Immune-mediated hemolytic anemia (IMHA) is one of the more commonly encountered causes of anemia in dogs and cats. IMHA can affect animals of any age, but it most commonly affects young adult and middle-aged dogs and cats. The condition can either be primary (nonassociative), in which the immune disease has no known causative trigger, or secondary (associative), in which the trigger or cause is an underlying condition. Practically speaking, although a cause for secondary IMHA can often be suspected on the basis of a temporal association with drug administration or underlying disease, proving causation is usually impossible. Although primary and secondary IMHA occurs in dogs and cats, primary IMHA is more common in dogs and secondary IMHA is more common in cats.

Primary IMHA: Although it has no obvious identifiable cause, primary IMHA is associated with an inherited predisposition in dogs, most commonly cocker spaniels, springer spaniels, and poodles.

Secondary IMHA: Associative IMHA has been strongly linked with organisms that infect red blood cells (RBCs) (e.g., Babesia species in dogs and Mycoplasma haemofelis in cats) and much more speculatively with feline leukemia virus infection, medications (particularly sulfur drugs in dogs and antithyroid medications in cats), recent vaccination, or neoplasia. Suspected secondary IMHA may also follow bee stings and elapid snake bites. However, for many of these proposed potential triggers, causation has not been definitively established.

PATHOPHYSIOLOGY
IMHA in dogs and cats is an antibody-mediated disease. It’s a classic example of a cytotoxic (type II) immune-mediated reaction in which antibody and complement attachment to the surface of RBCs leads to hemolysis. Hemolysis can be extravascular (antibody-coated RBCs are recognized and phagocytosed by macrophages in organs such as the spleen) or intravascular (antibody and complement on the RBC surface lead to direct cell lysis within the circulation).
Extravascular hemolysis: With the more common extravascular hemolysis, hemoglobin is released inside macrophages and eventually metabolized to bilirubin. Excessive bilirubin production can sometimes overwhelm hepatobiliary metabolic pathways, leading to hyperbilirubinemia and jaundice (FIGURE 1). Many patients with IMHA, however, never become clinically jaundiced.

Intravascular hemolysis: With the less common intravascular hemolysis, intracellular hemoglobin is released directly into the circulation, leading to hemoglobinemia, hemoglobinuria, and potentially kidney damage caused by hemoglobinuric nephrosis.

Intuitively, because hemolysis involves peripheral destruction of RBCs, resultant anemia would be expected to be highly regenerative as the marrow responds (within 3 to 5 days) by maximizing production of new RBCs. However, some cases of IMHA are actually poorly regenerative, either because antibodies against RBCs are also directed against marrow erythroid precursors or because the inflammation associated with IMHA leads to a functional iron deficiency (anemia of chronic disease). 4

CLINICAL PRESENTATION
Most commonly, dogs and cats with IMHA exhibit clinical features suggestive of moderate to severe anemia: pale mucous membranes, lethargy, exercise intolerance, and collapse. Physical examination will often reveal tachycardia, tachypnea, and strong (bounding) pulses associated with the sympathetic stimulation triggered by local tissue hypoxia. Patients with severe anemia often have a grade 1 to grade 2 systolic left-sided (hemic) murmur. Some patients with extravascular hemolysis will exhibit mild to marked jaundice, and patients with intravascular hemolysis will have hemoglobinemia (red-pink serum) and hemoglobinuria (dark “port wine” urine) (FIGURE 2).

Some patients also show signs consistent with enhanced inflammatory and mononuclear phagocytic processes, including inappetence, a low-grade fever, mild lymphadenopathy, and palpable splenomegaly. Such signs are often erroneously interpreted as evidence of infection. Occasionally, affected animals will have Evans syndrome, a combination of IMHA and immune-mediated thrombocytopenia; these patients may exhibit bleeding in the form of cutaneous and mucosal petechiae and ecchymoses, melena, and hematuria. A common complication of IMHA is pulmonary thromboembolism; affected patients will often exhibit acute onset of dyspnea.

FIGURE 1. Severe jaundice in a schnauzer that had received multiple transfusions for IMHA.

FIGURE 2. Necropsy images from a dog with severe intravascular hemolysis, demonstrating typical “port wine” appearance of hemoglobinuria (syringe) and dark discoloration of kidneys (“gun metal” kidneys) associated with hemoglobinuric nephrosis.
DIAGNOSIS

Minimum Database
Many diagnostically helpful clues can be provided by a complete blood count (CBC), serum biochemistry, and urinalysis.

Complete Blood Count
A CBC may reveal anemia, an inflammatory leukogram, and/or thrombocytopenia.

Anemia: Anemia may be mild to marked, usually with features of a regenerative response such as anisocytosis and polychromasia and associated RBC indices such as increased mean corpuscular volume and decreased mean corpuscular hemoglobin concentration.
- Marked autoagglutination, which is common in IMHA patients, can lead to inaccuracies in hematocrit, RBC counts, and other RBC indices.
- Reticulocytes most commonly increase; however, in up to one-third of IMHA patients, reticulocytes decrease.
- Analysis by automated hematology analyzers should be accompanied by direct examination of a stained blood smear for diagnostically useful features (e.g., spherocytes and ghost cells) and for conditions that trigger or mimic IMHA (e.g., babesiosis, mycoplasmosis, Heinz body hemolytic anemia, and microangiopathic hemolytic anemia [schistocytes]). The presence of spherocytes is strongly suggestive of IMHA. Spherocytes are small spherical RBCs that have lost their usual disk shape and central pallor. Spherocytes in IMHA patients are formed when phagocytes remove a piece of RBC membrane during attempted phagocytosis. Spherocytes are readily recognizable among the normal larger disk-shaped RBCs of dogs but are not easily identified in cats. The presence of ghost cells in freshly processed samples strongly suggests intravascular hemolysis. Ghost cells are hollow membrane remnants of RBCs that have been emptied of hemoglobin. However, in blood for which sample preparation was delayed, ghost cells are a common and diagnostically meaningless artifact.

Inflammatory Leukogram: A CBC will often also reveal a mild to marked inflammatory leukogram associated with the inflammation caused by immune-mediated RBC destruction. An inflammatory leukogram in patients with suspected IMHA, however marked, should not be misinterpreted as evidence of infection. Neutrophilia is sometimes profound and can mimic the extreme neutrophil counts seen with granulocytic leukemia (so-called leukemoid response).

Thrombocytopenia: Platelet counts in IMHA patients are occasionally low.
- Mild to moderate thrombocytopenia (<150,000 platelets/µL) is common, affecting about 55% of IMHA patients, and is most likely associated with platelet consumption within thrombi.³
- Marked thrombocytopenia (<50,000 platelets/µL) is less common, affecting about 25% of IMHA patients, and may indicate Evans syndrome.³⁻⁷

Serum Biochemistry
Serum biochemistry will often reveal mild to marked hyperbilirubinemia in about 66% of IMHA patients and elevated liver enzymes in more than 50% of patients.⁸
- Bilirubinemia is not present in all IMHA patients; it is most common in those that have severe acute hemolysis or have had multiple transfusions.
- Liver enzymes, particularly alanine aminotransferase (ALT), will often be mildly to moderately elevated, possibly caused by hepatic hypoxia.
- Hemoglobinemia may be noted by visual inspection of the serum of patients with intravascular hemolysis and can interfere with other serum biochemistry results.
- Serum protein levels in IMHA patients are typically within normal limits and, if low, may suggest undetected bleeding rather than hemolysis as the cause of anemia.
- Marked hypophosphatemia may be identified as a nonimmune cause of hemolytic anemia, particularly in patients receiving treatment for diabetic ketoacidosis or in those with suspected refeeding syndrome.

Urinalysis
Urinalysis results for IMHA patients are typically within normal limits, apart from dipstick detection of bilirubinuria or hemoglobinuria in some patients. Dipstick evaluation may lead to misinterpretation of hemoglobinuria as hematuria, but urine sediment examination will confirm the absence of RBCs, thereby ruling out hematuria.

Diagnostic Imaging
Diagnostic imaging (chest and abdominal radiography and abdominal ultrasonography) is not an essential
diagnostic tool for patients with suspected IMHA and often reveals no significant abnormalities. The main purpose of diagnostic imaging is to rule out conditions that mimic or trigger IMHA (e.g., zinc toxicity) or underlying neoplasia causing either associative IMHA (most commonly suspected with round cell tumors) or nonimmune microangiopathic hemolytic anemia (often seen with hemangiosarcoma).

Abdominal images of patients with primary IMHA are often unremarkable but may sometimes reveal splenomegaly, most likely caused by increased activity of the mononuclear phagocytic system. Ultrasonography may reveal thrombus formation in the vasculature of organs such as the spleen. Mild abdominal effusion is sometimes noted.

For any dyspneic IMHA patient with normal or near-normal thoracic radiographs, pulmonary thromboembolism should be strongly suspected. Although pulmonary thromboembolism can be radiographically silent, sometimes enlarged pulmonary arteries, focal interstitial or alveolar lung patterns, focal areas of lung hyperlucency caused by reduced blood flow distal to the thrombus (oligemia), and/or mild pleural effusion are observed (FIGURE 3). Suspected pulmonary thromboembolism can be confirmed, if

**FIGURE 3.** (A) Right lateral, (B) left lateral, and (C) ventrodorsal radiographs of a dog with a suspected pulmonary thromboembolism affecting the left caudal lung lobe. Radiographs reveal a moderate to severe diffuse unstructured interstitial and bronchial pulmonary pattern; the left caudal lung lobe is most severely affected (arrow).

**FIGURE 4.** Red speckles caused by autoagglutination in a heparinized tube of blood from a dog with severe IMHA.
needed, by use of advanced imaging techniques such as contrast-enhanced computed tomography and pulmonary scintigraphy.

Immunologic Testing
Strictly speaking, diagnosis of IMHA requires confirmation of the immune-mediated nature of the disease. Although many different immunologic tests have been used over the years, 2 particular tests have stood the test of time: in-saline agglutination testing and Coombs’ testing.

In-Saline Agglutination Testing: In many patients with IMHA, particularly those with high levels of antibody bound to cell membranes, RBCs can be strongly adhered to each other by antibodies attached to more than one RBC. Resultant RBC autoagglutination is noted by visible red speckles in anticoagulated blood (FIGURE 4) and by rapid separation of RBCs from plasma in blood samples that stand in tubes without mixing. This immune-mediated agglutination process is so strong that no amount of washing with saline will separate attached RBCs, whereas rouleaux formation (another process that causes RBCs to adhere to each other in sick patients and leads to visible speckles) is readily dispersed by saline. A positive in-saline agglutination test, therefore, strongly suggests a diagnosis of IMHA and is often thought to indicate a more severe disease process.

The simplest in-clinic version of in-saline agglutination testing is the slide agglutination test, in which 4 to 10 drops of saline are added to 1 drop of anticoagulated blood on a microscope slide (FIGURE 5) and the sample is gently mixed by tilting the slide while watching for gross agglutination (speckles) (FIGURE 6). The test should be performed with saline and blood at or above room temperature to avoid an erroneous false-positive result caused by cold agglutination, a result of dubious diagnostic significance. If gross agglutination is not observed, a cover slip is placed over the sample and the slide is inspected microscopically for microagglutination (strongly adhered RBC clumps). Both gross and microscopic agglutination support a diagnosis of IMHA. In-saline agglutination test specificity can be increased by adding saline washing steps before assessing for agglutination. Because RBC agglutination does not occur in many IMHA patients, a negative in-saline agglutination test result does not rule out IMHA.

Coombs’ Testing: The most common send-out test used to confirm a diagnosis of IMHA is the Coombs’ test, or direct antiglobulin test (DAT), which detects antibodies and/or complement bound to RBC membranes. Many laboratories use a polyvalent mix of antibodies directed against IgG, IgM, and complement. The end point of the DAT is RBC agglutination, and addition of antibodies that bind to IgG, IgM, or complement on the cell membrane increases the number of antibodies bound to RBCs, leading to agglutination in samples that would otherwise not have true autoagglutination. Test sensitivity is therefore increased compared with slide agglutination, albeit with potentially decreased test specificity. With use of a polyvalent mix of antibodies, DAT sensitivity is reported to typically range from 60% to a little over
80%, and test specificity is generally 95% or above.\textsuperscript{10,11} Modifications to the standard DAT that may increase diagnostic value include running the test at different temperatures and a wide range of titers and using individual monovalent antibodies against IgG, IgM, IgA, and complement as well as a standard polyvalent antibody/complement mix. Because, depending on the method used, the diagnostic accuracy of the DAT can vary from mediocre to highly accurate, a patient can potentially have IMHA despite a negative DAT result.\textsuperscript{10}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{algorithm.png}
\caption{Algorithm for diagnosis of immune-mediated hemolytic anemia (IMHA). Modified from Garden, et al.\textsuperscript{1}}
\end{figure}
Diagnostic accuracy of the DAT may be affected by prior corticosteroid therapy or transfusion.

Because the DAT is typically a send-out test in which results are invariably delayed, treatment for critical patients with suspected IMHA should be based on clinical suspicion and not delayed until results return. Arguably, if an in-saline slide agglutination test using washed RBCs is already positive, a DAT may not be required.

Other Testing
The degree of confidence in a diagnosis of primary IMHA is largely based on how aggressively causes of nonimmune hemolytic anemia or secondary IMHA have been excluded. Specific tests that may be indicated for selected patients are as follows.

- **Testing for infectious disease**
  - Testing of cats for retroviruses (feline leukemia virus, feline immunodeficiency virus)
  - Polymerase chain reaction (PCR) testing for *Mycoplasma haemofelis* (cats), *Babesia* species (dogs), and, arguably, *Mycoplasma haemocanis* (dogs). Serologic tests are also available to detect babesiosis in dogs.

- **Testing for inherited hemolytic anemia**
  - Genetic testing for pyruvate kinase deficiency and phosphofructokinase deficiency in some affected dog breeds
  - Osmotic fragility testing to detect hereditary increases in RBC fragility in affected breeds of cats and dogs. True IMHA, however, can also cause increased RBC osmotic fragility.

- **Testing for hemostasis**
  - Evaluation of prothrombin time, partial thromboplastin time, D-dimer, and antithrombin if hemolysis is suspected to result from microangiopathic RBC damage and an associated consumptive coagulopathy, particularly in patients for which schistocytes are seen on blood smear

- **Bone marrow evaluation (aspiration cytology and/or histopathology biopsy)**
  - Marrow evaluation for patients with suspected IMHA associated with precursor-targeted immune-mediated anemia
  - Marrow evaluation for patients with unexplained pancytopenia (all 3 major circulating cell lines affected) to rule out concurrent hematopoietic neoplasia, which may induce an immune-mediated anemia

Final Diagnosis
The American College of Veterinary Internal Medicine (ACVIM) recently published a comprehensive consensus statement regarding the diagnosis of IMHA in dogs and cats. Given that all tests can produce false-positive or -negative results for patients with IMHA, the consensus statement suggests a diagnostic algorithm based on multiple test results. The algorithm for an anemic patient categorizes the likelihood of a final diagnosis as diagnostic, supportive of IMHA, suspicious for IMHA, or not IMHA (FIGURE 7).

**Definitive:** Requires the presence of at least 2 indicators of immune-mediated destruction (positive slide agglutination, positive DAT, or spherocytes) and at least 1 indicator of hemolysis (jaundice/hyperbilirubinemia/marketed bilirubinuria, hemoglobinemia/hemoglobinuria, or ghost cells) in the absence of other obvious causes of anemia.

**Supportive:** Has several indicators of immune-mediated destruction or hemolysis but does not meet the strict criteria required for a definitive diagnosis.

**Suspected:** Requires the presence of only 1 indicator of immune-mediated destruction in the absence of indicators of hemolysis.

Another diagnostic clue for dogs and cats that are suspected to have IMHA but do not meet initial criteria for a definitive diagnosis is an appropriate response to immunosuppressive therapy.

**THERAPY**
Because IMHA is an immune-mediated disease, treatment has typically been centered on suppressing the immune system and providing supportive care to keep the patient stable until the immune-mediated component of the disease is controlled. Careful initial diagnostic evaluation is needed to ensure that the patient does not have nonimmune hemolytic anemia or IMHA secondary to an underlying trigger such as babesiosis or mycoplasmosis; otherwise, standard therapy will probably be at best ineffective and at worst dangerous.

**Glucocorticoids**
Typically, the cornerstone of IMHA treatment for dogs and cats is glucocorticoids. In fact, for many patients with IMHA, clinical remission can be attained with
glucocorticoids alone. For dogs, the standard recommended glucocorticoid therapy is oral prednisone or prednisolone at a starting dose of 2 mg/kg q24h (for large breed dogs, a lower dose of 1 to 1.5 mg/kg q24h or 50 to 60 mg/m² q24h is suggested). For dogs, no evidence indicates that twice daily dosing with prednisone or prednisolone is any more effective than once daily dosing, and side effects tend to be more pronounced with twice daily dosing.13 Cats typically need, and tolerate, a higher dosage of glucocorticoids; prednisolone (preferable to prednisone in cats) is typically commenced at 2 mg/kg PO q12h. For patients that do not tolerate oral therapy, injectable dexamethasone can be substituted, usually at approximately one-seventh of the calculated prednisone or prednisolone doses.

Recommended glucocorticoid starting doses are typically considered to be immunosuppressive, and such doses are indicated for patients with acute and severe IMHA. These starting doses, however, are poorly tolerated over the long term and are often associated with numerous unacceptable side effects including polyuria/polydipsia, polyphagia, panting and hyperventilation, muscle weakness and atrophy, hepatomegaly and a pot belly, alopecia, susceptibility to infection (e.g., pyoderma and urinary tract infections), calcinosis cutis, poor wound healing, and increased risk for pulmonary thromboembolism. For this reason, although starting doses of glucocorticoids are often effective at treating initial episodes of IMHA, tapering of starting doses should usually begin within a few weeks of commencing therapy.

Azathioprine
Azathioprine, a purine synthesis inhibitor that inhibits lymphocyte proliferation, has long been used to treat IMHA in dogs. The recommended starting dose for dogs is 2 mg/kg PO q24h. Azathioprine is usually well tolerated, but a reversible hepatopathy develops in up to 15% of treated dogs.17 For this reason, liver enzymes of dogs receiving azathioprine should be monitored regularly, and azathioprine should be discontinued if the ALT level rapidly rises beyond that expected from glucocorticoids alone. Less common side effects include mild anemia and (rarely) severe neutropenia. Azathioprine is dangerously myelosuppressive in cats; therefore, its use in cats is not recommended.

Mycophenolate Mofetil
Mycophenolate mofetil, another purine synthesis inhibitor, has recently gained popularity for treatment of IMHA in dogs. The recommended starting dose is 8 to 12 mg/kg PO q12h. The most common side effect, which occurs in about 20% of treated dogs, is diarrhea, which can sometimes be severe and is most common at doses higher than the currently recommended starting dose.

Cyclosporine
Cyclosporine, a calcineurin inhibitor that inhibits T-cell function, seems to be the most potent immunosuppressive agent currently available for veterinary use. The recommended starting dose for the treatment of IMHA in dogs is 5 mg/kg PO q12h of the most bioavailable modified (microemulsified) formulation of the drug. Unlike other immunosuppressive agents, cyclosporine has a veterinary-approved formulation, which enables accurate dosing in smaller patients. The most common
side effects are nausea and vomiting. Because cyclosporine has unpredictable bioavailability and efficacy, pharmacokinetic or pharmacodynamic therapeutic drug monitoring may be needed to ensure effective dosing. Unlike other immunosuppressive agents, cyclosporine has no marrow suppressive effects, making it the preferred agent for dogs with poorly regenerative IMHA.

**Leflunomide**
Leflunomide, a pyrimidine synthesis inhibitor, has not achieved widespread use in veterinary medicine but seems to be well tolerated by most patients. The recommended starting dose is 2 mg/kg PO q24h.

Regardless of the immunosuppressive drugs used, it is uncommon for patients with IMHA to respond to therapy in fewer than 5 to 10 days. In the meantime, aggressive supportive measures may be needed to maintain patient stability until immunosuppressive therapy takes effect. Clinicians should resist the temptation to use higher than recommended drug doses or to use “triple therapy” (3 immunosuppressive agents, including glucocorticoids, concurrently) because such measures are likely to increase the risk for infection without adding therapeutic benefit.18

**Transfusion**
Many patients with IMHA can tolerate anemia very well; therefore, transfusion is not indicated just because of anemia. Transfusion can, however, be lifesaving for patients with severe anemia (packed cell volume [PCV] <15%), particularly those that show overt clinical signs of anemia such as tachycardia, tachypnea, lethargy, and mental dullness. Transfusion adds more RBCs to a process that already involves excessive consumption of RBCs and therefore carries an associated risk of “fueling the fire.” Transfusion should not, however, be withheld from profoundly anemic patients.

For IMHA patients, packed RBC products, which provide RBCs without unnecessary plasma, are preferable to whole blood, although whole blood is acceptable in an emergency. Fresh or recently stored (for fewer than 10 days) products are preferable to long-stored blood products.19,20 Ideally, donor–patient compatibility matching via cross-match or blood typing should be performed before administering transfusion to dogs but may not be possible if autoagglutination interferes with the test method. Fortunately, for dogs, a single first-time unmatched and untyped transfusion is typically safe. For cats, blood type compatibility should always be verified before administering transfusion, and immunochromatographic typing kits that are not affected by agglutination are available for this species.

The target post-transfusion PCV in dogs with IMHA is about 25% or greater and in cats is about 20% or greater. In very severely affected animals, multiple transfusions (up to 2 transfusions/day) for up to a week or more may be needed to maintain patient stability until immunosuppressive therapy becomes effective.

**Other Therapeutic Options**
For patients with IMHA that is life-threatening and refractory to more standard therapy, other therapeutic options include splenectomy, intravenous human immunoglobulin, liposomal clodronate, and therapeutic plasma exchange. Although each of these more advanced or expensive options certainly seems to benefit some individual IMHA patients, strong evidence to support their routine use is minimal. Some clinicians also recommend oral melatonin as an adjunctive therapy for management of IMHA.

In cats, because IMHA commonly occurs secondary to *M. haemofelis* infection and because this organism can be hard to identify on blood smears, treatment with doxycycline or pradofloxacin, in addition to glucocorticoids, is often commenced at presentation while confirmatory PCR results are pending.

**PREVENTING PULMONARY THROMBOEMBOLISM**
In dogs with IMHA, pulmonary thromboembolism is a major cause of death. Therefore, during the initial treatment of IMHA, thromboprophylactic therapy is
recommended. For first-line therapy, anticoagulant therapy with drugs that inhibit the clotting cascade is recommended, including unfractionated heparin (starting dose 150 to 200 U/kg SC q6h or as a constant rate infusion, ideally with dosing adjustments based on inhibition of factor Xa assay when available), injectable low molecular weight heparins such as enoxaparin (0.8 to 1 mg/kg SC q6h) and dalteparin (150 U/kg SC q8h), or newer oral antiocoagulants such as rivaroxaban (0.9 mg/kg PO q24h). Oral antiplatelet agents such as clopidogrel (1 to 4 mg/kg q24h) and low-dose aspirin (1 mg/kg q24h) are less expensive than anticoagulant drugs and are therefore often used.

**PROGNOSIS**

Unfortunately, the mortality rate among dogs with IMHA continues to be high (>50%); most deaths occur within the first few months after presentation due to severe anemia, pulmonary thromboembolism, or euthanasia resulting from client intolerance of the high cost of therapy and drug side effects. In contrast, the long-term prognosis after survival of the first months of treatment is fair; relapse rates are up to about 20%. For most dogs, treatment can be discontinued within 6 to 12 months of presentation, although some require lifelong immunosuppressive therapy. Most cats with IMHA respond well to standard therapy. In recovered IMHA patients, no strong evidence indicates that routine preventative modalities (e.g., vaccination, heartworm prevention, or flea and tick control) will precipitate disease relapses. TVP

Andrew Mackin

Dr. Mackin is a professor and head of the department of Clinical Sciences at Mississippi State University. After graduating from Murdoch University, Australia, in 1983, he went on to complete an internship and residency in small animal medicine at the University of Melbourne, Australia, followed by an internal medicine residency at the Ontario Veterinary College in Canada. In 1993, Dr. Mackin became a Fellow of the Australian and New Zealand College of Veterinary Scientists and in 1994 he became an ACVIM Diplomate. His clinical and research focus is on hematology, hemostasis, immunosuppressive therapy, and transfusion medicine.

References

Immune-Mediated Hemolytic Anemia

1. Immune-mediated hemolytic anemia (IMHA) is a good example of which type of immune-mediated reaction?
   a. Type I (allergic)
   b. Type II (cytotoxic)
   c. Type III (immune complex)
   d. Type IV (delayed)

2. Which of the following clinical features does not strongly suggest the presence of intravascular hemolysis?
   a. Hemoglobinemia
   b. Hemoglobinuria
   c. Jaundice
   d. Ghost cells

3. Which organ is most likely to be damaged by the presence of intravascular hemolysis?
   a. Brain
   b. Heart
   c. Liver
   d. Kidney

4. Which of the following infectious diseases has been strongly associated with secondary IMHA in dogs?
   a. Brucellosis
   b. Leptospirosis
   c. Babesiosis
   d. Bartonellosis

5. Evans syndrome should be suspected in IMHA patients that have what abnormality on routine complete blood count evaluation?
   a. Marked thrombocytopenia
   b. Marked neutrophilia
   c. Pancytopenia
   d. Schistocytosis

6. Which red blood count abnormality strongly supports a diagnosis of IMHA in dogs?
   a. Heinz bodies
   b. Eccentrocytes
   c. Schistocytes
   d. Spherocytes

7. Which of the following immunosuppressive agents has no known marrow suppressive effects?
   a. Azathioprine
   b. Mycophenolate mofetil
   c. Leflunomide
   d. Cyclosporine

8. Which of the following immunosuppressive agents is considered to be highly dangerous in cats?
   a. Prednisolone
   b. Cyclosporine
   c. Mycophenolate mofetil
   d. Azathioprine

9. Which is the preferred blood product for transfusing dogs with IMHA?
   a. Fresh frozen plasma
   b. Packed red blood cells that are fresh or have been stored for fewer than 10 days
   c. Whole blood that is fresh or has been stored for fewer than 10 days
   d. Whole blood that has been stored for more than 10 days

10. Which of the following anticoagulants used to prevent pulmonary thromboembolism can be given orally?
    a. Unfractionated heparin
    b. Dalteparin
    c. Enoxaparin
    d. Rivaroxaban