Oxfordshire Clinical Commissioning Group
Referral Guidelines- Polycythaemia

DIAGNOSIS IN PRIMARY CARE AND REFERRAL PATHWAY
FOR PATIENTS WITH A RAISED HAEMATOCRIT

Document purpose
A raised haemoglobin or haematocrit is a common finding and can be a reason for referral. This document aims to facilitate investigation of such patients in Primary Care to reduce hospital referrals and follow-up appointments, and ensure that the most appropriate patients benefit from early specialist assessment.

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Notes

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1. Polycythaemia

(a) The commonest cause is a decrease in plasma volume. This is **apparent polycythaemia**.

b) True increase in the number of red blood cells. This can be a primary bone marrow problem e.g. **Polycythaemia Vera** (PV) (see below) or **secondary** to other medical conditions e.g. hypoxia.

**Classification of Polycythaemia (see Appendix 1 below)**

*Apparent polycythaemia*. Reduction in the plasma volume is usually related to modifiable factors – e.g. high body mass index, heavy smoking, excess alcohol consumption, use of thiazide diuretics. Patients with apparent polycythaemia are probably the **majority** of those who are referred of those with a high haematocrit. These patients are negative for the JAK2 mutation. They usually have a normal serum EPO level. A haematocrit > 0.6 male, > 0.56 female is less likely to be due to an apparent erythrocytosis.

**Polycythaemia Vera** (PV). Here acquired mutations in blood cells leads to inappropriate red cell proliferation. ~95% of PV patients have an acquired mutation in a gene called JAK2 that regulates erythropoiesis. The mutation is known as JAK2 V617F. As these patients have inappropriately high red cell numbers, they do not need as much erythropoietin (EPO) to drive red cell production. Thus, PV is characterised by the JAK2 mutation and low serum EPO levels.

**Secondary polycythaemia**. 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). The JAK2 mutation will be negative and the serum EPO level will usually be high. Very occasionally in EPO secreting tumours the EPO level may be low as the EPO-like agent is not detected by the assay. A **full list of secondary causes is listed in Appendix 1 below**.

**BACKGROUND**

Patients with high haemoglobin can be at risk of venous/arterial thrombo-embolic disease. There are two parts to management.

1. The haematocrit can be lowered. The target haematocrit is determined, in part, by diagnosis of polycythaemia.

   - In **PV** the target haematocrit is 0.45.
   - For **secondary and apparent polycythaemia**, the target haematocrit is usually 0.54. This can vary occasionally. For example, for patients with a thromboembolic history it may be prudent to keep the haematocrit lower (e.g. 0.5). This can be discussed with a haematology consultant or the primary hospital consultant looking after that patient.

2. It is important that **ALL** other additional risk factors for thrombosis, such as hypertension and smoking history, are addressed. This is critical to provide an integrated management strategy. These interventions are often best done in Primary Care.

Finally, and as a separate point, **PV patients need annual follow up which can be done in primary care to** detect the 2-8% that will transform myelofibrosis or the 1-3% that will transform to Acute Myeloid Leukaemia. **Patients without a primary myeloproliferative disorder do not have a risk of disease transformation.**
Patients with high haematocrit (Hct) >0.52 in men, >0.48 in women\(^1\) on two separate occasions (i.e. two months apart)\(^2\) OR a one off value of Hct >0.6 male, 0.56 female require investigation.

As patients with apparent polycythaemia (see ‘Diagnosis’ section above) are a significant proportion of those with a high haematocrit, the initial assessment should focus on lifestyle factors (smoking and excess alcohol), a history of thrombosis, and features causal of secondary polycythaemia (e.g. hypoxic lung disease).

Investigations recommended in Primary Care

- History and examination including smoking history and history of thrombosis
- Full blood count and film
- JAK2 mutation testing
- Serum erythropoietin level (EPO)
- Serum ferritin
- Renal and liver function tests
- Patients should be screened for hypertension, hyperlipidaemia, diabetes

The above blood tests can be requested by sending:

- 2 EDTA tubes (purple top) for blood count, blood film and JAK2 mutation testing and two SST tubes (yellow top) for serum ferritin 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?  (See Appendix 2 for flow chart)

1. **Patient is positive for the JAK2 mutation.** Refer to Haematology Outpatients.

2. **Patients negative for the mutation but with other features suggestive of a myeloproliferative disease.** High platelets and/or white count, enlarged spleen, family history of myeloproliferative disease, previous history of thrombosis - should also be referred. This will be rare group.

3. **Patients negative for the JAK2 V617 mutation but with an 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.

4. **Apparent polycythaemia.** These patients can be referred to commence a venesection programme if the haematocrit is persistently greater than 0.54. **Lifestyle risk factors should be addressed in primary care first.** Tackling cigarette smoking, excess alcohol intake, and changing from thiazide diurectics to alternative anti-hypertensive agents may reduce the haematocrit. **Patients with apparent polycythaemia and managed in this way should have a blood test every 3-6 months in primary care, and if their haematocrit is greater than 0.54 on two occasions, two months apart, then the patient should be referred for venesection.**

5. **Secondary Polycythaemia.** A small number of patients have an obvious secondary cause for the raised haematocrit such as hypoxic lung disease. These patients should be referred directly to the chest physicians in the first instance.
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## Referral Guidelines - Polycythaemia

<table>
<thead>
<tr>
<th>REFERRAL PROCESS</th>
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<tbody>
<tr>
<td>Refer appropriate new patients to Haematology through Dr Mead's secretary (details above).</td>
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<tr>
<td>To discuss the case prior to referral, please <strong>bleep the on-call Haematology SpR on bleep 1836 via switchboard (01865 741841).</strong></td>
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<th>ADDITIONAL INFORMATION</th>
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<td><strong>References</strong></td>
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## Classification of the absolute erythrocytoses

### Primary Myeloproliferative Disease
- Polycythaemia vera (PV) \( (\text{JAK}^2_{V617F} \text{ mutation positive or negative}) \)
- Exon 12 mutations

### Apparent Polycythaemia
- Heavy smoking
- High alcohol intake
- Hypertension particularly thiazide use

### Secondary Polycythaemia

#### Congenital
- High oxygen-affinity haemoglobin
- 2,3-Biphosphoglycerate mutase deficiency
- Erythropoietin receptor-mediated
- Chuvash erythrocytosis (VHL mutation)

#### Hypoxia-driven
- Central hypoxic process
- Chronic lung disease
- Right-to-left cardiopulmonary vascular shunts
- Carbon monoxide poisoning
- Smoker’s erythrocytosis
- Hypoventilation syndromes including sleep apnoea
- Local renal hypoxia
- Renal artery stenosis
- End-stage renal disease (more commonly associated with anaemia)
- Hydronephrosis
- Renal cysts (polycystic kidney disease)

#### Pathologic EPO production
- Tumours
- Hepatocellular carcinoma
- Renal cell cancer
- Cerebellar haemangioblastoma
- Parathyroid carcinoma/adenomas
- Uterine leiomyomas
- Pheochromocytoma
- Meningioma

#### Exogenous EPO
- Drug associated
- Treatment with androgen preparations

### Postrenal transplant erythrocytosis

### Idiopathic erythrocytosis
Which patients require referral?

- High HCT
  - True
  - Primary Polycythaemia Vera
    - JAK2 +ve EPO low
  - Secondary to high EPO
    - True with high EPO
    - Secondary to high EPO
    - Inappropriate
      - EPO-producing tumours: Renal, Hepatic, Cerebellar, Uterine
      - EPO-high
      - JAK2 –ve EPO normal
      - Hypoxia - lung disease, congenital cardiac conditions
      - JAK2 –ve EPO high (usually high - see text)

- Appropriate
- Inappropriate

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Management of Polycythaemia

Most patients with polycythaemia are asymptomatic. Consequently the rationale for treatment is to reduce the risks of arterial and venous thromboses, as well as bleeding, which are increased in these patients. Thus, a major aspect of managing these patients, involves reducing their thromboembolic risk factors, in particular smoking, diabetes, high cholesterol and hypertension. Equally important, are blood pressure monitoring, fasting lipid and glucose levels and smoking cessation advice where appropriate. It is also important to keep alcohol intake to a sensible level. Iron replacement should be avoided as this can cause a dangerous 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.

Specific management of primary polycythaemia (PV) most commonly requires aspirin (unless contraindicated) and regular venesections. At diagnosis, frequent venesection is performed to achieve a haematocrit under 0.45. Once the haematocrit is <0.45, venesections are usually only required every 6-12 weeks. More rarely cytoreductive therapy is indicated (hydroxycarbamide) for patients with PV associated with a raised platelet count and/or marked leucocytosis. This decision will be made by the Haematology Consultant.

Patients with apparent polycythaemia and some patients with secondary polycythaemia may require venesection usually with a target haematocrit of 0.54. Cytoreductive therapy with hydroxycarbamide is never indicated in these patients.

Patients being treated with venesection and/or hydroxycarbamide may be suitable for management by their GP with specialist input only when required. A similar shared care protocol for use of hydroxycarbamide in the management of essential thrombocythaemia has been very successfully implemented by GPs under a similar shared care agreement. Flow charts for the management of venesection and hydroxycarbamide in shared care are shown below.

Venesections can be arranged by directly contacting the Day Treatment Unit (Churchill Hospital) on 01865 235554 in order to schedule venesection as appropriate.

References:
1. Amendment to the diagnosis and investigation of polycythaemia/erythrocytosis

2. Guidelines for the Diagnosis, Investigation and Management of Polycythaemia/Erythrocytosis.
   British Journal of Haematology 2005; 130(2): 174-95
Figure 1: Flowchart for management of patients with Polycythaemia Vera (PV)

Management of patients with a High Haematocrit

All patients: Lifestyle advice and management of risk factors

Polycythaemia Vera (JAK2+ve)

Initial referral to haematology for assessment

Isolated polycythaemia

Initial venesection managed by haematology team to keep Hct <0.45

Once target haematocrit reached, referral for shared care maintenance venesection programme

Regular FBC (usually once every 6-12 weeks) with venesections as indicated to keep haematocrit <0.45

Polycythaemia with ↑plts or WBC

Hydroxycarbamide therapy commenced by haematology

Once established on hydroxycarbamide, referral for shared care

See separate flow chart

JAK2–ve polycythaemia

Referral for specialist opinion:
- e.g. chest clinic for patients with chronic hypoxic pulmonary disease

Referral to haematology in selected cases:
- Features suggestive of myeloproliferative disease
- Abnormal EPO level without chronic hypoxic disorder
- Haematocrit persistently >0.54 without chronic hypoxic disorder

Venection indicated in selected cases.
Usual target haematocrit <0.54

Initial venesection managed by haematology team to reduce haematocrit to below target (usually <0.54)

Once target haematocrit reached, referral for shared care

Regular FBC (usually once every 6-12 weeks) with venesections as indicated to keep haematocrit <0.54
Management of adult patients requiring Hydroxyurea (Hydroxycarbamide therapy) – shared care

Hydroxyurea is a cytoreductive agent used for the treatment of myeloproliferative disorders to control the platelet count, and occasionally other blood counts.

Dose and administration
- 20-30mg/kg/day PO, adjusted to platelet and neutrophil counts. For the majority of patients this is in the order of 0.5-2g/day

Preparations available
- Capsules (Hydrea, Squibb). 500mg capsules, pink/green

Adverse effects
- Neutropenia: this can be severe and life-threatening and patients’ neutrophil counts should be regularly monitored
- Anaemia: requires dose-adjustment
- Gastro-intestinal symptoms: eg anorexia, nausea, diarrhea. These are usually most prominent when the patient commences the treatment and settle within a couple of weeks
- Skin rash or skin/mucosal ulcers (may require cessation of treatment)

Contra-indications
- Renal impairment: dose should be reduced if GFR <50mL/min, but any dose reduction as a result of renal impairment should be carried out by the haematology department only.

Pregnancy and lactation
- These patients should be under specialist management only

Drug interactions (refer also to BNF or SPC)
- Can cause more severe myelosuppression if taken in conjunction with other cytotoxic drugs
- Dose may need adjustment if taken with uricosuric drugs

Monitoring
- Regular full blood count (minimum of 3-monthly if stable, otherwise more often as per flow-chart)

Patient information leaflet
Patients should be supplied with an information leaflet from the manufacturer.

Shared Care Responsibilities
Shared care assumes communication between the specialist, GP and patient. The intention to share care should be explained to the patient and accepted by them. Patients should be under regular follow-up which provides an opportunity to discuss drug therapy.

a) Hospital Consultant
- Write to the GP requesting shared care and outline shared care protocol criteria and individual patient's management plan i.e. frequency of venesection and/or current dose of hydroxycarbamide
- Liaise with GP regarding changes in disease management, drug dose, missed clinic appointments.
- Ensure clinical supervision of the patient is done by follow-up as appropriate.
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- Ensure the patient understands the nature and complications of drug therapy and their role in reporting adverse effects promptly.
- Be available to give advice to GP and patient.

b) GP

- Prescribe hydroxycarbamide once the dose is stable.
- Liaise with the patient and Haematology Day Treatment Unit to ensure appropriate monitoring of the blood count with venesections to maintain haematocrit below the target as indicated.
- Advise the hospital consultant of any clinical changes where appropriate.
- Monitor for adverse effects of hydroxycarbamide as detailed above.

c) Patient

- Report any adverse effects to their GP and/or consultant.
- Have regular monitoring and venesections as outlined above.
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Figure 2: Flowchart for shared care of adult Polycythaemia Vera patients treated with hydroxycarbamide

- **Full Blood Count**
  - Platelets >400 x 10^9/L and/or Hct >0.45
    - Increase dose by max 500 mg/day*
      - as long as neutrophils > 1.5 x 10^9/L, Hb >11/g/dL. Otherwise contact Haematology Laboratory Specialist Registrar though switchboard
    - Recheck FBC in one month
      - Improving counts, dose modification, as above
  - Platelets <200 x 10^9/L or Hb <11g/dl or Neutrophils <1.5 x 10^9/L
    - Decrease by max 500 mg/day
    - Recheck FBC in one month
  - Platelets 200-400 x 10^9/L and Hb >11g/dl and Neutrophils >1.5 x 10^9/L
    - Continue same dose
    - Recheck FBC in three months

**Indications for Haematology Specialist clinic review:**
- the patient requires ever increasing doses of HU to control the counts
- the counts cannot be controlled by 2.0 g/day HU
- the patient develops any adverse effects eg, GI disturbance, leg ulcer
- the patient complains of abdominal discomfort/ has an enlarging spleen
- the patient develops any thrombotic event
- neutrophil count drops to <1.0 x 10^3 / mm^3 or Hb <10.0 g/dL