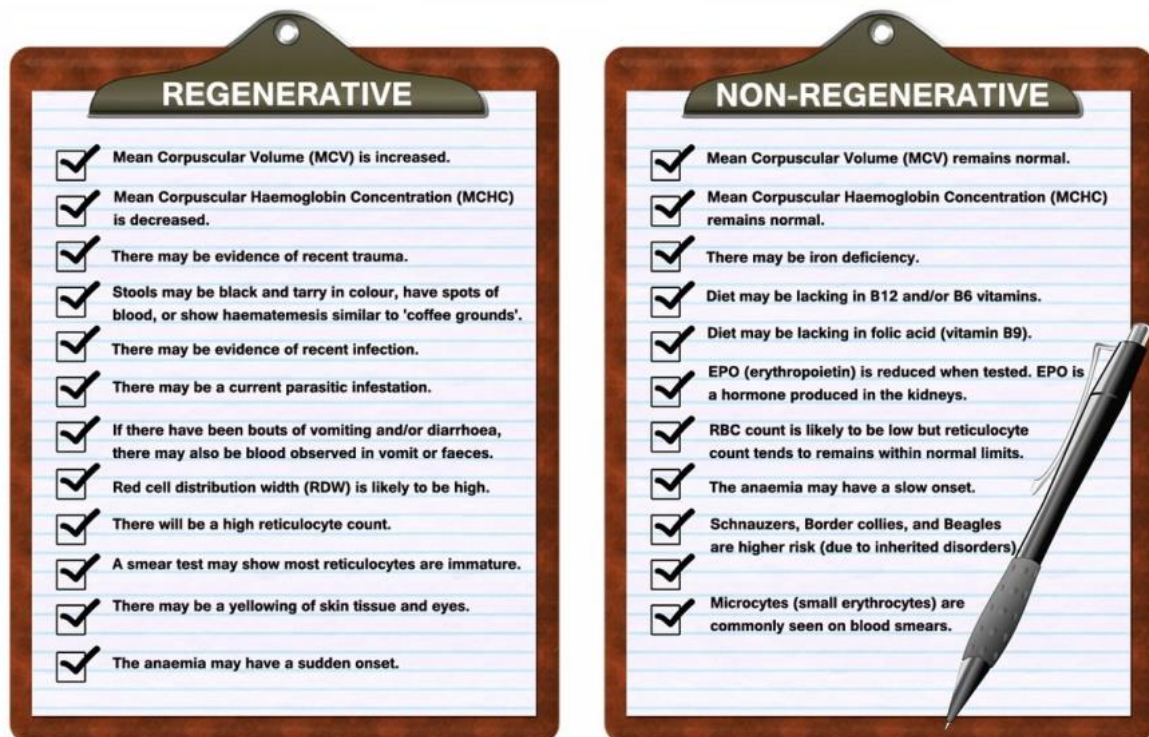


# Anaemia in Dogs with Chronic Kidney Disease

Anaemia is one of the frequent complications of kidney disease. The problem is it often occurs in the background and without any necessarily visible physical symptoms in the early stages. But it swiftly deteriorates if left untreated, adversely affecting just about every system of a dog's body. Recognising the fact that anaemia is present and obtaining the right treatment for the type occurring is crucial to the ongoing proactive management of the kidney disease itself.

## The Difference Between Regenerative and Non-Regenerative Anaemia



Anaemia occurs when there is an interruption to red blood cell (RBC) production in bone marrow, or when it increasingly becomes restricted or when it stops completely – or when these cells don't survive long enough in circulating blood and are not replaced by new ones to perform the vital role they have in maintaining good health. In canine kidney disease, dehydration often exacerbates the problem, because it masks the fact that anaemia is occurring. The lack of RBCs means oxygen is not carried to other body systems and organ cells, resulting in these systems underperforming and a slow deterioration of organ function. The heart and circulatory system are often critically affected when anaemia progresses, sometimes causing heart murmurs and other cardiac problems.

Anaemia more typically causes dogs to become increasingly lethargic, depressed, weak, and easily fatigued during or after minimal exercise. They commonly lose weight, show a heightened intolerance of cold conditions and are likely to have a rapid pulse and increased breathing rate. Additionally, bouts of fainting and seizures are typical events in later stages.

There are actually 400 different types of anaemia, which fall into 7 different classification groups. While most of these are irrelevant in terms of chronic kidney disease, owners must appreciate we are only describing those anaemias that pertain to or are commonly associated with renal disease. A veterinarian should always be consulted in all cases of suspected anaemia. There are a number of blood test references, blood composition and bodily components I will discuss throughout this article – and these include:

**Albumin** is a simple form of protein (like egg-white) found in blood serum.

**BUN** stands for Blood, Urea, Nitrogen, and is a measure of serum urea, a by-product of the breakdown of blood, muscle and protein.

**Creatinine** is a chemical waste molecule that is generated at the rate of 2% a day from muscle metabolism. Creatinine is transported through the bloodstream to the kidneys.

**Dehydration** is low circulating blood volume or negative fluid balance, which occurs when the body loses more fluid than it takes in.

**Erythropoietin (EPO)** is a hormone secreted by the kidneys in varying amounts depending on the need for red blood cells to be manufactured in bone marrow. The trigger for increased EPO comes primarily from falling levels of oxygen in tissues.

**Haematocrit (HCT)** is the ratio of red blood cell volume to the total volume of blood when it is tested.

**Haemoglobin (Hg)** is a red protein responsible for conveying oxygen in the blood.

**Haemolytic Anaemia** is a condition in which red blood cells are destroyed and removed from the bloodstream before their normal lifespan is over.

**Oedema** is an unhealthy build-up of fluid in the body which causes the affected tissue to become swollen.

**Packed Cell Volume (PCV)** is the percentage of red blood cells in circulating blood.

**Plasma** is the yellowish coloured liquid part of blood containing suspended blood cells, making up about 55% of the body's total blood volume.

**Pulmonary Oedema** is fluid accumulation in the tissue and air spaces of the lungs.

**Red blood cells (RBCs)** are concave disks in blood that contain oxygen-carrying haemoglobin.

**Reticulocytes** are young and immature red blood cells that have no nucleus.

**Urea** is a compound and the main nitrogenous by-product of protein metabolism that is cleared by the kidneys.

## **Why does anaemia occur?**

Different types of anaemia occur for various reasons in canine kidney disease. For example, blood loss through internal haemorrhage or trauma commonly causes 'regenerative anaemia'. Once the bleed has been satisfactorily treated, the ongoing creation of new replacement RBCs will usually solve the anemia. Blood loss might be due to an injury, a ruptured stomach ulcer, gastrointestinal irritation, or following prolonged periods of vomiting or diarrhoea. Prompt treatment to resolve the haemorrhage is critical under such circumstance because any delay will also adversely affect kidney function.

Diet can also play a role in causing anaemia. A lack of vitamin B12 and B6, Vitamin E, iron, niacin, riboflavin or folic acid inhibits RBC production in the bone marrow. Anticonvulsant drugs (typically given to dogs having seizures) and other medications that interfere with Vitamin B12 absorption are also known to cause anemia on occasions.

Low RBCs and anaemia have a direct connection to chronic kidney disease as the primary health concern. This commonly occurring secondary condition is known as non-regenerative anemia, whereby there is insufficient or zero RBC production. As RBCs have a short life-cycle of about 120 days, the volume of these cells in circulating blood continually reduces until there aren't enough to support the vital functions they need to undertake. While RBC counts are typically low in non-regenerative anaemia, the reticulocyte count invariably remains within normal limits.

But what is it about kidney disease that prevents adequate RBC production in the bone marrow?

The kidneys are responsible for producing a hormone called erythropoietin (EPO). In turn, EPO controls the manufacture of RBCs in bone marrow. When compromised kidneys cannot produce enough EPO, then reduced or zero RBC production is the result – and then non-regenerative anaemia occurs. Also, the increase of blood urea and other nitrogenous waste compounds (uraemia) usually eliminated by the kidneys also have the effect of shortening the life of RBCs, thus compounding the problem.

Chronic kidney disease also typically riddles a dog's body with inflammation – and the inflammation contributes to anaemia by creating a relative iron deficiency, which in turn makes iron unavailable for red blood cell production.

## **How can we identify anaemia in the early stages?**

The priority for owner and vet is to detect that anaemia is present - and then for the vet to clarify which type it is. Different types involve different treatments. The wrong treatment approach can make the anaemia worse and further reduce kidney function, so it's essential to get this right.

Initially, owners will see the ordinarily rich pink gums of their dog turn to a pale almost white pink. This change in colour is due to a lack of oxygenated red blood cells reaching the mouth. There will ordinarily also be a marked increase in lethargy and fatigue, along with some weakness of the legs and loss of balance. Dogs may be seen to shiver as their tolerance of cold environments decreases.

When anaemia is due to blood loss along the gastrointestinal tract, owners may see a darkening of stools and evidence of blood in diarrhoea or vomit. Iron deficiency related anaemia may first show as patchy jaundice (yellowing) of the eyes and skin.

As the anaemia worsens, short fainting spells and rapid breathing may develop along with an increase in the heartbeat. Dogs are likely to appear depressed, disinterested in their surroundings and the people around them, and generally 'out of sorts'. While some of these warning signs may already prevail due to the kidney disease, other pertinent symptoms convey to the owner that it's time to visit the vet.

### **Veterinary diagnosis and treatment**

Vets will want to undertake a Complete Blood Count to confirm anaemia is present. A low red blood cell (RBC) count is indicative of the condition, but not conclusive. Low haemoglobin (Hg) and haematocrit (HCT) levels will help support the diagnosis, but it's the Packed Cell Volume (PCV) count that is critical to determining anaemia in dogs. Anaemia is confirmed when PCV falls below 35%.

In regenerative anaemia, the body releases an increased volume of reticulocytes to try to correct the problem. This response is typical when trauma or other severe blood loss has caused the condition. These are immature red blood cells produced in the bone marrow. Reticulocytes are also seen on a blood smear, and this test is beneficial as it will occasionally also help find blood parasites responsible for destroying RBCs. A smear test might also show abnormal cells suggesting possible leukaemia.

Vets will commonly also want to test and check a dog's faeces for signs of parasites, as these can cause blood loss and significant anaemia.

When the vet is able to discount blood loss due to trauma and other possibilities, they will want to consider whether kidney disease is affecting EPO production (and therefore, the creation and management of circulating red blood cells). While this is the most likely cause of anaemia in dogs suffering from chronic kidney disease, it is crucial to explore other possibilities and discount them to prevent inappropriate and potentially damaging treatments starting. There is now a specific EPO blood test available for dogs, although not all vets may have immediate or easy access to it (depending on the efficacy of the surgery and the country of practice).

Approximately 85-90% of the body's EPO comes from the kidney, while the liver contributes 10-15%. The diseased kidneys consequently hinder the vast bulk of EPO production. When the laboratory blood test identifies low EPO production, it is logical to assume that treatment with replacement human EPO (created using recombinant DNA technology) will increase RBC production and resolve the anaemia. Unfortunately, this is not always the case, as it also depends on whether the bone marrow is capable of generating these blood cells after being stimulated to do so. Another worrying consideration is the fact that most replacement EPO like Epogen, Procrit, and Eprex originate from human variants of the hormone and a dog's immune system will commonly attack it as an alien body. That is bad enough on its own but, once triggered, the immune system response also tends to target the dog's own EPO as well, making the anaemia worse.

A new synthetic form of EPO has proved somewhat more successful. Darbepoetin (Aranesp) has no human albumin, so is less likely to invoke an immune system response, and it requires less frequent

administration. The consensus for starting treatment with Darbepoetin is when PVC or haematocrit (HCT) falls to a threshold of 20% or below. The downside of Darbepoetin treatment is that it's more expensive, but as it doesn't need using quite so often there is a reduction in the higher cost of longer-term treatment. More importantly, various studies and test treatment programs conducted suggest it is a much safer alternative for dogs. Management of the anemia with Darbepoetin usually takes 2 to 3 weeks before a positive blood-test response occurs. The goal is to increase PCV to 30% and then continue at a reduced Darbepoetin dose every two or three weeks with close PCV monitoring. The aim is to keep reducing the dose until it maintains a consistent and healthy PCV level (37%-55%).

It is worth noting that abnormally high or low levels of calcium in blood testing (hypo or hypercalcemia) and abnormal parathyroid hormone levels can adversely affect the success rate of using EPO supplementation. If these levels cannot be normalised it will inhibit EPO use in the bone marrow.

Iron is a necessary supplement for Darbepoetin injections, so the bone marrow has all the building block components needed for RBC production. However, iron overdose is a real possibility and can result in cellular oxidative stress (the cause of many serious illnesses), so guarded use and regular testing of iron levels are highly recommended. It is also crucial that vets closely monitor blood pressure because this can increase during treatment due to augmented RBC and plasma volume.

### **Can fluid therapy cause anaemia?**

Fluid therapy is a standard treatment for canine kidney disease when creatinine and BUN are high in blood tests. While it doesn't generally create the circumstances for anaemia to develop, it does have some relevance in conversely helping prevent anaemia. Dehydration and anaemia tend to occur together, so it is vital that dogs suffering from kidney disease are always adequately hydrated. When using fluid therapy, it is also important to make sure the dosage of daily fluids is right for the weight of the dog and the degree of serum-creatinine abnormality.

Michael Schaer, DVM, mentioned the danger of some vets misinterpreting symptoms in his address to the World Small Animal Veterinary Association World Congress: *'Intravenous fluids are sometimes used excessively in the anemic patient when the decrease in red blood cell mass is misinterpreted as total blood volume depletion, when in fact the plasma volume might even be expanded. To compensate for decreased tissue oxygen delivery, the heart rate increases, and if these patients are subjected to large fluid volumes over a short period of time, pulmonary oedema can occur.'*

Owners are probably wise to question a vet that suggests fluid dosing higher than the recommended regime, and particularly when anaemia is present as one of the secondary conditions of kidney disease. Pulmonary oedema (presenting asymptotically as laboured breathing) is a common symptom of fluid-overload.

Professor Maxey L Wellman, DVM, of the Ohio State University explains: *'Assessing hydration status is important in the interpretation of the PCV or HCT because relative anaemia can occur with overhydration and anaemia may be masked by dehydration.'*

### **Can certain medications cause anaemia?**

Nonsteroidal anti-inflammatory drugs (NSAIDs) are often prescribed to control pain and inflammation in dogs. In addition to these medications being associated with gastrointestinal ulcers and perforations, stomach or intestinal bleeding, as well as causing liver and kidney toxicity, their adverse effects can also cause anaemia (particularly iron-deficiency anaemia).

Anabolic steroids such as Stanozolol and Nandrolone are sometimes used to treat anaemia, improve appetite and promote weight gain – but they are not recommended as they are unlikely to resolve the anaemia or cure the complications of chronic kidney disease, but are likely to cause liver toxicity.

Cephalosporins (a class of antibiotics with trade names Biocef, Keflex and Keftab) are known to cause haemolytic anaemia on occasion. These antibiotics are commonly prescribed to treat bacterial infections of the skin, bones, joints, bladder, pneumonia and respiratory tract in dogs. Aspirin, ibuprofen, phenylbutazone and naproxen and pyroxicam can all cause irritated ulcers of the stomach and intestines to bleed profusely, resulting in anaemia.

### **In Conclusion**

Anaemia is a common secondary condition that occurs all too often in dogs suffering from kidney disease. Although non-regenerative anaemia is the more likely type to happen, proper diagnosis is crucial otherwise treatment using EPO will prove counterproductive. Recognising that anaemia is occurring involves the joint effort and duteous observation of both dog owner and vet – but that is just the start of the challenges that lie ahead to resolve it. Early diagnosis means treatment can begin promptly, creating the opportunity for a more positive outcome.

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