PEER REVIEWED

Management of Immune-Mediated Hemolytic Anemia

A Common Hematologic Disorder in Dogs & Cats

Todd Archer, DVM, MS, Diplomate ACVIM, and Andrew Mackin, BSc, BVMS, Diplomate ACVIM
Mississippi State University

*This article is the second in a 2-part series discussing the diagnosis and management of immune-mediated hemolytic anemia in dogs and cats. Read Part 1—**Diagnosis of Immune-Mediated Hemolytic Anemia** (July/August 2013 issue)—at **tvpjournal.com**.*

Immune-mediated hemolytic anemia (IMHA) is one of the most common immune-mediated hematologic disorders in dogs and cats.[1]

In dogs, IMHA is commonly primary or idiopathic in origin, but also occurs secondary to triggers, such as infectious, inflammatory, and neoplastic diseases; drugs; and vaccines. In cats, the condition is usually secondary to an underlying cause.[2]

DIAGNOSTIC REVIEW

There is no single test that is definitively diagnostic for IMHA. Instead, evidence from various analyses is used to determine the diagnosis (**Table 1**).

Initial diagnostics in an anemic patient should focus on identifying the cause of anemia. A diagnosis of anemia secondary to an underlying immune-mediated pathogenesis is based on evidence of accelerated red blood cell (RBC) destruction.

A diagnosis of primary IMHA is supported by the following signs and diagnostic results:

- Anemia
- Evidence of accelerated RBC lysis, such as hemoglobinemia/hemoglobinuria (intravascular hemolysis) or bilirubinemia/bilirubinuria
- Evidence of an immune-mediated process, such as autoagglutination (**Figures 1 and 2**), positive Coombs' test, or increased circulating spherocytes (**Figure 3**)

TABLE 1. IMMUNE-MEDIATED HEMOLYTIC ANEMIA DIAGNOSTIC OVERVIEW

No single test is definitively diagnostic for IMHA. Instead, evidence from various analyses is used to determine the diagnosis.

CATEGORY	DIAGNOSTIC TESTS
History & Examination	• Predilection • History • Clinical signs • Physical examination
Laboratory Diagnostics	• CBC/serum biochemical profile • Blood smear • Agglutination (anti-RBC antibodies) • Direct Coombs' test • Prothrombin time • Activated partial thromboplastin time • Urinalysis
Additional Diagnostics	• Bone marrow evaluation • Infectious disease identification • Imaging

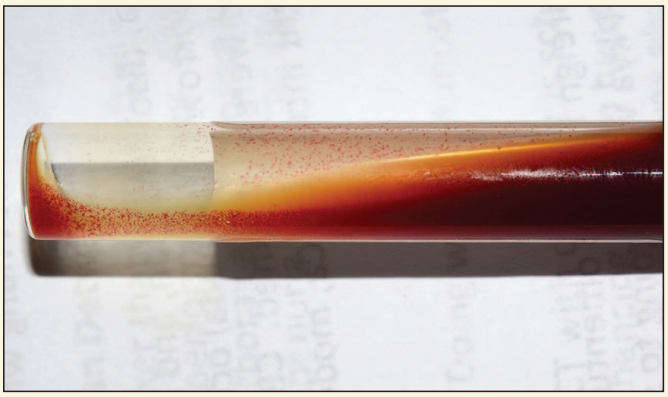

Figure 1. *Autoagglutination observed as red speckles in EDTA-anticoagulated blood from a dog with severe IMHA.*

- Lack of other identifiable causes of anemia.

An exhaustive search for underlying causes of IMHA is critical, because if there is a trigger factor, treatment success is dependent upon its removal. A comprehensive review of the diagnostic approach for IMHA trigger factors is described in Part 1 of this article (see **Article Archives**).

THERAPEUTIC APPROACH

The cornerstone of treatment for IMHA is immunosuppressive therapy. Immunosuppression is usually accomplished with glucocorticoids, with the addition of a second immunosuppressive agent, if needed. Therapy consists of 2 phases:

1. Acute phase, with induction of remission
2. Chronic maintenance phase.

Other than glucocorticoid administration, the following described therapies are not indicated for all patients and should be used on a case-by-case basis. **Table 2** provides the dosages of recommended medications.

GLUCOCORTICOID THERAPY

Glucocorticoids have multiple effects on the immune system, but the most important effect for IMHA patients is inhibition of macrophages within the mononuclear phagocytic system. Response to glucocorticoids often takes between 3 and 7 days.

Prednisolone/Prednisone

Dogs. Immunosuppressive dosages of prednisolone or prednisone range from **1 to 2 mg/kg PO Q 12 H**, with higher dosages not necessarily associated with improved remission rates. In large breed dogs, a dosage of 30 mg/m^2 is often used to minimize side effects.

Cats. Many clinicians advocate administering prednisolone at **4 mg/kg PO Q 24 H**, a higher immunosuppressive dosage than that used in dogs.

Prednisone is a prodrug that is metabolized into prednisolone. When cats receive oral prednisolone, higher plasma concentrations of prednisolone are achieved compared with cats administered oral prednisone; therefore, prednisolone is preferred for use in cats.

Dexamethasone

Dexamethasone may be used instead of prednisolone/prednisone, at a decreased dosage due to its greater potency. A dosage of 0.3 to 0.5 mg/kg IV Q 24 H is often administered in both cats and dogs.

SECOND-LINE IMMUNOSUPPRESSIVE THERAPY

Criteria that should prompt consideration of additional immunosuppressive agents include:

- Severe disease (intravascular hemolysis or transfusion dependency)
- Marked autoagglutination

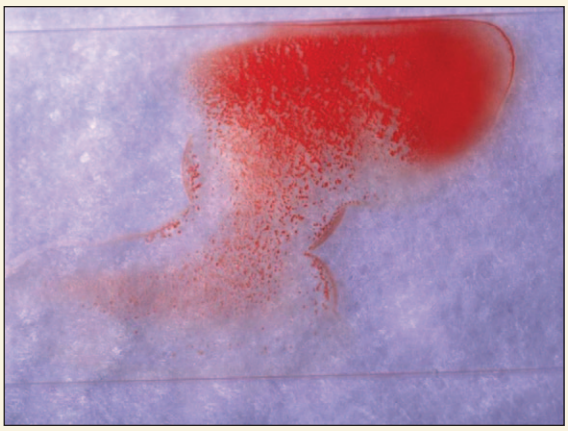

Figure 2. *Positive slide agglutination test in a dog with IMHA, demonstrating obvious macroagglutination.*

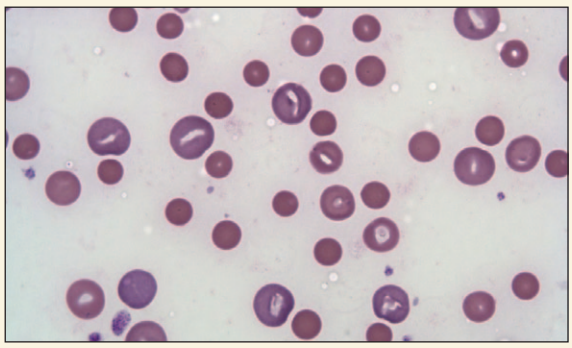

Figure 3. *Marked spherocytosis observed on a Wright's-stained blood smear from a dog with IMHA; spherocytes are recognized as smaller RBCs that lack central pallor. Spherocytosis is very suggestive of IHMA.*

TABLE 2. IMMUNE-MEDIATED HEMOLYTIC ANEMIA: MEDICATION DOSAGES

CLASS	DRUG	RECOMMENDED DOSAGE	
		Dogs	Cats
Immunosuppressive Agents	Azathioprine	**2 mg/kg** PO Q 24 H	Not recommended
	Chlorambucil	Not recommended	**2 mg/cat** (total dose) every second day, tapered over time to every third or fourth day*
	Cyclosporine	**5–10 mg/kg** PO Q 12 H	**1–5 mg/kg** PO divided Q 12 H
	Dexamethasone	**0.3–0.5 mg/kg** IV Q 24 H	**0.3–0.5 mg/kg** IV Q 24 H
	Leflunomide	**2–4 mg/kg** PO Q 24 H	**10 mg/cat** (total dose) PO Q 24 H
	Mycophenolate mofetil	**10 mg/kg** PO Q 12 H	**10 mg/kg** PO Q 12 H
	Prednisolone	**1–2 mg/kg** PO Q 12 H Consider 30 mg/m^2 in large breeds	**4 mg/kg** PO Q 24 H or divided Q 12 H
Anticoagulant Agents	Dalteparin	**150 U/kg** SC Q 8 H	**180 U/kg** SC Q 4–6 H
	Enoxaparin	**0.8 mg/kg** SC Q 6 H	**1.25 mg/kg** SC Q 6 H
	Unfractionated heparin	**200–500 U/kg** SC Q 8 H, adjusted (see Anticoagulants text)	**200–500 U/kg** SC Q 8 H, adjusted (see Anticoagulants text)
Antiplatelet Agents	Clopidogrel	Loading dose of **10 mg/kg** PO; followed by **2–3 mg/kg** PO Q 24 H	**18.75 mg** (¼ of a 75-mg tablet) PO Q 24 H
	Low-dose aspirin	**0.5–1 mg/kg** PO Q 24 H	**5 mg/cat** PO Q 72 H

Medications organized in alphabetical order within each class of agent
* Should be administered with a glucocorticoid

- Significant glucocorticoid side effects
- Lack of response to glucocorticoid therapy alone.

The addition of a second immunosuppressive agent is not benign—many drugs are expensive, can cause significant adverse effects, and may necessitate pharmacokinetic monitoring.

Therapy by Species

Dogs. Many clinicians initially administer a second immunosuppressive agent to reduce the side effects of steroids and allow more rapid glucocorticoid dose reduction. The most commonly used second-line immunosuppressive agents are azathioprine and cyclosporine, with other drugs such as mycophenolate mofetil and leflunomide being used more often in clinical practice.[3]

Cats. Because cats usually tolerate glucocorticoids well, for initial immunosupression, they receive steroids alone.[4] However, cyclosporine and chlorambucil can be used as second-line immunosuppressive agents when needed.

Azathioprine

Azathioprine is a relatively inexpensive purine antagonist that is often effective in IMHA patients; immunosuppression occurs mainly via T-cell suppression.[5] The initial dosage in **dogs is 2 mg/kg PO Q 24 H**.[5,6] This drug is not recommended for cats because they are very prone to its myelosuppressive effects.[1,5]

While previous literature has indicated that azathioprine can take many weeks or even months to exert its effects, clinically, the immunosuppressive effects in canine IMHA patients are usually observed within 1 to 2 weeks, a duration that is comparable to that observed with other immunosuppressive agents.

Significant side effects in dogs are uncommon to rare, and include gastrointestinal (GI) signs (anorexia, vomiting, diarrhea), myelosuppression, hepatotoxicity, and pancreatitis.[1,5] Slight anemia is commonly observed in dogs on azathioprine, but it is invariably too mild to be of clinical concern.

Cyclosporine

Cyclosporine is a calcineurin inhibitor that suppresses T-cell function by reducing cytokine expression.[6,7] The veterinary approved product, Atopica (ah.novartis.com), is a microemulsion that promotes increased bioavailability and consistent blood concentrations.[5] Starting dosage recommendations are:[5]

- *Dogs:* **5 to 10 mg/kg PO Q 12 H**
- *Cats:* **1 to 5 mg/kg/day PO divided twice daily.**

While the exact timing of the immunosuppressive effects of cyclosporine is unknown, pharmacodynamic work in normal dogs in our laboratory has shown suppressive effects on T cells at 3 days post dosing and maximal suppression after 7 days of dosing at 10 mg/kg PO Q 12 H.

Therapeutic drug monitoring is often used to ensure that blood drug levels are sufficient to initiate immunosuppression. Side effects include GI signs (inappetence, vomiting, diarrhea), gingival hyperplasia, hepatotoxicity, and secondary infections. Recent studies have also revealed that cyclosporine activates canine platelets, prompting concern that the drug may possibly increase the risk of pulmonary thromboembolism (PTE) in IMHA patients.[8]

Ketoconazole can be concurrently administered to reduce cyclosporine metabolism and decrease the oral dosage needed to attain immunosuppression.

Mycophenolate Mofetil

Mycophenolate mofetil, the prodrug of mycophenolic acid, induces immunosuppression by inhibiting inosine monophosphate dehydrogenase, targeting both B and T cells.

TAPERING IMMUNOSUPPRESSIVE DRUGS

Once a positive response to therapy is achieved (stable or rising hematocrit for at least 1–2 weeks), slowly taper drug dosages by approximately 25% to 50%, one drug at a time, every 2 to 4 weeks.

- **Taper the most expensive drug or one causing the most side effects first**, if a patient is receiving more than one immunosuppressive medication.

- **Check the patient's hematocrit** weekly during initial therapy after discharge from the hospital; then before, and 1 to 2 weeks after, each dose reduction.
- **Wean to the lowest effective dose to maintain disease remission**, which usually takes 3 to 6 months; some patients can eventually discontinue all medications.

Since any patient receiving potent immunosuppressive therapy is at risk for developing secondary infection, animals should be closely observed for signs of sepsis or infection, and tapering of drug doses should ideally begin shortly after disease remission is observed.

Its use is emerging in the literature for treatment of inflammatory and immune-mediated diseases in small animals. In a recent study evaluating prednisone combined with mycophenolate for treatment of IMHA, 77% of dogs survived to discharge, a rate that was comparable with other standard treatment regimes.[9]

While there are no veterinary approved products, mycophenolate is available as an oral human product in tablets, capsules, or an oral suspension. Starting dosage recommendations are:[5]

- *Dogs:* **10 mg/kg PO Q 12 H**
- *Cats:* **10 mg/kg PO Q 12 H.**

The most common side effects associated with mycophenolate mofetil, based on limited veterinary studies, include GI signs (inappetence, vomiting, diarrhea), lethargy, lymphopenia, and susceptibility to secondary infections. In humans, severe neutropenia has been reported as a rare side effect.

Leflunomide

Leflunomide induces immunosuppression through the inhibition of dihydroorotate dehydrogenase, an enzyme needed for pyrimidine synthesis. This ultimately targets and suppresses both B and T cells.

Similar to mycophenolate, the use of leflunomide is just beginning to emerge in the veterinary literature for treatment in clinical patients. A recent study described the use of leflunomide for the treatment of immune-mediated polyarthritis, with disease remission achieved in 8 of 14 dogs.[10]

While there are no veterinary approved products, leflunomide is available in a human tablet formulation. Starting dosage recommendations are:[5]

- *Dogs:* **2 to 4 mg/kg PO Q 24 H**
- *Cats:* **10 mg (total dose) per cat PO Q 24 H.**

The most common side effects associated with leflunomide, based on limited veterinary studies, include GI signs (inappetence, vomiting, diarrhea) and lethargy. In dogs, bone marrow suppression (leukopenia and thrombocytopenia) has been reported. Serious but rare side effects reported in human medicine include severe bone marrow suppression, dermatologic reactions (ie, toxic epidermal necrolysis), and hepatotoxicity.

Chlorambucil

Chlorambucil is a cell-cycle nonspecific alkylating agent that is used to treat certain cancers as well as induce immunosuppression in conditions, such as inflammatory skin diseases, inflammatory bowel disease, and immune-mediated blood disorders, particularly in cats.

Chlorambucil is available as a coated 2-mg tablet that cannot feasibly be divided, and, therefore, dosing recommendations in smaller patients are often provided in multiples of 2, and/or "pulsed" at infrequent dosing intervals in order to avoid overdose. For immunosuppressive therapy, chlorambucil is almost always given in combination with an oral glucocorticoid. The starting

dosage recommendation in cats is **2 mg (total dose) per cat every second day (with a glucocorticoid)**, tapered over time to every third or fourth day.[5]

Chlorambucil is relatively well tolerated, but does occasionally cause GI side effects, such as vomiting and diarrhea. Neurologic signs (including myoclonus, twitches, and seizures) have been reported in cats. The most common major adverse effect is myelosuppression, and complete blood counts must be monitored regularly (weekly at first) to watch for its development.

SUPPORTIVE MEDICAL CARE

Antithrombotic Medications

Antithrombotic medications, such as anticoagulants (ie, heparin) and antiplatelet medications (ie, aspirin, clopidogrel), are often administered in IMHA patients to reduce the incidence of PTE.[3,11]

IMHA patients are thought to have a hypercoagulable state and, therefore, are more prone to development of PTE. The pathogenesis of thromboembolism is thought to be multifactorial, including hypercoagulability (secondary to platelet activation as well as steroid administration), endothelial injury, and vascular stasis.

Anticoagulants

- Heparin products include unfractionated heparin and low molecular weight heparin (LMWH).
- Unfractionated heparin is often started at a dose of **200 to 500 U/kg SC Q 8 H** and adjusted to achieve either prolongation of activated partial thromboplastin time by 1.5 to 2 times pretreatment values *or* target range anti-Xa activity using a nomogram.[5,12-14]
- LMWH products include enoxaparin and dalteparin, which are both expensive but typically do not require monitoring of coagulation parameters.[5] Recommended doses are:
  - » *Enoxaparin:* **0.8 mg/kg SC Q 6 H** (dogs) and **1.25 mg/kg SC Q 6 H** (cats)
  - » *Dalteparin:* **150 U/kg SC Q 8 H** (dogs) and **180 U/kg SC Q 4–6 H** (cats).[5,12]

Antiplatelet Medications

- Low-dose aspirin is commonly used in IMHA patients at a dose of **0.5 to 1 mg/kg PO Q 24 H** (dogs) and **5 mg per cat PO Q 72 H** (cats).[5]
- Clopidogrel, a newer antiplatelet medication, irreversibly inhibits activation of platelet glycoprotein IIb/IIIa. For dogs with IMHA, a recent study demonstrated that an initial oral loading dose (**10 mg/kg**) followed by a daily maintenance dose (**2 to 3 mg/kg PO Q 24 H**) was safe and improved short-term survival at a comparable rate to low-dose aspirin.[15] For cats, the recommended dose is **18.75 mg (¼ of a 75-mg tablet) PO Q 24 H**.[5]

Gastric Protectants

Because glucocorticoids are possibly associated with GI gastrointestinal ulceration, some clinicians administer gastric protectants when treating IMHA patients; these protectants include sucralfate, omeprazole and famotidine.

Figure 4. *A schnauzer dog with IMHA receiving a blood transfusion.*

Intravenous Immunoglobulin

Human IV immunoglobulin is a sterile preparation of IgG derived from human plasma; it is thought to reduce Fc-mediated phagocytosis of IgG-coated RBCs by macrophages. IV immunoglobulin has been effective in a small number of dogs that were refractory to standard therapy.[16]

SUPPORTIVE NURSING CARE

Fluid Therapy

Fluid therapy is typically only warranted if the patient is dehydrated or has intravascular hemolysis and hemoglobinuria (since free hemoglobin is nephrotoxic). IV catheters should be removed as soon as fluids are no longer needed, as catheters are a possible risk factor for PTE. The same is true for central IV catheters, which should not be used in these patients.

Oxygen Carrying Support

Oxygen carrying support in the form of blood products—whole blood or, preferably, packed RBCs—is indicated when anemia is severe or associated with clinical evidence of tissue hypoxia, such as tachypnea, dyspnea, tachycardia, mental dullness, and weakness (**Figure 4**).

Many dogs with IMHA will require transfusion support, with some requiring multiple transfusions, especially during the first week of therapy.[11,17]

Article Archives
Read Part 1 of this series, **Diagnosis of Immune-Mediated Hemolytic Anemia,** at **tvpjournal.com** by entering "IMHA" in the Search box in the top right-hand corner of the homepage.

SUPPORTIVE SURGICAL & TECHNICAL CARE

Splenectomy

Splenectomy may be beneficial in patients who fail to respond to traditional therapy or those in which remission is only achieved with high doses of immunosuppressive agents, since the spleen is often a major organ responsible for RBC phagocytosis.

In 1 study, 10 dogs with IMHA had a splenectomy performed in addition to standard medical management. Nine dogs survived to 30 days without relapse, which suggests that splenectomy may be associated with an improved outcome in IMHA patients.[18]

Plasmapheresis

Plasmapheresis rapidly removes autoantibodies from plasma and may be effective in acute, severe cases of IMHA, but availability is very limited.

PROGNOSIS

Mortality rates in dogs with IMHA range from 26% to 70%, with PTE being a significant cause of death.[3,17,19] Abnormalities linked to an increased mortality rate include autoagglutination, thrombocytopenia, leukocytosis, elevated alkaline phosphatase, hyperbilirubinemia, and hypoalbuminemia.[3,11,17,20]

IMHA appears to have a more favorable prognosis in cats, with 1 study documenting a mortality rate of 23%.[4]

Death during medical therapy is typically due to, during the acute phase, lack of response to therapy, PTE, or treatment side effects and, during the maintenance phase, disease relapse or significant side effects associated with treatment. ■

GI = gastrointestinal; IMHA = immune-mediated hemolytic anemia; LMWH = low molecular weight heparin; PTE = pulmonary thromboembolism; RBC = red blood cell

References

1. McCullough S. Immune-mediated hemolytic anemia: Understanding the nemesis. *Vet Clin North Am Small Anim Pract* 2003; 33:1295-1315.
2. August J. Immune-mediated hemolytic anemia. *Consultations in Feline Internal Medicine*, vol 6. St. Louis: Saunders, 2006, pp 617-627.
3. Weinkle TK, Center SA, Randolph JF, et al. Evaluation of prognostic factors, survival rates, and treatment protocols for immune-mediated hemolytic anemia in dogs: 151 cases (1993-2002). *JAVMA* 2005; 226:1869-1880.
4. Kohn B, Weingart C, Eckmann V, et al. Primary immune-mediated hemolytic anemia in 19 cats: Diagnosis, therapy, and outcome (1998–2004). *J Vet Intern Med* 2006; 20:159-166.
5. Plumb D. *Plumb's Veterinary Drug Handbook*, 7th ed. Ames, IA: PharmaVet Inc, 2011, pp 112-117, 134-138, 263-266, 323-325, 352-357, 366-367, 502-504, 661-665, 788-790, 967-970.
6. Thacker EL. Immunomodulators, immunostimulants, and immunotherapies in small animal veterinary medicine. *Vet Clin North Am Small Anim Pract* 2010; 40:473-483.
7. Archer TM, Fellman CL, Stokes JV, et al. Pharmacodynamic monitoring of canine T-cell cytokine responses to oral cyclosporine. *J Vet Intern Med* 2011; 25:1391-1397.
8. Thomason J, Stokes J, Wallace M, et al. Effects of oral cyclosporine on platelet activity in normal dogs. *J Vet Intern Med* 2010; 24:682.
9. Wnag A, Smith JR, Creevy KE. Treatment of canine idiopathic immune-mediated haemolytic anaemia with mycophenolate mofetil and glucocorticoids: 30 cases (2007 to 2011). *J Small Anim Pract* 2013; 54:399-404.
10. Colopy SA, Baker TA, Muir P, et al. Efficacy of leflunomide for treatment of immune-mediated polyarthritis in dogs: 14 cases (2006-2008). *JAVMA* 2010; 236:312-318.
11. Carr AP, Panciera DL, Kidd L. Prognostic factors for mortality and thromboembolism in canine immune-mediated hemolytic anemia: A retrospective study of 72 dogs. *J Vet Intern Med* 2002; 16:504-509.
12. Helmond SE, Polzin DJ, Armstrong PJ, et al. Treatment of immune-mediated hemolytic anemia with individually adjusted heparin dosing in dogs. *J Vet Intern Med* 2010; 24:597-605.
13. Lunsford KV, Mackin AJ. Thromboembolic therapies in dogs and cats: An evidence-based approach. *Vet Clin North Am Small Anim Pract* 2007; 37:579-609.
14. Breuhl EL, Moore G, Brooks MB, Scott-Moncrieff JC. A prospective study of unfractionated heparin therapy in dogs with primary immune-mediated anemia. *JAAHA* 2009; 45(3):125-133.
15. Mellett AM, Nakamura RK, Bianco D. A prospective study of clopidogrel therapy in dogs with primary immune-mediated hemolytic anemia. *J Vet Intern Med* 2011; 25:71-75.
16. Kellerman DL, Bruyette DS. Intravenous human immunoglobulin for the treatment of immune-mediated hemolytic anemia in 13 dogs. J *Vet Intern Med* 1997; 11:327-332.
17. Burgess K, Moore A, Rand W, et al. Treatment of immune-mediated hemolytic anemia in dogs with cyclophosphamide. *J Vet Intern Med* 2000; 14:456-462.
18. Horgan JE, Roberts BK, Schermerhorn T. Splenectomy as an adjunctive treatment for dogs with immune-mediated hemolytic anemia: Ten cases (2003–2006). *J Vet Emerg Crit Care* 2009; 19:254-261.
19. Scott-Moncrieff JC, Treadwell NG, McCullough SM, et al. Hemostatic abnormalities in dogs with primary immune-mediated hemolytic anemia. *JAAHA* 2001; 37:220-227.
20. Grundy SA, Barton C. Influence of drug treatment on survival of dogs with immune-mediated hemolytic anemia: 88 cases (1989–1999). *JAVMA* 2001; 218:543-546.

***Todd M. Archer**, DVM, MS, Diplomate ACVIM, is assistant professor of small animal medicine in the Department of Clinical Sciences at Mississippi State University College of Veterinary Medicine. He received his DVM and completed an internship and residency at Mississippi State University.*

***Andrew Mackin**, BVMS, DVSc, Diplomate ACVIM, is professor and Ward Chair of Medicine at Mississippi State University College of Veterinary Medicine. He received his degree from Murdoch University in Western Australia; then completed an internship and residency in small animal medicine at University of Melbourne and an internal medicine residency at Ontario Veterinary College.*