Polycythemia

Polycythemia vera is a myeloproliferative disease that is independent of the erythropoietin (EPO) level. This disease is characterized by abnormal elevation of the packed cell volume (PCV), red blood cell (RBC) count, and hemoglobin concentration. The PCV of affected canine and feline patients can be >85%, but clinical signs do not show until the PCV is >60% (FIGURE 1). The clinical signs are secondary to increased blood viscosity and commonly include neurologic manifestations such as seizures, ataxia, and blindness. Generally, a diagnosis of polycythemia is not made until the PCV is >55%. Because of a lack of appreciation for the normal upper PCV limit in cats (45%) compared with the limit in dogs (55%), this disease is often underdiagnosed in cats. It is also important to note that greyhounds and dachshunds have normal RBC counts and hemoglobin levels that are higher than those of other canine breeds and, therefore, should not be considered polycythemic unless their PCV exceeds 65%.

Polycythemia is from the Greek words poly (many), cyto (cell), and haima (blood). Although polycythemia implies an increase in all cell lines (RBCs, white blood cells, and platelets), the disease typically increases only the number of RBCs. Some authors may prefer using the more accurate term erythrocytosis to refer to the disease; however, polycythemia is widely accepted.

Forms of Polycythemia

Polycythemia can be classified as relative or absolute (true) based on blood volume and RBC mass. These conditions require immediate attention and have contrasting therapeutic interventions (FIGURE 2).

Relative Polycythemia
Relative polycythemia is defined as an elevated PCV with a normal total RBC mass. This condition is associated with a decrease in plasma volume attributed to severe dehydration or an increase in the serum total protein concentration. Vomiting and diarrhea are common causes of dehydration, which can result in relative polycythemia.

Absolute Polycythemia

Absolute (true) polycythemia is defined as an elevated PCV (>65% in dogs; >55% in cats, with clinical signs showing at a PCV of >60%) with an increase in total RBC mass. A transient cause of absolute polycythemia is splenic contraction—a response to epinephrine that temporarily increases the number of RBCs in the circulation of dogs, but not in cats. Absolute polycythemia is further divided into primary or secondary, based on the level of involvement of EPO. EPO is a glycoprotein hormone responsible for regulating erythropoiesis (RBC production).

Primary Polycythemia (Polycythemia Vera)

Primary polycythemia is synonymous with polycythemia vera. Various forms of primary polycythemia may exist in dogs and cats.
In humans, polycythemia vera is one of several forms of primary polycythemia.\(^1\) The underlying molecular basis of polycythemia vera has not been determined.\(^4\) Polycythemia vera is thought to be EPO independent, and diagnosis of it is based partly on a low to untraceable serum EPO concentration.\(^5\) A myeloproliferative disease, polycythemia vera arises from the multipotent hemopoietic progenitor cells in bone marrow. When one of these stem cells gains a growth advantage and autonomy, it becomes the predominant source of marrow precursors, creating an excessive number of mature RBCs. Cytologically, these bone marrow cells appear normal and fully mature. An increase in the numbers of white blood cell precursors and megakaryocytes is typically not seen. Polycythemia vera can progress to erythroid leukemia.\(^3\)

**Secondary Polycythemia**

Secondary polycythemia, which is EPO dependent, is caused by excessive stimulation of RBC production. This form of polycythemia can be subdivided into physiologically appropriate or inappropriate. In patients with generalized tissue hypoxia, appropriate PCV increases are seen when RBCs behave as expected. This response can be due to high altitudes, cardiopulmonary disease such as right-to-left shunts (e.g., ventricular septal defects, reversed patent ductus arteriosus, tetralogy of Fallot) or congestive heart failure, or, uncommonly, chronic obstructive pulmonary disease.\(^3\) Inappropriate responses are typically associated with renal hypoxia or renal tumors (nephroblastomas and carcinomas).\(^2\) Some tumors produce EPO directly or interfere with its metabolism. Renal hypoxia can occur because of the sheer mass of the invading tumor. Renal disease, such as amyloidosis or renal inflammation or infection, may also cause local hypoxia and initiate EPO production; however, examples of this have been seen primarily in people.\(^1\)

**Pathophysiology**

Erythropoiesis (RBC production) is strictly regulated under normal physiologic conditions. EPO is produced in the peritubular capillary endothelial cells of the kidneys and liver. EPO production in the kidneys is localized to renal cells in the inner cortex, near the proximal tubules. The main mediator for production of hypoxia-inducible factor 1 (HIF-1) is renal hypoxia, rather than the mass or number of circulating RBCs. HIF-1 is a physiologic factor that responds to decreases in the oxygen level and influences EPO production by initiating EPO gene transcriptional activation.\(^4\) The number of EPO-generating cells activated is directly related to the degree of hypoxia. With increasing hypoxia, more EPO is released, increasing the plasma level. This stimulates mitosis and differentiation of RBC progenitor cells. The oxygen-carrying capacity of the blood is improved by the increased number of circulating RBCs, and renal oxygenation is subsequently enhanced. To complete the regulatory loop, when the hypoxia is corrected, the oxygen sensor is suppressed and HIF-1 and EPO levels are decreased.\(^4\)

In primary polycythemia, RBC production is independent of EPO production. Conversely, in secondary polycythemia, RBC production is EPO dependent. Secondary appropriate polycythemia is a direct result of hypoxia. Whether it is related to living at a high altitude or the mixing of venous and arterial blood with right-to-left shunting of blood, systemic hypoxia results in an increase in EPO production. Secondary inappropriate polycythemia generates an elevated serum EPO level in the absence of systemic hypoxia; instead, malignancies and renal disease cause local renal hypoxia, leading to EPO production.

**Clinical Findings**

Polycythemia vera most commonly affects middle-aged to older dogs and cats; however, the incidence of this disease is rare in both species.\(^3\) Clinical signs of polycythemia vera include hyperemic mucous membranes, erythematous skin, weakness, lethargy, injected scleral and retinal vessels, epistaxis, hematuria, melena, polyuria, polydipsia, sneezing, and splenomegaly. Nearly half of patients with polycythemia initially present because of neurologic signs observed by owners.\(^7\) Common neurologic signs include seizures,

### Glossary

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ataxia</td>
<td>Failure of muscular coordination</td>
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<tr>
<td>Epistaxis</td>
<td>Bleeding from the nose</td>
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<tr>
<td>Erythematous</td>
<td>Redness of the skin caused by congestion of the capillaries in the lower layers of the skin</td>
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<tr>
<td>Erythrocytosis</td>
<td>Increase in the total RBC mass secondary to a nonhematogenic systemic disorder in response to a known stimulus</td>
</tr>
<tr>
<td>Erythropoiesis</td>
<td>The formation of erythrocytes</td>
</tr>
<tr>
<td>Hyperemic</td>
<td>Excess blood in an area of the body</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>Diminished availability of oxygen to body tissues</td>
</tr>
<tr>
<td>Megakaryocyte</td>
<td>The giant cell of bone marrow from which platelets develop</td>
</tr>
<tr>
<td>Melena</td>
<td>Darkening of the feces by blood pigments</td>
</tr>
<tr>
<td>Myeloproliferative</td>
<td>Characterized by abnormal proliferation of bone marrow constituents</td>
</tr>
<tr>
<td>Myelosuppressive</td>
<td>Characterized by inhibition of bone marrow activity, resulting in decreased production of blood cells and platelets</td>
</tr>
<tr>
<td>Phlebotomy</td>
<td>Opening a vein by incision or puncture to remove blood as a treatment</td>
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<tr>
<td>Splenomegaly</td>
<td>Enlargement of the spleen</td>
</tr>
<tr>
<td>Syncope</td>
<td>Temporary suspension of consciousness due to cerebral anemia or fainting</td>
</tr>
<tr>
<td>Viscosity</td>
<td>A fluid's resistance to flow</td>
</tr>
</tbody>
</table>

\(^{\text{From Baillie's Comprehensive Veterinary Dictionary;}}\)
Polycythemia

ataxia, blindness, and behavior changes. Many of these clinical findings are secondary to hyperviscosity syndrome. With an increase in PCV comes an increase in blood viscosity (thickness). Because RBCs take up the greatest portion of blood volume, PCV is significant in determining blood viscosity. Increases in viscosity are nonlinear: a PCV >70% results in twice the normal viscosity.4 Impaired microcirculation to vital organs such as the brain may cause the neurologic signs of polycythemia.4

Diagnosis

Treatment depends on the type of polycythemia; therefore, differentiating between relative (due to dehydration) and absolute (due to an increase in RBC mass) polycythemia is imperative. Relative polycythemia can be ruled out by a physical examination, complete blood count (CBC), chemistry panel, and urinalysis and treated with fluid therapy. Diagnostic testing for absolute polycythemia may include a CBC, a serum chemistry panel, and urinalysis and treated with fluid therapy. Diagnostic testing for absolute polycythemia can be ruled out by a physical examination, complete blood count (CBC), chemistry panel, and urinalysis and treated with fluid therapy. Diagnostic testing for absolute polycythemia may include a CBC, a serum chemistry panel, a urinalysis, a reticulocyte count, a serum EPO level, an arterial blood gas evaluation, thoracic and abdominal radiography, cardiac and abdominal ultrasonography, and a bone marrow biopsy. Blood pressure measurement and a fundic examination may also be useful.1

A minimum database (i.e., a CBC with a reticulocyte count, a serum biochemistry profile, and a urinalysis) can help to initially differentiate between relative and absolute polycythemia and help assess erythropoietic activity. The serum EPO level can be measured (although very few laboratories currently provide this assay) to help differentiate between primary (EPO independent) and secondary (EPO dependent) polycythemia. Arterial blood gas evaluation is helpful for determining whether systemic hypoxia is present. Collection and measurement of an arterial blood sample may be challenging due to higher-than-normal blood viscosity. Therefore, it is recommended that before arterial blood collection (or other diagnostic evaluations, depending on the patient's condition at presentation), therapeutic phlebotomy should be performed. Phlebotomy does not change the patient's blood oxygen content. Pulse oximetry can be employed when arterial blood gas testing is not available, and a repeatable low saturation level is suggestive of hypoxia. If saturation values are abnormal, appropriate polycythemia should be suspected.1

Cardiac and pulmonary anomalies are investigated using cardiac ultrasonography, thoracic radiography, and electrocardiography. Abdominal ultrasonography and radiography can be useful for detecting renal disease, neoplasia, and splenomegaly. Bone marrow evaluation of patients with polycythemia vera can reveal extra-medullary hematopoiesis and a hyperplastic erythroid series. Bone marrow biopsy cannot differentiate between primary and secondary polycythemia, as the pathology of polycythemia vera is not associated with specific cytologic characteristics. However, combined with other diagnostic tests, bone marrow biopsy can help with the rule-out process, and polycythemia vera is a diagnosis of exclusion.1
Polycythemia

Treatment

Therapeutic phlebotomy is the initial treatment for absolute polycythemia if the PCV is >75% (this value varies depending on the source). The goal is to decrease blood viscosity by decreasing the number of circulating RBCs. Regular phlebotomies are performed until the target PCV (<55% in dogs; <50% in cats) is obtained or until clinical signs improve. The suggested amount of blood to withdraw is 10 to 20 mL/kg. A reduction that is too large can result in syncope, seizures, and hypoxia. The following formula can be used to determine the exact amount of blood to withdraw to achieve a desired PCV:

\[
\text{Blood to be removed (mL)} = \left( \frac{\text{Bodyweight [kg] } \times 0.09}{\text{Actual PCV}} \times 1000 \right) \times \frac{\text{Actual PCV} - \text{Desired PCV}}{\text{Actual PCV}}
\]

However, the resulting PCV is typically higher than the estimated PCV after the procedure, likely due to the release of extramedullary stores.

The technical process of phlebotomy varies slightly in the literature, but the fundamentals are the same. A central (jugular) vein is generally used because of the viscosity of the blood being withdrawn (FIGURE 3). A 19- or 21-gauge butterfly catheter attached to three 20-mL syringes (or a 60-mL syringe) is used to collect blood from the central vein (FIGURE 4). Syringe size is determined by personal preference; because the blood of affected patients is very viscous, drawing it into a large syringe can be more difficult. The syringe(s) may contain heparin (500 to 600 U diluted in 3 to 5 mL of saline) or sodium citrate as an anticoagulant. Chemical restraint may be required, depending on the patient’s demeanor; in my experience, chemical restraint is rarely required. Some sources recommend placement of a peripheral venous catheter and concurrent isotonic fluid infusion during phlebotomy to replace the volume being removed. Other sources recommend replacement of the patient’s own plasma after removal of RBCs. At my workplace, blood is collected from the medial or lateral saphenous vein to determine the PCV (FIGURE 5), followed by phlebotomy from alternating jugular veins (FIGURE 6, FIGURE 7). We use the saphenous veins to collect blood to obtain a PCV in case phlebotomy is not required on the same day, thereby saving the jugular vein. If we proceed with treatment, we alternate jugular veins so that only one of the veins is used per visit. Isotonic fluid is then delivered via the subcutaneous route, which we generally elect over the intravenous route to minimize the patient’s stress and time in the hospital (FIGURE 8). The amount of isotonic fluid delivered is equal to the amount of blood removed. Good technical skill is absolutely essential for maintaining the integrity and long-term sustainability of the jugular veins.

Although rarely used, leeching is another method of blood removal. This method, which must be administered in a hospital, has been used successfully when phlebotomy has not been possible. One text claims that four leeches reduced a feline patient’s hematocrit.
Polycythemia

from 79% to 56% within 48 hours. Leeching requires a client who is willing to allow it and a compliant patient.

The administration of myelosuppressive drugs combined with phlebotomy is another treatment option. The chemotherapeutic agent hydroxyurea is typically used because it induces bone marrow suppression by inhibiting DNA synthesis. Loading doses start at 30 to 50 mg/kg PO q24h; after 1 week, the dose is decreased to 15 mg/kg/d and then titrated to effect. Common adverse effects include myelosuppression (i.e., thrombocytopenia, anemia, leukopenia), gastrointestinal effects (e.g., vomiting, diarrhea, anorexia), hair loss, and pulmonary fibrosis. Adverse effects are reversible with discontinuation of the drug.

The CBC should be monitored every 1 to 2 weeks initially and then every 3 months while the patient receives this medication. The serum creatinine and blood urea nitrogen levels should be monitored before initial treatment and every 3 to 4 months thereafter. Chlorambucil, another myelosuppressive chemotherapeutic, is used less often to treat polycythemia vera. Alkylating agents such as melphalan, cyclophosphamide, and busulfan have also been used, with variable results.

Prognosis

The prognosis for patients with polycythemia vera is guarded; however, with appropriate treatment, patients have survived for more than 6 years with a reasonably good quality of life.

References

A patient with relative polycythemia requires
a. fluid therapy.
b. therapeutic phlebotomy.
c. no intervention.
d. chemotherapy.

2. Polycythemia vera is synonymous with _________ polycythemia.
   a. secondary
   b. relative
   c. primary
   d. absolute

3. Polycythemia vera is thought to be EPO _________, and diagnosis of it is based partly on a low serum EPO concentration.
   a. related
   b. independent
   c. appropriate
   d. dependent

4. Appropriate PCV increases are seen with generalized hypoxia in patients
   a. at high altitudes.
   b. with tetralogy of Fallot.
   c. with congestive heart failure.
   d. all of the above

5. EPO is produced in the endothelial cells of the
   a. kidneys and liver.
   b. kidneys only.
   c. spleen.
   d. heart.

6. Clinical signs of polycythemia vera include
   a. vomiting.
   b. melena.
   c. diarrhea.
   d. coughing.

7. Neurologic signs associated with polycythemia vera include
   a. seizures.
   b. ataxia.
   c. blindness.
   d. all of the above

8. The suggested amount of blood to withdraw for therapeutic phlebotomy is ______ mL/kg.
   a. 5 to 10
   b. 10 to 20
   c. 20 to 30
   d. none of the above

9. Therapeutic phlebotomy may require
   a. chemical restraint.
   b. the use of an anticoagulant.
   c. administration of isotonic fluid.
   d. all of the above

10. Examples of myelosuppressive drugs for treating polycythemia vera include
    a. melphalan and benazepril
    b. phenoxybenzamine and busulfan.
    c. hydroxyurea and chlorambucil.
    d. none of the above