BLOOD VISCOSITY DISORDERS: THE POLYCYTHEMIA GUIDE AND REVIEW

Mr. Abhay Vishal Dhumal*, Dr. Priyanka Kundlik Sabale, Prof. Jaydeep Babasaheb Pawar , Prof. Amarsinh Suresh Devdhe, Miss. Dnyaneshwari Suresh Kalane .

Department of Pharmacology, Shantiniketan College of Pharmacy Dhotre Bk. Tal-Parner, Dist-Ahilyanagar, Maharashtra, India 414304

Corresponding Authors Details: Mr. Abhay Vishal Dhumal, Second Year M. Pharmacy, Department of Pharmacology, Shantiniketan College of Pharmacy Dhotre Bk. Tal-Parner, Dist-Ahilyanagar, Maharashtra, India 414304

Email ID- abhaydhumal5555@email.com

Abstract:
Polycythemia is a hematological condition characterized by an increased red blood cell mass leading to elevated hemoglobin and hematocrit levels. It is broadly classified into primary polycythemia (Polycythemia Vera) and secondary polycythemia, which is driven either by hypoxia-induced erythropoietin (EPO) stimulation or by pathological non-hypoxic EPO overproduction. This review summarizes the etiological mechanisms, pathophysiological changes, clinical manifestations, diagnostic approach, and management strategies with an emphasis on hypoxia-driven secondary polycythemia. Understanding the underlying mechanism is essential for accurate diagnosis and appropriate therapeutic decisions to prevent complications such as thrombosis, hyperviscosity, and progression of underlying disease.

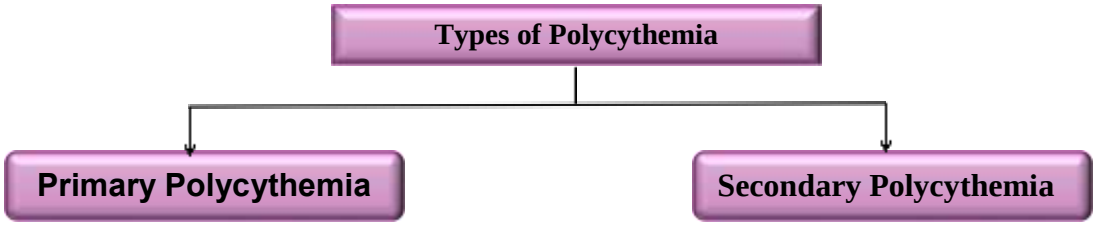
Keywords:
Polycythemia, Polycythemia Vera, Secondary Polycythemia, JAK2 mutation, Thrombosis, Red Blood Cell Mass

Introduction:

Polycythemia:
Definition:[1]
Polycythemia is a condition in which there is an abnormal increase in the total **red blood cell** (RBC) mass, leading to increased **hemoglobin** and **hematocrit** levels. This causes increased **blood viscosity, reduced blood flow,** and **risk of thrombosis**. Its primary form, Polycythemia Vera, is a type of **myeloproliferative blood cancer** caused by **JAK2** mutation.

Polycythemia = Increased RBC mass + high Hb/Hct + increased blood viscosity

Types: [2]



1] Primary Polycythemia or Polycythemia Vera (PV)

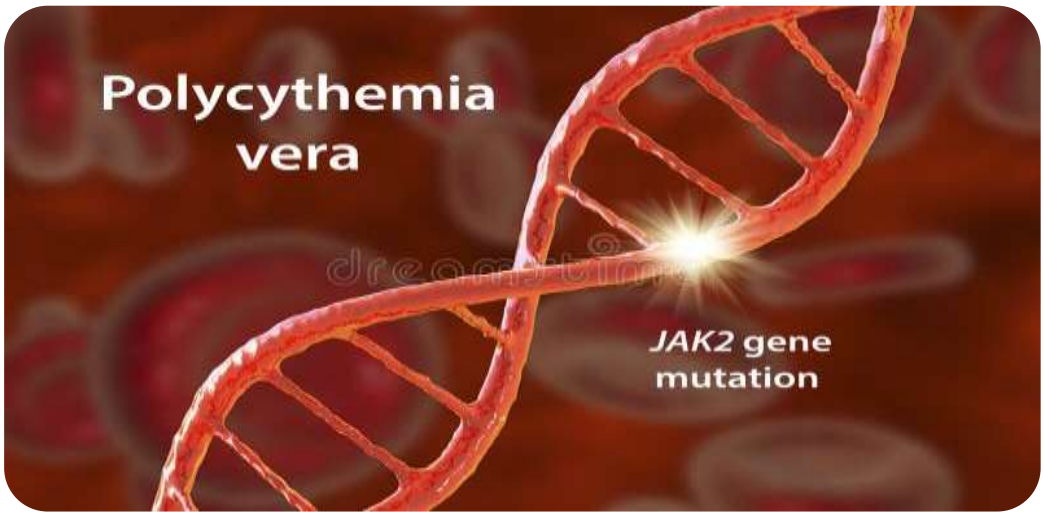


Figure No-1: Polycythemia Vera (PV)

Polycythemia Vera (PV) [3]

Polycythemia Vera (PV) is a chronic myeloproliferative neoplasm (MPN) characterized by clonal proliferation of RBCs, often with increased WBCs and platelets.

It is driven by a JAK2 gene mutation causing hypersensitive hematopoietic stem cells → overproduction of blood cells → hyperviscosity, thrombosis, and splenomegaly.

PV is independent of erythropoietin (low EPO level).

Polycythemia Vera Mechanisam

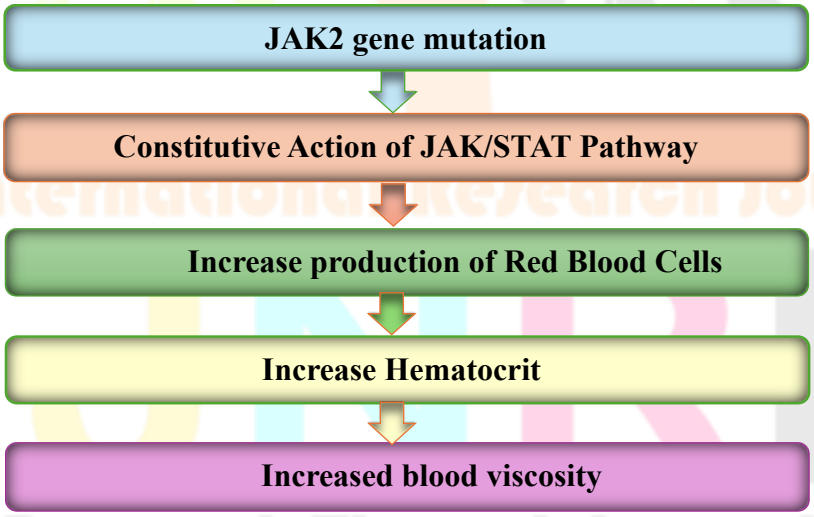


Figure No -2: Polycythemia Vera (PV) Mechanisam

Etiology / Causes [4, 6]

- **Primary Cause**
  1. JAK2 V617F mutation in 95% cases.
  2. JAK2 exon 12 mutation in most of the remaining cases.

Why JAK2 mutation is important? [5]

JAK2 is a tyrosine kinase involved in the EPO receptor signaling pathway.

Mutation → pathway stays permanently ON → RBCs produced even without EPO.

- **Risk factors:**[7]

(Not direct causes but associations)

1. Age > 60 years (common)
2. Environmental toxins (unclear evidence)
3. Slight male predominance

- **Pathophysiology:** [8,9,10,11,12]

1. Clonal abnormal stem cell in bone marrow acquires JAK2 mutation.

- **Causes:**

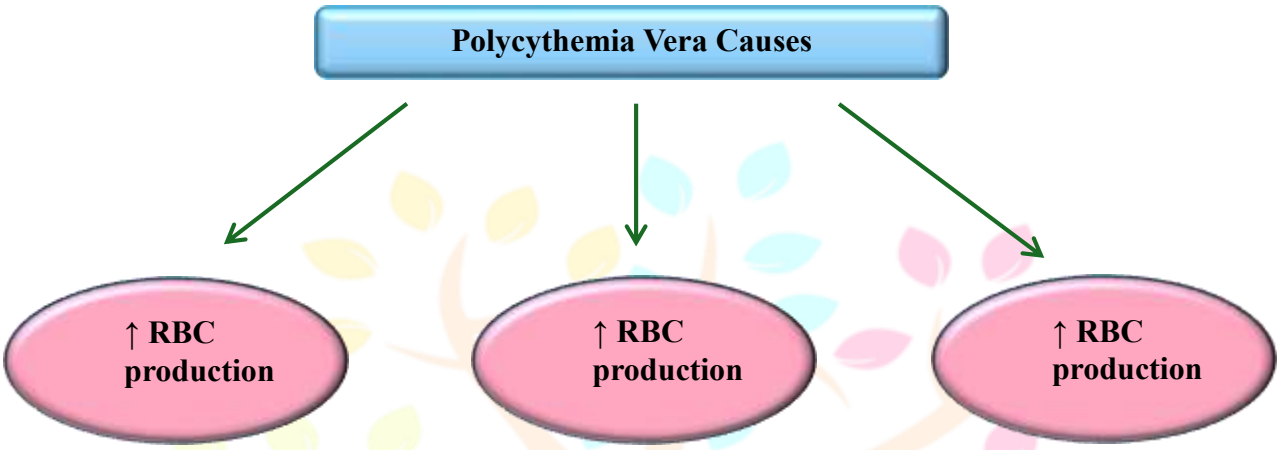


Figure No-3: Polycythemia Vera (PV) Causes

Leads to:

1. Increased blood viscosity → sluggish circulation
2. Thrombosis risk
3. Splenomegaly due to extramedullary hematopoiesis
4. Low EPO levels because body tries to compensate for high RBCs.
5. Over time → spent phase / myelofibrosis (fibrosis of bone marrow).
6. 10–15% risk → transformation into acute leukemia.

Symptoms [13, 14, 15]

A. Due to Hyperviscosity

- Headache
- Dizziness
- Visual disturbances
- Fatigue

B. Due to Increased RBC mass

- Red face (plethora)
- Hypertension

C. Microvascular Symptoms

- Erythromelalgia – burning pain in hands/feet
- Numbness, tingling

D. Histamine-related symptoms

- Aquagenic pruritus – severe itching after warm bath
- Peptic ulcer / gastritis (↑ histamine release from basophils)

E. Thrombotic events

- DVT
- Stroke
- MI

F. Bleeding

- Nosebleeds,
- gum bleeding

G. Organ enlargement

- Splenomegaly
- Hepatomegaly

Diagnosis [16, 17]

Table -1: Polycythemia Vera (PV) Diagnosis

Category	Criterion	Description
Major	1	Hb > 16.5 g/dL (men) / 16.0 g/dL (women) or Hct > 49% / 48%
Major	2	Bone marrow biopsy: hypercellularity + trilineage growth
Major	3	JAK2 mutation positive
Minor	1	Low serum EPO

Management [18, 19, 20]

Main Goals

- Reduce thrombotic risk
- Control hematocrit below 45%
- Reduce symptoms
- Prevent progression to myelofibrosis or leukemia

Table -2: Polycythemia Vera (PV) Treatment

Treatment	Target
Phlebotomy	**1. Target Hct < 45%** **2. Rapid relief of hyperviscosity**
Low-dose Aspirin (75–100 mg/day)	**1. Prevents thrombosis** **2. Reduces erythromelalgia**
Cytoreductive Therapy (Indications)	**Used in high-risk patients:** **1. Age > 60 years** **2. History of thrombosis** **3. Very high platelet count** **4. Severe symptomatic splenomegaly**

Drugs:

1) Hydroxyurea [21, 22]

Mechanism

a. Inhibits ribonucleotide reductase → blocks DNA synthesis
b. Decreases proliferation of RBC, WBC, and platelets
c. Reduces thrombosis risk

2) Ruxolitinib [23]

Mechanism

JAK1/JAK2 inhibitor

a. Directly blocks hyperactive JAK-STAT signaling due to mutation
b. Reduces splenomegaly, pruritus, cytokine symptoms

3) Interferon-α [24]

Mechanism

a. Suppresses hematopoietic progenitor cells
b. Modulates immune system
c. Decreases JAK2 mutation allele burden
d. Useful in young patients and pregnant females

4) Aspirin[25]

Mechanism

a. Irreversible inhibition of COX-1 in platelets
b. Decreases thromboxane A2 → reduces platelet aggregation
c. Prevents clot formation
d. Disease-modifying

5) Symptomatic treatment

a. Antihistamines for itching
b. PPIs for gastric symptoms
c. Manage cardiovascular risk factors (BP, lipids)

6) Monitoring

a. Regular CBC (every 3–6 months)
b. Monitor for thrombosis
c. Check spleen size

2] Secondary polycythemia [25, 26]

Secondary polycythemia is a condition in which RBC count, Hemoglobin (Hb), and Hematocrit (Hct) are increased, but the cause is not a bone-marrow disorder. Instead, it occurs due to increased erythropoietin (EPO) production.

Secondary Polycythemia = EPO high due to hypoxia, tumors, or drugs.

It is mainly a compensatory response to tissue hypoxia.

- **Pathophysiology** [27,28,29]

A) Hypoxia-Driven Mechanism

Low oxygen → Kidney pertubular cells sense hypoxia →HIF-1α activation → ↑ EPO secretion → Bone marrow stimulation → ↑ RBC production.

B) Non-Hypoxic Pathological EPO Overproduction

In non-hypoxic secondary polycythemia, certain tumors (e.g., renal cell carcinoma, hepatocellular carcinoma, hemangioblastoma, uterine fibroids) autonomously secrete excess erythropoietin (EPO) due to abnormal tumor gene expression, which stimulates the bone marrow to increase RBC

C) Drug-Induced Causes

1. **Testosterone therapy**
2. **Anabolic steroids**
3. **Recombinant EPO injections (athletes)**

These directly stimulate EPO or RBC production.

- **Etiology / Causes**

Secondary polycythemia develops due to conditions that increase erythropoietin (EPO) production. Its etiology is broadly classified into Hypoxia-dependent and Non-hypoxia-dependent categories. Each has distinct physiological triggers, which ultimately stimulate RBC production in the bone marrow.

1) Hypoxia-Dependent Etiology

These conditions reduce tissue oxygenation, triggering the kidneys to increase EPO release.

A) Chronic Lung Diseases [30]

Persistent lung dysfunction decreases oxygen exchange.

Mechanism: Alveolar hypoxia → kidneys sense low PaO□ → EPO ↑.

Examples:

- COPD (chronic bronchitis, emphysema)
- Interstitial lung diseases
- Severe bronchial asthma

B) Hypoventilation Disorders

Reduced breathing depth or rate → chronic low oxygen.

Examples:

- Obesity hypoventilation syndrome

- Neuromuscular disorders affecting respiration

C) High Altitude [31]

Atmospheric oxygen is low → arterial hypoxia → compensatory EPO rise.

Seen in mountain dwellers, trekkers, soldiers.

D) Congenital or Acquired Heart Diseases [32]

Defective heart structure causes right-to-left shunting → deoxygenated blood enters systemic circulation.

Examples:

- Tetralogy of Fallot
- Eisenmenger syndrome

E) Obstructive Sleep Apnea (OSA)[33]

Recurrent upper airway collapse during sleep → repeated hypoxic episodes → kidneys chronically increase EPO.

F) Carbon Monoxide Exposure (Smokers)

- Heavy smokers

CO binds to hemoglobin with high affinity → ↓ oxygen delivery despite normal oxygen levels.

Symptoms: [34]

A. General Symptoms

Headache

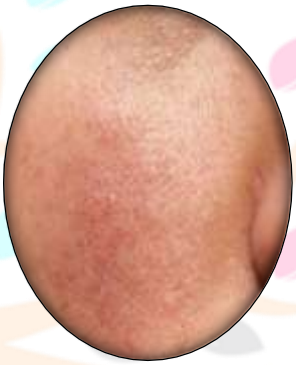
Weakness

Fatigue

Blurred vision

Tinnitus

Dizziness



Plethora

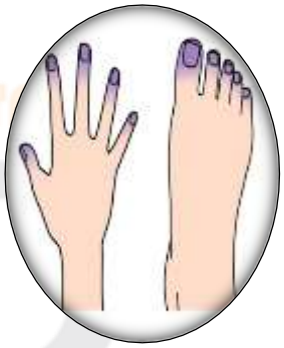
Itching

B] Hyperviscosity Symptoms

Chest Pain

Reduced Concentration

Burning in hands & feet



Cyanosis (bluish lips/nails)

Sleep apnea

Clubbing

Dyspnea

Investigations of Secondary Polycythemia: (SP) [35, 36, 37, 38]

Table -3: Investigations of Secondary Polycythemia

Investigations	Secondary Polycythemia (SP)
CBC	CBC ↑ RBC, ↑ Hb, ↑ Hct
EPO Level	High
Oxygen Saturation (SpO_2)	Low in hypoxic SP; normal in tumor/drug-induced SP
ABG	Shows hypoxia (↓ PaO_2)
JAK2 Mutation Test	Negative
Chest X-ray	Abnormal in COPD/ILD
Pulmonary Function Test	Obstructive/restrictive pattern
Sleep Study (Polysomnography)	Abnormal in OSA
ECG/Echo	Detects congenital heart disease, pulmonary HTN Normal
Carboxyhemoglobin Level	High in smokers
Bone Marrow Biopsy	Normal or increased erythroid activity

Management of Secondary Polycythemia: [39, 40, 41, 42, 43, 44]

Secondary polycythemia is treated by correcting the underlying cause, improving oxygenation, and reducing blood viscosity when necessary

1) Treat the Underlying Cause

Management depends on what is causing the increased RBC production.

A) Hypoxia-Related Causes

- **COPD, asthma** → bronchodilators
- **Obstructive sleep apnea** → CPAP therapy
- **High altitude** → descent or acclimatization
- **Obesity hypoventilation** → weight reduction
- **Congenital heart disease** → surgical correction
- **Smoking/CO exposure** → smoking cessation

2) Remove/Manage EPO-Secreting Tumors

If secondary polycythemia is due to non-hypoxic EPO overproduction:

- **Renal cell carcinoma** → nephrectomy
- **Hepatocellular carcinoma** → tumor management
- **Hemangioblastoma** → surgical removal

- **Uterine fibroids** → myomectomy or medical management

3) Oxygen Therapy

Used mainly for hypoxia-driven cases:

- Long-term oxygen therapy for COPD
- Nocturnal oxygen for OSA
- Oxygen support at high altitude

Restores oxygen levels → decreases EPO secretion.

4) Phlebotomy (Venesection)

Not routinely done because the increased RBC is compensatory.
But used when viscosity symptoms are significant:

Indications

- Hematocrit >55%
- Severe headache, dizziness, visual disturbance
- History of thrombosis
- Symptoms of hyperviscosity

Targets

- **Hct <52% in men**
- **Hct <48% in women**

Phlebotomy reduces blood thickness and improves circulation.

5) Low-Dose Aspirin

Used to lower the risk of thrombosis when viscosity is high.

- Typical dose: 75–100 mg/day
- Particularly helpful in smokers, COPD, and elderly patients.

7) Avoid Worsening Factors

- Avoid dehydration
- Stop testosterone/anabolic steroids
- Stop or reduce diuretics (cause hemoconcentration)
- Avoid high altitude travel if possible

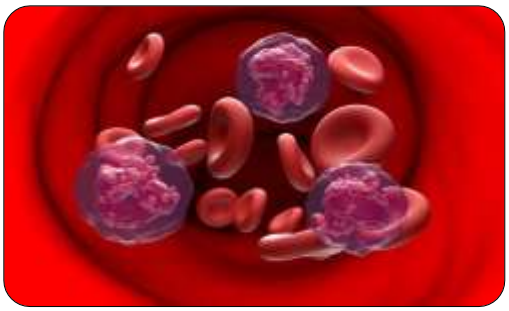
8) Lifestyle Modifications

- Adequate hydration
- Weight loss
- Smoking cessation
- Regular exercise
- Treat comorbidities (hypertension, diabetes)

9) Monitoring & Follow-Up

- CBC every 2–4 weeks initially
- Monitor oxygen saturation
- Check EPO levels if unclear etiology

- Regular evaluation for thrombosis risks
- Renal and liver imaging if tumor suspected



Complications [45, 46, 47, 48, 49, 50, 51]

1) Venous & arterial thrombosis

Polycythemia increases blood viscosity causing slow blood flow (stasis), which promotes clot formation.

Platelets become elevated and hyperactive, further increasing the risk of thrombosis.

Figure No-4: arterial thrombosis

2) Hemorrhage

Polycythemia causes hemorrhage because extremely high RBC and platelet counts lead to abnormal, dysfunctional platelets and fragile blood vessels, resulting in a paradoxical bleeding tendency

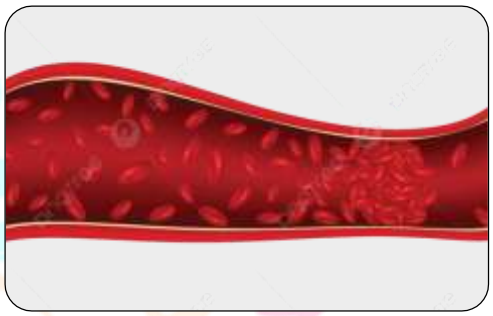


Figure No-5: Hemorrhage

3) Gout (↑ uric acid)

Gout occurs in polycythemia because increased cell turnover raises uric acid levels, which deposit as crystals in joints and cause inflammation and pain.

Figure No-6: Gout

4) Splenomegaly

Polycythemia causes splenomegaly because the spleen works extra to filter excess RBCs and blood cells, leading to congestion and enlargement.

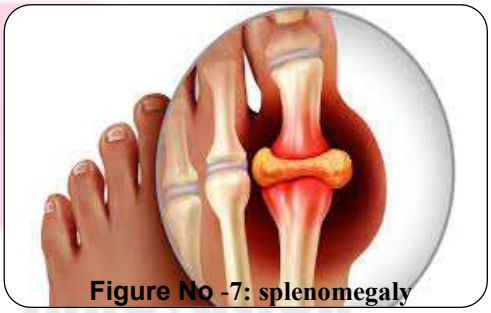


Figure No -7: splenomegaly

5) Acute myeloid leukemia transformation

Polycythemia can transform into acute myeloid leukemia because chronic JAK2-driven marrow overproduction causes genetic instability, eventually leading to malignant blast cell proliferation

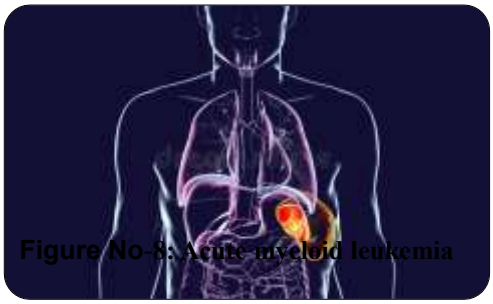


Figure No-8: Acute myeloid leukemia

Review Summary

- Polycythemia results from an increased circulating RBC mass leading to blood hyperviscosity. Primary polycythemia (PV) is a clonal myeloproliferative neoplasm associated with JAK2 mutations and presents with elevated RBCs along with raised WBCs and platelets. Secondary polycythemia can be physiological or pathological.
- Hypoxia-driven secondary polycythemia occurs due to chronic low oxygen levels stimulating EPO release (COPD, high altitude, cyanotic congenital heart disease, sleep apnea).
- Non-hypoxic pathological secondary polycythemia originates from autonomous EPO production by tumors (renal cell carcinoma, HCC, cerebellar hemangioblastoma) or drugs (androgens).
- Pathophysiologically, increased RBC mass raises blood viscosity causing sluggish blood flow, thrombosis, headaches, dizziness, plethora, and hypertension. Diagnosis requires CBC, EPO level, oxygen saturation, ABG, abdominal imaging, and JAK2 mutation testing to differentiate primary from secondary forms.
- Management focuses on treating the cause: phlebotomy for symptomatic hyperviscosity, oxygen therapy for hypoxic causes, CPAP for sleep apnea, withdrawal of offending drugs, and tumor removal when appropriate. PV requires cytoreductive therapy along with low-dose aspirin. Early diagnosis and targeted management prevent complications such as thrombosis, hemorrhage, gout, splenomegaly, and rarely transformation to acute leukemia.

References

1. Means TR. Erythrocytosis. In: Greer JP, Foerster J, Lukens JN, Rodgers GM, Paraskevas F, Glader B editors. Wintrobe's Clinical Hematology Vol 1.11th edn. Lippincott: Williams & Wilkins;2004 p.1225-1237.
2. Jadhav M.N, Patil P, Patil R.K, Kittur S.K, Kesarkhane M.M. A case of Polycythemia: diagnostic dilemma. Trop J Path Micro 2019;5(11):954-958.doi:10.17511/jopm.2019.i11.19
3. Polycythemia vera: MedlinePlus Medical Encyclopedia https://medlineplus.gov/ency/article/000589.htm
4. Barbui T, Barosi G, Birgegard G, Cervantes F, Finazzi G, Griesshammer M, Harrison C, Hasselbalch HC, Hehlmann R, Hoffman R, Kiladjian JJ, Kröger N, Mesa R, McMullin MF, Pardanani A, Passamonti F, Vannucchi AM, Reiter A, Silver RT, Verstovsek S, Tefferi A., European LeukemiaNet. Philadelphia-negative classical myeloproliferative neoplasms: critical concepts and management recommendations from European LeukemiaNet. J Clin Oncol. 2011 Feb 20;29(6):761-70. [PMC free article] [PubMed]
5. Jane Liesveld, MD, James P. Wilmot Cancer Institute, University of Rochester Medical Cente rReviewed By Ashkan Emadi, MD, PhD, West Virginia University School of Medicine, Robert C. Byrd Health Sciences CenterReviewed/Revised Sept 2025
6. Arber DA et al. The 2016 WHO classification of myeloid neoplasms. Blood. 2016;127(20):2391–2405.
7. Tefferi A, Barbui T. Polycythemia vera: 2024 update on diagnosis, risk-stratification, and management. Am J Hematol. 2023 Sep;98(9):1235–1248.
8. Hoffman R, Benz EJ, Silberstein LE. Hematology: Basic Principles and Practice. 7th ed. Elsevier; 2018.
9. Spivak JL. Polycythemia vera: myths, mechanisms, and management. Blood. 2019.
10. Tefferi A, Barbui T. Polycythemia vera: 2024 update on diagnosis, risk-stratification, and management. Am J Hematol. 2023.
11. Hoffman R, Benz EJ, Silberstein LE. Hematology: Basic Principles and Practices
12. Mesa RA, et al. Myeloproliferative neoplasms: pathophysiology and complications. Cancer J. 2020.
13. Barbui T, et al. Pathophysiology of ET and PV. Leukemia. 2021.
14. Singh N (2021) An Overview on Polycythemia its Types and Symptoms. J Hematol Thrombo Dis 9:464. DOI: 10.24105/2329
15. Polycythemia vera - Symptoms & causes - Mayo Clinic https://share.google/3jmqMtp72NJaphHsN
16. Carobbio A, et al. Laboratory features of polycythemia vera: A real-world cohort study. Leukemia Research. 2021.
17. McMullin MF. Investigation and management of erythrocytosis. British Journal of Haematology. 2019.

18. Pearson TC. Hemorheologic consequences of erythrocytosis. Seminars in Hematology. 2001.
19. Barosi G, et al. European LeukemiaNet (ELN) recommendations for management of PV. Leukemia. 2016.
20. Marchioli R, et al. Cardiovascular events and intensity of treatment in polycythemia vera. N Engl J Med. 2013.
21. Platt OS, et al. Hydroxyurea inhibits cellular proliferation by interfering with DNA synthesis. Journal of Clinical Investigation. 2014.
22. Yarbro JW. Mechanism of action of hydroxyurea. Seminars in Oncology. 1992.
23. Quintas-Cardama A, et al. Ruxolitinib inhibits JAK1 and JAK2 signaling in myeloproliferative neoplasms. Blood. 2010
24. Landolfi R, et al. Efficacy and safety of low-dose aspirin in polycythemia vera. N Engl J Med. 2004.
25. Secondary polycythemia: Its Symptoms, Diagnosis, Treatment, and Management https://www.webmd.com/a-to-z-guides/what-is-secondary-polycythemia
26. Marjorie Hecht Secondary Polycythemia (Secondary Erythrocytosis) on February 8, 2019
27. Wang GL, et al. Hypoxia-inducible factor (HIF) regulates erythropoietin gene expression. Science. 1995.
28. Jelkmann W. Regulation of erythropoietin production under hypoxic conditions. Physiological Reviews. 1992.
29. Krantz SB. Erythrocytosis due to autonomous or ectopic erythropoietin production. New England Journal of Medicine. 1988.
30. Criner GJ, et al. Hypoxemia in chronic lung disease and its hematologic effects. Am Rev Respir Dis. 1989.
31. West JB. High altitude–related erythrocytosis: physiologic adaptation. N Engl J Med. 2004.
32. Swenson ER. Chronic hypoxemia and erythrocytosis in congenital heart disease. Prog Cardiovasc Dis. 2005.
33. Sajkov D, et al. Polycythemia in obstructive sleep apnea syndrome. Chest. 1994
34. Middleton ET, et al. Carbon monoxide exposure and erythrocytosis. Thorax. 2000.
35. Mollan TL, et al. High-affinity hemoglobins and secondary erythrocytosis. Am J Hematol. 2009.
36. Agarwal R, et al. Renal lesions causing inappropriate EPO secretion. Kidney Int. 1999.
37. Sajkov D, et al. Sleep apnea and secondary polycythemia. Chest. 1994.
38. Krantz SB. Tumor-associated EPO production and diagnostic imaging. N Engl J Med. 1988.
39. Tefferi A. Management principles of secondary erythrocytosis. Mayo Clin Proc. 2003.
40. Cotes PM, et al. Oxygen therapy and reversal of hypoxia-induced erythrocytosis. Thorax. 1994.
41. Sajkov D, et al. CPAP therapy improves erythrocytosis in obstructive sleep apnea. Chest. 1994.
42. Shahani S, et al. Management of drug-induced erythrocytosis from testosterone/steroids. J Clin Endocrinol Metab. 2009.
43. Agarwal R, et al. Treatment of renal cyst–associated EPO overproduction. Kidney Int. 1999.
44. Spivak JL. Role of phlebotomy in secondary erythrocytosis. Blood. 2002.
45. Pearson TC. Hemorheologic consequences of increased RBC mass. Semin Hematol. 2001.
46. Braekkan SK, et al. Hematocrit and risk of venous thrombosis. J Thromb Haemost. 2010.
47. Kannel WB, et al. Hematocrit and cardiovascular disease risk. Circulation. 1967.
48. Weitzenblum E, et al. Secondary erythrocytosis and pulmonary hypertension in COPD. Eur Respir J. 1994.
49. Spivak JL. Clinical consequences of erythrocytosis. Blood. 2002.
50. Berlin NI. Iron deficiency following phlebotomy-induced depletion. Am J Med. 1975.
51. Sajkov D, et al. Cardiovascular impact of sleep apnea–related hypoxia. Chest. 1994.