



Erythrocytosis in Dogs and Cats: Diagnosis and Management

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ABSTRACT:

Erythrocytosis in dogs and cats has various causes. Relative erythrocytosis is associated with a normal red blood cell (RBC) mass, whereas absolute erythrocytosis (primary and secondary) is characterized by increased numbers of RBCs. Primary erythrocytosis is a rare myeloproliferative disease of dogs and cats and is somewhat similar to polycythemia vera in humans. Secondary erythrocytosis is often associated with renal neoplasia but may also occur with other neoplasms, hypoxic cardiopulmonary disease, high-altitude environment, hyperadrenocorticism, and severe obesity. Abnormalities in erythropoietin (EPO) regulation and concentration are associated with the absolute forms of erythrocytosis. Measurement of serum EPO levels in animals may be helpful, but lack of species-specific assays for the dog and cat may limit the clinical utility of currently available tests. Long-term survival of both dogs and cats with primary erythrocytosis may be realized by treatment with intermittent phlebotomy and hydroxyurea. Successful therapy for secondary erythrocytosis depends on identification and treatment of the underlying cause.

Erythrocytosis, also called *polycythemia*, is defined as an increase in the red blood cell (RBC) count, packed cell volume (PCV), and hemoglobin concentration. Older terms (e.g., polycythemia [rubra] vera, Gaisböck's syndrome, spurious polycythemia, pseudopolycythemia, erythrocythemia, stress polycythemia) often refer to a specific form of erythrocytosis and are considered archaic, although polycythemia is firmly entrenched in the medical literature. Erythrocytosis has been reported in both dogs and cats,¹⁻²⁰ and excellent reviews of polycythemia have been published.²¹⁻²⁵

Erythrocytosis can be classified by descriptive and etiologic classifications (Figure 1, Table 1). Erythrocytosis is usually either relative or absolute. Absolute erythrocytosis is either primary or secondary, with secondary causes further defined as physiologically appropriate or inappropriate. Primary erythrocytosis (polycythemia vera

[PV]) has been reported in dogs^{1-3,5,7,14,15} and cats.^{12,16-19} Although appropriate erythrocytosis associated with cyanotic heart disease has been reported in dogs,^{11,26,27} most cases of absolute erythrocytosis are secondary, inappropriate, and usually attributed to underlying neoplasia, often of renal origin.^{4,6,8-10,13,20}

NORMAL PHYSIOLOGY

Oxygen transport is the primary function of RBCs. Erythroid precursors in the bone marrow, primarily colony-forming unit erythroid cells, are stimulated by the hormone erythropoietin (EPO) to undergo growth and maturation to maintain an RBC mass capable of providing optimal oxygen delivery to body tissues. In normovolemic dogs, optimal oxygen delivery occurs with a PCV of 40% to 45%²³; however, alterations in blood volume, cardiovascular status, hemoglobin structure, and oxygen dissociation curve can significantly influence tissue oxygenation independent of the measured PCV.

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Breed differences are known to occur, with greyhounds and dachshunds often having higher values.²⁴ In cats, this number is slightly lower (35% to 45%), probably because of the smaller size of the feline erythron.

The site of origin of EPO has been debated. Although some controversy still exists, the kidney is the site of physiologically significant EPO production in mammals.²⁸ Two morphologically distinct cell types reside within the renal interstitium:

- **Type 1 (stellate) cells**, the interstitial fibroblasts, are presumed responsible for EPO production.
- **Type 2 cells** appear more lymphocytic and are thought to function in antigen presentation because of the expression of cell surface major histocompatibility complex molecules.

Type 1 cells reside at the level of the proximal convoluted renal tubule of the deep cortex and outer medulla and express cytoplasmic dendritic-like processes that contact both the renal tubule and the peritubular capillary. An abundance of rough endoplasmic reticulum suggests that these cells are synthetically active. The location of these cells, which are physiologic oxygen sensors, is considered both anatomically and functionally significant. At this level within the renal cortex, oxygen consumption is high and oxygen tension falls to 40 to 50 mm Hg. As oxygen tension declines (i.e., in hypoxia), a strategically placed sensor in this metabolically active region serves to protect function by increasing EPO production, with a subsequent increase in RBC numbers and a concomitant increase in oxygen-carrying capacity.²⁹⁻³⁴

ERYTHROPOIETIN

EPO is a heavily glycosylated, 34-kD polypeptide hormone belonging to a large group of hematopoietic growth factors.^{34,35} As with most hormones, EPO production is governed by negative feedback control. Under normal conditions, hypoxia increases the renal synthesis of EPO, which, in turn, stimulates bone marrow erythropoiesis. The resultant increase in hemoglobin concentration increases oxygen-carrying capacity. Increased tissue oxygenation then reduces EPO production, with a corresponding decrease in erythropoiesis. These controls serve to maintain an optimal RBC mass for adequate oxygen delivery to body tissues. The half-life of canine EPO is 6 to 9 hours.³⁶ Human, canine,^{37,38} and feline³⁹ EPOs have been sequenced, but only recombinant human EPO (rh-EPO) is commercially available

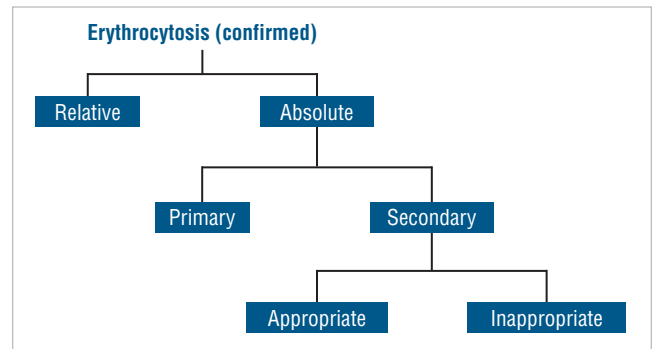


Figure 1. Descriptive classification of erythrocytosis.

(Epogen, Procrit [both epoetin alfa], Amgen). This product is widely used in both human and veterinary medicine to treat a variety of anemias, most often those associated with chronic renal failure or antineoplastic chemotherapy. Although the biologic activity of EPO from other mammalian species is similar to that of human EPO, there are species-specific antigenic differences. Dog EPO and cat EPO show an 85% sequence homology to human EPO.³⁹ Long-term use of rh-EPO in cats is known to result in anti-EPO antibody formation, with a resultant loss of effectiveness and a decline in RBC indices, although iron deficiency and impaired iron utilization (functional deficiency) caused by accelerated EPO-mediated erythropoiesis have also been suggested as causes of EPO-refractory anemia.^{40,41} These antigenic differences are also problematic for the use of human-based assays to accurately determine serum EPO levels in dogs and cats.^{34,35}

Measurement of Erythropoietin

Determination of serum EPO concentrations may be useful in some cases in which the cause is not clearly defined after a thorough diagnostic search, although a definitive diagnosis based on EPO levels alone is rarely achieved. EPO samples should be obtained before phlebotomy to prevent misleading results caused by phlebotomy-induced increases in EPO secretion.⁴²

Accurate measurement of EPO concentration in veterinary patients is an area of controversy and is complicated by the lack of commercial canine and feline species-specific EPO assays. EPO bioactivity has historically been evaluated by in-vivo and in-vitro bioassays. The cumbersome exhypoxic or hypertransfused polycythemic mouse assay used to detect increased EPO activity has remained the standard with which all other assays are compared. Although it is reliable for detecting

Table 1. Etiologic Classification of Erythrocytosis

Type	Cause
Relative	Dehydration, fluid redistribution Cutaneous loss (burns) Splenic contracture (dogs)
Absolute	
Primary	
• Primary erythrocytosis	Myeloproliferative disease
• Familial erythrocytosis	Genetic, autosomal dominant (humans)
Secondary	
• Appropriate: associated with hypoxic stimulus	Chronic respiratory disease Respiratory center depression Cyanotic heart disease Tetralogy of Fallot Right-to-left shunt Reverse patent ductus arteriosus Ventricular septal defect (i.e., Eisenmenger's complex) Atrial septal defect Aorticopulmonary window High-altitude environment Hemoglobinopathy (methemoglobin reductase deficiency) Severe obesity (pickwickian syndrome) Decreased 2,3-diphosphoglycerate levels
• Inappropriate: no hypoxic stimulus	Neoplasia Renal carcinoma Renal lymphoma Nasal carcinoma Central nervous system tumors Hepatic tumors Cecal leiomyosarcoma Uterine leiomyoma Ovarian carcinoma Pheochromocytoma Adrenocortical adenoma or adenocarcinoma Adrenal hyperplasia Renal disease Renal cysts Hydronephrosis Renal transplantation Pyelonephritis (dog)
Iatrogenic	Overzealous blood transfusion Exogenous EPO therapy

biologically active EPO, it is also labor-intensive, not widely available, expensive, and not sensitive enough to measure EPO levels in normal serum.³⁴ In-vitro bioassays using murine hematopoietic cell cultures to detect physiologically active EPO in test substances were reported^{23,34}; however, these assays provided conflicting

results in dogs, and their accuracy can be negatively affected by nonspecific inhibitory substances in test serum.^{34,35}

In the clinical laboratory setting, hemagglutination assays, radioimmunoassays (RIAs), and enzyme-linked immunosorbent assay (ELISA)-based tests have been widely used in human medicine and have been used to measure EPO levels in dogs and cats.^{34,35,42-44}

The accuracy of these tests can be limited, however, by the weak cross-reactivity of species-specific EPO in assays using monoclonal antibodies against rh-EPO.^{34,35,42} At least two RIAs can identify canine EPO.³⁵ A human EPO ELISA developed in Germany is used by Dr. Urs Giger and colleagues at the University of Pennsylvania School of Veterinary Medicine. This assay has been correlated to detection of canine and feline EPO. At present, I prefer this assay for measuring EPO levels in dogs and cats. Clinicians submitting samples for EPO determination are encouraged to consult with their laboratory service before submission. Samples must be handled and shipped according to the requirements of the laboratory conducting the assay. It may take 2 to 4 weeks before a report is available.

In humans, patients with primary erythrocytosis typically have low EPO concentrations, whereas secondary erythrocytosis is associated with increased serum EPO levels. Studies of dogs and cats reported similar, but inconsistent, findings.^{34,35,42-44} EPO levels in healthy dogs ranged from 5 to 15 mU/ml,^{34,35} and those in cats, 5 to 22 mU/ml.⁴³ In other reported studies using different methodologies, EPO levels in healthy dogs were 1.3 to 13.4 mU/ml⁴⁴ and 7 to

37 mU/ml⁴²; in cats, the values were 1.9 to 22.9 mU/ml⁴⁴ and 9 to 38 mU/ml.⁴² Dogs with appropriate erythrocytosis caused by cyanotic heart disease had slightly to markedly increased EPO levels, and EPO levels were markedly increased in animals with inappropriate erythrocytosis. Those with primary erythrocytosis

had low or low-normal EPO levels.³⁵ One study investigated a commercially available human RIA kit in normal, polycythemic, and anemic dogs and cats. In all evaluated groups, considerable overlap of EPO values within the normal range was found, which limited the diagnostic use of this assay.⁴² A definitive explanation for the wide variation and unexpected EPO levels in both primary and secondary erythrocytosis in some animals is lacking. Possible explanations include misdiagnosis, cyclic EPO secretion, postphlebotomy measurement,⁴² or hyperviscosity-induced local ischemia resulting in further inappropriate EPO secretion. Dogs with hyperadrenocorticism and moderate increases in PCV (52% to 58%) have demonstrated normal EPO levels, which suggests that the PCV increase is not mediated by EPO.³⁴

Undoubtedly, as commercial sources of canine and feline EPO become available, the development of a

slows, resulting in distention of small vessels and capillaries and increasing the risk of hypoxia, thrombosis, and vessel rupture.^{9,21-23} Polyuria and polydipsia have been proposed to be linked to an erythrocytosis-induced disturbance of urine-concentrating ability by the kidneys,⁹ and impaired vasopressin release has been documented in two dogs.⁵⁰

Relative Erythrocytosis

Relative erythrocytosis in dogs and cats is associated with an elevated venous PCV but normal RBC mass. The most common cause is derangement in fluid balance leading to decreased effective plasma fluid volume, which is seen with decreased intake, severe dehydration, cutaneous losses (i.e., extensive thermal or chemical burns), or vascular redistribution such as hemorrhagic gastroenteritis. In dogs, strenuous exercise, excitement, stress, or severe pain can result in significant splenic

Erythrocytosis in dogs and cats has most commonly been associated with dehydration, high-altitude environments, and renal and cardiovascular disease.

highly sensitive species-specific EPO assay will allow routine determination of EPO in both species with less potential for overlap of values and will increase the clinical value of EPO levels in the diagnostic approach to erythrocytosis.

EPO, not unlike other hormones, may possess other functions. EPO receptors are widely distributed throughout the body, and potential nonerythropoietic functions are beginning to be discovered. Although discussion of the role of EPO as a protective agent against ischemia and reperfusion injury is beyond the scope of this article, interest in this role has increased, and references are provided for the interested reader.⁴⁵⁻⁴⁹

PATHOPHYSIOLOGY

Clinical signs of erythrocytosis include plethora (e.g., skin and mucous membrane erythema); polyuria; polydipsia; episodic bleeding diatheses (e.g., epistaxis, hematuria, melena, hematochezia, hematemesis); and central nervous system disturbances such as mentation changes (e.g., lethargy, dementia), posterior weakness, ataxia, blindness, and seizures.²¹⁻²³ Signs are the result of hyperviscosity caused by increased RBC mass. Blood flow

contracture. Injection of concentrated splenic RBCs into the vascular compartment can produce mild relative erythrocytosis. Because of feline anatomic and functional splenic differences (nonsinusoidal versus sinusoidal), this event is less pronounced in cats. The elevation in PCV is often modest (55% to 65%) and, although definitive diagnosis may require RBC mass determination, relative erythrocytosis is most often recognized at the physical and clinical evaluation. Resolution of relative erythrocytosis occurs after volume repletion or removal of the inciting cause.

Absolute Erythrocytosis: Primary Versus Secondary

Absolute erythrocytosis, defined by an increase in RBC mass, may be either primary or secondary. Primary erythrocytosis (i.e., PV) is a myeloproliferative disorder characterized by clonal proliferation of neoplastic erythroid stem cells that require little or no EPO for clonal expansion, growth, and differentiation. Normal negative feedback inhibition of erythrocytosis does not occur, and EPO levels are usually low or undetectable. In a distinct subset of humans, primary polycythemia is due to a

familial and congenital genetic mutation of the EPO receptor. This truncated EPO receptor protein mutation lacks the cytoplasmic negative regulatory portion, resulting in nonneoplastic primary erythrocytosis.^{51,52} To date, this disorder has not been recognized in veterinary medicine. Primary erythrocytosis is well characterized in humans, and stringent criteria that have been established and revised, primarily by the National Polycythemia Vera Study Group, must be fulfilled before the diagnosis of primary erythrocytosis can be assigned (see box on this page). In dogs and cats, primary erythrocytosis is considered a rare neoplastic disease of young to middle-aged animals without apparent sex or breed predilection.^{21,22} In contrast to the situation in humans, leukocytosis, thrombocytosis, increased leukocyte alkaline phosphatase, and increased vitamin B₁₂ and vitamin B₁₂-binding capacity have not been reported in either feline or canine cases. Although splenomegaly in veterinary patients has been reported, hepatomegaly, hypertension, and hyperuricemia have not. In veterinary medicine, therefore, the term *primary erythrocytosis* is more appropriate than *polycythemia vera*.

Secondary erythrocytosis is caused by altered regulatory activity or excessive production of EPO. If systemic hypoxia is present, the increased EPO production results in an increased RBC mass capable of increased oxygen-carrying capacity, which represents an appropriate, compensatory response. As outlined in Table 1, appropriate secondary erythrocytosis most often results from cardiovascular disease, chronic pulmonary disease, hemoglobinopathies such as methemoglobin reductase deficiency (rare in veterinary patients), decreased 2,3-diphosphoglycerate (2,3-DPG) levels in RBCs, high-altitude environments, massive obesity, or neurologic disease causing depressed respiratory center function and decreased alveolar ventilation. Elevated EPO levels are expected in these situations.

Inappropriate secondary erythrocytosis is characterized by increased EPO levels without evidence of a hypoxic stimulus. In both veterinary and human patients, neoplasia is considered the most common cause. Both benign and malignant tumors have been reported in humans and include neoplasms of the kidney, lung, liver, uterus, ovaries, adrenal glands, thymus, and central nervous system. Renal cysts, hydronephrosis, and renal transplantation have also been reported as causes in humans. In the veterinary literature, most cases have been neoplastic in origin. Inappropriate secondary erythrocytosis caused by renal carcinoma, renal

Polycythemia Vera Study Group Criteria for Diagnosis in Humans

Category A	Criterion
A1	Increased RBC mass: Males: ≥ 36 ml/kg Females: ≥ 32 ml/kg
A2	Normal arterial oxygen saturation of $\geq 92\%$
A3	Splenomegaly
Category B	Criterion
B1	Thrombocytosis with platelet count $>400/\mu\text{l}$
B2	Leukocytosis with leukocyte count $>12,000/\mu\text{l}$ in the absence of fever or infection
B3	Increased leukocyte alkaline phosphatase score: >100 in the absence of fever or infection
B4	Increased vitamin B ₁₂ (>900 pg/ml) or unsaturated vitamin B ₁₂ -binding capacity ($>2,200$ pg/ml)

Analysis of Data

Where:

- RBC mass measured with RBCs tagged with ⁵¹Cr, ⁹⁹Tc, or ³²P
- Normal oxygen saturation used to exclude secondary polycythemia

Interpretation: Polycythemia vera is diagnosed

- If A1 and A2 and A3 are present
- or
- If A1 and A2 and any two of category B are present

Adapted from the Polycythemia Vera Study Group; available at 216.157.50.80/xdocs/docs_ch28/doc_ch28.11.html; accessed January 2004.

lymphoma, nasal fibrosarcoma, and cecal leiomyosarcoma was reported in dogs.^{6,8-10,13,20} Nonneoplastic inappropriate erythrocytosis was observed in a 5-year-old neutered male Labrador retriever with bilateral *Cryptococcus neoformans* pyelonephritis.⁹ Renal cysts, pyelonephritis, hydronephrosis, and other nonrenal neoplasms have also been demonstrated to result in inappropriate erythrocytosis. To this author's knowledge, idiopathic inappropriate erythrocytosis caused by excessive blood transfusions or exogenous EPO administra-

tion has not been reported and is considered a potential, albeit unlikely, cause.

Several mechanisms have been proposed to explain the elevated EPO levels found in neoplastic disease. Impaired renal parenchymal blood flow by an infiltrative or compressive solid or cystic tumor may induce excessive EPO production because of local tissue hypoxia. Systemic hypoxia induced by nonrenal tumors may also result in elevated EPO levels, but the exact mechanism by which this occurs is poorly defined. Impaired hepatic metabolism or excretion of EPO by tumors of the liver has also been proposed but appears to be an unlikely mechanism. Tumor-derived EPO or EPO-like substances (prostaglandins, androgens, corticosteroids) are generally accepted mechanisms for tumor-associated erythrocytosis.^{53,54} The presence of confirmed, repeatable, and unexplained erythrocytosis may provide a clue as to the presence of a neoplastic process in the early and potentially curable stage,²³ and every patient should be evaluated for neoplasia.

DIAGNOSIS

A logical, systematic approach to the diagnosis of erythrocytosis is imperative because the treatment

plan is determined by the cause. A thorough history and physical examination in conjunction with a complete blood cell count, blood chemistry panel, and urinalysis constitute the minimum database. The importance of this database cannot be overemphasized because relative erythrocytosis related to dehydration and fluid balance shifts is usually obvious based on findings of increased total serum protein levels, prerenal azotemia, and increased specific gravity of urine (>1.040). Hypoglycemia may occasionally occur with severe erythrocytosis because of increased glucose utilization and depletion of hepatic glycogen stores by the increased RBC mass.⁵⁵ Bone marrow cytology is rarely useful, as there are no characteristic erythroid markers for primary erythrocytosis, and a normal to low myeloid:erythroid ratio (resulting from erythroid hyperplasia) is consistently reported with all forms of absolute erythrocytosis.²⁴ Severe obesity or hyperadrenocorticism may also be identified at this stage of the clinical workup. A diagnostic algorithm is presented in Figure 2.

Although measurement of total RBC mass is not routinely available, it is the definitive method for differentiating relative from absolute erythrocytosis.^{9,21,23} RBC

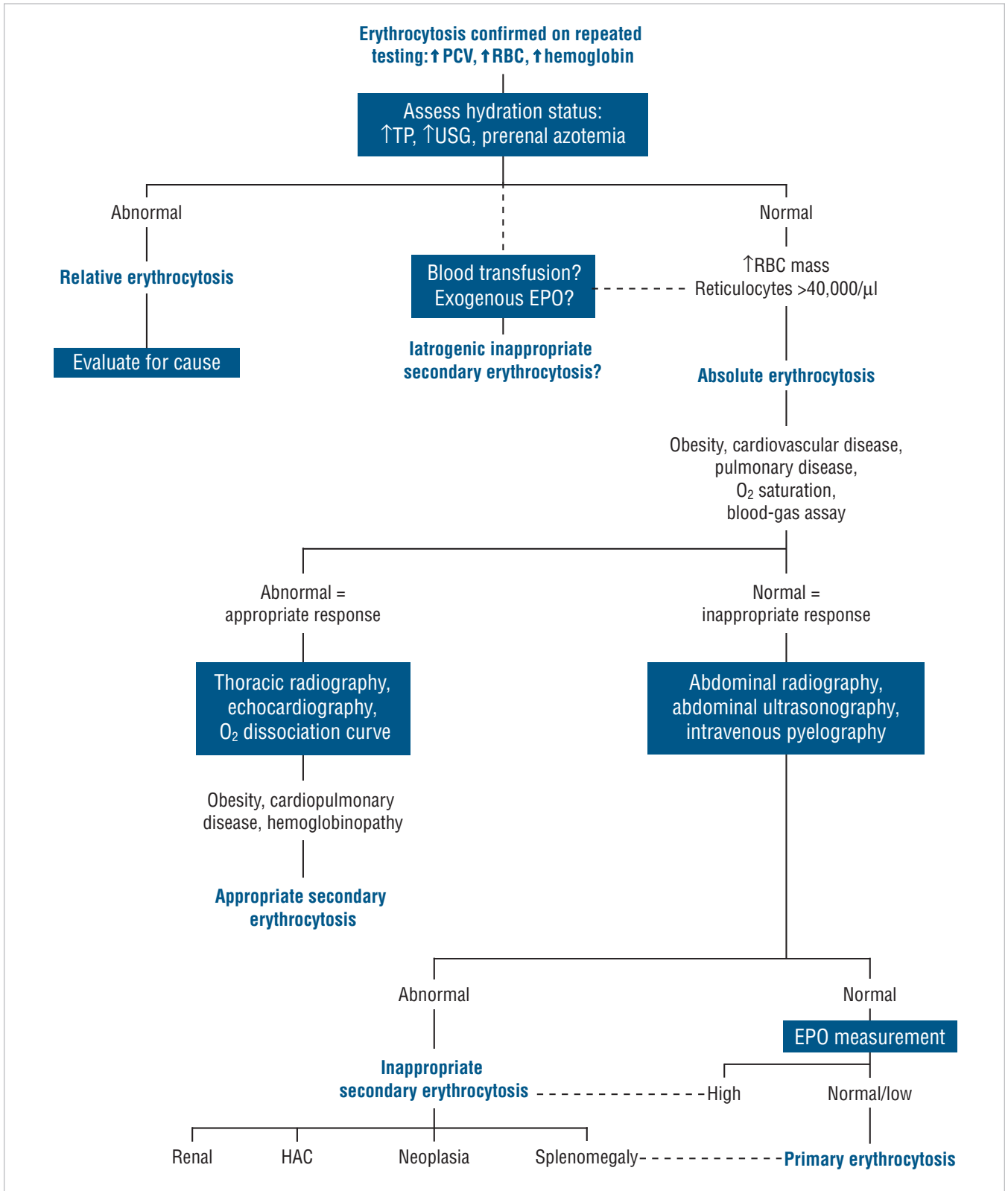


Figure 2. Diagnostic algorithm for erythrocytosis. (HAC = hyperadrenocorticism; TP = total serum protein level; USG = urine specific gravity)

mass is determined in vivo by the radioisotope dilution technique of isotope-tagged (^{51}Cr , ^{32}P , ^{99}Tc) autologous RBCs or estimation from plasma volume determined by ^{125}I -labeled albumin.²¹ From a clinical perspective, this assay is rarely necessary. An absolute reticulocyte count higher than 40,000/ μl in the presence of an elevated PCV is an inexpensive measure for detecting increased erythropoietic activity.²⁴ Relative erythrocytosis may be diagnosed based on clinical findings of dehydration, fluid losses, or, in dogs, evidence to support splenic contracture (pain, excitement, stress) and confirmed by normalization of the PCV with appropriate volume expansion or removal of the inciting cause.^{21–24,34}

After elimination of relative erythrocytosis as a diagnosis, the next step is to determine whether the increase in RBC mass is physiologically appropriate or inappropriate. The signalment, history, physical examination, identification of differential cyanosis, thoracic auscultation, thoracic radiography, echocardiography, and measurement of arterial blood-gas levels are useful for detecting underlying hypoxic disease. Erythrocytosis in conjunction with a low arterial oxygen tension or arterial oxygen saturation lower than 92% supports physiologically appropriate secondary erythrocytosis.^{9,21–23} Phlebotomy before blood-gas analysis may be necessary because increased blood viscosity may interfere with

EPO levels when accurately measured.^{34,35,42–44}

Because most criteria necessary for diagnosing primary erythrocytosis in humans have not been recognized in dogs and cats,^{21,22,42} primary erythrocytosis is often a diagnosis made by exclusion of hypoxic or neoplastic causes.^{24,34,35,42} Most patients have unremarkable results of diagnostic and imaging studies, except for hematologic abnormalities. Hyperviscosity may result in mild bronchointerstitial changes or ventricular hypertrophy, and splenomegaly may be detected in approximately 10% of dogs and 25% of cats.²⁴ A low to normal serum EPO concentration would be expected in primary erythrocytosis.

TREATMENT

Definitive therapy for erythrocytosis varies according to the underlying cause. Cases of relative erythrocytosis associated with fluid losses, fluid redistribution, dehydration, or splenic contracture resolve with appropriate volume expansion and removal of the inciting factor. Inappropriate secondary erythrocytosis caused by EPO-secreting tumors or masses is best treated by surgical removal of the inciting neoplasm after the patient's clinical status and PCV have stabilized. Preoperative support with phlebotomy and IV fluids to normalize the PCV is often indicated to decrease the risk of surgical hemorrhage and postoperative thromboembolism.^{22,23}

Intermittent phlebotomy, with or without adjunctive chemotherapy or radiotherapy, often results in long-term survival for patients with primary erythrocytosis.

accurate sampling.²⁴ Although hemoglobinopathies occur in humans, these disorders have rarely been reported as a cause of appropriate secondary erythrocytosis in dogs and cats.^{24,25}

After hypoxic causes have been eliminated, a diligent search for conditions associated with excessive EPO production (secondary inappropriate erythrocytosis) should be pursued. In both dogs and cats, renal neoplasia (renal carcinoma, lymphoma) is most common. Abdominal radiography, contrast radiography, and ultrasound evaluation can help identify structural lesions, and determination of EPO concentrations can be useful because an increased EPO level is considered diagnostic for secondary erythrocytosis.²⁴ Of the cases reported in the veterinary literature, most had normal to elevated

Postsurgical management of these patients should include regular monitoring of RBC parameters (i.e., RBC count, PCV, hemoglobin concentration), and, if serum EPO levels were evaluated preoperatively, the follow-up level should be checked. Successful treatment of EPO-secreting tumors would be expected to produce normalization of RBC parameters and a decrease in EPO levels to normal reference ranges⁹; return of erythrocytosis and elevated EPO levels may signal the return of the primary tumor or metastatic disease.

Absolute Erythrocytosis: Secondary

For nonneoplastic secondary erythrocytosis, a careful search for contributory causes should be undertaken and therapeutic phlebotomy should be performed with cau-

tion. Weight reduction should be stressed for severe obesity. If hyperadrenocorticism is diagnosed, definitive management with chemotherapy (e.g., mitotane) or surgical removal of an adrenal mass is advised. The presence of renal cysts or pyelonephritis may warrant ongoing medical therapy (aspiration of cystic fluid, antiinfective therapy) or possibly nephrectomy. As stated previously, successful resolution of the inciting cause of secondary erythrocytosis is expected to result in normalization of the RBC parameters. In fact, the final diagnostic confirmation in patients with secondary erythrocytosis is remission of erythrocytosis after removal of the cause.²³

Cases of appropriate erythrocytosis secondary to systemic hypoxia represent a unique subset of patients with regard to treatment. With chronic respiratory disease or cardiovascular pulmonary shunting, erythrocytosis represents a compensatory response to tissue hypoxia, and therapeutic phlebotomy is generally contraindicated.^{21,22} A PCV of 55% to 60% is considered optimum for these patients in which erythrocytosis provides a physiologic adaptation to chronic hypoxia. Systemic oxygenation begins to decline when the PCV exceeds 60%. Although an increased PCV is not optimum for cerebral blood flow, it is required to maintain adequate oxygen-carrying capability.²³ If the PCV in these patients increases to levels associated with increased blood viscosity and compromised blood flow resulting in clinical signs (e.g., weakness, neurologic, or visual deficits), judicious phlebotomy with careful fluid replacement to prevent sudden shifts in blood volume and plasma protein concentration should be considered.^{21-23,26} Many patients with absolute erythrocytosis, especially those with cardiopulmonary disease, are already volume expanded. Fluid administration in excess of replacement from phlebotomy may result in volume overload and signs of congestive failure.²⁵

Absolute Erythrocytosis: Primary

Phlebotomy is indicated for any patient in which erythrocytosis is considered detrimental. Phlebotomy as a single treatment modality has been used successfully in long-term control of erythrocytosis.²⁶ The goal is to reduce the PCV and the RBC mass to more normal ranges so that clinical signs are alleviated and the risk of vascular thrombosis and hemorrhage is reduced.²¹⁻²³ Phlebotomy is especially important in cases of primary erythrocytosis and represents the initial form of treatment.²³ The removal of 20 ml of blood/kg results in an

approximate 15% reduction in PCV.⁵ Phlebotomy is relatively safe but must be repeated at variable intervals to maintain an adequate PCV.^{21,22} Monitoring both PCV and plasma protein levels is prudent. The removal of large blood volumes, especially if done frequently, may result in both hypovolemia and hypoproteinemia and should be accompanied by infusion of 0.9% sodium chloride solution, plasma, or plasma expanders to replace lost plasma volume, plasma proteins, and coagulation factors and to reduce blood viscosity while decreasing the risk of tissue ischemia and thrombosis.^{3,5,23,25} Frequent phlebotomy can lead to iron deficiency, and dietary iron supplementation may become necessary. Approximately 50 mg of iron is lost with removal of each 100 ml of blood.⁵ The resultant microcytic, hypochromic anemia maintains the PCV within normal range for longer periods, although the cells in this type of anemia are less deformable, increase blood viscosity, and may further impair tissue oxygen delivery.²³

The optimal therapy for primary erythrocytosis is unknown, although phlebotomy is the initial therapy in any symptomatic patient. If phlebotomy is required more often than every 4 to 8 weeks, myelosuppressive therapy is indicated.²³ Phlebotomy in conjunction with radioactive phosphorous (³²P) or chemotherapeutic agents (e.g., chlorambucil, busulfan, uracil mustard, melphalan, hydroxyurea, pipobroman, recombinant interferon alfa, theophylline) as well as antithrombotics (e.g., aspirin, anagrelide) has reportedly been used in humans with primary erythrocytosis.⁵⁶⁻⁶¹ Treatment of humans with ³²P, chlorambucil, and hydroxyurea has caused an increased risk of myelofibrosis and leukemia, especially with long-term use.^{57,58,61} Selection of therapy for humans has been stratified on the basis of age, disease risk factors, and concern for development of treatment-induced neoplasia.⁵⁷ Some controversy exists, however, as there is evidence that progression to leukemia may represent the natural course of disease as a consequence of prolonged survival.⁶² Given the shorter life span of dogs and cats, these long-term therapeutic complications may be less of a concern.

Veterinary Patients

In dogs, treatment with repeated phlebotomy (10 to 20 ml/kg), ³²P, and hydroxyurea has been reported.^{15,21,23,27,62} In cats, therapeutic phlebotomy and hydroxyurea have been used^{17,18}; one case of medicinal leeching (with *Hirudo medicinalis*) before instituting phlebotomy and hydroxyurea was reported.¹⁹ Although

^{32}P is not routinely available for veterinary patients, when it is, it may be useful in dogs with primary erythrocytosis. In one study of eight dogs diagnosed with primary erythrocytosis and treated with ^{32}P , three showed a complete response with a survival time of 510 to 2300 days. A partial response was achieved in one dog; in two dogs, the disease stabilized for 1 year after treatment. No response was noted in the two remaining dogs, but survival times in these dogs ranged from 133 to 1,675 days. Myelofibrosis developed in one ^{32}P -treated dog.⁶³

Hydroxyurea, an inhibitor of DNA synthesis and member of the alkylating group of chemotherapeutic drugs, causes reversible myelosuppression without affecting RNA or protein synthesis. It is rapidly absorbed from the gastrointestinal (GI) tract and is excreted primarily in the urine. Hydroxyurea has been used to successfully manage primary and secondary erythrocytosis in both dogs and cats. In dogs, it is administered at an initial oral loading dosage of 30 mg/kg for 7 to 10 days; the dose is then decreased to daily oral maintenance with 15 mg/kg. A complete blood cell count, including platelet count, should be obtained every 7 to 14 days until the PCV normalizes and then every 3 to 4 months.^{21,23} The effects of hydroxyurea are enhanced if the PCV is first reduced to less than 50% by phlebotomy.²¹ The use of hydroxyurea in cats has been infrequently reported.^{17,18} Methemoglobinemia has been observed in cats given high weekly doses, and one study suggested starting feline patients at a total dosage of 125 mg every 2 days for 2 weeks, then 250 mg twice weekly for 2 weeks, and then increasing to 500 mg once weekly while observing for methemoglobinemia at each dose change.¹⁷ The dosages ranged from 300 to 875 mg/wk.¹⁷ As with dogs, the PCV, white blood cell count, and platelet count should be monitored weekly. Antithrombotic therapy with aspirin (1 mg/kg/day) has been suggested, although the overall risk of thrombosis and proof of prevention of thrombosis have not been established.²⁵ In addition, the risk of bleeding and GI irritation should be considered before instituting and during aspirin therapy.

The dose of hydroxyurea must be individualized for optimum control of primary erythrocytosis and may be higher or lower than the standard amounts just discussed. Monitoring the PCV and careful dose adjustment to achieve the desired effect are mandatory. If leukopenia, thrombocytopenia, or anemia develops during hydroxyurea treatment, the drug should be discontinued until blood counts normalize. Hydroxyurea is then reinstated

at a reduced dose to maintain adequate control. If erythrocytosis recurs, the dose should be increased for an additional 7 to 10 days or until the PCV returns to normal. Some dogs may require higher maintenance doses to prevent relapse.^{22,23} Because of the large dose formulations of commercially available hydroxyurea (Hydrea, 500-mg capsules, Bristol-Myers Squibb; Mylocel, 1000-mg tablets, Barr Laboratories), reformulation by a compounding pharmacy should be considered to ensure accurate dosing of small patients. Although the prognosis for primary erythrocytosis is guarded, extended survival for more than 6 years in dogs treated with hydroxyurea and intermittent phlebotomy has been reported.^{21,22,24}

Potential side effects of hydroxyurea therapy in animals include nausea, anorexia, vomiting, myelosuppression, bone marrow hypoplasia, spermatogenic arrest, and methemoglobin formation (cats).^{17,21,22} Sloughing of the toenails is a reported potential side effect in dogs²¹ and may be similar to the development of painful skin ulcers of the distal extremities in humans, often at multiple sites, that occurs with long-term hydroxyurea treatment. Resolution usually occurs after discontinuation of the drug.⁵⁹

SUMMARY

Clinically significant erythrocytosis is recognized by a repeatable increase in PCV. Differentiation of relative from absolute erythrocytosis is mandatory because treatment of the two forms differs significantly. Evidence of fluid loss, dehydration, or vascular redistribution consistent with relative erythrocytosis is usually identified at the initial evaluation, and these signs are easily correctable with replacement fluid therapy and resolution of the inciting cause. The finding of an elevated PCV and reticulocytosis is consistent with absolute erythrocytosis. More difficult, however, is the differentiation between primary and secondary causes. The history and physical examination findings, in addition to appropriate laboratory and imaging test results, may reveal an underlying cardiopulmonary (appropriate) or neoplastic (inappropriate) disease associated with EPO-dependent secondary causes of erythrocytosis. Primary erythrocytosis is a rare, EPO-independent hematopoietic neoplastic disease. The diagnosis is often made after a thorough search has excluded other causes of erythrocytosis and an appropriately low serum EPO level has been documented.

Phlebotomy is currently the primary therapy in all forms of clinically significant absolute erythrocytosis. Concurrent treatment with hydroxyurea or ^{32}P may be useful in some cases, although the small number of

reported cases in which these therapies have been used have typically combined drug therapy with phlebotomy. Therefore, it is difficult to state that these treatment modalities are superior to phlebotomy alone. It is equally difficult to predict long-term survival for the various forms of absolute erythrocytosis in veterinary patients because studies evaluating such survival have yet to be conducted. However, long-term survival of patients with primary erythrocytosis, and perhaps some forms of secondary erythrocytosis, may be expected with attentive medical management.

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ARTICLE #2 CE TEST

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1. By what cell in which organ is EPO in mammals produced?

- a. colony-forming unit erythroid cell; bone marrow
- b. type I interstitial cells; kidney
- c. type II interstitial cells; kidney
- d. chromophobe cells; pituitary
- e. Kupffer cells; liver

2. By which mechanism is EPO synthesis regulated under normal circumstances?

- a. total RBC count
- b. hemoglobin concentration
- c. 2,3-DPG levels
- d. tissue oxygenation
- e. EPO-stimulating hormone

3. EPO primarily stimulates

- a. pluripotential stem cells.
- b. blast-forming unit erythroids.
- c. colony-forming unit erythroids.
- d. metarubricytes.
- e. reticulocytes.

4. What is the plasma half-life of EPO?

- | | |
|-----------------------|----------------------|
| a. less than 1 minute | d. 6 to 9 days |
| b. less than 1 hour | e. more than 1 month |
| c. 6 to 9 hours | |

5. How is relative erythrocytosis most readily diagnosed in the clinical setting?

- a. measurement of RBC mass

- b. measurement of serum EPO levels
- c. measurement of arterial blood-gas concentrations
- d. measurement of serum protein levels
- e. measurement of PCV and clinical evidence of fluid losses, dehydration, or splenic contracture that normalizes with volume replacement

6. Appropriate erythrocytosis would be expected in which condition?

- a. PDA with left-to-right shunting
- b. tetralogy of Fallot
- c. myxomatous mitral valve degeneration
- d. severe obesity
- e. b and d

7. Primary erythrocytosis in dogs is characterized by

- a. normal to decreased EPO levels.
- b. increased EPO levels.
- c. neoplastic cells in the bone marrow.
- d. azotemia.
- e. renal neoplasia.

8. The primary initial therapy for symptomatic erythrocytosis is

- a. ^{32}P .
- b. phlebotomy.
- c. hydroxyurea.
- d. leeching.
- e. whole-body radiation therapy.

9. The optimum PCV for patients with cyanotic heart disease or chronic pulmonary disease is

- a. 35% to 40%.
- b. 40% to 45%.
- c. 45% to 50%.
- d. 50% to 55%.
- e. 55% to 60%.

10. Long-term use of hydroxyurea to manage absolute erythrocytosis may be associated with

- a. decreased RBC parameters.
- b. reversible bone marrow suppression.
- c. spermatogenic arrest.
- d. toenail sloughing.
- e. all of the above