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The diagnosis and management of erythrocytosis

Clodagh Keohane,¹ Mary Frances McMullin,² Claire Harrison¹

¹Haematology Department, Guy's and St Thomas' NHS Foundation Trust, London SE1 9RT, UK

²Haematology Department, Centre for Cancer Research and Cell Biology, Queen's University Belfast, Belfast, UK

Correspondence to: C Harrison
Claire.Harrison@gstt.nhs.uk

Cite this as: *BMJ* 2013;347:f6667
doi: 10.1136/bmj.f6667

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Erythrocytosis is an increase in the number of red blood cells. In a recent study from the United States, the prevalence of primary erythrocytosis (known as polycythaemia vera) was 44-57 per 100 000.¹ The prevalence of secondary erythrocytosis is considerably higher but is difficult to quantify owing to the diversity of causes and paucity of data. This review aims to provide an update on the diagnostic pathway for patients presenting with erythrocytosis, as well as up to date appraised data on the management of such patients.

What is the definition of erythrocytosis?

Erythrocytosis is suspected when haemoglobin is above 185 g/L or the packed cell volume is greater than 0.52 in a man or 165 g/L and 0.48, respectively, in a woman. The packed cell volume is a measure of the volume percentage of red blood cells in whole blood. In the past, the term polycythaemia was used synonymously with erythrocytosis; however, this is incorrect because polycythaemia implies an increase in all blood cells.² An absolute or true erythrocytosis is present only when the red cell mass (a highly specialised nuclear medicine test) is greater than 125% of that predicted for sex and body mass. A red cell mass test might show an absolute erythrocytosis or an apparent erythrocytosis (normal red cell mass but reduced plasma volume).

Factors associated with apparent erythrocytosis are obesity, alcohol excess, smoking, and hypertension. Circumstantial evidence from small non-randomised studies indicates that these patients have increased morbidity and mortality.³⁻⁵ However, it is not clear whether this increase is because of the raised packed cell volume, and there are no randomised studies to show that reducing the packed cell volume reduces morbidity or mortality. A retrospective study found that in 30% of patients, packed cell volume

SOURCES AND SELECTION CRITERIA

We searched PubMed to identify peer reviewed original articles, meta-analyses, and reviews. We considered only those papers that were written in English, published from 1966 until the present day, which described studies that had adequate scientific validity. The authors' own collections and older references generated from initial papers were also examined. Randomised trials and series of patients and single case reports were considered if appropriate.

returns to normal with serial measurements,⁶ and modification of risk factors such as smoking cessation can reduce packed cell volume. Guidelines from the British Committee for Standards in Haematology suggest that venesection should be considered only in patients with a recent thrombosis, additional risk factors for thrombosis, or a packed cell volume greater than 0.54 (three standard deviations above the mean).²

Why does erythrocytosis occur?

Regulation of erythropoiesis is a complex process that involves oxygen sensing and the production of erythropoietin. Erythrocytosis is defined as primary if a primary defect in the erythroid compartment of the bone marrow leads to increased red cell production and secondary if something external to the bone marrow (usually erythropoietin) is produced in excess and drives red cell production. For example, the most common cause of acquired primary erythrocytosis is polycythaemia vera, where patients have a mutation in the *JAK2* gene. This leads to an abnormal, constitutively active protein, which drives increased production of red and white cells and platelets. Rare congenital mutations in the erythropoietin receptor gene can also cause primary erythrocytosis. A variety of rare genetic abnormalities, such as mutations that cause high oxygen affinity haemoglobin, can cause congenital secondary erythrocytosis. More common conditions that underlie secondary erythrocytosis include hypoxia from respiratory disease (the most common of these secondary causes) and cardiac disease, renal disorders, and exogenous administration of erythropoietin (box 1). When no cause can be identified, the condition is termed idiopathic erythrocytosis.

What are the clinical consequences of erythrocytosis?

Apart from the risk of underlying disease that might need to be treated, there is a well defined association between erythrocytosis, rise in blood viscosity, and risk of thrombosis. For example, the 34 year follow-up of the Framingham cohort reported an association between being in the

SUMMARY POINTS

Erythrocytosis is a common reason for referral to haematology services and is usually secondary in origin
Referral thresholds for iron replete patients are packed cell volume persistently >0.52 in men and >0.48 in women
The cause can often be elucidated from a detailed medical and drug history
Common secondary causes include smoking, hypoxia, and diuretics
Intervention is not always indicated, and the decision to venesection is often made on a case by case basis after a risk-benefit assessment
True polycythaemia vera is rare. It carries an increased risk of thrombosis and progression to myelofibrosis or leukaemia and requires specialist management

Box 1 | Causes of erythrocytosis in clinical practice

Common causes

Hypoxia: Smoking, lung or cardiac disease, sleep apnoea
 Drugs: Diuretics, testosterone or anabolic steroids, erythropoietin
 Polycythaemia vera

Rare causes

Primary erythrocytosis (intrinsic to the red cells):
 erythropoietin receptor mutation
Congenital forms of secondary erythrocytosis (extrinsic to the red cells)

Altered affinity of oxyhaemoglobin:

- High oxygen affinity haemoglobin
- Bisphosphoglycerate mutase deficiency
- Methaemoglobinaemia

Oxygen sensing pathway defects:

- VHL gene mutation (Chuvash erythrocytosis)
- PHD2 mutations
- HIF2A mutations

Acquired forms of secondary erythrocytosis (extrinsic to the red cells)

Central hypoxic process:

- Carbon monoxide poisoning
- High altitude habitat

Local renal hypoxia:

- Renal artery stenosis
- End stage renal disease
- Hydronephrosis
- Renal cysts (polycystic kidney disease)
- Post-renal transplant erythrocytosis

Pathological erythropoietin production:

- Cerebellar haemangioblastoma
- Meningioma
- Parathyroid carcinoma or adenoma
- Hepatocellular carcinoma
- Renal cell carcinoma
- Pheochromocytoma
- Uterine leiomyoma

Idiopathic erythrocytosis

group with the highest packed cell volume (five groups in total) and the risk of cardiovascular mortality and morbidity.⁷ The multivariate adjusted odds ratio for cardiovascular morbidity was 1.6 (P=0.0018) for women and 1.29 (P=0.019) for men aged 35-64 years who were in this group. Box 2 lists the symptoms of raised blood viscosity.

The management of erythrocytosis needs to take into account whether the rise in packed cell volume is a physiological response. For example, in cyanotic heart disease, the physiological response to hypoxia is an increase in red cell production, which aids oxygen delivery, so treatment of erythrocytosis in this situation could worsen oxygen delivery to the tissues and the patient's symptoms, such as breathlessness.

How should erythrocytosis be investigated in primary care?

Erythrocytosis is often discovered incidentally. The full blood count should be repeated to see whether the rise

is transient (minimum of one week interval). As well as repeating the test, look to see if it has been done in the past and whether the raised packed cell volume is a new finding or whether the trend has been present for while. If present for some time, this suggests a true erythrocytosis. Once-off borderline increases in packed cell volume often return to the normal range when patients are reviewed in the haematology clinic.

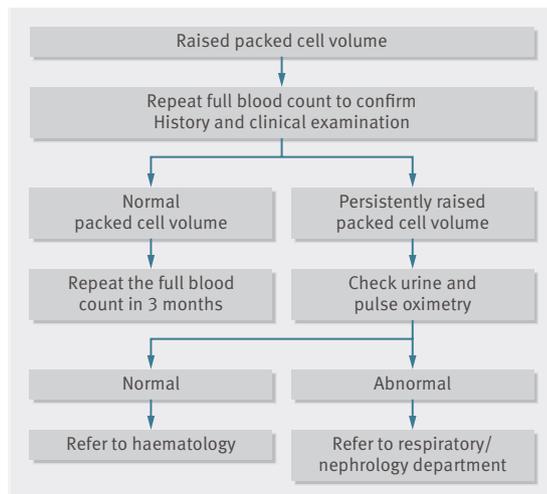
Undertake a clinical history and examination to search for the more common causes of a raised packed cell volume (box 1) and to look for symptoms related to raised blood viscosity (box 2). Ask about smoking and alcohol history; use of thiazide diuretics, testosterone, and anabolic steroids or any recent change in drugs that coincides with the increase in packed cell volume; and symptoms suggestive of obstructive sleep apnoea, such as daytime somnolence. Erythrocytosis as a result of serious medical comorbidities—such as cyanotic congenital heart disease or renal transplantation—is usually apparent from the medical history.

Initial investigations that can be performed in primary care to help identify the cause of persistently raised packed cell volume include pulse oximetry (for hypoxia) and urine dipstick (renal causes). Refer patients with haematuria or hypoxia to the appropriate specialists (figure).

What investigations will be carried out in the hospital setting?

Refer patients with persistent haemoglobin concentration or packed cell volume above the upper limit of normal and no obvious cause (box 1) to a haematologist for further investigation (box 3). Urgently refer patients with polycythaemia (raised white blood cell and platelet counts in addition to packed cell volume) and those with symptoms of raised viscosity (box 2). The diagnosis of these patients has been radically altered by the description of a mutation in JAK2, known as JAK2 V617F, because more than 95% of those with polycythaemia vera test positive for this mutation.^{8,9}

Patients with erythrocytosis need to be divided into those with a likely secondary cause, such as smoking or



Diagnostic pathway for general practitioners in patients with erythrocytosis

the recent addition of thiazide diuretic, and those with no clear cause (see box 3). *JAK2* testing is performed in patients without a clear cause in whom polycythaemia vera is likely. Baseline investigations for erythrocytosis in the haematology clinic include a blood film to look for features of myeloproliferative disease, such as basophilia; serum ferritin (because iron deficiency can mask the degree of erythrocytosis); and renal and liver profiles, to look for undiagnosed renal or hepatic disease (which can cause erythrocytosis; box 1). An abdominal ultrasound is often performed to assess for splenomegaly. An enlarged spleen is seen radiographically in two thirds of patients with polycythaemia vera, although this may not be clinically palpable.¹⁰ Ultrasound should be performed in all patients with a high index of suspicion of having polycythaemia vera and those with confirmed disease.

If *JAK2* testing is negative, measurement of serum erythropoietin can be helpful. A low value suggests a primary bone marrow disease and should prompt testing for the rarer exon 12 mutation of *JAK2*, which is present in 2% of patients with polycythaemia vera. Bone marrow aspiration and trephine biopsy should also be considered. If erythropoietin is raised, a cause of exogenous production of erythropoietin (box 1) should be sought. For patients without a *JAK2* mutation and normal erythropoietin, the next step is usually measurement of red cell mass—the definitive way to determine whether a true erythrocytosis exists. Bone marrow aspiration and trephine biopsy should also be considered, as well as investigation for rare mutations (box 1).

How is primary erythrocytosis managed?

British Committee for Standards in Haematology guidelines recommend that patients are individually managed according to their symptoms.² Polycythaemia vera is a rare lymphoproliferative disorder and patients have a 1.6 greater risk of thrombosis compared with the general population, so the main aim of treatment is to prevent thrombosis; paradoxically, haemorrhage may also be a problem, but this is usually confined to patients with severe thrombocytosis. The mechanism is not entirely clear, but it may be caused by acquired von Willebrand's disease. Patients with polycythaemia vera need long term follow-up in a specialist clinic. This is not only to manage cytoreductive treatment but to monitor signs of disease progression to the myelofibrotic stage (the “burnt out” phase, where the bone marrow is replaced by dense fibrous bands of reticulin and cytopenias are common, the incidence varying from 6% to 15% at 15 years).^{11 12} Using evidence based risk factors, patients with polycythaemia vera are stratified into those at low, intermediate, or high risk of thrombosis according to age, history of thrombosis, and cardiovascular risk factors. Patients can also have a raised platelet count and white cell count, which will increase the risk of thrombosis further.¹³ Cytoreductive treatment, which reduces packed cell volume as well as the numbers of leucocytes and platelets, is indicated for those with high risk disease but not usually for those with low risk disease. Treatment decisions for patients falling into the intermediate risk categories are decided on a case by case basis.

Venesection (usually 450 mL of blood; to maintain a target packed cell volume <0.45), together with low dose

Box 2 | Symptoms of hyperviscosity

Chest and abdominal pain
Myalgia and weakness
Fatigue
Headache
Blurred vision or symptoms to suggest amaurosis fugax
Paraesthesia
Slow mentation, sense of depersonalisation

Box 3 | What the haematologist will do

Initial investigations

Repeat full blood count and blood film
Iron studies/ferritin
Serum erythropoietin concentration
JAK2 mutation
Oxygen saturations and urine dipstick (if not previously done)
Renal and liver profile (if not previously done)

Secondary investigations

Abdominal ultrasound
Chest radiography
Referral for sleep study or lung function
Bone marrow aspirate and trephine
Measurement of red cell mass
JAK2 exon 12 mutation
Erythropoietin receptor gene analysis
VHL analysis

aspirin, is a mainstay of treatment in polycythaemia vera. Until recently, the only randomised study to compare phlebotomy with cytoreductive treatment was performed more than 30 years ago (PVSG-01 trial).¹⁴ In early 2013, the CYTO-PV Collaborative Group published the results of a large well conducted randomised trial. It found that patients with polycythaemia vera and a packed cell volume target of less than 0.45 had a significantly lower rate of death from cardiovascular disease and major thrombosis than did those with a target of 0.45-0.50 (4.4% v 10.9%; hazard ratio 2.69, 95% confidence interval 1.19 to 6.12; $P=0.02$).¹⁵ The ECLAP study, a double blind placebo controlled randomised trial of 518 patients, confirmed the safety and efficacy of aspirin in polycythaemia vera.¹⁶ Treatment with aspirin as compared with placebo reduced the risk of the endpoint of non-fatal myocardial infarction, non-fatal stroke, pulmonary embolism, major venous thrombosis or death from cardiovascular cause (relative risk 0.4; $P=0.03$). The incidence of major bleeding episodes was not significantly increased in the aspirin group.¹⁶

Several cytoreductive agents are used to treat high risk polycythaemia vera, some of which—such as busulfan and hydroxycarbamide (hydroxyurea)—have a long established role; others, such as Janus kinase (JAK) inhibitors, are novel and emerging treatments whose roles are yet to be clearly defined. Hydroxyurea (ribonucleotide reductase inhibitor) is the first line cytoreductive agent for the treatment of high risk polycythaemia vera in patients over the age of 60 years.² There is controversy surrounding the potential leukaemogenicity of this agent because acute myeloid leukaemia is part of the natural course of polycythaemia vera. Small studies report a variable risk

ADDITIONAL EDUCATIONAL RESOURCES

Resources for healthcare professionals

British Committee for Standards in Haematology (www.bcshguidelines.com)
—Guidelines for the diagnosis, investigation, and management of haematological diseases, including polycythaemia and erythrocytosis

Cranston JM, Crockett AJ, Moss JR, Alpers JH. Domiciliary oxygen for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2005;4:CD001744.

Review that includes the evidence for oxygen therapy reducing hypoxia driven erythrocytosis

Marchioli R, Finazzi G, Specchia G, Cacciola R, Cavazzina R, Cillonì D, et al. Cardiovascular events and intensity of treatment in polycythemia vera. *N Engl J Med* 2013;368:22-33. An important paper guiding therapeutic targets in polycythaemia

Resources for patients:

MPD Voice (www.mpdvoice.org.uk)

—Patient charity that provides information on polycythaemia vera including diagnosis, treatment, and clinical trials

of leukaemia, but larger studies have found that the risk is no different from that of untreated patients.^{17 18} However, it is clear that, over time, the use of multiple cytotoxic agents with leukaemic potential together with hydroxyurea increases the risk of transformation to leukaemia. Data from a long term follow-up study showed that at 10, 15, and 20 years, the cumulative incidence of acute myeloid leukemia/myelodysplastic syndrome was 6.6%, 16.5%, and 24% in patients randomised to hydroxyurea and 13%, 34%, and 52% in the pipobroman arm ($P=0.004$).¹⁹ Alternative cytoreductive agents are considered in young patients, such as interferon alfa, which is not teratogenic or leukaemogenic. Busulfan is an alkylating agent, and the European LeukaemiaNet guidelines suggest that its use should be limited to patients over 65 years owing to its well documented leukaemogenicity, especially when used sequentially with other agents, as is also the case for pipobroman.²⁰

How is secondary erythrocytosis managed?**Congenital erythrocytosis**

Rare congenital defects of haemoglobin, such as haemoglobin with a high affinity for oxygen, have been described. Affected patients have a variable phenotype but usually need treatment only if they develop viscosity-like symptoms (see box 2). Other congenital secondary causes include defects in the oxygen sensing pathway, such as *VHL* gene mutation (Chuvash erythrocytosis). Congenital erythrocytosis should be managed by a specialist haematology service. The mainstay of treatment in these patients will be venesection.

Hypoxia driven erythrocytosis

Cyanotic heart disease, pulmonary disease, and smoking can all cause an erythrocytosis as a compensatory mechanism in response to hypoxia. The challenge with these patients is to balance oxygen delivery against the effects of hyperviscosity from a raised packed cell volume. In patients with hypoxic pulmonary disease, the development of erythrocytosis is associated with an increased risk of cor pulmonale and a median survival of two to three years.²¹ A Cochrane review confirmed that long term oxygen therapy reduces mortality in patients with chronic

obstructive pulmonary disease and severe hypoxia (peto odds ratio of 0.45 and 0.42 for the two main randomised controlled trials).²² Long term oxygen therapy also reduces packed cell volume by improving oxygenation.²³⁻²⁵ Therefore, patients with pulmonary driven erythrocytosis should be referred to a specialist respiratory doctor for consideration of treatments to improve oxygenation and tackle the underlying cause for the compensatory erythrocytosis.

Obstructive sleep apnoea can also cause erythrocytosis, and these patients should also be reviewed by a respiratory doctor. Evidence from small case series suggests that venesection should be considered in patients who have symptoms associated with hyperviscosity or a packed cell volume greater than 0.56; a target packed cell volume of 0.50-0.52 has been shown to improve exercise tolerance.^{2 26-29}

In cyanotic congenital heart disease a compensatory erythrocytosis develops to maintain delivery of oxygen to the tissues. As the packed cell volume increases, symptoms of hyperviscosity may develop, although many patients remain symptom free even when the packed cell volume is greater than 0.70.^{30 31} The management of these patients is complex and they should be managed in a unit with an interest in cyanotic congenital heart disease. Venesection should be performed only in those with symptoms and in an isovolaemic manner, with a target decided on a case by case basis.²

A raised packed cell volume is well documented after renal transplantation, being seen in 10-15% of patients at 24 months. This increase has a multitude of causes, and it is associated with considerable morbidity. A review of 53 cases of erythrocytosis after renal transplantation reported an increase in thromboembolic events (18.9%) compared with transplant recipients without a raised packed cell volume (0%), although this finding is not consistent among all studies.³² Prospective randomised studies show that these patients usually respond well to angiotensin converting enzyme inhibitors or angiotensin receptor blockers, leading to a reduction in the packed cell volume within three months.^{33 34} Every measure should be taken to avoid dehydration in these patients by the judicious use of diuretics and rehydration if diarrhoea or vomiting occurs. Patients who do not respond to angiotensin converting enzyme inhibitors or angiotensin receptor blockers can be venesected to a target packed cell volume of less than 0.45, but iron deficiency may become a problem. As is the case in all instances of erythrocytosis, iron replacement therapy may be used judiciously, but the packed cell volume must be closely monitored. Adenosine facilitates the release of erythropoietin and is also thought to influence the bone marrow response to erythropoietin. In a study of eight patients with erythrocytosis after renal transplantation and five healthy controls, an eight week course of theophylline significantly reduced serum erythropoietin and packed cell volume in both groups.³⁵ However the reduction in erythrocytosis in response to theophylline is less predictable than that seen with angiotensin converting enzyme inhibitors or angiotensin receptor blockers, and detailed outcome data for the use of all of these agents are lacking.

Contributors: All authors reviewed the literature and drafted and edited the manuscript. CH is guarantor.

We have read and understood the BMJ Group policy on declaration of interests and declare the following interests: none.

Provenance and peer review: Commissioned; externally peer reviewed.

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ANSWERS TO ENDGAMES, p 36 For long answers go to the Education channel on bmj.com

PICTURE QUIZ Cerebral mass in HIV infection

- The image shows a 13 mm diameter ring enhancing lesion in the left superior frontal gyrus with perilesional oedema. Two similar lesions, with some enhancement in their walls but no surrounding oedema, are also seen in the left occipital and left parietal lobes.
- Cerebral toxoplasmosis, tuberculomas, cryptococcosis, primary central nervous system lymphoma, pyogenic cerebral abscesses, primary tumours of the central nervous system, solitary metastases, cerebral amoebiasis, neurosarcoidosis, mycotic granulomas, and neurocysticercosis.
- Magnetic resonance spectroscopy, erythrocyte sedimentation rate, cryptococcal antigen, and cysticercosis serology (enzyme linked immunosorbent assay (ELISA), immunoblotting) are useful. If lumbar puncture is not contraindicated, opening pressure should be measured and cerebrospinal fluid taken for microscopy, cell counts, biochemistry, and *Mycobacterium tuberculosis* culture and polymerase chain reaction (PCR). Other tests on spinal fluid include Epstein-Barr virus DNA; *Toxoplasma gondii* and JC virus PCR; and measurement of angiotensin converting enzyme, lysozyme, and β_2 microglobulin.
- In patients with HIV, the possibility of multiple diseases should be considered. If the CD4 count is greater than 300×10^6 cells/L, cerebral toxoplasmosis and cryptococcosis are unlikely. Spinal fluid is positive for Epstein-Barr virus DNA in all patients with primary central nervous system lymphoma. However, a brain lesion with mass effect is a contraindication for lumbar puncture. A high index of suspicion for neurocysticercosis is needed. Anthelmintics, together with anticonvulsants, can reduce seizure activity. Concomitant administration of steroids is indicated to suppress the inflammatory response induced by the destruction of live cysticerci.

STATISTICAL QUESTION

What is a non-inferiority trial?

Statements *a*, *b*, and *c* are all true.

ANATOMY QUIZ

An intraoperative cholangiogram: unusual anatomy

- A: Right hepatic duct
- B: Cystic duct; the cystic duct is seen opening into the right hepatic duct, an uncommon anatomical variant present in around 0.3% of the population
- C: Ampulla of Vater
- D: Left hepatic duct
- E: Common bile duct