Iron Deficiency in Dogs and Cats

By Patty Ewing, DVM, MS, DACVP  
(Anatomic and Clinical Pathology)  
angell.org/lab  
pathology@angell.org  
617 541-5014

INTRODUCTION
Iron is an essential trace mineral that has a variety of critical biologic functions. Iron is a component of hemoglobin, myoglobin, and cytochrome enzymes and is stored in the liver as ferritin or transferrin, which can be measured in the serum to assess iron status. The total amount of iron in the body is closely regulated by coordinating daily loss and intestinal absorption of iron. Iron deficiency results when iron demand by the body is not met by iron absorption by the intestine from the diet. Because iron is a critical component of hemoglobin, iron deficiency can result in life-threatening anemia. The major causes of iron deficiency include loss of iron via hemorrhage, and inadequate intake or absorption of iron (Table 1). Clinical signs of iron deficiency may include weakness, decreased activity, dyspnea (with severe anemia), altered behavior, gastrointestinal disorders secondary to decreased gastric acid secretion and intestinal malabsorption, and increased risk of infection.

IRON DEFICIENCY IN DOGS
At Angell Animal Medical Center, most cases of iron deficiency anemia (IDA) are due to chronic hemorrhage from gastrointestinal tumors. Diagnosis of uncomplicated and chronic iron deficiency is based on classic hematologic and biochemical abnormalities such as changes in erythrocyte indices (microcytic, hypochromic anemia) and decreased serum ferritin concentration (Table 2). Detection of early iron deficiency, before the appearance of those abnormalities, or iron deficiency in the presence of other diseases (e.g., neoplasia and inflammation) is a diagnostic challenge. In uncomplicated iron deficiency, the serum iron concentration and ferritin are typically low and the total iron binding capacity (TIBC) is usually high. Because iron is preferentially shunted to hemoglobin (Hb) formation, typical hematologic changes do not occur until late in iron deficiency, long after detrimental effects have occurred. Also, serum ferritin is an acute-phase reactant and concentrations may be increased with certain neoplastic and inflammatory diseases, which may make diagnosis of concurrent iron deficiency challenging. Although the immunologic assay for canine serum ferritin has been available for over a decade, its value in detecting IDA in chronically ill dogs is not reported. Many clinicians consider the evaluation of bone-marrow aspirates or biopsies (for the presence or absence of stainable iron) as a sensitive and reliable test for iron status assessment in dogs. However, some hematologists consider this invasive procedure to be subjective and imprecise. Thus, the true prevalence of iron deficiency may be unknown, and dogs with early iron deficiency masked by concurrent disease may remain undiagnosed and untreated.

<table>
<thead>
<tr>
<th>Table 1: Causes of Iron Deficiency in Dogs and Cats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient iron deficiency anemia (IDA) in neonates on all-milk diet</td>
</tr>
<tr>
<td>Blood-sucking parasites</td>
</tr>
<tr>
<td>Intestinal bleeding (tumors, ulcers, etc.) or intestinal malabsorption</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td>Urinary bleeding (bladder tumors)</td>
</tr>
<tr>
<td>Hemorrhagic disorders (diathesis, coagulopathy)</td>
</tr>
<tr>
<td>Latrogenic (blood donors)</td>
</tr>
</tbody>
</table>

> Continued on Page 2
Iron deficiency may occur if insufficient stores are accumulated during the last week of pregnancy. In the 1980s, iron deficiency anemia was reported to be common in five-week-old kittens. Kittens at this age had the highest frequency of microcytosis. At seven weeks of age, the kittens stopped producing microcytic cells. The age-related change implicated the all-milk diet in a rapidly growing animal. Milk is a poor source of iron, and iron requirements are usually higher than the intake. Now that kittens are transitioned to commercial diets typically consumed by three weeks of age, nutritional iron deficiency is infrequently reported, and the most common cause for iron deficiency in cats is parasitism (internal and external).

Iron deficiency anemia in adult cats has rarely been reported. Although red blood cell (RBC) fragmentation may occur in cats with iron deficiency anemia, hypochromasia is not reported as a common feature. Serum iron and percent transferrin saturation values decrease.1 An assay for ferrous ferric is commercially available. Determination of concentrations of serum iron and serum ferritin may be useful in the differentiation of anemia of chronic inflammation from IDA in cats.2

Cats may have greater gastrointestinal iron-absorptive capacities than other species.3,4 Additionally, detection of classic hematologic lesions of iron deficiency is more challenging than in dogs. This challenge is due to the lack of stainable iron in normal feline bone marrow, infrequency of hypochromasia, and the difficulty of detecting microcytosis by traditional hematologic methods in cats.2

TREATMENT

Transfusion of red blood cells (whole blood or packed red blood cells) should be considered for patients with IDA clinical signs. The patient hematocrit should be raised to 15–20%. The PCV is 20–25%. The first line of therapy for iron deficiency anemia is parenteral iron administration. Iron preparations administered intravenously may cause anaphylactic reactions, thus the intramuscular (IM) route is preferred.1 A small dose should be injected IM to test for hypersensitivity reactions. A maximal dose of 2 ml can be administered daily.4 Large doses of injectable iron may dissolve the serum brown, which can cause falsely elevated serum bilirubin values and falsely decrease serum calcium values.2 Iron deficiency in dogs is first addressed by administering iron dextran once at 10–20 mg/kg IM and then continuing therapy with oral iron. In dogs the dose for prevention of transient iron deficiency anemia in kittens is 50 mg of iron dextran IM at 18 days of age. The dose for definitive therapy with EPO treatment is 50 mg of iron dextran IM three to four times daily or oral supplementation. Oral iron therapy usually follows injectable iron (Table 4). Oral iron absorption varies widely based on the type of diet and other factors. Sustained-release iron formulations are not recommended as initial therapy, because they reduce the amount of iron that is present for the absorption by the duodenal villi. Gastrointestinal absorption of elemental iron is enhanced in the presence of an acidic gastric environment. This can be accomplished through concurrent intake of ascorbic acid (Vitamin C).5,6

Most common side effects of oral iron supplementation are gastrointestinal upset (most commonly constipation). Dividing the daily dose may reduce gastrointestinal upset. Although iron absorption occurs more readily when taken on an empty stomach, this increases the likelihood of stomach upset. Oral iron may result in black discoloration of feces and false-positive reactions with the guaiac occult blood test. A common product used for iron supplementation is Pet-Tinic (Pfizer Animal Health). It contains 12.5 mg of iron per tablespoon. For adequate iron supplementation; thus injections of iron dextran may be required in cases of chronic anemia.

REFERENCES

An Update on Pimobendan

By Adam Kane, DVM
angell.org/cardiology cardiology@angell.org 617 541-5038

Medical management of cardiac disease in veterinary patients is constantly evolving and improving. Either through the introduction of new medications or updated applications of existing medications, we have been able to afford our patients both improved quality and quantity of life. The advent of pimobendan (Vetmedin®) is one of the more recent examples of this beneficial evolution. In general, it is a medication that has been found to have great benefits with typically minimal side effects. However, as with any medication or therapy, appropriate use is paramount and guidelines established by evidence-based medicine and the subsequent peer-reviewed literature should be followed.

Pimobendan is a benzimidazole pyridazine derivative, approved by the FDA in 2007 for use in the treatment of congestive heart failure in canine patients. Because its mechanism of action does not affect endogenous catecholamines, stimulate cardiac adenrenergic receptors, or inhibit the Na+K+ATPase (sodium potassium) pump, it is classified as a nonsympathomimetic, nonglycoside, inotropic drug. Pimobendan is an inotrope that has both positive inotropic and vasodilatory effects.

In the failing heart, pimobendan exerts its positive inotropic effects primarily by increasing the binding affinity of cardiac troponin C for calcium. Calcium cycling is one of the primary determinants of myocardial contractility. The binding of calcium to cardiac troponin C allows for interaction between the contractile proteins of the cardiac myocytes, resulting in force generation and contractive force. The increased binding sensitivity for calcium results in an increased strength of contraction. Positive inotropy is also conferred by the medication’s phosphodiesterase-3 inhibitory effects within cardiac muscle cells. Phosphodiesterase-3 inhibition leads to phosphorylation of several cellular proteins involved in calcium uptake and release. The net result is a more rapid sequestration of calcium during diastole, and more profound release of calcium during systole, both of which contribute to an overall positive inotropic effect. Because the total intracellular concentration of calcium is not altered by pimobendan, this positive inotropy is achieved without increasing the myocardial oxygen demand.

Pimobendan is a mixed vasodilator (arterial and venodilator). This effect is also mediated by the medication’s phosphodiesterase-3 inhibitory properties. Through various signaling mechanisms in vascular smooth muscle cells, this causes an increase in sequestration of intracellular calcium, making less calcium available for smooth muscular contraction within the blood vessels. Pimobendan also has several other biologic activities of lesser importance, including mild immunomodulatory effects by decreasing pro-inflammatory cytokines, decreased catecholamine synthesis, and antiarrhythmic effects.

Side effects with the medication are uncommon, but typically include gastrointestinal signs such as decreased appetite and diarrhea. There has been concern surrounding possible arrhythmogenicity of pimobendan, due to prolongation of the cardiac action potential, but this concern has not been supported in various studies.

Pimobendan’s use in the treatment of canine chronic degenerative valvular disease has been evaluated in multiple studies involving both pre- and post-heart-failure patients. Unfortunately, no clear benefit has been established for patients with valvular disease prior to the onset of congestive heart failure. A study of asymptomatic dogs with valvular disease treated with pimobendan or benazepril showed worsened mitral regurgitation, with corresponding valvular and endocardial lesions in those dogs treated with pimobendan, despite an improvement in systolic function. These findings were corroborated by a case report of two dogs that developed similar lesions with long-term pimobendan therapy, the lesions resolved after discontinuation of the medication.

Conversely, several studies have underscored the benefits of pimobendan after the onset of heart failure in patients with valvular disease, and its use at this stage is supported by the veterinary cardiology community. The VetSCOPE study compared the use of pimobendan to that of benazepril in heart-failure patients. Those treated with pimobendan had a prolonged time to death or treatment failure, with an average of 415 days compared to 128 days for those in the benazepril treatment group. The QUEST study further supported these results, showing that the pimobendan-treated group had significantly longer time to the primary endpoint than the benazepril group (267 days versus 140 days).

Canine patients with dilated cardiomyopathy (DCM) may be the most common indication for pimobendan use in dogs with DCM and subsequent congestive heart failure has been supported for several years. One study compared the survival times of Cocker Spaniels and Dobebern Pinchers treated with pimobendan after the onset of DCM. The group that received pimobendan had a mean survival time of 416 days compared to 110 days for the group that received only supportive care. This study suggested that pimobendan may be beneficial in certain patients with DCM.

Pimobendan is a mixed vasodilator (arterial and venodilator). This effect is also mediated by the medication’s phosphodiesterase-3 inhibitory properties. Through various signaling mechanisms in vascular smooth muscle cells, this causes an increase in sequestration of intracellular calcium, making less calcium available for smooth muscular contraction within the blood vessels. Pimobendan also has several other biologic activities of lesser importance, including mild immunomodulatory effects by decreasing pro-inflammatory cytokines, decreased catecholamine synthesis, and antiarrhythmic effects.

Side effects with the medication are uncommon, but typically include gastrointestinal signs such as decreased appetite and diarrhea. There has been concern surrounding possible arrhythmogenicity of pimobendan, due to prolongation of the cardiac action potential, but this concern has not been supported in various studies.

Pimobendan’s use in the treatment of canine chronic degenerative valvular disease has been evaluated in multiple studies involving both pre- and post-heart-failure patients. Unfortunately, no clear benefit has been established for patients with valvular disease prior to the onset of congestive heart failure. A study of asymptomatic dogs with valvular disease treated with pimobendan or benazepril showed worsened mitral regurgitation, with corresponding valvular and endocardial lesions in those dogs treated with pimobendan, despite an improvement in systolic function. These findings were corroborated by a case report of two dogs that developed similar lesions with long-term pimobendan therapy, the lesions resolved after discontinuation of the medication.

Conversely, several studies have underscored the benefits of pimobendan after the onset of heart failure in patients with valvular disease, and its use at this stage is supported by the veterinary cardiology community. The VetSCOPE study compared the use of pimobendan to that of benazepril in heart-failure patients. Those treated with pimobendan had a prolonged time to death or treatment failure, with an average of 415 days compared to 128 days for those in the benazepril treatment group. The QUEST study further supported these results, showing that the pimobendan-treated group had significantly longer time to the primary endpoint than the benazepril group (267 days versus 140 days).

Canine patients with dilated cardiomyopathy (DCM) may be the most common indication for pimobendan use in dogs with DCM and subsequent congestive heart failure has been supported for several years. One study compared the survival times of Cocker Spaniels and Dobebern Pinchers treated with pimobendan after the onset of DCM. The group that received pimobendan had a mean survival time of 416 days compared to 110 days for the group that received only supportive care. This study suggested that pimobendan may be beneficial in certain patients with DCM.

One of the more interesting causes of vision loss in dogs is due to progressive rod cone degeneration (PRCD), a hereditary loss of photoreceptor function (often at times mistaken for cataract formation by clients). The disease is caused by a genetic mutation in the photoreceptors of the retina. The cells develop normally but in adolescence or early adulthood the mutation causes the retinas to degenerate over time, leading to blindness.

When a patient presents for vision loss and the visual axis is clear the attention turns to diseases causing retinal dysfunction including glaucoma, sudden acquired retinal degeneration (SARD), optic neuritis, other central nervous system (CNS) diseases, retinal dysplasia, or detachment, or one of the many congenital anomalies of retinal degeneration. The key points of differentiating photoreceptor degeneration from other types of retinal disease are a) the slow rate of progression; b) the characteristic nystagmus, or night vision loss, as the early indicator of a problem (day/night confusion often remains normal for a while); c) the absence of inflammation or ocular hypertension; and d) the often normal appearance of the retina early in the disease. Quite often the eyes are not red and the pupillary light reflexes (PLRs) may be normal early on. With genetic lineage it can be beneficial to identify carriers and limit propagation of the genetic disease.

There is no cure for PRCD and no accepted treatment for slowing the disease or prolonging vision. Causes for the disease have been theorized, and among those proposed ideas are changes in plasma lipid levels (docosahexaenoic acid, 22:6n-3). A few veterinary ophthalmologists have developed a neutraceutical product, Ocu-Glo™ (ocuglo.com), containing a mixture of antioxidants and vitamins that may support ocular health in the face of retinal disease. There is no proof that it slows down or reverses the damage caused by the genetic changes, but it may promote the optimal conditions for vision during disease progression. Large, randomized studies are needed to support any testimony that the product actually stabilizes or preserves retinal function and vision. We offer this product to clients who want to try something that may help, but we say up front there is no documented medicinal benefit by way of peer-reviewed papers at this time.

For more information about Angell’s Ophthalmology service, please visit angell.org/eyes. Drs. Coster and Bisser are available for consultations or referrals at 617 541-5095, or e-mail at ophthalmology@angell.org.
Proximal Tibial Epiphysiodesis (PTE): An Alternative Technique to Correcting the Cranial Cruciate Ligament Deficient Stifle in Growing Dogs

By Nick Trout, MA, VET MB, DACVS, EVCS
angell.org/surgery
surgery@angell.org
617 541-5048

Canine cruciate disease is arguably one of the most common orthopedic problems facing veterinarians today. In part, our awareness of stifle abnormalities has been heightened by an appreciation of effective surgical options for athletic or energetic dogs, in the form of tibial plateau leveling osteotomy (TPLO) and tibial tuberosity advancement (TTA). These procedures tend to be used on skeletally mature dogs of any breed, but what if your patient is still growing? Cruciate ligament injuries can occur at any age and, from time to time, four- to eight-old months will present with partial or complete cruciate tears. Should we wait until the proximal tibial growth plates are closed, or are we limited to stifle stabilization with a lateral suture technique?

Proximal tibial epiphysiodesis (PTE) offers an alternative technique to correcting the cranial cruciate ligament deficient stifle in growing dogs. Think of it as a “slow TPLO.” By prematurely closing the cranial portion of the tibia plateaus using a carefully positioned cannulated screw, growth can be impeded while allowing the caudal portion to continue growing. As long as the dog has sufficient residual growth potential, the result is a progressive decline in the tibial plateau angle. In the same way as a TPLO, PTE can eliminate the need for a cranial cruciate ligament to counteract tibial thrust, thereby achieving dynamic stifle stabilization.

Accurate screw placement using a small lateral arthrotomy can be accomplished. A tibial plateau angle of just over 30 degrees is appreciated (Figure 1) that this technique may not work in dogs over eight months of age or where the growth plate closes early. Screw removal has been reported to prevent overcorrection of the tibial plateau angle, though in my experience this has not proven necessary.

For large breeds or dogs that are disposed to be active, PTE offers dog owners a fantastic alternative to a lateral suture technique or the frustration of waiting until skeletal growth is complete.

For more information about this technique, please contact Angell’s Surgery service at 617 541-5048 or surgery@angell.org

REFERRAL CONTACT INFORMATION

Avian & Exotic Medicine Service
Referral Contact: Stacey Escallante
Referral Line: 617 541-5038
Referral Fax: 617 541-5039
E-mail: avianexotic@angell.org
angell.org/avianexotic

Cardiology Service
Referral Contact: Rebecca Stashe
Referral Line: 617 541-5038
Referral Fax: 617 541-5039
E-mail: cardiology@angell.org
angell.org/cardiology

Dentistry Service
Referral Contact: Michael Johnson
Referral Line: 617 541-5039
Referral Fax: 617 541-5040
E-mail: dentistry@angell.org
angell.org/dentistry

Dermatology Service
Referral Contact: Michael Johnson
Referral Line: 617 541-5039
Referral Fax: 617 541-5040
E-mail: dermatology@angell.org
angell.org/dermatology

Diagnostic Imaging
Referral Contact: Radiology Staff
Referral Line: 617 541-5039
Referral Fax: 617 541-5040
E-mail: diagnosticimaging@angell.org
angell.org/diagnosticimaging

Emergency/Critical Care Service
Referral Line: 617 541-5040
Referral Fax: 617 541-5041
E-mail: emergency@angell.org
angell.org/emergency

Internal Medicine
Referral Contact: Eleanor Cousino
Referral Line: 617 541-5040
Referral Fax: 617 541-5041
E-mail: internalmedicine@angell.org
angell.org/internalmedicine

Neurology Service
Referral Contact: Lisa Canale
Referral Line: 617 541-5040
Referral Fax: 617 541-5041
E-mail: neurology@angell.org
angell.org/neurology

Nutrition
Referral Contact: Eleanor Cousino
Referral Line: 617 541-5040
Referral Fax: 617 541-5041
E-mail: nutrition@angell.org
angell.org/nutrition

Oncology Service
Referral Contact: Slaney Escallante
Referral Line: 617 541-5041
Referral Fax: 617 541-5042
E-mail: oncology@angell.org
angell.org/oncology

Ophthalmology Service
Referral Contact: Rachel Daniels
Referral Line: 617 541-5041
Referral Fax: 617 541-5042
E-mail: ophthalmology@angell.org
angell.org/ophthalmology

Pathology Service (Clinical and Anatomical)
Referral Contact: Laboratory Staff
Referral Line: 617 541-5040
Referral Fax: 617 522-7356
E-mail: pathology@angell.org
angell.org/pathology

> An Update on Pimobendan (Continued from Page 4)

with pimobendan versus placebo after the onset of heart failure. Both breeds in the pimobendan group survived for a significantly longer period of time (1,037 days versus 537 days for the Cocker Spaniels, 321 days versus 50 days for the Doberman Pinschers). Similar findings were seen in a separate study evaluating Doberman Pinschers with congestive heart failure secondary to DCM. Those treated with pimobendan and other medications appropriate for heart failure survived for 130.5 days, while those given placebo plus other heart failure medications survived for only 14 days. More recently, the PROTECT study provided evidence for the benefits of pimobendan therapy in DCM patients prior to the onset of heart failure. The median time to the primary end point (congestive heart failure or sudden death) was 63% longer in the pimobendan group compared to the placebo group (718 days versus 441 days). The median survival time was also longer for the pimobendan-treated dogs (632 days versus 466 days). There is very little evidence to support the use of pimobendan in feline patients. As such, its use in cats is off-label at this time. Although it has been shown to be well tolerated, a recent pharmacologic study demonstrated that it can reach serum levels up to four times those seen in dogs with standard doses, and the serum half-life is approximately three times longer than that seen in dogs. While it has empirically been reported to be of benefit for feline patients with systolic dysfunction, the use of pimobendan, or any other positive inotrope, is contraindicated in patients with systolic anterior mitral valve motion, due to the possibility of causing worsened dynamic outflow tract obstruction.

Pimobendan has clear benefits when used appropriately in the treatment of canine patients with cardiac disease. Other uses and applications in these patients, as well as its general use in feline patients, require further evaluation.

For more information about Angell’s Cardiology service, please visit angell.org/cardiology. For consultations or referrals, please call 617 341-3038, or e-mail cardiology@angell.org.
Veterinary Referral News from Angell Animal Medical Center

350 South Huntington Ave.
Boston, MA 02130
angell.org

Saturday/Sunday/Evening/Early Morning Appointments:
Angell offers expanded appointment hours for many services. Please visit angell.org/hours.

Are your clients new to Angell?
Send them to angell.org/directions for detailed directions to our location. Ample free parking on site.

We encourage you to e-mail Angell’s specialists with questions. We hope you will use Angell as a resource, and we look forward to working with you as we continue our legacy of providing compassion and care for animals.

Main Phone: 617 522-7282
Veterinary Referrals: 617 522-5011

Chief of Staff
Ann Marie Manning, DVM, DACVECC
amanning@angell.org

Avian & Exotic Medicine
Elisabeth Simone-Freilicher, DVM, DABVP (Avian Practice)
esimonefreilicher@angell.org

Cardiology
Nancy Late, DVM, DACVIM (Cardiology)
nlaste@angell.org
Rebecca Malakoff, DVM, DACVIM (Cardiology)
malakoff@angell.org
Rebecca Quinn, DVM, DACVIM
rquinn@angell.org

Dentistry
William Rosenblad, DVM
wrosenblad@angell.org

Dermatology
Klaus Loft, DVM
klof@angell.org
Meghan Umstead, DVM
munstead@angell.org

Diagnostic Imaging
Rebecca Manley, DVM, DACVR
manley@angell.org
Joan Regan, VMD, DACVR
jregan@angell.org
Steven Tsai, DVM, DACVR
stsa@angell.org

Emergency & Critical Care Medicine
Kiko Bracker, DVM, DACVECC
kbracker@angell.org
Roxanna Khorzad, DVM
rkhhorzad@angell.org
Megan Whelan, DVM, DACVECC
mwhelan@angell.org

Internal Medicine
Doug Brum, DVM
dbrum@angell.org
Maureen Carroll, DVM, DACVIM
mccarroll@angell.org
Erika de Papp, DVM, DACVIM
depepapp@angell.org
Jean Marie Duddy, DVM
jduddy@angell.org
Kirstin Johnson, DVM, DACVIM
kjjohnson@angell.org
Shawn Kearns, DVM, DACVIM
skearns@angell.org
Susan O’Bell, DVM, MPH, DACVIM
sobell@angell.org

Neurology
Allen Sisson, DVM, MS, DACVIM (Neurology)
asisson@angell.org

Nutrition
Dana Hutchinson, DVM, DACVN
dhutchinson@angell.org

Oncology
Christine Anderson, DVM, MS, DACVIM (Oncology), DACVR (Radiation Oncology)
canderson@angell.org
Jennifer Mahoney, DVM, DACVIM (Oncology)
jmahoney@angell.org
Carrie Wood, DVM, DACVIM (Oncology)
cwood@angell.org

Ophthalmology
Daniel Biros, DVM, DACVO
dbiros@angell.org
Martin Coster, DVM, MS, DACVO
mcoster@angell.org

Pain Medicine
Lisa Moses, VMD, DACVIM, CVMA
lmoses@angell.org

Pathology (Clinical & Anatomical)
Patty Ewing, DVM, MS, DACVP
pewing@angell.org
Pamela Mouser, DVM, MS, DACVP
pmouser@angell.org

Surgery
Sue Casale, DVM, DACVS
scasale@angell.org
Michael Pavletic, DVM, DACVS
mpavletic@angell.org
Nicholas Trout, MA, VET MB, MRCVS, DACVS, DECVS
ntrout@angell.org

We mail one complimentary copy of our newsletter to each of our referring partners. Please circulate this copy within your practice.