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Polycythaemia: diagnosis and management

[1]R Kumar, [2]S Prem

[1]Professor, Department of Haematology, [2]Senior Resident (Academic), Department of Haematology, All India Institute of Medical Sciences, New Delhi, India

ABSTRACT Patients with raised haemoglobin or haematocrit need evaluation for the presence of polycythaemia. The term erythrocytosis should be used when only the red cells are affected, while polycythaemia is preferred for the clonal disorder involving all three haematopoietic cell lines, namely PV. Secondary erythrocytosis is far more common and is usually consequent to increased erythropoietin production. It is important to diagnose PV, as it has a high morbidity and mortality. The diagnostic criteria for PV are complex. Recently, an activating point mutation in the *JAK2* gene (*JAK2-V617F*) has been detected in a majority of PV patients, but is not specific, and needs more evaluation. Patients may present with plethora, thrombosis in arterial or venous circulations, erythromelalgia, pruritus, haemorrhage, splenomegaly, gout, leucocytosis, or thrombocytosis.

Management consists of reducing haematocrit to below 0·45, primarily by venesection. Low-dose aspirin should be administered to all patients unless contraindicated. Cyto-reductive therapy is indicated only if venesection is not tolerated, for high-risk illness, extreme thrombocytosis, and progressive disease. Hydroxycarbamide (previously known as hydroxyurea) is the simplest and most effective medication, being preferred in all except young patients. Interferon is also effective, but is more toxic and inconvenient to use. Anagrelide may be used to control platelet counts, but hydroxycarbamide appears superior. In the very elderly, ^{32}P or low-dose busulfan has a role because of the convenience, despite a greater risk of leukaemic transformation. With appropriate therapy, survival has improved from an average of two years to more than ten years. Special care is needed during pregnancy, prior to general surgery, and in the management of haemorrhage, pruritis, and splenomegaly.

KEYWORDS Cytoreduction, erythrocytosis, haemostasis, investigations, nomenclature, prognosis.

LIST OF ABBREVIATIONS Polycythaemia vera (PV), von Hippel Lindau (VHL), erythropoietin (EPO), haematocrit (Hct), red cell mass (RCM), International Committee for Standardisation in Haematology (ICSH), World Health Organization (WHO), low molecular weight heparin (LMWH), von Willebrand factor (vWF), von Willebrand disease (vWD), erythroid burst-forming units (BFU-E), British Committee for Standards in Haematology (BCSH), first line interferon alpha (IFN-α), psoralen with UV light A (PUVA), Radioactive phosphorus (^{32}P)

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Correspondence to ***R Kumar, Department of Haematology, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029, India***

tel. ***0091 11 2659 4809***

e-mail ***rajatkr@hotmail.com***

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INTRODUCTION

The term polycythaemia has been used in relation to a group of disorders with an increase in circulating red cells. It is recommended that the term erythrocytosis be used where only the red cells are involved, while polycythaemia is preferred for the clonal disorder involving three cell lineages, namely PV. In this article, a general approach to erythrocytosis is given, with detailed management of PV. A few common or unique forms of erythrocytosis are also discussed.

EVALUATION OF ERYTHROCYTOSIS

Haemoglobin values more than 17 g/dl in males, and more than 15 g/dl in females, or Hct values more than 0·51 in males and 0·48 in females, are considered elevated and require further evaluation. There are some differences in recommendations for evaluating and diagnosing erythrocytosis. The gold standard is measurement of the RCM by radionuclide studies. Traditionally the results are expressed in ml/kg and are abnormally high when >36 ml/kg in males and >32 ml/kg in females. This approach may be fallacious in obese individuals. The International

1. Apparent erythrocytosis (normal RCM)

a. Relative erythrocytosis: decreased plasma volume (dehydration, stress erythrocytosis or Gaisbock's syndrome).
b. Extreme 'high normal' values.

2. True erythrocytosis (increased RCM)

a. Primary: PV.
b. Secondary erythrocytosis
   - Congenital: high O_2 affinity haemoglobin, VHL gene mutation, activating mutation of EPO receptor.
   - Increased EPO related to central or peripheral hypoxia: high altitude, chronic lung disease, right to left cardiac shunts, sleep apnoea syndrome, renal artery stenosis (local hypoxia).
   - Increased EPO production by malignant or benign conditions: hepatocellular carcinoma, renal cell carcinoma, cerebellar haemangioblastoma, uterine leiomyoma, phaeochromocytoma, renal cysts.
   - Drug-associated: exogenous EPO, androgens.
c. Unknown mechanism: post-renal transplant erythrocytosis.

TABLE 1 Classification of erythrocytosis.

Committee for Standardisation in Haematology has recommended that the values be based on surface area for RCM. The diagnosis is made when an individual's measured RCM is more than 25% above their mean predicted value. Red cell mass studies may not be required if Hct values are above 0·60 in males and 0·56 in females, as these suggest absolute erythrocytosis. The WHO criteria accept a haemoglobin value of more than 18·5 g/dl in males and 16·5 g/dl in females as absolute erythrocytosis, but this has not been validated.

Erythrocytosis may be seen in a number of conditions and it is critical to differentiate between true and apparent erythrocytosis (see Table 1). If true erythrocytosis is confirmed, tests should be carried out to differentiate the more common secondary erythrocytosis from primary polycythaemia or PV.

POLYCYTHAEMIA VERA

Polycythaemia vera is a clonal disorder of unknown aetiology involving a multipotent haematopoietic progenitor cell giving rise to an increase in erythrocytes, granulocytes, and platelets. The primary increase is in erythrocytes. Erythropoeisis is autonomous, and erythropoeitin is not required for *in vitro* colony formation. Classically, two phases of PV can be recognised: (a) an initial proliferative polycythaemic phase and (b) a spent or post-polycythaemic phase, in which cytopenias are associated with ineffective haematopoeisis, bone marrow fibrosis, extramedullary haematopoesis, and hypersplenism. There are minor differences in the criteria recommended to diagnose PV from different organisations. The WHO guidelines are given in Table 2 along with the variations in the British guidelines. The differences relate to the availability of reliable tests in different parts of the world. Thus using RCM may not be possible in many centres. Using haemoglobin alone may not be sensitive or specific in all subgroups. In many cases of PV, the diagnosis is straightforward, with elevated haematocrit, neutrophilic leucocytosis, thrombocytosis, and splenomegaly. If there is no cause for secondary erythrocytosis and serum erythropoietin is low, the diagnosis is clear. However, there are patients where, initially, only the haemoglobin is raised. In these borderline cases, investigations to exclude secondary causes should be carried out, and long-term follow-up and re-evaluation will reveal the true diagnosis.

LABORATORY EVALUATION OF PATIENTS WITH ERYTHROCYTOSIS OR SUSPECTED POLYCYTHAEMIA VERA

The aim of evaluating a patient with erythrocytosis is to identify true erythrocytosis and then decide if it is secondary or primary PV. Confirmation of erythrocytosis is mandatory to diagnose PV.

Primary investigations

The following investigations should be carried out on all patients with true erythrocytosis as determined by either raised haemoglobin, haematocrit, or RCM according to British or WHO guidelines (see Table 2).

a. *Complete blood count/film:* for other features of PV. Thrombocytosis occurs in about 50% and neutrophilia, often with mild basophilia, occurs in approximately 60% of PV.
b. *Arterial oxygen saturation* (SaO_2): A pulse oximeter can be used. If SaO_2 <92%, erythrocytosis secondary to hypoxia is likely.
c. *Serum erythropoeitin level:* a low erythropoeitin level is a minor criteria for diagnosis of PV. An elevated level suggests secondary erythrocytosis and excludes PV but a normal level excludes neither PV nor hypoxia.
d. *Serum ferritin:* low ferritin levels are more often seen in PV than in secondary erythrocytosis. However, this may not always be helpful and is not included in the diagnostic criteria.
e. *Renal and liver function tests:* secondary erythrocytosis may be associated with renal and liver disease.
f. *Abdominal ultrasound:* to exclude secondary causes in the liver, kidneys, and uterus. A non-palpable splenomegaly on ultrasound (in the absence of liver disease) is a minor criterion for PV.
g. *Chest X-ray:* to exclude lung pathology, which may suggest secondary erythrocytosis.
h. *Carboxyhaemoglobin levels in smokers:* in smokers with polycythaemia, the erythropoietin is elevated but the SaO_2 may at times be normal. In these cases the plasma carboxyhaemoglobin levels are high suggesting a diagnosis of smoker's polycythaemia.

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WHO criteria	Differences from WHO criteria in Guidelines by British Committee for Standards in Haematology (2005)
A Criteria	
A1: Elevated RCM more than 25% above mean normal predicted value, or haemoglobin >18·5 g/dl in men and >16·5 g/dl in women, or >99th percentile of method specific range for age, sex, altitude of residence.	**A1:** Does not include haemoglobin. As an alternative to RCM, it includes Hct ≥0·60 in males, ≥0·56 in females.
A2: No cause of secondary erythrocytosis including: a. Absence of familial erythrocytosis. b. No elevation of EPO due to: • Hypoxia (arterial oxygen saturation ≤92%). • High oxygen affinity haemoglobin. • Truncated EPO receptor. • Inappropriate EPO production by tumour.	**A2:** Simply states 'Absence of cause for secondary erythrocytosis.'
A3: Splenomegaly	**A3:** Specifies 'palpable' splenomegaly
A4: Clonal genetic abnormality other than Ph chromosome or *bcr/abl* fusion gene in marrow cells.	**A4:** No difference.
A5: Endogenous erythroid colony formation *in vitro*.	**A5:** There is no A5 criterion (it is placed with B4).
B Criteria	
B1: Thrombocytosis >400x10⁹/L	**B1:** No difference.
B2: Leucocytosis >12x10⁹/L	**B2:** Specifies 'neutrophil leucocytosis (neutrophil count >10 ×10⁹/L in non-smokers; >12·5×10⁹/L in smokers)'.
B3: Bone marrow biopsy showing panmyelosis with prominent erythroid and megakaryocytic proliferation.	**B3:** Does not consider bone marrow histology, instead includes 'splenomegaly (demonstrated on isotope/ultrasound scanning)'.
B4: Low serum EPO levels.	**B4:** Also includes 'characteristic BFU-E growth' as alternative to low serum EPO levels.
Diagnose PV when A1 + A2 are present with any other A criteria or any two of B criteria.	

TABLE 2 Criteria for PV (comparison of WHO and BCSH criteria).

After these primary investigations, the patient should be referred to a specialist or haematologist if no obvious secondary cause is detected.

Secondary investigations

The following secondary investigation are selectively indicated, after primary work-up and clinical evaluation.

a. *Bone marrow studies:* bone marrow aspirate and biopsy studies are not essential to diagnose PV. Bone marrow may be sent for cytogenetic studies to establish clonality. Characteristically, the marrow is hypercellular with trilineage involvement and the iron stores are absent. This investigation is also useful as a baseline for future studies for evolution into myelofibrosis.
b. *Cytogenetics:* cytogenetic abnormalities are detected in about 10–20% of cases of PV at diagnosis, limiting its diagnostic utility. The common abnormalities are trisomy of chromosome 8 and 9, del (20q), del (13q), and del (1p).
c. *Culture studies for BFU-E:* for normal *in vitro* culture of erythroid progenitors, addition of erythropoietin is needed for growth of BFU-E. In PV, endogenous growth occurs in the absence of erythropoietin.
d. JAK2 *mutation:* until recently, there was no biological marker for PV. A number of studies in 2005 have shown that a single somatic activating point mutation in the *Janus kinase 2* (*JAK2*) gene is found in the great majority of patients with PV (65–97%). The mutation (*V617F*) may also be present in 23–57% with essential thrombocytosis or myelofibrosis and rarely in other myeloproliferative disorders. Thus the presence of the *JAK2* mutation can distinguish PV from secondary erythrocytosis but not from related myeloproliferative disorders. Further work is in progress for the possible development of a molecular targeted therapy.
e. *Other selected tests:*
• oxygen dissociation curve (P50) studies may be done to exclude high affinity haemoglobins in unexplained erythrocytosis;

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Feature	Characteristic
Thrombosis (15–60%)	Arterial (coronary, cerebral) or venous (hepatic, portal venous).
Haemorrhage	Mucosal, gastrointestinal.
Pruritis (20–25%)	Characteristically aquagenic.
Erythromelalgia	Red burning toes, feet, fingers.
Splenomegaly	In 50–75%.
Hepatomegaly	In 30%.
Peptic ulcer	3–5 times more common than in general population.
Hyperuricaemia (40%), gout	About 5% with hyperuricaemia develop gout.
Myeloid metaplasia	Increasing heptosplenomegaly, leucocytosis, anaemia.
Acute leukaemia	Mainly non-lymphoblastic.
Facial plethora, headache, vertigo, tinnitus, visual disturbances	May not be present in early cases.

TABLE 3 Clinical features and complications of PV.

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- sleep studies are indicated in suspected sleep apnoea;
- lung function tests are required for pulmonary disease;
- erythropoeitin receptor gene analysis may be done to exclude a rare erythropoietin receptor mutation.

CLINICAL FEATURES OF POLYCYTHAEMIA VERA

The peak age of onset is between 50 and 60 years. The clinical features are given in Table 3.

MANAGEMENT OF POLYCYTHAEMIA VERA

The aim of therapy is to decrease the risk of thrombosis and haemorrhage and to manage complications. This should be done in consultation with a haematologist. Thrombotic complications are common as the blood viscosity increases logarithmically at Hct values greater than 0·55. The recommended guidelines are given in Table 4. In summary, all patients should undergo venesection to achieve a target haematocrit of less than 0·45 and should take low-dose aspirin (unless contraindicated). In selected cases, cytoreductive therapy may be added. Cytoreduction is indicated if venesection is poorly tolerated, in high-risk cases (age >60 years or history of thrombosis), with increasing splenomegaly, and in extreme thrombocytosis.

The choice of cytoreductive therapy is age-related:

- *<40 years of age:* IFN-α; second line hydroxycarbamide (hydroxyurea) or anagrelide.
- *40–75 years:* first line hydroxycarbamide; second line IFN-α or anagrelide.
- *>75 years:* first line hydroxycarbamide; second line ^{32}P or intermittent low-dose busulfan.

Conventional risk factors for atherosclerosis such as hypertension, diabetes, and hyperlipidaemia should be corrected and smoking discouraged.

MANAGEMENT OF SPECIFIC PROBLEMS

1. *Increasing splenomegaly.* Hydroxycarbamide, IFN-α and busulfan are all effective in controlling moderate splenomegaly, but not massive splenomegaly.
2. *Pruritis.* Antihistaminic agents, cimetidine, and cytoreductive agents (hydroxycarbamide/IFN) and PUVA are effective.
3. *Surgery.* Elective surgery should be postponed until haematocrit is optimal for at least two months.
4. *Pregnancy.* All patients should be maintained on low-dose aspirin and careful venesection to maintain the haematocrit within the normal range appropriate for gestation. Cytoreduction should be avoided in pregnancy especially in the first trimester. If considered essential, IFN-α is the drug of choice. High-risk patients should receive LMWH throughout pregnancy and continued up to six weeks postpartum.
5. *Haemorrhage.* Patients with extreme thrombocytosis (usually >1,000–1,500x10^9/L) have a loss of large vWF multimers, similar to that seen in congenital type 2 vWD. This acquired vWD is related to the degree of thrombocytosis and resolves with platelet cytoreduction. Treatment for significant acute bleeding includes tranexamic acid or epsilon amino caproic acid and platelet transfusions despite a high count. For long-term control cytoreduction and avoidance of high doses of antiplatelet drugs is needed.
6. *Iron deficiency.* Repeated venesections induce a state of iron deficiency, which limits erythropoiesis and is one of the goals of phlebotomy. The frequency of venesections is thereby reduced. If symptomatic anaemia develops, iron replacement should be given judiciously and the patient's parameters closely monitored. Excessive iron may result in a sudden increase in RCM.

PROGNOSIS

Survival of untreated patients historically has been poor with a two-year survival of less than 50%. Adequately treated PV patients now have a life expectancy of more than ten years from diagnosis. Causes of death are thrombotic events, transformation to acute leukaemia, myelofibrosis, myelodysplasia, or haemorrhage.

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First line therapy: Recommended for all. Avoid aspirin if contraindicated.

Treatment	Method and rationale	Advantages	Disadvantages
Venesection	Repeated 2–3 times a week until haematocrit < 0·45. Later needed once every 2–3 months. Lowering the haematocrit reduces the risk of thrombosis and bleeding.	Most effective and simple. Induces mild iron deficiency to reduce erythroid production.	Not tolerated by some.
Low-dose aspirin	75–100 mg/day decreases risk of thrombosis and death from cardiovascular causes, without significantly increasing risk of haemorrhage.	Reduces thrombo-embolism, erythromelalgia.	Risk of bleeding in extreme thrombocytosis (platelets > 1,000–1,500x10^9/L).
Second line therapy: Cytoreduction therapy: Indications (a) venesection poorly tolerated, (b) high-risk cases (age > 60 years or history of thrombosis), (c) increasing splenomegaly, (d) extreme thrombocytosis.			
Hydroxycarbamide (hydroxyurea)	500 mg 2–3 times a day. Effective in controlling blood counts and haematocrit, reducing thromboembolism.	Risk of leukaemic transformation doubtful.	Continuous therapy needs monitoring of counts. Avoid in young and during pregnancy due to possible mutagenicity.
IFN-α	Subcutaneous injection in doses of 3–5 million units, three times a week, continuously. Controls erythrocytosis, thrombocytosis; often reduces splenomegaly and pruritis.	No increase in risk of leukaemic transformation.	Side-effects (fatigue, flu-like symptoms), parenteral route makes it inconvenient; withdrawal in 20–40%.
Low-dose busulfan	Alkylating agent, used as intermittent therapy (25–75 mg every 2–3 months).	Effective, less frequent monitoring, useful in elderly patients with limited longevity.	Risk of leukaemic transformation.
^{32}P	Intravenous route, repeated every three months if needed.		
Anagrelide	Antiplatelet drug, used for extreme thrombocytosis (>1500x10^9/L), less effective than hydroxycarbamide in a study for essential thrombocytosis.	No leukaemic transformation.	Non-compliance in 16% due to side-effects (cardiac, gastrointestinal, and neurological).

TABLE 4 Recommended therapy for PV.

MANAGEMENT OF SELECTED ERYTHROCYTOSIS

In secondary erythrocytosis, the underlying disease should be treated.

Apparent erythrocytosis or polycythaemia, Gaisbocks syndrome, or stress polycythaemia

In this condition, the Hct is raised, but RCM is normal. This is seen mainly in males, who are hypertensive smokers with non-specific symptoms of headache, dizziness, and fatigue. If there is a history of thrombosis, or Hct is persistently raised, (>0·54 despite stopping smoking, alcohol, and diuretics), venesection is recommended with a target Hct of <0·45.

Idiopathic erythrocytosis (benign erythrocytosis)

Some patients with true erythrocytosis cannot be classified as PV or secondary erythrocytosis. Venesection is recommended if Hct >0·54, or at lower levels if the risk of thrombosis is present, with a target Hct of <0·45.

Erythrocytosis in hypoxic pulmonary disease and cyanotic heart disease

Although erythrocytosis is compensatory, a very high

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blood viscosity may be harmful. Management should be in consultation with a specialist respiratory or cardiac physician. For pulmonary disease, if symptoms of hyperviscosity are present or Hct >0·56, venesection to reduce Hct to 0·50–0·52 is advisable. For cyanotic heart disease, isovolaemic venesection may be done if symptoms of hyperviscosity are present with individualisation of target Hct.

Post renal transplant erythrocytosis

In 10–15% of renal transplant patients, erythrocytosis develops 8–24 months later. The pathogenesis is likely to be multifactorial and includes abnormal erythroid sensitivity to erythropoietin and angiotensin II. It usually persists. Treatment: avoid dehydration, use angiotensin-converting enzyme inhibitors or angiotensin II receptor inhibitors. If there is no response, venesect to a Hct of 0·45.

KEYPOINTS

- Patients with raised haemoglobin merit detailed evaluation to determine the presence of true or apparent erythrocytosis and whether it is primary or secondary.
- Polycythaemia vera has a high morbidity and mortality due to thrombosis and haemorrhage.
- All patients with PV should undergo reduction of haematocrit to less than 0·45, preferably by venesection. Aspirin in low doses (75 mg/day) is recommended in all, unless contraindicated.
- In polycythaemia vera, cytoreductive therapy is indicated in high-risk or progressive disease with hydroxycarbamide or IFN-α, while in elderly patients busulfan or ^{32}P have a role. Anagrelide may be used for thrombocytosis.
- Discovery of a *JAK2* mutation is promising as a new diagnostic modality for PV and related myeloproliferative disorders.

FURTHER READING

- McMullin MF, Bareford D, Campbell P *et al.*; General Haematology Task Force of the British Committee for Standards in Haematology. Guidelines for the diagnosis, investigation and management of polycythaemia/erythrocytosis. *Br J Haematol* 2005; **130(2):**174–95.
- Pearson TC, Guthrie DL, Simpson J *et al.* Interpretation of measured red cell mass and plasma volume in adults: Expert Panel on Radionuclides of the International Council for Standardization in Haematology. *Br J Haematol* 1995; **89:**748–56.
- Pierre R, Imbert M, Thiele J, Vardiman JW, B running RD, Flandrin G. Polycythemia vera. In: Jaffe ES, Harris NL, Stein H, Vardiman JW (editors). *World Health Organisation (WHO) Classification of Tumours: Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues.* Lyon France: IARC Press; 2001; 32–4.
- Schafer AI. Molecular basis of the diagnosis and treatment of polycythemia vera and essential thrombocythemia. *Blood* 2006; **107(11):**4214–22.
- Tefferi A, Spivak JL. Polycythemia vera: scientific advances and current practice. *Semin Hematol* 2005; **42(4):**206–20.