September 2020

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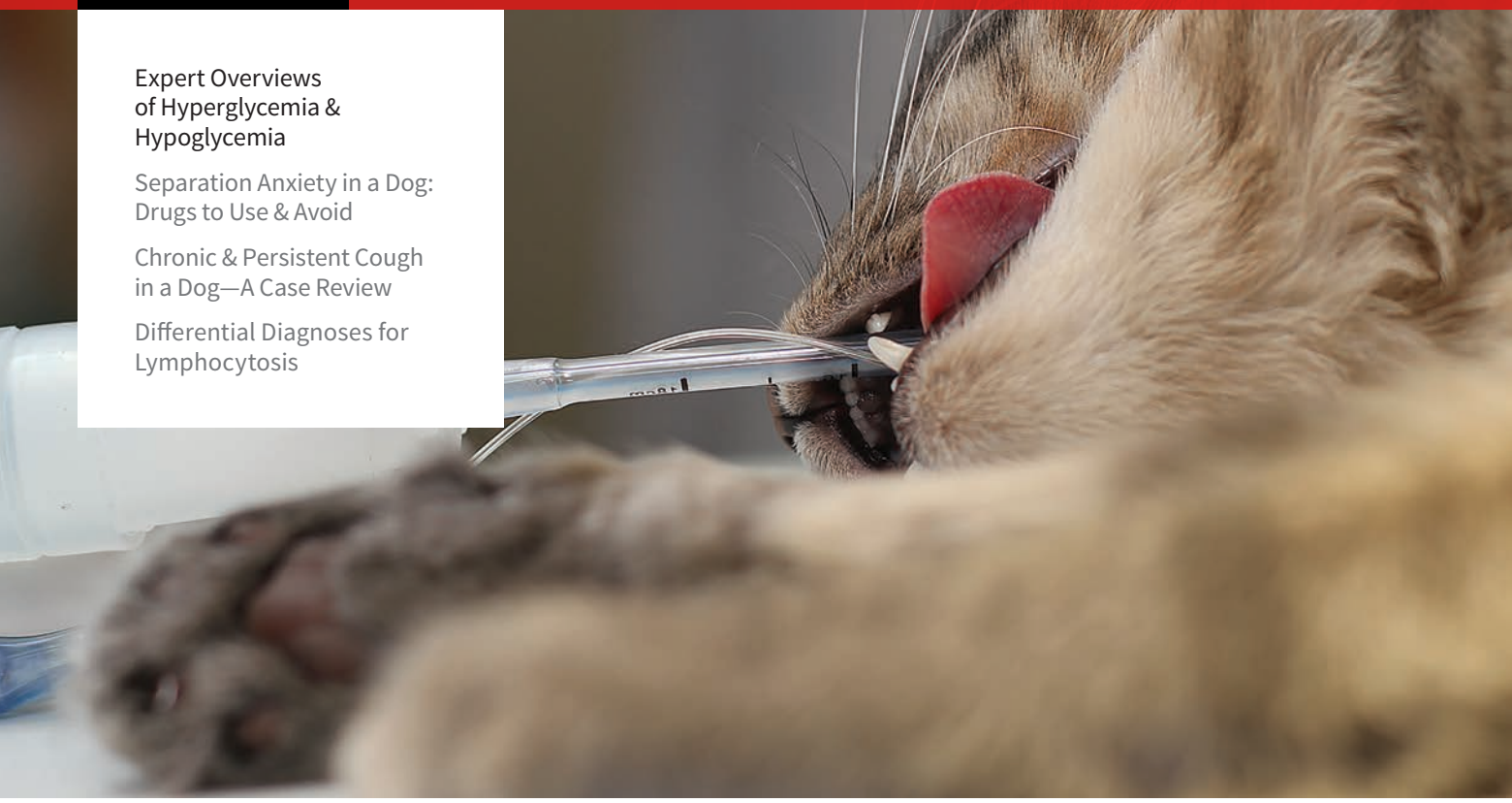
# ANESTHETIC MANAGEMENT DIFFERENCES IN DOGS & CATS

**IN THIS ISSUE**





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WSAVA Global Veterinary Community

clinician's brief
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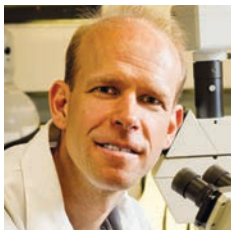











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"30 lbs; it was the whole Great Dane's abdomen and not hemangiosarcoma!"—*Camilo A*

"21 lbs; it barely fit in a litter box."—*Erin E*

"I assisted in a splenectomy that was 24 lbs."—*Laura F*

"18 lbs, from a golden retriever."—*Christine K*

### What unique items has a pet owner requested to take home after surgery?

"Placenta from a dog. The owner wanted to eat it for nutritional value."—*Chelsie T*

"Titanium plate from their cat's leg postcremation so they could make jewelry out of the plate"—*Sian B*

"Bladder stone. The owner said it would be the most expensive 'rock' she would ever own."—*Joni S*

"A large pus-filled pyometra from a French bulldog." —*Nanda K*

"We had an owner who made jewelry from her dog's gonads."—*Lacie S*

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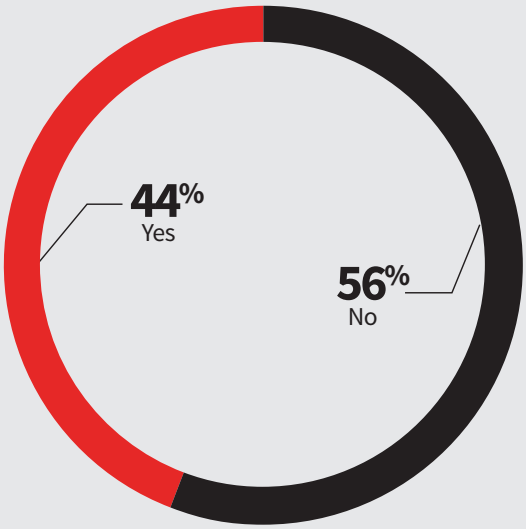


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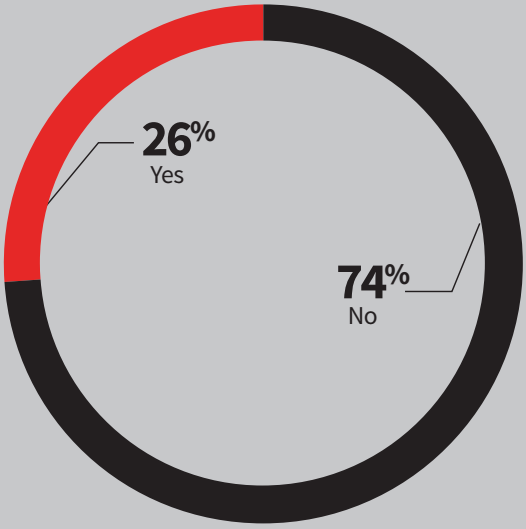


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HEARTWORM TESTING

# Heartworm Diagnostics: Antigen Tests Alone Aren't Enough

**LINDSAY STARKEY, DVM, PHD, DACVM-PARASITOLOGY**
ASSISTANT PROFESSOR,
DEPARTMENT OF PATHOBIOLOGY
AUBURN UNIVERSITY COLLEGE OF VETERINARY MEDICINE

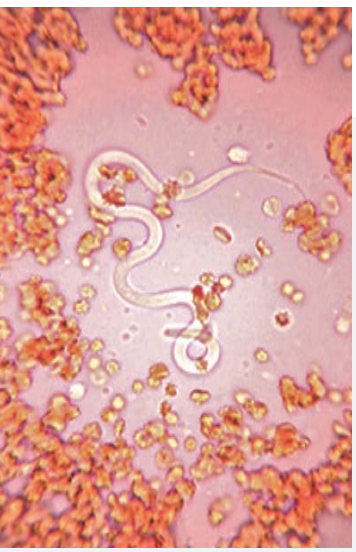
The American Heartworm Society (AHS) recommends heartworm antigen testing to screen dogs without clinical signs and verify suspected heartworm infections. While patient-side antigen tests provide a vital tool for the practice, a full understanding of their role in heartworm diagnosis is essential.

**Q. Today's commercial antigen tests have great utility in heartworm screening. Nevertheless, these tests also have certain limitations, don't they?**

**A.** Antigen tests detect circulating heartworm antigen from adult worms and are nearly 100% specific. While highly accurate in the vast majority of cases, even the most sensitive heartworm test can fail to detect the presence of antigen when levels of circulating antigen are low due to the presence of immature worms, male-only infection or few female worms. In other cases, sufficient antigen is present but bound by the antibodies produced as part of the body's response to infection. This is known as an immune complex formation.

**Q. The AHS recommends that microfilaria testing be conducted in addition to antigen testing as part of routine heartworm screening in dogs. Why?**

**A.** It's possible for dogs to test antigen-negative and microfilaria-positive (e.g. with immune complex formation) or antigen-positive and microfilaria-negative (e.g. during an occult infection). Conducting both antigen and microfilaria tests helps ensure that heartworm diagnoses will not be missed. Testing for the presence of microfilariae is an important component of the heartworm screening process, especially when the veterinarian has a high suspicion of infection or when the dog's prevention history is unknown.



*The AHS recommends conducting microfilaria tests in tandem with antigen tests. (Image credit: Stephen Jones, DVM)*

**Q. What should be done if heartworm testing yields an unexpected or ambiguous result?**

**A.** False-positive results with heartworm antigen tests are rare. However, there are times when a "no antigen detected" (NAD) result on a heartworm test belies what our clinical judgment is telling us—particularly when we strongly suspect heartworm infection given the patient's history (e.g. a rescue dog with no history of prevention from a highly endemic area), the presence of clinical signs, and/or the presence of microfilariae. When this happens, the following steps should be considered:

- **Immune complex dissociation.** Antigen tests are usually sensitive enough to yield an accurate result despite some antigen being bound, but in certain cases immune complex formation can lead to an NAD finding in patients with adult heartworms. Heat or acid pretreatment of the serum or plasma sample dissociates the immune complexes and allows for released antigen to be detected. This testing is offered by a number of state and commercial diagnostic laboratories.
- **Retest in six months.** Following infection, it can require six to seven months for a dog to test positive on an antigen test. In the case of a dog with a high likelihood of infection but an NAD result, waiting for the worms to mature may be necessary. A retest in six months vs. waiting 12 months until the next annual check-up will ensure that the dog is diagnosed and treatment implemented early in the disease process while also reducing confusion and concern regarding the efficacy of the heartworm preventive utilized in the interim.
- **Consider other diagnostics.** Depending on the age of the dog and the presence of clinical signs, further evaluation, including comprehensive bloodwork with a urinalysis, ultrasonography, radiographs and/or echocardiography, may provide important information.

# OUR AUTHORS

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**TOP 5 PAGE 11**

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**CASE IN POINT PAGE 63**

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**CONSULT THE EXPERT PAGE 28**

**LESLIE SINN**, CPDT-KA, DVM, DACVB, maintains Behavior Solutions for Pets in Leesburg, Virginia. She earned her DVM from University of Georgia, where she also completed an internship in small animal medicine and surgery. Dr. Sinn is a board-certified veterinary behaviorist and a certified professional dog trainer. She has lectured worldwide and is the author of numerous articles and book chapters.

**RED LIGHT, GREEN LIGHT PAGE 70**

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Khursheed Mama, DVM, DACVAA

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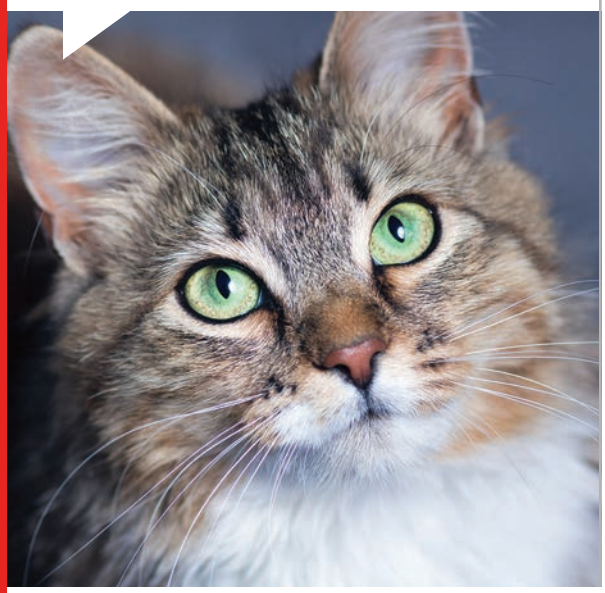

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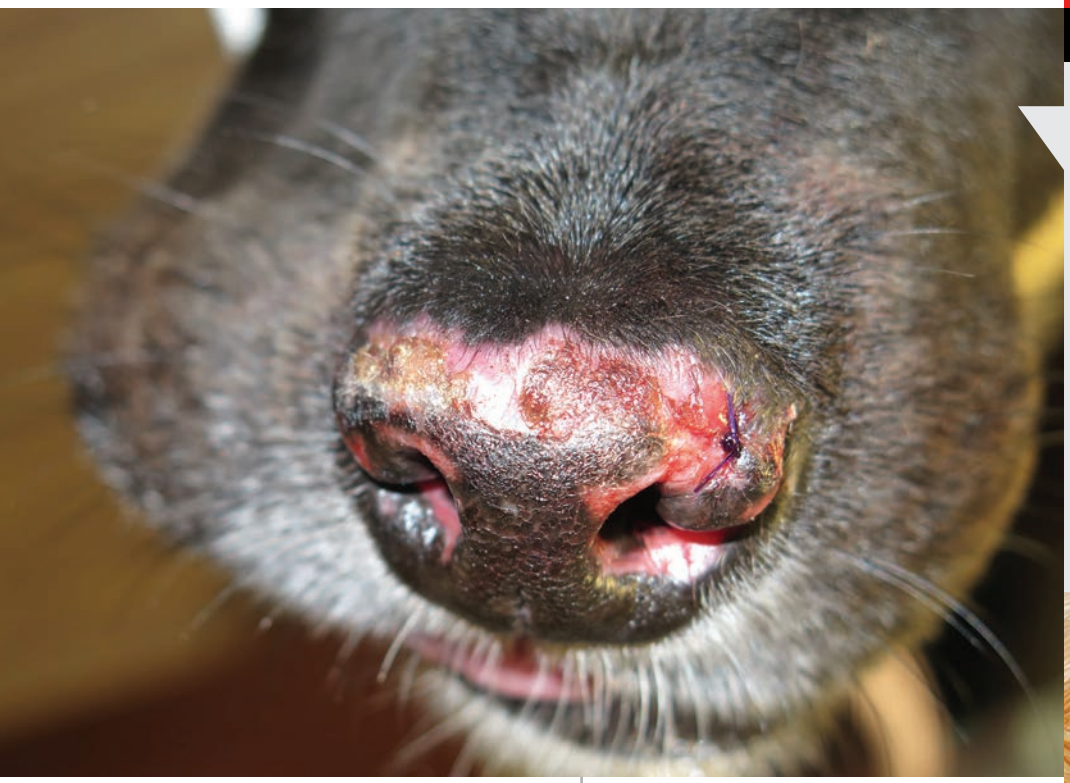

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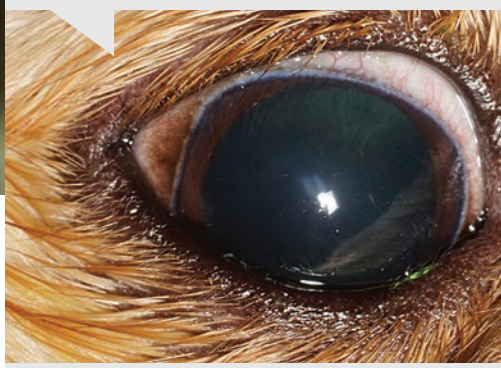




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# Top 5 Anesthetic Management Differences Between Dogs & Cats

**Khursheed Mama, DVM, DACVAA**
*Colorado State University*

When planning for and managing anesthesia in cats and dogs, there are differences beyond size that should be considered.

Following are 5 of the most common key differences in anesthetic management for cats and dogs according to the author.

## 1 Restraint & Instrumentation

Minimal restraint is frequently most effective in achieving efficiency, which is key when working with cats. Previsit oral medications (eg, gabapentin and trazodone) given at home have been shown to minimize anxiety and stress and increase compliance.[1-3] Alfaxalone and dexmedetomidine can also help alleviate agitation; these drugs are typically administered IM after the overall health of the cat has been evaluated.

Because of the small size of cats, IV catheterization can be more challenging in cats than in dogs. Although the cephalic vein can be catheterized in both cats and dogs, the medial saphenous vein is more commonly catheterized in cats, and the lateral saphenous vein is more commonly catheterized in dogs. Intubation can also be more challenging in cats because of the size and reactivity of

### TOP 5 ANESTHETIC MANAGEMENT DIFFERENCES BETWEEN DOGS & CATS

the upper airway. If care is not used, a greater incidence of tracheal tears following intubation is possible[4,5]; however, use of topical lidocaine on the arytenoids and an appropriate tube without a stiff stylet can greatly minimize these problems. Diligent cuff inflation and disconnection of the tube from the breathing circuit are also important when turning the patient.

Postanesthesia, cortical blindness also has been reported in cats (but not in dogs) and associated with the influence of spring-loaded mouth gags on maxillary artery blood flow[6,7]; therefore, it is important that use of these devices be minimized or avoided when anesthetizing cats for bronchoscopy, endoscopy, or dentistry.

## 2 Anesthetic Equipment

A nonrebreathing circuit (eg, Bain) is commonly used to anesthetize cats weighing <11 lb (5 kg). These circuits must be appropriately assembled and used in order to minimize complications, including excessive pressure in the system. A nonrebreathing system also requires higher flow rates on a per-kilogram basis to minimize rebreathing of carbon dioxide, which can dry the respiratory tract and increase patient cooling. Although not routinely used during anesthetic management, there are tools that can help alleviate these concerns by heating and humidifying the breathing system. Pediatric circle systems can be used in cats, but inspiratory and expiratory valves and carbon dioxide absorbent increases the work required for breathing in spontaneously ventilating animals, possibly resulting in fatigue and hypoventilation.

**Opioid-associated sedation may contribute to lack of hyperthermia in dogs.**

Similar considerations relative to breathing circuits exist for small dogs. Larger dogs can typically be maintained on circle breathing systems with appropriately sized hoses and rebreathing bags.

## 3 Medications & Patient Response

Cats differ in their requirements for and responses to numerous medications commonly used in the perianesthetic period. Acepromazine is considered an effective tranquilizer in dogs, particularly when used in combination with other drugs, but equivalent acepromazine-associated tranquilization in cats may not result, despite signs suggesting efficacy (eg, a raised third eyelid). Conversely, dexmedetomidine provides good sedation in both dogs and cats. The anesthetic induction dose needed to facilitate intubation is lower following dexmedetomidine premedication than with acepromazine.[8]

Opioids are reported to cause a higher degree of signs of euphoria or dysphoria in cats than in dogs, especially with IV administration.[9] The analgesic- and inhalant-sparing effects in cats also differ from those in dogs, and a ceiling effect (ie, increased dose does not result in additional clinical benefits) may occur at a lower dose.[10] Unlike in dogs, large or repeated doses of opioids may result in hyperthermia in cats.[11] The cause of hyperthermia is unknown. Elevations in body temperature are not typically reported in dogs, even when panting is observed following administration. Opioid-associated sedation may contribute to lack of hyperthermia in dogs.

Lidocaine given IV with a bolus or constant-rate infusion has been increasingly used in dogs for its anesthesia-sparing effects and possible analgesic

benefits. However, IV lidocaine is not routinely recommended in cats because the associated cardiovascular depression is worse than an equivalent dose of inhalant, and drug-related toxicity is possible.[12] When comparing isoflurane requirements, the minimum alveolar concentration is higher in cats than in dogs.[13]

## 4 Monitoring

Cardiovascular and respiratory monitoring can be challenging in cats because of their size and limitations with monitoring equipment not specifically developed for use in cats. For example, many oscillometric noninvasive blood pressure monitors provide only intermittent readings in cats, and obtaining a reliable signal from a Doppler crystal can be difficult. These obstacles can be further complicated by the use of certain drugs (eg, dexmedetomidine) that cause vasoconstriction, bradycardia, and decreased cardiac output. Similar challenges can occur with the use of a pulse oximeter to monitor oxygen saturation. Amplitude of the electrocardiogram may also hinder accurate heart rate measurement and assessment of rhythm changes in cats as compared with dogs. Typically, cats have higher heart rates than dogs, but their blood pressure during anesthesia tends to be more labile or stimulus-responsive. It is therefore important to evaluate physiologic monitors to be used during anesthesia in the clinic to ensure functionality. In addition, using an appropriately sized Doppler crystal or an alternate site (eg, tail vs distal limb) may help improve performance. Similarly, for pulse oximeter probes, placement of a moist gauze sponge over the tongue prior to probe placement can be beneficial.

When a nonrebreathing system is used, sidestream capnography can result in significant underestimation of the end-tidal carbon dioxide tension because of the constant flow of oxygen diluting exhaled gas at the sampling site. A mainstream capnometer can alleviate this issue, but weight on the endotracheal tube can cause kinking or dislodging.

Pain assessment in cats is also more difficult and requires close observation of specific behaviors and interaction with the patient as needed.[14] There are an increasing number of pain scales and assessment tools available.

## 5 Support

Fluid therapy during anesthesia is critical for maintaining blood pressure and vital organ perfusion during anesthesia in cats and dogs. Because older cats are frequently diagnosed with varying stages of renal disease, fluid support is essential in the perianesthetic period.[15] To account for blood volume differences (ie, ≈60-70 mL/kg in cats vs ≈80-90 mL/kg in dogs), the volume of both fluids and blood products should be lowered for cats, especially when administered via bolus. Because universal feline donors do not exist, all cats, including naive cats, should be typed and crossmatched to donors in cases in which use of blood products is anticipated.

## Conclusion

Although anesthesia in cats is often thought to be more challenging than in dogs, knowledge of species-specific requirements and responses can help improve patient management during the perianesthetic period.

**All cats should be typed and crossmatched to donors in cases in which use of blood products is anticipated.**

See next page for references

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See page 14 for product information summary.

**References: 1.** Semintra® (telmisartan oral solution) Prescribing Information. Boehringer Ingelheim Vetmedica, Inc. 2018.
**2.** Zimmering T. Ease of use of Semintra® and its effects on quality of life—update on cat owner feedback ("EASY Programme") [abstract]. In: Proceedings from the 21st Federation of European Companion Animal Veterinary Associations (FECAVA); October 15–17, 2015; Barcelona, Spain. Poster.




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# Hyperglycemia

**Thomas Schermerhorn, VMD, DACVIM (SAIM)**
*Kansas State University*

Hyperglycemia is defined as an increase in blood glucose levels above the physiologic range for a given species. Hyperglycemia may be physiologic or pathologic and is always secondary to a disorder that disrupts one or more of the homeostatic mechanisms that maintain euglycemia.

## Background & Pathophysiology

Glucose is a principal fuel metabolized to produce adenosine triphosphate for use in cellular-energy–requiring processes and is vital for normal cell function. Homeostatic mechanisms maintain blood glucose levels within narrow physiologic limits (ie, euglycemia).[1] Glucose ranges in dogs and cats vary slightly but generally measure ≈90 mg/dL.[2]

Glucose homeostasis is a balance between glucose appearing in and disappearing from the blood (***Figure***). Normoglycemia is maintained by the complex interactions of a group of hormones that exert hyperglycemic or hypoglycemic actions by altering the metabolic pathways that produce or consume glucose.[3] Insulin, produced by β cells in the pancreatic islets, is the most important hormone for maintaining glucose homeostasis. Insulin secretion is precisely regulated by glucose. In circulation, it exerts potent hypoglycemic actions by promoting cellular uptake of glucose, stimulating hepatic glycogenesis, and suppressing hepatic gluconeogenesis.[4] Several hormones that promote hyperglycemia oppose insulin's hypoglycemic actions. Glucagon, also of pancreatic islet origin, activates hepatic glycogenolysis and gluconeogenesis pathways that increase net glucose production by the liver.[3] Thyroid hormones exert a hyperglycemic action, especially when secreted in excess, as in hyperthyroidism.[3] Adrenal catecholamines (eg, epinephrine, norepinephrine),[5] cortisol,[6] and growth hormone[7] also antagonize insulin action. Glucagon, growth hormone, catecholamines, and

cortisol are collectively called "counterregulatory hormones" to reflect their functions as insulin antagonists. These hormones are the physiologic foundation of hyperglycemia that develops as part of the "fight-or-flight" response, but individual hormones play roles in various disorders that have insulin resistance as a common pathology.[8]

## Mechanisms of Action

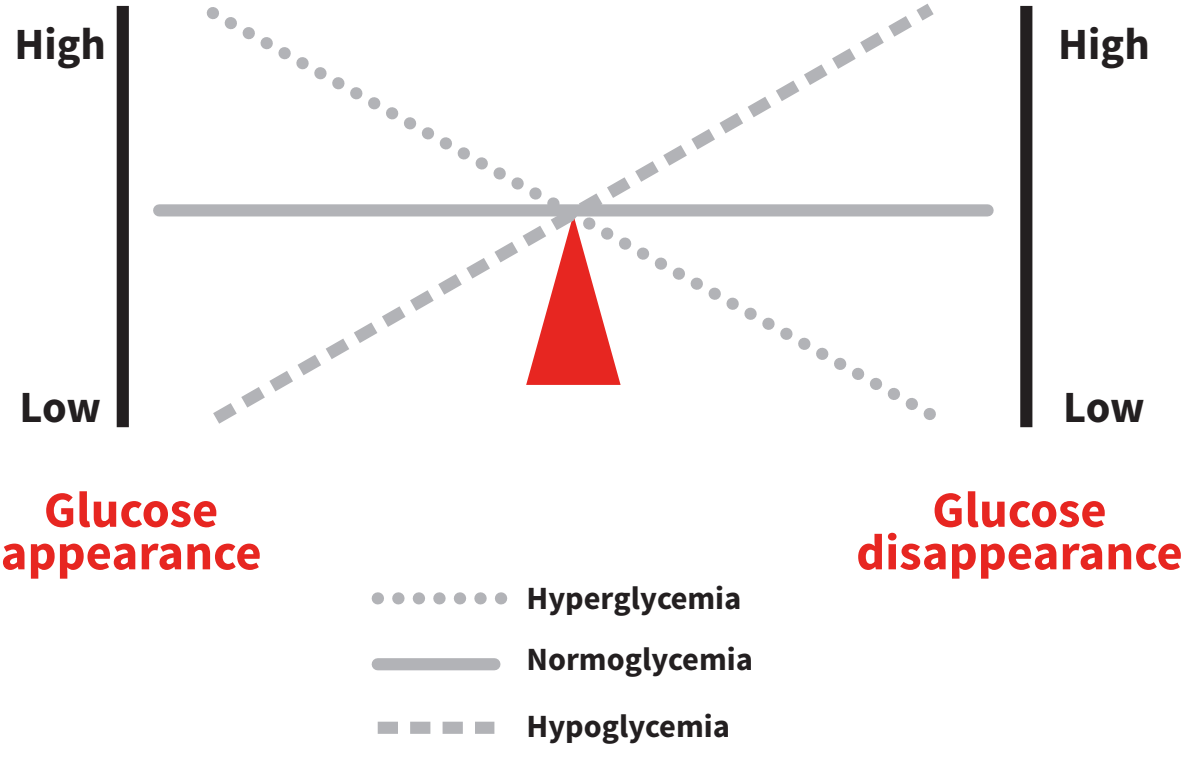
Homeostatic mechanisms responsible for normoglycemia maintenance are robust and persistent. Hyperglycemia does not occur when physiologic pathways are intact; instead, it appears when glucose enters the blood faster than it can be removed (***Figure***). Pathologic hyperglycemia develops when physiologic mechanisms that suppress glucose are lacking (as in hypoinsulinemic states) or attenuated (as in insulin-resistant states).[9] Once hyperglycemia is established, chronic elevation of blood glucose levels exacerbates the existing defects in pathways for β-cell secretion and insulin action in target tissue, a phenomenon termed *glucose toxicity*.

### Hypoinsulinemia

Hypoinsulinemia is an absolute or a relative decrease in blood insulin levels. Absolute hypoinsulinemia is caused by β cell loss, whereas relative hypoinsulinemia occurs when insulin is unable to mount an appropriate response to increased blood glucose levels. Hypoinsulinemia is a hallmark of advanced diabetes mellitus in dogs and cats, regardless of the underlying pathology.[10]

### Insulin Resistance

Insulin resistance is a metabolic state in which target tissues resist the hypoglycemic actions of




▲ **FIGURE** The relative rates of glucose appearance into and disappearance from the blood affects glycemic status. Normoglycemia (***solid line***) is maintained when the rates of appearance and disappearance are balanced. Hyperglycemia (***dotted line***) results when the rate of appearance exceeds the rate of disappearance, and hypoglycemia (***dashed line***) occurs when disappearance exceeds appearance.

insulin (ie, decreased insulin sensitivity). Insulin resistance interferes with insulin-mediated cell signaling and reduces glucose uptake in peripheral tissues, especially skeletal muscles and adipose tissue.[4] With reduced insulin effects at the cellular level, the pancreas must produce more insulin. This insulin resistance results in hyperinsulinemia, an early feature of hyperglycemia (ie, hyperinsulinemic hyperglycemia). However, patients that are chronically insulin-resistant may develop β-cell failure and hypoinsulinemia (ie, hypoinsulinemic hyperglycemia).[4]

Hyperglycemia produces pathology by inducing hyperosmolality (which underlies the commonly observed clinical signs) and producing advanced glycation end products (AGEs), a process that is associated with end-organ damage in vascular and neuronal cells.[11]

## Pathology

Glucose is a serum osmole but contributes little (3-5 mOsm/L) to the total serum osmolality in normoglycemic dogs and cats.[12,13] The osmolar contribution of glucose parallels the magnitude of hyperglycemia and can be substantial in cases of severe hyperglycemia (eg, >50 mOsm/L when glucose exceeds 1000 mg/dL).[12] Complications of hyperosmolality observed with severe hyperglycemia include vomiting, neurologic impairment, seizures, and coma.[13] The onset of hyperosmolality initially triggers corrective physiologic responses, including thirst and reduced renal excretion of free water.[14] Chronic hyperosmolality induces additional adaptations, including expanded blood volume and altered water metabolism.

Hyperglycemia also permanently alters cellular and serum proteins through a nonenzymatic glycation reaction that produces a series of AGEs.[11] Some glycated proteins (eg, hemoglobin $A_{1c}$ and fructosamine) serve as clinical biomarkers that reflect average blood glucose levels over time.[15] Other AGE proteins interact with specialized receptors of AGEs that are expressed by vascular and neuronal tissues, a reaction that is implicated in long-term diabetes complications, such as microangiopathy and neuropathy.[11]

## Common Conditions Associated with Hyperglycemia

Numerous causes of hyperglycemia have been identified in dogs and cats (see ***Causes of Hyperglycemia***). Several frequently encountered endocrine causes illustrate how pathologic disorders disrupt normal homeostatic mechanisms to cause this disorder.

### Diabetes Mellitus

Diabetes mellitus (DM) is the most frequently encountered and clinically significant hyperglycemic disorder in small animals. Hyperglycemia in DM arises from the combined influences of hypoinsulinemia and insulin resistance. However, the proportional contribution of each mechanism may vary, depending on underlying diabetes pathology or even the stage of disease. Hyperglycemia in humans with type 1 diabetes is caused by severe hypoinsulinemia that develops as a result of autoimmune-mediated destruction of β cells.[16] Likewise, marked hypoinsulinemia is a typical finding in canine DM, which shares certain pathogenic features with human type 1 diabetes. In humans, an islet defect causes disordered glucose sensing and an abnormal insulin secretion pattern in response to a glucose challenge.[16] Affected humans retain the ability to make and secrete insulin, but the quantity and timing of insulin release is insufficient to maintain euglycemia, and hyperglycemia develops.[16] Islet defects are not well described in canine DM and, if present, occur early in the development of DM and are not recognized clinically. In cats with overt DM due to insulinopenia, the early role of abnormal insulin secretion (the consequence of an islet defect) is not appreciated due to profound islet loss. However, the presence of an islet defect is suggested when islet mass is adequate but there is evidence for impaired glucose tolerance. For example, an islet defect is suggested by the abnormal glycemic response to a glucose challenge in obese cats at risk for DM and the abnormal glucose tolerance documented in cats that have entered diabetic

remission.[17] These cats are normoglycemic and have no requirement for exogenous insulin.[17] Insulin resistance is a major pathologic feature of type 2 diabetes in humans, which may contribute to islet exhaustion and, eventually, hypoinsulinemia.[16] Insulin resistance is not a major feature of uncomplicated canine DM but seems to play a role in pathogenesis and progression of feline DM.[18]

### Catecholamine & Cortisol Excess

Conditions associated with elevated concentrations of catecholamines and/or cortisol produce hyperglycemia by inducing insulin resistance. Catecholamines contribute to the phenomenon of stress hyperglycemia, which serves a physiologic function and is frequently encountered in veterinary patients.[5,19] The stress response is transient and typically results in mild to moderate hyperglycemia; severe hyperglycemia can occur but is uncommon. Excessive production and secretion of norepinephrine by neuroendocrine paraganglioma, as is seen in adrenal medullary tumors (pheochromocytoma), can produce hyperglycemia in ≈25% of affected dogs.[20]

Hypercortisolemia caused by canine hyperadrenocorticism can cause persistent hyperglycemia of varying severity via several mechanisms, including inhibition of insulin secretion and exacerbation of peripheral insulin resistance.[21] Hyperglycemia due to insulin resistance can resolve when hypercortisolemia is addressed, but persistent severe insulin resistance can lead to β cell exhaustion and hypoinsulinemia that results in permanent DM.[21]

### Growth Hormone Excess

Growth hormone (GH), or somatotropin, antagonizes insulin action and, in excess, induces severe insulin resistance. The best example in companion animals is feline acromegaly, which is caused by a functional GH-secreting pituitary adenoma. Cats with acromegaly are usually initially presented for signs related to GH excess, including glucose intolerance, insulin resistance, or, frequently, overt DM.[22] In addition to commonly reported anatomic changes that accompany acromegaly, large pituitary

## CAUSES OF HYPERGLYCEMIA[2]

**Common Causes[2]***

- Physiologic (ie, stress hyperglycemia) hyperglycemia (cats, dogs)
- Diabetes mellitus (cats, dogs)
- Hyperadrenocorticism (dogs)
- Acromegaly (cats)
- Acute pancreatitis (cats, dogs)
- Drug- and toxin-induced hyperglycemia (cats, dogs)
  - Glucocorticoids
  - Progestogens
  - $\alpha_2$-receptor agonists
  - β blockers
  - Glucose-containing crystalloid fluid
  - Parenteral feeding solution
  - Ethylene glycol ingestion

**Uncommon & Miscellaneous Causes**

- Postprandial hyperglycemia
- Pancreatic neoplasia
- Diestrus (dogs)
- Critical illness or sepsis
- Pheochromocytoma
- Hyperthyroidism (cats)
- Head injury/trauma

*Although these etiologies are diverse, common mechanisms underlie the development of hyperglycemia. Hyperglycemia in these conditions is caused by either a pathophysiologic disturbance in the ability to produce/secrete normal amounts of insulin or, more commonly, induction of insulin resistance. For some disorders (eg, pancreatitis), both mechanisms may contribute to hyperglycemia.

AGE = advanced glycation end products
DM = diabetes mellitus
GH = growth hormone

tumors may produce neurologic signs through compression and damage to local brain structures.[22]

## History

Patient history will vary depending on the underlying cause of hyperglycemia. DM is the most frequently encountered disorder associated with clinically significant hyperglycemia. Patients may have a subtle history that includes weight loss, often despite maintaining a normal appetite, along with increased water consumption and changes in urination habits. Patients with complicated diabetes may appear to be ill and exhibit lethargy, diminished appetite, reduced water consumption, or vomiting.[2]

Dogs with hyperadrenocorticism typically demonstrate profound polydipsia and polyuria secondary to hypercortisolemia, so any additive effects of hyperglycemia may go unnoticed in this setting. In some cases, the development of polydipsia or polyuria in a dog with well-controlled hyperadrenocorticism signals the onset of diabetes.[21]

Cats with acromegaly are often presented with uncontrolled DM. They show typical signs of DM but uniquely display persistent hyperglycemia despite provision of high doses of insulin (>2.2 U/kg/dose). It is only after other signs are recognized (eg, increased body mass, organomegaly, changes in facial structure) that acromegaly is suspected.[22]

**Diabetes mellitus is a likely diagnosis when hyperglycemia is the sole or primary finding and clinical signs are present.**

## Clinical Signs

The primary clinical signs of hyperglycemia are polyuria and polydipsia.[2,9] These signs are most obvious with the onset of moderate to severe hyperglycemia, specifically when blood glucose levels begin to exceed the ability of the proximal tubules to reclaim filtered glucose. Glucose is freely filtered at the glomerulus, but avid reabsorption in the proximal tubules ensures that normal urine does not contain glucose. Glucosuria occurs when the amount of filtered glucose exceeds the capacity of the proximal tubules to reclaim glucose from filtrate. The renal threshold for glucose is exceeded when serum glucose levels range from ≥180 to 200 mg/dL in dogs and ≥250 to 280 mg/dL in cats.[2] Polyuria and polydipsia are interrelated and develop as a result of glucose-mediated plasma hyperosmolality (which stimulates thirst and drinking behavior) and glucose-mediated osmotic diuresis (which increases the volume of urine and frequency of urination).[23]

## Diagnosis

Hyperglycemia is diagnosed using any of several widely available laboratory methods. In most clinical situations, glucose is measured as part of most routine serum chemistry profiles but can also be measured using other methods, such as a portable glucometer or interstitial glucose monitor. Mild hyperglycemia in the absence of clinical suspicion of a hyperglycemic disorder may be transient physiologic hyperglycemia and should be re-evaluated; persistent hyperglycemia, even if relatively mild, warrants a diagnostic investigation. DM is a likely diagnosis when hyperglycemia is the sole or primary finding and clinical signs are present. However, careful evaluation is necessary to avoid DM misdiagnosis in patients presented under circumstances that might induce stress hyperglycemia (eg, severe illness, fear, anxiety), which is frequent in cats and can be marked in some patients.

In rare circumstances, it may be challenging to confirm a DM diagnosis in a patient with hyperglycemia due to illness or stress. Fasting hyperglycemia or hyperglycemia that persists over multiple

sampling periods or marked glucose elevation (>250 mg/dL) is suggestive of DM rather than a stress response. Although glucosuria is not essential for a diagnosis of DM, most dogs and cats have glucosuria at the time of diagnosis. Glucosuria may occur secondary to marked stress hyperglycemia in some cases and is present without concurrent hyperglycemia with conditions associated with renal tubule dysfunction (eg, primary renal glucosuria, Fanconi's syndrome, acute renal tubular injury).[24]

## Treatment & Management

Principal management of hyperglycemia aims to address the underlying cause. Hyperglycemia caused by insulin resistance may be ameliorated as the associated condition resolves, endocrine pancreatic function (eg, glucose-sensing, insulin secretion) normalizes, and an appropriate insulin response can be mounted. For example, hyperglycemic humans with obesity-associated insulin resistance may return to normoglycemia after weight loss. Hyperglycemia associated with glucocorticoid excess resolves when hyperadrenocorticism is addressed if β cell function is normal. Likewise, although hyperglycemia is an infrequent finding with functional canine pheochromocytoma, normoglycemia is expected to be restored after successful adrenalectomy. The insulin resistance that accompanies feline acromegaly is severe and often only fully resolves with appropriate therapy that effectively addresses excessive growth hormone.

Hyperglycemia caused by hypoinsulinemia is treated with insulin replacement. Most patients requiring insulin replacement have permanent DM, although the diabetic state can resolve under some circumstances. For example, severe pancreatitis may be accompanied by hyperglycemia, which, if severe enough, warrants use of insulin to restore euglycemia. Hyperglycemia in this setting is due to the combined effects of insulin resistance (secondary to marked inflammation) and hypoinsulinemia (secondary to islet cell injury or loss). In some cases of pancreatitis-associated DM, the need for exogenous insulin decreases and eventually resolves with resolution of pancreatitis.

## Prognosis & Clinical Follow-Up

The pathologic consequences of untreated chronic hyperglycemia are similar regardless of the underlying cause. Risk for complications increases with the duration and magnitude of hyperglycemia. Microvascular injury caused by chronic hyperglycemia causes the common diabetic complications in humans (eg, retinopathy, nephropathy). Hyperglycemia also has a role in cataract formation in dogs and diabetic neuropathy in dogs and cats, as well as in humans.

Hyperglycemia is a common clinical problem in dogs and cats. The prognosis is difficult to determine because it depends on whether the underlying cause can be effectively controlled. DM in dogs and cats carries a guarded prognosis, depending on the establishment of an effective control protocol. Canine hyperadrenocorticism has a variable prognosis, depending on the initiating pathology (ie, pituitary, adrenal), but prognosis for return to euglycemia is good if hypercortisolemia is effectively controlled. Hyperglycemia associated with feline acromegaly carries a poor prognosis, primarily because diabetes control is difficult, options for treatment of growth hormone excess and pituitary adenoma are limited, and cats are often presented with advanced disease.

**Glucosuria may occur secondary to marked stress hyperglycemia in some cases.**

DM = diabetes mellitus

See next page for references

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0920-663-I01A

See page 22 for product information summary.

# Comparison of Essential Nutrients in Plant-Based Pet Foods with Nutrient Requirements of Dogs & Cats

This study investigated multiple essential nutrients in commercial plant-based diets fed to dogs and cats. Some pet owners feed plant-based diets as either part (7.9% of owners) or all (1.3% of owners) of their facultative carnivorous dog's or obligate carnivorous cat's diet. Proximate analyses, amino acids, fatty acids, minerals (excluding selenium and iodine), vitamin A, vitamin B12, and vitamin D3 were measured in single samples of all plant-based cat and dog foods commercially available in Canada ($n$ = 26). Essential nutrient analyses were compared with Nutritional Research Council nutrient requirements for maintenance and growth of the labeled species and life stage.

Twenty percent of the canine and none of the feline adult diets met adult maintenance requirements. No canine or feline growth diets met all requirements for growth. One canine growth diet met adult maintenance requirements. Of the diets, 85% failed to meet the nutrient profile for which they were intended. Of greatest concern was failure to meet calcium, phosphorus, and vitamin D3 requirements for growing dogs and cats and sulfur amino acid requirements for both growing and adult dogs and cats. Dogs and cats fed plant-based diets should be closely monitored for signs of malnutrition, especially those related to sulfur amino acid and bone metabolism (eg, skeletal deformities, abnormal growth, failure to thrive).—*Dodd SAS*

# Alterations of Serum Amino Acid Profiles in Cats with Chronic Kidney Disease

Cats with chronic kidney disease (CKD) are typically older and are often presented with change in appetite (usually decreased), decreased weight and muscle mass, and increased colonic protein fermentation metabolites. These metabolites are considered detrimental to the patient. Alterations in serum amino acids may provide a useful focus for treatment. Serum amino acids in healthy senior cats were compared with those in cats affected by CKD; concentrations of essential amino acids (ie, leucine, methionine, phenylalanine, threonine, tryptophan, valine) were significantly decreased in CKD patients, as were concentrations of nonessential amino acids (ie, serine, tyrosine, proline, asparagine). Cats with CKD also had elevated levels of taurine and nonessential amino acids (ie, citrulline, aspartic acid). In cats with CKD, 3-methylhistidine was also elevated and positively correlated with serum creatinine; this is indicative of skeletal muscle breakdown, making elevated 3-methylhistidine possibly useful as a marker for muscle wasting.—*Summers S*

# Clinical Assessment of Transdermal Gabapentin in Cats

In cats, gabapentin has been used as an alternative to opioids and NSAIDs, but dosages and administration can be difficult for some cat owners when the drug is given chronically. This study aimed to determine whether transdermal administration of gabapentin permeates feline skin in vivo and the response of painful cats to transdermal gabapentin.

In the first phase, 8 healthy cats were treated with gabapentin at either 5 mg/kg or 10 mg/kg transdermally applied to the ear pinnae or cervical region three times daily. Serum samples to measure gabapentin levels were collected preadministration and at days 1 and 5 after treatment was started. Gabapentin was measurable in all samples at days 1 and 5 with no differences detected between doses or administration locations.

In the second phase, 15 cats with underlying disease (ie, International Renal Interest Society [IRIS] stage 2 chronic kidney disease, osteoarthritis, obesity) were given gabapentin at 10 mg/kg transdermally 3 times daily for 5 days. Two validated pain assessment scales were evaluated preadministration and on days 1, 5, and 8 after treatment was started. There was a significant increase in serum gabapentin concentration on day 5 as compared with day 1. There was also significant improvement in pain scores on day 5 versus preadministration or day 1. Pain scores on day 8 were not significantly different than at preadministration. The authors concluded that further study for chronic gabapentin use in cats is warranted.—*Slovak JE*


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# Comparing Adipose-Derived Mesenchymal Stem Cells to Prednisolone for the Treatment of Feline Inflammatory Bowel Disease

Feline adipose-derived mesenchymal stem cells (fMSCs) have been proposed for the treatment of chronic enteropathy in cats. This small preliminary study compared the efficacy of fMSCs versus prednisolone in cats with inflammatory bowel disease (IBD); 12 cats with IBD were included. A patient history was obtained, and physical examination, CBC, serum chemistry profile, urinalysis, fecal sample, total thyroxine ($T_4$), and GI panel were performed to exclude major concurrent disease; a 2-week dietary trial was performed to rule out food-responsive diarrhea. Multisite histopathology, immunohistochemistry, PCR for antigen receptor rearrangements (PARR), and flow cytometry were conducted to confirm IBD.

Enrolled cats were randomly assigned to the prednisolone ($n$ = 6) or fMSC ($n$ = 6) group and received both treatment and appropriate placebo. Pet owners were blinded to the grouping. The fMSC treatment (or placebo for the prednisolone group) was administered as 2 SC injections given 2 weeks apart; fMSCs came from a specific pathogen-free donor. Prednisolone (or placebo for the fMSC group) was given at 1-2 mg/kg PO every 24 hours and tapered based on clinical effect after 2 months. Patients were reassessed after 6 months using a standardized questionnaire (ie, Feline Chronic Enteropathy Activity Index [FCEAI]). One cat in each group failed treatment at 2 months, but the remaining 5 cats in each group responded well to therapy. At the 6-month recheck, the mean FCEAI score for the prednisolone group rose slightly from 3.4 to 3.7 (range, 0.5-9) and for the fMSC group fell from 3.7 to 1.0 (range, 0-1.5). These results suggest that fMSCs are at least as effective as prednisolone in the treatment of feline IBD.—*Webb CB*

# Antibiotic Administration Results in Long-Term Changes to the Immature Feline Fecal Microbiome

This study evaluated the effect of antibiotic treatment (AT) on GI bacterial groups possibly associated with dysbiosis in kittens. Previous findings in humans and research animals demonstrated that GI microbial composition and function are significantly affected by AT during early life. Human infants and children with antibiotic-induced intestinal dysbiosis have an increased risk for GI and non-GI–related disorders.

Kittens (≈8 weeks of age) given AT were randomly treated with amoxicillin/clavulanic acid (group 2; $n$ = 22) for 20 days or doxycycline (group 3; $n$ = 20) for 28 days. Group 1 was the control group and consisted of 23 healthy kittens. DNA was extracted from naturally passed fecal samples on days 0, 20 (group 2) or 28 (group 3), 60, 120, and 300. Quantitative PCR was performed for total bacteria, *Turicibacter* spp, *Clostridium hiranonis*, *Faecalibacterium* spp, *Streptococcus* spp, *Escherichia coli*, *Blautia* spp, *Fusobacterium* spp, and *Bifidobacterium* spp. There were no differences among groups on day 0. On day 20, group 2 had decreases in total bacteria, *Streptococcus* spp, and *C hiranonis* as compared with group 1 and in *Faecalibacterium* spp and *Blautia* spp as compared with group 1 and group 3. As compared with group 1, *E coli* was increased on day 20 in group 2 and on day 60 in group 3. *Faecalibacterium* spp and *Bifidobacterium* spp were increased in group 2 as compared with group 1 on day 120. Group 2 and group 3 had increased total bacteria as compared with group 1 on day 300.

The authors concluded that amoxicillin/clavulanic acid and doxycycline can influence bacteria commonly associated with GI dysbiosis in kittens, and these changes can be seen for at least 10 months after antibiotics are discontinued.—*Stavroulaki E*

# Hypoglycemia

**Thomas Schermerhorn, VMD, DACVIM (SAIM)**
*Kansas State University*

Hypoglycemia is a manifestation of a pathologic process—not a diagnosis. It is always secondary to a disorder that disrupts or overwhelms one or more of the homeostatic mechanisms responsible for maintenance of normoglycemia.

## Background & Pathophysiology

Glucose is a dietary carbohydrate used as a substrate for adenosine triphosphate production via anaerobic and aerobic pathways. Its use as a cellular source of fuel requires regulation at multiple points during metabolism. As a result, glucose homeostatic pathways are highly integrated to maintain blood glucose levels within precise physiologic limits.[1]

Hypoglycemia is defined as a decrease in blood glucose below the physiologic range and is considered clinically relevant when levels decrease below 60 mg/dL.[2]

### Blood Glucose Regulation

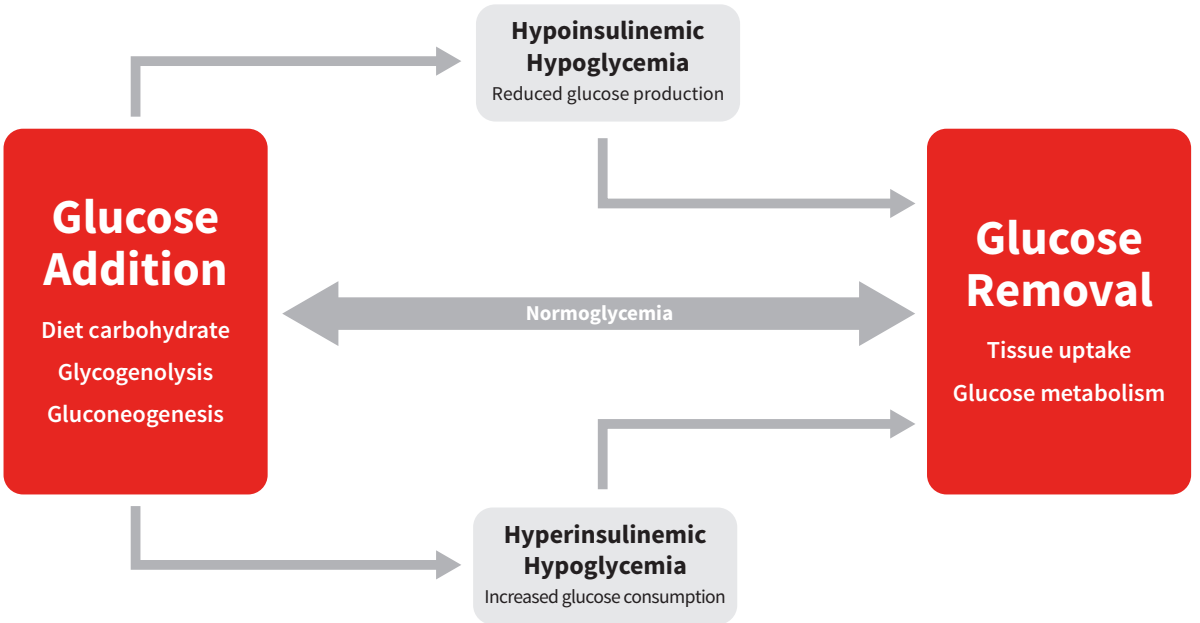
Normoglycemia is maintained by the actions of multiple hormones that regulate the metabolic pathways responsible for glucose addition and removal from blood (***Figure***). Insulin and glucagon are the most important hormones involved in glucose homeostasis. The major pathways through which glucose is added to blood are intestinal absorption of dietary glucose and hepatic glucose production via glycogenolysis and gluconeogenesis.[3] Insulin and glucagon play opposite roles in blood glucose regulation. Insulin exerts hypoglycemic effects through actions that stimulate glucose uptake by target tissues and reduce hepatic glucose output.[3] Glucagon has no effect on cellular glucose uptake but potently increases the rate of glucose appearance in blood through stimulation of glycogenolysis and gluconeogenesis.[4] It is the balanceof these hormones—the insulin:glucagon ratio—that determines whether there is a net gain or loss of glucose from blood.

When glucose decreases below its physiologic set point, insulin secretion is typically inhibited and glucagon secretion is stimulated; when the decrease in glucose levels is rapid, a marked counterregulatory response serves to rescue the organism from severe hypoglycemia.[5] The counterregulatory response is mediated through the actions of hormones such as cortisol and other glucocorticoids, catecholamines, and growth hormone, which induce a degree of insulin resistance that helps increase blood glucose. Hypoglycemia occurs when the rate of glucose removal exceeds the rate of its addition to blood.[1] Endogenous or exogenous substances that mimic or potentiate insulin action or enhance or accelerate glucose metabolism increase glucose removal, whereas failure of endogenous glucose production decreases the rate of glucose addition to blood. Disruptions of the pathways responsible for glucose addition or removal may overwhelm homeostatic mechanisms and produce clinical hypoglycemia.

## Mechanisms of Action

Hypoglycemia has been associated with a variety of clinical conditions but is a consistent feature of relatively few disorders. Because artifactual and factitious causes for hypoglycemia are fairly common, it is important to rule out the possibility of preanalytic (eg, improper sample collection, handling or storage) or analytic (eg, inaccurate glucometer) errors before accepting the validity of a test result consistent with hypoglycemia, especially when clinical signs are lacking or the finding is unexpected. Confidence in the result can be improved by repeating the analysis or using a different technique to measure glucose. Clinical disorders produce hypoglycemia through one or more pathophysiologic mechanisms. Clinical hypoglycemia can be broadly divided into several categories: hyperinsulinemic hypoglycemia, hypoinsulinemic hypoglycemia, and miscellaneous disorders (***Table*** 1, next page).[6]

Hyperinsulinemic hypoglycemia is the most common mechanism of hypoglycemia in dogs and cats, with relative or absolute insulin excess being a common feature (***Table 1***, next page). Exogenous insulin administered to diabetic patients is




▲ **FIGURE** Normoglycemia represents balance between glucose addition and removal from the blood. Hypoglycemia results when the rate of glucose addition falls below the removal rate (ie, hypoinsulinemic hypoglycemia) or when the rate of removal exceeds the addition rate (ie, hyperinsulinemic hypoglycemia).

TABLE 1

## PATHOPHYSIOLOGIC MECHANISMS & MAJOR CAUSES OF HYPOGLYCEMIA

| | Mechanism of Action |
|---|---|
| **Hypoinsulinemic hypoglycemia** | |
| Congenital portosystemic shunt | Reduced hepatic glycogen storage and gluconeogenesis |
| Liver failure (acute or chronic) of any cause, including feline hepatic lipidosis | Impaired or reduced hepatic glucose production due to hepatocellular dysfunction, injury, or loss |
| Hypoglycemia of fasting | Limited hepatic glycogen stores are exhausted after a short fast. Hepatic glucose production is less efficient in young puppies and kittens than in adults due to reduced glycogen stores and limited gluconeogenic substrates. Fasting does not cause hypoglycemia in healthy adult animals. |
| Glycogen storage disorders | Genetic condition that causes impaired glycogen metabolism |
| Counterregulatory hormone deficiency | Deficiency results in decreased antagonism of insulin action, which favors development of hypoglycemia. |
| Polycythemias | Increased cellular glucose use |
| **Hyperinsulinemic hypoglycemia** | |
| Insulin overdose | Accidental or intentional administration of excess dose of exogenous insulin |
| Insulinoma | Neuroendocrine tumor of islet cells secretes endogenous insulin in excess |
| Paraneoplastic hypoglycemia | Tumor produces an insulin-like substance. |
| Xylitol toxicity | Stimulation of insulin release in dogs |
| **Miscellaneous** | |
| Sepsis | Cause is not fully understood; multiple mechanisms have a role. |
| Infections, toxins, and drugs | Various mechanisms |
| Idiopathic or episodic hypoglycemia | Unknown cause; multiple factors (eg, prandial state, level of anxiety/excitement, level of exertion, diet) are likely to be involved. |

## Clinical Notes

| |
|---|
| Signs observed at young age. Breed conveys risk in dogs. Signs are similar for intra- and extrahepatic shunt locations. |
| Frequently accompanied by elevated levels of hepatic transaminases and bilirubin; however, blood levels of other hepatic function markers (eg, urea, albumin, cholesterol) will be low. |
| Most common cause for hypoglycemia in neonatal and young puppies and kittens |
| |
| Type 1 (von Gierke's disease) and type 3 (Cori's disease) are rare conditions that have been described in dogs. |
| Clinical disorders include cortisol deficiency (hypoadrenocorticism) and growth hormone deficiency (eg, pituitary dwarfism). |
| Infrequent complication of hematologic cancers and other disorders associated with marked erythrocytosis (eg, polycythemia vera) or leukocytosis (eg, leukemias) |
| |
| Affected patients have a history of diabetes mellitus; many are considered poorly regulated diabetics. Inadvertent overdose of prescribed insulin is the most common error. Using insulin to cause intentional harm is reported in humans but appears rare in veterinary medicine. |
| Vague, nonspecific signs may precede onset of hypoglycemia. Recent weight gain is reported before diagnosis in some patients. |
| Some nonpancreatic tumors release a humoral factor that causes hypoglycemia; tumor may produce other signs along with hypoglycemia. Increased glucose consumption by very large tumors may also contribute to hypoglycemia. |
| Hypoglycemia is secondary to increased insulin secretion but may be exacerbated in dogs with xylitol-associated liver failure. |
| |
| Hypoglycemia is related to more severe cases of sepsis and may signify a worse prognosis. |
| Infections infrequently associated with hypoglycemia include bartonellosis and babesiosis.[2] Hypoglycemia can result from ethylene glycol toxicity or ethanol intoxication (rare in dogs and cats) and has been observed in a dog after oleander ingestion.[2] Hypoglycemia due to drugs (other than insulin), including oral hypoglycemic drugs, is rare in dogs and cats. |
| Episodes of hypoglycemia occur in an otherwise healthy animal. Triggering events or circumstances may be identified; clinical examples include small-breed hypoglycemia and hunting dog hypoglycemia. Hypoglycemia may rarely develop during pregnancy in dogs. |

responsible for most cases of hyperinsulinemic hypoglycemia in veterinary medicine; typically, the cause is insulin overdose, although pharmacologic doses of insulin given to diabetic cats may result in onset of diabetes remission with subsequent hypoglycemia.[7,8] Accidental or nefarious injection of insulin has been described in nondiabetic humans but is an unlikely cause of hyperinsulinemic hypoglycemia in animals.[9]

Insulinoma, a neuroendocrine tumor of the pancreas, is the most common disorder associated with hyperinsulinemic hypoglycemia due to excess production of endogenous insulin.[10] Insulin excess due to islet cell hyperplasia has been suspected in some dogs.[11,12] In humans, oral hypoglycemic drugs (eg, sulfonylureas) that stimulate release of endogenous insulin can cause hyperinsulinemic hypoglycemia. However, these drugs are infrequently used in veterinary medicine, so this effect is unlikely to be encountered clinically.[13]

Ingestion of xylitol, an artificial sweetener used in many products intended for human use, causes profound hypoglycemia in dogs.[14] Uniquely in dogs, xylitol is a potent stimulator of insulin release, and toxicity occurs after ingestion of more than 0.1 g/kg.[15,16] Hypoglycemia results from insulin excess with or without concurrent failure of hepatic glucose output, which is caused by xylitol-induced liver damage.

Hypoinsulinemic hypoglycemia describes hypoglycemia that develops independent of insulin; in associated conditions, blood insulin is appropriately low with hypoglycemia. Non-insulin–mediated hypoglycemia may develop via one of several mechanisms (***Table 1***, page 30). Several tumor types (eg, hepatomas, hepatocellular carcinomas, leiomyomas, leiomyosarcomas) produce humoral insulin-like substances (eg, insulin-like growth factor-1) that promote hypoglycemia.[2,6,17] Hypoinsulinemic hypoglycemia can also occur with disorders that increase use of glucose by body tissues or those associated with failure of hepatic glucose production.[18]

## History & Clinical Signs

Hypoglycemia is a manifestation of disease rather than a specific diagnosis. Patient age and breed, previous diagnoses (eg, diabetes), and information about the conditions that elicit signs (eg, fasting, exercise) provide clues about possible causes. Patients may not share a consistent history except when the only signs displayed are those of hypoglycemia. Signs of hypoglycemia can be divided into signs related to impaired tissue energetics (neuroglycopenic) and those related to sympathetic activation (neurogenic; see ***Signs of Hypoglycemia***).[19] Acute hypoglycemia can produce a variety of nonspecific signs, including muscle tremors or weakness, ataxia, nausea, vomiting, behavior changes, confusion, collapse, seizures, and coma.[2] Chronic or intermittent hypoglycemia is often associated with vague signs of decreased activity or reduced energy, which may be accompanied by signs that are usually associated with acute exacerbations.[19]

## Diagnosis

Hypoglycemia is diagnosed when the measured blood glucose level is below the reference range, which is generally centered around 90 to 100 mg/dL and ranges from 70 to 120 mg/dL. Clinically, signs are most likely to appear when the glucose level is ≤60 mg/dL.[2,19] Hypoglycemia may be documented using a variety of clinical testing methods, including serum chemistry profile, whole blood testing using a portable glucometer, or interstitial fluid analysis using a continuous glucose monitor. Artifactual hypoglycemia is a preanalytic error that occurs when glucose in the sample is consumed by blood cells during processing. Some examples include consumption by RBCs when clot removal is delayed during serum processing or by WBCs when severe leukocytosis is present.[20] If laboratory error is eliminated as a cause, persistent or recurrent hypoglycemia should be investigated. Because recognition of hypoglycemia per se is not sufficient to make a diagnosis, patient history, physical examination, and other diagnostic findings must be carefully evaluated to identify the underlying cause. A diagnosis of clinically relevant hypoglycemia is

confirmed by satisfying the criteria of Whipple's triad: 1) clinical signs of hypoglycemia, 2) concurrent biochemical hypoglycemia, and 3) resolution of clinical signs with correction of hypoglycemia. In many cases, a series of diagnostic tests and imaging studies are needed to identify an underlying cause for hypoglycemia.

## Treatment & Management

Treatment aims to eliminate the clinical signs of hypoglycemia and address any underlying pathology (***Table 2***, next page). Mild hypoglycemia may be alleviated by feeding, especially in young animals or small-breed dogs in which hypoglycemia may develop due to rapid depletion of glycogen. Blood glucose can be increased rapidly via oral or IV glucose supplementation. Oral glucose is usually provided as corn syrup or honey, both of which contain large amounts of glucose in the form of simple sugars.[19] IV glucose is usually supplied via bolus injection or CRI of a glucose solution prepared from a sterile 50% dextrose solution. Infusion of glucagon, a hormone that antagonizes insulin-mediated inhibition of gluconeogenesis and promotes hepatic glucose production, has been used to treat hypoglycemia associated with insulin overdose and insulinoma in dogs.[21,22]

Some medications are useful for addressing chronic hypoglycemia associated with specific disorders. Glucocorticoids (eg, prednisone, dexamethasone) are used as replacement therapy for cortisol deficiency that accompanies hypoadrenocorticism.[23] Given at doses sufficient to induce insulin resistance, these drugs are also used as adjunctive treatment for insulinoma-associated hypoglycemia.[10] Anecdotally, L-carnitine supplementation may help ameliorate hypoglycemic events in susceptible small-breed puppies, including those with hypoglycemia caused by portosystemic shunting.

## Prognosis

Correction of hypoglycemia is readily accomplished with glucose supplementation. However,

### SIGNS OF HYPOGLYCEMIA[19]

- Signs may be triggered under such circumstances as fasting, stress, or exercise.
- Severity of signs depends on hypoglycemia duration and severity.
- Marked hypoglycemia may be tolerated in dogs and cats with chronic or episodic hypoglycemia.

**Neurogenic Signs**

- Restlessness
- Hunger/food seeking
- Nausea/vomiting
- Tachycardia
- Tremors
- Signs reported in humans include feeling shaky, sweating, and anxiety, but equivalent signs are difficult to define in dogs and cats.

**Neuroglycopenic Signs***

- Weakness
- Unusual behaviors, confusion, apparent vision abnormalities
- Ataxia
- Lethargy
- Seizure
- Coma

*Severe or prolonged neuroglycopenia may be fatal.

TABLE 2

## TREATMENT OF HYPOGLYCEMIA

| Treatment | Formulations & Dosing Guidelines |
|---|---|
| Food | A small snack or meal portion of a commercial balanced diet is a source of carbohydrates as well as substrates that support gluconeogenesis. |
| Glucose-containing syrup | • Corn syrup or honey contains a high percentage of glucose as the simple sugar.<br>• 50% dextrose for injection (0.5 g glucose/mL); can be given PO if IV access is not available<br>• Apply liberally along gingiva and buccal mucosa; allow ingestion if patient is able to swallow. |
| Glucose solution | 50% dextrose for injection (50-mL vial); each vial contains 25 g dextrose<br>**Glucose bolus**<br>• IV injection is administered at 0.5-1.0 g/kg (1-2 mL/kg) over 10-15 minutes; the dose is diluted 1:4 with 0.9% sodium chloride before administration.<br>**Glucose CRI**<br>• A 5% glucose infusion solution is prepared by adding 25 g dextrose/500 mL isotonic fluid (eg, lactated Ringer's solution).<br>• A glucose bolus may be given at the start of CRI.<br>• The infusion rate is started at 2-3 mL/kg/hour and titrated to achieve normoglycemia. |
| Glucagon | Available in 1-mg vials for rescue treatment of hypoglycemia in diabetic humans; drug is administered via CRI for veterinary applications<br>**CRI preparation and dosing**<br>1. Glucagon is reconstituted using supplied diluent.<br>2. The infusion solution (1 µg glucagon/mL) is prepared by adding the entire reconstituted volume (containing 1 mg glucagon) to 1 L bag of 0.9% sodium chloride solution.<br>3. A bolus injection of glucagon (0.05 µg/kg) IV can be given before starting CRI.<br>4. The initial CRI dose is 0.005-0.01 µg/kg/min IV and is titrated to achieve normoglycemia.<br>5. Blood glucose should be monitored hourly until normoglycemia is achieved.<br>6. CRI can be maintained until blood glucose is stable and the rate tapered with monitoring to ensure normoglycemia is sustained. |
| **Adjunctive treatment** | |
| Glucocorticoids | **Prednisone**<br>• Dose for hormone replacement is 0.1-0.2 mg/kg daily.<br>• Dose to induce insulin resistance is 1-2 mg/kg daily (higher dose is also immunosuppressive).<br>**Dexamethasone**<br>• More potent than prednisone and requires appropriate dose reductions<br>• Replacement dose is 0.01-0.02 mg/kg/day.<br>• Dose sufficient to induce insulin resistance is 0.1-0.2 mg/kg/day. |
| L-carnitine | A recommended empiric dose is 50 mg/kg twice daily.<br><br>The use of L-carnitine for this purpose is based on anecdotal reports and the author's clinical experience. |

**Clinical Notes**

- Only indicated for treatment of mild hypoglycemia
- Requires patient to be alert and have the ability to swallow normally
- Not suitable for emergency treatment of hypoglycemia
- Small meals fed frequently may be part of an effective strategy for hypoglycemic management in some patients.

- Owners should be advised to start therapy as soon as hypoglycemia is recognized.
- Caregivers should be warned to take care not to be bitten during administration and to withhold treatment if patient is nonresponsive or unable to swallow.

- An indwelling catheter is recommended to avoid complications (eg, phlebitis, pain) associated with injection of hypertonic glucose solutions.
- Bolus injection will rapidly correct hypoglycemia but may stimulate insulin release in nondiabetic patients. In such cases, the effect of the bolus may wane rapidly, necessitating administration of multiple boluses; beginning a glucose CRI should be considered.
- In a study of insulin overdose in dogs and cats, glucose supplementation was continued for a median of 18 hours and 8.5 hours, respectively, until euglycemia was restored.[7] The same study found that the total amount of glucose needed to restore normoglycemia was >1 g/kg, with some patients requiring much greater quantities.

- Glucagon infusion is reported in dogs and has been used to treat hypoglycemia due to insulinoma[9,24] and insulin overdose.[9,25]
- Glucagon infusion is effective and well-tolerated in dogs[24] and should be considered when glucose infusion fails to maintain blood glucose.

- Use of low-dose glucocorticoids as hormone replacement is only indicated for treatment of hypoglycemia caused by cortisol deficiency associated with hypoadrenocorticism. The dose is insufficient to induce insulin resistance.
- Adverse effects (eg, polydipsia, polyuria, weight gain) occur when doses exceed the replacement dose.
- Glucocorticoid induction of insulin resistance is a helpful adjunctive treatment for insulinoma when definitive therapy is not pursued. Improvement or resolution of insulinoma-induced hypoglycemia is usually temporary, although some dogs will remain subclinical for several months.

- L-carnitine is believed to increase the metabolic efficiency of mitochondria and to improve cellular energy production.[26]
- L-carnitine is commercially available as a nutritional supplement. The powder form is easily given mixed with food.
- L-carnitine supplementation may be useful for decreasing the frequency and severity of hypoglycemia in young animals. Supplementation can usually be discontinued after the animal matures.
- Anecdotally, L-carnitine may provide similar benefits for animals with liver impairment secondary to portosystemic shunting and animals with some forms of idiopathic hypoglycemia.

initial improvement will wane if the underlying pathology of hypoglycemia is not addressed or resolved. Frequent or continuous glucose supplementation may be needed to support patients with hypoglycemia caused by insulin overdose until the exogenous insulin is fully metabolized. Insulin excess due to insulinoma causes a similar problem, but release of endogenous insulin from insulinoma is ongoing and may be unpredictable. Some of these tumors may retain the ability to secrete insulin in response to hyperglycemia, which may develop during bolus glucose administration. The severity of hypoglycemic episodes experienced by juvenile animals or small-breed dogs may decrease with treatment and time as the animal matures and grows.

Idiopathic hypoglycemia carries a good prognosis if triggering factors can be identified and avoided. Prognosis for paraneoplastic hypoglycemia depends on whether effective treatment of the underlying neoplasm is possible. Hypoglycemia secondary to liver failure subsequent to cirrhosis or other disorders carries a poor prognosis, whereas hypoglycemia in patients with portovascular anomaly is expected to resolve after shunt closure.

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# Busy times call for simpler flea and tick treatment.

## ONE chew every 12 weeks*

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***BRAVECTO Chews for Dogs** kill fleas, prevents flea infestations, and kills ticks (black-legged tick, American dog tick, and brown dog tick) for 12 weeks. **BRAVECTO Chews** also kills lone star ticks for 8 weeks.

The most commonly reported adverse reactions include vomiting, decreased appetite, diarrhea, lethargy, polydipsia, and flatulence. **BRAVECTO Chews for Dogs** 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. **VIEW PRESCRIBING INFORMATION**



See page 38 for product information summary.

# BRAVECTO®
*(fluralaner)*
*Chews*

Flavored chews for dogs.

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

**Description:**
Each chew is formulated to provide a minimum dose of 11.4 mg/lb (25 mg/kg) body weight.

The chemical name of fluralaner is (±)-4-[5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]-2-methyl-N-[2-oxo-2-(2,2,2-trifluoroethylamino) ethyl]benzamide.

**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.

**Dosage and Administration:**
Bravecto should be administered orally as a single dose every 12 weeks according to the **Dosage Schedule** below to provide a minimum dose of 11.4 mg/lb (25 mg/kg) body weight.

Bravecto may be administered every 8 weeks in case of potential exposure to *Amblyomma americanum* ticks (see **Effectiveness**).

Bravecto should be administered with food.

**Dosage Schedule**

| Body Weight Ranges (lb) | Fluralaner Content (mg) | Chews Administered |
|---|---|---|
| 4.4 – 9.9 | 112.5 | One |
| >9.9 – 22.0 | 250 | One |
| >22.0 – 44.0 | 500 | One |
| >44.0 – 88.0 | 1000 | One |
| >88.0 – 123.0* | 1400 | One |

*Dogs over 123.0 lb should be administered the appropriate combination of chews

Treatment with Bravecto may begin at any time of the year and can continue year round without interruption.

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

**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 (see **Effectiveness**).

**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: Percentage of Dogs with the AR During the 182-Day Study (n=224 dogs) | Active Control Group: Percentage 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.

**Clinical Pharmacology:**
Peak fluralaner concentrations are achieved between 2 hours and 3 days following oral administration, and the elimination half-life ranges between 9.3 to 16.2 days. Quantifiable drug concentrations can be measured (lower than necessary for effectiveness) through 112 days. Due to reduced drug bioavailability in the fasted state, fluralaner should be administered with food.

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

**Effectiveness:**
Bravecto began to kill fleas within two hours after administration in a well-controlled laboratory study. In a European laboratory study, Bravecto killed fleas and *Ixodes ricinus* ticks and reduced the numbers of live fleas and *Ixodes ricinus* ticks on dogs by > 98% within 12 hours for 12 weeks. In a well-controlled laboratory study, Bravecto demonstrated 100% effectiveness against adult fleas 48 hours post-infestation for 12 weeks. In well-controlled laboratory studies, Bravecto demonstrated ≥ 93% effectiveness against *Dermacentor variabilis, Ixodes scapularis,* and *Rhipicephalus sanguineus* ticks 48 hours post-infestation for 12 weeks. Bravecto demonstrated ≥90% effectiveness against *Amblyomma americanum* 72 hours post-infestation for 8 weeks, but failed to demonstrate ≥90% effectiveness beyond 8 weeks.

In a well-controlled U.S. field study, a single dose of Bravecto reduced fleas by ≥ 99.7% for 12 weeks. Dogs with signs of flea allergy dermatitis showed improvement in erythema, alopecia, papules, scales, crusts, and excoriation as a direct result of eliminating flea infestations.

*Palatability:* In a well-controlled U.S. field study, which included 559 doses administered to 224 dogs, 80.7% of dogs voluntarily consumed Bravecto within 5 minutes, an additional 12.5% voluntarily consumed Bravecto within 5 minutes when offered with food, and 6.8% refused the dose or required forced administration.

**Animal Safety:**
*Margin of Safety Study:* In a margin of safety study, Bravecto was administered orally to 8- to 9-week-old puppies at 1, 3, and 5X the maximum label dose of 56 mg/kg at three, 8-week intervals. The dogs in the control group (0X) were untreated.

There were no clinically-relevant, treatment-related effects on physical examinations, body weights, food consumption, clinical pathology (hematology, clinical chemistries, coagulation tests, and urinalysis), gross pathology, histopathology, or organ weights. Diarrhea, mucoid, and bloody feces were the most common observations in this study, occurring at a similar incidence in the treated and control groups. Five of the twelve treated dogs that experienced one or more of these signs did so within 6 hours of the first dosing. One dog in the 3X treatment group was observed to be dull, inappetant, with evidence of bloody diarrhea, vomiting, and weight loss beginning five days after the first treatment. One dog in the 1X treatment group vomited food 4 hours following the first treatment.

*Reproductive Safety Study:* Bravecto was administered orally to intact, reproductively- sound male and female Beagles at a dose of up to 168 mg/kg (equivalent to 3X the maximum label dose) on three to four occasions at 8-week intervals. The dogs in the control group (0X) were untreated.

There were no clinically-relevant, treatment-related effects on the body weights, food consumption, reproductive performance, semen analysis, litter data, gross necropsy (adult dogs), or histopathology findings (adult dogs and puppies). One adult 3X treated dog suffered a seizure during the course of the study (46 days after the third treatment). Abnormal salivation was observed on 17 occasions: in six treated dogs (11 occasions) after dosing and four control dogs (6 occasions).

The following abnormalities were noted in 7 pups from 2 of the 10 dams in only the treated group during gross necropsy examination: limb deformity (4 pups), enlarged heart (2 pups), enlarged spleen (3 pups), and cleft palate (2 pups). During veterinary examination at Week 7, two pups from the control group had inguinal testicles, and two and four pups from the treated group had inguinal and cryptorchid testicles, respectively. No undescended testicles were observed at the time of necropsy (days 50 to 71).

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

**Storage Information:**
Do not store above 86°F (30°C).

**How Supplied:**
Bravecto is available in five strengths (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.

Approved by FDA under NADA # 141-426

Distributed by:
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Fluralaner (active ingred.) Made in Japan.
Formulated in Austria



Rev. 04/19

# Lymphocytosis

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

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

Following are differential diagnoses for patients presented with lymphocytosis.

- Age-related cause (eg, dogs and cats <6 months of age often have mild lymphocytosis due to vaccination or exposure to novel antigens)
- Antigenic stimulation
  - Immune-mediated disease (rare; eg, immune-mediated hemolytic anemia in cats)
  - Infection (most commonly, *Ehrlichia canis*; rarely, protozoal [eg, *Leishmania infantum*], *Spirocerca lupi*, FIV)
- Endocrine disease
  - Hyperthyroidism (cats; usually mild; can be seen prior to diagnosis [possibly epinephrine-related] or secondary to methimazole treatment)
  - Hypoadrenocorticism (primarily dogs; lack of a stress leukogram in a sick patient can indicate disease)
- Lymphoid neoplasia
  - Acute lymphoblastic leukemia
  - Chronic lymphocytic leukemia (± small cell lymphoma)
- Nonlymphoid neoplasia (eg, thymoma)
- Physiologic (eg, epinephrine-induced) response (primarily cats)

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Brief Summary
NADA 141-213, Approved by FDA

# Metacam®

(meloxicam oral suspension )
**1.5 mg/mL (equivalent to 0.05 mg per drop) /0.5 mg/mL (equivalent to 0.02 mg per drop)**
Non-steroidal anti-inflammatory drug for oral use in dogs only

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

**Warning: Repeated use of meloxicam in cats has been associated with acute renal failure and death. Do not administer additional injectable or oral meloxicam to cats. See Contraindications, Warnings, and Precautions for detailed information.**

**Description:** Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) of the oxicam class. Each milliliter of METACAM Oral Suspension contains meloxicam equivalent to 0.5 or 1.5 milligrams and sodium benzoate (1.5 milligrams) as a preservative. The chemical name for Meloxicam is 4-Hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1, 1-dioxide. The formulation is a yellowish viscous suspension with the odor of honey.

**Indications:** METACAM Oral Suspension is indicated for the control of pain and inflammation associated with osteoarthritis in dogs.

**Contraindications:** Dogs with known hypersensitivity to meloxicam should not receive METACAM Oral Suspension. **Do not use METACAM Oral Suspension in cats. Acute renal failure and death have been associated with the use of meloxicam in cats.**

**Warnings:** Not for use in humans. Keep this and all medications out of reach of children. Consult a physician in case of accidental ingestion by humans. **For oral use in dogs only.**

As with any NSAID all dogs should undergo a thorough history and physical examination before the initiation of NSAID therapy. Appropriate laboratory testing to establish hematological and serum biochemical baseline data is recommended prior to and periodically during administration. Owner should be advised to observe their dog for signs of potential drug toxicity and be given a client information sheet about METACAM.

**Precautions:** The safe use of METACAM Oral Suspension in dogs younger than 6 months of age, dogs used for breeding, or in pregnant or lactating dogs has not been evaluated. Meloxicam is not recommended for use in dogs with bleeding disorders, as safety has not been established in dogs with these disorders. As a class, cyclo-oxygenase inhibitory NSAIDs may be associated with gastrointestinal, renal and hepatic toxicity. Sensitivity to drug-associated adverse events varies with the individual patient. Dogs that have experienced adverse reactions from one NSAID may experience adverse reactions from another NSAID. Patients at greatest risk for renal toxicity are those that are dehydrated, on concomitant diuretic therapy, or those with existing renal, cardiovascular, and/or hepatic dysfunction. Concurrent administration of potentially nephrotoxic drugs should be carefully approached. NSAIDs may inhibit the prostaglandins that maintain normal homeostatic function. Such anti-prostaglandin effects may result in clinically significant disease in patients with underlying or pre-existing disease that has not been previously diagnosed. Since NSAIDs possess the potential to induce gastrointestinal ulcerations and/or perforations, concomitant use with other anti-inflammatory drugs, such as NSAIDs or corticosteroids, should be avoided. If additional pain medication is needed after administration of the total daily dose of METACAM Oral Suspension, a non-NSAID or non-corticosteroid class of analgesia should be considered. The use of another NSAID is not recommended. Consider appropriate washout times when switching from corticosteroid use or from one NSAID to another in dogs. The use of concomitantly protein-bound drugs with METACAM Oral Suspension has not been studied in dogs. Commonly used protein-bound drugs include cardiac, anticonvulsant and behavioral medications. The influence of concomitant drugs that may inhibit metabolism of METACAM Oral Suspension has not been evaluated. Drug compatibility should be monitored in patients requiring adjunctive therapy.

**Adverse Reactions:** Field safety was evaluated in 306 dogs.[1] Based on the results of two studies, GI abnormalities (vomiting, soft stools, diarrhea, and inappetance) were the most common adverse reactions associated with the administration of meloxicam.

The following adverse events are based on post-approval adverse drug experience reporting. Not all adverse reactions are reported to FDA/CVM. It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product exposure using these data. The following adverse events are listed in decreasing order of frequency by body system.

*Gastrointestinal*: vomiting, anorexia, diarrhea, melena, gastrointestinal ulceration
*Urinary*: azotemia, elevated creatinine, renal failure
*Neurological/Behavioral:* lethargy, depression
*Hepatic:* elevated liver enzymes
*Dermatologic*: pruritus

Death has been reported as an outcome of the adverse events listed above. **Acute renal failure and death have been associated with use of meloxicam in cats.**

**Information for Dog Owners:** METACAM, like other drugs of its class, is not free from adverse reactions. 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, dark or tarry stools, increased water consumption, increased urination, pale gums due to anemia, yellowing of gums, skin or white of the eye due to jaundice, lethargy, incoordination, seizure, or behavioral changes. **Serious adverse reactions associated with this drug class can occur without warning and in rare situations result in death (see Adverse Reactions). Owners should be advised to discontinue METACAM and contact their veterinarian immediately if signs of intolerance are observed.** The vast majority of patients with drug related adverse reactions have recovered when the signs are recognized, the drug is withdrawn, and veterinary care, if appropriate, is initiated. Owners should be advised of the importance of periodic follow up for all dogs during administration of any NSAID.

**Effectiveness:** The effectiveness of meloxicam was demonstrated in two field studies involving a total of 277 dogs representing various breeds, between six months and sixteen years of age, all diagnosed with osteoarthritis. Both of the placebo-controlled, masked studies were conducted for 14 days. All dogs received 0.2 mg/kg meloxicam on day 1. All dogs were maintained on 0.1 mg/kg oral meloxicam from days 2 through 14 of both studies. Parameters evaluated by veterinarians included lameness, weight-bearing, pain on palpation, and overall improvement. Parameters assessed by owners included mobility, ability to rise, limping, and overall improvement. In the first field study (n=109), dogs showed clinical improvement with statistical significance after 14 days of meloxicam treatment for all parameters. In the second field study (n=48), dogs receiving meloxicam showed a clinical improvement after 14 days of therapy for all parameters; however, statistical significance was demonstrated only for the overall investigator evaluation on day 7, and for the owner evaluation on day 14.[1]

**Reference: 1.** FOI for NADA 141-213 METACAM (meloxicam oral suspension).

**Manufactured for:**
Boehringer Ingelheim Vetmedica, Inc.
St. Joseph, MO 64506 U.S.A.



601401-08/601413-04/6015161-10/6015268-04
Revised 07/2016

18490
06/2018

Brief Summary
NADA 141-219, Approved by FDA

Boehringer Ingelheim

# Metacam®

(meloxicam)
**5 mg/mL Solution for Injection**
Non-steroidal anti-inflammatory drug for use in dogs and cats only

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

**Warning: Repeated use of meloxicam in cats has been associated with acute renal failure and death. Do not administer additional injectable or oral meloxicam to cats. See Contraindications, Warnings, and Precautions for detailed information.**

**Description:** Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) of the oxicam class. Each mL of this sterile product for injection contains meloxicam 5.0 mg, alcohol 15%, glycofurol 10%, poloxamer 188 5%, sodium chloride 0.6%, glycine 0.5% and meglumine 0.3%, in water for injection, pH adjusted with sodium hydroxide and hydrochloric acid.

**Indications:**
**Dogs:** METACAM (meloxicam) 5 mg/mL Solution for Injection is indicated in dogs for the control of pain and inflammation associated with osteoarthritis.

**Contraindications:** Dogs with known hypersensitivity to meloxicam should not receive METACAM 5 mg/mL Solution for Injection.

**Warnings:** Not for use in humans. Keep this and all medications out of reach of children. Consult a physician in case of accidental ingestion by humans. For IV or SQ injectable use in dogs. All dogs should undergo a thorough history and physical examination before administering any NSAID. Appropriate laboratory testing to establish hematological and serum biochemical baseline data is recommended prior to, and periodically during use of any NSAID in dogs.

**Owner should be advised to observe their dogs for signs of potential drug toxicity.**

**Precautions:** The safe use of METACAM 5 mg/mL Solution for Injection in dogs younger than 6 months of age, dogs used for breeding, or in pregnant or lactating bitches has not been evaluated. Meloxicam is not recommended for use in dogs with bleeding disorders, as safety has not been established in dogs with these disorders. Safety has not been established for intramuscular (IM) administration in dogs. When administering METACAM 5 mg/mL Solution for Injection, use a syringe of appropriate size to ensure precise dosing. As a class, cyclo-oxygenase inhibitory NSAIDs may be associated with gastrointestinal, renal and hepatic toxicity. Sensitivity to drug-associated adverse events varies with the individual patient. Dogs that have experienced adverse reactions from one NSAID may experience adverse reactions from another NSAID. Patients at greatest risk for renal toxicity are those that are dehydrated, on concomitant diuretic therapy, or those with existing renal, cardiovascular, and/or hepatic dysfunction. Concurrent administration of potentially nephrotoxic drugs should be carefully approached. NSAIDs may inhibit the prostaglandins that maintain normal homeostatic function. Such anti-prostaglandin effects may result in clinically significant disease in patients with underlying or preexisting disease that has not been previously diagnosed. Since NSAIDs possess the potential to induce gastrointestinal ulcerations and/or perforations, concomitant use with other anti-inflammatory drugs, such as NSAIDs or corticosteroids, should be avoided. If additional pain medication is needed after the administration of the total daily dose of METACAM Oral Suspension, a non-NSAID or noncorticosteriod class of analgesia should be considered. The use of another NSAID is not recommended. Consider appropriate washout times when switching from corticosteroid use or from one NSAID to another in dogs. The use of concomitantly protein-bound drugs with METACAM 5 mg/mL Solution for Injection has not been studied in dogs. Commonly used protein-bound drugs include cardiac, anticonvulsant and behavioral medications. The influence of concomitant drugs that may inhibit metabolism of METACAM 5 mg/mL Solution for Injection has not been evaluated. Drug compatibility should be monitored in patients requiring adjunctive therapy. The effect of cyclo-oxygenase inhibition and the potential for thromboembolic occurrence or a hypercoagulable state has not been studied.

**Adverse Reactions:**
**Dogs:** A field study involving 224 dogs was conducted.[1] Based on the results of this study, GI abnormalities (vomiting, soft stools, diarrhea, and inappetance) were the most common adverse reactions associated with the administration of meloxicam.

The following adverse reactions are based on post-approval adverse drug event reporting. The categories are listed in decreasing order of frequency by body system:

Gastrointestinal: *vomiting, diarrhea, melena, gastrointestinal ulceration*
Urinary: *azotemia, elevated creatinine, renal failure*
Neurological/Behavioral: *lethargy, depression*
Hepatic: *elevated liver enzymes*
Dermatologic: *pruritus*

Death has been reported as an outcome of the adverse events listed above. **Acute renal failure and death have been associated with the use of meloxicam in cats.**

**Information For Dog Owners:** Meloxicam, like other NSAIDs, is not free from adverse reactions. Owners should be advised of the potential for adverse reactions and be informed of the clinical signs associated with NSAID intolerance. Adverse reactions may include vomiting, diarrhea, lethargy, decreased appetite and behavioral changes. Dog owners should be advised when their pet has received a meloxicam injection. Dog owners should contact their veterinarian immediately if possible adverse reactions are observed, and dog owners should be advised to discontinue METACAM therapy.

**Effectiveness:**
**Dogs:** The effectiveness of METACAM 5 mg/mL Solution for Injection was demonstrated in a field study involving a total of 224 dogs representing various breeds, all diagnosed with osteoarthritis.[1] This placebo-controlled, masked study was conducted for 14 days. Dogs received a subcutaneous injection of 0.2 mg/kg METACAM 5 mg/mL Solution for Injection on day 1. The dogs were maintained on 0.1 mg/kg oral meloxicam from days 2 through 14. Variables evaluated by veterinarians included lameness, weight-bearing, pain on palpation, and overall improvement. Variables assessed by owners included mobility, ability to rise, limping, and overall improvement.

In this field study, dogs showed clinical improvement with statistical significance after 14 days of meloxicam treatment for all variables.

**Reference: 1.** FOI for NADA 141-219 METACAM (meloxicam) 5 mg/mL Solution for Injection.

**Manufactured for:**
Boehringer Ingelheim Vetmedica, Inc.
St. Joseph, MO 64506 U.S.A.



601307-07
Revised 08/2014

18490
06/2018

# Previcox® (firocoxib)

## CHEWABLE TABLETS

***Brief Summary: Before using* PREVICOX, *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.

***Indications:*** PREVICOX (firocoxib) Chewable Tablets are indicated for the control of pain and inflammation associated with osteoarthritis and for the control of postoperative pain and inflammation associated with soft-tissue and orthopedic surgery in dogs.

***Contraindications:*** Dogs with known hypersensitivity to firocoxib should not receive PREVICOX.

***Warnings:*** Not for use in humans. Keep this and all medications out of the reach of children. Consult a physician in case of accidental ingestion by humans.

***For oral use in dogs only. Use of this product at doses above the recommended 2.27 mg/lb (5.0 mg/kg) in puppies less than seven months of age has been associated with serious adverse reactions, including death (see Animal Safety). Due to tablet sizes and scoring, dogs weighing less than 12.5 lb (5.7 kg) cannot be accurately dosed.***

All dogs should undergo a thorough history and physical examination before the initiation of NSAID therapy. Appropriate laboratory testing to establish hematological and serum baseline data is recommended prior to and periodically during administration of any NSAID. ***Owners should be advised to observe for signs of potential drug toxicity (see Adverse Reactions and Animal Safety) and be given a Client Information Sheet about* PREVICOX *Chewable Tablets.***

For technical assistance or to report suspected adverse events, call 1-877-217-3543. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDAVETS or http://www.fda.gov/AnimalVeterinary/SafetyHealth

***Precautions:*** This product cannot be accurately dosed in dogs less than 12.5 pounds in body weight. Consider appropriate washout times when switching from one NSAID to another or when switching from corticosteroid use to NSAID use.

As a class, cyclooxygenase inhibitory NSAIDs may be associated with renal, gastrointestinal and hepatic toxicity. Sensitivity to drug-associated adverse events varies with the individual patient. Dogs that have experienced adverse reactions from one NSAID may experience adverse reactions from another NSAID. Patients at greatest risk for adverse events are those that are dehydrated, on concomitant diuretic therapy, or those with existing renal, cardiovascular, and/or hepatic dysfunction. Concurrent administration of potentially nephrotoxic drugs should be carefully approached and monitored. NSAIDs may inhibit the prostaglandins that maintain normal homeostatic function. Such anti-prostaglandin effects may result in clinically significant disease in patients with underlying or pre-existing disease that has not been previously diagnosed. Since NSAIDs possess the potential to produce gastrointestinal ulceration and/or gastrointestinal perforation, concomitant use of PREVICOX Chewable Tablets with other anti-inflammatory drugs, such as NSAIDs or corticosteroids, should be avoided. The concomitant use of protein-bound drugs with PREVICOX Chewable Tablets has not been studied in dogs. Commonly used protein-bound drugs include cardiac, anticonvulsant, and behavioral medications. The influence of concomitant drugs that may inhibit the metabolism of PREVICOX Chewable Tablets has not been evaluated. Drug compatibility should be monitored in patients requiring adjunctive therapy. If additional pain medication is needed after the daily dose of PREVICOX, a non-NSAID class of analgesic may be necessary. Appropriate monitoring procedures should be employed during all surgical procedures. Anesthetic drugs may affect renal perfusion, approach concomitant use of anesthetics and NSAIDs cautiously. The use of parenteral fluids during surgery should be considered to decrease potential renal complications when using NSAIDs perioperatively. The safe use of PREVICOX Chewable Tablets in pregnant, lactating or breeding dogs has not been evaluated.

***Adverse Reactions:***

**Osteoarthritis:** In controlled field studies, 128 dogs (ages 11 months to 15 years) were evaluated for safety when given PREVICOX Chewable Tablets at a dose of 2.27mg/lb (5.0 mg/kg) orally once daily for 30 days. The following adverse reactions were observed. Dogs may have experienced more than one of the observed adverse reactions during the study.

**Adverse Reactions Seen in U. S. Field Studies**

| *Adverse Reactions* | PREVICOX *(n=128)* | *Active Control (n=121)* |
|---|---|---|
| Vomiting | 5 | 8 |
| Diarrhea | 1 | 10 |
| Decreased Appetite or Anorexia | 3 | 3 |
| Lethargy | 1 | 3 |
| Pain | 2 | 1 |
| Somnolence | 1 | 1 |
| Hyperactivity | 1 | 0 |

PREVICOX (firocoxib) Chewable Tablets were safely used during field studies concomitantly with other therapies, including vaccines, anthelmintics, and antibiotics.

**Soft-tissue Surgery:** In controlled field studies evaluating soft-tissue postoperative pain and inflammation, 258 dogs (ages 10.5 weeks to 16 years) were evaluated for safety when given PREVICOX Chewable Tablets at a dose of 2.27 mg/lb (5.0 mg/kg) orally approximately 2 hours prior to surgery and once daily thereafter for up to two days. The following adverse reactions were observed. Dogs may have experienced more than one of the observed reactions during the study.

**Adverse Reactions Seen in the Soft-tissue Surgery Postoperative Pain Field Studies**

| *Adverse Reactions* | *Firocoxib Group (n=127)* | *Control Group* (n=131)* |
|---|---|---|
| Vomiting | 5 | 6 |
| Diarrhea | 1 | 1 |
| Bruising at Surgery Site | 1 | 1 |
| Respiratory Arrest | 1 | 0 |
| SQ Crepitus in Rear Leg and Flank | 1 | 0 |
| Swollen Paw | 1 | 0 |

**Sham-dosed (pilled)*

**Orthopedic Surgery:** In a controlled field study evaluating orthopedic postoperative pain and inflammation, 226 dogs of various breeds, ranging in age from 1 to 11.9 years in the PREVICOX-treated groups and 0.7 to 17 years in the control group were evaluated for safety. Of the 226 dogs, 118 were given PREVICOX Chewable Tablets at a dose of 2.27 mg/lb (5.0 mg/kg) orally approximately 2 hours prior to surgery and once daily thereafter for a total of three days. The following adverse reactions were observed. Dogs may have experienced more than one of the observed reactions during the study.

**Adverse Reactions Seen in the Orthopedic Surgery Postoperative Pain Field Study**

| *Adverse Reactions* | *Firocoxib Group (n=118)* | *Control Group* (n=108)* |
|---|---|---|
| Vomiting | 1 | 0 |
| Diarrhea | 2** | 1 |
| Bruising at Surgery Site | 2 | 3 |
| Inappetence/ Decreased Appetite | 1 | 2 |
| Pyrexia | 0 | 1 |
| Incision Swelling, Redness | 9 | 5 |
| Oozing Incision | 2 | 0 |

A case may be represented in more than one category.
*Sham-dosed (pilled).
**One dog had hemorrhagic gastroenteritis.

***Post-Approval Experience (Rev. 2009):*** The following adverse reactions are based on post-approval adverse drug event reporting. The categories are listed in decreasing order of frequency by body system:

Gastrointestinal: *Vomiting, anorexia, diarrhea, melena, gastrointestinal perforation, hematemesis, hematachezia, weight loss, gastrointestinal ulceration, peritonitis, abdominal pain, hypersalivation, nausea*

Urinary: *Elevated BUN, elevated creatinine, polydypsia, polyuria, hematuria, urinary incontinence, proteinuria, kidney failure, azotemia, urinary tract infection*

Neurological/Behavioral/Special Sense: *Depression/lethargy, ataxia, seizures, nervousness, confusion, weakness, hyperactivity, tremor, paresis, head tilt, nystagmus, mydriasis, aggression, uveitis*

Hepatic: *Elevated ALP, elevated ALT, elevated bilirubin, decreased albumin, elevated AST, icterus, decreased or increased total protein and globulin, pancreatitis, ascites, liver failure, decreased BUN*

Hematological: *Anemia, neutrophilia, thrombocytopenia, neutropenia*

Cardiovascular/Respiratory: *Tachypnea, dyspnea, tachycardia*

Dermatologic/Immunologic: *Pruritis, fever, alopecia, moist dermatitis, autoimmune hemolytic anemia, facial/muzzle edema, urticaria*

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

For a complete listing of adverse reactions for firocoxib reported to the CVM see: http://www.fda.gov/downloads/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/UCM055407.pdf

***Information For Dog Owners:*** PREVICOX, like other drugs of its class, is not free from adverse reactions. 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, dark or tarry stools, increased water consumption, increased urination, pale gums due to anemia, yellowing of gums, skin or white of the eye due to jaundice, lethargy, incoordination, seizure, or behavioral changes. **Serious adverse reactions associated with this drug class can occur without warning and in rare situations result in death (see Adverse Reactions). Owners should be advised to discontinue PREVICOX therapy and contact their veterinarian immediately if signs of intolerance are observed.** The vast majority of patients with drug-related adverse reactions have recovered when the signs are recognized, the drug is withdrawn, and veterinary care, if appropriate, is initiated. Owners should be advised of the importance of periodic follow up for all dogs during administration of any NSAID.

***Effectiveness:*** Two hundred and forty-nine dogs of various breeds, ranging in age from 11 months to 20 years, and weighing 13 to 175 lbs, were randomly administered PREVICOX or an active control drug in two field studies. Dogs were assessed for lameness, pain on manipulation, range of motion, joint swelling, and overall improvement in a non-inferiority evaluation of PREVICOX compared with the active control. At the study's end, 87% of the owners rated PREVICOX-treated dogs as improved. Eighty-eight percent of dogs treated with PREVICOX were also judged improved by the veterinarians. Dogs treated with PREVICOX showed a level of improvement in veterinarian-assessed lameness, pain on palpation, range of motion, and owner-assessed improvement that was comparable to the active control. The level of improvement in PREVICOX-treated dogs in limb weight bearing on the force plate gait analysis assessment was comparable to the active control. In a separate field study, two hundred fifty-eight client-owned dogs of various breeds, ranging in age from 10.5 weeks to 16 years and weighing from 7 to 168 lbs, were randomly administered PREVICOX or a control (sham-dosed-pilled) for the control of postoperative pain and inflammation associated with soft-tissue surgical procedures such as abdominal surgery (e.g., ovariohysterectomy, abdominal cryptorchidectomy, splenectomy, cystotomy) or major external surgeries (e.g., mastectomy, skin tumor removal ≤8 cm). The study demonstrated that PREVICOX-treated dogs had significantly lower need for rescue medication than the control (sham-dosed-pilled) in controlling postoperative pain and inflammation associated with soft-surgery. A multi-center field study with 226 client-owned dogs of various breeds, and ranging in age from 1 to 11.9 years in the PREVICOX-treated groups and 0.7 to 17 years in the control group was conducted. Dogs were randomly assigned to either the PREVICOX or the control (sham-dosed-pilled) group for the control of postoperative pain and inflammation associated with orthopedic surgery. Surgery to repair a ruptured cruciate ligament included the following stabilization procedures: fabellar suture and/or imbrication, fibular head transposition, tibial plateau leveling osteotomy (TPLO), and 'over the top' technique. The study (n = 220 for effectiveness) demonstrated that PREVICOX-treated dogs had significantly lower need for rescue medication than the control (sham-dosed-pilled) in controlling postoperative pain and inflammation associated with orthopedic surgery.

***Animal Safety:*** In a targeted animal safety study, firocoxib was administered orally to healthy adult Beagle dogs (eight dogs per group) at 5, 15, and 25 mg/kg (1, 3, and 5 times the recommended total daily dose) for 180 days. At the indicated dose of 5 mg/kg, there were no treatment-related adverse events. Decreased appetite, vomiting, and diarrhea were seen in dogs in all dose groups, including unmedicated controls, although vomiting and diarrhea were seen more often in dogs in the 5X dose group. One dog in the 3X dose group was diagnosed with juvenile polyarteritis of unknown etiology after exhibiting recurrent episodes of vomiting and diarrhea, lethargy, pain, anorexia, ataxia, proprioceptive deficits, decreased albumin levels, decreased and then elevated platelet counts, increased bleeding times, and elevated liver enzymes. On histopathologic examination, a mild ileal ulcer was found in one 5X dog. This dog also had a decreased serum albumin which returned to normal by study completion. One control and three 5X dogs had focal areas of inflammation in the pylorus or small intestine. Vacuolization without inflammatory cell infiltrates was noted in the thalamic region of the brain in three control, one 3X, and three 5X dogs. Mean ALP was within the normal range for all groups but was greater in the 3X and 5X dose groups than in the control group. Transient decreases in serum albumin were seen in multiple animals in the 3X and 5X dose groups, and in one control animal. In a separate safety study, firocoxib was administered orally to healthy juvenile (10-13 weeks of age) Beagle dogs at 5, 15, and 25 mg/kg (1, 3, and 5 times the recommended total daily dose) for 180 days. At the indicated (1X) dose of 5 mg/kg, on histopathologic examination, three out of six dogs had minimal periportal hepatic fatty change. On histopathologic examination, one control, one 1X, and two 5X dogs had diffuse slight hepatic fatty change. These animals showed no clinical signs and had no liver enzyme elevations. In the 3X dose group, one dog was euthanized because of poor clinical condition (Day 63). This dog also had a mildly decreased serum albumin. At study completion, out of five surviving and clinically normal 3X dogs, three had minimal periportal hepatic fatty change. Of twelve dogs in the 5X dose group, one died (Day 82) and three moribund dogs were euthanized (Days 38, 78, and 79) because of anorexia, poor weight gain, depression, and in one dog, vomiting. One of the euthanized dogs had ingested a rope toy. Two of these 5X dogs had mildly elevated liver enzymes. At necropsy all five of the dogs that died or were euthanized had moderate periportal or severe panzonal hepatic fatty change; two had duodenal ulceration; and two had pancreatic edema. Of two other clinically normal 5X dogs (out of four euthanized as comparators to the clinically affected dogs), one had slight and one had moderate periportal hepatic fatty change. Drug treatment was discontinued for four dogs in the 5X group. These dogs survived the remaining 14 weeks of the study. On average, the dogs in the 3X and 5X dose groups did not gain as much weight as control dogs. Rate of weight gain was measured (instead of weight loss) because these were young growing dogs. Thalamic vacuolation was seen in three of six dogs in the 3X dose group, five of twelve dogs in the 5X dose group, and to a lesser degree in two unmedicated controls. Diarrhea was seen in all dose groups, including unmedicated controls. In a separate dose tolerance safety study involving a total of six dogs (two control dogs and four treated dogs), firocoxib was administered to four healthy adult Beagle dogs at 50 mg/kg (ten times the recommended daily dose) for twenty-two days. All dogs survived to the end of the study. Three of the four treated dogs developed small intestinal erosion or ulceration. Treated dogs that developed small intestinal erosion or ulceration had a higher incidence of vomiting, diarrhea, and decreased food consumption than control dogs. One of these dogs had severe duodenal ulceration, with hepatic fatty change and associated vomiting, diarrhea, anorexia, weight loss, ketonuria, and mild elevations in AST and ALT. All four treated dogs exhibited progressively decreasing serum albumin that, with the exception of one dog that developed hypoalbuminemia, remained within normal range. Mild weight loss also occurred in the treated group. One of the two control dogs and three of the four treated dogs exhibited transient increases in ALP that remained within normal range.

Made in France
Marketed by: Merial, Inc., Duluth, GA 30096-4640, U.S.A.
1-877-217-3543
NADA 141-230, Approved by FDA
Rev. 09-2015

# Outpatient to Outdoorsy

## We've got the *proof* on pain.

While others talk about pain management, our pain portfolio is proven in more than 20 favorable studies. When you prescribe METACAM® (meloxicam) or PREVICOX® (firocoxib) for your post-operative (PREVICOX only) and canine osteoarthritis patients, the research stands with you, so that you can get your patients back to living the life they love.







Previcox® (firocoxib)

Metacam® (meloxicam)

**IMPORTANT SAFETY INFORMATION: METACAM (meloxicam oral suspension) and PREVICOX (firocoxib) Chewable Tablets are for use in dogs only. METACAM (meloxicam) Solution for Injection is approved for use in dogs or cats (not indicated for osteoarthritis in cats). Repeated use of meloxicam in cats has been associated with acute renal failure and death. Do not administer additional injectable or oral meloxicam to cats.** As a class, cyclooxygenase inhibitory NSAIDs like METACAM and PREVICOX may be associated with gastrointestinal, kidney, or liver side effects. Dogs should be evaluated for pre-existing conditions and currently prescribed medications prior to treatment with METACAM or PREVICOX, then monitored regularly while on therapy. Concurrent use with another NSAID, corticosteroid, or nephrotoxic medication should be avoided or monitored closely. Please refer to the package insert or product website for complete product information.



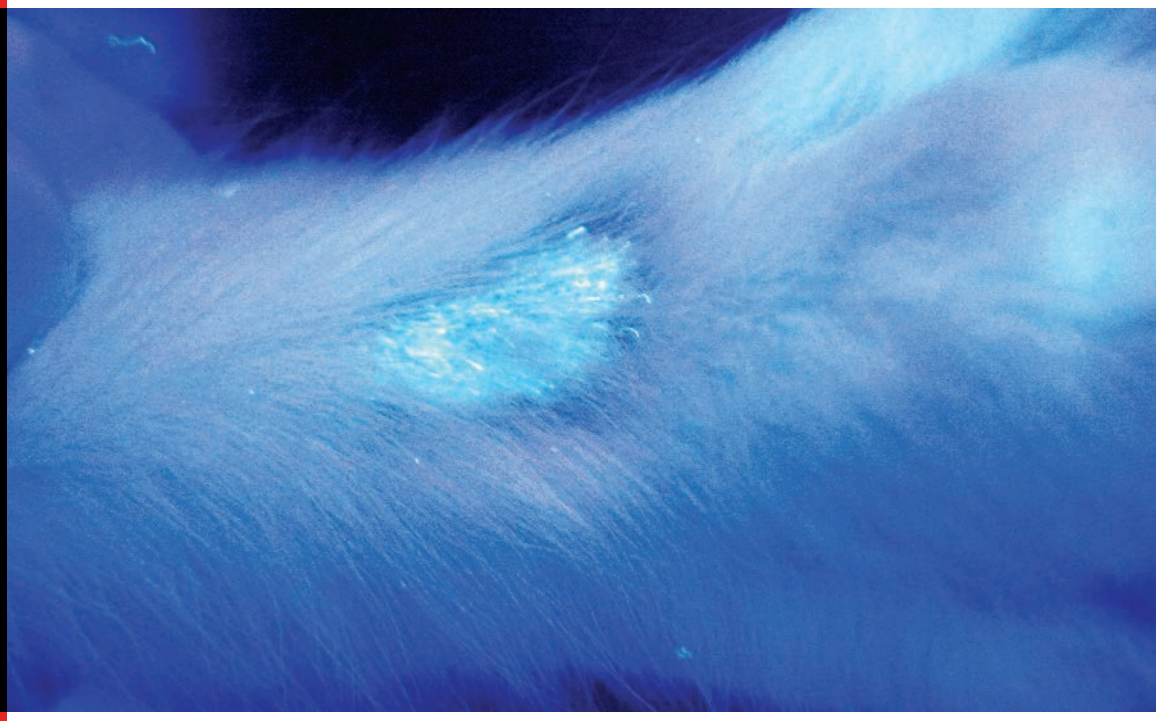
TOGETHER, WE ARE MORE THAN MEDICINE.

Boehringer Ingelheim

See pages 40 & 41 for product information summary.

# 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.





RESEARCH NOTES

# Environmental Decontamination for Ringworm

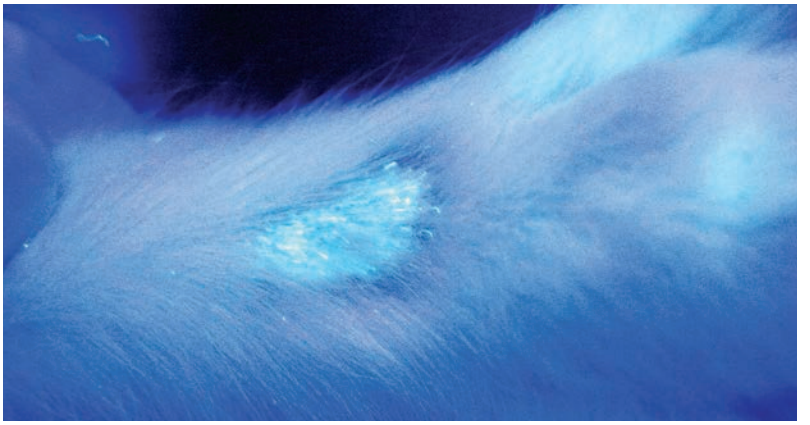
**Alison Diesel, DVM, DACVD**
*Texas A&M University*

**In the literature**

Moriello KA. Decontamination of 70 foster family homes exposed to *Microsporum canis* infected cats: a retrospective study. *Vet Dermatol*. 2019;30(2):178-e55.

## FROM THE PAGE ...

As part of successful treatment of dermatophytosis, environmental decontamination is recommended to eliminate infective material in the home environment. Although environmental contamination is considered an unlikely source of dermatophyte transmission, many pet owners may be fearful of persistent organisms in the environment and/or frustrated at the perception of difficult successful home decontamination.



▲ **FIGURE** Positive Wood's lamp fluorescence result in a kitten with *Microsporum canis* dermatophytosis

Continues ▶

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# Baytril® Otic

## (enrofloxacin/silver sulfadiazine) Antibacterial-Antimycotic Emulsion

**For Ototopical Use In Dogs**

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

Federal law prohibits the extralabel use of this drug in food-producing animals.

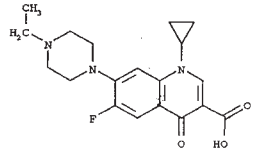
**PRODUCT DESCRIPTION:**

Each milliliter of Baytril® Otic contains: enrofloxacin 5 mg (0.5% w/v), silver sulfadiazine (SSD) 10 mg (1.0% w/v), benzyl alcohol (as a preservative) and cetylstearyl alcohol (as a stabilizer) in a neutral oil and purified water emulsion. The active ingredients are delivered via a physiological carrier (a nonirritating emulsion).

**CHEMICAL NOMENCLATURE AND STRUCTURE:**

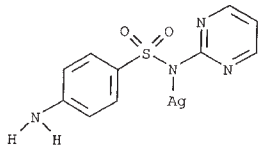
**Enrofloxacin**

1-Cyclopropyl-7-(4-ethyl-1-piperazinyl)-6-fluoro-1, 4-dihydro-4-oxo-3-quinolinecarboxylic acid.



**Silver Sulfadiazine**

Benzenesulfonamide, 4-amino-N-2-pyrimidinyl-monosilver



**ACTIONS:**

Enrofloxacin, a 4-fluoroquinolone compound, is bactericidal with activity against a broad spectrum of both Gram negative and Gram positive bacteria. Fluoroquinolones elicit their bactericidal activities through interactions with two intracellular enzymes, DNA gyrase (DNA topoisomerase II) and DNA topoisomerase IV, which are essential for bacterial DNA transcription, synthesis and replication. It is believed that fluoroquinolones actively bind with bacterial DNA:ENZYME complexes and thereby inhibit the essential processes catalyzed by the enzymes (DNA supercoiling and chromosomal decatenation).[1] The ultimate outcome of the fluoroquinolone intervention is DNA fragmentation and bacterial cell death.[2,3]

Silver sulfadiazine (SSD) is synthesized from silver nitrate and sodium sulfadiazine.[4] This compound has a wide spectrum of antimicrobial activity against Gram negative and Gram positive bacteria and is also an effective antimycotic.[5,6] SSD suppresses microbial growth through inhibition of DNA replication and modification of the cell membrane.

**MICROBIOLOGY:**

In clinical field trials, Baytril® Otic demonstrated elimination or reduction of clinical signs associated with otitis externa and *in vitro* activity against cultured organisms. Baytril® Otic is effective when used as a treatment for canine otitis externa associated with one or more of the following organisms: *Malassezia pachydermatis, coagulase-positive Staphylococcus spp., Pseudomonas aeruginosa, Enterobacter spp., Proteus mirabilis, Streptococci spp., Aeromonas hydrophila, Aspergillus spp., Klebsiella pneumoniae,* and *Candida albicans.*

*In vitro* assays, such as disk-diffusion and agar/broth-dilution, are used to determine the susceptibilities of microbes to antimicrobial therapies. Results of agar/broth-dilution assays are reported as a Minimal Inhibitory Concentration (MIC) which represents the lowest antimicrobial concentration, expressed in µg/mL, capable of inhibiting the growth of a pathogenic microorganism. MICs are used in conjunction with pharmacokinetics to predict the *in vivo* efficacy of systemically administered antimicrobials. Topical administration of Baytril® Otic to an exudate and debris-free canal, however, will generally result in local antimicrobial concentrations that greatly exceed serum and tissue levels resulting from systemic therapy. Therefore, when using Baytril® Otic as a treatment for canine otitis externa, interpret susceptibility data cautiously.

**INDICATIONS:**

Baytril® Otic is indicated as a treatment for canine otitis externa complicated by bacterial and fungal organisms susceptible to enrofloxacin and/or silver sulfadiazine (see Microbiology section).

**EFFECTIVENESS:**

Due to its combination of active ingredients, Baytril® Otic provides antimicrobial therapy against bacteria and fungi (which includes yeast) commonly encountered in cases of canine otitis externa.

The effectiveness of Baytril® Otic was evaluated in a controlled, double-blind, multi-site clinical trial. One hundred and sixty-nine dogs (n=169), with naturally occurring active otitis externa participated in the study. The presence of active disease was verified by aural cytology, microbial culture and otoscopy/clinical scoring. Qualified cases were randomly assigned to either Baytril Otic treatment (n=113) or to a comparable placebo-based regimen (n=56). Treatments were administered twice daily for up to 14 days. Assessment of effectiveness was based on continued resolution of clinical signs 3 to 4 days following administration of the last dose.

At study conclusion, Baytril® Otic was found to be a significantly more effective treatment for canine otitis externa than the placebo regimen. Based on the scoring system used to assess treatment response, therapeutic success occurred in 67% of Baytril® Otic-treated infections compared to 14% with placebo (r-value[2] 0.001) after 14 days of treatment.

**CONTRAINDICATIONS:**

Baytril® Otic is contraindicated in dogs with suspected or known hypersensitivity to quinolones and/or sulfonamides.

**HUMAN WARNINGS:**

Not for human use. Keep out of the reach of children. Avoid contact with eyes. In case of contact, immediately flush eyes with copious amounts of water for 15 minutes. In case of dermal contact, wash skin with soap and water. Consult a physician if irritation develops or persists following ocular or dermal exposures. Individuals with a history of hypersensitivity to quinolone compounds or antibacterials should avoid handling this product. In humans, there is a risk of user photosensitization within a few hours after excessive exposure to quinolones. If excessive accidental exposure occurs, avoid direct sunlight.

**PRECAUTIONS:**

The use of Baytril® Otic in dogs with perforated tympanic membranes has not been evaluated. Therefore, the integrity of the tympanic membrane should be evaluated before administering this product. If hearing or vestibular dysfunction is noted during the course of treatment, discontinue use of Baytril® Otic.

Quinolone-class drugs should be used with caution in animals with known or suspected Central Nervous System (CNS) disorders. In such animals, quinolones have, in rare instances, been associated with CNS stimulation which may lead to convulsive seizures.

Quinolone-class drugs have been associated with cartilage erosions in weightbearing joints and other forms of arthropathy in immature animals of various species.

The safe use of Baytril® Otic in dogs used for breeding purposes, during pregnancy, or in lactating bitches, has not been evaluated.

**ADVERSE REACTIONS:**

During clinical trials, 2 of 113 (1.7%) dogs exhibited reactions that may have resulted from treatment with Baytril® Otic. Both cases displayed local hypersensitivity responses of the aural epithelium to some component within the Baytril® Otic formulation. The reactions were characterized by acute inflammation of the ear canal and pinna.

For medical emergencies or to report adverse reactions, call 1-800-422-9874. For customer service or to obtain product information, including Material Safety Data Sheet, call 1-800-633-3796.

**SAFETY:**

**General Safety Study:**

In a target animal safety study, Baytril® Otic was administered in both ears of 24 clinically normal beagle dogs at either recommended or exaggerated dosages: 10, 30 or 50 drops applied twice daily for 42 consecutive days. A control group of 8 beagle dogs was treated by administering 50 drops of vehicle in one ear twice daily for 42 consecutive days, with the contralateral ear untreated. Erythema was noted in all groups, including both treated and untreated ears in the controls, which resolved following termination of treatment.

**Oral Safety Study:**

In order to test safety in case of ingestion, Baytril® Otic was administered, twice daily for 14 consecutive days, to the dorsum of the tongue and to the left buccal mucosa of 6 clinically normal dogs. No adverse local or systemic reactions were reported.

**DOSAGE AND ADMINISTRATION:**

Shake well before each use.

Tilt head so that the affected ear is presented in an upward orientation. Administer a sufficient quantity of Baytril® Otic to coat the aural lesions and the external auditory canal. As a general guide, administer 5-10 drops per treatment in dogs weighing 35 lbs. or less and 10-15 drops per treatment in dogs weighing more than 35 lbs. Following treatment, gently massage the ear so as to ensure complete and uniform distribution of the medication throughout the external ear canal. Apply twice daily for a duration of up to 14 days.

**STORAGE:**

Store between 4° and 25°C (40 - 77°F). Store in an upright position. Do not store in direct sunlight.

**HOW SUPPLIED:**

Baytril® Otic (enrofloxacin/silver sulfadiazine)

| Size | Presentation |
|---|---|
| 15 mL | Oval plastic bottle with dropper tip and extended tip closure |

**REFERENCES:**


1. Hooper DC and Wolfson JS. Mechanisms of quinolone action and bacterial killing in quinolone antimicrobial agents. Washington DC, American Society for Microbiology, 2nd ed., 1993: 53-75.
2. Gootz TD and Brightly KE. Fluoroquinolone antibacterial: mechanism of action, resistance and clinical aspects. Medicinal Research Reviews 1996: 16 (5): 433-486.
3. Drlica K and Zhoa X. DNA gyrase, topoisomerase IV and the 4-quinolones. Microbiology and Molecular Biology Reviews 1997: 61(3): 377-392.
4. Fox CL. Silver sulfadiazine: a new topical therapy for Pseudomonas in burns. Archives of Surgery 1968: 96:184-188.
5. Wlodkowski TJ and Rosenkranz HS. Antifungal activity of silver sulfadiazine. Lancet 1973: 2:739-740.
6. Schmidt A. In vitro activity of climbazole, clotrimazole and silver sulfadiazine against isolates of Malassezia pachydermatis. J of Vet Medicine Series B 1997: 44: 193-197.



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This retrospective study evaluated the success of decontamination of homes in which *Microsporum canis*-infected cats lived as part of a foster program. Seventy homes were evaluated over a 10-year period as part of establishing a dermatophyte treatment program for shelters. Foster families were instructed to confine cats to a single room. Once the cat left the home, the environment was cleaned and sampled for residual contamination. The cleaning process involved removal of all visible debris, followed by wiping of surfaces with an over-the-counter household detergent. Once excess water was removed, all surfaces were disinfected with either 1:100 household bleach or 1:16 accelerated hydrogen peroxide.

Culture results were negative after a single cleaning in 38 of the 70 homes. In the other homes, complete decontamination was achieved after an additional 1 to 3 cleanings. Cultures were taken from furnace filters and room vents in 9 homes and were all negative. There were no reports of dermatophyte transmission to animals or humans during the study period.

**By incorporating multimodal therapy with routine cleaning and disinfection, it is possible to eliminate environmental contamination.**

## … TO YOUR PATIENTS

Key pearls to put into practice:

1. Dermatophytosis affects adoptable populations of animals, primarily puppies and kittens. The infectious nature of this condition is troublesome for shelters; some elect to "recognize and euthanize" to keep disease transmission to a minimum. There have, however, been several successful dermatophyte treatment programs developed in animal shelters, many of which use foster care families to aid in treatment delivery. By incorporating multimodal therapy (ie, combination of oral and topical antifungal therapy) with routine cleaning and disinfection, it is possible to eliminate environmental contamination and thereby reduce risk for reinfection and contagion.

2. Dermatophytosis is considered to be a generalized infection in cats due to the increased amount of infective material (ie, infective spores) present and distributed over the body as part of normal grooming behavior. This is different than in dogs, in which infection may be resolved with localized topical therapy. For cats, a combination of topical (eg, lime sulfur dips, miconazole/chlorhexidine combination shampoos) and systemic (eg, itraconazole, terbinafine) therapy is typically recommended.[1]

3. For most cats with alopecia, dermatophytosis should be considered a possible differential diagnosis. Positive Wood's lamp fluorescence results will only be seen with *Microsporum canis* infections; a negative result does not rule out infection. Fungal culture remains the preferred diagnostic method to confirm disease, although dermatophyte PCR can also provide a rapid result to help confirm clinical suspicion.

### Reference

1. Moriello KA, Coyner K, Paterson S, Mignon B. Diagnosis and treatment of dermatophytosis in dogs and cats: Clinical Consensus Guidelines of the World Association of Veterinary Dermatology. *Vet Dermatol*. 2017;28(3):266-e68.

## Research Note:
# Potential Use of Activity Monitor to Evaluate Osteoarthritis in Cats

This study evaluated data signatures from an activity monitor of jumps performed by 13 healthy cats that had no evidence of osteoarthritis or degenerative joint disease. Each cat was encouraged to jump up, jump down, or jump horizontally during a 5- to 8-hour observation period. Mean misclassification error rate per cat was 5.4%, which indicates this model is reliable in correctly identifying jumping events in healthy cats. Further studies are expected to show similar results in cats with signs of pain and may be useful in early detection of osteoarthritis and joint pain and in identifying objective end points to assess treatment efficacy.

**Source**

Sharon KP, Thompson CM, Lascelles BDX, Parrish RS. Novel use of an activity monitor to model jumping behaviors in cats. *Am J Vet Res*. 2020;81(4):334-343.

## Research Note:
# Cleaning Procedures & Bacterial Contamination of Feline Inhalation Chambers

Inhalation chambers are commonly used to deliver aerosol drugs to cats with lower airway disease. Manufacturers recommend different cleaning procedures to minimize bacteria buildup in these spacer devices, but no studies have been performed to evaluate their effectiveness. The investigators in this study placed standardized inoculations of *Pseudomonas aeruginosa* into spacer devices from 2 different manufacturers. Devices were then cleaned according to manufacturer recommendations. Chambers were air dried for 24 hours, and samples were obtained from 3 sites and submitted for bacterial culture testing. No bacterial contamination was detected in any of the devices tested. The authors concluded that successful bacterial decontamination occurs when inhalation chambers are cleaned following manufacturer instructions.

**Source**

Klenk FK, DeSimoi V, Wolf G, Schulz BS. Evaluation of different cleaning methods for feline inhalation chambers after bacterial contamination. *J Feline Med Surg*. 2020. doi: 10.1177/1098612X20913352

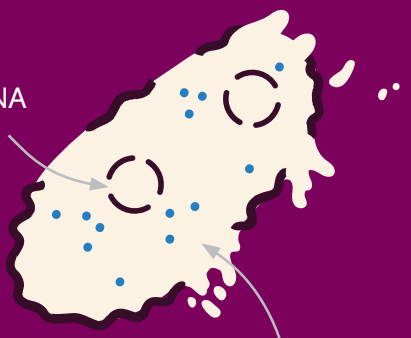
# Baytril® Otic

(enrofloxacin/silver sulfadiazine) Emulsion

# Your go-to for fighting *Pseudomonas* ear infections

**ENROFLOXACIN**

- Attacks on the inside
- Destroys bacterial DNA
- Effective against Gram (+) cocci and Gram (–) rods




**SILVER SULFADIAZINE**

- Attacks on the outside
- Breaks down cell walls/membranes
- Effective against Gram (+) cocci, Gram (–) rods and budding yeast

**DEEP-REACHING ACTION**
**NON-IRRITATING**

Only Baytril® Otic (enrofloxacin/silver sulfadiazine) Emulsion fights *Pseudomonas* with two mechanisms of action.

**Stock Baytril® Otic for your toughest otitis externa cases.**

**CAUTION:** Available only from a licensed veterinarian. Federal law prohibits the extra-label use of this drug in food-producing animals. **PRECAUTIONS:** The safe use of Baytril® Otic in dogs used for breeding purposes, during pregnancy, or in lactating bitches has not been evaluated. The use of Baytril® Otic in dogs with perforated tympanic membranes has not been evaluated. Therefore, the integrity of the tympanic membrane should be evaluated before administering this product. If hearing or vestibular dysfunction is noted during the course of treatment, discontinue use of Baytril® Otic. **CONTRAINDICATIONS:** Baytril® Otic is contraindicated in dogs with suspected or known hypersensitivity to quinolones and/or sulfonamides.



See page 46 for product information summary.

# WHEN IS COMFORT FROM ALLERGY SYMPTOMS NOT ENOUGH?

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# Allergies & CCDs: **What You Need to Know**

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Canine atopic dermatitis is a complex, multifactorial disease. Allergen immunotherapy (AIT; ie, hyposensitization) is considered to be the only treatment that can impact the course of disease. The gold standard for identifying allergens for immunotherapy has traditionally been intradermal testing (IDT); however, there is no clear evidence that AIT based on IDT results is more effective than AIT based on immunoglobulin E (IgE) serum allergy testing, and not all pet owners have access to IDT.[1,2,6]

## Serum Allergy Testing Benefits

Serum allergy testing has some practical advantages over IDT. IDT can be traumatic for some patients and requires the withdrawal of comfort medications (eg, antihistamines [7 days], short-acting glucocorticoids [14 days]), which can potentially impact patient quality of life.[3-5] Similar withdrawals are not required for serum allergy testing.[4]

Unlike IDT, serum allergy testing generally does not require referral,[6] allowing testing to be performed by the primary veterinarian. This can be helpful for owners who may prefer to work with a team they already know and trust or for those with whom cost may be a factor. In addition, serum allergy testing does not require sedation or the shaving of fur and typically takes less time.[3]

## Challenges in Allergy Testing

There is increasing concern regarding inconsistencies between and within both allergy testing methodologies. This has led to speculation regarding whether standardization could further improve AIT outcomes.

With IDT, the allergens tested, test concentrations, and volumes injected vary, even with tests conducted in a specific geographic area and allergens purchased from the same source.[7] There are also inconsistencies in the interpretation of results[8] and only fair to moderate consistency between interevaluator wheal scoring.[9]

Multiple studies have found variability in and among different serum allergy testing laboratories,[10-13] with one study indicating that interlaboratory agreement is only slightly higher than chance.[10] Differences may stem from variability in cut-off values, laboratory methodology, batches of allergen extract, and nonspecific binding interactions, among others.[10]

IDT and serum allergy testing of the same patient may also have discordant results, with the most common cause being positive IgE results when IDT is negative.[6,14,15] Cross-reactive carbohydrate determinants (CCDs) may be a cause of this discrepancy.

## CCDs

CCDs are antigens with carbohydrate epitopes that stimulate the formation of IgE antibodies and have broad cross-reactivity but no apparent clinical significance.[16] CCDs appear to occur in 22% to 35% of atopic humans[17] and 17% to 73% of atopic dogs.[18] When present, CCDs usually result in multiple false-positive or clinically irrelevant serum allergy testing results that correlate poorly with IDT results, particularly with regard to pollens.[16,19]

CCD blockers can improve the specificity of serum allergy testing.[16,17,19] Their efficacy may be impacted by test protocol.[17,19-21]

When testing was performed against 94 potential allergens in US patients, the use of Spectrum's proprietary CCD blocker reduced the average number of allergens testing positive by 19.[21] The environmental allergens most impacted were the pollens of weeds and trees. This new methodology has also been shown to increase the assay sensitivity and intra-assay reproducibility.

Eliminating false-positive results decreases unnecessary allergens included in a patient's individualized AIT plan. Fewer treatment vials decrease costs and improve long-term compliance.

## Conclusion

Allergies impact the lives of animals and their owners[5] and are a top source of pet insurance claims.[22] AIT based on serum allergy testing appears to result in similar success rates as compared with IDT but has additional key advantages. Choosing a test that has quality control features, including those available through Spectrum Veterinary's SPOT Platinum+ panel, may help ensure more reproducible results and improve AIT recommendations. Further research should be conducted to assess the additional potential benefits in safety and efficacy of AIT when CCD blocking is utilized in conjunction with serum allergy testing.

For references, please see **cliniciansbrief.com/article/allergies-ccds-what-you-need-know**

# Animal Toxicosis to Human Topical Dermatologic Products

**Sarah Gray, DVM, DACVECC**
*Horizon Veterinary Specialist*
*Ventura, California*

**In the literature**

Tater KC, Gwaltney-Brant S, Wismer T. Dermatological topical products used in the US population and their toxicity to dogs and cats. *Vet Dermatol*. 2019;30(6):474-e140.

## FROM THE PAGE ...

This study aimed to describe the range of topical dermatologic medications used in human medicine in the United States and their potential toxicity to dogs and cats. Prescription data from 2011 to 2014 were collected from the National Health and Nutrition Examination Survey (NHANES) database, which provided a dataset of 10,170 individuals representative of 311,065,381 US residents. Results revealed that 1.33% (±0.21%) of the US population used prescription topical dermatologic medications; 50 different products were identified. This information was paired with a description of the epidemiology of dog and cat exposures to dermatologic products (both human and veterinary).

A data search from the ASPCA Animal Poison Control Center from 2001 to 2018 revealed 61,169 exposures (dogs, 46,289; cats, 14,880) to 177 veterinary and human topical dermatologic products. These exposures resulted in clinical signs in 37.5% (22,910) of cases. Human-labeled products were involved in 15.1% (3,463) of cases, 73.5% (2,545) of which involved a prescription topical dermatologic drug. Clinical outcomes were categorized as mild (ie, non-life–threatening, transient signs, minimal veterinary intervention), moderate (ie, more intense or longer duration of clinical signs, some veterinary intervention), major (ie, potentially life-threatening, intensive intervention, and/or long-term or permanent sequelae), and death (ie, found dead, died, or were euthanized as a result of toxicosis). Of the identified human-labeled products, 56% (28/50) showed medium to high risk for toxicity. Exposure to human-labeled products was primarily via oral exposure (94.2% of cases); dermal (ie, dermal only or dermal + oral) exposures accounted for 5.3% of cases. Clinical outcomes were mild in 68.2% of cases and moderate, major, or death in 31.2% of cases; of the latter cases, 44 active ingredients were involved in the toxicosis.

The data presented in this study are broad and extrapolated from 2 databases. One database allowed collection of representative human topical dermatologic agents used and potentially accessible to pets. In the NHANES database, humans were selected through complex, multistage, highly stratified cluster samples of households; these data allowed collection of the topical products used but may not be comprehensive or all-inclusive. Pet information was collected from the ASPCA Animal Poison Control Center, which limits the reports of pet cases, as these calls and data may alternatively be documented by company adverse-effect reporting call centers or other animal poison centers in the United States.

## … TO YOUR PATIENTS

Key pearls to put into practice:

1. Most of the literature on toxicoses from human-labeled topical dermatologic products involves individual case reports. Thus, this study is a useful reference to evaluate possible adverse effects caused by topical dermatologic agents in dogs and cats, as the study attempts to aggregate a plethora of information, although broad, into a single source.
2. Clinicians should be aware of the risk for topical dermatologic human (and veterinary) products to result in moderate or major clinical patient outcomes.
3. Increased public awareness of the risks these products pose to pets may help decrease toxic exposures, particularly in regard to home storage practices.

### Suggested Reading

Centers for Disease Control and Prevention. National health and nutrition examination survey. CDC website. https://www.cdc.gov/nchs/nhanes/index.htm. Updated June 30, 2020. Accessed July 15, 2020.

# Effect of Expiratory Phase in Detecting Left Heart Enlargement

**Ashley E. Jones, DVM, DACVIM (Cardiology)**
*Trillium Veterinary Cardiology*
*Ontario, Canada*

### In the literature

Chhoey S, Lee SK, Je H, Jung JW, Jang Y, Choi J. Effect of expiratory phase for radiographic detection of left heart enlargement in dogs with mitral regurgitation. *Vet Radiol Ultrasound*. 2020;61(3):291-301.

## FROM THE PAGE ...

Myxomatous mitral valve disease (MMVD) is the most common acquired heart disease diagnosed in dogs.[1] Echocardiography is the gold standard for diagnosing MMVD but is not always readily available. Left atrial (LA) size correlates with the severity of mitral regurgitation; thus, echocardiographic assessment of LA size is most commonly performed using the left atrial:aortic root ratio (LA:Ao). A variety of methods have been described for radiographically assessing LA and overall heart size, and phase of respiration has been shown to influence some radiographic findings (eg, pulmonary opacity, relative cardiac size).

This study investigated whether the phase of respiration on thoracic radiographs would influence detection of left heart enlargement in normal dogs and dogs with MMVD. The study group included 100 dogs with echocardiographic documentation of mitral regurgitation (MR) secondary to MMVD. To be included in the study, patients had to have inspiratory and expiratory thoracic radiography performed the same day as the echocardiogram and could not have any concurrent diseases affecting the cardiovascular system or evidence of congestive heart failure. The healthy group consisted of 20 purpose-bred beagles. LA:Ao was measured on standard right parasternal short axis view, and a LA:Ao >1.5 was used to define LA enlargement. Quantitative measurements of LA size on thoracic radiographs consisted of vertebral heart size (VHS) and vertebral LA size, a recently described radiographic measurement.[2] Qualitative radiographic assessment of the left heart was also performed; on the lateral view, presence or absence of dorsally deviated carina was noted, and bulging of the caudal cardiac waist in the region of the left atrium was graded 0 to 3, with 0 representing no bulging and 3 representing severe bulging. Similarly, on the ventrodorsal view, the severity of bulges associated with the left auricular appendage and left ventricle were also graded on a scale of 0 to 3.

For the normal group, respiratory phase did not affect radiographic measurements or heart assessments. For dogs with MMVD, with the exception of qualitative assessment of left ventricular bulge on expiration, all radiographic measurements on both inspiration and expiration had moderate positive correlation with echocardiographic-derived LA:Ao. Vertebral LA size measured larger on inspiration, whereas qualitative assessments of bulges associated with the LA, left auricular appendage, and left ventricle were greater on expiration. Moreover, there was a higher chance of false-positive assessment of LA enlargement on expiratory views. There was no difference in VHS on inspiratory and expiratory views.

Overall, use of both inspiratory and expiratory thoracic radiography can be helpful in assessing left heart enlargement in dogs with mitral regurgitation due to MMVD. Caution should be used when interpreting expiratory radiographs, as LA enlargement can be overestimated, but, ultimately, several radiographic assessments described in this study showed good correlation with echocardiographic measurement of LA:Ao.

## … TO YOUR PATIENTS

Key pearls to put into practice:

1. Expiratory thoracic radiography can be helpful in detecting left heart enlargement, but caution should be used, as LA enlargement can be overestimated.
2. VHS assessment remains stable regardless of the phase of respiration.
3. When echocardiography is not readily available, thoracic radiography can be used to assess LA size as a surrogate for severity of MMVD. In this study, all assessments of LA size and VHS had moderate positive correlation with echocardiographic-derived LA:Ao.

## References


1. Parker HG, Kilroy-Glynn P. Myxomatous mitral valve disease in dogs: does size matter? *J Vet Cardiol*. 2012;14(1):19-29.
2. Malcolm EL, Vissver LC, Phillips KL, Johnson LR. Diagnostic value of vertebral left atrial size as determined from thoracic radiographs for assessment of left atrial size in dogs with myxomatous mitral valve disease. *J Am Vet Med Assoc*. 2018;253(8):1038-1045.

# Ultra-Low–Fat Diets in Dogs with Protein-Losing Enteropathy

**Jan S. Suchodolski, DrMedVet, PhD, AGAF, DACVM**
*Gastrointestinal Laboratory*
*Texas A&M University*

## In the literature

Nagata N, Ohta H, Yokoyama N, et al. Clinical characteristics of dogs with food-responsive protein-losing enteropathy. *J Vet Intern Med*. 2020;34(2):659-668.

## FROM THE PAGE ...

Protein-losing enteropathy (PLE) is characterized by intestinal protein loss, often as a consequence of various intestinal disorders (eg, intestinal lymphangiectasia, chronic enteropathy). Therapies involve immunosuppressive agents and dietary modifications (ie, novel or hydrolyzed protein, fat restriction). Dogs with PLE carry a poor prognosis, with many becoming refractory to standard therapy. Recent studies have suggested that ultra-low–fat diets may be of benefit to dogs with PLE, especially those with intestinal lymphangiectasia.[1-4]

This retrospective study describes clinical characteristics of dogs with PLE ($n = 33$). Diagnosis of PLE was based on presence of hypoalbuminemia (albumin <2.6 g/dL) after exclusion of other causes of hypoalbuminemia. Dogs with concurrent disorders (eg, intestinal lymphoma, pancreatitis, hepatic dysfunction), with other causes of hypoalbuminemia (eg, renal protein loss), and/or that were lost to follow-up were excluded.

Continues ▶

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See page 56 for product information summary.

Of the 33 dogs, 27 received a homemade, boiled, ultra-low–fat diet as initial management. The diet consisted of 1 part skinless chicken breast and 2 parts rice or white potato without skin.[4] Fat content was 0.35 g/100 kcal.

Response was defined as a decrease in clinical activity (see ***Suggested Reading***), and responders were subclassified as complete (ie, normal serum albumin [≥2.6 g/dL], no requirement for additional prednisolone treatment) or partial (ie, only partial improvement in serum albumin and/or required additional prednisolone). Of the 27 dogs receiving the ultra-low–fat diet, 23 (85%) responded; of those, 12 were classified as complete and 11 as partial. Median duration to response was 15 days (range, 6-32 days). Responders had significantly lower clinical activity scores as compared with nonresponders. Survival times were longer in responders as compared with nonresponders.

After initial improvement, dogs were gradually transitioned (median, 47 days) to either a commercial dry low-fat (fat content, 2.03 g/100 kcal or 2.3 g/100 kcal) or hydrolyzed diet (fat content, 4.25 g/100 kcal) to prevent secondary nutritional deficiencies.

## … TO YOUR PATIENTS

Key pearls to put into practice:

1. Dietary modifications are crucial in the management of dogs with chronic enteropathy, with several studies showing that most dogs respond to dietary intervention alone. However, because of the complexity of PLE, there is no one-size-fits-all approach, and clinicians should experiment with different diet types. This study confirms that a homemade ultra-low–fat diet can be beneficial in dogs with PLE. After initial response, some dogs can be transitioned to a commercial low-fat or hydrolyzed protein diet.

2. Ultra-low–fat diets have a considerably lower fat content than commercial low-fat diets. It is important for clinicians to correctly assess the macronutrient content (ie, fat, protein, fiber) of different diets. When comparing diets, it is best to assess these nutrients per caloric concentration (eg, grams of fat per 100 or 1000 kcal).

3. Incorporating clinical activity scores (see ***Suggested Reading***) when assessing the patient can add valuable information about the prognosis and clinical response to therapy. Although both the canine inflammatory bowel disease activity index (CIBDAI) and canine chronic enteropathy clinical activity index (CCECAI) are used, the CCECAI may be more useful for dogs with PLE, as it incorporates serum albumin concentrations, which are important when monitoring response to treatment in dogs with PLE.

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## Suggested Reading


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# Feline Osteoarthritis Pain: Tools for Clinicians & Pet Owners

Tamara Grubb, DVM, PhD, DACVAA

## KEY POINTS

- Owners should be educated that cats experience pain from OA, which impacts health, QOL, and behavior. Behavioral and QOL scores and mobility animations such as those available through Zoetis can be useful tools on educating owners how to recognize OA-associated pain (see ***Education & Diagnostic Tools***, next page).
- Using pain-specific questionnaires and performing feline-friendly, OA pain-specific examinations can help expedite a diagnosis of pain (see ***Education & Diagnostic Tools***, next page).
- Feline OA patients should be treated with the drugs and techniques currently available, but clinicians should stay abreast of future data and new treatment options as they emerge.

ZOETIS PETCARE

Osteoarthritis (OA), a form of degenerative joint disease (DJD), is the most common cause of chronic pain in mammals, including cats. More than 90% of adult cats may have radiographic evidence of OA, with the presence/severity of disease expected to increase by >10% each year.[1]

Pain can be classified as either adaptive (physiologic) or maladaptive (pathologic). Adaptive pain facilitates tissue protection and healing, whereas maladaptive pain negatively impacts health, quality of life (QOL), and behavior, which can impact the human–animal bond, potentially leading to surrender or euthanasia of the pet.[2] OA is a nonhealing disease, with OA-associated pain having no protective benefit; thus, OA causes maladaptive pain that, without treatment, progressively worsens as peripheral and central sensitization and neuropathic pain develop.[1]

Although OA is not curable, if identified and treated early, the progression of the intensity of OA pain can be slowed, providing a prolonged period of controllable pain and good QOL (likely a normal lifespan). Because OA is more common in geriatric cats,[1,3] OA screening should begin when cats reach 7 to 10 years of age.

## Recognizing OA-Associated Pain

OA-associated pain may not be obvious—to owners and to veterinary teams.[4] Because cats are evolutionarily both predators and prey, their natural instinct is to hide any vulnerability that could increase predation, including pain. Tools such as checklists, animations, and videos can help owners and veterinary teams accurately recognize and assess pain associated with OA in cats.

### Tools for Owners

Although the expected prevalence of OA is similar between dogs and cats, cat owners may be less likely than dog owners to identify pain in their pet.[4] However, educating owners on the prevalence of OA-associated pain and available treatment options may make owners more likely to bring their cat to the clinic.[5]

Owner education starts with an understanding of feline behavior and mobility. Owners should understand that the clinical signs of OA-associated pain are rarely what is expected but the impact of pain (ie, pain-mediated changes in behavior, activity, and mobility) can still be identified. Behavior and activity changes related to urination/defecation, grooming, and social interactions (with humans and/or other pets) are often indicators of pain and, if not due to pain, could be due to other conditions that may require medical attention. Cats are largely sedentary, making

pain-related mobility changes challenging to observe. Cats are also often semi-nocturnal, so owners may be sleeping when cats exhibit mobility changes. Feline OA is often idiopathic and bilateral as compared with canine OA, which is primarily secondary and unilateral.[6-8] Thus, classic limping as exhibited by dogs is unlikely to be exhibited by cats. In addition, cats also spend more time moving vertically (eg, jumping, climbing) as compared with dogs. Vertical mobility changes, which most owners do not know how to identify, are important indicators of OA-associated pain.

Checklists can be useful in a variety of settings, including medical diagnostics. Using checklists with specific pain-related behavior/activity questions can educate the owner on the potential presence of pain and expedite diagnosis by alerting the clinician to pain-related concerns (see ***Education & Diagnostic Tools***). Questions on a checklist should focus on the cat's behavior and activity. Mobility discussions should center on the cat's ability to jump and climb.

Videos and animations may help owners understand mobility in patients with OA, as the owner may more readily identify with observing the cat in motion. Detailed animations are available and can be effective diagnostic tools, comparing the movement of a cat with healthy, nonpainful joints with a cat with painful osteoarthritic joints as the cats climb up and down stairs, jump up and down, and jump to/from elevated surfaces, among others (see ***Education & Diagnostic Tools***). Providing mobility animations on the clinic website and/or social media can also be beneficial; they can also be displayed on TV or computer screens in the lobby or examination rooms.

Infographics describing changes in behavior-related pain are also available (see ***Education & Diagnostic Tools***). Clinicians should strive to be a pre-eminent resource for animal health information. Thus, infographics and questionnaires should be shared on the clinic website and/or social media and hard-copies made available in the clinic. Information regarding this material can also be included by audio in the clinic's on-hold phone recording.

### Tools for Clinicians

In a study of 90 geriatric cats with radiographic changes of DJD, only 4 had DJD or arthritis mentioned in their medical records.[3] Although radiographic changes do not consistently predict the presence of pain, there is some correlation,[9] and it could therefore be assumed that >4 of these 90 cats were painful.

Identifying feline pain can be difficult for the clinician if not specifically investigated. Clinicians rarely observe a cat walking at the clinic as commonly occurs with dogs; thus, gait analysis is not typically a normal part of a non-pain–related examination. Having the owner explore checklists and mobility animations prior to the visit can increase the likelihood of pain being identified, as the owner's input will provide a template for pointed pain-related, cat-specific questions.

A feline-friendly musculoskeletal examination focused on joint-specific pain and mobility using gentle palpation and range of motion should be a part of any examination for patients in which pain is a potential problem and for every examination for cats >7 to 10 years of age. Detailed videos on feline-friendly, pain-focused musculoskeletal examinations in cats are available (see ***Education & Diagnostic Tools***) and include thorough evaluative descriptions of the patient and several joints, including the hip, stifle, tarsus, and elbow—common locations for feline OA. Asking the owner to video their cat at home can also help facilitate diagnosis, as mobility and behavior can be more accurately assessed when the cat is in an environment it is familiar with. Radiography can provide valuable information and is recommended; however, some patients will have radiographic lesions with no pain, and some patients may have pain that is worse than the radiographic evidence.[7,10] Regardless, pain should be the focus of treatment, not the radiographic changes.

## Treatment of Feline OA

There are no research-backed, FDA-approved, easy-to-administer, long-lasting analgesic treatments for chronic pain in cats. NSAIDs are currently the most effective treatment option but are not approved in the United States for chronic use in cats and can cause adverse effects, including renal dysfunction, which is a common concern in cats.[11] NSAIDs are typically a first-line treatment option in all species but often do not control pain—especially moderate to severe pain—when used alone. Other pharmaceuticals can be used to treat OA pain in cats, but most have little to no demonstrated efficacy in cats and typically require oral administration. For advantages and disadvantages of drugs commonly used to treat chronic pain in cats, see ***Table***.

**Article continues on page 4**

## EDUCATION & DIAGNOSTIC TOOLS

- Feline Examination Videos: **felineOAexam.com**
- Feline OA Owner Checklist: **catOAchecklist.com**
- The International Veterinary Academy of Pain Management: Animal Pain Awareness Month: **ivapm.org/animal-pain-awareness-month**
- Role of Nerve Growth Factor in OA Pain: **thenewscienceofOApain.com**
- Zoetis Technical Bulletin: Current & Future State of Disease: **felineOApain.com**

**TABLE**

## COMMON MEDICATIONS USED TO TREAT CHRONIC PAIN IN CATS: ADVANTAGES, DISADVANTAGES, & DOSAGES

| Drug & Class | Dose, Frequency, & Route | Advantages | Disadvantages | Notes |
|---|---|---|---|---|
| Robenacoxib (NSAID) | 1-2.4 mg/kg PO every 24 hours* | Class is effective against OA-associated pain | Oral administration, which may be difficult for owners<br>Adverse effects are possible with NSAIDs, which can frequently be an owner concern | Approved outside the United States for treatment of chronic pain in cats<br>No limit on duration of therapy |
| Meloxicam (NSAID) | 0.1 mg/kg PO first day, then 0.05 mg/kg every 24 hours thereafter* | Class is effective against OA-associated pain | Oral administration, which may be difficult for owners<br>Adverse effects are possible with NSAIDs, which can frequently be an owner concern | Approved outside the United States for treatment of chronic pain in cats<br>No limit on duration of therapy<br>Doses as low as 0.01-0.03 mg/kg every 24 hours may be effective[17] |
| Gabapentin | 3-20 mg/kg PO every 8-12 hours | Minimal adverse effects<br>One study has indicated efficacy for treatment of OA-associated pain in cats[18] | Oral twice- to three-times-daily administration<br>Can cause sedation<br>Often a controlled drug | Proven effective for calming prior to transport to the clinic, which may decrease pain, as pain causes anxiety and anxiety exacerbates pain |
| Amantadine (NMDA-receptor antagonist) | 3-5 mg/kg PO every 12 hours | Minimal adverse effects<br>Potential for significant pain relief due to monoamine oxidase inhibition | Oral twice-daily administration<br>Efficacy can be difficult to determine | Dosing is based on one canine study and may be inadequate<br>Neither pharmacokinetics nor pharmacodynamics have been studied in cats |
| Ketamine (NMDA-receptor antagonist) | 4-10 µg/kg/min IV following a loading dose of 0.5 mg/kg | Minimal adverse effects<br>Potential for significant pain relief due to monoamine oxidase inhibition | Patient must be hospitalized for infusion<br>Repeat infusions may be necessary | Proven effective in other species, particularly in patients with pain of central sensitization<br>Most effective dose and infusion duration are unknown and are likely highly individual |
| Amitriptyline (tricyclic antidepressant) | 3-4 mg/kg PO every 12 hours | Minimal adverse effects | Oral twice-daily administration<br>Cats typically do not like the taste | Serotonin-reuptake inhibition may provide analgesia through the descending inhibitory limb of the pain pathway |
| Tramadol (opioid) | 1-2 mg/kg PO every 12 hours | Two studies indicate efficacy for treatment of OA-associated pain in cats[19,20] | Cats typically do not like the taste<br>Oral twice- to three-times-daily administration<br>Can cause sedation or dysphoria<br>Controlled drug | Adverse effects like dysphoria, sedation, and diarrhea are common at the effective dose[19] |
| Buprenorphine (opioid) | 0.02-0.05 mg/kg oral transmucosal every 8-12 hours | Opioid-level pain relief | Potential adverse effects<br>Oral twice- to three-times-daily administration<br>Controlled drug<br>Opioids are not ideal for treatment of chronic pain | Oral transmucosal absorption is fairly low, potentially leading to the need for higher doses |

*Dosage used outside the United States to treat chronic pain

Nonpharmacologic treatment (eg, acupuncture, laser and physical therapy) should be considered, although these techniques are largely unproven by research and require frequent treatment visits. Nutraceuticals and specific joint diets may be effective and could be added to the protocol as multimodal therapy but also have little to no demonstrated efficacy in cats. Most of these compounds are likely most effective at slowing disease progression, which may potentially delay the onset of worsening pain, than they are at providing analgesia directly.

## The Future of Treating OA-Associated Pain

Nerve growth factor (NGF) is a cytokine that has recently been recognized as a major factor in the generation, propagation, and sensation of pain.[12-14] Once released from damaged tissue, including tissue in an osteoarthritic joint, NGF rapidly escalates pain due to its impact on multiple pain pathway components, resulting in maladaptive pain.[12-14] NGF binds to tropomyosin receptor kinase A (trkA receptors) and causes nociceptor sensitization, which can lead to hyperalgesia and/or allodynia; this is augmented by the release of other inflammatory mediators (eg, histamine, bradykinin) and additional NGF following NGF binding to trkA receptors on proinflammatory cells (eg, mast cells). In addition, the NGF/trkA receptor complex is internalized and transported to the neuronal cell body in the dorsal root ganglion, where it promotes the expression and/or upregulation of a variety of other pronociception ion channels and receptors, including transient receptor potential vanilloid receptor 1, which is integral for development of central sensitization.[12-14] Because of profound pronociceptive involvement and the ability to rapidly produce both peripheral and central sensitization, NGF is an obvious target for the control of OA pain. Monoclonal antibodies could potentially be an option for anti-NGF therapeutics; they can bind to specific target molecules, including cytokines, and block the activity of the target. Specified (felinized and caninized) anti-NGF monoclonal antibodies for dogs and cats are in development but not yet available.[15,16] In proof-of-concept studies, anti-NGF monoclonal antibodies have shown promise for relief of OA-associated pain for ≈1 month following SC injection.

## Conclusion

OA can cause maladaptive, potentially excruciating, pain in cats. Although owners may struggle to identify pain in their cat, educating owners on the prevalence of OA-associated pain and available treatment options may make owners more likely to bring their cat to the clinic. Education can be provided through numerous resources, such as posters, questionnaires, and mobility animations. Providing education to owners through these means can also help expedite a diagnosis of OA, as pointed questions regarding changes in behavior and vertical movement can help more quickly identify pain. Incorporating these tools for both the owner and the clinician can help to more readily identify and treat feline OA-associated pain, improving patient quality of life.

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# Chronic & Persistent Coughing in a Dog

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## Clinical History & Signalment

Louie, an 11-year-old, 53-lb (24-kg) neutered male Labrador retriever–poodle crossbreed, was presented for intense, productive coughing, gagging, and retching of 8 days' duration. He had no known travel history or recent exposure to other dogs, and he was current on vaccinations and heartworm preventive. His owners reported no chronic respiratory signs, including voice change and/or coughing or gagging while eating or drinking.

## Physical Examination

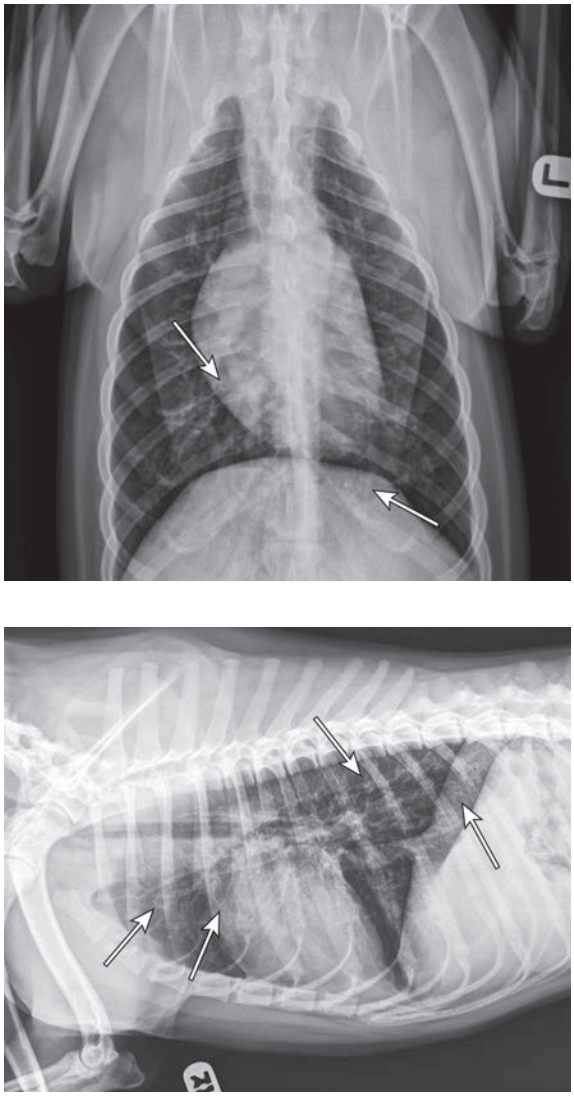
On physical examination, Louie was bright, alert, and responsive. Vital signs were within normal limits. His temperature was 101.3ºF (38.5ºC), heart rate was 80 bpm, respiratory rate was 30 bpm with normal effort, and capillary refill time was <2 seconds. Cardiac, pulmonary, laryngeal, and tracheal auscultation were all normal. No ocular or nasal discharge was present. Mild tracheal sensitivity was noted on direct palpation; abdominal palpation was normal. Several freely movable, homogeneous, subcutaneous masses were appreciated.

## Diagnosis

Differential diagnoses for acute onset cough should include canine infectious respiratory disease complex, pulmonary edema (cardiogenic or noncardiogenic), tracheal collapse, aspiration tracheitis/pneumonia, eosinophilic bronchopneumopathy (EBP), inhaled foreign bodies, and infectious disease (eg, fungal, protozoal, parasitic). Additional considerations include acute presentations of chronic processes, including bronchitis (eg, eosinophilic, chronic) or neoplasia.

Canine infectious respiratory disease complex was considered less likely based on lack of exposure to other dogs. Tracheal collapse and lung lobe torsion were of lower likelihood due to signalment, and fungal disease was considered less likely due to age and lack of exposure to enzootic areas. Heartworm disease was considered less likely based on chronic heartworm preventive administration, annual heartworm testing, and low geographic prevalence. Pulmonary edema was considered unlikely based on normal pulmonary auscultation, lack of heart murmur, and normal respiratory effort.

Thoracic radiographs revealed a moderate, diffuse, bronchointerstitial pattern (***Figure 1***). The cardiac silhouette, pulmonary vasculature, and extrathoracic structures were normal. Airway sampling via bronchoscopy was recommended based on radiographic findings. CBC and serum chemistry profile were performed prior to sedation. Serum chemistry results were within normal limits. CBC revealed leukocytosis (24.3 x $10^3$/µL; normal range, 4.9-17.6 x $10^3$/µL) characterized by marked eosinophilia (10.4 x $10^3$/µL; normal range, 0.07-1.49 x $10^3$/µL), monocytosis (1.4 x $10^3$/µL; normal range, 0.13-1.15 x $10^3$/µL), and band neutrophilia (729/µL; normal range, 0-170/µL). Heartworm antigen test was negative.



▲ **FIGURE 1** Thoracic radiographs showing a characteristic diffuse, patchy bronchointerstitial pattern (***arrows***)

EBP = eosinophilic bronchopneumopathy

Bronchoscopic visualization revealed a moderate amount of thick, adherent, greenish-yellow mucus in the trachea and secondary and tertiary bronchi; mucosa was moderately irregular and erythematous (***Figure 2***). There was no evidence of airway collapse. Samples were collected via bronchoalveolar lavage for cytology, aerobic culture, and *Mycoplasma* spp culture.

Cytologic evaluation revealed a marked eosinophilic inflammatory response with no evidence of bacteria or sepsis; eosinophils made up 96% of total nucleated cells. The remaining cells were consistent with nondegenerate neutrophils (2%) and alveolar macrophages (2%) (***Figure 3***, page 66).

*Mycoplasma* spp culture was negative. Aerobic culture demonstrated small growth of *Citrobacter freundii*, *Klebsiella pneumoniae*, and *Stenotrophomonas maltophilia*, all of which were suspected to be contaminants in the absence of septic cytology.

A Baermann test and fecal centrifugation via zinc sulfate were performed because of the peripheral eosinophilia and eosinophilic cytology; results of both were negative. Repeat Baermann testing was not pursued due to the low clinical concern; however, repeat testing may increase sensitivity in populations with higher prevalence (ie, young dogs, immunosuppressed dogs, research dogs).

## DIAGNOSIS:
## EOSINOPHILIC BRONCHOPNEUMOPATHY

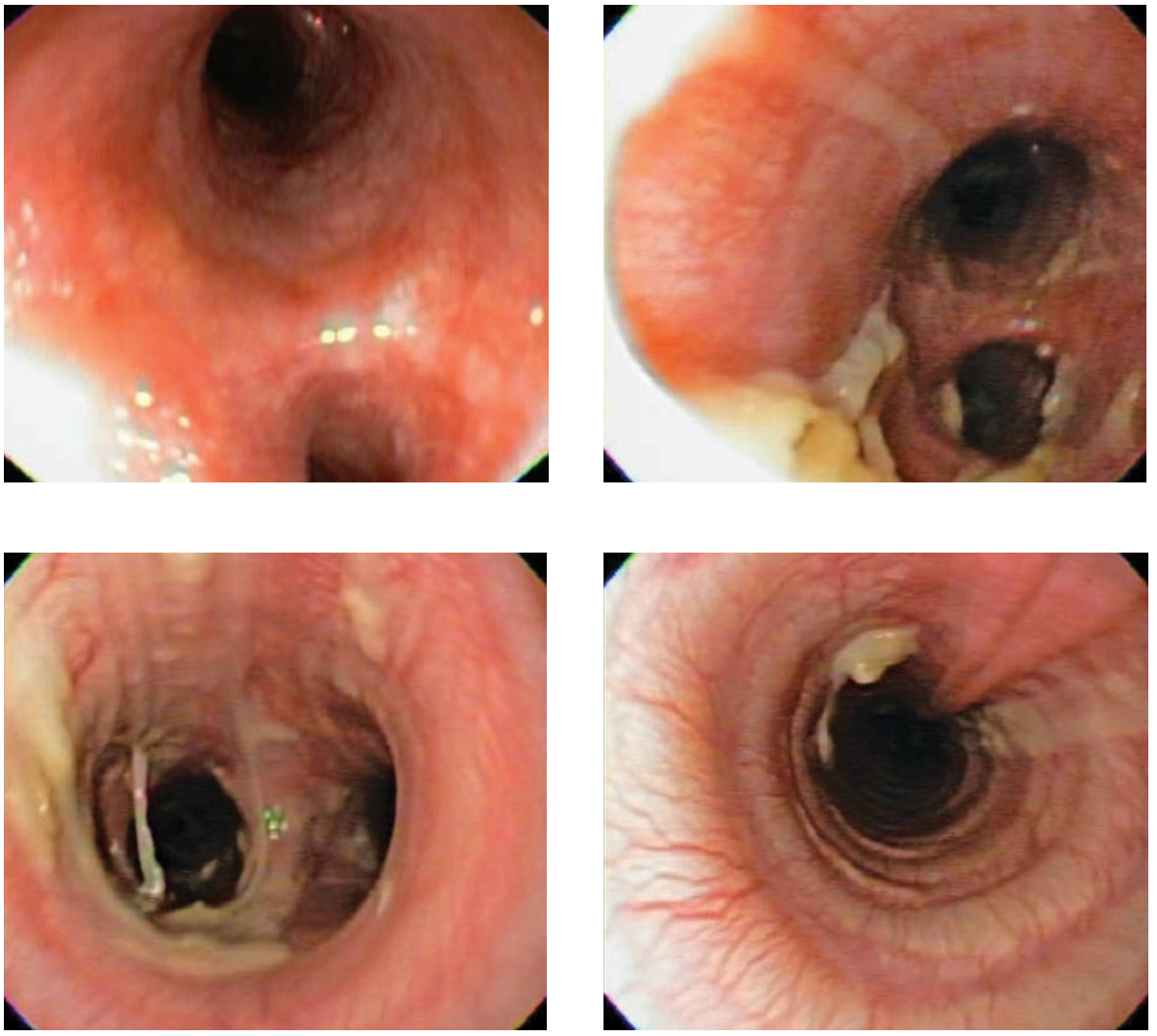
### Treatment & Long-Term Management

Treatment for EBP requires anti-inflammatory medications (see ***Treatment at a Glance***, page 66). Louie was discharged on fenbendazole (1500 mg

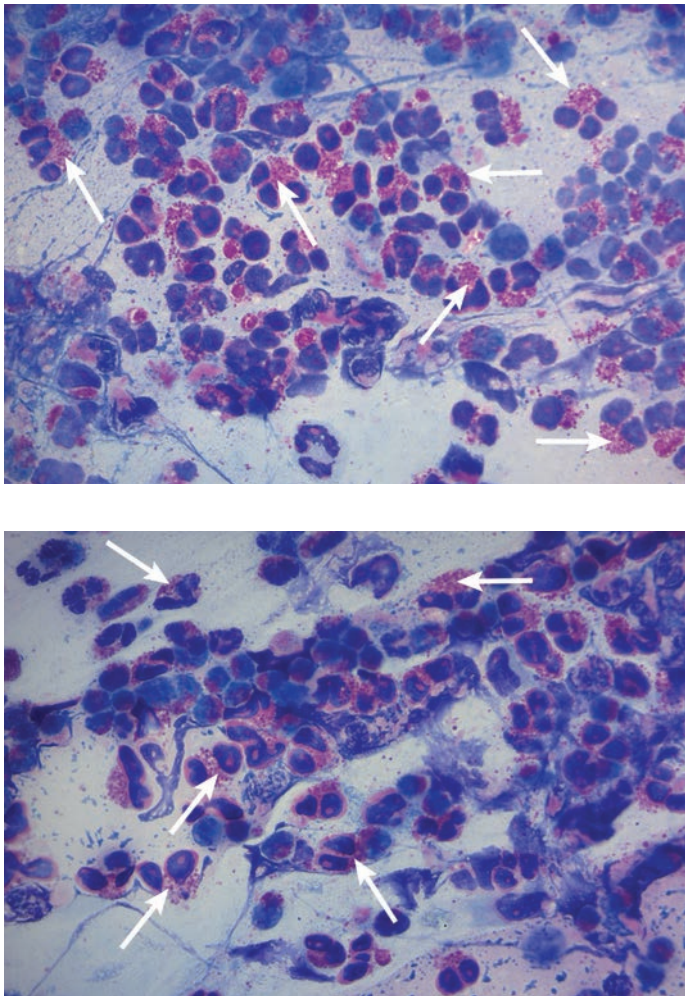
[50 mg/kg] once daily for 14 days) and prednisone (30 mg every 12 hours [2 mg/kg/day] for 5 days tapered to 20 mg every 12 hours [1.5 mg/kg/day] for 5 days; 15 mg every 12 hours [1 mg/kg/day] for 2 weeks; 10 mg every 12 hours for 2 weeks [0.67 mg/kg/day]; 10 mg every 24 hours for 2 weeks [0.33 mg/kg/day]; and finally 10 mg every 48 hours [0.33 mg/kg every other day]. Based on Louie's clinical response, eventual discontinuation of steroids could have been considered.

Louie's owner was asked to report any clinical signs (eg, coughing, gagging, retching) and corticosteroid adverse effects before each taper. Recheck examination and repeat radiography were recommended 1 month after discharge.

Treatment of inflammation should include corticosteroids, with or without immunomodulating medications, which should be gradually and slowly tapered. In endemic regions, concurrent treatment for parasitic disease (fenbendazole, 50 mg/kg for 10-14 days) should be considered to address migrating nematodes and/or primary pulmonary



▲ **FIGURE 2** Bronchoscopy results demonstrating mucosal irregularity, hyperemia, and characteristic greenish-yellow airway exudate



▲ **FIGURE 3** Characteristic cytologic eosinophilic inflammation. Pink granules typical of eosinophils can be seen (***arrows***).

or tracheal parasites (eg, *Paragonimus kellicotti*, *Filaroides* spp, *Crenosoma vulpis*, *Oslerus osleri*), as false-negative results from traditional fecal testing are possible.

## Prognosis & Outcome

At 1 week after discharge, Louie's owner reported he had marked improvement in coughing (ie, ≈80% reduction) and increased energy; however, his owner also noted Louie had excessive thirst, urination, and appetite. At 2 weeks, his owner reported intermittent coughing and persistent signs of corticosteroid excess.

At 1 month after discharge, thoracic radiography was repeated and revealed marked improvement in diffusion of the bronchointerstitial pattern (***Figure 4***). Prednisone was tapered over the next 6 weeks to 10 mg every other day. Intermittent coughing returned, and the dosage was increased to 10 mg once daily (0.33 mg/kg/day), which maintained clinical control. Because this regimen did not result in significant adverse effects and maintained clinical control, adjunctive or alternative anti-inflammatory medications were not prescribed.

Louie was managed on a low dose of prednisone (10 mg once daily) for 5 years with no complications. The primary care clinician attempted to taper prednisone but was unsuccessful—coughing returned as the frequency of medication was reduced.

## TREATMENT AT A GLANCE

- Treatment should be provided for parasitic disease if necessary (ie, fenbendazole 50 mg/kg every 24 hours for 10 to 14 days.
- Prednisone should be initiated at 1 to 2 mg/kg/day.
- Prednisone should be tapered gradually, ideally every 1 to 2 weeks to the lowest effective dose.
- Clinical signs should be monitored, and regular communication with the pet owner is recommended.
- Radiography should be repeated to assess the patient's response to treatment.
- Relapse is common, and long-term therapy may be necessary.
- Steroid adverse effects should be minimized; if these are excessive, alternative medications may include other immunosuppressants (eg, cyclosporine, azathioprine) and/or inhaled corticosteroids (eg, fluticasone, beclomethasone).

## Discussion

EBP (historically known as pulmonary infiltrates with eosinophils) is a disease characterized by eosinophilic infiltration of lung and bronchial mucosa and an important differential diagnosis for patients presented with chronic cough, acute onset of respiratory distress, and/or exercise intolerance.[1,2] Cough is typically harsh and may be associated with gagging and retching.

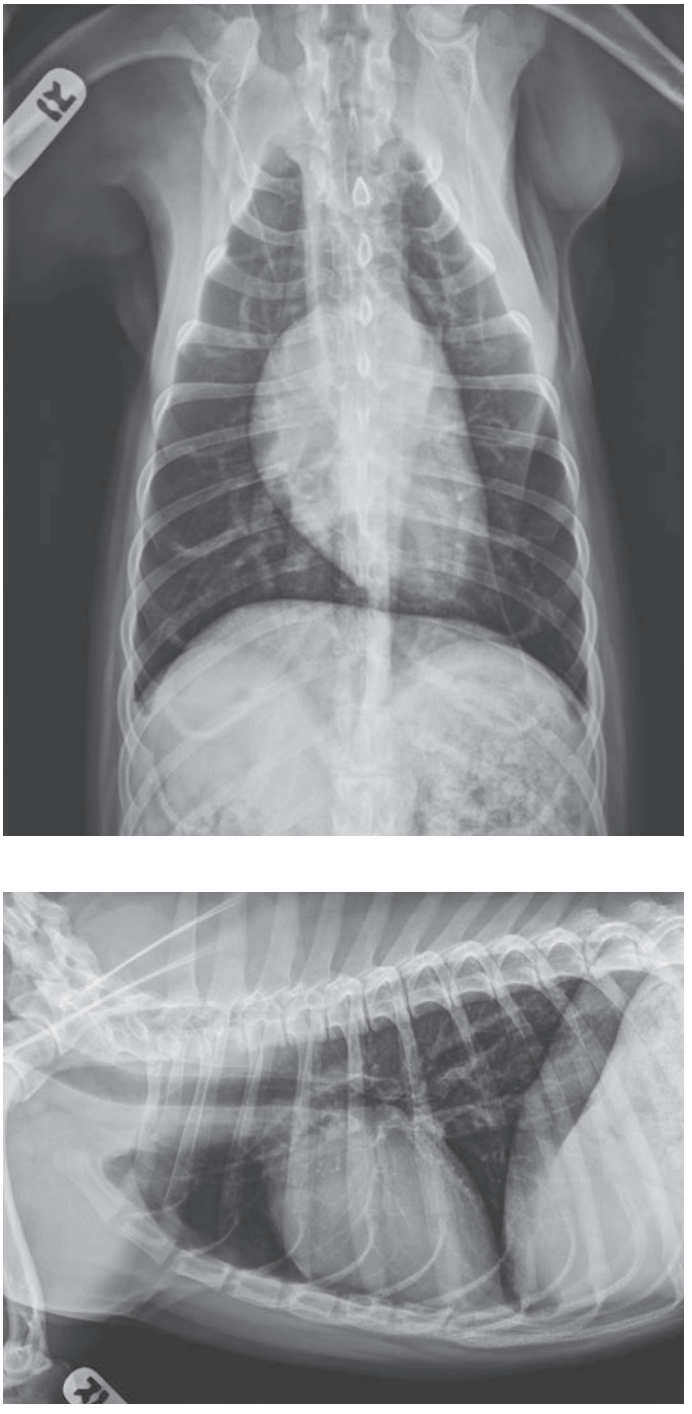
This disease can be seen at any age; however, dogs 4 to 6 years of age are most commonly represented.[1-3] Although Siberian huskies and Alaskan malamutes may be overrepresented,[2] the disease can occur in any dog breed.

Physical examination findings may reveal abnormal lung sounds, but auscultation can be normal.[1,2] In addition, ≤24% of patients may have concurrent nasal discharge.[1,2,4]

Diagnosis requires strong clinical suspicion, as EBP is an uncommon cause of the primary clinical signs (ie, coughing, gagging, exercise intolerance). CBC may reveal an inflammatory leukogram (eg, eosinophilia, neutrophilia) in ≤60% of cases.[4] Eosinophilia may raise clinical suspicion, but its absence does not rule out disease, as it is only present in 50% to 60% of cases.[1,2,5]

Thoracic radiographs are generally characterized by a diffuse bronchointerstitial pattern with peribronchial cuffing and thickening of the bronchial walls. In some cases, bronchiectasis or alveolar infiltration may be observed.[2,6-8] Occasionally, patchy pulmonary opacities create a nodular appearance.[4] Radiography is critical for ruling out other common causes of cough and/or acute respiratory distress. Concurrent disease processes (eg, cardiomegaly, tracheal collapse) can complicate diagnosis.

EBP on thoracic computed tomography has been characterized by parenchymal abnormalities (93%) and bronchial wall thickening (87%) in most dogs. Many dogs also had mucus and/or debris that occluded the bronchial lumen (73%),



▲ **FIGURE 4** Radiograph 1 month after therapeutic initiation showing an improved bronchointerstitial pattern

EBP = eosinophilic bronchopneumopathy

lymphadenopathy (67%), or bronchiectasis (60%).[9] Approximately 33% of dogs had pulmonary nodules, as has been identified on radiographs.[4,9]

Cytologic evaluation of the airways confirms eosinophilic inflammation, which is the hallmark of diagnosis. The percentage of eosinophils (mean, 61% of the total nucleated cell population[4]) exceeds that of healthy dogs (5%-24%).[2,5,10] Samples can be obtained via tracheal wash or bronchoscopy. Bronchoscopy allows for visualization of more characteristic airway associated changes (eg, greenish-yellow secretions, irregular mucosa, hyperemia).[2,5,11] Occasionally, intraluminal granulomas may be present,[4] allowing for mucosal brush samples or biopsies that can further support a diagnosis. Tracheal washes provide appropriate cytologic samples in most cases. Bronchoscopy is generally reserved for patients with more focal radiographic disease, concerns for neoplasia, or suspicion for concurrent structural disorders (eg, bronchial collapse, tracheal collapse).

Cytologic evaluation is critical to help rule out parasitic disease that can also result in eosinophilic inflammatory response. Fecal testing (ie, Baermann test, fecal centrifugation) for parasitic disease is recommended; however, because negative results do not rule out parasitic disease, repeat testing and/or empirical therapy is advisable, particularly in at-risk patients.[12] Heartworm testing is also indicated because heartworm disease may be associated with pneumonitis and eosinophilic inflammation (***Table***).[13]

Eosinophilic bronchitis (EB), eosinophilic granuloma (EG), and EBP have been retrospectively evaluated and may provide information regarding therapeutic response, indications for chronic therapy, and overall prognosis.[4] EB is associated with less severe airway remodeling, reduced eosinophilic inflammation (ie, percent of nucleated cells in airway samples), reduced total inflammation (bronchoalveolar lavage total nucleated cell count/μL), and lower incidence of peripheral eosinophilia. Patients with EG demonstrate intraluminal granulomas/masses not present in EBP. Overlap still exists among these disorders, and the impact on therapeutic outcome is not yet known; however, EB may be more responsive and EG less responsive to therapy.[4] Eosinophilic pulmonary granulomatosis may also be associated with eosinophilic inflammation, but it is least common and may represent a spectrum of disease characterized by masses that involve the pulmonary parenchyma (not exclusively luminal). EPG may also have systemic organ involvement and be the least responsive to therapy.[14,15]

Corticosteroids are the mainstay of therapy. Prednisone is typically initiated at 1 to 2 mg/kg/day and gradually tapered to the lowest effective dose.[1,2,4] It is important to note that clinical relapse is common and can reach ≈30% after corticosteroids are tapered.[5] In some cases, medications can be discon-

**TABLE**

## COMMON FINDINGS IN EOSINOPHILIC BRONCHOPNEUMOPATHY

| | |
|---|---|
| Clinical signs | Coughing<br>Acute respiratory distress |
| Radiographic evaluation | Bronchointerstitial pattern<br>Peribronchial cuffing<br>Alveolar disease<br>Bronchiectasis<br>Nodular pattern |
| CBC | Leukocytosis ± eosinophilia |
| Airway cytology | Eosinophilic ± neutrophilic airway cytology |
| Airway culture | Generally negative |
| Bronchoscopy | Greenish-yellow secretions<br>Irregular, hyperemic mucosa<br>± nodular changes |

tinued after months with no evidence of relapse. Some clinicians may taper the drug faster, but the author believes that tapering faster than 1 to 2 weeks may increase the rate of relapse.

Patients with severe signs (eg, hypoxemia, oxygen dependency, alveolar disease) may also benefit from higher doses initially.

Alternative options for management include inhaled corticosteroids or additional immunosuppressive medications. Fluticasone has been evaluated and may be successful in some cases but is not always adequate for maintaining clinical remission.[16] The author has successfully used cyclosporine in some cases in which corticosteroid adverse effects were intolerable. However, cyclosporine and other immunosuppressive drugs (eg, azathioprine, mycophenolate) have not been evaluated in randomized, controlled studies despite sporadic clinical use. Cyclosporine has been used for the treatment of other eosinophilic disorders in dogs.[17,18]

## TAKE-HOME MESSAGES

- EBP should be considered in patients with chronic cough and in patients with acute respiratory distress.
- Radiographs may reveal nodules, mimicking neoplasia.
- Absence of eosinophilia does not rule out the disease.
- Diagnosis requires cytologic evaluation.
- Parasitic disease can mimic EBP and cannot be definitively ruled out with negative testing.
- Corticosteroids (ie, prednisone) are the hallmark of therapy.
- Patient relapse is common and may necessitate long-term management.
- Inhaled steroids may not always control the disease.

EB = eosinophilic bronchitis
EBP = eosinophilic bronchopneumopathy
EG = eosinophilic granuloma

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# Separation Anxiety in a Dog with Fear-Based Behavior

**Leslie Sinn, CPDT-KA, DVM, DACVB**
*Behavior Solutions for Pets*
*Hamilton, Virginia*

A 6-year-old spayed terrier crossbreed is presented for a 2-month history of crying and barking when left at home alone. The behavior began 2 weeks after the patient was adopted from a local animal shelter. She becomes increasingly agitated (eg, panting, whining, following her owners) when her owners prepare to leave the home; when the owners return, she exuberantly greets them, engaging in marked attention-seeking behaviors (eg, standing on hindlimbs, frantically pawing at the owners) and requiring at least 15 minutes to settle.

The owners provide a video of the patient vocalizing when crated (see ***Video***, page 74) and report that she pants, paces, vocalizes, and chews and paws at doors and window frames when not crated. These behaviors continue for the duration of the owners' absence. The owners have crated the dog, offered long-lasting chews before departures, and used verbal reprimands, none of which have impacted her behavior. The dog does not have a history of aggression toward humans or other animals.

No abnormalities are observed on physical examination. CBC, serum chemistry profile, total thyroxine, and urinalysis are unremarkable. On examination, the patient is visibly trembling, refuses food, and remains crouched on the owner's lap with ears down, tail tucked, and eyes averted. To avoid exacerbating her fearful response to handling, temperature is not obtained.

Diagnoses of separation anxiety and fear-based behaviors in the veterinary setting are made.

# Which of the following drugs would be appropriate for this patient's separation anxiety?

Based on the information provided, how would you grade the following drugs and why?

RED = do not use  YELLOW = proceed with caution  GREEN = safe

| | | | |
|---|---|---|---|
| **Alprazolam** | RED | YELLOW | GREEN |
| **Acepromazine** | RED | YELLOW | GREEN |
| **Trazodone** | RED | YELLOW | GREEN |
| **Gabapentin** | RED | YELLOW | GREEN |
| **Clonidine** | RED | YELLOW | GREEN |
| **Fluoxetine** | RED | YELLOW | GREEN |
| **Clomipramine** | RED | YELLOW | GREEN |
| **Dog-Appeasing Pheromone** | RED | YELLOW | GREEN |
| **L-Theanine** | RED | YELLOW | GREEN |
| **Rescue Remedy** | RED | YELLOW | GREEN |
| **α-Casozepine** | RED | YELLOW | GREEN |

**TURN THE PAGE TO COMPARE YOUR RESULTS**

# Did you answer?

The following represents the best responses based on drug metabolism, pharmacokinetics, species, diagnostic differentials, clinical and laboratory data, and other pertinent findings.

## Alprazolam

CORRECT RESPONSE 

Alprazolam is a short-acting benzodiazepine that exerts anxiolysis by enhancing the effect of the inhibitory neurotransmitter γ-aminobutyric acid (GABA). Alprazolam should be administered 30 to 60 minutes prior to the stressful event (eg, departure of pet owners, arrival to the veterinary clinic).[1,2] Because time to onset is variable and paradoxical reactions (eg, increased restlessness, hyperactivity) may be observed, the owners should be advised to administer a test dose prior to using this medication in a stressful situation. Because alprazolam is short-acting (ie, 4-6 hours), a longer-lasting maintenance medication will also be needed to treat this patient's separation anxiety.

## Acepromazine

CORRECT RESPONSE 

Acepromazine is a phenothiazine tranquilizer that blocks dopamine receptors and increases the dopamine turnover rate. It is a CNS depressant that induces sedation and muscle relaxation. Acepromazine has poor anxiolytic properties and should never be used as a sole agent when treating anxiety disorders. The only exception is when the drug is used in conjunction with an anxiolytic to prevent self-injury or trauma.

## Trazodone

CORRECT RESPONSE 

Trazodone is a serotonin antagonist and reuptake inhibitor that functions by enhancing serotonin, dopamine, and norepinephrine, resulting in antidepressant, hypnotic, and anxiolytic effects. This drug has been demonstrated to be an efficacious adjunctive medication for the treatment of separation anxiety.[3] Trazodone has a mild sedative effect, which can be highly advantageous in animals that panic and/or are destructive.[3] Occasionally, paradoxical reactions (eg, restlessness, hyperactivity) are observed; owners should be advised to administer a test dose before using trazodone in a stressful situation. Trazodone should be administered 2 hours prior to departures or veterinary visits. Because trazodone is short-acting, a longer-lasting maintenance medication will also be needed to treat this dog's separation anxiety.

## Gabapentin

CORRECT RESPONSE 

Gabapentin functions by inhibiting calcium channels. It is used to treat pain and epilepsy in humans and has anxiolytic and sedative properties. Sleepiness is a common adverse effect and may be advantageous in the treatment of separation anxiety. Gabapentin should be administered 1 to 2 hours prior to veterinary visits or departures. Because gabapentin is short-acting, a longer-lasting maintenance medication will also be needed to treat this patient's separation anxiety. Of note, gabapentin remains a frequent choice as a short-acting departure medication used in the treatment of separation anxiety despite little research supporting its use.

## Clonidine

CORRECT RESPONSE 

Clonidine is a selective $\alpha_2$-receptor agonist that blocks norepinephrine release in the locus coeruleus, which induces noradrenergic stimulation. It is short-acting and requires 1 to 2 hours to reach full effect. Clonidine has been shown to be an effective adjunctive medication for treatment of canine separation anxiety.[4] Because it is a hypotensive agent, clonidine should be used with caution (ie, not as a first-choice drug) in older patients and patients with cardiovascular disease. Adverse effects may include increased water intake, incoordination, sedation, and constipation.[4] Owners should be advised to administer a test dose before using this drug in a stressful situation. Because clonidine is short-acting, a longer-lasting maintenance medication will also be needed to treat this patient's separation anxiety.

## Fluoxetine

CORRECT RESPONSE 

Fluoxetine is a selective serotonin reuptake inhibitor that provides anxiolysis by increasing serotonin levels in the neurosynaptic cleft. Common adverse effects include drowsiness, loss of appetite, and occasional diarrhea. Fluoxetine is FDA-approved for the treatment of separation anxiety in dogs in conjunction with behavior modification. Although improvement may be seen as soon as the first week, in most cases, the medication must be administered daily for 4 to 6 weeks to be effective.[5] Thus, a short-acting medication should be used prior to departures to provide additional needed support. Some dogs can tolerate separation once the maintenance medication is initiated, whereas others require lifelong departure drugs and maintenance medication.

## Clomipramine

CORRECT RESPONSE 

Clomipramine is a tricyclic antidepressant that helps reduce anxiety by the selective inhibition of neuronal reuptake of serotonin and has lesser effects on neuronal reuptake of norepinephrine. It must be administered daily as a maintenance medication. Common adverse effects include drowsiness, loss of appetite, urine retention, and occasional diarrhea. Clomipramine is FDA-approved for the treatment of separation anxiety in dogs in conjunction with behavior modification. Improvement can be seen as quickly as 1 week, but maximum effectiveness in most cases takes 8 to 12 weeks[6]; a short-acting medication should therefore be used prior to departures to provide needed support. Some dogs can tolerate separation once the maintenance medication is initiated, whereas others require lifelong departure drugs and maintenance medication.

## Dog-Appeasing Pheromone

CORRECT RESPONSE 

Dog-appeasing pheromone is a mimic of the pheromone released from nursing dams that provides a sense of reassurance and calm to help dogs adjust to stressful situations (eg, triggering noises, travel) and new environments. The efficacy of dog-appeasing pheromone for treatment of separation anxiety has been demonstrated.[7] This product is appropriate for mild cases of separation anxiety and fear-based behaviors and when used as a component of a comprehensive treatment plan.

## L-Theanine

CORRECT RESPONSE 

The available research on L-theanine is limited but appears promising.[8,9]

Theanine is an amino acid found in green tea that binds to glutamate receptors in the brain, countering neural stimulation at these sites. This effect causes a subsequent rise in GABA, thereby inhibiting neural transmission and excessive firing associated with anxiety.[8] Although it can be used as a sole agent to help address mild distress due to separation, theanine is best used as part of a comprehensive treatment plan with other psychoactive medications when clinical signs of separation anxiety are escalated.

Continues ▶

### Rescue Remedy

CORRECT RESPONSE 

Rescue Remedy contains extracts of rockrose, impatiens, clematis, Star of Bethlehem, and cherry plum. No research is available regarding its efficacy in animals. A double-blind, placebo-controlled study in humans demonstrated no effect.[10] When discussing this product with owners, the clinician should keep in mind that the placebo effect can be as high as 45%.[11]

### α–Casozepine

CORRECT RESPONSE 

α–Casozepine is a supplement derived from milk protein. It affects GABA receptors and has benzodiazepine-like properties, resulting in an anxiolytic effect. α–Casozepine can be used as a sole agent to help address mild fear and anxiety or as part of a comprehensive treatment plan in conjunction with other psychoactive medications.[12,13] Although it can be used as a sole agent to help address mild distress due to separation, α–casozepine is best used as part of a comprehensive treatment plan with other psychoactive medications when clinical signs of separation anxiety are marked.

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## VIDEO

To watch a video of the patient's behavior when crated, scan the QR code or go to **cliniciansbrief.com/article/separation-anxiety-dog-fear-based-behavior**

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

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

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Package Insert for Dogs

# ProZinc®
## (protamine zinc recombinant human insulin)

**40 IU/mL**

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

**Description:** PROZINC® is a sterile aqueous protamine zinc suspension of recombinant human insulin.

**Each mL contains:**

| | |
|---|---|
| recombinant human insulin | 40 International Units (IU) |
| protamine sulfate | 0.466 mg |
| zinc oxide | 0.088 mg |
| glycerin | 16.00 mg |
| dibasic sodium phosphate, heptahydrate | 3.78 mg |
| phenol (added as preservative) | 2.50 mg |
| hydrochloric acid | 1.63 mg |
| water for injection (maximum) | 1005 mg |

pH is adjusted with hydrochloric acid and/or sodium hydroxide.

**Indication:** PROZINC (protamine zinc recombinant human insulin) is indicated for the reduction of hyperglycemia and hyperglycemia-associated clinical signs in dogs with diabetes mellitus.

**Dosage and Administration:** USE OF A SYRINGE OTHER THAN A U-40 SYRINGE WILL RESULT IN INCORRECT DOSING.

FOR SUBCUTANEOUS INJECTION ONLY.

DO NOT SHAKE OR AGITATE THE VIAL.

**PROZINC should be mixed by gently rolling the vial prior to withdrawing each dose from the vial.** Once mixed, PROZINC suspension has a white, cloudy appearance. Clumps or visible white particles can form in insulin suspensions: do not use the product if clumps or visible white particles persist after gently rolling the vial.

Using a U-40 insulin syringe, the injection should be administered subcutaneously on the back of the neck or on the side of the dog.

Always provide the Client Information Sheet with each prescription.

**Starting dose:** The recommended starting dose for PROZINC is 0.2-0.5 IU insulin/pound of body weight (0.5-1.0 IU/kg) **once daily**. The recommended starting dose for naïve dogs is the lower end of the dose range. The recommended starting dose for dogs with poorly controlled diabetes mellitus and transitioning from another insulin product is the mid to higher end of the dose range based on the veterinarian's experience with the dog's medical history and previous insulin dose. When transitioning from another insulin, the dog's blood glucose and general condition should be closely monitored. **When transitioning from another insulin, PROZINC should be started once daily, regardless of the frequency of prior insulin use.**

The dose should be given concurrently with or right after a meal. The veterinarian should re-evaluate the dog at appropriate intervals and adjust the dose and frequency based on both clinical signs and laboratory test results (the blood glucose curve values and shape, nadir, and fructosamine) until adequate glycemic control has been attained. In the effectiveness field study, glycemic control was considered adequate if the glucose nadir from a 9-hour blood glucose curve was between 80 and 125 mg/dL, the maximum blood glucose was ≤ 300 mg/dL, and clinical signs of hyperglycemia such as polyuria, polydipsia, or weight loss were improved.

**Changing to twice daily dosing:** Twice daily dosing should be considered if the duration of insulin action is determined to be inadequate with once daily dosing. Use caution when adjusting from once daily to twice daily dosing because PROZINC may have prolonged duration of action in some dogs (see Clinical Pharmacology). The veterinarian should closely monitor the duration of action using blood glucose curves to avoid the increased risk of hypoglycemia. If twice daily dosing is initiated, the two doses should each be approximately 25% less than the once daily dose required to attain an acceptable glucose nadir. For example, if a dog receiving 10 units of PROZINC once daily has an acceptable nadir but inadequate duration of activity, the dose should be changed to 7 units twice daily (round down to the nearest whole unit).

Further adjustments in the dosage may be necessary with changes in the dog's diet, body weight, or concomitant medication, or if the dog develops concurrent infection, inflammation, neoplasia, or an additional endocrine or other medical disorder.

**Contraindications:** PROZINC is contraindicated in dogs sensitive to protamine zinc recombinant human insulin or any other ingredients in PROZINC. PROZINC is contraindicated during episodes of hypoglycemia.

**Warnings:**
**User Safety:** For use in dogs and cats. Keep out of the reach of children. Avoid contact with eyes. In case of contact, immediately flush eyes with running water for at least 15 minutes. Accidental injection may cause hypoglycemia. In case of accidental injection, seek medical attention immediately. Exposure to product may induce a local or systemic allergic reaction in sensitized individuals.

**Animal Safety:** Owners should be advised to observe for signs of hypoglycemia (see Client Information Sheet). Use of this product, even at established doses, has been associated with hypoglycemia. A dog with signs of hypoglycemia should be treated immediately. Glucose should be given orally or intravenously as dictated by clinical signs. Insulin should be temporarily withheld and, if indicated, the dosage adjusted.

Any change in insulin should be made cautiously and only under a veterinarian's supervision. Changes in insulin strength, manufacturer, type, species (human, animal) or method of manufacture (rDNA versus animal-source insulin) may result in the need for a change in dosage.

Appropriate diagnostic tests should be performed to rule out other endocrinopathies in diabetic dogs that are difficult to regulate.

**Precautions:** Dogs presenting with severe ketoacidosis, anorexia, lethargy, and/or vomiting should be stabilized with short-acting insulin and appropriate supportive therapy until their condition is stabilized. As with all insulin products, careful patient monitoring for hypoglycemia and hyperglycemia is essential to attain and maintain adequate glycemic control and to prevent associated complications. Overdose can result in profound hypoglycemia and death.

Glucocorticoids, progestogens, and certain endocrinopathies can have an antagonistic effect on insulin activity. Glucocorticoid and progestogen use should be avoided.

The safety and effectiveness of PROZINC in breeding, pregnant, and lactating dogs has not been evaluated.

The safety and effectiveness of PROZINC in puppies has not been evaluated.

**Adverse Reactions:** In a 182-day field study, 276 dogs received PROZINC. The most common adverse reactions were lethargy, anorexia, hypoglycemia, vomiting, seizures, shaking, diarrhea, and ataxia.

Table 1 summarizes the adverse reactions reported in the study. Clinical signs of hypoglycemia varied and included seizure, collapse, ataxia, staggering, trembling, twitching, shaking, disorientation, lethargy, weakness, and vocalization. In Table 1, the individual clinical signs that were observed during the episodes of hypoglycemia are captured as separate adverse reactions and a single dog may have experienced more than one clinical sign of hypoglycemia.

Table 1. Adverse reactions seen in the safety population (276 dogs)

| Adverse Reaction | Number and Percentage |
|---|---|
| Lethargy (lethargy, depression, listless, and tiredness) | 45 (16.3%) |
| Anorexia (anorexia, decreased appetite, inappetence, and not eating) | 28 (10.1%) |
| Hypoglycemia with clinical signs | 24 (8.9%) |
| Vomiting | 21 (7.6%) |
| Seizures | 16 (5.8%) |
| Shaking/trembling/twitching | 13 (4.7%) |
| Ataxia (ataxia, balance problem, stumbling gait) | 11 (4.0%) |
| Diarrhea (includes bloody diarrhea) | 9 (3.3%) |
| Disorientation/confusion | 9 (3.3%) |
| Weakness | 8 (2.9%) |
| Restlessness/anxiety/agitation | 6 (2.2%) |
| Cataract | 6 (2.2%) |
| Panting (panting and tachypnea) | 6 (2.2%) |
| Hematuria | 4 (1.5%) |

**Clinical pathology:** The only change seen in complete blood count, serum chemistry, and urinalysis results was an elevation in mean cholesterol at Day 182 (432.6 mg/dL, normal range 131-345 mg/dL) compared to Day -1 (333.7 mg/dL).)

**Injection site reactions:** Seven dogs had injection site reactions, including observations of thickened skin, swelling, bumps at the injection site, and redness. All injection site reactions resolved without cessation of PROZINC therapy. Reaction to the injection, including vocalization, was observed in four dogs.

**Hypoglycemia:** There were 80 hypoglycemic episodes recorded during the study with some dogs experiencing more than one episode; 37 episodes were associated with clinical signs in 24 dogs, 40 episodes were without clinical signs in 27 dogs, and 3 were with unknown signs in 2 dogs. Clinical signs of hypoglycemia varied and included seizure, collapse, ataxia, staggering, trembling, twitching, shaking, disorientation, lethargy, weakness, and vocalization. Some dogs required hospitalization and intravenous dextrose while most recovered after receiving oral supplementation with a meal and/or oral glucose such as syrup. Two dogs were euthanized when the hypoglycemia did not resolve with supportive care. Hypoglycemia without clinical signs was defined as two consecutive blood glucose curve values < 60 mg/dL unaccompanied by clinical signs.

**Diabetic ketoacidosis and pancreatitis:** Eleven dogs were diagnosed with diabetic ketoacidosis. Four of these 11 dogs died or were euthanized, one after one dose of PROZINC. Twenty-one dogs were diagnosed with pancreatitis. Seven of these 21 dogs died or were euthanized due to complications of pancreatitis. Four dogs had concurrent diabetic ketoacidosis and pancreatitis, three of which died or were euthanized. Not all the deaths were considered related to PROZINC.

**Deaths:** Thirty-six (36) dogs died or were euthanized, six of which were possibly related to PROZINC. One dog died from recurrent episodes of pancreatitis, and one died after developing severe vomiting and diarrhea followed by a seizure. Four dogs were euthanized: one developed severe pancreatitis and azotemia, one had recurrent episodes of pancreatitis and diabetic ketoacidosis, and two for lack of effectiveness.

To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Boehringer Ingelheim at 1-888-637-4251.

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

**Clinical Pharmacology:** PROZINC was administered subcutaneously to 10 healthy Beagles using an incomplete crossover design at doses of 0.5 IU/kg (5 dogs), 0.8 IU/kg at a single site (10 dogs), or 0.8 IU/kg at three separate sites (6 dogs). Insulin and glucose concentrations were measured over 24 hours. The shapes of insulin and glucose curves were variable among dogs; and the relationship between insulin dose, concentration, and glucose-lowering effect was nonlinear (Table 2).

Table 2. Pharmacodynamics of three dosing groups

| Dose group | Onset of Action | Time to nadir | Duration of Action |
|---|---|---|---|
| 0.5 IU/kg at a single site | 1 to 14 hours | 6 to 16 hours | 16 to >24 hours |
| 0.8 IU/kg at a single site | 0.5 to 10 hours | 5 to >24 hours | 16 to >24 hours |
| 0.8 IU/kg divided at three sites | 1 to 10 hours | 8 to 20 hours | 18 to >24 hours |

**Information for Dog Owners:** Please refer to the Client Information Sheet for Dogs for more information about PROZINC. PROZINC, like other insulin products, is not free from adverse reactions. Owners should be advised of the potential for adverse reactions and be informed of the associated clinical signs. Potential adverse reactions include hypoglycemia, insulin antagonism/resistance, rapid insulin metabolism, insulin-induced hyperglycemia (Somogyi Effect), and local or systemic reactions. The most common adverse reaction observed is hypoglycemia. Signs may include weakness, depression, behavioral changes, muscle twitching, and anxiety. In severe cases of hypoglycemia, seizures and coma can occur. Hypoglycemia can be fatal if an affected dog does not receive prompt treatment. Appropriate veterinary monitoring of blood glucose, adjustment of insulin dose and regimen as needed, and stabilization of diet and activity help minimize the risk of hypoglycemic episodes. The attending veterinarian should evaluate other adverse reactions on a case-by-case basis to determine if an adjustment in therapy is appropriate, or if alternative therapy should be considered.

**Effectiveness:** A total of 276 client-owned dogs were enrolled in an 84-day field study followed by a 98-day extended-use phase with 276 dogs receiving PROZINC. The dogs included various purebred and mixed breed dogs ranging in age from 2 to 16 years and in weight from 3.3 to 123 pounds. There were 128 neutered males, 8 intact males, 134 spayed females and 6 intact females. Two hundred twenty-four dogs (224) were included in the effectiveness analysis. Dogs were started on PROZINC at a dose of 0.2-0.5 IU/lb (0.5-1.0 IU/kg) once daily. Dogs were evaluated at 7, 14, 21, 28, 42, 63 and 84 days after initiation of therapy. The dose was adjusted based on clinical signs and results of 9-hour blood glucose curves on Days 7, 14, 21, 28, 42, 63 and 84.

Effectiveness was based on successful control of diabetes which was defined as improvement in at least one laboratory variable (blood glucose curve mean, blood glucose curve nadir, or fructosamine) and at least one clinical sign (polyuria, polydipsia, or weight loss). Based on this definition, 162 of 224 cases (72%) were considered successful.

**How Supplied:** PROZINC is supplied as a sterile injectable suspension in 10 mL and 20 mL multi-dose vials. Each mL of PROZINC contains 40 IU recombinant human insulin.

**Storage Conditions:** Store in an upright position under refrigeration at 36-46°F (2-8°C). Do not freeze. Protect from light. **Use the 10 mL vial within 60 days of first puncture. Use the 20 mL vial within 80 days of first puncture.**

Approved by FDA under NADA # 141-297

**Marketed by:**
Boehringer Ingelheim Animal Health USA Inc. Duluth, GA 30096

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Boehringer Ingelheim

Package Insert for Cats

# ProZinc®
## (protamine zinc recombinant human insulin)

**40 IU/mL**

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

**Description:** PROZINC® is a sterile aqueous protamine zinc suspension of recombinant human insulin.

Each mL contains:

| | |
|---|---|
| recombinant human insulin | 40 International Units (IU) |
| protamine sulfate | 0.466 mg |
| zinc oxide | 0.088 mg |
| glycerin | 16.00 mg |
| dibasic sodium phosphate, heptahydrate | 3.78 mg |
| phenol (added as preservative) | 2.50 mg |
| hydrochloric acid | 1.63 mg |
| water for injection (maximum) | 1005 mg |

pH is adjusted with hydrochloric acid and/or sodium hydroxide.

**Indication:** PROZINC (protamine zinc recombinant human insulin) is indicated for the reduction of hyperglycemia and hyperglycemia-associated clinical signs in cats with diabetes mellitus.

**Dosage and Administration:** USE OF A SYRINGE OTHER THAN A U-40 SYRINGE WILL RESULT IN INCORRECT DOSING.

FOR SUBCUTANEOUS INJECTION ONLY.

DO NOT SHAKE OR AGITATE THE VIAL.

**PROZINC should be mixed by gently rolling the vial prior to withdrawing each dose from the vial.** Once mixed, PROZINC suspension has a white, cloudy appearance. Clumps or visible white particles can form in insulin suspensions: do not use the product if clumps or visible white particles persist after gently rolling the vial.

Using a U-40 insulin syringe, the injection should be administered subcutaneously on the back of the neck or on the side of the cat.

Always provide the Client Information Sheet with each prescription.

The initial recommended PROZINC dose is 0.1 – 0.3 IU insulin/pound of body weight (0.2 – 0.7 IU/kg) every 12 hours. The dose should be given concurrently with or right after a meal. The veterinarian should re-evaluate the cat at appropriate intervals and adjust the dose based on both clinical signs and glucose nadirs until adequate glycemic control has been attained. In the effectiveness field study, glycemic control was considered adequate if the glucose nadir from a 9-hour blood glucose curve was between 80 and 150 mg/dL and clinical signs of hyperglycemia such as polyuria, polydipsia, and weight loss were improved.

Further adjustments in the dosage may be necessary with changes in the cat's diet, body weight, or concomitant medication, or if the cat develops concurrent infection, inflammation, neoplasia, or an additional endocrine or other medical disorder.

**Contraindications:** PROZINC is contraindicated in cats sensitive to protamine zinc recombinant human insulin or any other ingredients in PROZINC. PROZINC is contraindicated during episodes of hypoglycemia.

**Warnings: User Safety:** For use in cats and dogs only. Keep out of the reach of children. Avoid contact with eyes. In case of contact, immediately flush eyes with running water for at least 15 minutes. Accidental injection may cause hypoglycemia. In case of accidental injection, seek medical attention immediately. Exposure to product may induce a local or systemic allergic reaction in sensitized individuals.

**Animal Safety:** Owners should be advised to observe for signs of hypoglycemia (see Client Information Sheet). Use of this product, even at established doses, has been associated with hypoglycemia. A cat with signs of hypoglycemia should be treated immediately. Glucose should be given orally or intravenously as dictated by clinical signs. Insulin should be temporarily withheld and, if indicated, the dosage adjusted.

Any change in insulin should be made cautiously and only under a veterinarian's supervision. Changes in insulin strength, manufacturer, type, species (human, animal) or method of manufacture (rDNA versus animal-source insulin) may result in the need for a change in dosage.

Appropriate diagnostic tests should be performed to rule out other endocrinopathies in diabetic cats that are difficult to regulate.

**Precautions:** Cats presenting with severe ketoacidosis, anorexia, lethargy, and/or vomiting should be stabilized with short-acting insulin and appropriate supportive therapy until their condition is stabilized. As with all insulin products, careful patient monitoring for hypoglycemia and hyperglycemia is essential to attain and maintain adequate glycemic control and to prevent associated complications. Overdose can result in profound hypoglycemia and death.

Glucocorticoids, progestogens, and certain endocrinopathies can have an antagonistic effect on insulin activity. Glucocorticoid and progestogen use should be avoided.

The safety and effectiveness of PROZINC in breeding, pregnant, and lactating cats has not been evaluated.

The safety and effectiveness of PROZINC in kittens has not been evaluated.

**Adverse Reactions:** Effectiveness Field Study

In a 45-day effectiveness field study, 176 cats received PROZINC. Hypoglycemia (defined as a blood glucose value of < 50 mg/dL) occurred in 71 of the cats at various times throughout the study. Clinical signs of hypoglycemia were generally mild in nature (described as lethargic, sluggish, weak, trembling, uncoordinated, groggy, glassy-eyed or dazed). In 17 cases, the veterinarian provided oral glucose supplementation or food as treatment. Most cases were not associated with clinical signs and received no treatment. One cat had a serious hypoglycemic event associated with stupor, lateral recumbency, hypothermia and seizures.

All cases of hypoglycemia resolved with appropriate therapy and if needed, a dose reduction.

Three cats had injection site reactions which were described as either small, punctate, red lesions; lesions on neck; or palpable subcutaneous thickening. All injection site reactions resolved without cessation of therapy.

Four cats developed diabetic neuropathy during the study as evidenced by plantigrade stance. Three cats entered the study with plantigrade stance, one of which resolved by Day 45. Four cats were diagnosed with diabetic ketoacidosis during the study. Two were euthanized due to poor response to treatment. Five other cats were euthanized during the study, one of which had hypoglycemia. Four cats had received PROZINC for less than a week and were euthanized due to worsening concurrent medical conditions.

The following additional clinical observations or diagnoses were reported in cats during the effectiveness field study: vomiting, lethargy, diarrhea, cystitis/hematuria, upper respiratory infection, dry coat, hair loss, ocular discharge, abnormal vocalization, black stool, and rapid breathing.

Extended Use Field Study

Cats that completed the effectiveness study were enrolled into an extended use field study. In this study, 145 cats received PROZINC for up to an additional 136 days. Adverse reactions were similar to those reported during the 45-day effectiveness study and are listed in order of decreasing frequency: vomiting, hypoglycemia, anorexia/poor appetite, diarrhea, lethargy, cystitis/hematuria, and weakness. Twenty cats had signs consistent with hypoglycemia described as: sluggish, lethargic, unsteady, wobbly, seizures, trembling, or dazed. Most of these were treated by the owner or veterinarian with oral glucose supplementation or food; others received intravenous glucose. One cat had a serious hypoglycemic event associated with seizures and blindness. The cat fully recovered after supportive therapy and finished the study. All cases of hypoglycemia resolved with appropriate therapy and if needed, a dose reduction.

Fourteen cats died or were euthanized during the extended use study. In two cases, continued use of insulin despite anorexia and signs of hypoglycemia contributed to the deaths. In one case, the owner decided not to continue therapy after a presumed episode of hypoglycemia. The rest were due to concurrent medical conditions or worsening of the diabetes mellitus.

To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Boehringer Ingelheim at 1-888-637-4251.

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.

**Information for Cat Owners:** Please refer to the Client Information Sheet for Cats for more information about PROZINC. PROZINC, like other insulin products, is not free from adverse reactions. Owners should be advised of the potential for adverse reactions and be informed of the associated clinical signs. Potential adverse reactions include: hypoglycemia, insulin antagonism/resistance, rapid insulin metabolism, insulin-induced hyperglycemia (Somogyi Effect), and local or systemic reactions. The most common adverse reaction observed is hypoglycemia. Signs may include: weakness, depression, behavioral changes, muscle twitching, and anxiety. In severe cases of hypoglycemia, seizures and coma can occur. Hypoglycemia can be fatal if an affected cat does not receive prompt treatment. Appropriate veterinary monitoring of blood glucose, adjustment of insulin dose and regimen as needed, and stabilization of diet and activity help minimize the risk of hypoglycemic episodes. The attending veterinarian should evaluate other adverse reactions on a case-by-case basis to determine if an adjustment in therapy is appropriate, or if alternative therapy should be considered.

**Effectiveness:** A total of 187 client-owned cats were enrolled in a 45-day field study, with 176 receiving PROZINC. One hundred and fifty-one cats were included in the effectiveness analysis. The patients included various purebred and mixed breed cats ranging in age from 3 to 19 years and in weight from 4.6 to 20.8 pounds. Of the cats included in the effectiveness analysis, 101 were castrated males, 49 were spayed females, and 1 was an intact female.

Cats were started on PROZINC at a dose of 0.1-0.3 IU/lb (0.2-0.7 IU/kg) twice daily. Cats were evaluated at 7, 14, 30, and 45 days after initiation of therapy and the dose was adjusted based on clinical signs and results of 9-hour blood glucose curves on Days 7, 14, and 30.

Effectiveness was based on successful control of diabetes which was defined as improvement in at least one blood glucose variable (glucose curve mean, nadir, or fructosamine) and at least one clinical sign (polyuria, polydipsia, or body weight). Based on this definition, 115 of 151 cases (76.2%) were considered successful. Blood glucose curve means decreased from 415.3 mg/dL on Day 0 to 203.2 mg/dL by Day 45 and the mean blood glucose nadir decreased from 407.9 mg/dL on Day 0 to 142.4 mg/dL on Day 45. Mean fructosamine values decreased from 505.9 µmol/L on Day 0 to 380.7 µmol/L on Day 45.

Cats that completed the effectiveness study were enrolled in an extended use field study. The mean fructosamine value was 342.0 µmol/L after a total of 181 days of PROZINC therapy.

**How Supplied:** PROZINC is supplied as a sterile injectable suspension in 10 mL and 20 mL multi-dose vials. Each mL of PROZINC contains 40 IU recombinant human insulin.

**Storage Conditions:** Store in an upright position under refrigeration at 36-46°F (2-8°C). Do not freeze. Protect from light. **Use the 10 mL vial within 60 days of first puncture. Use the 20 mL vial within 80 days of first puncture.**

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Boehringer Ingelheim Animal Health USA Inc.
Duluth, GA 30096



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Boehringer Ingelheim

# QUIZ CORNER

## QUIZ YOURSELF

**on this issue's features**

**Quiz Corner** is offered by the publisher for entertainment purposes only and does not apply toward CE credit. Questions are provided by editorial staff and are not subject to peer review.

1 **TOP 5** **PAGE 11**

_____ is considered to be an effective tranquilizer in dogs but may not result in equivalent tranquilization in cats.

A. Butorphanol
B. Oxymorphone
C. Xylazine
D. Acepromazine

2 **CONSULT THE EXPERT** **PAGE 16**

The renal threshold for glucose in dogs is ≥180 to 200 mg/dL. What is the renal threshold for glucose in cats?

A. ≥180 to 200 mg/dL
B. ≥200 to 230 mg/dL
C. ≥250 to 280 mg/dL
D. ≥300 to 320 mg/dL

3 **CONSULT THE EXPERT** **PAGE 28**

Which of the following statements regarding diagnosis of hypoglycemia is *false*?

A. Patient history, physical examination, and other diagnostic findings must be carefully evaluated to identify the underlying cause of disease.
B. Hypoglycemia must be documented using a portable glucometer as the sole clinical method.
C. A diagnosis of clinically relevant hypoglycemia is confirmed by satisfying the criteria of Whipple's triad.
D. Artifactual hypoglycemia may occur if clot removal is delayed during serum processing of a blood sample.

4 **CASE IN POINT** **PAGE 63**

The hallmark of diagnosis of eosinophilic bronchopneumopathy is _____.

A. Thoracic radiography
B. CBC
C. PCR testing
D. Cytologic evaluation of airways

5 **RED LIGHT, GREEN LIGHT** **PAGE 70**

Which of the following could be used as a long-acting maintenance medication for the treatment of canine separation anxiety?

A. Fluoxetine
B. Alprazolam
C. Trazodone
D. Gabapentin

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

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**ProZinc®**
**(protamine zinc recombinant human insulin)**

*PROZINC is approved for twice-daily use in cats.[3]

**IMPORTANT SAFETY INFORMATION:** PROZINC is for use in dogs and cats only. Keep out of the reach of children. Animals presenting with severe ketoacidosis, anorexia, lethargy, and/or vomiting should be stabilized with short-acting insulin and appropriate supportive therapy until their condition is stabilized. As with all insulin products, careful patient monitoring for hypoglycemia and hyperglycemia is essential to attain and maintain adequate glycemic control and to prevent associated complications. Overdose can result in profound hypoglycemia and death. The most common adverse reactions were lethargy, anorexia, hypoglycemia, vomiting, seizures, shaking (dogs only), diarrhea, and ataxia. Many of the adverse reactions, such as lethargy, seizures, shaking (dogs only), and ataxia, are associated with hypoglycemia. Glucocorticoid and progestogen use should be avoided. The safety and effectiveness of PROZINC in puppies, kittens, or breeding, pregnant, and lactating animals has not been evaluated. PROZINC is contraindicated during episodes of hypoglycemia and in animals sensitive to protamine zinc recombinant human insulin or any other ingredients in PROZINC. **For more information, please see full prescribing information.**

**References:**
[1] Data on file at Boehringer Ingelheim.
[2] ProZinc® (protamine zinc recombinant human insulin) [Freedom of Information Summary]. Duluth, GA: Boehringer Ingelheim Animal Health USA, Inc.; 2019.
[3] ProZinc® (protamine zinc recombinant human insulin) [Freedom of Information Summary]. St. Joseph, MO: Boehringer Ingelheim Vetmedica, Inc.; 2009.



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See pages 78 & 79 for product information summary.