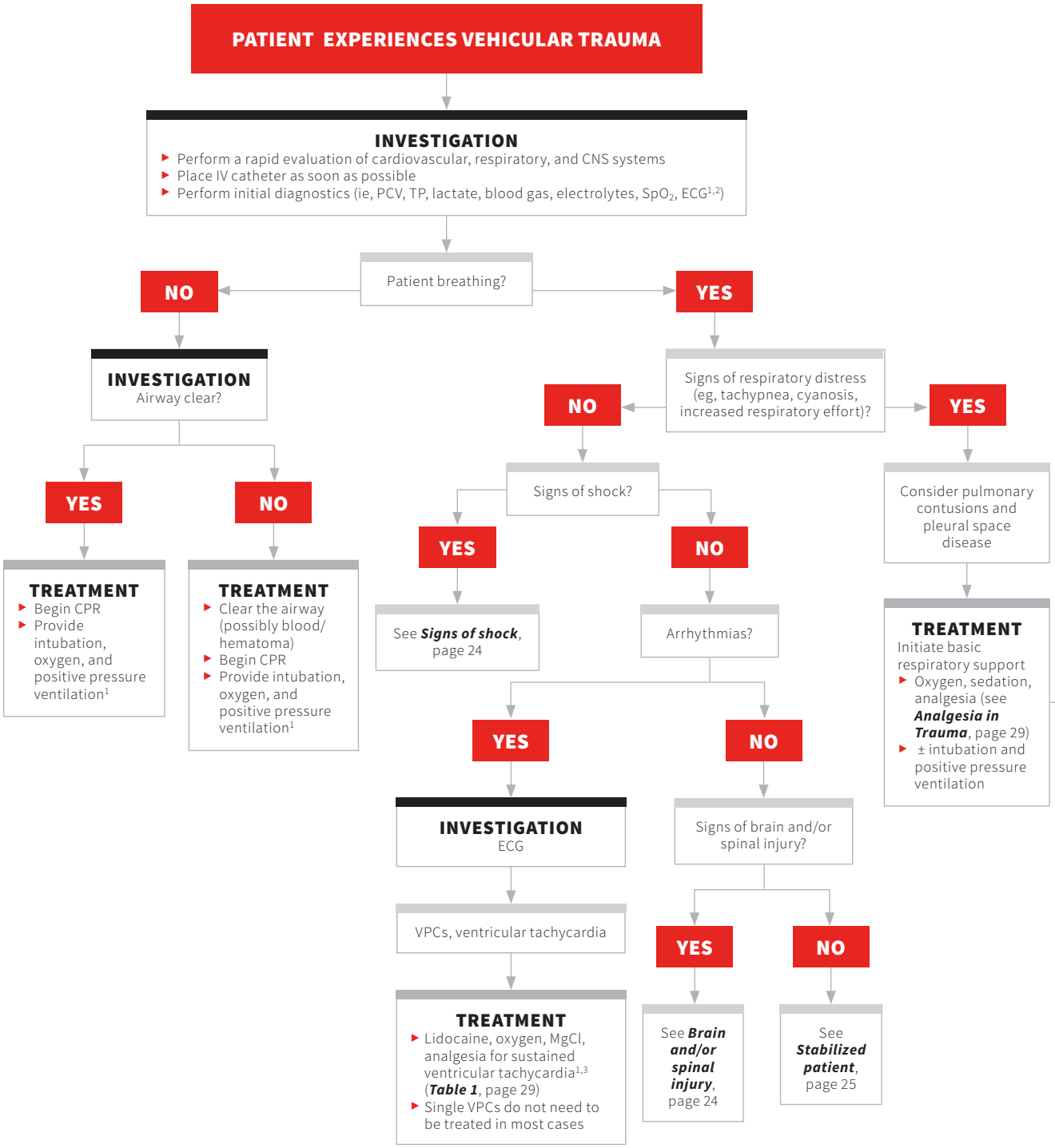
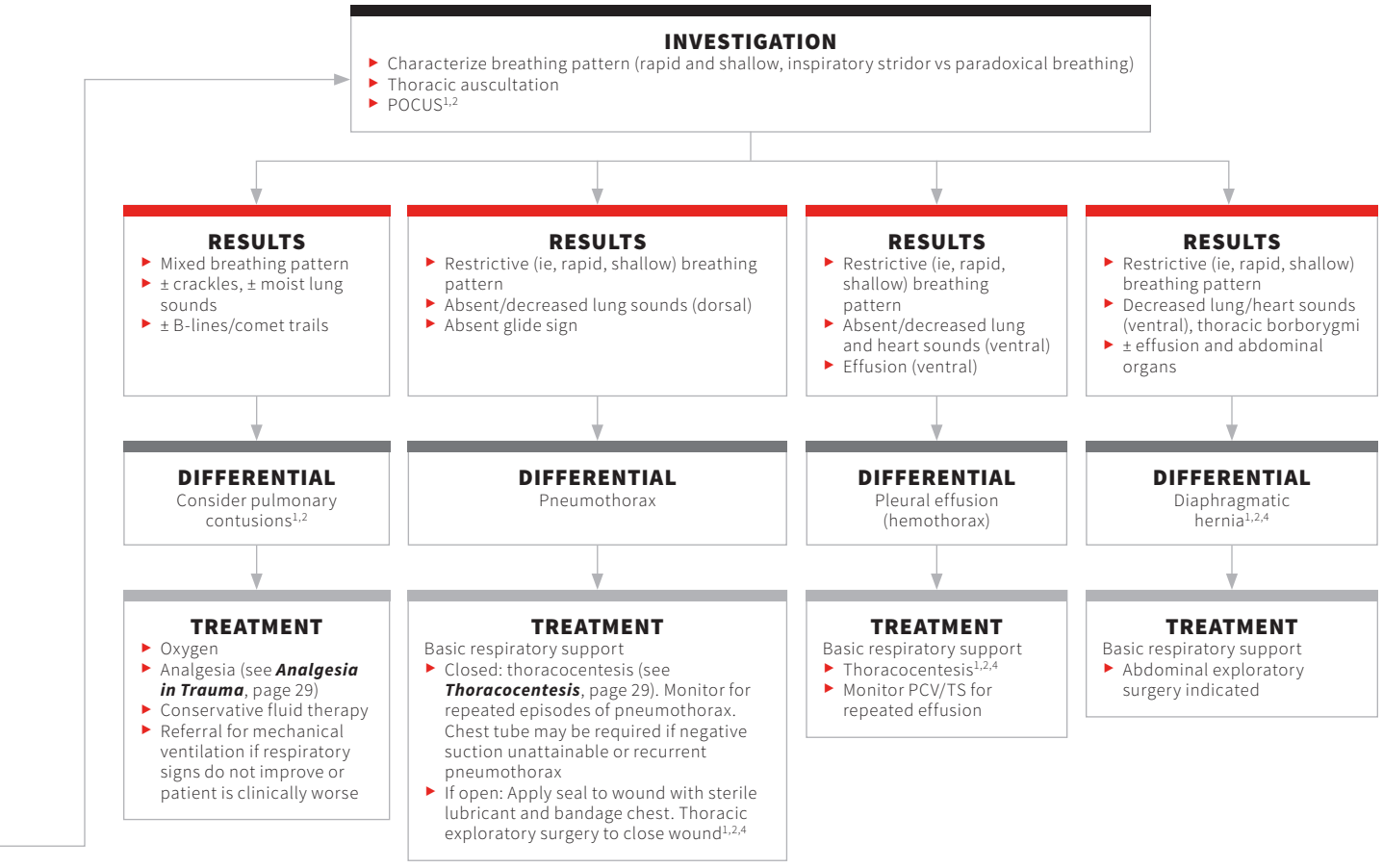
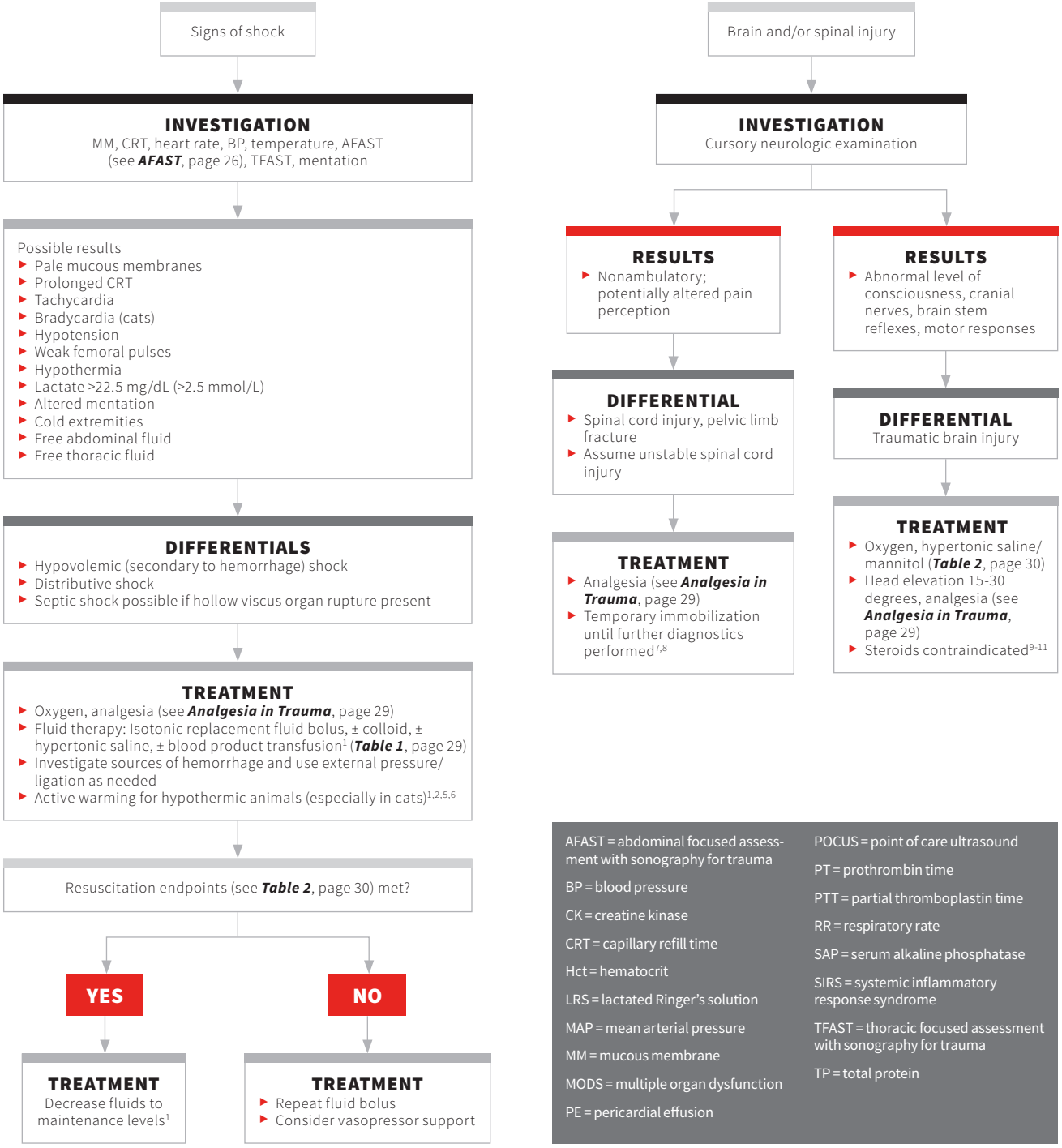




CPR = cardiopulmonary resuscitation
MgCl = magnesium chloride
PCV = packed cell volume
POCUS = point-of-care ultrasound
SpO_2 = oxygen saturation
TS = total solids
VPC = ventricular premature contraction

Continues ▶



AFAST = abdominal focused assessment with sonography for trauma

BP = blood pressure

CK = creatine kinase

CRT = capillary refill time

Hct = hematocrit

LRS = lactated Ringer's solution

MAP = mean arterial pressure

MM = mucous membrane

MODS = multiple organ dysfunction

PE = pericardial effusion

POCUS = point of care ultrasound

PT = prothrombin time

PTT = partial thromboplastin time

RR = respiratory rate

SAP = serum alkaline phosphatase

SIRS = systemic inflammatory response syndrome

TFAST = thoracic focused assessment with sonography for trauma

TP = total protein

STABILIZED PATIENT

INVESTIGATION

Admit to hospital for at least 24 hours

- Closely monitor RR, respiratory effort, demeanor, and level of pain
- Perform serial PE, AFAST, TFAST (every 15 minutes to 12 hours as needed)
- CBC, serum chemistry profile, ± PT/PTT (repeat as necessary)
- Monitor urine output (at least 1-2 mL/kg/hour)[7]
- See ***Systemic Consequences of Trauma***, page 30

Therapeutic plan

- Fluid therapy with isotonic crystalloids (40-90 mL/kg/day)
- Continue analgesia with opioids. Consider NSAIDs (eg, robenacoxib, 2 mg/kg PO every 24 hours) if normotensive and ideally eating on own
- Provide oxygen if oxygen dependent
- Address any cutaneous wounds
- Antibiotic therapy as indicated for wounds, open fractures, or septic peritonitis
- Monitor Hct, BP, oxygenation, level of pain, mentation, and cranial nerve signs
- Recumbency care if not moving on own

Discharge criteria

- Eating and drinking well
- No longer oxygen dependent (based on primary clinical signs, respiratory rate, effort)
- Pain well-managed with oral analgesics
- Adequate plan for follow-up care depending on injuries sustained

Perform diagnostic evaluations

INVESTIGATION
Thoracic radiography

INVESTIGATION
See ***Orthopedic radiography***, page 26

INVESTIGATION
See ***Abdominal radiography***, page 26

INVESTIGATION
See ***POCUS (AFAST)***, page 26

RESULTS

- Incomplete diaphragmatic silhouette
- Obscured cardiac silhouette
- ± gas filled loops/stomach in thorax

DIFFERENTIAL
Diaphragmatic hernia

TREATMENT

Surgery

Ideally delayed 3-5 days to allow improvement of pulmonary contusions if present. Indications for emergency surgery:

- Herniated stomach
- Strangulated bowel/organ
- Inability to oxygenate properly despite appropriate treatment
- Ruptured viscera

RESULTS

- Silhouette effect
- Retraction of lung lobes
- Fissure lines
- Atelectasis

DIFFERENTIAL
Pleural effusion (hemothorax)

TREATMENT

- Typically resolves with supportive care. Thoracocentesis may be required if large volume of effusion. Oxygen support and blood transfusion may also be required.
- Assess coagulation times. Rarely requires surgical intervention, but emergent surgery may be required if large-volume bleed present[1,4,12]

RESULTS

- Widened radiolucent pleural space
- Atelectasis
- Elevation of heart from the sternum

DIFFERENTIAL
Pneumothorax

TREATMENT

- Thoracocentesis
- If thoracocentesis is needed twice within a very short period (ie, patient with recurrent pneumothorax) or negative suction cannot be obtained, consider thoracostomy tubes[1,4]

RESULTS

- Interstitial to alveolar pulmonary infiltrates

DIFFERENTIAL
Pulmonary contusions

TREATMENT

- Supportive care
- Rest, monitor for 24 hours
- May not be appreciable on radiographs for 24 hours[1,4]

RESULTS

- ***Fractures(s)*** (see ***Fracture[s]*** under ***Orthopedic radiography*** page 26)

Continues ▶


INVESTIGATION
Orthopedic radiography
RESULTS
Fracture(s)
RESULTS
Pelvic, appendicular, rib fractures
TREATMENT
Pain management
External coaptation when possible
± internal fixation
Cage rest
Flail chest: place affected side down[1,7,8]
RESULTS
Spinal fracture(s)
Minimally displaced
Minimal neurologic deficits
Cervical trauma
See Three Compartment Model, page 30
TREATMENT
Pain management
External coaptation
Cage rest
Refer for CT ± MRI
± surgery[7,8]
RESULTS
Spinal fracture(s)
Significant neurologic deficits
Penetrating injury
2 of 3 spinal compartments affected indicates patient is unstable (see Three Compartment Model, page 30)
TREATMENT
Pain management
Immobilize
Refer for CT ± MRI
± surgery as soon as possible[7,8]
INVESTIGATION
Abdominal radiography
RESULTS
Free gas
DIFFERENTIAL
Pneumoperitoneum
TREATMENT
Stabilization and emergency abdominal exploratory surgery
RESULTS
Peripheral blood to abdominal fluid glucose difference ≥20 mg/dL
Effusion lactate ≥22.5 mg/dL (≥2.5 mmol/L) (dogs)
Cytology: Neutrophils (often degenerate), presence of intracellular bacteria
DIFFERENTIAL
Septic abdomen
TREATMENT
Stabilize, initiate broad spectrum antibiotics and emergency abdominal exploratory surgery to evaluate and repair possible damage
INVESTIGATION
POCUS (AFAST)
RESULTS
Free abdominal fluid
INVESTIGATION
Abdominocentesis
Compare PCV/TS, creatinine/potassium, bilirubin, glucose, and lactate of effusion to peripheral blood and cytology
RESULTS
Effusion:serum bilirubin ratio >2
Cytology: bile pigments
DIFFERENTIAL
Biliary rupture
TREATMENT
Emergency abdominal exploratory surgery to evaluate and repair possible damage as soon as patient is stable[1]
RESULTS
PCV/TS of effusion ≈ PCV/TS of peripheral blood
DIFFERENTIAL
Traumatic hemoabdomen
TREATMENT
Most respond to supportive care, fluid therapy, blood transfusion, and restricted activity. May consider abdominal compression wrap, but it must be done correctly to be valuable. Surgical intervention is rarely required
Abdominal exploratory and surgical intervention required when hemorrhage is profound and ongoing and patient cannot be stablized[1]
RESULTS
Effusion:serum creatinine ratio >2
Effusion: serum potassium ratio >1.9 (cats) >1.4 (dogs
DIFFERENTIAL
Uroabdomen
TREATMENT
Place urinary catheter. An abdominal drain may be needed if urinary catheter is not fully draining the abdomen.
Consider contrast study to identify source of leakage (eg, urethra, urinary bladder, ureter).
Surgery can be delayed for 6-24 hours if the abdominal cavity is properly drained and there is no evidence of septic peritonitis.
Urethral tears usually heal on their own without surgical intervention[1]

Continues ▶

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ANCILLARY MATERIAL TO VEHICULAR TRAUMA

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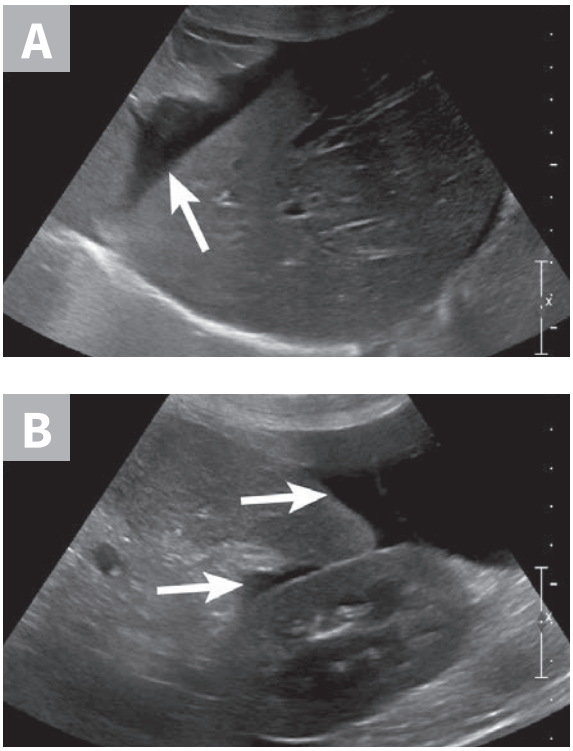
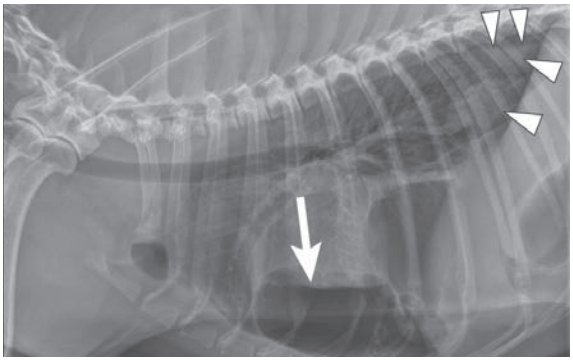
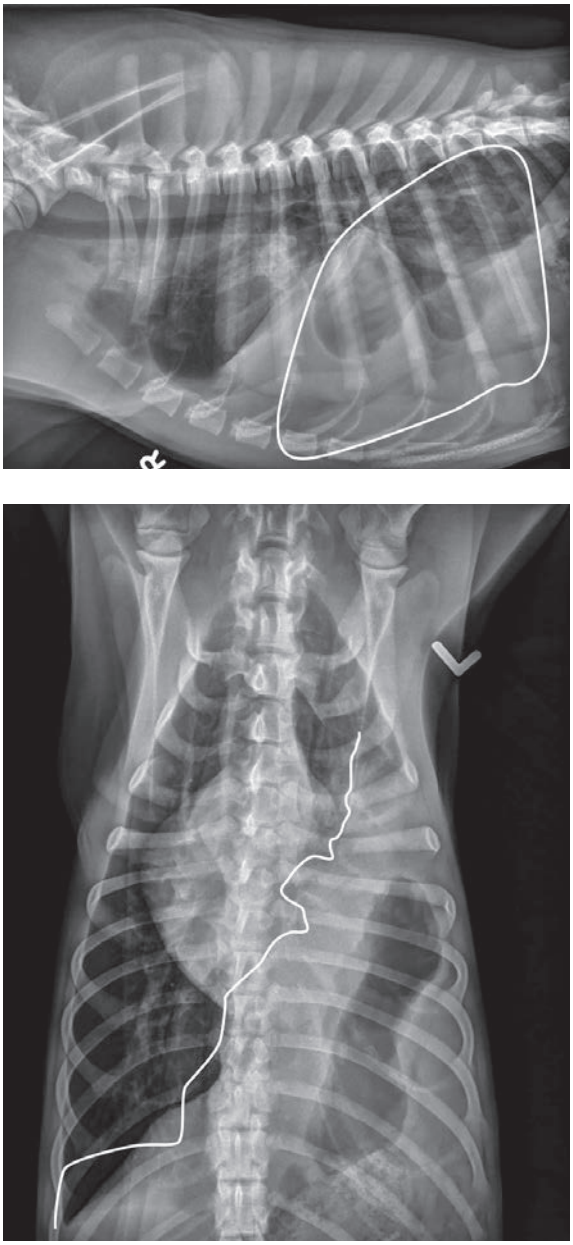


▲ **FIGURE 1** AFAST: Anechoic free abdominal fluid (***arrows***) at the diaphragmatico-hepatic view (***A***) and splenorenal site (***B***). *Images courtesy of Silke Hecht, DACVR, DECVDI*



▲ **FIGURE 2** Lateral thoracic radiograph of the pneumothorax in a dog. Increased gas opacity in the pleural space, retraction of the lung lobes from the thoracic wall and diaphragm (***arrowheads***), separation of the cardiac silhouette from the sternum (***arrow***), and diffusely increased opacity of the lungs due to atelectasis can be seen. *Image courtesy of Silke Hecht, DACVR, DECVDI*



▲ **FIGURE 3** Thoracic radiographs of diaphragmatic hernia in a dog. Cranial displacement of abdominal viscera (***circle***), loss of normal diaphragm outline (***line***), and displacement of thoracic structures can be seen. *Images courtesy of Silke Hecht, DACVR, DECVDI*

TABLE 1

GENERAL GUIDELINES FOR FLUID RESUSCITATION & BLOOD TRANSFUSION IN PATIENTS WITH TRAUMA

Perfusion Parameters	Normal Endpoints
Whole blood[5]	Dogs: 20-30 mL/kg given over 30 minutes to 4 hours, depending on how critical the patient is Cats: 50-60 mL/cat (NOT mL/kg) given over same time period as for dogs
Packed RBCs[5]	Dogs: 15 mL/kg given over same time frame as whole blood Cats: 30-40 mL/cat (NOT mL/kg) given over same time frame as for dogs
Synthetic colloid (controversial)[5]	1-5 mL/kg given over 15 minutes
Fresh frozen plasma[5]	15-30 mL/kg for patients with coagulopathy and active hemorrhage
Isotonic fluid shock bolus (LRS, Norm-R, 0.9% sodium chloride, Plasma-Lyte)[5,9]	10-25 mL/kg given over 15 minutes. End goals should be reassessed; may be repeated until entire shock dose administered. Dog shock dose: 90 mL/kg/hour; cat shock dose: 50-60 mL/kg/hour
Hypertonic saline[5,9]	4-6 mL/kg given over 15 minutes; may be repeated 2-3 times in 24 hours
Mannitol[9]	0.5-1.5 g/kg IV given over 15 minutes, may be repeated 2-3 times in 24 hours
Lidocaine[3]	2 mg/kg IV bolus, followed by 50-80 µg/kg/minute if rhythm converts

THORACOCENTESIS

Thoracocentesis is often a life-saving treatment that should be performed during initial stabilization, ideally prior to radiographic confirmation of pneumothorax or pleural effusion to prevent patient decompensation in radiology.[1,2,4]

ANALGESIA IN TRAUMA

Quick and effective analgesia is essential for patients with vehicular trauma. Opioids are the drug of choice because of their efficacy and limited adverse effects. NSAIDs should be avoided until the patient is hemodynamically stable. In addition, butorphanol has minimal analgesic effects and should not be used. IM or SC administration of pure µ-receptor agonists may cause vomiting; IV administration is strongly preferred.[1,13]

- Morphine (0.1-0.5 mg/kg IV every 4 hours)
- Hydromorphone (0.05-0.2 mg/kg IV every 4-6 hours)
- Methadone (0.1-0.5 mg/kg IV every 4-6 hours)
- Fentanyl (2-5 µg/kg bolus, then 2-6 µg/kg/hour IV CRI)
- Buprenorphine (0.01-0.03 mg/kg IV or IM every 6-8 hours)

Continues ▶

ANCILLARY MATERIAL TO VEHICULAR TRAUMA CONTINUED

THREE COMPARTMENT MODEL

- Dorsal column: laminae, spinous processes and their ligaments
- Middle column: dorsal longitudinal ligament, dorsal annulus, dorsal cortex of the vertebral bodies
- Ventral column: ventral longitudinal ligament, ventral annulus, ventral cortex of the vertebral bodies

SYSTEMIC CONSEQUENCES OF TRAUMA

- Common metabolic consequences[6,12]
  - –Activation of the coagulation cascade
  - –Hypothermia
  - –GI disturbance (eg, vomiting, diarrhea)
  - –Systemic inflammation (eg, SIRS, MODS)
- Common clinical pathologic abnormalities[2,6,12]
  - –Hyperglycemia
  - –Hyperlactatemia
  - –Metabolic acidosis
  - –Hypoalbuminemia
  - –Anemia
  - –Thrombocytopenia
  - –Increased ALT
  - –Increased CK
  - –Prolonged PT/PTT

TABLE 2

RESUSCITATION ENDPOINTS

Perfusion Parameters	Normal Endpoints
Heart rate	Dogs: 60-120 bpm Cats: 160-220 bpm
MM color	Pink
CRT	1-2 seconds
Temperature	99°F-102.5°F (37.2°C-39.2°C)
Mentation	Alert
SAP (systolic BP)	>90 mm Hg
MAP (mean BP)	>70 mm Hg
Urine output	1-2 mL/kg/hour
Lactate	<22.5 mg/dL (2.5 mmoL)

BP = blood pressure
CRT = capillary refill time
MAP = mean arterial pressure
MODS = multiple organ dysfunction
PT = prothrombin time
PTT = partial thromboplastin time
SIRS = systemic inflammatory response syndrome

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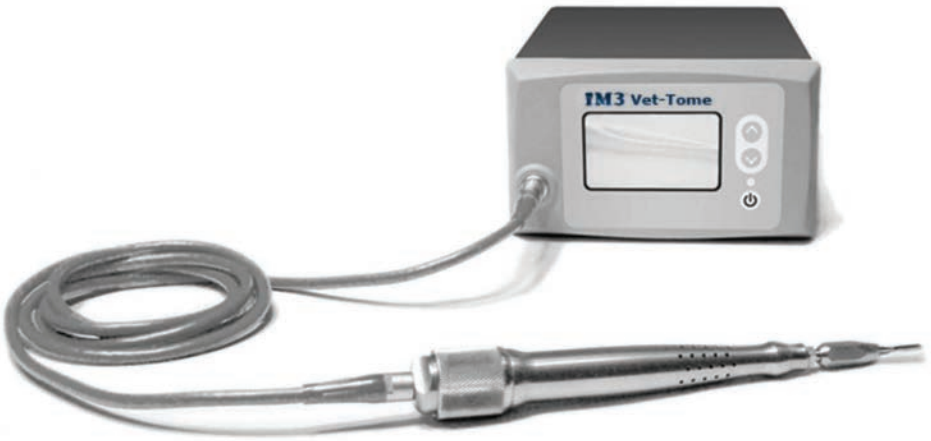

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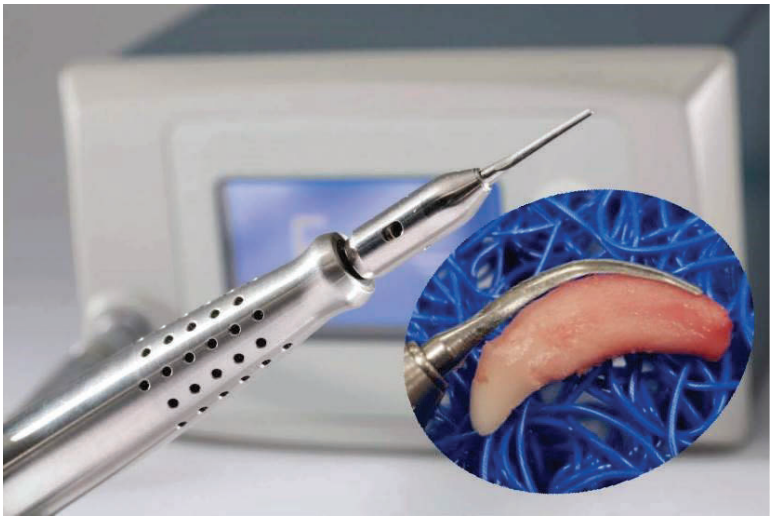

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FROM PAGE TO PATIENT

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.

Virbac

STELFONTA®

(tigilanol tiglate injection)

1 mg/mL

For intratumoral injection in dogs only
Antineoplastic
Single use vial

WARNING: SEVERE WOUND FORMATION IN HUMANS; EXTENSIVE WOUND FORMATION, MAST CELL DEGRANULATION, AND DEATH IN DOGS DUE TO MAST CELL DEGRANULATION

Human Safety

- **Accidental self-injection of STELFONTA® may cause severe wound formation. To decrease the risk of accidental self-injection, sedation of the dog may be necessary (see Dosage and Administration, Human Warnings and Adverse Reactions).**

Dog Safety

- **Always administer a corticosteroid (e.g. prednisone or prednisolone), an H1 receptor blocking agent (e.g. diphenhydramine), and an H2 receptor blocking agent (e.g. famotidine) when treating with STELFONTA to decrease the potential for severe systemic adverse reactions, including death, from mast cell degranulation (see Contraindications and Dosage and Administration).**
- **Do not inject STELFONTA into subcutaneous mast cell tumors located above the elbow or hock (e.g. on the body, head, or neck). This may result in accumulation of necrotic debris in the subcutaneous space increasing the risk of systemic adverse reactions, including death, from mast cell degranulation (see Contraindications, Warnings and Adverse Events).**
- **Treatment with STELFONTA has been associated with cellulitis and severe tissue sloughing extending away from the treated site resulting in extensive wounds that require additional treatment and prolonged recovery times (see Warnings, Precautions and Adverse Events).**

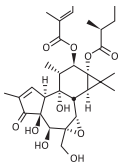
CAUTION

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

DESCRIPTION

The active ingredient for tigilanol tiglate injection is a phorbol ester that activates alpha, beta I, beta II, and gamma isoforms of protein kinase C. The chemical name is (4S,5S,6R,7S,8R,9R,10S,11R,12R,13S,14R)-12-(2E)-2-methylbut-2-enoatyl-13-[(2S)-2-methylbutyroyl]-6,7-epoxy-4,5,9,12,13,20-hexahydroxy-1-tigliaen-3-one. The molecular formula is $C_{30}H_{42}O_{10}$ and its molecular weight is 562.65 g mol^{-1}. Each mL of STELFONTA contains 1 mg tigilanol tiglate and sterile water for injection (60% v/v), propylene glycol (40% v/v), sodium acetate (<0.1% w/v), and glacial acetic acid (<0.1% w/v).

The chemical structure for tigilanol tiglate is:



INDICATION

STELFONTA injection is indicated for use in dogs for the treatment of:

- non-metastatic cutaneous mast cell tumors
- non-metastatic subcutaneous mast cell tumors located at or distal to the elbow or the hock

DOSAGE AND ADMINISTRATION

ALWAYS PROVIDE THE CLIENT INFORMATION SHEET TO THE DOG OWNER BEFORE DOSE ADMINISTRATION.

Concomitant medications

Administer the following medications to decrease the potential for severe systemic adverse reactions from mast cell degranulation:

- **Corticosteroid (e.g. oral prednisone or prednisolone at anti-inflammatory dose):** Start medication 2 days prior to STELFONTA treatment and continue for 8 days post-treatment (10 days total).
- **H1 receptor blocking agent (e.g. oral diphenhydramine):** Start medication on the day of STELFONTA treatment and continue for a total of 8 days.
- **H2 receptor blocking agent (e.g. oral famotidine):** Start medication on the day of STELFONTA treatment and continue for a total of 8 days.

Dosing Instructions

Administer STELFONTA as an intratumoral injection at a dose of 0.5 mL per cm^3 of tumor volume, as determined by the following calculations:

- **Determine the Tumor Volume in cm^3:**
  0.5 x [length (cm) x width (cm) x height (cm)]
- Confirm the Tumor Volume does not exceed 10 cm^3. Do not use STELFONTA if tumor volume is >10 cm^3.
- **Calculate the Dose Volume (mL) of STELFONTA to inject:**
  Tumor Volume x 0.5 mL
- Confirm the dose of STELFONTA does not exceed 0.25 mL/kg body weight.
- Do not exceed 5 mL per dog, regardless of tumor volume or body weight.
- The minimum dose of STELFONTA is 0.1 mL, regardless of tumor volume or body weight. If the calculated dose is <0.1 mL, administer 0.1 mL.

Administration of STELFONTA:

Sedation may be necessary to safely and accurately administer STELFONTA to decrease the chance of accidental self-injection. Wear gloves, eye protection, and lab coat or gown in the preparation and administration of STELFONTA. Care should be taken to restrict injections to the tumor only. STELFONTA should not be injected into the margins, beyond the periphery, or deep to the tumor.

- Shave the tumor site. Avoid manipulation of the tumor.
- Draw the calculated volume of STELFONTA into a sterile Luer-lock syringe with a 23 gauge needle.
- Identify an appropriate injection point on the edge of the tumor. See Figure 1. Insertion of the needle depends on the tumor's location, form, and appearance. If a tumor protrudes above the surface of the skin, insert the needle at an oblique angle of approximately 45°.
- Insert and embed the needle in the tumor through a single injection site and draw the syringe plunger back slightly to ensure STELFONTA is not injected into a blood vessel. While applying even pressure on the syringe plunger, move the needle back and forth in a fanning manner to inject STELFONTA into the tumor. See Figure 1. The drug should fully perfuse the entire tumor.
- When the total dose of STELFONTA has been administered, pause to allow tissue dispersion before removing the needle from the tumor. Pull back on the syringe plunger to create a small negative pressure before removing the needle to minimize leakage from the injection site.
- After the needle is withdrawn, apply light pressure for 30 seconds over the needle exit hole using a gloved finger. If leakage does occur, rinse injection site with saline to wash STELFONTA from the skin surface. Do not re-administer.
- To minimize risk of accidental self-injection, do not recap the needle. Dispose of the needle and syringe.

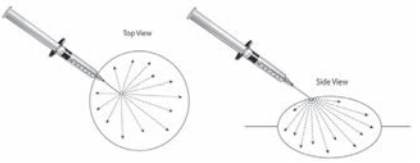


Figure 1: Dispersion of STELFONTA throughout the tumor.

CONTRAINDICATIONS

Do not inject STELFONTA into subcutaneous mast cell tumors located above the elbow or hock (e.g. on the body, head, or neck). This may result in accumulation of necrotic debris in the subcutaneous space increasing the risk of systemic adverse reactions, including death, from mast cell degranulation (see **Adverse Reactions**).

WARNINGS

Human Safety

NOT FOR USE IN HUMANS. KEEP THIS AND ALL MEDICATIONS OUT OF REACH OF CHILDREN.

Caution is required during treatment to avoid accidental self-injection. Dogs undergoing treatment with STELFONTA should be adequately restrained and sedation used if necessary. Use a Luer-lock syringe to administer STELFONTA. Do not recap the needle. Accidental self-injection may result in local inflammatory reactions, including swelling, redness and severe wound formation. In case of accidental self-injection, immediately rinse the area with water, seek medical advice immediately, and show the package insert to the physician.

Wear personal protective equipment consisting of disposable gloves, protective eye wear, and a lab coat or gown when handling STELFONTA. STELFONTA is an irritant and accidental exposure to skin, eye, or by ingestion should be avoided. In case of dermal or ocular exposure, repeatedly wash the exposed skin or eye with water. If wearing contacts, rinse the eyes first then remove contacts and continue to rinse with water. If symptoms such as local signs of redness and swelling occur, or if there has been ingestion, seek the advice of a physician and show them the package insert.

Limited data is available on the potential teratogenic effects of STELFONTA. Therefore, STELFONTA should not be administered by women who are pregnant or planning to become pregnant.

People with known hypersensitivity to tigilanol tiglate or to any of the excipients should avoid contact with STELFONTA.

Animal Safety

Dogs should be monitored during and for 5-7 days after intratumoral treatment with STELFONTA for signs of systemic mast cell degranulation such as vomiting, diarrhea, lethargy, anorexia/hyporexia, altered breathing, hypotension, urticaria, edema at or away from the treated site, or bruising at or away from the treated site. If signs are observed, appropriate treatment should be started immediately.

Always administer the recommended concomitant medications (corticosteroids, H1, and H2 receptor blocking agents) with STELFONTA. Death has occurred following mast cell degranulation when these concomitant medications were not administered according to this Package Insert (see **Dosage and Administration** and **Adverse Reactions**).

STELFONTA can induce a substantial local inflammatory reaction which may result in pain, bruising, and swelling. During this time, an analgesic may be needed in addition to the use of corticosteroids and both H1 and H2 receptor blocking agents.

Treatment with STELFONTA causes tumor necrosis which is part of the mechanism of action of the drug. Bruising, heat, pain, and swelling may begin at the site within 2 hours of treatment. By day 7 after treatment, wound formation including full thickness dermal necrosis with exudate, peripheral tissue edema, erythema, skin discoloration, tissue sloughing, and necrotic eschar may occur.

In addition to tumor necrosis, treatment with STELFONTA has been associated with cellulitis and severe tissue sloughing extending away from the treated site resulting in extensive wounds (see **Adverse Reactions**).

Do not inject STELFONTA into normal subcutaneous tissue or adjacent tissues (e.g. beyond tumor margins) because severe edema, erythema and necrosis of the injected tissue may occur.

PRECAUTIONS

STELFONTA has not been evaluated in dogs with signs of systemic disease due to the mast cell tumor(s).

STELFONTA is not intended for the treatment of metastatic mast cell tumors.

The safe and effective use of STELFONTA has not been evaluated for simultaneous treatment of more than one mast cell tumor.

The safe and effective use of STELFONTA has not been evaluated in dogs with a mast cell tumor volume >10 cm^3.

Use STELFONTA with caution in tumors located within mucocutaneous regions (e.g., eyelids, vulva, prepuce, and anus) as tumor necrosis could cause a change in morphology of the mucocutaneous region resulting in loss of functional integrity.

Use STELFONTA with caution in mast cell tumors with significant ulceration as leakage of the drug from the ulcerated area may occur following treatment potentially reducing effectiveness.

The safe use of STELFONTA has not been evaluated in dogs with concurrent diseases that may result in delayed wound healing.

After treatment with STELFONTA, dogs may require additional care of the treated site to aid in the healing process. An Elizabethan collar or a non-constricting dry gauze bandage may be needed to prevent the dog from self-traumatizing the treated site.

After treatment with STELFONTA, separation from other household animals may be necessary to prevent grooming and trauma to the treated site.

The safe use of STELFONTA under conditions of use has not been evaluated in dogs younger than 3.5 years old.

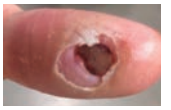
The safe use of STELFONTA has not been evaluated in dogs that are pregnant, lactating, or intended for breeding.

ADVERSE REACTIONS

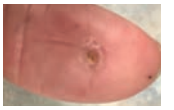
Human Exposure

There was one human exposure during the field study where the veterinarian had a needle stick injury to the thumb at completion of tumor treatment and was injected with an unknown amount of STELFONTA. The incident resulted in pain and necrosis of the center of the thumb at the point of needle stick. The wound healed over a period of three months. See Pictures 1 and 2 below. A separate needle stick injury was reported with a maximum potential dose of 0.1 mL tigilanol tiglate into the distal extremity of the left index finger, resulting in a localized burning sensation, local inflammation, bruising, muscular pain up the left arm, and localized tissue necrosis. Muscular pain resolved in the first 12-24 hours and the wound healed in 8 weeks. There have been other needle stick injuries reported, with at least one injection into a thumb, with minimal (stinging, pain, and swelling) to no adverse events associated with these accidental self-injections.

Picture 1. Thirteen days after self-injection



Picture 2. Seventy-four days after self-injection



Field Study

In a well-controlled, multi-center, randomized, double-masked field study evaluating the effectiveness and safety of STELFONTA for the treatment of cutaneous and subcutaneous mast cell tumors in dogs, 117 dogs treated with STELFONTA and 42 dogs receiving sham treatment (untreated control) were evaluated for safety. Eighty-one dogs were treated with STELFONTA on Day 0. Thirty-six previously untreated control dogs were treated with STELFONTA on Day 30. In addition, 18 dogs treated with STELFONTA on Day 0 had the same tumor re-treated with STELFONTA on Day 30 due to incomplete response. The most common adverse reactions included wound formation, injection site pain, lameness in the treated limb, vomiting, diarrhea, and hypoalbuminemia. Wound formation, vomiting, and diarrhea were mainly observed within the first 7 to 10 days after treatment. Injection site pain and lameness in the treated leg were mainly observed within the first 2 days after treatment. Hypoalbuminemia was mainly observed within the first 28 days after treatment. All dogs received concomitant medications as noted in the Effectiveness section. The adverse reactions during the study are summarized in Table 2 below.

Table 2: Adverse Reactions During the Field Study

Adverse Reaction	STELFONTA 1st Treatment (n = 117)	STELFONTA 2nd Treatment (n = 18)	UNTREATED CONTROL (n = 42)
Wound formation	110 (94.0%)	12 (66.7%)	3 (7.1%)
Injection site pain	61 (52.1%)	7 (38.9%)	1 (2.4%)
Lameness in treated limb	29 (24.8%)	2 (11.1%)	1 (2.4%)
Vomiting	24 (20.5%)	3 (16.7%)	4 (9.5%)
Diarrhea	24 (20.5%)	3 (16.7%)	2 (4.8%)
Hypoalbuminemia[a]	21 (18.0%)	2 (11.1%)	1 (2.4%)
Injection site bruising/ erythema/edema/ irritation	20 (17.1%)	3 (16.7%)	1 (2.4%)
Anorexia	14 (12.0%)	2 (11.1%)	3 (7.1%)
Regional lymph node swelling/enlargement	13 (11.1%)	1 (5.6%)	1 (2.4%)
Tachycardia	12 (10.3%)	0 (0.0%)	1 (2.4%)
Weight loss	12 (10.3%)	3 (16.7%)	5 (11.9%)
Cystitis	10 (8.6%)	1 (5.6%)	2 (4.8%)
Dermatitis	9 (7.7%)	1 (5.6%)	1 (2.4%)
Personality/behavior change	8 (6.8%)	0 (0.0%)	2 (4.8%)
Infection at injection site	8 (6.8%)	0 (0.0%)	0 (0.0%)
Tachypnea	7 (6.0%)	2 (11.1%)	1 (2.4%)
Pruritus	6 (5.1%)	3 (16.7%)	2 (4.8%)
Lethargy/Depression	6 (5.1%)	1 (5.6%)	1 (2.4%)
Pyrexia	3 (2.6%)	2 (11.1%)	0 (0.0%)

[a] There was a statistically significant decrease in albumin and albumin/globulin ratios at Day 7 in the STELFONTA group compared to the control group. The hypoalbuminemia ranged from 2.0 to 2.6 g/dL (reference range 2.7-3.9 g/dL).

Note: If an animal experienced the same adverse reaction more than once, only the highest grade was tabulated.

Adverse reactions were graded using the Veterinary Co-operative Oncology Group – Common Terminology Criteria for Adverse Events (VCOG-CTCAE).[1] Most adverse reactions were Grade 1 (mild) or 2 (moderate). Grade 3 (severe) and 4 (life-threatening) adverse reactions in dogs treated with STELFONTA included: lameness in the treated limb (6 dogs), injection site pain (4 dogs), wound formation (3 dogs), lethargy/depression (3 dogs), anorexia (2 dogs), infection at injection site (1 dog), pruritis (1 dog), and tachycardia (1 dog).

Adverse reactions associated with use of the required concomitant corticosteroids were similarly reported in STELFONTA and untreated control dogs and included elevated alkaline phosphatase, polyuria, and polydipsia.

Wound Formation

Tumor observations were conducted at 2, 4, 8, and 24 hours and 4 days after treatment. The 81 dogs treated with STELFONTA on Day 0 were reported most frequently with swelling, bruising, pain and heat at all tumor observation timepoints. The following were reported at 24 hours post treatment:

- Swelling: 97.5% (79/81 dogs)
- Bruising: 91.4% (74/81 dogs)
- Pain: 69.1% (56/81 dogs)
- Heat: 53.1% (43/81 dogs)

At 24 hours post treatment, intact skin was reported in 71.6% (58/81 dogs) of STELFONTA® (tigilanol tiglate injection) treated dogs. On Day 4 intact skin was reported in 17.3% (14/81 dogs) of STELFONTA treated dogs. On Day 4, the following observations were reported with the highest frequency:

- Necrosis: 55.6% (45/81 dogs)
- Crater pockets: 37.0% (30/81 dogs)
- Exudate: 37.0% (30/81 dogs)
- Eschar: 28.4% (23/81 dogs)
- Ulceration: 11.1% (9/81 dogs)

A wound healing assessment was performed on the effectiveness dataset which included 80 dogs in the STELFONTA group and 38 dogs in the untreated control group. Wounds developed in 92.5% (74/80) of STELFONTA treated dogs and 2.6% (1/38) of untreated control dogs by Day 7. On Day 28, the presence of wounds was 40% (32/80) in the STELFONTA group and 2.6% (1/38) in the

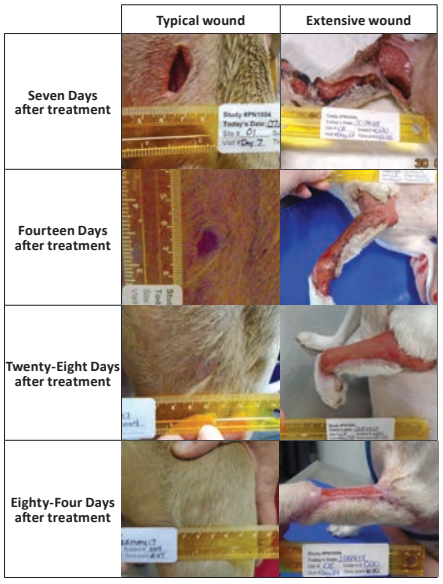
untreated control group. On Day 42 and Day 84, the presence of wounds was 27.1% (16/59) and 1.8% (1/57), respectively, in the STELFONTA group.

Exudate from the treated site including serous, serosanguinous, sanguineous, seropurulent, and purulent discharges were seen mainly on Day 7 and to a lesser extent on Day 14. Sloughing of the treated site was observed from Day 7 to Day 42, with decreasing frequency after Day 7. Peripheral pitting or non-pitting edema and erythema of the surrounding area were observed from Day 7 to Day 28, with decreasing intensity and frequency after Day 7. Necrotic eschar and epithelialization of the treated site was observed from Day 7 to Day 84, with decreasing frequency after Day 14. Granulation or hyper-granulation of the treated site was observed from Day 7 to Day 84, with decreasing frequency after Day 14.

The average wound size at Day 7 for a STELFONTA treated dog was 3.3 cm x 2.4 cm (original average tumor size 1.9 x 1.6 x 0.9 cm). On Day 28, the average wound size was 2.0 x 1.4 cm.

The largest total wound for a STELFONTA treated dog was reported seven days after treatment. The treated tumor was located on the left caudal stifle and the original tumor size measured 2.4 x 2.1 x 1.4 cm. The wound area initially consisted of three individual wounds recorded on the treated limb (both medial and lateral sides): 7.5 x 4.5 cm, 7.0 x 3.5 cm, and 11.5 x 7.0 cm. The wounds had reduced to 3.5 x 1.4 cm, 3.9 x 1.5 cm, and 9.7 x 4.3 cm 28 days after treatment, and 0.5 x 0.7 cm and 2.5 x 2.9 cm 42 days after treatment and were no longer present at 84 days after treatment.

One dog treated with STELFONTA was reported with an extensive wound formation (wound size 25.0 x 9.5 cm) with severe tissue slough (Grade 3) nine days after treatment of a mast cell tumor on the left metacarpal area (original tumor size 2.5 x 1.9 x 1.3 cm). The wound extended proximally up the leg to the shoulder and required bandaging of the leg and antibiotics. Scar contracture formed, requiring treatment under sedation to release the scar tissue. Clinical pathology abnormalities included elevated band neutrophils, anemia, and hypoalbuminemia. The wound had not fully healed by the end of the study 89 days after treatment. See pictures below comparing progression of this extensive wound formation versus commonly observed wound progression.



One dog treated with STELFONTA was reported with a bacterial infection and cellulitis in the right rear leg 9 days after treatment of a mast cell tumor on the right rear paw. There was bruising of the upper thigh and necrotic skin on the caudal right thigh and cranial aspect of the hock. Bloody discharge under the necrotic tissue revealed rod bacteria and toxic neutrophils. The dog was treated with intravenous fluids and antibiotics.

Systemic Mast Cell Degranulation and Death

Two dogs from two separate pilot studies died from a suspected mast cell degranulation reaction. Both dogs were treated with STELFONTA for a subcutaneous mast cell tumor located above the hock and did not receive the concomitant medications as prescribed.

In a pilot field study, one dog with a large (10 cm^3) subcutaneous mast cell tumor on the right hip was treated with STELFONTA. The dog had a partial Response Evaluation Criteria in Solid Tumors Guideline (RECIST)[2] response to the initial STELFONTA injection and was re-treated with STELFONTA, 30 days following the initial injection. The patient did not receive any of the recommended concomitant medications of prednisolone, chlorpheniramine and famotidine from 24 hours after the second STELFONTA injection. On Day 2 following the second STELFONTA injection, the dog became anorexic, painful, and lethargic and had marked swelling of the right hind limb extending to the chest with hemorrhagic, ruptured blisters near the hock joint. Blood work showed anemia, hypoproteinemia, liver enzyme elevations, and white blood cell changes (leukocytosis, neutrophilia, monocytosis, and thrombocytopenia). The dog was hospitalized, received a blood transfusion, and was administered intravenous fluids, prednisolone, chlorpheniramine and tramadol. Pitting edema progressed to the neck by four days following treatment. Despite supportive care, the dog died five days following treatment likely due to degranulation of the mast cell tumor and internal necrotic discharge of the tumor.

In a separate pilot field study, one dog with a moderate (2.53 cm^3) subcutaneous mast cell tumor on the left caudal hindlimb was treated with STELFONTA. The dog was treated with chlorpheniramine and meloxicam on treatment day (Day 0) and Day 1 only. The dog did not receive further concomitant medication. On Day 3 the dog was lethargic and there was significant edema at the injection site. While intravenous fluid and antibiotic therapy was initiated on Day 3, the dog rapidly deteriorated and died on the following day likely due to degranulation of the mast cell tumor. Pathology findings included widespread cellulitis, panniculitis (likely of bacterial origin), and septic peritonitis.

To report suspected adverse reactions, to obtain a Safety Data Sheet (SDS), or for technical assistance, call 800-338-3659. For additional information about adverse drug experience reporting for animal drugs, contact the FDA at 1-888-FDA-VETS or www.fda.gov/reportanimalae.

INFORMATION FOR DOG OWNERS

Owners should be given the Client Information Sheet to read before STELFONTA is administered and should be advised to observe their dog for potential side effects, including signs of degranulation and excessive wound formation, as described in the sheet. Advise dog owners about possible adverse reactions, when to contact a veterinarian, and how to care for the treated tumor site.

Some discharge from the site following treatment is expected. The site can be cleaned with warm water as necessary. Advise owners to wear disposable gloves when cleaning the area.

CLINICAL PHARMACOLOGY

Mechanism of Action

In non-clinical pharmacology studies, tigilanol tiglate has been shown to have three inter-related effects that are responsible for its anti-tumor effectiveness. The first effect is to cause oncolysis of tumor cells that are in direct contact with tigilanol tiglate. The oncolysis occurs within the first hours following treatment and results from the disruption of mitochondrial functioning. Secondly, at the same time, tigilanol tiglate activates a protein kinase C (PKC) signaling cascade which propagates throughout the tumor, resulting in an acute inflammatory response with swelling and erythema extending to the tumor margins and immediate surroundings. This inflammatory response is normal and necessarily contributes to the activity of tigilanol tiglate by (a) restricting blood and oxygen supply to the tumor (causing localized hypoxia) and (b) recruiting and activating innate immune cells (principally neutrophils and macrophages), which then target the tumor and release reactive oxygen species, proteases, and cytokines that function in an antimicrobial role. This acute inflammatory response generally resolves within 48 to 96 hours. The third component of the antitumor activity of tigilanol tiglate is associated with direct effects of the drug in increased permeability of the tumor vasculature (via activation of the Beta-II isoform of PKC) leading to tumor vascular destruction. The resulting outcome is tumor destruction with a deficit or wound remaining where the tumor was located. Complete healing of the resulting wound following tumor destruction by STELFONTA is typically within 6 weeks.

Pharmacokinetics

Pharmacokinetic properties of STELFONTA were evaluated in a pilot study monitoring systemic levels following intratumoral injection, with a dose delivered according to the size of the mast cell tumor. A dose of 0.5 mg/cm^3 (0.5 mL/cm^3) was used in dogs with tumor volumes ranging from 0.1 to 6.8 cm^3 resulting in doses ranging from 0.002 mg/kg to 0.145 mg/kg and total doses ranging from 0.05 mg to 3.4 mg per dog. A total of 6 cutaneous and 5 subcutaneous mast cell tumors were treated in 10 dogs (one dog had two tumors treated consecutively). The following range of pharmacokinetic parameters were determined for STELFONTA in plasma: 1) elimination half-life ($t_{1/2}$): 2.85 to 36.87 hours; 2) maximum plasma concentration (C_{max}): 0.356 ng/mL to 13.8 ng/mL; and 3) area under the plasma concentration time-curve to the last quantifiable plasma concentration (AUC_{last}): 2.25 h*ng/mL to 31.24 h*ng/mL. There was no relationship between drug exposure (C_{max} and AUC_{last}) with tumor location (cutaneous or subcutaneous) or with total dose. In an evaluation of the pharmacokinetic data from the 5 dogs with cutaneous tumors, dose levels ranged from 0.002 mg/kg to 0.145 mg/kg. The highest C_{max} was 11.1 ng/mL and the highest AUC_{last} was 31.24 h*ng/mL at a dose of 0.125 mg/kg. For the other 5 dogs with subcutaneous tumors, doses ranged from 0.049 mg/kg to 0.094 mg/kg. The highest Cmax was 13.8 ng/mL and the highest AUC_{last} was 30.81 h*ng/mL at a dose of 0.094 mg/kg.

EFFECTIVENESS

The effectiveness of STELFONTA was evaluated in a well-controlled, multi-center, randomized, double-masked, field study in client-owned dogs. Enrolled dogs had non-metastatic World Health Organization stages Ia (one tumor confined to the dermis, without regional lymph node involvement) and IIIa (multiple dermal tumors; large infiltrating tumors without regional lymph node involvement) mast cell tumors that were (i) cutaneous, or (ii) subcutaneous and located at or distal to the elbow or the hock). A total of 123 client-owned dogs with a mast cell tumor measuring less than or equal to 10 cm^3 were randomized to treatment with a single injection of STELFONTA (n=81) or untreated control (n=42). On the day of treatment, the average tumor volume was 1.7 cm^3 (range 0.1 to 9.8 cm^3).

A total of 118 dogs were included in the effectiveness analysis; 80 dogs were in the STELFONTA group and 38 dogs were in the untreated control group. Response to treatment was evaluated using the RECIST[2], where complete response (CR) is resolution of the target tumor, partial response (PR) is at least a 30% decrease in the longest diameter of target tumor, stable disease (SD) is a decrease of less than 30% or increase of less than 20% of the longest diameter of the target tumor, and progressive disease (PD) is greater than a 20% increase in the longest diameter of the target tumor.

The primary effectiveness variable compared CR rates of the target tumor between groups 28 days after treatment. At 28 days after treatment, a statistically significantly greater proportion of dogs in the STELFONTA treated group (60/80; 75%) achieved CR compared to dogs in the untreated control group (2/38; 5.3%) (p<0.0001). An objective tumor response (CR + PR) was observed in 64/80 (80%) of the STELFONTA treated dogs. Of the 60 dogs in the STELFONTA group that experienced CR at Day 28, response assessment was conducted for 59 dogs at Day 42 and for 57 dogs at Day 84. At Day 42, 59/59 (100%) were disease-free at the injection site, and at Day 84, 55/57 (96%) were disease-free at the injection site.

For all dogs, corticosteroids (prednisone or prednisolone) were initiated 2 days prior to treatment at a dose of 0.5 mg/kg orally twice daily and continued for 7 days total (2 days before, on the day of treatment and 4 days after treatment), then 0.5 mg/kg once daily for an additional 3 days. An H1 receptor blocking agent (diphenhydramine [2 mg/kg orally twice daily]) and H2 receptor blocking agent (famotidine [0.5 mg/kg orally twice daily]) were initiated on the day of treatment and continued for 7 days.

Other medications prescribed based on veterinary discretion included antibiotics, analgesics, and sedatives. The majority of antibiotics were used to treat injection site infections. The majority of analgesics were used to treat tumor pain and were mainly initiated on the day of or day after treatment. Sedatives were used for treatment administration, conducting diagnostics, anxiety, and temperament issues.

Quality of Life (QoL)[3] was assessed by owners throughout the study and the mean scores for the QoL assessment was similar between the STELFONTA and untreated control groups at all time points.

Eighteen of the 20 STELFONTA treated dogs without CR received a second treatment. Twenty-eight days following the second treatment, CR was observed in 8/18 (44.4%) of these dogs. Forty-two days following the second treatment, CR was observed in 7/18 (38.9%) of treated dogs.

TARGET ANIMAL SAFETY

The margin of safety and toxicity of STELFONTA was evaluated in one laboratory safety study and one laboratory cardiovascular study utilizing final market formulation, and one pilot field study that used non-commercial formulation.

Laboratory Safety Study

In a 4-week laboratory safety study, 48 healthy Beagle dogs 6 to 8 months old were administered STELFONTA intravenously over a 15-minute infusion once a week for four weeks on Days 1, 8, 15, and 22, at doses of 0, 0.025, 0.05, or 0.075 mg/kg body weight (ranges between 0.02-0.036, 0.039-0.056, and 0.06-0.08 mg/kg, respectively due to dosing variability). Control dogs (0 mg/kg) received a vehicle control at a volume equal to the 0.075 mg/kg dose. The intravenous route was chosen for this study because subcutaneous injection was too toxic and intratumoral administration was not possible.

There were twelve dogs per group (6 male, 6 female). Four dogs/sex/group were necropsied two days following the last dose and two dogs/sex/group were necropsied following a 2-week recovery period.

All dogs survived the study, and there were no STELFONTA-related effects on body weight, body temperature, ophthalmic exam, electrocardiographic parameters, and organ weights.

The following were observed only in dogs in the groups administered STELFONTA: decreased food consumption from Days 22-29, vomiting/retching during infusion or immediately post-infusion, wound formation at the infusion site after the second or third dose, decrease in activity sporadically throughout the study, and elevations in alanine aminotransferase on Day 23.

The following were observed in all groups, including vehicle control and increased in a dose dependent manner: limited use of the leg that received the infusion occurred soon after dosing, weakness after the first dose, salivation and infusion site edema and erythema increased in frequency and severity throughout the study, and tremors occurred immediately post-infusion and increased in severity with dose.

Vomiting, retching, or tremors were typically transient and resolved within 1 hour of dosing while salivation also typically resolved within 4 hours.

Loose feces were observed in all groups in a non-dose dependent manner. Polydipsia occurred in the control, 0.05 and 0.075 mg/kg groups. Trending towards decreasing hematocrit (but still within reference intervals) was observed in all groups. One dog in the 0.05 mg/kg group was mildly anemic during recovery. Monocytosis and elevated fibrinogen were seen on Days 2 and 23 in a dose-dependent manner.

Gross pathology findings at the infusion site included inflammation, redness, and thickening of the skin. Correlative histopathology findings of the infusion site included hemorrhage, edema, inflammation, mixed cell infiltration, fibrosis, and chronic organizing thrombosis. Only one of the recovery dogs had changes at the infusion site consisting of proliferation of the intima. One dog in the 0.075 mg/kg group had a severe wound, confirmed on histopathology as ulcerative inflammation and severe necrosis with bacteria present. Gross pathology findings also included red, mottled, firm, and enlarged lymph nodes in all dose groups, including recovery dogs, confirmed on histopathology as inflammation, lymphoid hypercellularity, hemorrhage, and sinus histiocytosis. Pituitary cysts were observed in 7 dogs in all STELFONTA treated groups. One dog each from the 0.075 mg/kg group was observed to have kidney tubular vacuolation, dilation of the ventricles of the brain, and chronic inflammation of both the left thigh skeletal muscle and left sciatic nerve.

Laboratory Cardiovascular Study

In a 12-day laboratory cardiovascular study, 4 healthy male conscious telemeterized Beagle dogs approximately 2-4 years old were administered STELFONTA as a single intravenous infusion. Treatment consisted of four groups: vehicle control and STELFONTA at doses of 0.01, 0.025 and 0.075 mg/kg body weight. All four dogs received all treatments with at least a 3-day wash-out period.

All dogs survived the study and there were no STELFONTA-related effects on body temperatures, blood pressure, or electrocardiograms. The following were observed only after administration of STELFONTA in all dose groups: salivation, vocalization, incoordination, tremors, red feces, and decreased feces output. Retching, vomiting, incoordination, and changes in activity levels (increased and decreased) occurred in the 0.075 mg/kg group only. Tachycardia was seen for the first 2.5 hours after the 0.075 mg/kg dose only. The following were observed after administration of control or STELFONTA: excessive panting, decreased appetite, and limited usage/swelling of leg or paw. All dogs lost weight during the study. Clinical signs resolved around 4 hours post dosing.

Pilot Field Study

In a 28-day unmasked field study, 10 client-owned dogs, 6-14 years old were administered tigilanol tiglate (non-commercial formulation) once as an intratumoral injection at a dose of 0.5 mg tigilanol tiglate per cubic centimeter (cm^3) of tumor volume, not exceeding 0.25 mg/kg body weight (maximum dose of 5 mg). One dog was enrolled a second time to treat a second mast cell tumor after successful treatment of the first tumor. See pharmacokinetic results from this study under **Clinical Pharmacology**.

The most common observations after tigilanol tiglate administration were injection site reactions including necrosis, swelling (localized edema and edema extending well beyond the tumor injection site), pain, restlessness, inflammation, erythema, bleeding ulcerations, bruising/discoloration, sloughing of tissue, open wound, mild drainage, malodor, and presence of granulation tissue. Three dogs experienced dermatitis with or without skin necrosis in a region nearby but distinct from the tumor injection site. One dog experienced non-weight bearing lameness, muscle atrophy and enlarged popliteal lymph node. One dog vomited after administration. Three dogs required longer healing times beyond 28 days, with the longest requiring 5 months. Hypoalbuminemia was observed in 5 dogs with hypoproteinemia observed in 1 of these 5 dogs on Day 7 and was resolved by Day 28.

STORAGE INFORMATION

Store STELFONTA vials refrigerated at 2°C to 8°C (35°F to 46°F).

Do not freeze.

Keep the vial in the carton at all times to protect the vial from light.

For single use only.

Dispose of any unused product in accordance with disposal for routine medical waste.

HOW SUPPLIED

STELFONTA is supplied as a sterile, colorless liquid in a 5 mL clear, single-use glass vial containing 2 mL of STELFONTA at a concentration of 1 mg/mL tigilanol tiglate in sterile water for injection.

REFERENCES

1. Veterinary Cooperative Oncology Group – common terminology criteria for adverse events (VCOG-CTCAE) following chemotherapy or biologic antineoplastic therapy in dogs and cats v1.1. *Vet Compar Oncol.* 20 Jul 2011.
2. Eisenhauer EA, Therase P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1), *Eur J Cancer.* 2009; 45(2):228-247.
3. Lynch S, Savary-Bataille K, Leeuw B, Argyle DJ. Development of a questionnaire assessing health-related quality-of-life in dogs and cats with cancer. *Vet Compar Oncol.* 2011; 9 (3):172-82.

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Brucella canis in Dogs from South Dakota Reservations

Radford G. Davis, DVM, MPH, DACVPM
Iowa State University

In the literature

Daly R, Willis KC, Wood J, et al. Seroprevalence of *Brucella canis* in dogs rescued from South Dakota Indian reservations, 2015-2019. *Prev Vet Med*. 2020;184:105157.

FROM THE PAGE ...

Brucella canis is a long-recognized cause of abortion, reproductive failure, and many other health disorders in dogs, including epididymitis, orchitis, prostatitis, diskospondylitis, osteomyelitis, and meningoencephalitis.[1,2] Zoonotic transmission can occur through contact with the reproductive fluids, blood, urine, feces, saliva, and nasal secretions of infected dogs.[1,2] Treatment failure and relapse are common in dogs, and euthanasia is frequently chosen. This disease carries significant emotional and economic hardships for dog owners and breeders, and management can be challenging for clinicians, shelters, and public health officials. The full impact of *B canis* on human health and the true prevalence in dogs remain unknown.[1,2]

This study examined the seroprevalence of *B canis* in stray and owner-surrendered dogs on 2 reservations and surrounding areas in South Dakota from 2015 to 2019.[1] Rescue groups operate in and around these reservations, where stray dogs are common. Investigators aimed to characterize the seroprevalence of infection among dogs from these reservations and adjacent areas after an adopted dog was discovered to be seropositive for *B canis*, as this could have a negative impact on future rescue operations.

In the first year of the study, dogs were tested via indirect immunofluorescence assay; positive results were confirmed with agarose gel immunodiffusion. In subsequent years, testing was done using the rapid slide agglutination test, followed by the 2-mercaptoethanol test in cases with initial positive results. There was no significant difference in seropositivity rates between the testing methods. The overall apparent seroprevalence was 6.8% of 3,898 dogs tested, with an estimated true prevalence in the population of 29.4%. Higher seropositivity rates were noted in intact and older dogs (especially those >2 years of age). No sex predisposition was noted. Dogs originating from one reservation were much more likely to be positive than those from the other reservation or surrounding areas; the reason for this is unknown.

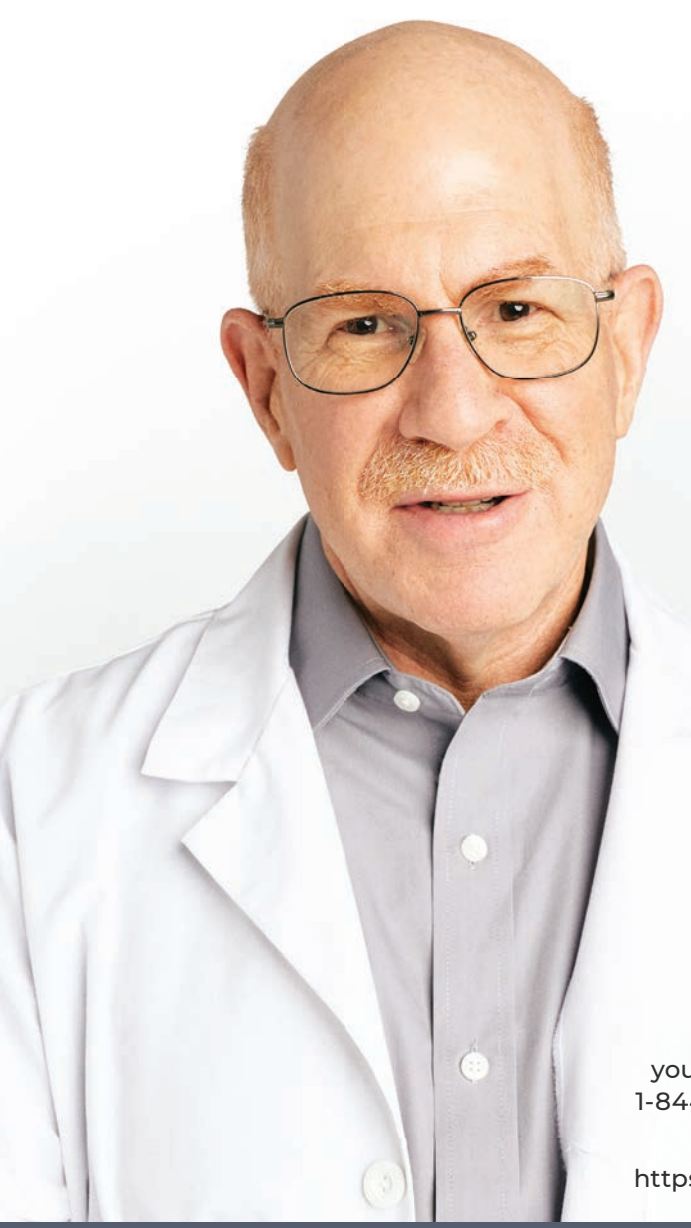
... TO YOUR PATIENTS

Key pearls to put into practice:

1. The true prevalence of *B canis* among dogs is unknown and varies by geographic region, individual, age, and reproductive status.[1,2]
2. Infection is transmitted between dogs venereally or through oral contact with reproductive fluids and tissues.[1]
3. Infection is likely to be higher among stray dogs than owned dogs or those surrendered to a shelter.[1]

References

1. Daly R, Willis KC, Wood J, et al. Seroprevalence of *Brucella canis* in dogs rescued from South Dakota Indian reservations, 2015-2019. *Prev Vet Med.* 2020;184:105157.
2. Hensel ME, Negron M, Arenas-Gamboa AM. Brucellosis in dogs and public health risk. *Emerg Infect Dis.* 2018;24(8):1401-1406.



STELFONTA®
(tigilanol tiglate injection)
1 mg/mL

SEEING IS BELIEVING

"Mast cell tumor removal in a single treatment?

Sounded crazy to me, then I tried it."

Dr Samuel Geller,
Veterinarian

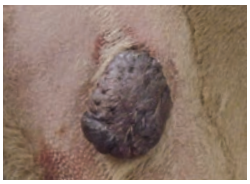
To place an order, contact your Virbac representative, or call 1-844-4-VIRBAC (1-844-484-7222).

To learn more, visit https://vet-us.virbac.com/stelfonta.

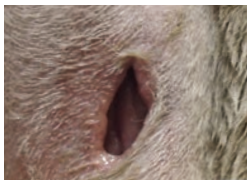
SCAN ME

STELFONTA® (tigilanol tiglate injection)

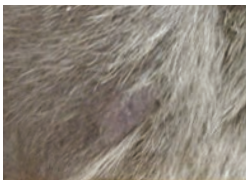
4 HOURS



7 DAYS



6 WEEKS



Hours: visible changes

Days: tumor destruction

Weeks: tumor site typically healed

IMPORTANT SAFETY INFORMATION

Accidental self-injection of STELFONTA® (tigilanol tiglate injection) may cause severe wound formation. To decrease the risk of accidental self-injection, sedation of the dog may be necessary. In dogs, do not inject STELFONTA into subcutaneous mast cell tumors located above the elbow or hock. Formation of wounds, possibly extensive, is an intended and likely response to treatment with STELFONTA along with associated swelling, bruising and pain; these wounds are expected to heal. Appropriate pre- and post-treatment medications must be given, including a corticosteroid plus blocking agents for both H1 and H2 receptors, in order to decrease the potential for severe systemic adverse reactions, including death, from mast cell degranulation. For full prescribing information, contact VIRBAC at 1-800-338-3659 or visit https://vet-us.virbac.com/stelfonta.

Please see full prescribing information on pages 34-35.

Virbac Shaping the future of animal health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IT'S FOR LIFE

With the introduction of BRAVECTO® 1-MONTH Chews, BRAVECTO will now be able to protect dogs across all life stages.

BRAVECTO 1-MONTH CHEWS

EXTENDED-DURATION BRAVECTO® CHEWS

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Once puppies reach **6 months of age, they can transition** to extended-duration BRAVECTO Chews.

BRAVECTO® (fluralaner) Chews

To learn more, contact your Merck Animal Health sales representative.

IMPORTANT SAFETY INFORMATION:

BRAVECTO 1-MONTH Chews are for dogs 8 weeks of age and older. Side effects may include itching, diarrhea, vomiting, decreased appetite, elevated ALT, lethargy, and weight loss. Fluralaner 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. **BRAVECTO 1-MONTH Chews** are not effective against A. americanum in puppies less than 6 months of age. **BRAVECTO Chews for Dogs:** The most commonly reported adverse reactions include vomiting, decreased appetite, diarrhea, lethargy, polydipsia, and flatulence. **BRAVECTO Chews** have not been shown to be effective for 12-weeks' duration in puppies less than 6 months of age. **BRAVECTO Chews** are not effective against lone star ticks beyond 8 weeks of dosing. Fluralaner 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. For complete product information, refer to the product insert on page 40.

Approved by FDA under NADA # 141-532

BRAVECTO® 1-MONTH

(fluralaner) Chews for Dogs

BRIEF SUMMARY (For full Prescribing Information, see package insert)

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

Indications:
Bravecto 1-Month 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), *Dermacentor variabilis* (American dog tick) and *Rhipicephalus sanguineus* (brown dog tick)] for one month in dogs and puppies 8 weeks of age and older, and weighing 4.4 pounds or greater.

Bravecto 1-Month is also indicated for the treatment and control of *Amblyomma americanum* (lone star tick) infestations for one month in dogs and puppies 6 months of age and older, and weighing 4.4 pounds or greater.

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

WARNINGS
Human Warnings:
Not for human use. Keep this and all drugs out of the reach of children. 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. Wash hands thoroughly with soap and water immediately after use of the product.

Keep Bravecto 1-Month in a secure location out of reach of dogs, cats, and other animals to prevent accidental ingestion or overdose.

Precautions:
Fluralaner 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.

Bravecto 1-Month is not effective against *A. americanum* in puppies less than 6 months of age.

The safety of Bravecto 1-Month has not been evaluated in breeding, pregnant and lactating dogs.

Adverse Reactions:
In a well-controlled U.S. field study, which included 271 dogs (201 dogs were administered Bravecto 1-Month every 30 days and 70 dogs were administered an oral active control [an isoxazoline] every 30 days), there were no serious adverse reactions associated with treatment. Over the 90-day study period, all observations of potential adverse reactions were recorded.

Dogs with Adverse Reactions in the Field Study

Adverse Reaction (AR)	Fluralaner Group: Percentage of Dogs with the AR during the 90-Day Study (n= 201 dogs)	Active Control Group: Percentage of Dogs with the AR during the 90-Day Study (n= 70 dogs)
Pruritus	7.0%	10.0%
Diarrhea	3.0%	4.3%
Vomiting	3.0%	4.3%
Decreased Appetite	3.0%	0.0%
Liver enzymes (serum ALT or ALP) greater than twice the upper reference range*	1.0%	1.4%
Lethargy	1.0%	1.4%
Weight loss (>15%)	0.5%	0.0%

*Alanine aminotransferase (ALT); alkaline phosphatase (ALP)

One dog in the Bravecto 1-Month group with a history of seizures managed with anticonvulsant medication had seizure activity 28 days after its first dose; the dog received its second dose later the same day. No additional seizures occurred during the study. One dog in the control group with no history of seizures had seizure activity 12 days after its second dose. The dog was started on anticonvulsant medication and no additional seizures occurred during the study.

During the palatability assessment, four dogs coughed within 1 hour of dosing with Bravecto 1-Month. Palatability was not assessed in the control group.

In well-controlled laboratory effectiveness studies, one dog and three puppies administered Bravecto 1-Month had diarrhea (with or without blood).

Post Approval Experience (2019):
The following adverse events are based on post-approval adverse drug experience reporting for fluralaner. 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: Vomiting, lethargy, diarrhea (with or without blood), anorexia, pruritus, polydipsia, seizure, allergic reactions (including hives, swelling, erythema), dermatitis (including crusts, pustules, rash), tremors and ataxia.

Contact Information:
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.

How Supplied:
Bravecto 1-Month is available in five strengths (45, 100, 200, 400, and 560 mg fluralaner per chew). Each chew is packaged individually into aluminum foil blister packs sealed with a peelable paper backed foil lid stock. Product may be packaged in 1, 3, or 4 chews per package.

Rev: 03/20

Approved by FDA under NADA # 141-426

BRAVECTO®

(fluralaner) flavored chew for dogs

BRIEF SUMMARY (For full Prescribing Information, see package insert)

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

Indications:
Bravecto 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), *Dermacentor variabilis* (American dog tick), and *Rhipicephalus sanguineus* (brown dog tick)] for 12 weeks in dogs and puppies 6 months of age and older, and weighing 4.4 pounds or greater.

Bravecto is also indicated for the treatment and control of *Amblyomma americanum* (lone star tick) infestations for 8 weeks in dogs and puppies 6 months of age and older, and weighing 4.4 pounds or greater.

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. 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. Wash hands thoroughly with soap and water immediately after use of the product.

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

Precautions:
Fluralaner 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.

Bravecto has not been shown to be effective for 12-weeks duration in puppies less than 6 months of age. Bravecto is not effective against *Amblyomma americanum* ticks beyond 8 weeks after dosing.

Adverse Reactions:
In a well-controlled U.S. field study, which included 294 dogs (224 dogs were administered Bravecto every 12 weeks and 70 dogs were administered an oral active control every 4 weeks and were provided with a tick collar); there were no serious adverse reactions. All potential adverse reactions were recorded in dogs treated with Bravecto over a 182-day period and in dogs treated with the active control over an 84-day period. The most frequently reported adverse reaction in dogs in the Bravecto and active control groups was vomiting.

Percentage of Dogs with Adverse Reactions in the Field Study

Adverse Reaction (AR)	**Bravecto Group: Percent of Dogs with the AR During the 182-Day Study (n=224 dogs)**	**Active Control Group: Percent of Dogs with the AR During the 84-Day Study (n=70 dogs)**
Vomiting	7.1	14.3
Decreased Appetite	6.7	0.0
Diarrhea	4.9	2.9
Lethargy	5.4	7.1
Polydipsia	1.8	4.3
Flatulence	1.3	0.0

In a well-controlled laboratory dose confirmation study, one dog developed edema and hyperemia of the upper lips within one hour of receiving Bravecto. The edema improved progressively through the day and had resolved without medical intervention by the next morning.

Post-Approval Experience (2019):
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 fluralaner: Vomiting, lethargy, diarrhea (with and without blood), anorexia, pruritis, polydipsia, seizure, allergic reactions (including hives, swelling, erythema), dermatitis (including crusts, pustules, rash), tremors and ataxia.

Contact Information:
For a copy of the Safety Data Sheet (SDS) or to report suspected adverse drug events, 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 http://www.fda.gov/AnimalVeterinary/SafetyHealth.

How Supplied:
Bravecto is available in five strengths for use in dogs (112.5, 250, 500, 1000, and 1400 mg fluralaner per chew). Each chew is packaged individually into aluminum foil blister packs sealed with a peelable paper backed foil lid stock. Product may be packaged in 1, 2, or 4 chews per package.

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Formulated in Austria

Rev. 04/19
356271 R3

Use of Hydrolyzed Diets in Cats with Enteropathy

Jennifer Larsen, DVM, PhD, DACVN
University of California, Davis

In the literature

Kathrani A, Church DB, Brodbelt DC, Pegram C, O'Neil DG. The use of hydrolysed diets for vomiting and/or diarrhoea in cats in primary veterinary practice. *J Small Anim Pract*. 2020;61(12):723-731.

FROM THE PAGE ...

Although vomiting and diarrhea are frequently seen in cats, the cause is often unknown. Laboratory and fecal testing, imaging, and biopsies are recommended for definitive diagnosis.[1] However, diet, antimicrobials, and/or glucocorticoids are used in many cases without a full diagnostic profile first being pursued. The outcomes in cats treated with ≥1 of these empiric therapies have not been previously reported.

This study sought to describe responses of cats with chronic vomiting and/or diarrhea of unknown etiology that were given a hydrolyzed diet with or without a concurrent antibiotic and/or glucocorticoid. Medical records of cats (n = 977) meeting the inclusion criteria were evaluated. Poor response was defined as needing antibiotics and/or glucocorticoids for vomiting and/or diarrhea at a subsequent visit after the diet was started or death associated with clinical signs within 6 months of follow-up.

Of the 977 cats, most (n = 697) were first prescribed a hydrolyzed diet only, and a small percentage of these (34%) had a poor response. Of cats initially prescribed both diet and antibiotics (n = 127), 56% had a poor response. Of cats initially prescribed both diet and glucocorticoids with or without antibiotics (n = 153), 65% had a poor response. Cats concurrently treated with either antibiotics or glucocorticoids plus diet and those given one or both (ie, antibiotics, glucocorticoids) before diet was tried had significantly increased odds of a poor response. Cats 6 years of age or older also had increased odds of having a poor response; however, other characteristics (eg, sex, neuter status, breed) were not significant.

Regardless of treatment, 42% of cats with suspected chronic inflammatory enteropathy had poor response. Due to the retrospective and uncontrolled nature of this study, it was not possible to determine efficacy of hydrolyzed diets in feline enteropathy. In addition, it is unknown if disease chronicity, severity, or exact pathophysiology (especially neoplasia[2,3]) could explain the higher proportion of poor response in cats prescribed nondietary therapies.

... TO YOUR PATIENTS

Key pearls to put into practice:

1. There are many potential underlying causes of vomiting and diarrhea in cats; comprehensive diagnostic testing is recommended to enable targeted therapy.
2. Efficacy of antibiotic therapy in GI disease is unknown. These drugs should be used cautiously due to concerns regarding intestinal dysbiosis and antibiotic resistance.[4]
3. Hydrolyzed diet as an initial sole therapy may be a rational approach for treatment of suspected inflammatory enteropathy in cats.

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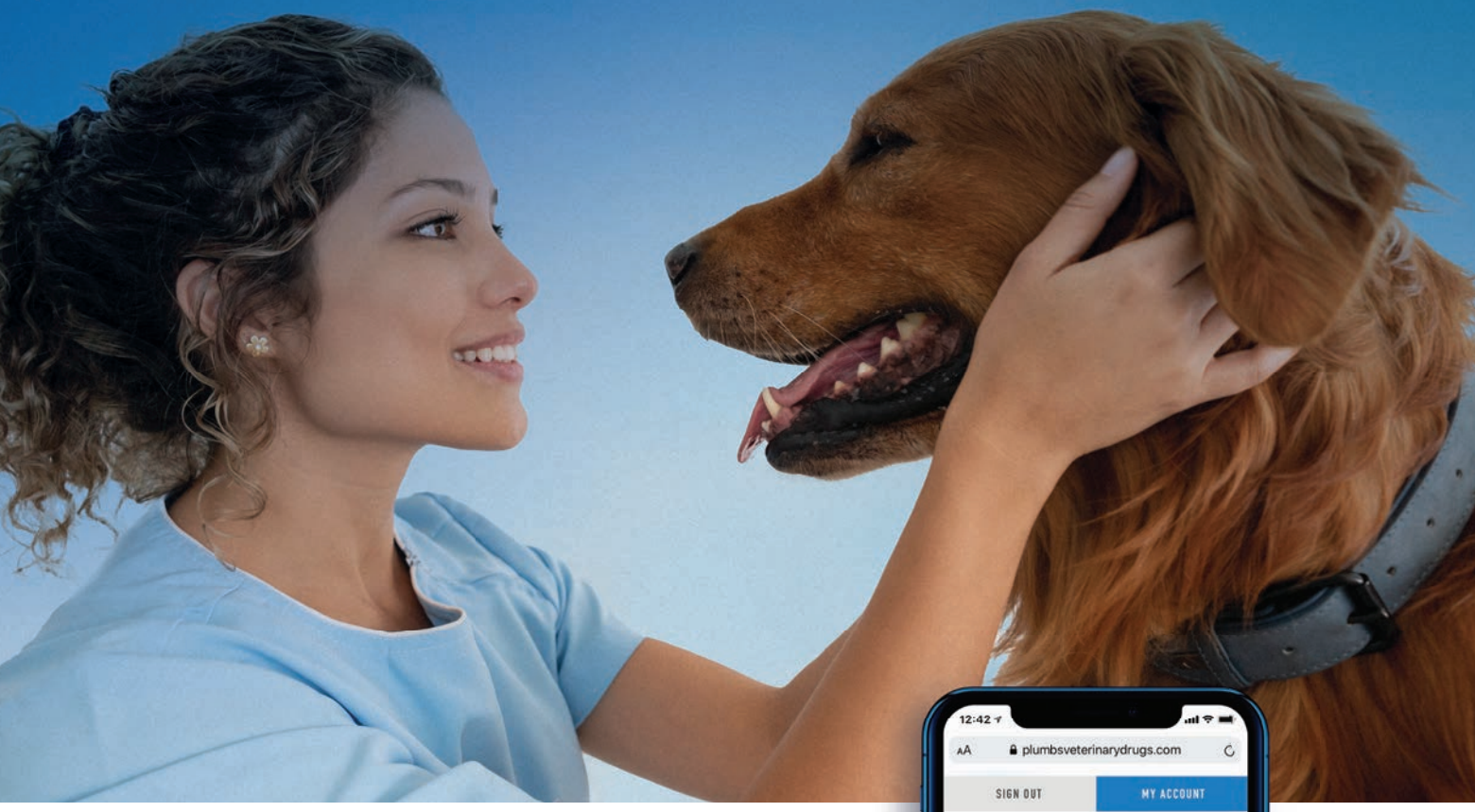

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Using Artificial Intelligence to Predict Risk for Chronic Kidney Disease

Taylor Gin, DVM
Craig Gin, PhD
Shelly Vaden, DVM, DACVIM, PhD
North Carolina State University

In the literature

Biourge V, Delmotte S, Feugier A, Bradley R, McAllister M, Elliott J. An artificial neural network-based model to predict chronic kidney disease in aged cats. *J Vet Intern Med*. 2020;34(5):1920-1931.

FROM THE PAGE ...

Early detection of feline chronic kidney disease (CKD) can be challenging, as even the most reliable markers of kidney dysfunction can be influenced by extrarenal factors. Patient history, physical examination, and laboratory diagnostics (eg, BUN, creatinine, urine specific gravity [USG], packed cell volume, electrolytes) are typically used to determine whether kidneys are functioning properly, but evaluation of laboratory results only provides (at best) an indication of kidney dysfunction at 75% nephron loss.[1] Newer diagnostics to determine risk factors or biological markers for renal dysfunction are therefore of utmost importance.

This study* used machine learning to attempt to predict whether enrolled cats would develop CKD within 12 months. The model recognized subtle combinations of laboratory tests (eg, BUN, creatinine, USG) that serve as early markers of CKD risk in cats ≥7 years of age. Two strategies to determine a cutoff between cats with high and low risk for developing CKD were considered. The first strategy maximized both sensitivity (87%) and specificity (70%) and appeared most appropriate for scenarios in which correctly identifying cats that will not develop CKD within 12 months is considered more important than correctly identifying cats that will develop CKD (ie, high negative predictive value). The second strategy maximized specificity (98%) but had lower sensitivity (42%). Because this strategy has a higher positive predictive value (87%), it is more appropriate for attempting to limit false-positive results. Clinicians should be aware of the sensitivity and specificity of the exact strategy being used when applying it to clinical practice.

*This study was funded by Royal Canin SAS, a subsidiary of Mars, Inc.

... TO YOUR PATIENTS

Key pearls to put into practice:

1. The model in this study may help predict the risk for developing CKD within 12 months in cats ≥7 years of age but should not be applied to cats <7 years of age.
2. Although the model in this study does not provide a diagnosis of CKD, it is important to increase monitoring of laboratory tests (specifically BUN, creatinine, USG, electrolytes, and blood pressure) to every 3 to 4 months in cats considered at risk based on this model.
3. This study only looked at laboratory results from the patient's most recent visit. Careful review of patient history—especially as it pertains to trends in BUN, creatinine, USG, body weight, and clinical signs—may provide more information.

Reference

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Suggested Reading

Bradley R, Tagkopoulos I, Kim M, et al. Predicting early risk of chronic kidney disease in cats using routine clinical laboratory tests and machine learning. *J Vet Intern Med*. 2019;33(6):2644-2656.

Alternative Heartworm Adulticide Protocol in Dogs

Craig Datz,* DVM, MS, DABVP, DACVN
University of Missouri

In the literature

Alberigi B, Fernandes JI, Paiva JP, et al. Efficacy of semi-annual therapy of an extended-release injectable moxidectin suspension and oral doxycycline in *Dirofilaria immitis* naturally infected dogs. *Parasit Vectors*. 2020;13(1):503.

FROM THE PAGE ...

Canine heartworm disease caused by *Dirofilaria immitis* continues to be a significant problem in many areas of the world despite the availability of effective testing and preventive medications.[1,2] In the United States, the only FDA-approved adulticidal treatment is melarsomine dihydrochloride, but this drug is relatively expensive and not available in all countries.[3] Alternatives to melarsomine have been explored, and several studies have demonstrated that a combination of topical moxidectin and oral doxycycline can be effective in treating adult heartworms.[3-5] Moxidectin is also available as a long-acting injection for the prevention of heartworm disease. In this study,† researchers in Brazil aimed to determine if injectable moxidectin combined with oral doxycycline is an effective adulticidal protocol in dogs naturally infected with *D immitis*.

Twenty dogs with naturally occurring *D immitis* infection were enrolled in the study. Dogs ranged from 1 to 8 years of age (mean, 4.85 years), were clinically healthy, and had not received macrocyclic lactones or doxycycline in the 6 months prior to the study. Each dog was treated with a 12-month extended-release injectable moxidectin suspension (0.5 mg/kg SC once) and doxycycline (10 mg/kg PO twice daily for 30 days) every 6 months. Exercise was not restricted, but pet owners were instructed to help their pet avoid excessive activity.

Physical examination and diagnostic testing (ie, heartworm antigen and microfilaria [mf] count, CBC, serum chemistry profile, thoracic radiography, echocardiography) were performed at baseline and then every 6 months until 2 consecutive negative antigen tests were obtained. Eleven dogs (55%) became antigen negative on day 180, 7 dogs (35%) on day 360, 1 dog (5%) on day 540, and 1 dog (5%) on day 810. Microfilariae decreased from a geometric mean of 4,587 mf/mL at baseline to 2,584 mf/mL at day 30. All dogs were negative for microfilariae on day 150.

The number of dogs with pulmonary signs (ie, cough, dyspnea, harsh expiratory sounds) decreased significantly from baseline to the first negative antigen test. Radiographic signs of enlargement of the main and caudal pulmonary arteries also decreased over time, although no significant reductions in pulmonary bronchial and interstitial patterns were noted. In some dogs, micronodular patterns increased on the first negative antigen test, then returned to baseline on the second negative test. Echocardiography showed normal systolic right ventricular function and no worsening of pulmonary hypertension throughout the study. No adverse effects on body weight or clinical health were noted, and blood work results remained in the normal reference range.

* Craig Datz is also affiliated with Royal Canin.
† This study was funded by Zoetis Brasil.

… TO YOUR PATIENTS

Key pearls to put into practice:

1 Melarsomine is the standard recommended treatment for adult heartworms in dogs[6,7]; however, alternative protocols may be considered in cases in which melarsomine is unavailable or cost-prohibitive or in dogs that cannot tolerate the drug.

2 Long-acting injectable moxidectin combined with oral doxycycline administered every 6 months appears to be as safe and effective as protocols using topical moxidectin or other macrocyclic lactones. However, this study was not controlled or masked and may not be directly comparable with other studies.

3 Injectable moxidectin as used in this study is extra-label and not approved by the FDA or the drug manufacturer. Informed owner consent should be obtained before attempting this protocol in dogs with heartworm disease.

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7. Companion Animal Parasite Council. Heartworm. CAPC website. https://capcvet.org/guidelines/heartworm. Updated July 2020. Accessed January 2021.

Research Note:

Absorbable Fixation Straps for Total Laparoscopic Gastropexy in Dogs

Prophylactic gastropexy has been used to prevent occurrence or recurrence of gastric dilatation-volvulus in large- and giant-breed dogs. Various surgical techniques have been described, with incisional gastropexy being the most common. Minimally invasive gastropexy techniques, including laparoscopic-assisted gastropexy and total laparoscopic gastropexy, can have lower postoperative morbidity and faster recovery rates. Absorbable fixation straps are used for laparoscopic repair of abdominal wall hernias in humans. This cadaveric study compared load-to-failure results for absorbable fixation straps with absorbable knotless (barbed) sutures for total laparoscopic gastropexy. The authors found this technique required no intra-abdominal sutures, may be technically less demanding, and had similar loads to failure as compared with other techniques; therefore, further prospective studies with long-term follow-up are warranted.

Source

Fracassi L, Crovace AM, Staffieri F, Lacitignola L. Biomechanical evaluation of an absorbable fixation strap for use in total laparoscopic gastropexy in dogs. *Am J Vet Res*. 2020;81(7):594-599.

Minimally invasive gastropexy techniques, including laparoscopic-assisted gastropexy and total laparoscopic gastropexy, can have lower postoperative morbidity and faster recovery rates.

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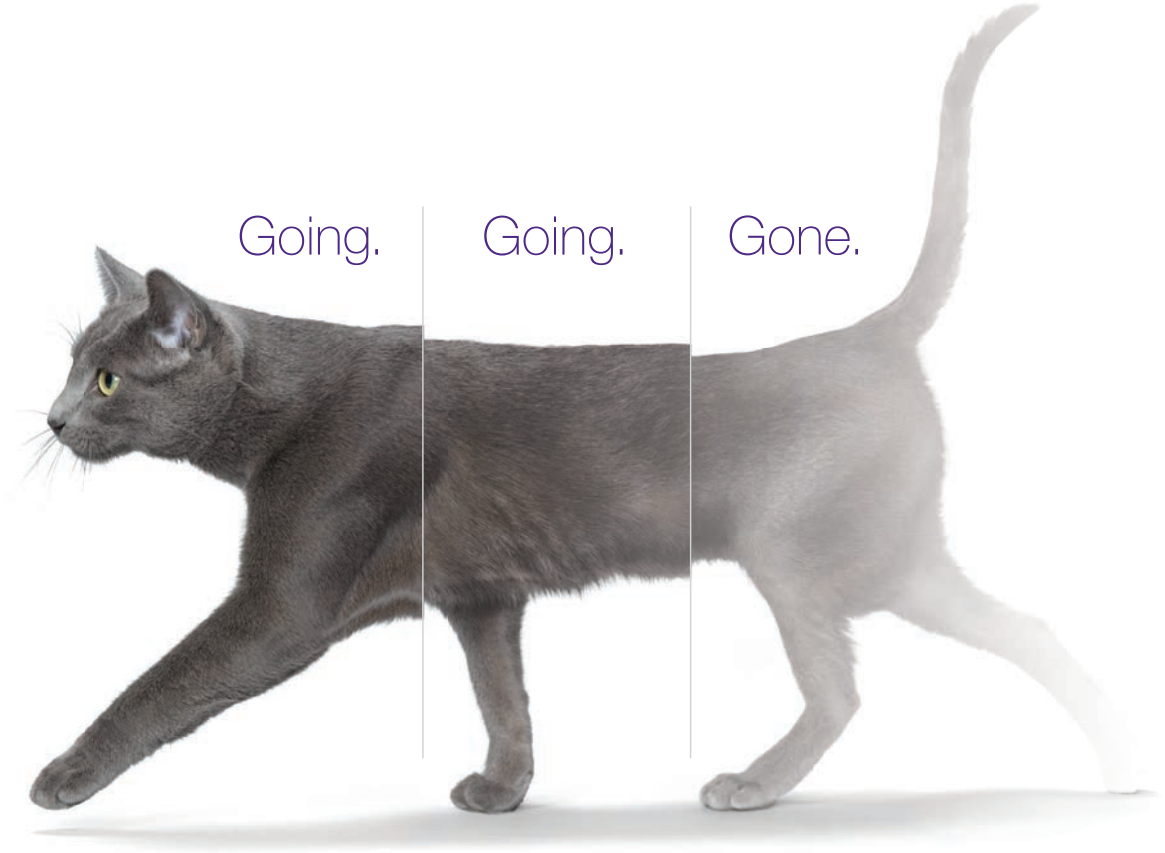

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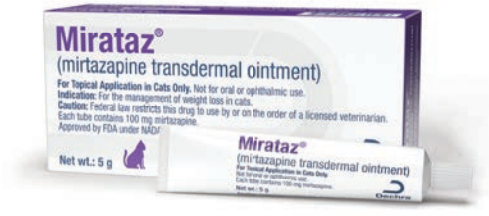

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References: 1. Agnew W, Korman R. Pharmacological appetite stimulation: rational choices in the inappetent cat. *J Feline Med Surg.* 2014;16(9):749-756. **2.** Poole M, Quimby JM, Hu T, et al. A double-blind, placebo-controlled, randomized study to evaluate the weight gain drug, mirtazapine transdermal ointment, in cats with unintended weight loss. *J Vet Pharmacol Ther.* 2019;42(2):179-188. doi:10.1111/jvp.12738.

Research Note: **Transanal Minimally Invasive Surgery in Canine Cadavers**

This study evaluated the use of transanal minimally invasive surgery (TAMIS), which can provide an alternative approach to resection of rectal tumors, for submucosal rectal resection in 6 large-breed canine cadavers. The median length of resected rectal mucosa was 24.5 mm, and no dogs had evidence of iatrogenic full-thickness surgical penetration of the rectum (ie, a complication that could lead to septic peritonitis). Based on these results, transanal minimally invasive surgery may be a promising alternative to more invasive surgery (eg, rectal pull-through—a technique that may lead to higher incidence of complications or diminished ability to achieve clean margins).

Source

Mayhew PD, Balsa IM, Guerzon CM, et al. Evaluation of transanal minimally invasive surgery for submucosal rectal resection in cadaveric canine specimens. *Vet Surg*. 2020;49(7):1378-1387.

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[1] Data on file at Boehringer Ingelheim. [2] Data on file at Boehringer Ingelheim. [3] Ascarid for Dog. Companion Animal Parasite Council. https://capcvet.org/guidelines/ascarid/. Accessed December 2, 2020. [4] Hookworms for Dog. Companion Animal Parasite Council. https://capcvet.org/guidelines/hookworms/. Accessed December 2, 2020.

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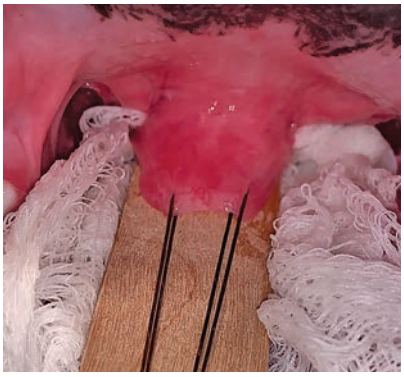
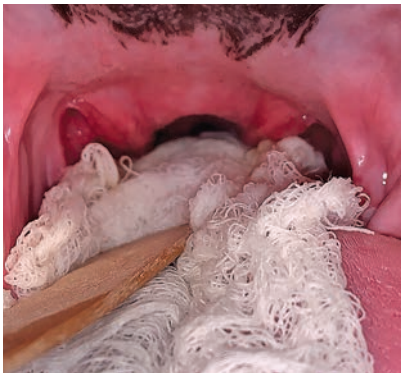
See page 48 for product information summary.

Recent Updates on Brachycephalic Airway Syndrome

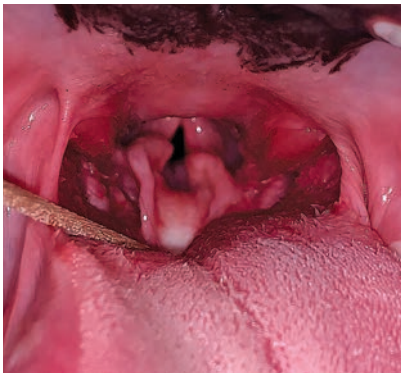
Susanna Hinkle Schwartz, DVM, DACVS
MedVet
Cincinnati, Ohio



▲ **FIGURE 1** Preoperative elongated soft palate. Stay sutures are in place to pull the elongated soft palate rostrally. A laser is used to trim to the mid- to distal one-third of the palate.



▲ **FIGURE 2** Trimmed palate. Postoperative laser resection was done on the mid- to distal one-third of the elongated soft palate.



▲ **FIGURE 3** Everted saccules. Stage 1 laryngeal collapse (ie, everted laryngeal saccules) demonstrates there has been significant negative pressure in the oronasopharynx, causing the saccules to evert.

In the literature

Lindsay B, Cook D, Wetzel J-M, Siess S, Moses P. Brachycephalic airway syndrome: management of post-operative respiratory complications in 248 dogs. *Aust Vet J*. 2020;98(5):174-180.

FROM THE PAGE ...

Brachycephalic airway syndrome (BAS; ie, brachycephalic obstructive airway syndrome) is a combination of upper respiratory tract abnormalities that result in decreased air passage and typically consist of stenotic nares, elongated soft palate, everted laryngeal saccules, abnormal turbinates, and (eventually) laryngeal collapse and tonsillar protrusion from the crypt. Hypoplastic trachea is common in brachycephalic dogs and contributes to airway distress, but it is not a component of BAS. Decreased air flow as a result of these abnormalities can lead to increased upper airway resistance, hypoxia, and elevated proinflammatory cytokines.[1] Affected dogs have also been found to have decreased arterial oxygen saturation, increased carbon dioxide levels, and hypertension.[2] GI tract lesions (eg, gastritis) were also found in up to 98% of dogs.[3] Due to the severe physiologic consequences of BAS, surgery is recommended for ideal long-term health and exercise tolerance. Staphylectomy can be performed with sharp resection (potentially resulting in more hemorrhage and swelling), a carbon dioxide laser,[4] or a ligature vessel-sealing device.[5] The carbon dioxide laser technique resulted in a similar prognosis as sharp resection but was much faster and easier, with potentially less hemorrhage and edema. A bipolar sealing device can be safely used and resulted in no mortalities.[5]

This study retrospectively reviewed medical records of 248 dogs for data on incidence and management strategies of postoperative complications following surgical correction of ≥1 components of BAS. Dogs ranged in age from 31 days to 15.8 years; Cavalier King Charles spaniels were significantly older than the rest of the study population. Other breeds were primarily brachycephalic, with pugs, Cavalier King Charles spaniels, and British bulldogs predominating. Prior to anesthesia, thoracic radiography was performed in all dogs to assess for pneumonia. Surgeries performed included vertical wedge resection, staphylectomy with sharp resection, everted saccule resection, and tonsillectomy. In this population, 23.4% of patients developed complications, including varying levels of dyspnea (25.1%), aspiration pneumonia (4%), and respiratory or cardiac arrest (2.4%). Of the 10 dogs with aspiration pneumonia, 4 had clinical evidence preoperatively. Dogs that had significant complications were older than those that did not develop complications; this differs from a previous study[6] that found younger dogs developed more complications than older dogs. Overall complications (23.4%) were higher in this study than in previous studies, but overall mortality (2.4%) was similar.[7,8] Vomiting and regurgitation were associated with significantly higher risk for postoperative respiratory complications. Temporary tracheostomy placement was also more common in this study and was present in 8.9% of cases; however, 5 of these dogs were presented to the referral hospital with the tracheostomy in place.

Due to the severe physiologic consequences of BAS, surgery is recommended for ideal long-term health and exercise tolerance.

… TO YOUR PATIENTS

Key pearls to put into practice:

1. Surgical correction of BAS should be performed early for ideal long-term health and a better prognosis.
2. Preoperative radiography should be obtained to determine if pneumonia is present, and surgery should potentially be postponed until pneumonia has resolved.
3. Proactive postoperative supplementation with oxygen may prevent respiratory compromise and shorten time of recovery from anesthesia. Close monitoring with 24-hour care is imperative because complications are more likely to occur in the immediate postoperative period.
4. Further studies are indicated to determine whether prokinetics, antacids, or antiemetics may be beneficial in decreasing the risk for regurgitation/vomiting; this may result in a lower incidence of respiratory compromise.

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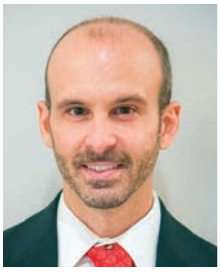


BRIAN DIGANGI, DVM, DABVP
(CANINE & FELINE PRACTICE, SHELTER MEDICINE PRACTICE)
SENIOR DIRECTOR OF SHELTER MEDICINE, ASPCA

THE SHORT ANSWER

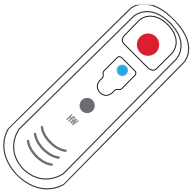
Following several simple steps can ensure dogs can be safely transported without posing a risk for further heartworm transmission.

A In an ideal world, a dog like this would first undergo heartworm treatment and post-treatment recovery before being transported,* but "ideal" is not how many such cases are described.

You have two clear priorities in this case: (1) **to protect the health of the infected patient**; and (2) **to prevent this infected dog from serving as a reservoir of infection to other pets**. While not exhibiting clinical signs, the dog is unquestionably harboring adult heartworms, making it important to initiate heartworm treatment as soon as possible. It is also vital to eliminate the microfilaria; otherwise, unprotected pets in the vicinity will be at risk. Meanwhile, if the dog's long-term survival is highly dependent on his being rehomed as soon as possible, that is clearly a vital consideration.

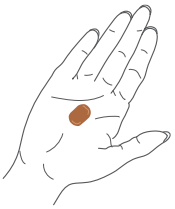
These priorities may seem to be in conflict with each other, but they don't have to be. The American Heartworm Society (AHS) and the Association of Shelter Veterinarians (ASV) recently collaborated on a series of recommendations for safe and responsible transport of heartworm-positive dogs *(visit heartwormsociety.org/relocating for complete details).*

The principles of these new recommendations include the following:



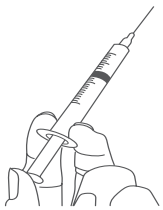
1. Test all dogs greater than 6 months of age for microfilariae and heartworm antigen within 30 days of transport.

You have already done this. But it should be emphasized that knowing the health status of dogs undergoing transport—whether they are homeless dogs being relocated, pet dogs accompanying owners or caretakers on vacations, or dogs whose families are moving—is essential.



2. Determine which steps of the heartworm treatment protocol should be performed before and after transport.

The AHS treatment protocol for heartworm in dogs has several steps, including administration of a heartworm preventive and doxycycline to minimize pulmonary pathology and melarsomine injections. With a patient such as this, a variety of protocols can be used to disrupt the transmission cycle during transport and prior to adulticidal therapy. Timing of doxycycline administration (before or after transport) can be tailored to the situation. Meanwhile, transporting dogs that are exhibiting clinical signs of heartworm infection should be avoided.



3. Once heartworm-positive dogs have been safely transported, complete heartworm treatment according to the AHS Guidelines.

Ensuring dogs with heartworm infection are treated as soon as possible helps ensure the best possible outcome. The AHS heartworm treatment protocol is detailed in our canine guidelines on heartwormsociety.org.

** Transportation and importation of companion animals must be performed in accordance with state and/or federal regulations.*

Changing Methadone Metabolism to Prolong Analgesia

Tamara Grubb, DVM, PhD, DACVAA
Washington State University

In the literature

KuKanich B, KuKanich K, Rankin DC, et al. Perioperative analgesia associated with oral administration of a novel methadone-fluconazole-naltrexone formulation in dogs undergoing routine ovariohysterectomy. *Am J Vet Res*. 2020;81(9):699-707.

FROM THE PAGE ...

Opioids are potent analgesic drugs commonly used to control acute pain (eg, pain caused by surgery or traumatic injury). When administered orally to humans, methadone has a high bioavailability, prolonged elimination time, and results in 6 to 12 hours of analgesia.[1] Opioid effects are terminated via hepatic cytochrome P450 enzymes, which is a species-specific process.[2,3] In a previous study, there was no measurable plasma methadone in a majority of dogs following oral administration[4]; this is unlike pharmacokinetics in humans. Drugs with opioid potency, long duration of action, and efficacy following oral administration are desirable for veterinary patients but are not currently available.

As an alternative to the discovery and development of new drugs, effects of existing drugs can be modified through a variety of mechanisms, including changing the rate and/or extent of drug metabolism via manipulation of hepatic enzymes using pharmacokinetic enhancers (eg, fluconazole, ketoconazole, chloramphenicol). In dogs, enhancers coadministered with oral methadone have been shown to increase the bioavailability and prolong the elimination time of methadone.[4-6] However, the clinical impact of this was previously unknown.

In this clinical study, dogs undergoing ovariohysterectomy were either given methadone (0.5 mg/kg SC every 4 hours) alone or methadone with fluconazole and naltrexone in 2 oral drug combinations (ie, methadone [0.5 mg/kg], fluconazole [2.5 mg/kg], and naltrexone [0.125 mg/kg] or methadone [1 mg/kg], fluconazole [5 mg/kg], and naltrexone [0.25 mg/kg]) PO every 12 hours.[7] Pain scores (using the Glasgow Composite Measure Pain Scale Short Form) were compared among groups every 4 hours, which is the expected analgesic duration following IV administration. A significant difference in scores was identified at only one time point, and no dog required rescue analgesia, indicating adequate analgesia was provided by both protocols. All dogs also received carprofen, which may mask minor methadone insufficiency but does not change the utility of the results, as the drugs would be used together in clinical protocols.

As with all drugs, both efficacy and safety should be considered. A major safety concern of potent opioids is diversion to human use. Naltrexone, an orally administered long-duration opioid antagonist, was added to the methadone/fluconazole combination as an abuse deterrent. Although naltrexone could potentially reverse some of the analgesia provided to the patient, the drug combination was shown to be effective in this study, and opioid-mediated adverse effects (eg, vomiting) were not eliminated.

The results in this study are promising, as they demonstrate that long-duration analgesia can potentially be achieved in dogs using currently available drugs. The authors state that the efficiency of oral twice-daily administration, as compared with injectable administration every 4 hours, is expected to increase the probability patients will receive adequate analgesic treatment.

Continues ▶

… TO YOUR PATIENTS

Key pearls to put into practice:

1. Drug metabolism is often species-specific, and the effects of drugs in humans cannot be extrapolated to veterinary species.
2. Orally administered methadone (2 mg/kg) without an enhancer like fluconazole is not bioavailable in dogs and should not be administered for analgesia.
3. As shown by pain scores in this study and others,[7-9] ovariohysterectomy is painful, and adequate analgesia—along with pain scoring to assess treatment efficacy—should be a standard component of patient care.

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Research Note:
Stored Packed RBCs for Blood Transfusion

This study evaluated the impact of storage time on canine packed RBCs over 28 days. Packed cell volume increased from 70% to 78.33%, lactate increased 627%, potassium content increased 183%, hemolysis reached 0.69%, and pH decreased 9% after 28 days. There was no determined negative effect on dogs receiving transfusions. The authors concluded that, despite alterations that occur during storage, packed RBCs stored ≤21 days are effective and safe for transfusion therapy.

Source

Rodrigues RR, Kayano CK, dos Santos VP, Moroz LR, Fantoni DT, Ambrósio AM. Evaluation of hematologic, biochemical, and blood gas variables in stored canine packed red blood cells, and the impact of storage time on blood recipients. *Vet Clin Pathol*. 2020;49(2):198-206.

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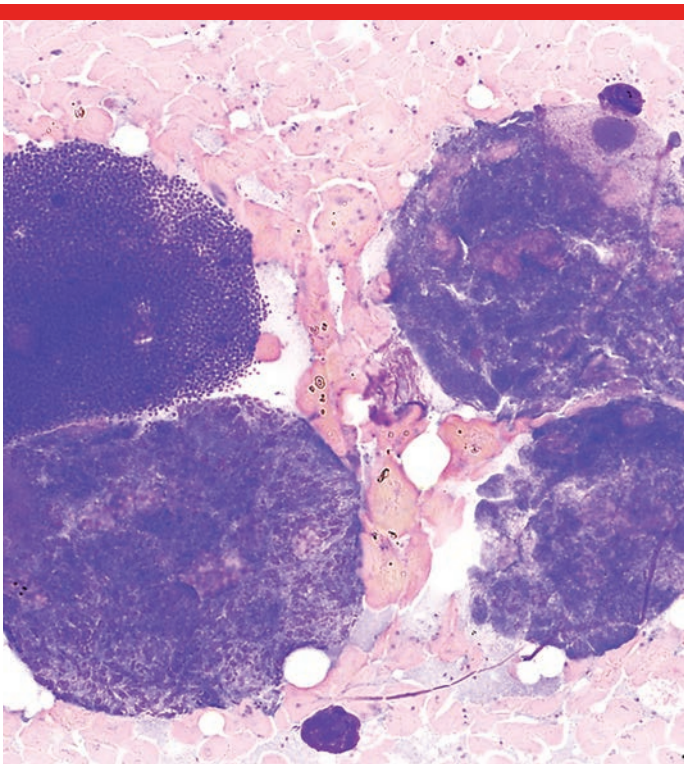
*For this assessment, a common brand pairing is defined as having been purchased for more than 25,000 dogs. 591,200 pet owners paired *NexGard* for flea and tick control with HEARTGARD Plus for heartworm disease prevention – more than any other possible pairing.

1. Data on file at Boehringer Ingelheim. **2.** Data on file at Boehringer Ingelheim. **3.** Data on file at IDEXX Laboratories, Inc. Westbrook, Maine USA. **4.** Data on file at Boehringer Ingelheim. **5.** Data on file at Boehringer Ingelheim.

Boehringer Ingelheim

Pancytopenia & Icterus in a Cat



Alex Knetsche, DVM candidate
Lisa M. Pohlman, DVM, MS, DACVP
Kansas State University

Clinical History & Signalment

Scar, an 11-year-old, spayed domestic shorthair cat, was presented after her owner noted lethargy and vocalization outside the home. Her owners reported she had a poor appetite the previous couple days, and she refused food on the day of presentation. Scar was an indoor/outdoor cat that usually stayed close to home; however, she had reportedly started roaming more than normal after a puppy was introduced to the household ≈7 weeks prior to presentation. No previous health problems were reported. She was free-fed commercial cat food and commercial cat treats several times a week. Flea and tick preventives were up to date.

Physical Examination

Abnormal findings on physical examination included vocalization, dehydration (5%-7%), fever (105.1ºF [40.6ºC]), icterus, lymphadenopathy, splenomegaly, and hepatomegaly.

Diagnosis

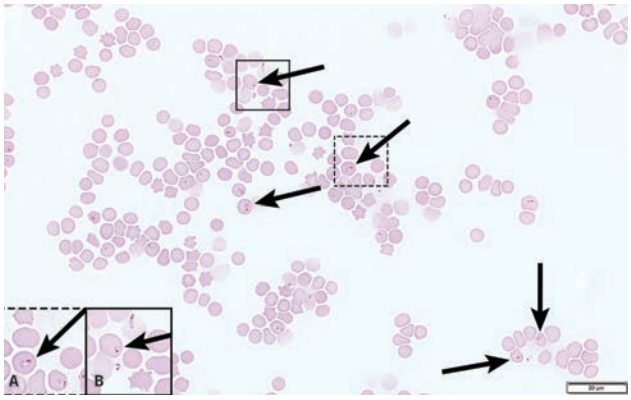
CBC revealed pancytopenia characterized by nonregenerative anemia (hematocrit, 28%; reference interval [RI], 30%-45%), leukopenia (1,900 WBC/µL; RI, 5,500-19,000/µl) due to neutropenia (1,520 neutrophils/µL; RI, 2,500-12,500/µL), and thrombocytopenia (23,000 platelets/µL; RI, 180,000-500,000/µL). Peripheral blood smear examination revealed frequent signet-ring–shaped piroplasms within RBCs (***Figure 1***, next page).

Serum chemistry profile revealed mild hyperglycemia (184 mg/dL; RI, 70-140 mg/dL) likely due to stress, as well as increased total bilirubin (4.4 mg/dL; RI, <0.2 mg/dL), alkaline phosphatase (75 U/L; RI, 15-50 U/L), and γ-glutamyl transferase (20 U/L; RI, 0-10 U/L); all of which are consistent with cholestasis.

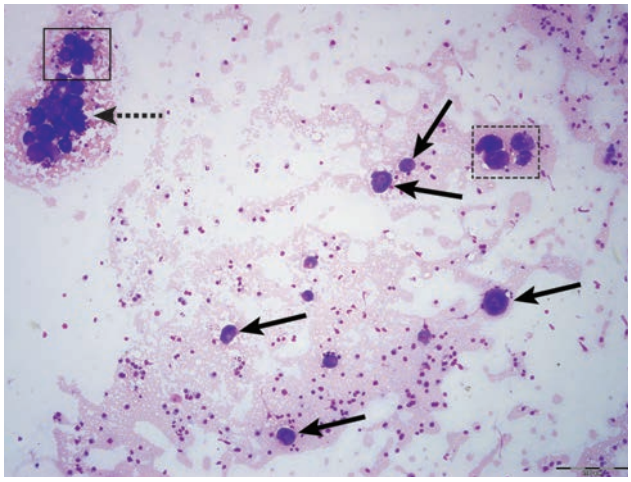
Coagulation testing was not performed in this case.

Ultrasound-guided aspirates of the spleen (***Figures 2-4***, next page) and liver (***Figure 5***, page 59) were collected, and cytologic assessment found abundant schizonts in various stages of maturation.

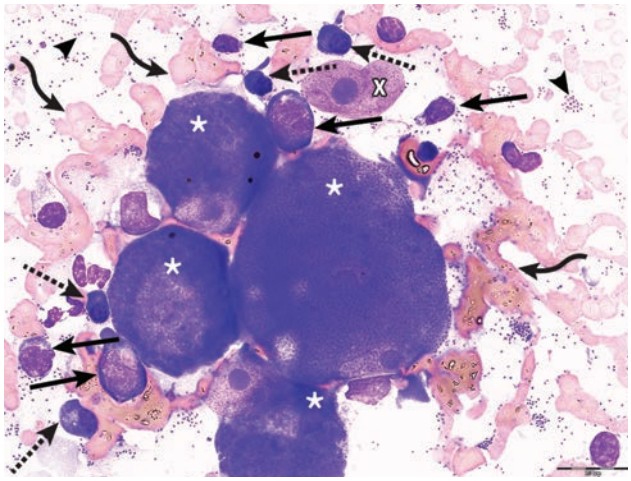
RI = reference interval



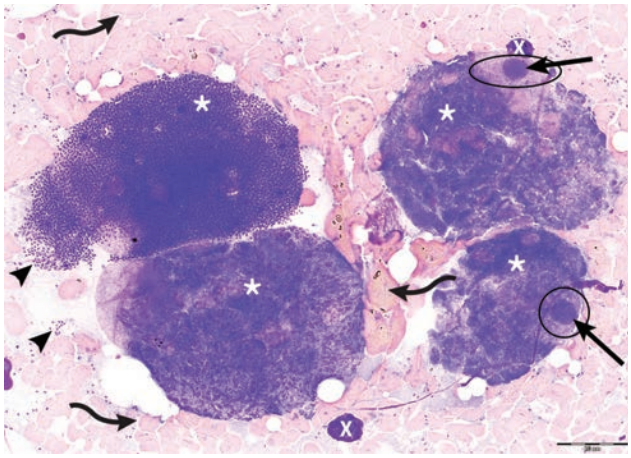
▲ **FIGURE 1** Peripheral blood smear (feathered edge) from Scar; signet-ring–shaped piroplasms (***arrows***) within RBCs can be seen. Not all organisms are indicated. *Modified Wright's stain, 1000× magnification*



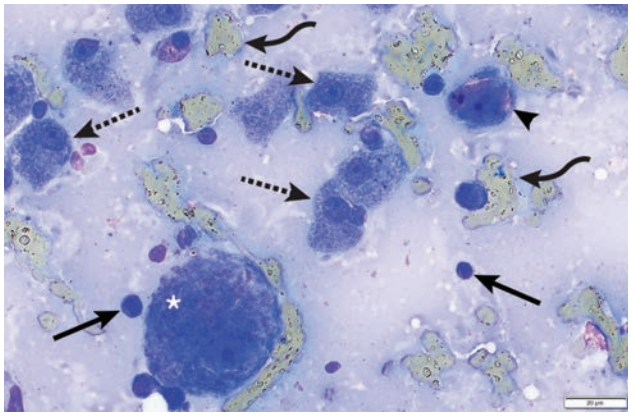
▲ **FIGURE 2** Splenic aspirate from Scar; frequent, large schizont-containing monocytes (also simply referred to as *schizonts*) in various stages of development can be seen. Schizonts are present individually (***solid arrows***) and in clusters (***dashed arrow*** and ***boxes***). The background is composed of RBCs and WBCs. Higher magnifications of the areas in the dashed and solid boxes are in shown in ***Figures 3*** and ***4***, respectively. *Modified Wright's stain, 100× magnification*



▲ **FIGURE 3** Splenic aspirate from Scar; 4 schizonts (***asterisks***) in various stages of development, lymphocytes (***solid arrows***), plasma cells (***dashed arrows***), individual and clusters of RBCs (***curved arrows***), and free merozoites (***arrowheads***) can be seen. A free nucleus (***X***), from a ruptured cell, with a large nucleolus is also present; this cell should not be interpreted. *Modified Wright's stain, 1000× magnification*



▲ **FIGURE 4** Splenic aspirate from Scar; 4 large schizont-containing monocytes (***asterisks***) in various stages of development can be seen. Large monocyte nuclei (***circles***) are pushed to the edge of the cell; a large, prominent nucleolus is also present in each of these nuclei (***arrows***). Free merozoites (***arrowheads***) and a naked nuclei (the remainder of a ruptured cell; ***Xs***) can also be seen. RBCs are distributed individually and clumped (***curved arrows***). *Modified Wright's stain, 1000x magnification*



▲ **FIGURE 5** Liver aspirate from Scar; 1 schizont (***asterisk***) can be seen among the hepatocytes (***dashed arrows***), macrophage (***arrowhead***), scattered lymphocytes (***solid arrows***), and RBC clumps (***curved arrows***). *Modified Wright's stain, 1000× magnification*

TREATMENT AT A GLANCE

- A combination of atovaquone suspension (15 mg/kg PO every 8 hours given with a fatty meal)[3] and azithromycin (10 mg/kg PO every 24 hours) for 10 days is considered the most effective therapy for treating cytauxzoanosis.[3,4]
- Supportive care with crystalloid fluids, oxygen, and analgesic medication is key to helping recovery by improving hydration, increasing organ perfusion, and decreasing high pain levels.[1,4]
- Blood transfusion may be necessary.[4]
- In cases in which DIC is present, heparin therapy (200 units/kg SC every 8 hours) may be indicated in intensive care settings where coagulation parameters can be monitored.[4]
- An esophageal feeding tube to administer medications and keep the cat hydrated with adequate nutrition may be indicated.[1,4]
- Minimal stress and handling, as well as a quiet, dark environment in the cage, may be helpful.

DIC = disseminated intravascular coagulation

DIAGNOSIS:

CYTAUXZOONOSIS

Treatment

Prognosis for cats with acute *Cytauxzoon felis* infection is guarded, even with supportive treatment and antiprotozoal medication.[1,2] A combination of atovaquone suspension (15 mg/kg PO every 8 hours with a fatty meal[3]) and azithromycin (10 mg/kg PO every 24 hours) for 10 days is considered the most effective therapy for treating cytauxzoonosis in cats.[3,4] Supportive care with crystalloid fluids, oxygen therapy, and analgesic medication is key to helping in recovery by improving hydration, increasing organ perfusion and oxygenation, and decreasing high pain levels.[1,4] Coagulation testing is recommended, as acute cytauxzoonosis (ie, a form of sepsis) may lead to disseminated intravascular coagulation (DIC). In these cases, some clinicians advocate for heparin therapy (200 units/kg SC every 8 hours) in intensive care settings in which coagulation parameters can be monitored.[4] Blood transfusion may be required during the hemolytic stage, which occurs late in the disease.[4] To further aid recovery, placement of an esophageal feeding tube is often necessary for adequate nutrition and administration of medications.[4] Minimal stress and handling as well as a quiet, dark environment in the cage may be helpful in achieving a positive outcome.

Outcome

Due to the high cost of treatment and poor prognosis even with therapy, Scar's owners elected euthanasia.

Discussion

C felis, a hemoprotozoan parasite, causes cytauxzoonosis in cats. This disease is most common when the tick vector is most active (ie, in spring to early autumn).[1] Transmission of *C felis* occurs via *Amblyomma americanum* (ie, lone star tick) and *Dermacentor variabilis* (ie, American dog tick), with *A americanum* being considered the more competent vector.[2] Ticks become infected with *C felis* when merozoite-infected erythrocytes are ingested from a reservoir species—typically bobcat and domestic cat carriers that survive infection. Replication occurs in both the salivary glands and gut of the tick to form sporozoites,[1,5] which are then transmitted to the cat via tick bite. Endothelial monocytes are then

infected.[1] Transmission of *C felis* from *A americanum* can occur as early as 36 hours after attachment by the tick.[2] Once sporozoites are present in monocytes, they undergo replication that leads to formation of schizonts.[1] In the late stages of disease, schizonts rupture to release merozoites, which infect erythrocytes; these piroplasms are detectable in erythrocytes on a blood smear.[1]

The most consistent clinical signs of acute cytauxzoonosis are lethargy,[4,6] pyrexia,[4] and anorexia.[4,6] Vocalization,[4] lymphadenomegaly,[6] icterus,[4] and dyspnea[4] are also frequently reported. Cats may be hypothermic late in the disease process (ie, just prior to death).[4] Clinical signs are typically apparent 10 to 14 days postinfection.[5] Pancytopenia, hyperbilirubinemia, bilirubinuria, and increase in liver enzymes are common[1]; however, pancytopenia is not always recognized, and any combination of neutropenia, lymphopenia, thrombocytopenia, and nonregenerative anemia can be consistent with *C felis* infection. DIC may also be seen in some cats.[4]

TAKE-HOME MESSAGES

- Piroplasms within erythrocytes indicate late-stage disease.[1,6]
- Detection of schizonts in cytologic preparations of the lymph node, liver, and spleen can help determine the diagnosis in earlier stages of disease, prior to piroplasmosis.[1]
- Clinical signs of *C felis* appear 10 to 14 days postinfection, and *C felis* can be fatal in as little as 1 week after the appearance of clinical signs.[1,5]
- *C felis* has a high mortality rate; without aggressive treatment, most cats with acute infection die.[4]
- Even with aggressive treatment, only 60% of acutely infected cats survive.[4]
- *A americanum* and *D variabilis* are vectors for *C felis*, so administering a tick preventive and keeping cats indoors can decrease the incidence of *C felis* in endemic areas.[2,4]
- Two acaricides—imidacloprid 10%/flumethrin 4.5% collar[7] and topical selamectin/sarolaner[8]—have demonstrated efficacy in preventing *C felis* transmission by *A americanum* under experimental conditions.[7,8]

The mortality rate is high (40%-100%) and depends on whether appropriate, aggressive, and timely treatment was initiated. Even with aggressive treatment, only 60% of acutely infected cats survive.[4] Cats that survive infection may be lifelong carriers of the parasite and thereby potential sources of infection for other cats.[1]

Most pathologic tissue damage that results in clinical signs is due to the schizogenous phase of parasitemia, which causes obstruction of small veins and capillaries of the spleen, lymph nodes, liver, lungs, and other organs, resulting in hypoxic tissue damage and copious release of inflammatory cytokines.[4] As a result, lymphadenopathy, splenomegaly, and hepatomegaly are typically present.[6] Piroplasms can be detected on a blood smear ≈14 days postinfection.[1,6] However, because clinical signs usually precede the presence of piroplasms in the blood, visualization of schizonts on cytologic preparations of the liver, spleen, and lymph node can confirm acute disease[1] when blood film analysis is equivocal.[4] *C felis* can be fatal in as little as 1 week after clinical signs appear due to thrombosis, tissue infection, and multisystemic inflammation and organ failure caused by schizont dissemination.[1,4,5]

Due to the poor prognosis and short tick-attachment time required for infection, prevention is ideal; however, in outdoor cats that live in endemic areas, prevention can be difficult even with the use of preventives.[2] Acaricides that minimize the time a tick is able to attach to cats, regular manual tick checks and tick removal, and keeping cats indoors in endemic areas (ie, south-central, southeastern, and mid-Atlantic United States), especially during peak tick season, can significantly decrease the likelihood of infection.[2,4] Two acaricides—imidacloprid 10%/flumethrin 4.5% collar[7] and selamectin/sarolaner topical solution[8]—have demonstrated efficacy in preventing *C felis* transmission by *A americanum* under experimental conditions.[7,8]

DIC = disseminated intravascular coagulation

See page 61 for references.

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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 is indicated for the prevention of heartworm disease caused by *Dirofilaria immitis* and for 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. SIMPARICA TRIO kills adult fleas (*Ctenocephalides felis*) and is indicated for the treatment and prevention of flea infestations, and 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) 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

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Kalamazoo, MI 49007

Revised: August 2020

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- **TICKS & FLEAS**
- **ROUNDWORMS & HOOKWORMS**

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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 62.**

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

ZOETIS PETCARE

Top 5 Situations for Judicious NSAID Use

Natalie Smith, DVM
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NSAIDs are commonly used in veterinary medicine to control pain and inflammation and include COX inhibitors (eg, carprofen, deracoxib) and grapiprant, a newer prostaglandin-receptor antagonist. NSAIDs act by reducing the production or action of proinflammatory prostaglandins and are generally well-tolerated, although potential adverse effects may include GI upset, nephrotoxicity, and hepatotoxicity.

Following are the authors' 5 most common uses of NSAIDs, along with important considerations for patient safety.

TOP 5 SITUATIONS FOR JUDICIOUS NSAID USE

1. Osteoarthritis
2. Management of Postoperative Pain
3. Fever
4. Antineoplastic Therapy
5. Musculoskeletal Injury

1 Osteoarthritis

A common application of NSAIDs is the management of osteoarthritis (OA). Because OA is characterized by both chronic and acute flare-ups of pain and inflammation secondary to joint pathology, the analgesic and anti-inflammatory properties of NSAIDs can be helpful with intermittent or continuous

therapy.[1,2] Numerous NSAIDs (eg, carprofen, meloxicam, firocoxib, deracoxib, grapiprant) are labeled for management of OA in dogs; however, no NSAIDs are currently FDA-approved for long-term use in cats.

Although NSAIDs are typically well-tolerated in veterinary patients, sustained use to treat OA in older patients warrants close monitoring for potential adverse effects in the GI tract, kidneys, and liver. GI adverse effects have been linked to a variety of mechanisms (eg, direct irritation of the GI mucosa, inhibition of prostaglandin E_2) and potentially include ulceration, gastritis, enteritis, and perforation.[3] COX expression in the kidneys can lead to production of prostaglandins, which help maintain renal homeostasis by affecting renal blood flow and glomerular filtration rate, among other functions.[4] Thus, use of NSAIDs in dogs may exacerbate underlying chronic kidney disease or lead to acute kidney injury, reversible renal insufficiency, or papillary necrosis.[5-8]

Adverse effects in the liver are uncommon and can be attributed to idiosyncratic reactions.[9] Hepatopathy has been suggested or documented with NSAID use.[10-15] Idiosyncratic hepatotoxicity that occurs with carprofen administration typically involves acute hepatic necrosis, and signs of toxicosis (eg, marked increase in serum ALT) usually occur ≈2 to 4 weeks after exposure.[11]

COX-1 and COX-2 expression play a major role in maintaining renal blood flow.

OA = osteoarthritis

In patients receiving long-term NSAID therapy, baseline laboratory work, (ie, patient hematocrit, liver enzymes, kidney values, and urinalysis) should be performed to help determine whether the patient has underlying renal or hepatic dysfunction. In addition, ongoing clinical monitoring of renal and hepatic parameters is recommended, and the pet owner should monitor for evidence of GI intolerance (eg, inappetence, vomiting, diarrhea, melena) at home. The authors recommend blood work be rechecked ≈2 to 4 weeks after initiation of NSAID treatment, then every 3 to 6 months. In patients that develop adverse effects while receiving an NSAID, the drug should be stopped and laboratory work (minimum CBC and serum chemistry profile) repeated to assess for possible drug toxicity.

2 Management of Postoperative Pain

NSAIDs are frequently used to provide analgesia during surgical procedures (eg, ovariohysterectomy, fracture repair, mass removal) but are generally contraindicated in patients undergoing GI surgery, as there are risks for ulceration and delayed healing.[16-21] COX-1 and COX-2 expression is increased in inflammatory conditions (eg, those induced during surgery). NSAIDs inhibit COX-1 and COX-2 expression, thus decreasing the production of inflammatory mediators (eg, prostaglandins, thromboxanes) responsible for peripheral and central sensitization to pain stimuli.[3,22]

A primary consideration in patients with postsurgical pain is the timing of NSAID administration in the perioperative period. NSAIDs have been shown to provide better postsurgical analgesia when administered prior to surgery rather than immediately following surgery.[23-30] However, human and veterinary patients have frequently experienced hypotension while under anesthesia, and the kidneys are highly vulnerable to hypotensive insult.[31] COX-1 and COX-2 expression play a major role in maintaining renal blood flow, particularly during hypotension, and preoperative inhibition of COX expression by NSAIDs may contribute to postoperative renal dysfunction.[32] Several studies

evaluating renal function after NSAID administration as anesthesia have not found evidence of significant dysfunction; however, these studies primarily included young, healthy dogs, with the oldest being 89 months of age.[24-26,33,34] Accordingly, preoperative use of NSAIDs may be reasonable in healthy patients that do not have underlying renal disease or increased risk for hypotensive events; blood pressure monitoring is recommended in patients under anesthesia. Because patients with existing renal disease may be at increased risk for hypotensive events, NSAIDs as anesthesia should not be used in these patients.

3 Fever

NSAIDs are also used to provide clinical relief from fever, as their antipyretic effects are mediated by central and peripheral thermoregulatory mechanisms. The primary antipyretic action decreases prostaglandin E_2 levels in the hypothalamus by inhibiting COX.[35] Fever at sites of tissue inflammation is reduced via suppression of pyrogenic cytokines, increased release of endogenous antipyretics and anti-inflammatory molecules, and decreased adhesion molecule expression to reduce endothelial cell interactions with leukocytes.[35] This can allow NSAIDs to rapidly reduce fever, potentially controlling life-threatening febrile reactions and significantly improving patient comfort.

NSAIDs should be used with caution in patients with fever of unknown origin, especially in cases in which infectious disease has not been ruled out or immune-mediated disease is likely.

OA = osteoarthritis

Although NSAIDs are effective at reducing fever, they usually do not treat the underlying cause. Resolution of a low- to moderate-grade fever can indicate the appropriate treatment is being used (eg, antimicrobials for system infection, glucocorticoids for immune-mediated polyarthritis). Patients with fever of unknown origin that were referred for further diagnostics and given NSAIDs, glucocorticoids, or antibiotics within 24 hours of presentation had significantly prolonged time to diagnosis as compared with patients not treated within this period.[36] In addition, pyrogenic fever is a protective mechanism in patients with sepsis or fungal infections. A mild febrile response in humans with pyrogenic fever secondary to infection has been shown to improve clinical outcomes.[37] Thus, NSAIDs should be used with caution in patients with fever of unknown origin, especially in cases in which infectious disease has not been ruled out or immune-mediated disease is likely; treatment with glucocorticoids may be indicated.

4 Antineoplastic Therapy

NSAIDs used in conjunction with metronomic chemotherapy are important in the management of cancer patients and can be used as a single-agent treatment for some tumors.[38-40] For metronomic chemotherapy, conventional oral cytotoxic chemotherapy agents can be given at relatively low doses and regular intervals (eg, every 24-48 hours) over a sustained period. Metronomic chemotherapy agents are often delivered with other agents (eg, NSAIDs, small-molecule inhibitors).[38] Therapy is aimed at altering tumor microenvironment, primarily via antiangiogenic mechanisms, rather than directly targeting the tumor cells. COX-2 inhibition via NSAIDs can decrease cell proliferation, reduce production of proangiogenic factors (eg, vascular endothelial growth factor), and increase the rate of apoptosis.[39] Adjuvant metronomic chemotherapy has been explored in a variety of tumor types (eg, hemangiosarcoma, soft tissue sarcoma) and can safely be incorporated in treatment regimens for cancer patients.[38]

Carcinomas (eg, urothelial carcinoma, mammary carcinoma, nasal adenocarcinoma, anal sac adenocarcinoma) express COX-2.[40-43] NSAIDs have activity against canine urothelial carcinoma, with several different COX inhibitors (eg, piroxicam, deracoxib, firocoxib) reported.[44-46] NSAIDs may be recommended as part of standard therapy for carcinomas because of their potential antitumor activity and ability to provide analgesia. One study reported a median survival time of 181 days in dogs with urothelial carcinoma treated with piroxicam alone as compared with 291 days in dogs treated with piroxicam in combination with mitoxantrone.[46] Single-agent NSAIDs may be more effective when combined with conventional chemotherapy agents for treatment of urothelial carcinoma but can be used alone when conventional chemotherapy is not possible.

The effectiveness of NSAIDs for antineoplastic therapy should be balanced against possible adverse effects. GI adverse effects may limit the use of NSAIDs, especially in patients also being treated with conventional chemotherapy agents or small-molecule inhibitors that may independently cause GI adverse effects. NSAIDs should not be used concurrently with glucocorticoids, which are often used in the treatment of round cell neoplasias (eg, lymphoma, mast cell tumors). Owners of patients treated with NSAIDs as part of antineoplastic therapy should be advised to monitor for signs of GI adverse effects. Baseline and follow-up laboratory work is also recommended (as described for OA; see ***Osteoarthritis***, page 64).

5 Musculoskeletal Injury

NSAIDs are also frequently used in patients with acute musculoskeletal injuries. Pain associated with acute injuries persists during both the inflammatory and healing phases and may last up to 3 months before being considered chronic.[17] During the inflammatory phase, prostaglandin expression may increase up to 80-fold, making COX inhibition a valuable target for therapeutic intervention.[47]

Patients with acute musculoskeletal injuries are typically given shorter courses of NSAID therapy, reducing the risk for potential adverse effects in the kidneys, GI tract, and liver, as compared with patients given sustained NSAID therapy. However, caution is recommended in patients with pre-existing GI disease, and screening for renal or hepatic dysfunction should be done prior to NSAID administration, especially in older patients.

Conclusion

NSAIDs are important therapeutics because of their ability to reduce inflammation and provide effective analgesia. With appropriate monitoring for GI, renal, and hepatic adverse effects, NSAIDs can be used safely to treat a variety of conditions in small animal patients.

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Nutritional management of chronic enteropathies in cats

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Background:

Feline noninfectious, inflammatory chronic enteropathies (CE) can be treated using nutritional management, modulating bacterial populations in the gut, pharmacologic therapy to decrease inflammation, and environmental enrichment to decrease the role of stress.[1] The most important step in diagnosing a CE is eliminating the possibility of systemic disorders as well as ruling out several primary gastrointestinal diseases (e.g. infectious, neoplastic) that may not be dietary responsive.[2] Nearly half of cats with CE will respond to nutritional management alone, and that is the focus of this article.[3,4]

Nutritional Management of Feline Noninfectious Inflammatory CE

Limited ingredient, hydrolyzed, highly digestible, and modified fiber diets are used for management of CE in cats (Table 1).[5,a-c] Low-fat diets will not be covered here due to lack of evidence for their use in feline CE.[6,7] In a study of 8 cats with small intestinal IBD fed a hydrolyzed diet, clinical signs resolved in all cats within 4-8 days. Challenge with the original diet resulted in all cats relapsing, and with reintroduction of the hydrolyzed diet, clinical signs resolved again in 7 cats.[8] Another study demonstrated a 40-67% response rate in cats fed various highly digestible diets.[9] This is supported by another study using two different highly digestible diets and another using a hydrolyzed diet.[10,11] These data indicate that limited ingredient, hydrolyzed, as well as highly digestible diets have utility for treating feline CE with small bowel signs (Table 1). Individual studies with each of these diet types have shown good outcomes, and there are currently no comparative studies to identify the optimal approach. Therefore, when based solely on the criteria of diet type, there is no specific first line choice. Recent, informal polls of veterinarians specializing in gastroenterology, in the Comparative Gastroenterology Society, demonstrated a fairly even distribution of expert opinion on the best strategy. Therefore, for the clinician in practice, considering holistic nutrition goals and examining other aspects of the diet nutrient profile (e.g. caloric content, macronutrient content, etc.) may assist in choosing specific diets and strategies for the individual patient.

If signs of colitis predominate, there is some evidence for utilizing either a highly digestible, limited ingredient, or a modified fiber diet (Table 1). In an early study of 12 cats treated with either diet alone or diet in addition to ancillary medications, complete resolution was observed in 7 of the cats, all of which were managed long-term on diet alone. Another 3 cats exhibited a partial response to dietary management. The most common diet type utilized in the study was modified fiber.[12] A smaller case series that preceded that study demonstrated a response in 6 cats to a home-cooked lamb and rice diet. One cat in this study was initially concurrently managed with anti-inflammatory medications, but ultimately diet alone was sufficient.[13]

Indirect evidence shows that a true immunologic food allergy may occur in one-third of cats with CE. Food allergy cats often display a wide variety of clinical signs; however, vomiting and small bowel diarrhea with concurrent dermatologic signs should increase the clinician's suspicion.[14] If a food allergy is suspected, limited ingredient or hydrolyzed diets based on a complete diet history should be fed to avoid potential previous exposure as well as the most common allergens in cats (e.g beef, dairy products, fish) (Table 1).[15,16,17] Additionally, diet trials longer than 2 weeks are required in true food allergy cases. In food allergy cases, diet trials of at least 8-12 weeks are required for diagnosis.[16]

Clinical Summary

Feline CE can be effectively managed with diet, which offers many advantages over other therapies and should be a focus during treatment planning. A variety of options exist, and patient factors and clinical signs may guide empirical dietary management choices made by the clinician. The optimal approach between these diet types in cats is unknown, and it may be beneficial to attempt multiple diet trials utilizing different diet types (easily digestible, hydrolyzed, limited ingredient, and modified fiber diets) if initial attempts with one specific diet type fail.

Footnotes:

[a] Dethioux F, Marniquet P, Petit P, et al. Importance of proteins together with soluble and insoluble fibers on a cat's digestive tolerance. In: Preventative Nutrition for Major Health Risks in Cats. Royal Canin Focus, 2005;37-50.

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TABLE 1: UNDERSTANDING TYPES OF GASTROINTESTINAL DIETS

DIET TYPE	KEY POINTS	DIETARY CONCEPT	EXAMPLE DIETS	REFERENCES
Hydrolyzed	These diets have undergone processing to alter macronutrient structure to reduce its antigenic potential.	*Typically made with a single protein source. *Processing is not perfect. If food allergy is suspected consider hydrolyzed protein source. *These diets are often highly digestible. *Side effects associated with hydrolyzed diets (e.g. osmotic diarrhea) have not been studied in cats.	*BLUE Natural Veterinary Diet HF Hydrolyzed *Royal Canin Veterinary Care Nutrition Hydrolyzed Protein HP. *Hill's Prescription Diet Food Sensitivities z/d *Purina Pro Plan Veterinary Diets HA Hydrolyzed	1. Cave NJ. Hydrolyzed protein diets for dogs and cats. *Vet Clin North Am Small Anim Pract* 2006;36:1251-1268, vi. 2. Clapper GM, Grieshop CM, Merchen NR, et al. Ileal and total tract nutrient digestibilities and fecal characteristics of dogs as affected by soybean protein inclusion in dry, extruded diets. *J Anim Sci* 2001;79:1523-1532. 3.
Limited Antigen	These diets provide limited protein and carbohydate source[s]. If there is no previous exposure to these ingredients, the diet is also considered a 'novel ingredient' diet.	*Variable macronutrient profiles in these diets allow for flexibility in combining nutritional goals. *Over the counter limited antigen/ingredient diets frequently contain additional ingredients which may act as antigens and are not listed in the ingredient list.	*BLUE Natural Veterinary Diet NP Novel Protein *Royal Canin Veterinary Care Nutrition Selected Protein PR/PV *Hill's Prescription Diet Food Sensitivities d/d	1. Raditic DM, Remillard RL, Tater KC. ELISA testing for common food antigens in four dry dog foods used in dietary elimination trials. *J Anim Physiol Anim Nutr* (Berl) 2011;95:90-97. 2. Willis-Mahn C, Remillard R, Tater K. ELISA testing for soy antigens in dry dog foods used in dietary elimination trials. *J Am Anim Hosp Assoc* 2014;50(6):383-389.
Highly Digestible	These diets are frequently reported to have over 90% digestiblity of major macronutrients.	*Digestibility varies between animals, as it is affected by mechanical, enzymatic, bacterial, and chemical digestion. *There is no set definition for 'highly digestible'. Each component of a highly digestible diet can be altered to affect digestibility, resulting in a lack of a consistent phenotype of a highly digestible diet. *Highly digestible diets tend to be more calorically dense than other dietary groups.	*BLUE Natural Veterinary Diet GI Gastrointestinal Support *Royal Canin Veterinary Care Nutrition Gastrointestinal *Hill's Prescription Diet Digestive Care i/d. *Purina Pro Plan Veterinary Diets EN Gastroenteric	1. Schunemann CM, A.; Junker, S.; Wilfarth, H.; Meyer, H. Praecaecale und postileale verdaulichkeit verschiedener starken sowie pH-werte und gehalte an organischen sauren in darmchumus and faeces. *Adv Anim Physiol Anim Nutr* 1989;19:44-57.
Modified Fiber	These diets have modified fiber content to improve clinical response through their solubility fermentability. Fiber is defined as complex, nondigestible carbohydrates of plant origin.	*Soluble fiber sources are typically more readily fermented, ultimately producing volatile fatty acids, which can benefit enterocytes and augment the microbiota. *Insoluble fiber sources are less fermentable and can contribute to gut motility and passage of gut contents in the gastrointestinal tract. *Total dietary fiber is a more useful descriptor of fiber content in a diet than crude fiber, as total dietary fiber includes both soluble and insoluble fiber. *Fiber can function as a prebiotic.	*Royal Canin Veterinary Care Nutrition Gastrointestinal Fiber Response *Hill's Prescription Diet Gastrointestinal Biome	1. de-Oliveira LD, Takakura FS, Kienzle E, et al. Fibre analysis and fibre digestibility in pet foods x– a comparison of total dietary fibre, neutral and acid detergent fibre and crude fibre. *J Anim Physiol Anim Nutr* (Berl) 2012;96:895-906. 2. Slavin J. Fiber and prebiotics: mechanisms and health benefits. *Nutrients* 2013;5:1417-1435.

*It is important to note that the nutrient profiles of diets frequently change and up-to-date profiles should be acquired every 6 to 12 months. Canned and dry varieties of the same diet, as well as diets that come in a variety of flavors, may have variable nutrient profiles and should not necessarily be used interchangeably.

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Consistently Low Neutrophil Count in a Healthy Dog

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Clinical History & Signalment

Cain, a 5.5-year-old, 79.6-lb (36.2-kg), neutered male crossbreed dog, was presented for his annual examination, heartworm test, serum chemistry profile, and CBC. Clinical history was insignificant except for previously diagnosed bilateral coxofemoral degenerative joint disease.

Physical Examination

On physical examination, Cain was bright, alert, and responsive. Vital signs were within normal limits and BCS was 5/9. He had mild periodontal disease and decreased range of motion on bilateral hip extension. Remainder of the examination was unremarkable.

Diagnosis

Results of routine heartworm antigen testing (including associated testing for *Ehrlichia* spp, *Anaplasma* spp, and *Borrelia burgdorferi* antibodies) were negative. Serum chemistry profile did not indicate clinically significant abnormalities. CBC revealed mild neutropenia (1.79 K/µL; reference range, 2.7-8.9 K/µL; see ***Table***, next page).

Neutropenia is caused by decreased production, increased destruction, increased demand, and sequestration.[1,2] Common differential diagnoses include infectious disease, neoplasia, bone marrow disease, drug toxicity, and uncommon genetic disease (see ***Causes of Neutropenia***, page 75).[1-4]

CBC was repeated 16 days after presentation to confirm neutropenia before additional diagnostics were performed. Moderate neutropenia (0.92 K/µL) and mild thrombocytopenia were noted.[4] Because the neutrophils were <1 K/µL, prophylactic antibiotic therapy was recommended to reduce the risk for sepsis pending further testing for definitive diagnosis and therapy.[1,5-9] However, the pet owner chose to routinely monitor Cain's temperature at home and have CBC rechecked on day 20, which revealed progressive neutropenia and a normal platelet count.

Cain's owner had recently moved to wooded property; therefore, in-house tick-borne disease testing was repeated and showed a faint positive result for *Ehrlichia* spp antibodies. Because antibodies indicate exposure—not necessarily infection—a vector-borne disease PCR panel (including *Anaplasma* spp, *Babesia* spp, *Bartonella* spp, *Ehrlichia* spp, *Mycoplasma* spp, and *Rickettsia* spp) was submitted to a reference laboratory to determine whether an active infection was present. Pending these results, Cain was empirically treated with doxycycline (10 mg/kg PO every 24 hours for 30 days) for possible ehrlichiosis. In addition, due to the worsening neutropenia, enrofloxacin (10 mg/kg PO every 24 hours) was administered prophylactically to reduce the risk for sepsis.[1,5-9] Enrofloxacin has a better gram-negative spectrum and is bacteriocidal, whereas doxycycline is bacteriostatic.

On day 31, results of the vector-borne PCR panel were positive for *Mycoplasma haematoparvum* and negative for *Ehrlichia* spp. Cain was not anemic; thus, the positive mycoplasmal PCR was suspected to be incidental, evidence of early infection, or a false-positive result. Given the negative PCR result and no clinical signs indicating ehrlichiosis (eg, fever, lethargy, petechiae, ecchymoses, lymphadenomegaly, splenomegaly), *Ehrlichia* spp was excluded as a cause for Cain's leukopenia.[10] A repeat CBC indicated worsening, severe neutropenia and recurrence of mild thrombocytopenia (***Table***). Additional diagnostic tests for causes of neutropenia were performed. Thoracic radiographs and abdominal ultrasound revealed no abnormalities. Because no causes were found for the neutropenia or thrombocytopenia, bone marrow sampling was recommended.[1,2] Presence of a persistent cytopenia or multiple cytopenias increase the possibility of bone marrow disease.[2] A bone marrow aspirate for cytology and a core biopsy sample were obtained with the patient under general anesthesia.

Bone marrow cytology was consistent with myeloid hyperplasia, with an increased number of immature neutrophils, indicating an appropriate response to the peripheral neutropenia. In addition, there were

IMN = immune-mediated neutropenia

TABLE

CBC RESULTS

	Day 1	Day 16	Day 20	Day 31	Day 47	Day 61
WBC (5-13 K/µL)	*4.34*	*4.01*	*3.23*	*3.24*	*4.17*	5.66
Platelets (134-396 K/µL)	168	*125*	*132*	*116*	153	203
Fibrinogen (0.1-0.4 g/dL)	0.3	0.4	0.1	*0.5*	*<0.1*	0.3
Neutrophils (2.7-8.9 K/µL)	*1.79*	*0.92*	*0.72*	*0.53*	*2.5*	3.58
Lymphocytes (0.9-3.4 K/µL)	2.02	2.4	1.83	1.98	1.2	1.49
Monocytes (0.1-0.8 K/µL)	0.14	*0.08*	0.12	0.13	0.38	0.3
Eosinophils (0.1-1.3 K/µL)	0.37	0.56	0.54	0.6	0.13	0.27
Basophils (0-0.1 K/µL)	0.01	0	0.01	0	0	0.01

Abnormal values are indicated in italic.

adequate to increased megakaryocytes consistent with an appropriate response to the intermittent peripheral thrombocytopenia. There was no evidence of inflammation, infection, or neoplasia. Based on these cytologic findings, the core biopsy was unlikely to yield additional information and was not submitted for histopathology.

Based on cytology results and negative findings for other causes, a diagnosis of immune-mediated neutropenia (IMN) was made. In humans, flow cytometry is used to detect antineutrophil antibodies and is considered the gold standard for diagnosis of IMN; however, this test is not as specific, sensitive, or readily available in veterinary medicine.[2,3,11,12] IMN is an uncommon, usually idiopathic, primary condition diagnosed by exclusion of other causes of neutropenia.[1,3,11] In dogs with persistent peripheral neutropenia due to IMN, the most common finding on bone marrow cytology is myeloid hyperplasia.[2,3,11,12] However, some dogs may have hypoplasia, which indicates destruction of precursor cells in the bone marrow.[11]

DIAGNOSIS:
IMMUNE-MEDIATED NEUTROPENIA

Treatment & Long-Term Management

Cain was treated with prednisone (1.5 mg/kg/day; 50 mg/m^2) on day 35. CBC was rechecked on days 47 and 61, and resolution of neutropenia and thrombocytopenia was noted (***Table***). Enrofloxacin was discontinued on day 47, as the neutrophil count was >1 K/µ/L. Doxycycline was continued for the remainder of the month-long treatment of *M haematoparvum*, as significance of the positive PCR result was uncertain.

The most common treatment of IMN is immunosuppressive doses of glucocorticoids (eg, prednisone), in which a variety of dosages have been used, with the most common being 2 mg/kg PO every 24 hours.[2,3,11,12] Due to the severe adverse effects of glucocorticoids seen in large-breed dogs, recent recommendations are to consider a dose

CAUSES OF NEUTROPENIA

- Bacterial
  - –*Ehrlichia* spp ± other rickettsial disease
  - –Sepsis
  - –Pneumonia
  - –Dog bite infection
  - –Peritonitis
- Viral
  - –Canine parvovirus
  - –FeLV
  - –FIV
  - –Feline panleukopenia
- Fungal
  - –Histoplasma capsulatum
  - –Cryptococcus neoformans
- Marked inflammation
  - –Organ torsion
  - –Bile peritonitis
  - –Pancreatitis
  - –Hemolytic anemia
- Neoplasia
  - –Leukemia
  - –Lymphoma
  - –Multiple myeloma
- Primary bone marrow disease
  - –Leukemia
  - –Myelodysplasia
  - –Myelofibrosis
  - –Aplasia
- Drug toxicity
  - –Chemotherapeutic agents
  - –Estrogens
  - –Trimethoprim sulfamethoxazole and other antibiotics
  - –Phenobarbital
  - –Methimazole
- Immune-mediated disease
  - –Primary
  - –Secondary to inciting cause
- Genetic
  - –Cyclic hematopoiesis in gray-coated collies
  - –Cobalamin deficiency/malabsorption in giant schnauzers
  - –Trapped neutrophil syndrome in border collies

based on body surface area (50 mg/m^2 in dogs >55 lb [25 kg]), as was used in this case.[13] In most cases, dogs respond to corticosteroid treatment within 7 to 10 days.[2,3,11,12] Once the neutrophil count is normal, prednisone can be slowly tapered over 1 to 6 months.[11] Some dogs may require additional immunosuppressive medications if they are not responding well to steroids or steroids are not tolerated well. Azathioprine (initial dosage, 2 mg/kg/day or 50 mg/m^2) is also commonly used.[2] Serum chemistry profile should be routinely monitored, as azathioprine can cause liver toxicosis. Some dogs may require long-term or lifelong therapy.

Prognosis & Outcome

CBC was repeated after Cain had been receiving prednisone for 1 month (day 61) and showed a neutrophil count of 3.58 K/µL. Prednisone was slowly tapered over the next several months, with CBC checked 1 week after each dose change. Cain continued to be healthy and was no longer receiving prednisone at the time of publication.

Prognosis for remission is good and typically fast after prednisone is instituted.[2,11,12] A study of 11 dogs showed rapid remission with prednisone and no relapse as corticosteroids were tapered.[12] However, in a recent study of 35 dogs, 12 developed a relapse of neutropenia when prednisone treatment was tapered or discontinued.[11] Additional long-term studies are needed for more accurate assessment of relapse and to determine the number of dogs needing lifelong immunosuppressant therapy.

TREATMENT AT A GLANCE

- Prednisone should be started at an immunosuppressive dosage (2 mg/kg/day or 50 mg/m^2 in dogs >55 lb [25 kg]) and CBC rechecked in 1 week.
- If the neutrophil count is <1 K/µL, a broad-spectrum antibiotic to cover aerobic gram-positive and gram-negative bacteria should be considered to reduce the risk for sepsis.[1,5-9]
- If the patient does not respond to prednisone alone, another immunosuppressant (eg, azathioprine [2 mg/kg/day or 50 mg/m^2]) can be added.
- If azathioprine must be discontinued due to liver toxicosis, other immunosuppressants (eg, cyclosporine, mycophenolate, leflunomide) can be attempted.

IMN = immune-mediated neutropenia

See page 79 for references.

TAKE-HOME MESSAGES

- IMN is an uncommon condition diagnosed based on exclusion of other causes of neutropenia.
- Common differential diagnoses include infectious disease, neoplasia, bone marrow disease, drug toxicity, and genetic disease.
- The most common clinical signs are fever and lethargy; however, neutropenia may be an incidental finding on routine blood work.
- Physical examination should be aimed at finding any nidus for infection that could cause neutropenia, particularly a heart murmur secondary to endocarditis, abscesses, spinal pain for discospondylitis, enlarged lymph nodes, and abdominal palpation abnormalities.
- Diagnosis involves sequential CBCs with blood smear analysis, serum chemistry profile, urinalysis, thoracic radiography, abdominal ultrasonography, tick-borne and other infectious disease testing, FeLV/FIV testing in cats, and bone marrow cytology and/or histopathology. In patients with clinical signs, urine and possibly blood cultures can be considered to rule out sources of infection.
- Treatment should begin with prednisone; most dogs respond within 7 to 10 days.

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CASE IN POINT
CONTINUED FROM PAGE 76

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1 **CONSULT THE EXPERT** **PAGE 14**

Which of the following statements regarding heartworm antigen testing in dogs is false?

A. Male-only single sex infections are not detected.
B. Prepatent infections (ie, worms <5 months of age) are not routinely detected.
C. If all worms are killed, adult antigens should be cleared from the blood by 9 months after treatment.
D. These tests are quantitative; the color of the test correlates with the worm burden.

2 **DIAGNOSTIC/MANAGEMENT TREE** **PAGE 22**

A 2-year-old male crossbreed dog is presented after getting hit by a car. Physical examination and thoracic auscultation reveal a restrictive breathing pattern with rapid, shallow breaths and decreased ventral lung and heart sounds with thoracic borborygmi. What is the most likely differential?

A. Pulmonary contusions
B. Diaphragmatic hernia
C. Pulmonary effusion
D. Pneumothorax

3 **CASE IN POINT** **PAGE 57**

How soon after attachment by an *Amblyomma americanum* tick does transmission of *Cytauxzoon felis* occur?

A. 12 hours
B. 24 hours
C. 36 hours
D. 72 hours

4 **TOP 5** **PAGE 64**

Because of NSAIDs potential antitumor activity and ability to provide analgesia, these drugs may be recommended as part of standard therapy for which of the following types of cancer?

A. Carcinoma
B. Sarcoma
C. Leukemia
D. Lymphoma

5 **CASE IN POINT** **PAGE 73**

The most common treatment for immune-mediated neutropenia in dogs is _____.

A. Mycophenolate
B. Azathioprine
C. Immunosuppressive doses of glucocorticoids
D. Cyclophosphamide

Answer Key:
1: D 2: B 3: C 4: A 5: C

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