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.

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>DIAGNOSTIC TESTS</th>
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<tbody>
<tr>
<td>History &amp; Examination</td>
<td>• Predilection</td>
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<tr>
<td></td>
<td>• History</td>
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<tr>
<td></td>
<td>• Clinical signs</td>
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<td></td>
<td>• Physical examination</td>
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<tr>
<td>Laboratory Diagnostics</td>
<td>• CBC/serum biochemical profile</td>
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<tr>
<td></td>
<td>• Blood smear</td>
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<tr>
<td></td>
<td>• Agglutination (anti-RBC antibodies)</td>
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<td></td>
<td>• Direct Coombs’ test</td>
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<tr>
<td></td>
<td>• Prothrombin time</td>
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<tr>
<td></td>
<td>• Activated partial thromboplastin time</td>
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<tr>
<td></td>
<td>• Urinalysis</td>
</tr>
<tr>
<td>Additional Diagnostics</td>
<td>• Bone marrow evaluation</td>
</tr>
<tr>
<td></td>
<td>• Infectious disease identification</td>
</tr>
<tr>
<td></td>
<td>• Imaging</td>
</tr>
</tbody>
</table>

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.
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/m² 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 1. Autoagglutination observed as red speckles in EDTA-anticoagulated blood from a dog with severe IMHA.](image1)

![Figure 2. Positive slide agglutination test in a dog with IMHA, demonstrating obvious macroagglutination.](image2)

![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.](image3)
Management of Immune-Mediated Hemolytic Anemia

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 pharmaco-kinetic 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.7

Cats. Because cats usually tolerate glucocorticoids well, for initial immunosupression, they receive steroids alone.6 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.7 The initial dosage in dogs is 2 mg/kg PO Q 24 H.6 This drug is not recommended for cats because they are very prone to its myelosuppressive effects.8

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.9 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.4,7 The veterinary approved product, Atopica (ah.novartis.com), is a microemulsion that promotes increased bioavailability and consistent blood concentrations.7 Starting dosage recommendations are:3

Table 2. Immune-Mediated Hemolytic Anemia: Medication Dosages

<table>
<thead>
<tr>
<th>CLASS</th>
<th>DRUG</th>
<th>RECOMMENDED DOSAGE</th>
<th>Dogs</th>
<th>Cats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunosuppressive</td>
<td>Azathioprine</td>
<td>2 mg/kg PO Q 24 H</td>
<td>Not recommended</td>
<td></td>
</tr>
<tr>
<td>Agents</td>
<td>Chlorambucil</td>
<td>Not recommended</td>
<td>2 mg/cat (total dose) every second day, tapered over time to every third or fourth day*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cyclosporine</td>
<td>5–10 mg/kg PO Q 12 H</td>
<td>1–5 mg/kg PO divided Q 12 H</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dexamethasone</td>
<td>0.3–0.5 mg/kg IV Q 24 H</td>
<td>0.3–0.5 mg/kg IV Q 24 H</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Leflunomide</td>
<td>2–4 mg/kg PO Q 24 H</td>
<td>10 mg/cat (total dose) PO Q 24 H</td>
<td></td>
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<tr>
<td></td>
<td>Mycophenolate</td>
<td>10 mg/kg PO Q 12 H</td>
<td>10 mg/kg PO Q 12 H</td>
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<tr>
<td></td>
<td>mofetil</td>
<td></td>
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<tr>
<td></td>
<td>Prednisolone</td>
<td>1–2 mg/kg PO Q 12 H</td>
<td>Consider 30 mg/m² in large breeds</td>
<td>4 mg/kg PO Q 24 H or divided Q 12 H</td>
</tr>
<tr>
<td></td>
<td>Dextran</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Dalteparin</td>
<td>150 U/kg SC Q 8 H</td>
<td>180 U/kg SC Q 4–6 H</td>
<td></td>
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<tr>
<td></td>
<td>Enoxaparin</td>
<td>0.8 mg/kg SC Q 6 H</td>
<td>1.25 mg/kg SC Q 6 H</td>
<td></td>
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<tr>
<td></td>
<td>Unfractionated</td>
<td>200–500 U/kg SC Q 8 H, adjusted (see Anticoagulants text)</td>
<td>200–500 U/kg SC Q 8 H, adjusted (see Anticoagulants text)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>heparin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clopidogrel</td>
<td>Loading dose of 10 mg/kg PO; followed by 2–3 mg/kg PO Q 24 H</td>
<td>18.75 mg (¼ of a 75-mg tablet) PO Q 24 H</td>
<td></td>
</tr>
<tr>
<td>Antiplatelet Agents</td>
<td>Low-dose aspirin</td>
<td>0.5–1 mg/kg PO Q 24 H</td>
<td>5 mg/cat PO Q 72 H</td>
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</tr>
</tbody>
</table>

Medications organized in alphabetical order within each class of agent

* Should be administered with a glucocorticoid
**Management of Immune-Mediated Hemolytic Anemia**

**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.

- **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.

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.

\[ \text{Mycophenolic acid} \rightarrow \text{Mycophenolate} \rightarrow \text{Mycophenolic acid} \rightarrow \text{Inosine} \rightarrow \text{Hypoxanthine} \rightarrow \text{Adenine} \]

Side effects reported in human medicine include severe 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{5,12-14}
- LMWH products include enoxaparin and dalteparin, which are both expensive but typically do not require monitoring of coagulation parameters.\textsuperscript{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).\textsuperscript{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).\textsuperscript{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.\textsuperscript{9} For cats, the recommended dose is 18.75 mg (¼ of a 75-mg tablet) PO Q 24 H.\textsuperscript{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.

**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.\textsuperscript{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.\textsuperscript{11,17}
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%.7

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