

GUIDELINES FOR THE DIAGNOSIS, INVESTIGATION AND MANAGEMENT OF POLYCYTHAEMIA/ERYTHROCYTOSIS

Writing Group

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Traditionally, polycythaemia has been used to identify a group of varied disorders with an increase in circulating red cells which are typified by a persistently raised haematocrit (Hct). Since only the red cell lineage is involved, the term erythrocytosis has more validity and will be used throughout this article. Polycythaemia will be retained in relation to the clonal disorder, polycythaemia vera (PV) in which three cell lineages are involved.

Aim

The purpose of this guideline is to provide a rational approach to diagnosis, investigation and management of patients with an erythrocytosis. This will include recommendations on the management of polycythaemia vera, apparent and relative erythrocytosis, idiopathic erythrocytosis and the secondary erythrocytoses due to high oxygen affinity haemoglobin, hypoxia due to chronic lung disease, congenital cyanotic heart disease and post renal transplantation.

Methods

The guideline group was selected to include UK based medical experts. The drafting group met (real or virtual) on four occasions and communicated by email. Each member of the group was allocated responsibility for the preparation of a selected component of the first draft. Medline, CANCELIT and EMBASE were systematically searched for publications in English from 1966 to June 2004. Relevant literature in group members own collections and older references generated from initial papers were also examined. The Cochrane controlled trials register and the Cochrane optimal search strategy for randomised controlled trials was searched but no additional material was identified. Randomised trials and series of patients and single case reports if appropriate were considered. Meeting abstracts were not included in the systematic search strategy. The group leader synthesized the draft components which were subsequently revised by consensus. No recommendations are included for which full consensus was not achieved. The guideline was reviewed by sounding boards and BSCH and comments incorporated where appropriate. Criteria used to quote levels and grades of evidence are outlined in Table 1.

Diagnosis of Erythrocytosis

Patients with a persistently raised venous haematocrit (Hct) (>0.52 males, >0.48 females for > 2 months) should, in general, be investigated by measurement of their red cell mass (RCM). A number of physiological factors have been shown to influence the Hct value, although in practice the use of only minimal or no venous occlusion when taking the blood sample is the most important. In addition, Coulter 'S' and Coulter 'S Plus' analysers are known to underestimate Hct (approximately 7% at reduced MCH values). As a result a correction factor should be applied (Guthrie and Pearson 1982)

Males and females with Hct values above 0.60 and 0.56 respectively, however, can be assumed to have an absolute erythrocytosis and do not require confirmatory studies (Pearson 1991). The WHO criteria which accept a haemoglobin of greater than 18.5 in males and 16.5 in females has not been verified. PV can be masked in patients that present with iron deficient anaemia and it may be necessary to administer iron to correct the anaemia. If this is done, it should be done extremely judiciously with at least weekly monitoring of Hct as the Hct can rise very rapidly and may precipitate thromboembolic events.

Red Cell Mass

Recommended methods for the measurement of RCM have been drawn up by the Radionucleotide Panel of the International Committee for Standardization in Haematology (ICSH) (Anonymous 1980). These methods have now been widely adopted and provide within-method accuracy in the order of 2-3%. Traditionally, results and normal ranges have been expressed in terms of ml/kg total body weight. Indeed the widely quoted Polycythemia Vera Study Group (PVSG) criteria include RCM values expressed in ml/kg (Berlin 1975). However, this approach can lack precision in obese individuals as, since adipose tissue is relatively avascular, it may result in high predicted normal values and low measured values. In order to overcome this limitation, the ICSH prediction formulae based on surface area for RCM showed that the scatter of results from 98% of males and 99% of females fall between +/- 25% of the mean value at any given surface area (Pearson *et al*, 1995). Therefore, using these limits as the reference range, the diagnosis of absolute erythrocytosis is made when an individual's measured RCM is more than 25% above their mean predicted value.

Individuals with a raised venous Hct but whose RCM falls within the reference range have an apparent erythrocytosis. "Relative erythrocytosis" as a pathological state where the RCM is in the normal reference range and the plasma volume is below the reference range generally only exists in true pathological states of dehydration (Brown *et al*, 1971).

Recommendations: Red Cell Mass and Terminology

RCM should be expressed in relation to surface area as recommended by the ICSH.

The term 'relative erythrocytosis' should be reserved for states of dehydration.

Apparent erythrocytosis should be used for those individuals who have a raised venous haematocrit but with a red cell mass within the reference range.

The Investigation of Absolute Erythrocytosis

The classification of the absolute erythrocytoses is shown in Table 2. Once an absolute erythrocytosis has been confirmed it is desirable to identify the underlying aetiology although this may not be possible either initially or after prolonged investigation. Nevertheless, the starting point is knowledge of the underlying causes of a secondary erythrocytosis (Table 2) and the diagnostic criteria of PV (Table 3). Frequently, it can be difficult to prove conclusively that an erythrocytosis is either secondary or primary and dual pathologies resulting in an erythrocytosis should be considered, especially in the elderly. Two stages of diagnostic tests are listed in Table 4 (see below for comment). The number and order of tests and intensity of investigation depends on the clinical features after assessment. However, stage one investigations, including serum erythropoietin (EPO) levels and blood gas measurements, should be undertaken in all patients and can facilitate the diagnosis in the majority of cases. Selected tests in stage 2 are undertaken following an evaluation of the initial results.

Stage 1 Investigations

Full Blood Count (FBC)

A neutrophilia is present in approximately two-thirds and thrombocytosis in 50% of PV cases (Berlin 1975) and, as a result, provide useful minor criteria for the diagnosis of PV (Pearson and Messinezy 1996). It should be noted that smokers have significantly higher neutrophil counts than non-smokers (Whitehead *et al*, 1995) and it has been suggested that in smokers the upper limit of normal for neutrophil count should be taken as to $12.5 \times 10^9/l$.

Serum Ferritin and vitamin B₁₂

Low serum ferritin levels are more commonly seen in PV than secondary erythrocytosis. Indeed the absence of iron stores is a frequent finding in PV marrow histology. Although an elevated B₁₂ level is characteristic of PV, resulting from transcobalamin release from an increased granulocytic mass, it is not an essential investigation.

Renal and Liver Function

Erythrocytosis may be associated with both renal and hepatic disease. A serum calcium should be included to exclude the very rare secondary erythrocytosis caused by parathyroid adenomas or carcinoma.

Arterial Oxygen Saturation

The measurement of arterial oxygen saturation (SaO₂), a sensitive indicator of tissue hypoxia, is most easily achieved with the use of a pulse oximeter. However, there are three situations causing hypoxic erythrocytosis in which the SaO₂ can be misleading: carbon monoxide poisoning, the presence of high oxygen affinity haemoglobins and sleep apnoea syndrome. Most instruments provide carbon monoxyhaemoglobin (COHb) measurements and this value should be subtracted to give an accurate SaO₂ result. Smokers generally have higher COHb levels, although a secondary erythrocytosis due to smoking alone is uncommon (Smith and Landaw 1978). High oxygen affinity haemoglobins, as well as congenitally low 2,3 BPG levels, will give rise to a normal SaO₂, despite tissue hypoxia and measurement of the p50 is important to exclude these rare conditions. A SaO₂ below 92% has been taken to indicate a causal relationship with an absolute erythrocytosis (Berlin 1975). A normal daytime SaO₂ can also be seen in the sleep apnoea syndrome and supine hypoventilation due to premature airway closure. It is important therefore to consider these conditions and to enquire about symptoms relating to nocturnal oxygen desaturation, for example snoring, nocturnal restlessness and daytime somnolence. Nocturnal reduction in SaO₂, usually but by no means exclusively seen in obesity (Pearson and Treacher 1990), may be found in 10-20% of patients who would otherwise have been classified as having idiopathic erythrocytosis (Moore-Gillon *et al*, 1986). Review by a chest or sleep physician (to assess the need for a respiratory sleep study) is recommended in patients with erythrocytosis of all types who are known to snore heavily and either have unwanted daytime somnolence (defined as an Epworth Score >10/24 [www.stanford.edu/~dement/epworth.html]) (Johns 1993) or who are significantly overweight (BMI>30kg/m²). A chest X ray is also recommended to exclude lung pathology.

Serum Erythropoietin Levels

Since erythrocyte production is controlled by EPO, a serum EPO level can provide information as to whether the erythrocytosis is hormonally mediated or autonomous. In patients with erythrocytosis secondary to hypoxia, serum EPO levels are typically raised. In contrast, EPO levels in patients with PV are characteristically reduced and remain low in the majority of cases even following adequate venesection (Messinezy *et al*, 2002b). EPO values below the reference range, however, can be seen in idiopathic erythrocytosis, a fact that lowers the specificity of low EPO levels for PV. In addition, a normal serum EPO level excludes neither hypoxia nor PV as the cause of erythrocytosis. Nevertheless, with the availability of specific, sensitive and reproducible EPO assays a low serum EPO levels can now be used as a minor criterion in the diagnosis of PV (Messinezy *et al*, 2002a).

Abdominal Ultrasound

Abdominal ultrasound is an essential investigation in all patients with a proven absolute erythrocytosis to exclude underlying renal and hepatic pathology. In the absence of liver disease, a palpable spleen is a reliable sign of PV and as such has been adopted as a major criterion for its diagnosis. Splenomegaly can be found in two thirds of PV cases by various imaging techniques, although ultrasound is the simplest (Messinezy *et al*, 1997). However, in view of the significant inter-observer error of scanning detection of non-palpable splenomegaly, it has been proposed that this finding be taken as a minor criterion (Table 3). In females pelvic ultrasound would detect leiomyomas which have occasionally been found to be a cause of secondary erythrocytosis.

Stage 2 Investigations

Bone Marrow Examination

Bone marrow aspirate and trephine biopsy are not required to meet the diagnostic criteria for PV (Table 3). However these investigations provide useful information including confirmation of the diagnosis of PV, differentiation from secondary erythrocytosis and other MPDs, and assessment of the degree of fibrosis. They also provide a baseline which can be compared to subsequent bone marrow examinations to assess disease progression or response to therapy. The finding of a chromosomal abnormality establishes clonality

In PV, aspirated bone marrow is expected to have dense particles and cellular trails. There is usually marked erythroid hyperplasia with moderate to marked hyperplasia of granulopoiesis and megakaryopoiesis. As well as increased cells of the neutrophil lineage, eosinophils and basophils are increased but not monocytes. Wide variation in megakaryocyte size, including larger variants with hyperlobated nuclei are characteristic. Iron stores typically are absent.

The bone marrow trephine core is hypercellular for the patient's age. There is trilineage involvement, not selectively and only rarely preferentially erythroid (Pierre *et al*, 2001). Erythroid maturation is maintained and is normoblastic, although erythropoietic nests may be abnormally located abutting trabeculae. Granulocyte maturation is also maintained. It may be left-shifted and distributed in a disorderly fashion, involving loss of the usual preferential localisation of promyelocytes and myelocytes at trabecular margins. There is increased variation in megakaryocyte cell size. Large variants are often predominant and may have uneven or reduced nuclear lobulation. Clusters of megakaryocytes are common and typically pleomorphic, i.e.,

contain mixed large and small cells. There is usually a mild to moderate increase in stromal reticulin (grade 2-3). (Imbert *et al*, 2001).

Histological features supporting a diagnosis of secondary erythrocytosis rather than PV include the presence of stromal inflammatory features such as increased plasma cells, increased haemosiderin in stromal macrophages and evidence of abundant background apoptotic activity (Thiele *et al*, 2001b).

Bone marrow histology is a B criterion in the WHO Classification and is helpful in distinguishing PV from reactive conditions with secondary erythrocytosis. However, there is histological overlap with other Chronic Myeloproliferative Disorders (CMPD) which currently limits the usefulness of histology in sub-classification (Pierre *et al*, 2001).

(In doubtful diagnostic situations it may be helpful to refer the sample to a haematopathologist with expertise in trephine biopsy interpretation).

Karyotype

Cytogenetic Abnormalities are found in 10-20% of patients with PV. The abnormalities trisomy of chromosomes 8 and 9, del(20q), del (13q) and del (1p) are the most commonly found. An abnormal karyotype, a clonality marker, is a major diagnostic criteria. Patients who progress to myelodysplastic syndrome or acute leukaemia almost always have a karyotypic abnormality (Pierre *et al*, 2001).

Culture Studies of BFU-E (burst forming units-erythroid)

The culture of the mononuclear non-adherent fraction of peripheral blood cells or bone marrow cells of patients with PV in serum-containing medium without the addition of EPO leads to the growth of BFU-E – so-called ‘endogenous erythroid colonies’. This feature, which is not usually found in normal individuals or patients with secondary erythrocytoses, has been shown to be a good marker for PV (Partanen *et al*, 1989). Despite these observations, culture techniques are not standardised and are expensive. It is for these reasons that the finding of endogenous erythroid colonies is best regarded as a minor diagnostic criteria.

Oxygen Dissociation Curve (p50)

It is important to examine the p50 in patients with unexplained erythrocytosis to exclude a high affinity haemoglobin. There are a large number of beta-chain haemoglobin variants that have increased oxygen affinity and a resultant left shifted oxygen dissociation curve. (For this test, contact Special Haematology St Thomas’s, London on 0207188 3421 or Department of Haematology, City Hospital, Birmingham on 0121 507 4577 to discuss. A 5ml EDTA sample will be required from the patients and a normal control, bled at the same time).

Erythropoietin Receptor and von Hippel-Landau (VHL) gene mutation analysis

Patients with an unexplained erythrocytosis and low serum EPO levels should be considered for investigation of an EPO receptor mutation (Percy *et al*, 1998). The Chuvash form of erythrocytosis, an autosomal recessive disorder common to a large number of families in central Russia, has been shown to result from mutations in the VHL gene. Recently, a small number of patients of Asian and Western European ancestry with erythrocytosis have also been reported to have *VHL* mutations (Percy *et al*, 2003). These patients have inappropriately normal or high EPO

levels for their Hct. (Investigation of *EPOR* and *VHL* gene mutations can be analysed by sending an EDTA sample by post to Dr. M Percy, Dept of Haematology, C Floor, Belfast City Hospital, Lisburn Road, Belfast, 02890329241 ext. 3361)

PRV-1 and Other Investigations

A novel cell surface receptor *PRV-1* (*Polycythaemia rubra vera-1*) has been found to be overexpressed in granulocytes from PV patients. Decreased c-MPL protein expression has been found in platelets from patients with PV. These tests are interesting but not currently useful diagnostic tests (Kralovics *et al*, 2003).

Polycythaemia Vera

PV presents at a median age of 60 years. The incidence is the same in males and females. Reports of the annual incidence of PV vary widely from 0.2 / 10⁶/yr (Kurita 1974) to the highest of 28 / 10⁶/yr in Goteborg, Sweden (Kutti and Ridell 2001). Patients often present with either arterial or venous vascular occlusive events (Barabas *et al*, 1973). Coronary and cerebral events are prominent and microvascular disturbances can also occur (Gruppo Italiano Studio Policitemia (GISP) 1995). Occasionally they can present with haemorrhage particularly involving the skin and gastrointestinal tract. Splenic pain, pruritus, gout and constitutional symptoms such as fatigue may also be presenting features.

The disease may progress over time in various ways. Thrombosis and haemorrhage continue to occur. Splenomegaly may develop and increase. A few patients will proceed to develop massive splenomegaly and some myelofibrosis but there is variation in the terminology used. Older terms such as 'spent phase', 'burnt out PV', and 'postpolycythaemic myeloid metaplasia' are poorly elucidated. Modern definitions have relied on the demonstration of significantly increased bone marrow reticulin staining (grade III-IV on a four point scale) together with a clinical syndrome of one or more of progressive splenomegaly, anaemia, leukoerythroblastosis and constitutional symptoms (Thiele *et al*, 2001a). With this definition, the rates of myelofibrotic transformation range from <5% at 10 years in some studies (Berk *et al*, 1995;Tatarsky and Sharon 1997), and up to 15% at 10 years (Najean and Rain 1997b). Acute leukaemia is part of the natural history of PV occurring in untreated patients and in those treated with venesection only (Berk *et al*, 1986). Untreated PV has historically had a dismal prognosis as shown by an early retrospective cohort study (Chievitz and Thiede 1962), where the median survival in untreated patients was 18 months, with thrombosis being the dominant cause of death.

The aims of treatment of PV are therefore to:

- 1) reduce the risk of thrombosis and haemorrhage
- 2) minimize the risk of transformation to acute leukaemia and myelofibrosis
- 3) manage complications which may occur including thrombosis, haemorrhage and pruritus and
- 4) manage pregnancy. These aims were used when assessing the evidence and developing management advice.

Management of Polycythaemia Vera

Randomised Clinical Trials

There have been six randomised clinical trials of treatment for PV (Table 5). Most trials have used the PVSG definition for the diagnosis of PV as the inclusion criterion, ensuring that the study populations are broadly comparable. None of the trials are without methodological problems. Most of these arise in studies of any disease with a long, indolent course, aging patient populations and significant late complications. It also proved difficult to keep patients on allocated treatment when new information became available. No trial had an objective of controlling the platelet count. They have also been reported in different ways. The issue of incidence of leukaemia is particularly problematic as in some cases the actual incidence of acute leukaemia of a group of patients on a particular treatment is reported and in others the calculated actuarial risk on an intention to treat basis is reported. These figures are not comparable. However, there are many clear conclusions about the short and longer-term consequences of various therapeutic options that can be reached from review of the clinical trial data.

The PVSG-01 study established venesection as the first line therapy for PV. In comparison to ^{32}P and chlorambucil, overall survival was significantly longer in the venesection arm, and associated with much lower risks of leukaemia and non-haematological malignancy. An increased risk of thrombosis was seen in the venesection arm, but this was predominantly observed during the first three years when the target Hct was 0.52, (Berk *et al*, 1995). In later years it was reduced to 0.45. There was a large degree of cross-over between arms, with 91% of patients randomised to venesection having changed to alternative treatments by ten years in the French subgroup of patients in the trial (Najean *et al*, 1994). Thus the role of purely using venesection as treatment for PV is unclear.

PVSG-05 was a two arm study comparing ^{32}P to venesection plus high doses of anti-platelet agents, aspirin (300mg tid) and dipyridamole (75mg tid) (Tartaglia *et al*, 1986). The rationale for this trial was to use anti-platelet agents to reduce the increased risk of thrombosis that was observed initially in the phlebotomy arm of PVSG-01. The haemorrhage and death rate was significantly increased in the venesection and antiplatelet arm and the trial was therefore stopped. In the majority of cases a high platelet count was found at the time of haemorrhage but the platelet count was controlled by ^{32}P in the other arm.

The EORTC conducted a trial comparing ^{32}P to busulphan (Cooperative Group, European Organization for Research on Treatment of Cancer (E.O.R.T.C.) 1981). Venesection was added in each arm to maintain the Hct between 0.42 and 0.47. Overall survival was significantly better in the busulphan group with the major reason for the difference being an increase in vascular complications. There were no differences between the arms for other complications such as leukaemia, myelofibrosis or non-haematological malignancy.

The French Polycythaemia Study Group (FPSG) published two randomised trials in 1997. The first was a two arm comparison of ^{32}P alone against ^{32}P with maintenance hydroxycarbamide in patients over the age of 65 years (Najean and Rain 1997b). Significant numbers of patients crossed between the two treatment arms. Median survival was not significantly different. No differences were observed for vascular end-points or progression to myelofibrosis. The actuarial risk of leukaemia was significantly greater for the ^{32}P and hydroxycarbamide group, with the difference becoming apparent after 5 years, and the gap continuing to widen up to the 15th year. In

addition, the actuarial risk of non-haematological malignancy was also much greater for the ³²P and hydroxycarbamide arm, with a similar 5-15 year latency observed.

The second trial from the FPSG was a comparison of hydroxycarbamide therapy with pipobroman in patients under the age of 65 years (Najean and Rain 1997a). Overall actuarial survival was 70% in the two arms at 14 years, compared to an estimated 84% for the age- and sex-matched population. There were no differences between the two groups in vascular end-points or rates of leukaemia or non-haematological malignancy. Myelofibrosis risk was significantly increased in the hydroxycarbamide arm, and tended to occur earlier.

The FPSG (Najean *et al*, 1994) also document very long follow-up in their patients entered into PVSG trials. They had 48 patients in PVSG-01 on chlorambucil, 60 in PVSG -01 and 21 in PVSG-05 on ³²P, 56 in PVSG -01 and 19 in PVSG-05 managed with venesection. Of the original 75 patients randomized to venesection 91% were treated with chemotherapy or radiotherapy. The numbers are thus so small that any analysis of survival is of very dubious accuracy. However the patients in the phlebotomy arm developed myelofibrosis earlier but had very long survival. Therefore intention to treat analysis is not valid. The risk of myelofibrosis was higher if treated by phlebotomy alone.

The ECLAP study establishes the therapeutic benefit of aspirin in PV (Landolfi *et al*, 2004), which followed an earlier pilot study (Anonymous 1997). Patients were randomised between aspirin 100mg daily and placebo. Aspirin significantly reduced the risk of the combined end-point of nonfatal thromboembolic events, or death from cardiovascular causes. The risk of major or minor thrombosis was also significantly decreased. There was no significant increase in haemorrhage. The results of this large, well designed multicentre trial eliminate the concerns about the efficacy and safety of aspirin raised by the earlier, smaller PVSG-05 trial (Tartaglia *et al*, 1986) and provide evidence for the use of aspirin in the management of PV.

The Role of the Platelet Count

Hyperviscosity secondary to the raised Hct is a well-recognised cause of thrombosis in PV. There is a direct and striking correlation between the Hct and rates of thrombosis (Pearson and Wetherley-Mein 1978). However platelets may also be part of the problem. Circumstantial evidence for the benefit of reducing the platelet count is provided by studies in essential thrombocythaemia (ET) where reducing the platelet count significantly reduced the incidence of vascular events (Cortelazzo *et al*, 1995). The role of thrombocytosis in vascular events in PV is controversial. In the PVSG-01 trial, there was no correlation between a raised platelet count and thrombotic events (Berk *et al*, 1986). However, aspirin reduces the incidence of thrombosis in PV (Landolfi *et al*, 2004), suggesting a key role for platelets in thromboembolic events.

Different treatments vary little in the frequency of myelofibrotic transformation, although one randomised trial did show a greater incidence for hydroxycarbamide compared to pipobroman (Najean and Rain 1997a). In this trial, poor control of the platelet count was strongly associated with progression to myelofibrosis. This suggests that controlling the platelet count will reduce thromboembolic events and influence the rate of transformation to myelofibrosis

Venesection

An uncontrolled Hct has been associated with increased morbidity and mortality in surgical patients (Wasserman and Gilbert 1964) and therefore ideally the Hct should be controlled for 3

months before elective surgery. Venesection can be used to control the Hct in PV. In a retrospective study, patients with PV who were treated with venesection and chemotherapy, mainly busulphan, the incidence of arterial and venous thromboembolic events increased as the Hct increased. The cerebral blood flow was significantly below normal in PV patients with a raised Hct and improved by 73% when the Hct was less than 0.45 (Thomas *et al*, 1977). Thus we recommend that the Hct is reduced to below 0.45 by venesection. There is currently no evidence to support a different level of Hct in males and females.

Isovolaemic erythropheresis has been used to reduce the RCM (Kaboth *et al*, 1997). To be used generally it would have significant resource implications but it could be used acutely in the very occasional patient with an evolving ischaemic event.

Recommendation: Venesection

Venesection: The Hct should be maintained at less than 0.45 by venesection. The volume removed should be commensurate with the patient's size and comorbidities

Grade B Recommendation: Evidence Level IIa

Cytoreductive Therapy

Chlorambucil

The alkylating agent chlorambucil was included in the randomized trial PVSG-01 (Berk *et al*, 1981) as listed in Table 5. It was associated with a higher risk of acute leukaemia. The risk of acute leukaemia was higher with higher doses of chlorambucil. Chlorambucil is not now recommended in the treatment of PV.

Busulphan

The alkylating agent Busulphan was used in the EORTC randomized trial and found to be superior to ³²P (Cooperative Group, European Organization for Research on Treatment of Cancer (E.O.R.T.C.) 1981) (see table 5) although both treatments had a low incidence of acute leukaemia at a median follow-up of 8 years. In a single centre retrospective study (Messinezy *et al*, 1985) patients treated with venesection and low dose busulphan were presented. The median survival was 11.1 years. Acute leukaemia and myelofibrosis deaths were significantly increased above the normal population but there were some long survivors with myelofibrosis. These studies show that low dose busulphan is efficacious in controlling PV but since busulphan is an alkylating agent it should be reserved for the elderly.

Pipobroman

Pipobroman is a bromide derivative of piperazine, similar to alkylating agents, which inhibits DNA and RNA polymerase and reduces incorporation of pyrimidine nucleotides into DNA. It has been used extensively in Europe but not in the UK. It has been used in a number of series of patients and one randomised trial (Najejan and Rain 1997a). Rates of acute leukaemia from 4% to 6% have been reported except in one series where a rate of 19.5% was observed (Kiladjian *et al*,

2003) some of whom had other agents added. Rates of myelofibrosis from 0% to 8.5% have been reported.

Hydroxycarbamide

Hydroxycarbamide (formerly known as hydroxyurea) acts by a non-alkylating mechanism by inhibiting the enzyme ribonucleotide reductase which has a rate-limiting role in the regulation of DNA synthesis. It has been used in a phase II study, PVSG-08, and a number of case series. The PVSG-08 study was a Phase II efficacy study that included untreated and previously treated patients (Donovan *et al*, 1984). One year failure free survival was 73% in the previously untreated and 59% in the previously treated. This study showed that hydroxycarbamide was efficacious but recommended dose reduction due to toxicity. The previously untreated patients in this study were compared to historical venesected controls randomised to venesection in PVSG -01 (Kaplan *et al*, 1986) with the Hct maintained at less than 50%. There was less thrombosis including in the early period after the start of therapy and no difference in the rate of leukaemia. With prolonged follow-up, there was no statistical difference in the incidence of myelofibrosis (spent phase) between the groups (Fruchtman *et al*, 1997). Therefore hydroxycarbamide is efficacious using the historical comparison.

In the series of reports of the use of hydroxycarbamide the incidence of acute leukaemia varies from 0% to 6% in patients treated with hydroxycarbamide alone, with the exception of one small single centre series who reported an actual rate of 10.5% (Tatarsky and Sharon 1997; Weinfeld *et al*, 1994). Hydroxycarbamide is thus useful in controlling blood counts in PV. However the FPSG randomized trial in the under 65 year olds showed that pipobroman had a lower rate of progression to leukaemia and other cancers compared to the combination, ³²P and hydroxycarbamide. In the over 65 year olds trial they also showed that progression to myelofibrosis occurred significantly more frequently on hydroxycarbamide but this was related to higher platelet counts in the hydroxycarbamide treated group (Najean and Rain 1997b).

There has been much debate on the leukaemogenicity of hydroxycarbamide. The literature discussed above does not present conclusive evidence for increased leukaemogenicity of hydroxycarbamide given the issue of the development of acute leukaemia in PV. There is some related evidence that should be considered in evaluating hydroxycarbamide. Over 10 years experience of the use of hydroxycarbamide in patients with sickle cell disease is now available and only 4 malignancies have been reported 2 of which occurred soon after starting treatment and are probably not associated (Halsey and Roberts 2003). A study of patients with MPD exposed to hydroxycarbamide *in vivo* showed no increase in acquired DNA mutations compared to controls (Hanft *et al*, 2000). A series of patients with essential thrombocythaemia treated with hydroxycarbamide with 17p deletions is often referred to as proof of the leukaemogenicity of hydroxycarbamide (Sterkers *et al*, 1998). The risk of leukaemia in this series was low at 3.5% in the patients treated with hydroxycarbamide alone. The association with the particular cytogenetic abnormality is not proven in this group as there is no difference in the rate of 17p deletion in those treated with hydroxycarbamide alone and the rate in those not receiving cytotoxic agents. Therefore the case for the leukaemogenicity of hydroxycarbamide is not proven. It is effective in controlling the counts and reducing the thromboembolic events.

Hydroxycarbamide is generally good at controlling PV. Continuous treatment is required and some patients will find this follow-up difficult. There will be some patients who will experience significant side effects including gastrointestinal disturbance and skin pigmentation and leg

ulcers. As there is still some anxiety about the possibility of leukaemia transformation its use should be limited in younger patients

Radiotherapy and radioactive phosphorus ^{32}P

The first patient was treated with ^{32}P in 1940 (Lawrence 1940). Within a few years cases of acute leukaemia were observed. A number of series of patients have been reported over the last 40 years. These series are often retrospective, of patients referred to tertiary centres and are likely to be selected cases which may have aggressive or problematic disease. It is of note that Osgood (Osgood 1964) reported rates of acute leukaemia of 14% in PV patients and 2.5% in CLL patients given the same treatment. This argues that acute leukaemia is part of the inherent nature of PV. The incidence in randomised trials after ^{32}P alone is 2.5 to 15%.

^{32}P is good at controlling PV, intermittent treatment is required and follow-up can therefore be limited. However it does increase the leukaemic transformation rate and therefore its use should be limited to the elderly.

Other Cytotoxic Agents

Melphalan an alkylating agent was used in one small series. Counts were well controlled but acute leukaemia developed in 15% and myelofibrosis in 14% (Logue *et al*, 1970). The antimetabolite 6-Thioguanine, which is a purine antagonist analogue of guanine, was used in one single centre small series and is of some efficacy (Milligan *et al*, 1982). The alkylating agent, carboquone and other agents were given in a single centre series (Higuchi *et al*, 1995). High rates of acute leukaemia resulted.

Interferon- α

Interferon- α (IFN- α) suppresses the proliferation of haematopoietic progenitors both pluripotent and lineage-committed. *In vivo* an inhibitory effect on progenitor cells is consistent with suppression of proliferation as the major mechanism controlling thrombocytosis and erythrocytosis. There are a number of small, single centre series of patients treated with IFN- α for the control of PV. Complete response rates between 29% and 86% have been reported (Taylor *et al*, 1996; Foa *et al*, 1998; Heis *et al*, 1999). The definition of response varies but IFN- α controls the blood counts, reduces or obviates the need for venesection and often reduces the amount of splenomegaly. It is also effective in many cases in reducing symptomatic pruritus. This agent has not been implicated as a possible leukaemogenic agent. However, it is not well tolerated in many patients as shown by the withdrawal rate of between 0% and 41%. One study (Heis *et al*, 1999) also documented a reduced rate of venous thrombosis on treatment but not the rate of arterial thrombosis compared to the rates on prior treatments.

IFN- α is theoretically superior for treating PV as it is effective in controlling counts and there is no risk of leukaemogenesis. Treatment is usually continuous but occasionally can be stopped for prolonged periods of time. The rate of side effects may make it difficult to tolerate. It is most likely to be tolerated in younger patients for whom it is recommended.

Busulphan, hydroxycarbamide and IFN- α can all reduce slight to modest splenomegaly but none are particularly efficacious in reducing massive splenomegaly.

Anagrelide

Anagrelide is a quinazolon derivative which inhibits cyclic nucleotide phosphodiesterase and the release of arachidonic acid from phospholipase possibly by inhibiting phospholipase A₂. It was shown to control the platelet count in MPD patients including PV and side effects included cardiac, gastrointestinal and neurologic. At 5 years 16% of patients had discontinued this treatment because of side effects (Anagrelide Study Group 1992). When the results of the MRC PT-1 trial are available more information on the efficacy of anagrelide may be available. Anagrelide is megakaryocyte specific. It is effective in controlling the platelet count but probably does not control progression of PV for example increasing splenomegaly. The side effect profile may make it difficult for some patients to tolerate.

Recommendations

Drawing together the evidence available from randomised trials and other evidence we make the following recommendations for the management of PV.

Recommendations: Management of Polycythaemia Vera

- 1. Venesection to maintain the Hct to < 0.45**
- 2. Aspirin 75 mg/day unless it is contraindicated**
- 3. Cytoreduction should be considered if:**
 - **Poor tolerance of venesection**
 - **Symptomatic or progressive splenomegaly**
 - **Other evidence of disease progression e.g. weight loss, night sweats**
 - **Thrombocytosis**
- 4. Choice of cytoreductive therapy, if indicated:**
 - **< 40 years: 1st line Interferon, 2nd line hydroxycarbamide or anagrelide**
 - **40-75 years: 1st line Hydroxycarbamide, 2nd line interferon or anagrelide**
 - **>75 years: 1st line Hydroxycarbamide, 2nd line ³²P or intermittent low dose busulphan**

Grade C Recommendation: Evidence Level IV

Thrombotic and Haemorrhagic complications

Thrombotic risk assessment

Thrombotic events are a major cause of morbidity and mortality in PV. Clearly part of this risk relates to derangement of the full blood count principally the Hct and platelet count but other factors may also be important. Conventional risk factors for atherosclerosis, including hyperlipidaemia and hypertension, have been assessed in myeloproliferative disorders (MPD) with variable results. Little work has specifically been performed in PV. Recent recommendations for the management of atherosclerosis would suggest that this patient group would benefit from

aggressive risk management with the use of antihypertensives to maintain normal blood pressure and the use of a statin. The utility of inherited thrombophilia screening in patients without MPD and with previous VTE has recently been questioned (Baglin *et al*, 2003). A recent report suggests that F V Leiden may be more common in MPD patients with recurrent VTE (Ruggeri *et al*, 2002). Although hyperhomocysteinaemia has been documented in patients with ET and PV, this appears neither to be associated with thrombosis nor the MTHFR polymorphism (Faurischou *et al*, 2000). Thus there is no evidence as yet that identification of an inherited thrombophilic abnormality adds to the management of patients with MPD. Clinical studies are required to resolve this issue. Increased prevalence of antiphospholipid syndrome (aPL) has been described in ET and associated with increased risk of thrombosis (Harrison 2002). There have been no reports thus far in this field for patients with PV. Patients with persistent antiphospholipid antibodies should be managed according to guidelines for this condition (Greaves *et al*, 2000).

Recommendations: Assessing risk of thrombosis

- **Patients should be screened for hypertension, hyperlipidaemia, diabetes and a smoking history taken**
- **Conventional risk factors for atherosclerosis should be managed aggressively. All patients should be requested to stop smoking**
- **No current evidence to support routine thrombophilia screening in PV**

Grade C Recommendation: Evidence Level IV

Management of an acute thrombotic event and pharmacoprophylaxis

Acute thrombotic events should be managed according to current guidelines, individual risk factors should be examined and control of the Hct and platelet count optimized. Low-dose aspirin has clear benefit in the secondary prevention of atherosclerosis in haematologically normal patients. However its role in preventing similar complications for patients with MPDs has been controversial with the documented ability of aspirin to uncover a latent bleeding tendency (Tartaglia *et al*, 1986). Two subsequent studies of low dose aspirin (100 mg/day) in ET documented its safety (if plt < 1000 x 10⁹/L and no prior haemorrhage) as well as potential ability to reduce arterial thrombotic complications (van Genderen *et al*, 1995). As discussed the recent ECLAP study (Landolfi *et al*, 2004) supports the safety and utility of aspirin in prevention of non-fatal thrombotic events in PV. Unlike aspirin current risk benefit analysis would suggest no role for oral anticoagulants such as warfarin in the primary prevention of thrombosis. For secondary prevention of venous thromboembolism it remains unclear whether to give a short course (standard practice) or to continue with long term warfarinisation. The only clear indication in this context is if the patients have antiphospholipid syndrome.

The role of the ADP-receptor antagonist clopidogrel in MPD patients is currently unclear. In patients with established atherosclerosis who do not have MPD, the recent CURE study (Clopidogrel in Unstable Angina to Prevent Recurrent Events) showed that combination therapy produced a 20% relative risk reduction of cardiovascular events and death but was associated with a relative increased risk of major bleeding events of 38% (Yusuf *et al*, 2001). This must be of concern in the MPD patient populations. Evidence exists for its benefit in patients with ongoing

evidence of platelet activation whilst receiving aspirin (Nurden *et al*, 1996). These agents may be useful for patients with peptic ulcer disease or aspirin allergy.

Haemorrhage

Haemorrhage is both a less frequent and generally less severe clinical complication of PV than thrombosis. The principal sites affected are skin, mucous membranes and gastrointestinal tract. Haemorrhage is often reported in association with high platelet counts, acquired von Willebrand's disease (Budde *et al*, 1984) and high doses of anti-platelet therapy (Tartaglia *et al*, 1986). Low dose aspirin is infrequently associated with haemorrhagic complications (Landolfi *et al*, 2004). A wide variety of platelet function defects are reported in PV but they are not predictive of bleeding.

Clinically significant bleeding may paradoxically require platelet transfusion (Terasako and Sasai 1998) and a role for epsilon amino caproic acid and tranexamic acid are suggested by some (Spivak 2002). Other measures to consider in the commoner less acute situation include better control of blood counts, adjustment of any concomitant anti-platelet and/or anti-coagulant therapy. The utility of recombinant FVIIa is unknown in MPD patients with uncontrolled life-threatening bleeding and worthy of further study.

Pruritus

Pruritus, typically aquagenic, can be a severe clinical problem in PV. Antihistamines may be of benefit (Weick *et al*, 1982). There have been a number of small studies which have tried to address this problem. Some benefit has been shown with cimetidine (Weick *et al*, 1982) and phototherapy using psoralen and ultraviolet A light (Jeanmougin *et al*, 1996). One study showed improvement in pruritus with iron replacement but the pruritus recurred when iron had to be stopped (Hct controlled to 0.55) (Salem *et al*, 1982). Some studies, (Taylor *et al*, 1996) describe improvements with treatment with IFN- α . Finally Tefferi (Tefferi and Fonseca 2002) reported 10 patients with PV who were treated with selective serotonin re-uptake inhibitors for other reasons and had great improvement in pruritus. There are thus a number of agents which may be useful on an individual case basis.

Pregnancy and Polycythaemia Vera

There is only limited information in the medical literature about the management of PV in pregnancy. Of the 20 pregnancies reported there were 12 live births but 3/12 suffered early neonatal death, 17/20 were reported before 1988. A recent series of pregnancies (Robinson *et al*, 2004) reviewed a further 16 pregnancies in 8 women and documented significantly greater chance of live birth with aggressive management. The risks of pregnancy in PV are probably similar to those for patients with ET where there is a more extensive literature with an overall incidence of first trimester miscarriage of 36% (about twice that expected) and an increased chance of intrauterine growth retardation, intrauterine death and stillbirth described (8%) (Harrison 2002).

An overview of the literature does not enable confident management guidelines to be drawn up. These recommendations are based on current knowledge of PV, ET and the management of antiphospholipid syndrome which all have placental dysfunction as a common pathogenic feature. Therapeutic strategies for PV in pregnancy are influenced by the patients' disease status and prior obstetric history. If any of the following factors are present then the pregnancy is likely to be at high risk of complication to the mother and/or fetus:

- previous venous or arterial thrombosis in mother (whether pregnant or not)
- previous haemorrhage attributed to PV (whether pregnant or not)
- previous pregnancy complication that may have been caused by PV e.g.
 - ≥ 3 first trimester or ≥ 1 second or third trimester pregnancy loss birthweight $< 5^{\text{th}}$ centile for gestation
 - intrauterine death or still birth (with no obvious other cause, evidence of placental dysfunction and growth restricted fetus)
 - significant ante- or postpartum haemorrhage (requiring red cell transfusion)
- severe preeclampsia (necessitating preterm delivery < 37 weeks) or development of any such complication in the index pregnancy
- platelet count rising to $>1,000 \times 10^9/l$

Therapeutic options include antithrombotic treatment, venesection and cytoreductive agents. Although the expected natural fall of the platelet count and Hct during pregnancy may anyway obviate or reduce the need for the latter. The Hct could be controlled with either careful venesection or cytoreductive therapy. The target Hct for a non-pregnant female has yet to be determined but in pregnancy the Hct should be maintained within the normal range appropriate for gestation. There is currently no evidence for maintaining Hct less than this in pregnancy.

Cytoreduction should be avoided in pregnancy, particularly in the first trimester. None of the cytoreductive agents have a product licence for use in pregnancy. Where cytoreduction is deemed necessary (see above), IFN- α is the drug of choice. There are no reports of teratogenic effects in animals or adverse effects in the admittedly small numbers of pregnancies exposed to this drug. However, some evidence suggests that IFN- α may decrease fertility (Griesshammer *et al*, 1998) and so it may be better to avoid it in women who have difficulty in conceiving. Few pregnancies in CML patients treated with hydroxycarbamide have been published (Patel *et al*, 1991; Jackson *et al*, 1993) most without fetal complications. However one still-birth and one malformed infant and teratogenicity in animals have been reported. Hence hydroxycarbamide is probably contraindicated at the time of conception (this also applies to male patients) and during pregnancy. Anagrelide is not recommended because of insufficient documentation of its use in pregnancy. Thus hydroxycarbamide or anagrelide should be gradually withdrawn 3-6 months prior to conception and IFN- α may be substituted if necessary.

Low dose aspirin is safe in pregnancy (Anonymous 1994) and seems advantageous (Griesshammer *et al*, 1998). We recommend that in the absence of clear contraindications all patients should be on aspirin (initially 75mg o.d.) throughout the pregnancy and for 6 weeks after delivery (grade C recommendation, evidence level IV).

Low molecular weight heparin (LMWH) has been used successfully in pregnancies at high risk of thrombosis (Hunt *et al*, 2003). It reduced fetal morbidity (Rai *et al*, 1997), and is safe and has a lower risk of heparin induced thrombocytopenia and osteoporosis compared with unfractionated heparin (Sanson *et al*, 1999). Thus it has been used anecdotally in women with PV and previous thrombosis and/or fetal morbidity. If the patient has had a previous venous or arterial thrombosis,

then the use of LMWH thromboprophylaxis is indicated during pregnancy. Use of unmonitored intermediate dose LMWH is widely used (e.g. enoxaparin 40mg OD) increased to 40mg twice daily from 16 weeks, dropping to 40mg daily for 6 weeks post partum. The recent guidelines for thromboprophylaxis in pregnancy recommend constant reassessment of venous thrombotic risk during pregnancy. The British Society for Haematology guidelines recommend (Walker *et al*, 1993) (grade C evidence level IV) that all women with previous VTE or a thrombophilia should be encouraged to wear graded elastic compression stocking (GECS) throughout their pregnancy and for 6-12 weeks after delivery. The use of GECS is also recommended for pregnant women travelling by air (Kelman *et al*, 2003).

During the pregnancy the patient should be monitored regularly and management is summarized in figure 1. It is important to discuss the implications of the use of thromboprophylaxis with the obstetric anaesthetist for epidural or spinal anaesthesia. During labour dehydration should be avoided, attention should be given to dosing of LMWH and the use of GECS should be considered. In the puerperium we recommend thromboprophylaxis with 6 weeks LMWH for all women with MPD. Breast feeding is safe with heparin and warfarin (providing baby receives adequate vitamin K). Breast feeding is contra-indicated with the cytoreductive agents (IFN α , anagrelide and hydroxycarbamide). The first six weeks post-partum are a high risk time for venous thrombosis blood counts may rise rapidly, thus on-going haematological monitoring is important.

Apparent Erythrocytosis

Evidence that apparent erythrocytosis is associated with increased mortality comes from small non-randomised studies in which the survival of patients with apparent erythrocytosis is compared with the expected death rate of age and sex match controls in the general population. Burge (Burge *et al*, 1975) studied 32 men and 3 women with a Hct of 0.50, RCM of 36ml/kg or below and a plasma volume of 36ml/kg or below. Twenty seven of these patients were followed up for a minimum of 4 years. There was a significant excess of deaths in this patient group over the expected death rate. Weinreb and Shih (Weinreb and Shih 1975) investigated 69 men with a red cell mass of <36ml/kg who were referred for evaluation of a Hct of >0.52. Patients were subdivided depending on whether their RCM was in the upper normal range (group 1) or was no greater than 1 standard deviation from the normal mean (group 2). Patients in group 2 had a significantly lower plasma volume than those in group 1. The survival of patients in group 2 was poorer than in group 1 and group 2 patients had a poorer survival than age matched controls in the general population.

Circumstantial evidence for an increase in morbidity and mortality in apparent erythrocytosis comes from studies showing that individuals with a Hct which is in the upper normal range, or slightly elevated, may be associated with an increase in thrombotic events and cardiovascular mortality compared to those with a Hct in the middle or lower part of the normal range (Lowe 1999).

It is not clear that the increase in mortality associated with apparent erythrocytosis is due to the high Hct, nor are there randomised studies to show that reducing the Hct in apparent erythrocytosis reduces morbidity or mortality. Current management of apparent erythrocytosis may be based on the following observations.

Serial measurements of the Hct in untreated patients with apparent erythrocytosis show that the Hct returns to within the normal range in up to 30% of patients (Messinezy and Pearson 1990).

Modifications in the factors which are associated with apparent erythrocytosis such as obesity, smoking and hypertension may lead to a reduction in Hct (Pearson 1991).

Venesection of male patients with apparent erythrocytosis due to a low plasma volume resulted in a fall of mean Hct from 0.5 to 0.43, with a rise in plasma volume without a reduction in overall blood volume (Humphrey *et al*, 1980).

There is a need for more data on the clinical consequences of apparent erythrocytosis. If it is confirmed to be an independent risk factor for thrombosis, then randomised studies of treatment to lower the Hct are required, on which to base rational management.

Recommendations: Management of apparent erythrocytosis

Confirm that the elevated Hct is persistent, with at least 2 measurement of the Hct under standardised conditions over a 3 month period.

Advise reduction or elimination of factors which may contribute to apparent erythrocytosis, for example, a reduction in smoking and alcohol intake and control of hypertension (without the use of a thiazide diuretic)

Consider venesection in the following circumstances:

- **Patients with a recent history of thrombosis, or with additional risk factors for thrombosis.**
- **Patients whose Hct exceeds 0.54 (>3 standard deviations above the mean), based on the increased risk of thrombosis in idiopathic erythrocytosis and low incidence of normal individuals with a haematocrit of >0.54.**
- **Untreated patients should be monitored to exclude a further rise in Hct and possible evolution to absolute erythrocytosis.**

There is no data on which to base a target Hct for patients undergoing venesection, but a figure of <0.45 has been proposed based on data from patients with PV and idiopathic erythrocytosis (Pearson 1991).

Grade C recommendation; evidence level IV.

Idiopathic Erythrocytosis

The term idiopathic erythrocytosis applies to patients who have an increased RCM and who on investigation do not have any form of known primary or secondary erythrocytosis. It has also been termed 'benign erythrocytosis' but these patients do not always have a benign course (Modan and Modan 1968) and 'pure erythrocytosis' as it was thought to be a pure red cell disorder ((Najean *et al*, 1981). However secondary erythrocytosis is also a pure red cell disorder, therefore idiopathic erythrocytosis is the preferred term. There is a male preponderance in several of the published series (Modan and Modan 1968; Pearson and Wetherley-Mein 1979). The incidence of

vascular complications is high, 46.6% at presentation in one series and 17% of the total patients died of cerebrovascular accidents (Pearson and Wetherley-Mein 1979). In another study the incidence of fatal thromboembolic and haemorrhagic events was the same as in patients with PV (Modan and Modan 1968). A management plan must take this into account.

Recommendations : Idiopathic erythrocytosis

- **Venesection to reduce the Hct to < 0.45 if Hct is > 0.54**
- **Venesection to reduce the Hct to < 0.45 if < 0.54 and there is increased risk of thrombosis i.e evidence of ischaemia, previous history of thrombosis, peripheral vascular disease, diabetes or hypertension**
- **Cytoreductive therapy is contraindicated**

Grade B recommendation; evidence level III.

High Oxygen Affinity Haemoglobins

The physiological adaptations to the inheritance of a high oxygen affinity haemoglobin include a rise in Hct, which is often modest, and an increase in cardiac output. Healthy individuals with a high oxygen affinity haemoglobin and comparable p50 values have differing haemoglobin concentrations, suggesting heterogeneity in the adaptive responses (Charache *et al*, 1978). There have been no randomised studies on venesection therapy for patients with high oxygen affinity haemoglobins, and proof of the efficacy of this treatment is lacking.

Recommendations for venesection are based on, and influenced by, the following observations:

1. Most individuals remain asymptomatic.
2. Experimentally, isovolaemic venesections performed in asymptomatic individuals with a high oxygen affinity haemoglobin, and resulting in a reduction in Hct from mean values of 0.55 to 0.41, can reduce exercise performance (Butler *et al*, 1982; Winslow *et al*, 1983).
3. Hyperviscosity symptoms and thromboembolic episodes have been reported (Fairbanks *et al*, 1971; Weatherall *et al*, 1977).
4. In some families thrombotic episodes have been confined to individuals who are compound heterozygotes for both a high oxygen affinity haemoglobin and a thrombophilic defect (Berruyer *et al*, 1994; Hanss *et al*, 2002).
5. Individuals with dizziness, dyspnoea or angina may derive clinical benefit from venesection (Fairbanks *et al*, 1971; Grace *et al*, 1992).

Recommendations: High Oxygen Affinity Haemoglobins

Possible indications for venesection include the following:

- **Presence of symptoms such as dizziness, dyspnoea or angina, for which a raised Hct is considered to be a contributory factor**
- **One or more previous thrombotic episodes.**
- **Asymptomatic individuals in whom a family member with a high oxygen affinity haemoglobin, similar haemoglobin concentration, and comparable risk factors for thrombosis, has developed thrombotic problems.**

Consideration of a partial exchange transfusion should be given for individuals with a Hct above 0.60 requiring major surgery (Larson *et al*, 1997).

Do not attempt to reduce the Hct to within the normal range. Venesection to maintain the Hct below 0.60 has been recommended (Weatherall *et al*, 1977)

When thrombosis or symptoms compatible with hyperviscosity develop at a lower Hct, a target Hct of 0.52 has been suggested (Pearson T, personal communication)

Grade C recommendation; evidence level IV

Hypoxia

Erythrocytosis secondary to hypoxia occurs in different ambient circulatory conditions from the other forms of erythrocytosis. This influences the compensatory mechanisms for blood flow and also impacts upon management of the erythrocytosis. The challenge in managing these patients is balancing oxygen transport against the effects of increased viscosity due to the elevated Hct. Two areas will be considered in detail: hypoxic pulmonary disease (HPD) and cyanotic congenital heart disease (CCHD).

Hypoxic Pulmonary Disease (HPD)

The development of an erythrocytosis in patients with HPD is associated with an increased risk of the development of cor pulmonale and poor median survival of 2-3 years (Criner 2000). Additional factors affecting circulatory compromise and tissue oxygen delivery include carbon monoxide in smokers, extent of hypercapnia, renal blood flow, acid-base balance (pH), capacity of the bone marrow to respond to erythropoietic drive, position of the oxygen dissociation curve and changes in the peripheral vascular circulation (Harrison and Stokes 1982). Furthermore for an individual patient co-existent age-related vascular disease may also affect therapy.

Long term oxygen therapy improves survival in patients with chronic obstructive pulmonary disease and severe hypoxaemia (PaO₂ below 7.3kPa or <8.0kPa with nocturnal hypoventilation) (Crockett *et al*, 2001). This also reduces the Hct by improving oxygenation. All patients with

erythrocytosis consequent upon HPD should be evaluated by a respiratory physician for consideration of long-term oxygen therapy or alternative methods of improving oxygenation. If they are smokers they should be strongly advised to stop. In addition to supplemental oxygen, nocturnal oxygenation may also be improved by the use of non-invasive ventilation in the case of Type II respiratory failure (Simonds and Elliott 1995) or continuous positive airways pressure, in the case of obstructive sleep apnoea (Jenkinson *et al*, 1999). Therefore failure to achieve adequate oxygenation in HPD should not be accepted without review by a specialist respiratory physician. In addition a clinically relevant minority of patients with erythrocytosis have nocturnal oxygen desaturation due to obstructive sleep apnoea (Moore-Gillon *et al*, 1986) and such patients should be referred for appropriate investigation (Eisensehr and Noachtar 2001).

Benefit of limited venesection in patients with HPD was demonstrated by Weiss (Weisse *et al*, 1975) who showed that reducing the Hct to 0.50-0.52 led to an improvement in exercise tolerance, but a further staged reduction to Hct of 0.45 did not give additional benefit. Numerous other non-controlled patient series have also suggested that control of the Hct reduces pulmonary vascular resistance (Harrison and Stokes 1982;Weisse *et al*, 1975;Segel and Bishop 1966;Harrison *et al*, 1973), improving cerebral blood flow and psychometric testing (Menon *et al*, 1981;Wedzicha *et al*, 1983) as well as subjectively helping confusion and headache (Wade *et al*, 1981). Not all studies however have demonstrated beneficial effects of venesection in these patients (Dayton *et al*, 1975) and there are reports of venesection fatalities (Constantinidis 1979).

It is therefore of interest that a number of other agents have been reported to reduce the Hct in small uncontrolled studies these include dapsons and pyrimethamine (Pengelly 1966) as well as theophyllines (Oren *et al*, 1997) and losartan (Vlahakos *et al*, 1999).

Recommendations: Hypoxic Pulmonary Disease

- **Patients with HPD who develop an erythrocytosis should be evaluated by a respiratory physician for consideration of long-term oxygen therapy or alternative therapy (Grade A, Level 1a).**
- **Patients who are symptomatic of hyperviscosity or have a Hct > 0.56 should have venesection to reduce this to 0.50-0.52 (Grade B, Level III).**
- **There is limited evidence to suggest that therapy with drugs such as ACE inhibitors or angiotensin receptor antagonists could be used in patients who do not tolerate venesection (Grade B recommendation: Evidence Level IIa)**

Cyanotic Congenital Heart Disease (CCHD)

In CCHD a compensatory erythrocytosis develops to maintain tissue oxygen delivery. The underlying heart defects fall into 2 large categories. 1) Patients with absent or poorly developed central pulmonary arteries with pulmonary blood flow via collateral arteries from the aorta or branches and a large right to left shunt (typically pulmonary atresia with a ventricular septal defect and major aorto-pulmonary collateral arteries). 2) Patients with pulmonary vascular disease where the intra-pulmonary arterioles and capillaries have undergone obliterative changes secondary to high pressure and high flow shunts in a variety of simple and complex congenital heart defects and occasionally as a result of palliative surgical shunting procedures (Eisenmenger syndrome). Many of these patients are currently seen only in adult cardiology or haematology

departments (Rosenthal and Anderson 1998) who might now be eligible for corrective or palliative surgery or catheter interventions to decrease the cyanosis and the erythrocytosis.

As the erythrocytosis increases, patients may experience symptoms of hyperviscosity though many may remain free from symptoms for many years even with haematocrits in excess of 70% (Perloff *et al*, 1988).

Thrombosis has been documented in several series of patients with CCHD. Interestingly children, to whom this guideline is NOT intended to apply, appear to have a significantly increased risk of cerebral venous thrombosis that is particularly linked to iron deficiency (Phornphutkul *et al*, 1973). In adults however there is evidence of the occurrence of cerebral arterial and microarterial thrombi and particularly in patients with Fallots' tetralogy pulmonary thrombotic events (Rich 1948; Berthrong and Sabiston 1951). Direct evidence linking thrombus to increased viscosity however remains at best circumstantial in that older patients with cerebral thrombosis tend to be those with the highest Hct values (Phornphutkul *et al*, 1973). A similar link was not been shown in other case series (Perloff *et al*, 1993) but the series was probably not sufficiently powered to detect a difference (Bridges 1994). A statistically significant correlation has also been suggested between stroke, microcytosis and history of phlebotomy in one study of 162 adults with CCHD (Ammash and Warnes 1996). It was not clear from this study when the stroke occurred in relationship to the venesection. There has also been a report of myocardial ischaemia directly related to high Hct in these patients (Yeager and Freed 1984).

CCHD patients who experience symptoms of hyperviscosity (table A) respond with a reduction in these symptoms with venesection. Venesection also results in reduced peripheral vascular resistance, and increased stroke volume, cardiac output and systemic blood flow (Rosenthal *et al*, 1970; Oldershaw and Sutton 1980). Repeated exercise tests two weeks after venesection in one study showed increased oxygen uptake and reduced oxygen debt (Oldershaw and Sutton 1980). The clinical difficulty arises is in discriminating hyperviscosity from heart disease related symptomatology, and a pitfall to be avoided is deciding whether to venesect based upon the Hct alone. Furthermore excessive venesection renders these patients both hypoxic and anaemic reducing tissue oxygenation and reducing exercise tolerance (Somerville 1997).

There have also been concerns when venesection renders patients iron deficient that this may further increase blood viscosity and increase the risk of thrombosis (Linderkamp *et al*, 1979; Hutton 1979). There are several pitfalls in this field, firstly inaccurate Hct estimation in the presence of microcytic indices, and conflicting evidence as to whether iron deficient red cells are more rigid than normal red blood cells. On balance the literature would suggest however that iron deficient red cells are at least as deformable as normal red cells (Pearson 2001). However a key problem when iron deficiency develops in CCHD is that oxygen carrying capacity is no longer optimum (Gidding and Stockman 1988). For example at an MCH value of 20pg and Hct of 0.50, the haemoglobin and hence also oxygen carrying capacity is 11% less than for normal red cells (Van de Pette *et al*, 1986). The corollary is that iron deficient patients with hypochromic cells will have a higher Hct and increased viscosity (and symptoms) than iron replete patients with a similar haemoglobin value and oxygen carrying capacity.

A significant feature of the erythrocytosis in patients with CCHD (when compared to PV) is the absence of a thrombocytosis – indeed the platelet count is frequently low – and evidence for platelet dysfunction. In addition, clotting factors II, V, VII and IX are reduced and may explain the mild bleeding diathesis in these patients (Territo and Rosove 1991). These factors would seem to be theoretically advantageous in preventing stroke produced by the raised viscosity from the

erythrocytosis. Indeed it has been shown and is recommended that these patients should undergo a venesection 24 hours before elective non-cardiac surgery to improve the clotting function (Wedemeyer and Lewis 1973).

(Thorne 1998) suggested isovolumic venesection should only be performed for symptomatic patients if the Hct is greater than 0.65 and the patients had adequate iron stores. If the Hct is below 0.65, iron deficiency should be suspected and if present this should be cautiously treated first as the hyperviscosity symptoms could be due to the iron deficiency itself (Perloff *et al*, 1993). Iron replacement, however, has been documented to cause a rapid rise in Hct or unstable erythrocytosis (Rosove *et al*, 1986) and so there are practical difficulties with these guidelines. A reasonable evidence based approach would be to venesect only symptomatic patients; if iron deficiency occurred then a small amount of iron could be administered with close supervision. Once the haematocrit began to rise – often with in a week – it should be stopped to prevent an exaggerated rise in the Hct. There are anecdotal reports of ischaemic symptoms with iron therapy and control of the Hct by venesection (Sondel *et al*, 1981).

In the absence of strong evidence associating the erythrocytosis with stroke development or evidence for a benefit from routine venesection in these patients, the development of symptoms from excessive venesection in some and the potential for stroke in those rendered iron deficient it seems reasonable for venesection to be restricted to those with symptoms of hyperviscosity. Antiplatelet agents and anticoagulation therapy for the prevention of stroke should be avoided given the increased bleeding tendency unless there are additional risk factors for stroke development such as atrial fibrillation, poor ventricular function or a documented TIA. With continuing advances in surgical, catheter interventional and medical management of these patients, it would be reasonable to suggest that the management of CCHD patients is primarily in a specialist adult congenital heart disease unit with haematological support for the management of hyperviscosity symptoms (Table 6).

Recommendations: Cyanotic Congenital Heart Disease

- Patients with CCHD and an erythrocytosis represent a complex management problem and should be managed primarily in a congenital heart disease unit so that advances in surgery, catheter interventional and medical management that may improve (rarely cure) the erythrocytosis are not missed. Level IV, Grade C. Level IV, Grade C.
- Isovolumic venesection should be performed when the patient has symptoms of hyperviscosity but no general target Hct can be suggested and treatment should be individualised. Level III Grade B
- Excessive venesection may produce iron deficiency which may compromise oxygen delivery and raise the viscosity for a given level of Hb thereby causing a recurrence of symptoms., Iron therapy in this setting should be used judiciously as it may provoke a rapid rise in Hct. Level III Grade B.

Post Renal Transplant Erythrocytosis (PTE) and its Management

The correction of anaemia after a successful renal transplantation is dependent on the adequate production of EPO by the donor organ and the elimination of marrow inhibitors that characterise the uraemic state (Besarab *et al*, 1987). Following a successful transplant, the EPO production usually increases within a few days and results in a correction of the anaemia within three months. However, approximately 10-15% of renal transplant recipients develop an erythrocytosis between 8-24 months later, a condition referred to as post-renal transplant erythrocytosis (PTE) reviewed

in Vlahakos et al, 2003 (Vlahakos *et al*, 2003). Predisposing factors include smoking, diabetes, transplant renal artery stenosis, rejection free course with a well functioning renal graft and adequate erythropoiesis prior to transplantation. The pathogenesis of PTE is poorly understood and is likely to be multifactorial involving abnormal erythroid precursor sensitivity to EPO or altered EPO production, abnormal erythroid sensitivity to angiotensin II or altered angiotensin II production and an elevated concentration of insulin-like growth factor I and its binding proteins (Gaston *et al*, 1994; Julian *et al*, 1998; Brox *et al*, 1998). PTE usually persists, with only 25% undergoing spontaneous remission, and presents clinically in most patients with malaise, headache, lethargy and dizziness. Importantly, PTE can contribute to the onset of hypertension or worsen pre-existing hypertension, and in addition, constitutes a serious thromboembolic risk factor. In one series, 10-30% of cases developed a thrombo-embolic event, that involved both veins and arteries, and which ultimately led to the patients' death in 1% to 2% of cases (Wickre *et al*, 1983).

Management

It is important to prevent further increases in Hct levels by meticulous avoidance of extracellular volume reduction, for example excessive diuresis, diarrhoea and vomiting. PTE was originally treated with repeated venesection although this approach led to severe iron deficiency.

Recently, the beneficial effects of ACE inhibitors (ACEI) and angiotensin II receptor antagonists have been reported (Vlahakos *et al*, 2003). ACEI, including captopril, enalapril, lisinopril, are well tolerated and a dose dependent decrease in Hct is seen within the first month of treatment with maximal effect being reached by 3 months. Similar results have been reported for the angiotensin II receptor antagonist, losartin. The minority of patients (5% to 10%) who fail to respond to one ACEI are not likely to respond to other ACEIs or to losartin, although an occasional patient may respond to a combination of an ACEI and theophylline (Rostaing *et al*, 1995). In the absence of response to these therapeutic interventions, venesection remains the only effective therapy and should be undertaken to achieve a target Hct of 0.45 (Barenbrock *et al*, 1993).

Recommendations: Post Renal Transplant Erythrocytosis

- **Avoid excessive dehydration.**
- **Treat with ACEI or an angiotensin II receptor antagonist**
- **Venesect to Hct of 0.45**

Grade C Recommendation: Evidence level IV.

Useful Web Site

<http://www.acor.org/mpd/>

Table 1

Classification of evidence levels

- Ia Evidence obtained from meta-analysis of randomised controlled trials.
- Ib Evidence obtained from at least one randomised controlled trial
- IIa Evidence obtained from at least one well-designed controlled study without randomisation.
- IIb Evidence obtained from at least one other type of well-designed quasi-experimental study*.
- III Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.
- IV Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.

Classification of grades of recommendations

- A Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing specific recommendation.
(Evidence levels Ia, Ib).
- B Requires the availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation.
(Evidence levels IIa, IIb, III).
- C Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality.
(Evidence level IV).

* Refers to a situation in which implementation of an intervention is outwith the control of the investigators, but an opportunity exists to evaluate its effect.

Table 2

Classification of the Absolute Erythrocytoses

Primary Erythrocytosis
Polycythaemia vera

Secondary erythrocytosis

Congenital

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

Acquired

EPO mediated

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
(High-altitude habitat)

Local renal hypoxia

Renal artery stenosis
End stage renal disease
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

Post - renal transplant erythrocytosis

Idiopathic erythrocytosis

EPO = erythropoietin

Table 3

Proposed modified criteria for the diagnosis of polycythaemia vera. (Pearson and Messinezy 1996)

Major

- A1 Raised red cell mass (>25% above mean normal predicted value¹) or Hct \geq 0.60 males; \geq 0.56 females
- A2 Absence of cause for secondary erythrocytosis (consider possibility of dual pathology)
- A3 Palpable splenomegaly²
- A4 Clonality marker i.e. acquired abnormal marrow karyotype

Minor

- B1 Thrombocytosis (platelet count > 400 x 10⁹/l)
- B2 Neutrophil leucocytosis (neutrophil count > 10 x 10⁹/l in non-smokers;>12.5 x 10⁹/l in smokers)
- B3 Splenomegaly (demonstrated on isotope/ultrasound scanning)^{2,3}
- B4 Characteristic BFU-E growth or reduced serum erythropoietin⁴.

A1+A2+A3 or A4 establishes PV

A1+A2+ any 2 B criteria establishes PV

¹RCM – mean normal predicted value - for males = (1486 x S*) – 825 mls
for females = (1.06 x age) + (822 x S*) mls. (*S=Surface Area).

²Without evidence of a secondary cause such as portal hypertension

³Splenomegaly can be calculated from the ultrasound result (Messinezy *et al*, 1997)

⁴Serum erythropoietin level varies depending on the assay used (Messinezy *et al*, 2002a)

Table 4

Stage 1 and 2 investigations in patients with an absolute erythrocytosis

Stage 1	Stage 2
FBC/Film	Bone marrow aspirate/trephine
Arterial oxygen saturation	Cytogenetics
Ferritin	BFU-E culture
Renal and liver function tests	Oxygen dissociation curve (p50)
Abdominal ultrasound	Sleep study
Serum erythropoietin	Lung function tests
Chest X-Ray	Erythropoietin receptor gene analysis
	<i>VHL</i> gene analysis

Table 5

Randomised trials in polycythaemia vera with rates of important end-points for each of the treatment arms. ⊗ indicates estimates which have been derived from actuarial survival curves for the purposes of this table. * indicates variables which are significantly different between arms in the trial.+ selected patients not intention to treat.

Trial	Therapy	No	Follow-up (yrs)	Median Survival	Thrombosis	Acute Leukaemia	Cancer	MF
PVSG-01 ¹	<i>Phleb</i>	134	Min. 12 Max 18	12.6 yr *	40%* ⊗ (5yr)	1.5%*+ (10 yr)	No ↑*	9% (12 yr)
	³² P	156		10.9 yr *	23%* ⊗ (5 yr)	9.6%* (10 yr)	2.5x↑*	9% (12 yr)
	<i>Cbl</i>	141		9.1 yr *	17%* ⊗ (5 yr)	13.5%* (10 yr)	3.5x↑*	9% (12 yr)
PVSG-05 ²	<i>Phleb+</i> <i>Anti-plt</i>	83	1.2		7 pts			
	³² P	83			2 pts			
EORTC ³	<i>Bu</i>	147	8	70% * (10 yr)	5% deaths *	2%	3%	5%
	³² P	146		55% * (10 yr)	17% deaths*	1%	5%	4%
FPSG >65 yr ⁴	³² P	242	0.3 to 16	11.2 yr	22% ⊗ (10 yr)	12% * ⊗ (10 yr)	15% * ⊗ (10 yr)	8% ⊗ (10 yr)
	³² P + HU	219		9.1 yr	36% ⊗ (10 yr)	20% * ⊗ (10 yr)	20% * ⊗ (10 yr)	15% ⊗ (10 yr)
FPSG <65 yr ⁵	<i>HU</i>	150	0.3 to 16	70% (14 yr)	16% ⊗ (10 yr)	3% ⊗ (10 yr)	4% ⊗ (10 yr)	17% ⊗* (10 yr)
	<i>Pipob</i>	142		70% (14 yr)	15% ⊗ (10 yr)	5% ⊗ (10 yr)	8% ⊗ (10 yr)	2% ⊗* (10 yr)
ECLAP ⁶	<i>Aspirin</i>	253	3		6.7% *			
	<i>Placebo</i>	265			15.5% *			

1. (Berk *et al*, 1995)
2. (Tartaglia *et al*, 1986)
3. (Cooperative Group, European Organization for Research on Treatment of Cancer (E.O.R.T.C.) 1981)
4. (Najean and Rain 1997b)
5. (Najean and Rain 1997a)
6. (Landolfi *et al*, 2004)

Table 6

Symptoms of hyperviscosity in CCHD with erythrocytosis

Chest and abdominal pain

Myalgia and weakness

Fatigue

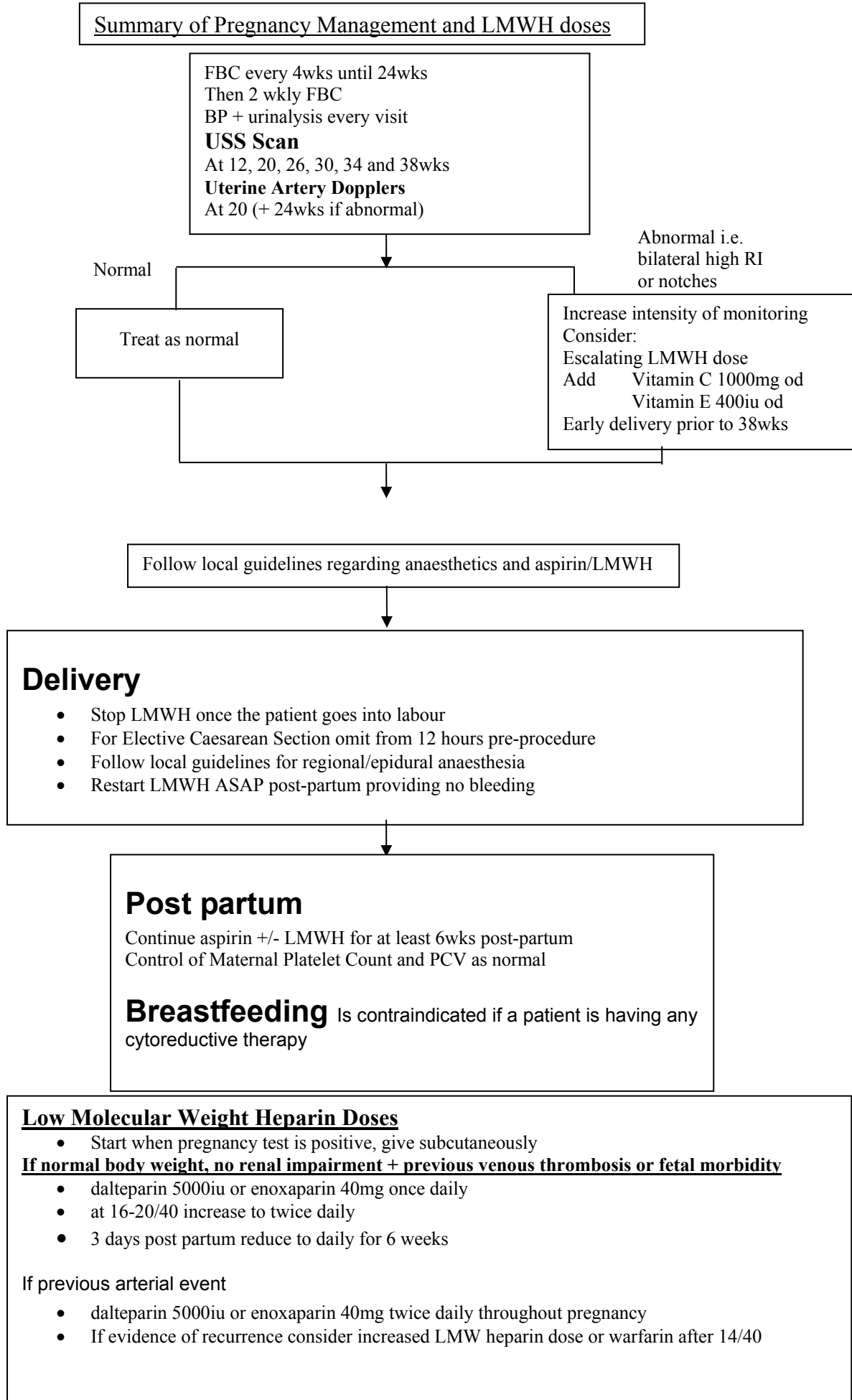
Headache

Blurred vision or symptoms to suggest amaurosis fugax

Paraesthesiae

Slow mentation, sense of depersonalization

FIGURE 1



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