Iron Deficiency Anemia: Pathophysiology, Diagnosis, and Emerging Therapies

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Abstract: **Iron is essential for nearly all living organisms and plays a vital role in various metabolic functions. One of its most important roles is oxygen transport in hemoglobin. In dogs and cats, iron deficiency anemia is often caused by chronic blood loss and may be discovered incidentally, as these animals can adapt to the anemia over time. Severe iron deficiency leads to a type of anemia characterized by microcytic and hypochromic red blood cells, and the regenerative response can vary. This text will review iron metabolism and homeostasis, followed by a discussion on diagnostic testing and therapeutic recommendations for iron deficiency anemia.**

Keywords: **Anemia, Deficiency, Iron, Diagnostic**

INTRODUCTION

Iron deficiency anemia in dogs and cats usually occurs as a result of chronic external blood loss and only develops after the body's iron stores have been depleted. Treatment involves addressing the underlying cause of the blood loss and replenishing the iron stores. Iron deficiency anemia in dogs and cats usually occurs as a result of chronic external blood loss and only develops after the body's iron stores have been depleted. Treatment involves addressing the underlying cause of the blood loss and replenishing the iron stores.

The Intricacies of Iron Metabolism and the Balance of Homeostasis

Iron is essential for various metabolic functions, including the transportation of oxygen in hemoglobin. Additionally, iron is a crucial component of many enzymes, such as cytochromes, which are necessary for energy production and drug metabolism. Iron can exist in either a reduced ferrous (Fe2+) or an oxidized ferric (Fe3+) state due to the donation or acceptance of an electron. The majority of functional iron is found in hemoglobin, with smaller amounts present in myoglobin and cytochromes. The liver produces iron transport proteins and stores iron primarily as ferritin or hemosiderin. Ferritin is a soluble and diffuse protein that serves as the body's primary storage form of iron. In contrast, hemosiderin has a similar structure to ferritin but contains a higher ratio of iron to protein and is insoluble. Iron storage also occurs in the reticuloendothelial cells of the bone marrow and spleen; however, it is not commonly found in the bone marrow of cats. [1234]

Dietary iron is primarily absorbed in the duodenum. Only ferrous iron can be absorbed, and it is transported across the apical membrane of the enterocyte by a protein known as divalent metal transporter 1. After absorption, iron is moved from the enterocyte to the basolateral membrane through an unknown mechanism. Once it reaches the basolateral membrane, iron is exported from the enterocyte by ferroportin. It then binds to transferrin in the plasma, allowing it to be transported to target organs or stored for future use. [1234]

The body tightly regulates its iron stores to ensure there is enough iron for cellular needs while avoiding the toxicity associated with excess iron. Since the body does not have a mechanism to excrete excessive iron, homeostasis is maintained by limiting iron absorption in the intestines through impaired release from enterocytes. This release of iron is controlled by hepcidin, a hormone produced by liver cells (hepatocytes). When iron levels in the body are adequate or high, hepcidin is released and binds to ferroportin, a protein responsible for iron export from enterocytes. This binding leads to the internalization and destruction of ferroportin, resulting in a decrease in iron being released into the bloodstream from dietary sources. Consequently, the iron remains trapped in the enterocyte and is lost when the cell

sheds. On the other hand, when iron levels are low, the production and secretion of hepcidin are suppressed, which enhances the release of iron from enterocytes into the bloodstream. The body tightly regulates its iron stores to ensure there is enough iron for cellular needs while avoiding the toxicity associated with excess iron. Since the body does not have a mechanism to excrete excessive iron, homeostasis is maintained by limiting iron absorption in the intestines through impaired release from enterocytes. This release of iron is controlled by hepcidin, a hormone produced by liver cells (hepatocytes). [1,2,3]

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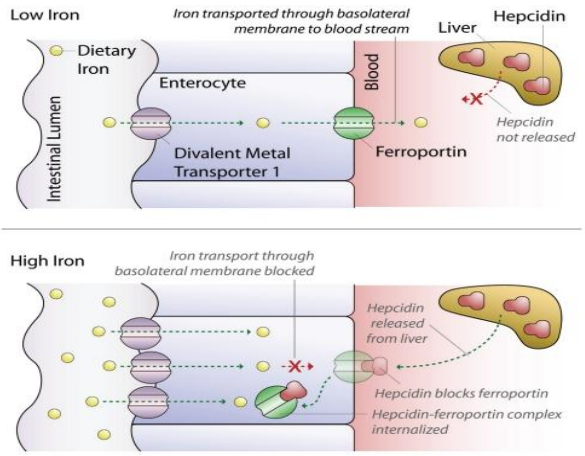

Figure 1 Mechanism of intestinal iron absorption at low and high serum iron levels.

Tight regulation of iron levels is essential, as excessive iron buildup in liver cells can lead to pathological damage known as hemochromatosis. As a result, increased fibrosis and cirrhosis may develop. Iron deficiency results in the depletion of the body's iron stores, which can lead to iron deficiency anemia and various metabolic dysfunctions. The duodenum has limited capability to absorb dietary iron, although this can be increased in response to needs. However, the increase in iron absorption due to chronic blood loss and subsequent iron deficiency may not be sufficient to restore proper iron balance, even after the cause of blood loss has been addressed. [1,3,6]

Causes of iron deficiency anemia

Iron deficiency occurs when the dietary intake of iron does not meet the body's needs or when there is chronic external blood loss. For adult dogs and cats, the estimated dietary iron requirement is around 80 mg per kg of dry matter. This requirement is higher for puppies and kittens due to their rapid growth. Inadequate intake of iron is uncommon, except in nursing animals, as milk contains a low concentration of iron. While dogs and cats that are fed commercial pet foods typically do not experience inadequate dietary iron intake, it can occur with home-cooked or vegetarian diets lacking appropriate iron supplementation. Foods that are rich in iron include meat products such as liver, heart, and muscle, as well as brewer's yeast, wheat germ, egg yolks, oysters, certain dried beans, and some fruits. Green vegetables, cereals, fish, and fowl provide a moderate amount of iron. In contrast, foods low in iron include milk, dairy products, and most non-green vegetables. [1,4,6,8,9]

During acute blood loss, the body typically has enough iron stored to support accelerated red blood cell production. In such cases, the subsequent iron uptake is usually sufficient to restore normal iron levels. However, iron deficiency anemia can develop over weeks to months in cases of chronic or recurrent blood loss in both juvenile and adult animals. Chronic external blood loss can be caused by ectoparasitism, endoparasitism, hematuria, epistaxis, hemorrhagic skin disorders, coagulopathy, thrombocytopenia, thrombocytopathia, and gastrointestinal bleeding. Gastrointestinal hemorrhage can occur due to primary gastrointestinal diseases, such as benign or malignant neoplasms, ulceration, or arteriovenous fistula. It can also result from ulcerogenic drugs, particularly non-steroidal anti-inflammatory agents and corticosteroids. Additionally, it may be secondary to systemic diseases, including renal and hepatic disorders, bleeding disorders, and hypoadrenocorticism. [1,3,10,11,12,15,16]

Nursing animals are especially susceptible to iron deficiency anemia due to lower body iron stores, increased requirements, and reduced intake from a milk-based diet. [1,13,14] The surgical removal of the entire duodenum can result in iron malabsorption. Iron deficiency anemia may also occur due to excessive blood donations from animals, as each

donation of 450 mL removes approximately 200 mg of iron from the body. Additionally, repeated blood draws for diagnostic and monitoring purposes in smaller animals can lead to iron deficiency anemia. It is important to note that the volume of blood drawn should not exceed 1% of the animal's body weight per week. [10]

Pathogenesis of iron deficiency anemia

Iron deficiency anemia can be classified into three stages: storage iron deficiency, iron-deficient erythropoiesis, and iron deficiency anemia. Initially, during blood loss, the body preferentially uses its iron stores to support increased red blood cell production (erythropoiesis). Once the body's iron stores are depleted, the production of red blood cells and other iron-containing proteins, such as myoglobin, becomes limited, resulting in overt iron deficiency anemia. Anemia worsens as the iron-deficient red blood cells have a shorter lifespan due to their fragility, which increases their removal and destruction by reticuloendothelial cells. The morphological changes seen in erythrocytes due to iron deficiency reflect severely impaired hemoglobin synthesis. These changes are characterized by hypochromasia (paleness) and microcytosis (smaller-than-normal red blood cells). Additionally, hemoglobin-deficient erythroid precursors are thought to undergo extra cell divisions to achieve adequate levels of cytoplasmic hemoglobin, which further exaggerates microcytosis. [1,2,3,13,18]

Normocytic normochromic erythrocytes contain approximately one-third of hemoglobin. However, in animals with iron deficiency anemia, red blood cell indices show progressive decreases in mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and mean corpuscular volume. Early stages of iron deficiency may go unnoticed, as the anemia can initially appear normocytic and normochromic. Nevertheless, examining the erythrogram and reticulocyte count, along with newer parameters such as reticulocyte hemoglobin content, may provide earlier indications of iron deficiency anemia once these tests become available in canine and feline commercial laboratories. Initially, there may be reticulocytosis due to increased production and release of reticulocytes as a response to anemia. However, as iron stores deplete and iron deficiency becomes more severe, the absolute reticulocyte count may no longer be adequate for the level of anemia. Additionally, due to insufficient heme and reduced hemoglobin synthesis, red blood cells can become more fragile, potentially leading to mild hemolysis and exacerbating the anemia. [4,6,13,19]

Functional iron deficiency can occur in disease states when iron is unavailable for heme synthesis, even though there are normal to increased levels of body iron stores. One example of this is anemia of inflammatory disease, which may be confused with iron deficiency anemia based on blood tests. In this condition, serum iron levels decrease due to iron being sequestered in the liver, spleen, and bone marrow. This leads to functional iron deficiency, defective heme synthesis, and the production of microcytic and possibly hypochromic erythrocytes despite having adequate iron stores in the body. Animals suffering from chronic renal disease often develop anemia, which is typically normocytic, normochromic, and non-regenerative. This type of anemia is primarily caused by a reduced synthesis of erythropoietin by the kidneys. Additionally, chronic low-grade gastrointestinal bleeding that results in iron loss, along with anemia of inflammatory disease, can also play a role in this process. Treatment with recombinant human erythropoietin may further limit iron reserves, thus impairing erythropoiesis stimulated by erythropoietin. In dogs with congenital portosystemic shunts, microcytosis, hypochromasia, and low serum iron concentrations have been observed, although these features are not typically seen in other liver diseases. The exact cause of this apparent functional iron deficiency is not well understood, but it is likely a direct consequence of the portosystemic shunt. These abnormal features tend to normalize after surgical intervention. Rare genetic defects in the regulation of ferroportin and hepcidin have been reported to cause iron refractory iron deficiency anemia in humans, though such cases have not been documented in animals. However, a currently unpublished case involving a cocker spaniel has been identified by the authors, which involves a defect in the hepcidin regulator known as *Tmprss6*. [1,2,3,4,10,12,14,20,21]

Physical examination findings

Clinical signs of anemia in dogs and cats can vary widely and may result from the underlying disease process, anemia itself, or both. Since iron deficiency anemia develops gradually, many pets can adapt and compensate, often exhibiting only mild symptoms like pallor, even in severe cases. Significant clinical signs typically do not emerge until the anemia is severe, and they can include lethargy, decreased

exercise tolerance, weakness, weight loss, stunted growth, and general malaise. While these signs are common in any type of anemia, the development of pica (the urge to eat non-food items) is unique to iron deficiency anemia. The clinical signs are thought to stem not only from the anemia but also from a deficiency of iron-containing proteins such as myoglobin, cytochrome c, and various metabolic enzymes. Additionally, indications of blood loss, such as melena (dark, tarry stools), hematuria (blood in urine), or bleeding from other sites, may be observed by pet owners or noted during a veterinary examination. [1,3,6,10]

Physical examination results may appear normal, except for signs of pallor, or they may indicate an underlying disease process. The presence of fleas, other ectoparasites, or hemorrhagic skin lesions can be observed. In cases of severe anemia, bounding pulses, arrhythmias, and a systolic heart murmur may be noted. Melena or hematochezia may be discovered during a fecal examination, a digital rectal examination, or when using a thermometer, but these symptoms may only be visible intermittently. Animals are typically normovolemic or may even be slightly hypervolemic. While some animals can develop significant compensatory cardiomegaly to increase cardiac output, symptoms such as tachypnea and tachycardia are uncommon in cases of iron deficiency anemia. [10]

Diagnostic approach to iron deficiency anemia

The diagnostic process for iron deficiency anemia involves identifying the underlying cause or trigger through a comprehensive history, physical examination, and diagnostic evaluation. The patient's history should include a detailed review of medications, diet, existing medical conditions, stool characteristics, flea and tick exposure, and careful questioning of the owner about potential sources of blood loss. Minimum diagnostic tests, such as fecal examinations for color and endoparasites, microscopic blood smear evaluations, packed cell volume assessments, and total protein measurements, may be sufficient for diagnosing juvenile anemic animals with suspected ectoparasite and/or endoparasite infestations. However, in many cases, further diagnostic evaluations are necessary. These may include a complete blood count (CBC) with reticulocyte count, fecal occult blood tests, serum iron parameters, coagulation parameters, a biochemical profile (which includes albumin, globulins, and liver and kidney function tests), urinalysis, and abdominal imaging. Animals experiencing chronic blood loss often exhibit significant reactive thrombocytosis, which may exceed 1 × 10^6/μL. The mechanism causing this condition remains unclear. Additionally, decreased neutrophil production due to iron deficiency may lead to neutropenia, although the underlying mechanism for this is also unknown. [6,10,22]

If melena or hematochezia is not apparent and no blood loss can be detected, fecal occult blood tests should be conducted. Various commercial tests are available to identify occult blood in feces that may not be visible through visual inspection. However, false positive results can occur with oral iron supplementation and meat-based diets, while they are much less likely with commercial animal diets due to the presence of dietary myoglobin, hemoglobin, or plant peroxidases. To accurately interpret the results, it may be necessary to withdraw iron supplementation and meat-based diets for three days. Additionally, a fecal occult blood test may return negative if gastrointestinal bleeding is intermittent. Therefore, repeated testing and a color assessment by the owner are recommended in cases of elusive iron deficiency anemia. In some instances, serum total protein levels may also be low due to the concurrent loss of plasma. [23,24]

Iron status is further assessed by measuring serum iron parameters. In animals with iron deficiency anemia, serum iron concentration is typically very low. However, mildly low to low-normal serum iron values can also be seen in cases of anemia associated with inflammatory diseases. [3,13] Serum iron levels can be temporarily increased due to the lysis of red blood cells within the bloodstream, recent blood transfusions, or iron supplementation. These factors can complicate the interpretation of laboratory results. Additionally, corticosteroids administered externally have been shown to raise serum iron levels through an unclear mechanism. The total iron-binding capacity (TIBC) measures the plasma's ability to transport iron and indicates the maximum amount of iron that can be bound by transferrin in the plasma. Although this test is often included in an iron panel, it has limited clinical value in small animals since it does not evaluate serum or tissue iron levels, nor does it change significantly during disease. Iron saturation (IS) indicates the percentage of iron bound to transferrin and is typically low (< 20%) in cases of iron deficiency anemia. Lastly, the unsaturated iron-binding capacity (UIBC) measures the available

binding sites on transferrin, which are elevated in iron deficiency anemia.. [25]

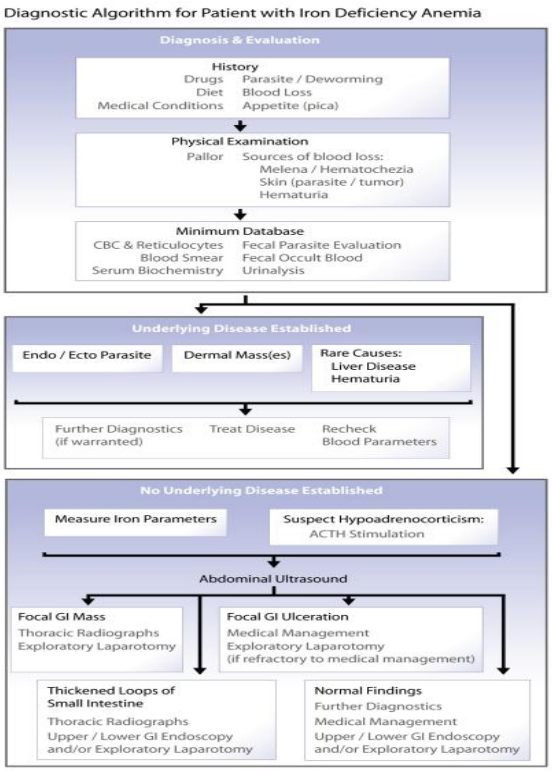

Figure 2. Diagnostic algorithm for a patient with iron deficiency anemia.

Table 1. Expected serum parameters in iron deficiency anemia and anemia of inflammatory disease

Inflammatory disease	Iron deficiency anemia	Anemia of inflammatory disease
Hematocrit	↓ to ↓ ↓ ↓	↓ to ↓ ↓
MCV	↓ to ↓ ↓ ↓	Normal to ↓
MCHC	↓	Normal
Serum iron	↓ to ↓ ↓ ↓	Normal to ↓ ↓
Serum TIBC	Normal to ↑	Normal to ↓
Serum ferritin	↓ to ↓ ↓	Normal to ↑ ↑
Stainable iron in the marrow	Absent	Normal to ↑
Reticulocytes	Normal to ↓	↓

Ferritin is a protein found in serum that serves as a reliable indicator of the body's iron stores. However, since the ferritin assay is specific to each species, it is not widely available for all animals. Ferritin levels decrease in cases of iron deficiency anemia, while they increase when there are elevated total body iron stores. Additionally, ferritin functions as an acute-phase protein, meaning that hyperferritinemia can occur in the presence of certain underlying conditions, such as inflammatory diseases, cancers, liver disorders, or hemolytic diseases. Despite this, low serum ferritin concentrations can effectively differentiate iron deficiency anemia from anemia caused by inflammatory diseases. [3,13,25].

Body iron stores can be assessed qualitatively by staining aspirates, impression smears, or biopsy sections taken from the liver, spleen, or bone marrow using a Prussian blue stain. Furthermore, iron concentration can be quantified in biopsy samples from tissues such as the liver and spleen. However, these methods are invasive and are typically not used in cases of known iron deficiency anemia. If iron is detected in these samples, it can help rule out iron deficiency. It's important to note that healthy, non-anemic cats with proper iron homeostasis usually do not have stainable iron in their bone marrow. [3,28]

Diagnostic imaging may be necessary to investigate iron deficiency anemia further. An abdominal ultrasound is recommended to visualize the abdominal organs and evaluate the gastrointestinal tract for any signs of ulceration, wall thickening, or masses. Common gastrointestinal tumors that can lead to ulceration and chronic blood loss include leiomyoma, leiomyosarcoma, carcinoma, and round-cell tumors. If a primary gastrointestinal issue is suspected and no abnormalities are found through abdominal imaging, gastroduodenal or colonic endoscopy (or both) may be required to check for ulceration and to obtain biopsies. Additionally, an exploratory laparotomy may be indicated in some cases. [1,4]

Therapeutic approach to iron deficiency anemia

The general principles for treating animals with iron deficiency anemia include preventing further blood loss, correcting the anemia when it is severe, starting iron supplementation, and addressing any underlying diseases. Animals with severe anemia may not display significant clinical signs initially, but they can quickly deteriorate shortly after arriving at the clinic. Therefore, they should be handled with caution. A blood transfusion may be necessary before receiving results from diagnostic evaluations if the animal is severely anemic and showing signs of hypoxemia. Blood samples for a complete blood count (CBC), as well as ideally a serum biochemical profile, coagulation profile, and iron parameters, should be collected before administering a blood transfusion. It is best to slowly administer compatible packed red blood cell products, but fresh or stored whole blood can also be transfused gradually. It is important to

note that fluid overload can easily occur in these animals due to rapid or excessive blood transfusions or intravenous fluid administration, as they are typically normovolemic or even hypervolemic. This differs from patients experiencing acute to peracute blood loss anemia, where fluid resuscitation is appropriate. [1,29]

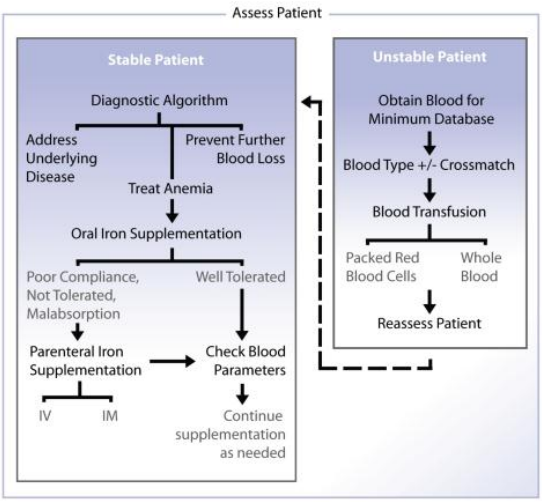

Figure 3. Diagnostic approach to a patient with iron deficiency anemia.

Transfusions of red blood cell products can effectively address anemia and provide a good source of bioavailable iron. There is no specific transfusion trigger; compared to other causes of anemia, animals with iron deficiency can tolerate even severe anemia well unless they are stressed or challenged. Therefore, blood transfusions are primarily indicated in cases of severe anemia that lead to tissue hypoxia to stabilize a decompensated patient or before general anesthesia and surgery in animals with moderate to severe anemia. The amount of packed red blood cells to be transfused can be calculated as follows:

Volume to be transfused (ml)= desired packed cell volume (PCV) x body weight (Kg)

Blood transfusions are associated with certain risks, including acute hemolytic reactions, hypersensitivity reactions, hemolysis, transmission of infectious diseases, and volume overload. Before administering a first transfusion, it is essential to perform blood typing: use dog erythrocyte antigen (DEA) 1.1 for dogs and AB blood typing for cats. This ensures that compatible blood donors are selected. If the animal has had a prior transfusion, it's crucial to conduct both a major and minor cross-match test to verify blood compatibility. There are no specific guidelines that dictate when a transfusion is necessary; the decision should be based on clinical and laboratory evaluations of the patient. [1,30]

Iron supplementation is typically necessary to restore iron balance in the body and should be guided by several factors, including the severity of anemia, the underlying cause, red blood cell count, serum iron levels, and the morphology of erythrocytes. These same parameters are also used to assess the ongoing need for additional iron supplementation. While supplemental iron is effective in treating iron deficiency anemia, it is not recommended for other types of anemia and may even be harmful due to the risk of iron overload. Iron can be administered to animals via supplemental iron products, which can be given orally or through injections, including blood transfusions. [10]

In stable patients, oral iron therapy is generally preferred over parenteral iron administration in small animals due to its low cost and higher safety profile. Both ferrous and ferric forms of iron are available, but only the ferrous form is recommended because of its superior absorption. Ferrous sulfate is the most commonly used option, although ferrous gluconate and fumarate can also be utilized. When determining the dosage, it's important to note that published doses may be expressed in terms of either milligrams of iron salt or elemental iron. The recommended dosage for ferrous sulfate is 15 mg of iron salt per kg of body weight (which equates to 5 mg of elemental iron per kg), divided and administered every 8 to 12 hours. One common side effect of oral iron supplementation is gastrointestinal irritation, which can be minimized by dividing the daily dose into several smaller doses. It's also important to be aware of drug interactions with iron, as it can bind to certain medications, such as tetracycline, reducing the effectiveness of both. If these medications need to be given together, they should be administered several hours apart. Additionally, the bioavailability of iron is decreased when taken with antacids, eggs, or milk, so these should also be avoided if iron supplements are to be taken effectively. [4,10,31]

Parenteral forms of iron, apart from red blood cell products, can be administered under certain conditions, such as when oral supplementation causes side effects, is ineffective due to malabsorption, when the animal is vomiting, or if there are compliance issues. Additionally, a single dose of iron may be given parenterally before starting oral supplementation. Iron dextran, when given via intramuscular injection, is primarily absorbed by the

lymphatic system, with approximately 70% of the iron being absorbed from the injection site within a few days. For dogs, iron dextran can be administered at a dose of 10 mg of elemental iron per kg of body weight weekly, while for cats, a dose of 50 mg can be given once every 3 to 4 weeks. It is advisable to start with a small dose first, as hypersensitivity reactions can occur. Other potential side effects from intramuscular iron administration include irritation and pain at the injection site. [4,10,31,32]

Administering intravenous iron in dogs and cats is uncommon, though it is more frequent in humans. Several intravenous iron preparations are available for human use, including iron gluconate, iron sucrose, iron dextran, and ferric carboxymaltose, with iron sucrose being considered the safest option. In human patients, an initial test dose is given, and if there are no adverse effects, the remaining dose is administered over several hours. Rapid infusion can lead to adverse reactions such as hypotension, tachycardia, dyspnea, and phlebitis. Currently, there is no established intravenous iron dosage for dogs and cats. However, based on anecdotal evidence, a weight-proportional dose similar to that used in humans—approximately 10 mg of elemental iron per kg of body weight—administered roughly once every three weeks is likely to be both effective and safe. [1,33]

It may take several months of iron supplementation for red blood cell parameters to return to normal. Treatment should continue even after these parameters normalize, as it takes much longer for the body's iron stores to be fully replenished. While serum iron levels might be normal or even high during active iron supplementation, it is important to closely monitor red blood cell indices to evaluate the response to therapy and to confirm the resolution of functional iron deficiency. After completing iron supplementation, assessing body iron stores is typically not performed. However, measuring serum ferritin and other iron parameters is advisable to ensure that iron levels have normalized. [1,14]

CONCLUSION

In conclusion, iron is an essential element that plays a crucial role in various metabolic functions, particularly in oxygen transport through hemoglobin. Iron deficiency anemia often develops due to chronic blood loss after the body's iron stores have been depleted. This condition is characterized by the presence of microcytosis and hypochromasia, along with insufficient regeneration and low levels of serum iron, iron saturation, and ferritin. If iron deficiency is not treated, it may progress to severe anemia, which many animals can surprisingly tolerate well unless they experience stress. Samples for diagnostic testing should be collected before initiating any treatment. Therapy for iron deficiency anemia involves preventing further blood loss, providing oral and/or parenteral iron supplementation, and addressing the underlying disease. With appropriate treatment, patients with iron deficiency anemia can have a positive prognosis, provided that the underlying condition is managed effectively.

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