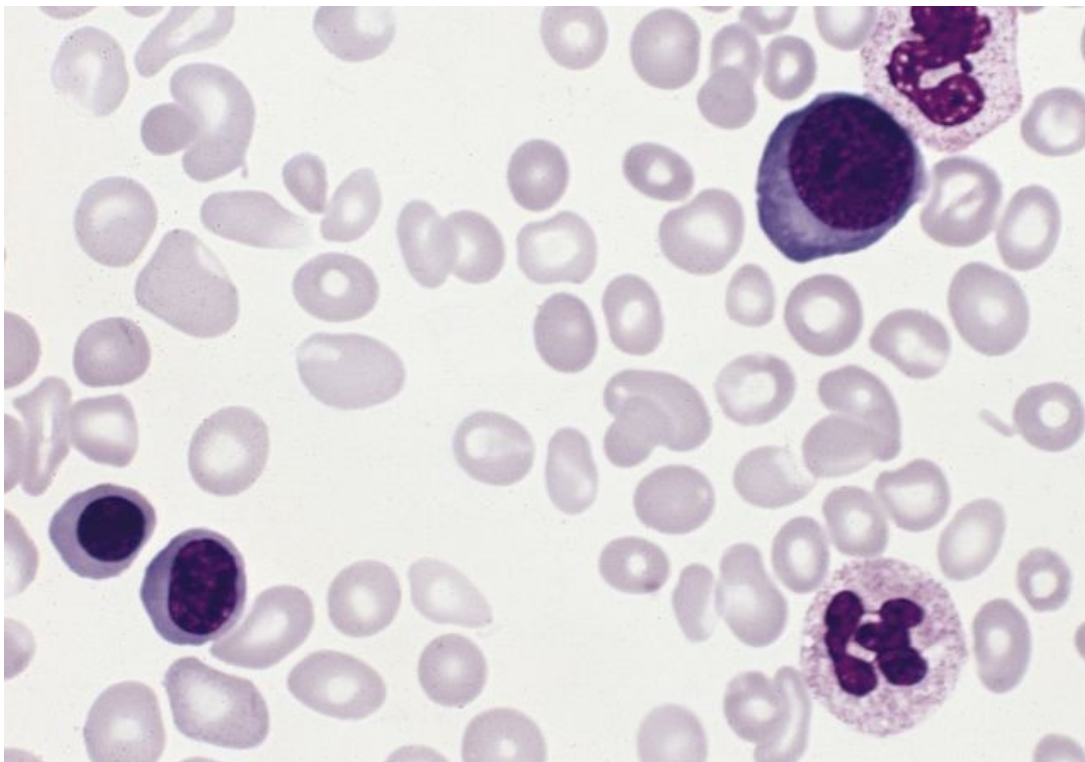


# Polycythemia — Symptoms, Causes and Treatment

[See online here](#)

**Red blood cells perform an important function of supplying adequate oxygen to all tissues. Increased synthesis of these red blood cells, arising either de novo or secondary to other conditions, is called polycythemia. Read on to find out more about the different types of polycythemia and how they may present.**



## Definition

Polycythemia is an increased number of red blood cells (RBC) in circulation. This makes the blood more difficult to pump around the body.

## Pathophysiology

Polycythemia is defined as an **increased red blood cell mass** of the blood. RBC mass is estimated by hematocrit value that is the percentage of RBC's in a given volume of blood. Newborns have a higher hematocrit (51%+-7%) as compared to adults (36%-54%). This is accompanied by a **rise in the packed cell volume (PCV)**, as well as **hemoglobin (Hb)**. The extra red blood cells increase the viscosity of blood and because of increased viscosity and small diameter of blood vessels, the resistance of blood increases that in

turn gives rise to decreased perfusion and may cause thromboembolic and ischemic complications.

Depending on the cause, polycythemia can be classified into two major types:

**Primary Polycythemia:** It is also called **Polycythemia Vera (PV)**. This condition is an acquired stem cell disorder characterized by the **unregulated** de novo synthesis of RBCs by the bone marrow cells.

**Secondary polycythemia:** There is an increased production of RBCs due to a **physiologic** increase in the demand for oxygen by the body.

## Polycythemia Vera

### Definition

Polycythemia vera, also called polycythemia rubra vera or primary polycythemia, is one of the four **myeloproliferative disorders**; the others being **essential thrombocytosis (ET)**, **primary myelofibrosis (PMF)**, and **chronic myelogenous leukemia (CML)**. Myeloproliferative disorders are acquired clonal stem cell disorders characterized by abnormal development and functioning of the bone marrow cells.

In polycythemia vera, all three cell lineages (red blood cells, granulocytes and platelets) is increased, most prominently the red blood cells.

## Etiology and Epidemiology of Polycythemia Vera

The etiology of polycythemia vera is not fully understood.

This disease is presumed to have a genetic basis. Most patients have a mutation in the **JAK2 (Janus kinase 2) gene**, located on chromosome 9. This gene encodes a protein that is essential for RBC production and its mutation is instrumental in the onset of PV.

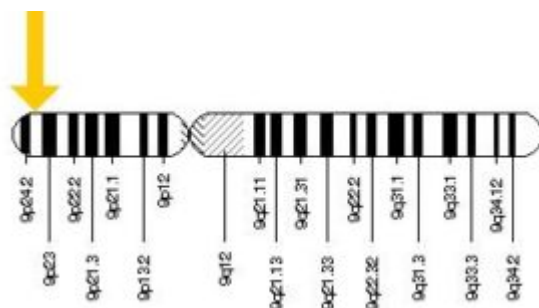


Image: "Locus 9p24 of the human chromosome 9, on which is located the JAK2 gene" by Genetics Home Reference - <http://ghr.nlm.nih.gov/gene/JAK2>. License: Public Domain

The prevalence of PV is higher amongst the Eastern European Jews than amongst other European or Asian populations. The incidence of PV is 2.8 per 100,000 males and 1.3 per 100,000 females. Several small studies have shown that PV is prevalent in 22 of 100,000 people.

The incidence of PV increases with age and is more common in the 50 - 70 years age group.

# Clinical Features and Complications of Polycythemia Vera

Many patients with PV remain **asymptomatic** for years owing to the extremely slow development of this disease and are found incidentally on routine blood counts revealing increased hemoglobin levels.

Most of the symptoms of PV occur due to the **increased blood viscosity**, secondary to increased red blood cell mass. The thick, viscous blood causes sluggish circulation, blocks vessels, and interferes with oxygen delivery to the cells that may result in the following symptoms:

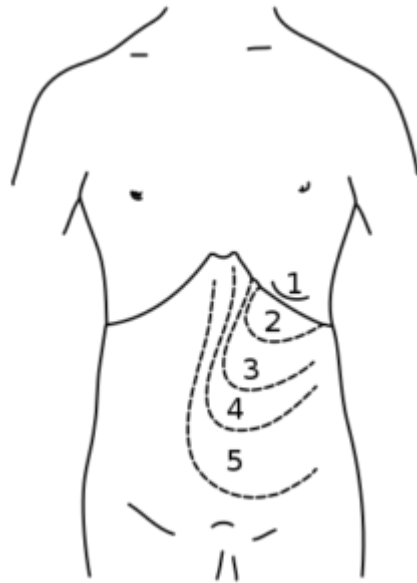


Image: "Splenomegaly in Different Grades." by Furfur - Own Work. License: [CC BY-SA 4.0](https://creativecommons.org/licenses/by-sa/4.0/)

- A headache, dizziness, and fatigue
- Visual disturbances
- **Dyspnea**
- **Splenomegaly**
- Tinnitus
- Intermittent claudication- crampy muscular pain in limbs
- Itching, more prominent after a warm bath
- Bleeding from multiple sites and gums- seen in 1% cases
- Abnormal sensations in the hands and feet
- Angina pectoris
- Weight loss
- In rare cases, osteopathic pain

The patients with PV have a ruddy complexion. Splenomegaly is a common physical finding, present in 75% of cases. Hepatomegaly is also present in one-third of patients. Epigastric tenderness may occur due to gastritis or a peptic ulcer.

The prominent itching after a warm bath occurs due to the increased histamine release from increased basophils and mast cells. Peptic ulcers and gastritis symptoms also occur in these patients due to an increased histamine release and may lead to gastrointestinal

bleeding.

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### Complications

The blood hyperviscosity may result in **thromboembolic complications**, such as myocardial ischemia, transient ischemic attack, [stroke](#), or hepatic vein thrombosis. The **bleeding** complications such as epistaxis, ecchymosis, and gum bleeding occur due to platelet dysfunction.

In rare cases, PV may progress to **acute myeloblastic leukemia** (AML) or **myelofibrosis**.

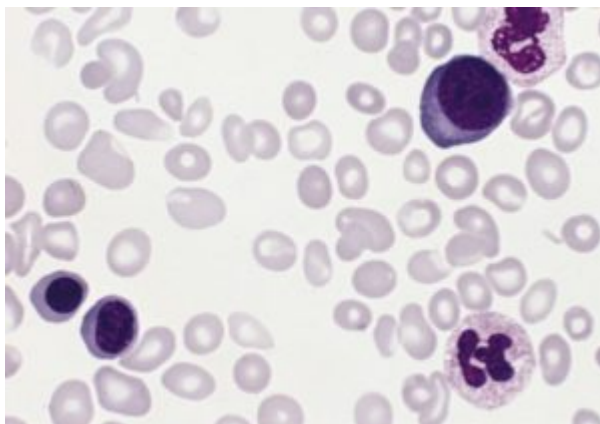
## Diagnosis of Polycythemia Vera

As previously mentioned, polycythemia vera is often an **incidental diagnosis** detected during routine blood counts. Once the diagnosis of polycythemia is confirmed, it is essential to find out whether it is primary or secondary polycythemia.

**Primary or secondary polycythemia** can be differentiated based on the past medical history and clinical examination of the patient. The serum **erythropoietin** (EPO) level helps in the differentiation of these two types of polycythemia.

In **primary** polycythemia (PV), the level of EPO is **subnormal**, whereas, in **secondary** polycythemia, the level of EPO is **normal or raised**.

The tests done for PV include the following:



**Image:** "Blood smear from a 68-year-old woman with a 13-year history of polycythemia vera treated with phlebotomy, 32-P, and hydroxyurea." by The Armed Forces Institute of Pathology (AFIP) - PEIR Digital Library (Pathology image database). Image# 404905.  
Image and description are from the AFIP Atlas of Tumor Pathology. License: Public Domain

1. **CBC:** Raised Hb or hematocrit can be indicative of PV. The counts of RBCs, granulocytes, and platelets may also be increased.
2. **Blood smear:** An increased RBC number and abnormal blood cell types may be seen, especially in PV associated with AML or myelofibrosis.
3. **Serum Erythropoietin:** Measurement of the EPO level helps to differentiate between primary and secondary polycythemia, as described above.

4. **Bone marrow examination:** An increase in RBC production is highly suggestive of PV.
5. **JAK2 mutation analysis:** The presence of the *JAK2* mutation (along with low EPO) confirms the diagnosis of polycythemia vera.

The World Health Organisation (WHO) has proposed the following diagnostic criteria for polycythemia vera.

<b>Major criteria</b>	Hemoglobin > 18.5 g/dL in men, > 16.5 g/dL in women or other evidence of increased red cell volume, Hematocrit>49% in males and >48% in females.
	Presence of JAK2 V617F or other functionally similar mutation such as JAK2 exon 12 mutation
<b>Minor criteria</b>	Bone marrow biopsy showing hypercellularity for age with trilineage expansion
	Serum erythropoietin level below the reference range for normal
	Endogenous erythroid colony formation in vitro

Table 1: WHO Criteria for Polycythemia Vera

**According to WHO criteria, the diagnosis of polycythemia vera requires:**

- (i) The presence of both major criteria plus one minor criterion (Or)
- (ii) The presence of the first major criterion plus two minor criterion.

## Treatment and Prevention of Polycythemia Vera

PV is a chronic disease which has **no cure**. However, patients with PV can be managed efficiently for many years. Multiple modalities may be needed for the effective management of the disease. Their goal is to lower the RBC mass, decreasing blood viscosity, and the subsequent risks of [myocardial infarction](#), [stroke](#), and other thromboembolic complications. It also ensures adequate oxygen supply to all the tissues. Patients undergoing treatment usually lead a normal life. However, for prevention, as well as treatment of complications, medical supervision is necessary.

**The treatment modalities that help in the reduction of the red blood cell count are:**

**Phlebotomy:** It is the treatment of choice. In this procedure, about one unit of venous blood (approximately 500 ml) is removed from the patient's body at regular intervals until the hematocrit is maintained at less than 45%.

**Medications:** Hydroxyurea and interferon-alpha are commonly used for cytoreductive drugs. **Hydroxyurea** is an anti-cancer drug that improves blood flow by decreasing the RBC counts. **Interferon-  $\alpha$  (IFN-  $\alpha$ )** is a substance normally produced by our body. It prompts the [immune system](#) to suppress RBC production and thereby reduces the effects of polycythemia.

**JAK inhibitors:** Ruxolitinib is a newer drug that inhibits JAK 1 and 2 enzyme subtypes. It is used in patients with PV who have failed to respond to hydroxyurea and alpha-interferon.

**Radiation therapy:** Over-activity of the bone marrow cells can be suppressed by radiation therapy. This causes a reduction in the RBCs and thus reduces the blood viscosity.

**Low-dose aspirin:** Low-dose aspirin is used for its anti-thrombotic effect that decreases the chances of blood coagulation. It is also helpful in the treatment of bone pain and the burning sensation of hands and feet. However, aspirin can cause **gastric and intestinal**

**hemorrhage** and thus should only be taken under supervision.

The use of **antihistaminics** in the treatment of pruritus is not very promising. The itching may be brought under control by avoiding the use of warm water and vigorous rubbing after bathing. Starch baths may also help soothe the skin. **Paroxetine**, a selective serotonin reuptake inhibitor (SSRI), is used experimentally to treat pruritus.

There are no known preventive strategies for primary polycythemia. It is, however, possible to control the symptoms and complications of this disease by adequate treatment.

## Secondary Polycythemia

Secondary polycythemia, as the name indicates, occurs secondary to certain underlying causes, which increase the oxygen demand of our body. These **hypoxic** conditions cause our bodies to release excess **erythropoietin**, a hormone that increases the RBC count to increase the oxygen-carrying capacity of the blood. Secondary polycythemia is, thus, characterized by **increased** erythropoietin levels. It has **no association with the JAK2 gene**.

## Etiology and Symptoms of Secondary Polycythemia



[Image](#): "Significant Hydronephrosis of the Left Kidney." by James Heilman, MD - Own Work. License: [CC BY-SA 3.0](#)

**Chronic hypoxia** is the main cause of secondary polycythemia. The causes of chronic hypoxia are chronic respiratory diseases, sleep apnea syndrome, smoking, obesity, hypoventilation syndrome, testosterone replacement therapy, erythropoietin secreting tumors, residence at high altitude levels and congenital heart diseases with a right-to-left cardiac shunt. Such conditions increase the oxygen demand of the body.

**Kidneys** are the major site of erythropoietin (EPO) production and, hence, polycythemia may be a prominent feature of some renal diseases such as single or multiple cysts, hydronephrosis or renal artery stenosis.

EPO and erythropoietin-like substances are also secreted by malignancies including renal cell carcinoma, hepatoma, uterine fibroids, cerebellar hemangioblastoma, and pheochromocytoma. Erythrocytosis is reported in up to 5% of patients with renal cell carcinoma.

### Clinical Features

Symptoms of secondary polycythemia are similar to those of PV. The only difference is in the level of EPO. **In primary** polycythemia, EPO is **subnormal** whereas, in **secondary** polycythemia, EPO is **normal or raised**.

## Treatment and Prevention of Secondary Polycythemia

In contrast to polycythemia vera, secondary polycythemia is triggered by conditions causing long-standing hypoxia. Hence, treating the underlying cause of hypoxia cures the polycythemia. Smoking, high altitudes, mountain climbing, etc. should be avoided to prevent secondary polycythemia. Phlebotomy is indicated in patients with severe symptoms and with a high risk of thrombosis.

The risk of thromboembolic complications is very low in secondary polycythemia, as compared to primary polycythemia, although some thrombotic events were reported in patients with a right-to-left cardiac shunt. Competitive athletes may indulge in blood doping with recombinant human EPO in certain scenarios.

## Prognosis

Prognosis of secondary polycythemia is associated with the underlying disease. However, patients with physiological polycythemia have a normal life span as it is not associated with complications.

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