Thames Valley
Strategic Clinical Network

Investigations of Raised Haematocrit and Management of Polycythaemia Vera in Primary Care

For shared care protocol of hydroxycarbamide for Polycythaemia Vera, please visit the Oxfordshire CCG website [LINK]

Background

Apparent Polycythaemia

Apparent polycythaemia is the commonest cause of a raised haematocrit (Hct), and due to a decrease in plasma volume. This can be due to dehydration (relative polycythaemia), excess alcohol, heavy smoking, high BMI or thiazide diuretics, or anabolic steroid use.
Key diagnostic features:

- Negative for JAK2 mutation
- Typically, the erythropoietin (EPO) level is normal but in some cases the EPO level can be low or high

Hct usually not higher than 0.6 in men and 0.56 in women

True Polycythaemia

A true increase in the number of red blood cells can be due to a primary bone marrow disorder, e.g. Polycythaemia Vera (see below) or can be secondary to other, non-haematological conditions e.g. hypoxia.

In Polycythaemia Vera (PV), acquired mutations in bone marrow cells lead to inappropriate red cell production. ~95% of PV patients have an acquired mutation in a gene called JAK2, known as the JAK2 V617F mutation, which causes excessive production of blood cells. In a minority of patients, PV can transform to the more severe conditions myelofibrosis (~10% patients) and acute myeloid leukaemia (~5%).
Key diagnostic features:

- JAK2 mutation detected
- Low serum EPO levels.

Secondary polycythaemia

This usually results from increased serum EPO in response to chronic hypoxia, or, more rarely, due to malignant or benign tumours releasing erythropoietin-mimetic agents (e.g. renal or hepatic cancer or uterine fibroids). Very occasionally in EPO secreting tumours, the EPO level may be low as the EPO-like agent is not detected by the assay.
Key diagnostic features:

- JAK2 mutation is negative
- Serum EPO level usually high but can be normal.

A full list of secondary causes is listed in Appendix 1 below.

Clinical Assessment and Investigations (see Flow Chart below)

- History and examination including smoking history and history of thrombosis
- Screening for hypertension, hyperlipidaemia, diabetes
- Full blood count
- JAK2 mutation testing
- Serum erythropoietin level (EPO)
- Serum ferritin, iron and transferrin saturations
- Renal and liver function tests

The above blood tests can be requested by sending 2 EDTA tubes (purple top) for blood count and JAK2 mutation testing and two SST tubes (yellow top) for iron studies and EPO level. Send these to Haematology Laboratory, JR site. One Lithium Heparin tube (green top) for renal, liver enzymes, lipid profile and (fluoride) blood sugar tests to Biochemistry Laboratory, JR site

Which patients require referral?

The following patients should be referred to haematology through the myeloid haematology secretary. To discuss the case prior to referral, please contact the on-call Haematology SpR.

1. Patients positive for the JAK2 mutation.
2. Patients negative for the JAK2 mutation but with other features suggestive of a myeloproliferative disease. This includes high platelets and/or white count, enlarged spleen, family history of myeloproliferative disease, previous history of thrombosis or low EPO level. This will be a rare group.
3. Patients negative for the JAK2 mutation but with a persistently abnormal serum EPO level *without* a chronic hypoxic disorder. Refer to haematology to exclude an EPO secreting malignancy or uncommon JAK2 exon 12 mutations, or other rare causes of secondary polycythaemia.

Notes: **Patients with apparent polycythaemia with Hct <0.60:** In general, these patients *do not* need referral to haematology. See management suggestions below.

Secondary Polycythaemia: Patients with an obvious secondary cause for the raised haematocrit such as hypoxic lung disease should be referred directly to the chest physicians in the first instance.

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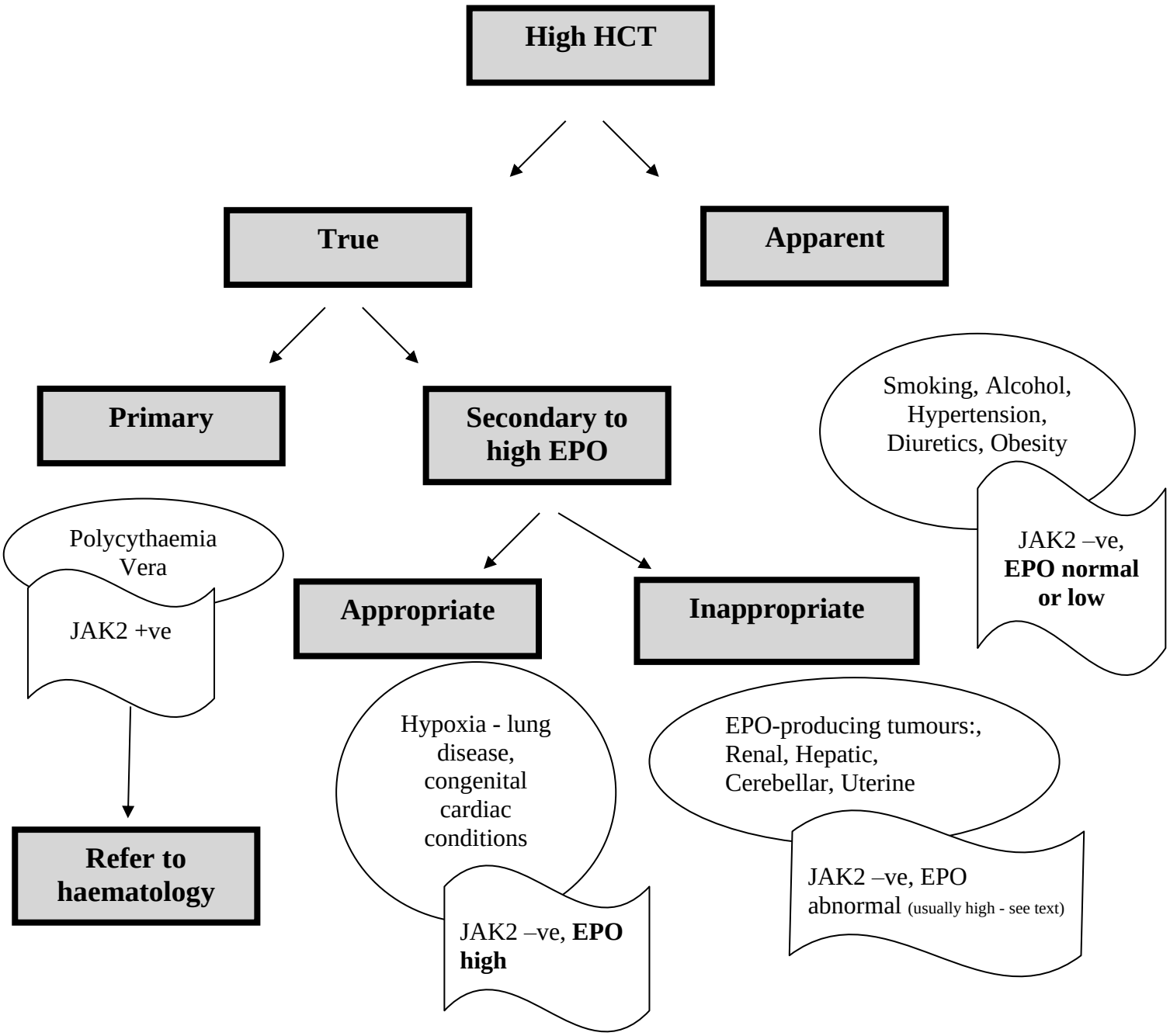
Flow Chart: Overview of investigation of polycythaemia



Management of apparent polycythaemia/ secondary polycythaemia

A pragmatic approach is required for these patients with rigorous control of vascular risk factors such as diabetes, hypertension or smoking and use of aspirin in cases where this would be otherwise clinically indicated for primary or secondary prevention. Lifestyle risk factors should be addressed in primary care first. Tackling cigarette smoking, excess alcohol intake, and changing from thiazide diuretics to alternative anti-hypertensive agents (e.g. ACEi) may reduce the haematocrit. These interventions are often best done in Primary Care.

There is no evidence to support that venesection is beneficial in these cases, and management is primarily focused on treatment the underlying cause and modification of lifestyle factors. In rare patients in whom the raised haematocrit is considered to have contributed to a thrombosis or vascular event, or other symptoms/complications then venesection can be considered on a per patient basis.

Cytoreductive therapy with hydroxycarbamide is never indicated in patients with apparent or secondary polycythaemia. As these patients do not have a primary haematological problem, they are rarely followed up in the haematology clinic.

Management of Polycythaemia Vera

Patients with polycythaemia vera can be asymptomatic, or may present with arterial or venous vascular occlusive events, microvascular disturbances e.g migraine or severe headaches, or occasionally haemorrhage. Symptoms relating to splenic pain and/or enlargement, pruritus, gout and constitutional symptoms such as fatigue are frequently present.

Mortality is related to arterial and venous thrombosis, which is significantly increased in these patients, and therefore management is directed to reduce these risks. This requires lowering the haematocrit. The target haematocrit for patients with PV is 0.45.

Another major aspect of managing these patients, involves reducing any other thromboembolic risk factors, in particular smoking, diabetes, high cholesterol and hypertension. It is also important to keep alcohol intake to a sensible level. Iron replacement should be avoided as this can cause rebound polycythaemia. In rare circumstances where iron replacement may be indicated this can be discussed with the haematology team on a case-by-case basis.

Assessment and management by Clinical Haematology specific to Polycythaemia Vera

The haematology specialist will confirm the diagnosis and plan management according to the risk of vascular events.

A bone marrow aspirate and trephine biopsy may be performed to confirm the diagnosis and to assess for bone marrow fibrosis, although is often not necessary in patients in whom a JAK2 mutation is detected.

All patients with PV should receive low dose aspirin (75-100mg OD) unless contraindicated, and modification of additional cardiovascular risk factors should be considered. In older patients (>75 years) a PPI should be routinely co-prescribed with aspirin.

Management is largely based on the patient's risk category as follows:

Risk category	**Definition**	**Management**
Low	≤ 65 years of age AND No history of thrombosis	Phlebotomy to maintain Hct <0.45 (initially intensive phlebotomy, then usually only required 3-6 times/year). Low dose aspirin (consider PPI).
High	Age >65 AND/OR history of PV-associated thrombosis	Cytoreduction with hydroxycarbamide to maintain Hct <0.45 +/- phlebotomy. Low dose aspirin (consider PPI, especially if >75yrs). Interferon may be used as an alternative to hydroxycarbamide especially in younger patients. These patients will be managed in the haematology clinic.

Cytoreductive therapy (e.g. hydroycarbamide) may be indicated in low-risk patients who have other thrombotic risk factors, e.g. a raised platelet count and/or marked leukocytosis.

APPENDIX 1: CLASSIFICATION AND DEFINITIONS OF POLYCYTHAEMIA

TRUE POLYCYTHAEMIA (raised Hct due to increased red cell mass)

Primary myeloproliferative **disorder**

- Polycythaemia Vera (PV) – 95% due to JAK2V617F mutation, rare cases have JAK2 Exon 12 mutation

Secondary polycythaemia

Congenital causes

- High oxygen-affinity haemaglobin
- 2,3-biphosphoglycerate mutase deficiency
- Erythropoietin receptor-mediated
- Chuvash erythrocytosis (VHL mutation)

Hypoxia Driven increased EPO

- Central hypoxic process
- Chronic lung disease
- Right-to-left cardiopulmonary vascular shunts
- Carbon monoxide poisoning
- Smoker's erythrocytosis
- Hypoventilation syndromes e.g. sleep apnoea
- Local renal hypoxia
- Renal Artery Stenosis
- End-stage renal disease (more commonly associated with anaemia)
- Hydronephrosis
- Renal cysts e.g. polycystic kidney disease

Pathological EPO production

- Tumours
- Hepatocellular carcinoma
- Renal cell cancer
- Cerebellar haemangioblastoma
- Parathyroid carcinoma/adenoma
- Uterine leiomyomas
- Phaeochromocytoma
- Meningioma

Exogenous EPO

- Drug associated
- Treatment with androgen preparation

Post renal transplant erythrocytosis

Idiopathic erythrocytosis – no cause identified

APPARENT POLYCYTHAEMIA (raised Hct but normal red cell mass)

- Heavy smoking
- High alcohol intake
- Hypertension particularly thiazide use
- Dehydration ("relative" erythrocytosis)

CONTACT INFORMATION

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2. Amendment to the diagnosis and investigation of polycythaemia/erythrocytosis British Journal of Haematology 2007; 138 (6): 821-2
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REVIEW

Name	Revision	Date	Version	Review date
Dr Bethan Psaila, Consultant Haematologist	New document	Oct 2019	1.0	Oct 2021
Prof Adam Mead, Consultant Haematologist NSSG Myeloid Group	Updated contact information, annual protocol meeting	Nov 2021	1.1	Nov 2023
Zishaan Ramzan, Haematology Pharmacist. NSSG Myeloid group	Annual protocol meeting	Sep 2023	1.2	Nov 2025