

Guideline for investigation and management of adults and children presenting with a thrombocytosis

Claire N. Harrison,¹ David Bareford,² Nauman Butt,³ Peter Campbell,⁴ Eibhlean Conneally,⁵ Mark Drummond,⁶ Wendy Erber,⁷ Tamara Everington,⁸ Anthony R. Green,⁹ Georgina W. Hall,¹⁰ Beverley J. Hunt,¹ Christopher A. Ludlam,¹¹ Richard Murrin,¹² Catherine Nelson-Piercy,¹ Deepti H. Radia,¹ John T. Reilly,¹³ Jon Van der Walt,¹ Bridget Wilkins¹ and Mary F. McMullin¹⁴
 Writing group: British Committee for Standards in Haematology

¹Guy's and St Thomas' NHS Foundation Trust, London, ²Russells Hall Hospital, Dudley, West Midlands, ³Arrowe Park Hospital Arrowe Park Road Upton Wirral, ⁴Wellcome Trust Sanger Institute, Hinxton, Cambridge, ⁵St. James Hospital, James Street, Dublin, ⁶Gartnavel General Hospital 21 Shelley Road Glasgow, ⁷Addenbrooke's Hospital, Cambridge, ⁸Salisbury Healthcare NHS Trust, Salisbury, Wiltshire, ⁹Cambridge Institute for Medical Research, Hills Road, Cambridge, ¹⁰John Radcliffe Hospital, Headley Way, Headington, Oxford, ¹¹Royal Infirmary, Little France Crescent, Edinburgh, ¹²Sandwell and West Birmingham Hospitals, Dudley Road, Birmingham, ¹³Royal Hallamshire Hospital, Glossop Road, Sheffield, and ¹⁴Belfast City Hospital, Lisburn Road Belfast, UK

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Introduction

The guideline group was selected to be representative of UK-based medical experts. MEDLINE and EMBASE were searched systematically for publications in English from 1966 until October 2009 using a variety of key words. The writing group produced the draft guideline which was subsequently revised by consensus by members of the Haemostasis and Thrombosis and Haemato-oncology Task Forces of the British Committee for Standards in Haematology. The guideline was then reviewed by a sounding board of approximately 50 UK haematologists, the British Committee for Standards in Haematology (BCSH) and the British Society for Haematology Committee and comments incorporated where appropriate. Criteria used to quote levels and grades of evidence are as outlined in the Procedure for Guidelines Commissioned by the BCSH (Table I). The objective of this guideline is to provide healthcare professionals with clear guidance on the investigation and management of thrombocytosis in both adult and paediatric patients. The guidance may not be appropriate to all patients with thrombocytosis and in all cases individual patient circumstances may dictate an alternative approach.

Guideline update

There is no previous guideline for this topic.

Correspondence: Dr C. N. Harrison, BCSH Secretary, British Society for Haematology, 100 White Lion Street, London N1 9PF, UK.

E-mail: bcsh@b-s-h.org.uk

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Aim

The purpose of this guideline is to provide an approach to the diagnosis, investigation and management of patients with a thrombocytosis (i.e., a platelet count $>450 \times 10^9/l$). This will include advice on how to distinguish reactive thrombocytosis from true haematological disease and how to distinguish essential thrombocythaemia (ET) from other myeloproliferative neoplasms (MPN), myelodysplastic syndromes (MDS) or overlap syndromes. Recommendations for the management of complications of ET, such as splanchnic vein thrombosis, blast crisis and post-ET myelofibrosis are given, as well as advice on management of pregnancy and children with ET.

Diagnostic process

Thrombocytosis is a common finding and is a frequent cause of referral for further investigation. There is a wide range of primary and secondary causes as well as false or 'spurious' conditions mimicking thrombocytosis (Table II). Establishing the cause therefore requires consideration of clinical features, haematological parameters, bone marrow aspirate and trephine biopsy morphological features and the presence or absence of clonal genetic abnormalities. The definitions of specific neoplastic entities are guided by diagnostic criteria and algorithms within the world Health Organization (WHO) Classification of Tumours of Haematopoietic and Lymphoid Tissues (Swerdlow, 2008). These definitions are based on combinations of clinical and pathological characteristics which may be major (required) or minor (supportive). This most recent iteration of the WHO classification emphasizes the neoplastic nature of the previously termed myeloproliferative diseases and renamed them MPN. The guideline group however discussed and agreed specific diagnostic criteria for ET (Table III) that are subtly different from those of the WHO

Table I. Evidence statements and grades of recommendations.

| | |
|---|---|
| Classification of evidence levels | |
| Ia: | Evidence obtained from meta-analysis of randomized controlled trials |
| Ib: | Evidence obtained from at least one randomized 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 randomized 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 randomized 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 out with the control of the investigators, but an opportunity exists to evaluate its effect.

2008 classification based upon evidence from the analysis of data from a randomized controlled trial (Wilkins *et al*, 2008). The diagnostic features, including detailed morphological descriptions of the common myeloid entities associated with thrombocytosis, are provided below and are intended to act as a useful reference to supplement, but not replace, the WHO monograph. The guideline group also developed a diagnostic

algorithm to synthesize practice in undertaking the investigation of thrombocytosis (Fig 1).

The quantification of stromal reticulin fibres and detection of collagen fibrosis are fundamental to the classification and assessment of progression in MPN. Several different semi-quantitative methods for grading reticulin and collagen fibrosis have been developed, ranging from 4 to 6 grades (reviewed in Kuter *et al*, 2007). The WHO 2008 classification has adopted the European consensus grading scheme (Thiele *et al*, 2005), developed specifically in the context of MPN trephine histology assessment. This defines four grades, grade 0 being normal and grades 1–3 representing progressive increments above normal. Both grade 2 and grade 3 allow the presence of varying amounts of collagen fibrosis. While the various systems have not been compared in prospective studies, this scheme has the potential advantage of allowing separation of cases with small foci of collagen from those with more extensive fibrosis. A description of this scoring system is illustrated in Fig 2 and in Table IV.

Reactive thrombocytosis

The most common secondary (or reactive) causes of thrombocytosis are infection, inflammation, iron deficiency, tissue damage, haemolysis, severe exercise, malignancy, hyposplenism and other causes of an acute phase response (Table II). These are usually, but not always, characterized by an elevated C-reactive protein, or erythrocyte sedimentation rate. The platelets are mostly small with a normal mean platelet volume. The blood film may show other features to indicate an underlying cause, including acute infective, or inflammatory, processes. A bone marrow aspirate or trephine is not usually required for reactive thrombocytosis. If one has been performed due to diagnostic uncertainty, this will show megakaryocytic hyperplasia with normal mature and left-shifted

Table II. Causes of thrombocytosis.

| Primary | Secondary | Spurious |
|---|---|---------------------------------------|
| Essential thrombocythaemia | Infection | Microspherocytes (e.g. severe burns) |
| Polycythaemia vera | Inflammation | Cryoglobulinaemia |
| Primary myelofibrosis | Tissue damage | Neoplastic cell cytoplasmic fragments |
| Myelodysplasia with del(5q) | Hyposplenism | Schistocytes |
| Refractory anaemia with ring sideroblasts associated with marked thrombocytosis | Post-operative | Bacteria |
| Chronic myeloid leukaemia | Haemorrhage | Pappenheimer bodies |
| Chronic myelomonocytic leukaemia | Iron deficiency | |
| Atypical chronic myeloid leukaemia | Malignancy | |
| MDS/MPN-U | Haemolysis | |
| | Drug therapy (e.g. corticosteroids; adrenaline) | |
| | Cytokine administration (e.g. thrombopoietin) | |
| | Rebound following myelosuppressive chemotherapy | |

MDS/MPN-U, myelodysplastic/myeloproliferative neoplasms, unclassifiable.

Table III. Proposed diagnostic criteria for essential thrombocythemia.

| Diagnosis requires A1–A3 or A1 + A3–A5 | |
|--|--|
| A1 | Sustained platelet count $>450 \times 10^9/l$ |
| A2 | Presence of an acquired pathogenetic mutation (e.g. in the <i>JAK2</i> or <i>MPL</i> genes) |
| A3 | No other myeloid malignancy, especially PV*, PMF†, CML‡ or MDS§ |
| A4 | No reactive cause for thrombocytosis and normal iron stores |
| A5 | Bone marrow aspirate and trephine biopsy showing increased megakaryocyte numbers displaying a spectrum of morphology with predominant large megakaryocytes with hyperlobated nuclei and abundant cytoplasm. Reticulin is generally not increased (grades 0–2/4 or grade 0/3) |

*Excluded by a normal haematocrit in an iron-replete patient; PV, polycythaemia vera.

†Indicated by presence of significant marrow bone marrow fibrosis (greater or equal to 2/3 or 3/4 reticulin) AND palpable splenomegaly, blood film abnormalities (circulating progenitors and tear-drop cells) or unexplained anaemia (Barosi *et al*, 1999; Mesa *et al*, 2007b); PMF, primary myelofibrosis.

‡Excluded by absence of *BCR-ABL1* fusion from bone marrow or peripheral blood; CML, chronic myeloid leukaemia.

§Excluded by absence of dysplasia on examination of blood film and bone marrow aspirate; MDS, myelodysplastic syndrome.

These criteria are modified from WHO diagnostic criteria (Swerdlow, 2008).

megakaryocyte morphology. The megakaryocytes will have a normal interstitial distribution and not show clustering. Reticulin is typically not increased. In chronic infective or inflammatory processes there may also be granulocytic hyperplasia and features of the anaemia of chronic disease.

Essential thrombocythemia (ET)

The diagnosis of ET requires a sustained thrombocytosis of $>450 \times 10^9/l$ and the exclusion of reactive causes. The blood film shows a thrombocytosis with varying degrees of platelet anisocytosis. Platelet morphology can vary from those of normal size and granulation to larger atypical forms that may be hypogranular. Features of iron deficiency may be seen if there has been an associated chronic blood loss: while iron deficiency may also mask an underlying polycythaemia vera (PV). Leucoerythroblastosis and poikilocytosis are not seen in ET. An elevated white blood cell count may be detected. Bone marrow examination (aspirate and trephine biopsy) is required according to the WHO classification (Swerdlow, 2008) to make the diagnosis of ET. However, in elderly patients where a clonal marker, such as *JAK2* V617F or *MPL* 515L/K has been detected, without features suspicious of MDS or primary myelofibrosis (PMF), a bone marrow examination may not be

necessary. This represents a departure from the WHO classification. However the guidelines group agreed that this was justified for at least two reasons; first, in view of data from the PT-1 histology review demonstrating poor reproducibility in interpreting some trephine biopsy features (Wilkins *et al*, 2008) and second, that the most recent WHO diagnostic criteria for all stages of PMF requires the presence of additional features such as splenomegaly, leucoerythroblastic film, or significant constitutional symptoms, that bone marrow examination was not always necessary. Nevertheless it is recommended to perform a bone marrow biopsy where there are atypical features, or if during the course of treatment a change in management is planned, such as change of cytoreductive therapy, or if transformation is suspected. The guideline group therefore proposed a modification of the WHO diagnostic criteria for ET (Table III).

In ET, the bone marrow is normocellular for age or mildly hypercellular. Megakaryocytes are increased in number and mostly present as single cells; they may form occasional small, loose clusters within the interstitium of the marrow. Large or giant megakaryocytes with hyperlobated ('staghorn') nuclei are prominent and these may show increased emperipoiesis. The WHO Classification states that large or giant megakaryocytes predominate but smaller forms may also be seen, particularly if immunohistochemistry is used to aid megakaryocyte identification in trephine biopsy sections. Megakaryocytes with normal morphology, including nearly-bare end-stage variants with pyknotic nuclei are also present. This spectrum of megakaryocyte morphology is typical of ET. Erythropoiesis and granulopoiesis are generally normal. Significant dyserythropoiesis and/or dysgranulopoiesis are not features of ET and favour myelodysplasia. Iron stores may be reduced and siderotic granulation is normal. Reticulin is generally not increased (grades 0–2/4 or grade 0/3, depending on the grading system used, see above).

A clonal genetic abnormality can be demonstrated in approximately 60% of cases of ET. The *JAK2* V617F mutation is detectable in 50% and the *MPL* mutation in up to 10% (Pardanani *et al*, 2006; Pikman *et al*, 2006; Beer *et al*, 2008; Vannucchi *et al*, 2008). The presence of the *BCR-ABL1* rearrangement (diagnostic of chronic myeloid leukaemia) excludes ET and testing for this should be performed if atypical features are present, such as basophilia, left shift of neutrophils or atypical trephine features. Routine karyotyping is not always required but a karyotypic abnormality where present may be a useful future marker for disease progression.

Polycythaemia vera (PV)

PV is characterized by an elevated haemoglobin, haematocrit and red cell mass, although up to 15% of patients may present with a marked thrombocytosis and clinical features such as pruritis would add weight to a diagnosis of PV. Bone marrow examination (though not always essential) shows a pan-myelosis with normal erythroid and granulocytic

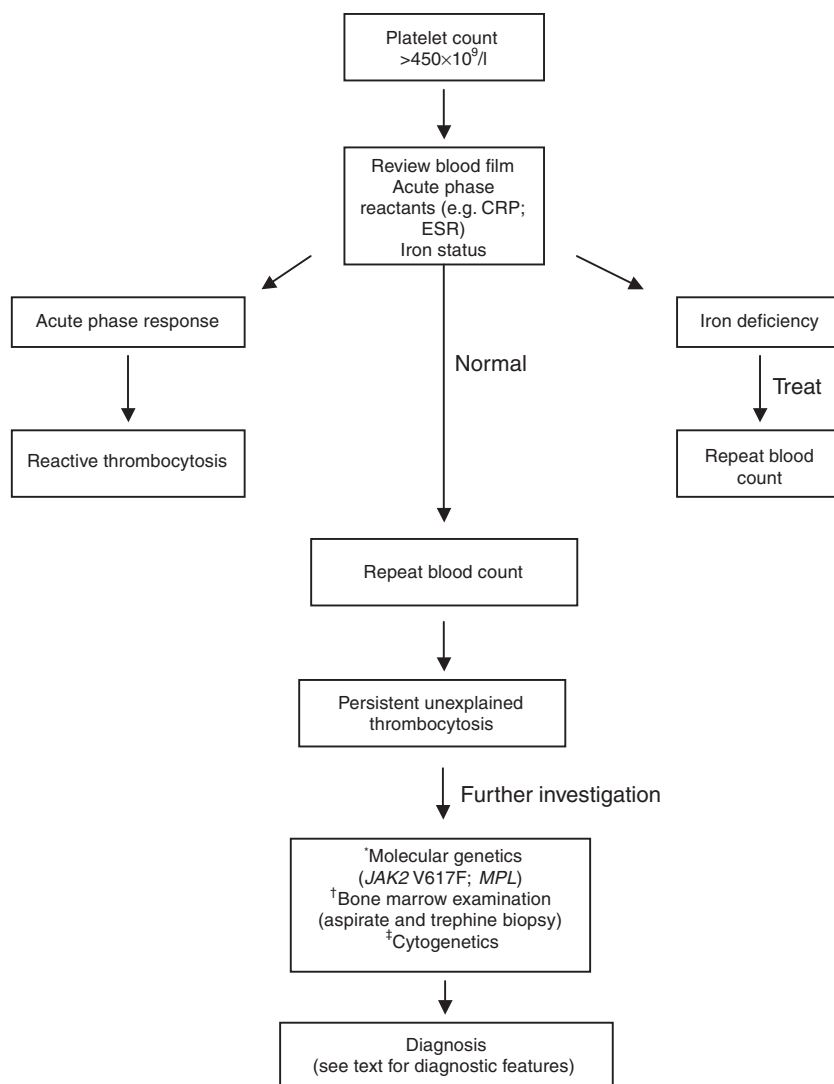


Fig 1. Diagnostic pathway for the investigation of thrombocytosis. **BCR-ABL1* testing is only recommended if there are atypical features on the blood count and/or film (e.g. basophilia). †Bone marrow examination is recommended to confirm the diagnosis, as per the WHO Classification. In some circumstances this may not be clinically indicated. ‡The need for Cytogenetics on the bone marrow should be guided by the blood and bone marrow morphology.

differentiation but with spatial disorganisation. In contrast to ET, the megakaryocytes show marked pleomorphism with a higher than normal nuclear:cytoplasmic ratio plus a characteristic mixture of large and small variants; loose clustering of megakaryocyte is usual. The giant megakaryocytes with hyperlobated nuclei that are a feature of ET are not seen in PV. Iron deficiency is common in those patients whose presentation overlaps with ET and should be investigated to exclude a second pathology. The *JAK2* V617F mutation is present in more than 97% of PV patients and a further 1–2% will have an exon 12 mutation of *JAK2* (Scott *et al*, 2007),(Pietra *et al*, 2008). Exon 12 mutations have not been documented in the context of ET or PMF. The ability to discriminate between ET and PV on the basis of trephine evaluation has never been tested, or evaluated in a formal setting.

Primary myelofibrosis (PMF)

Primary myelofibrosis can present with a marked thrombocytosis, with or without anaemia, teardrop poikilocytosis, leucocytosis and a leuco-erythroblastic blood film. Clinical features again are similar to ET. Platelets tend to show marked anisocytosis with large forms. Bone marrow aspiration may yield a 'dry tap' or show hypercellular particles with hypocellular trails. Bone marrow trephine histology shows a spectrum of findings including increased overall cellularity, particularly of granulocytes and megakaryocytes: commonly, there is also reduced erythropoiesis. Granulopoiesis may have a disordered distribution and may be left-shifted but is usually not dysplastic. In PMF the megakaryocytes are markedly abnormal. They have an abnormal distribution and pattern, including adjacency to bone trabeculae and within sinuses.

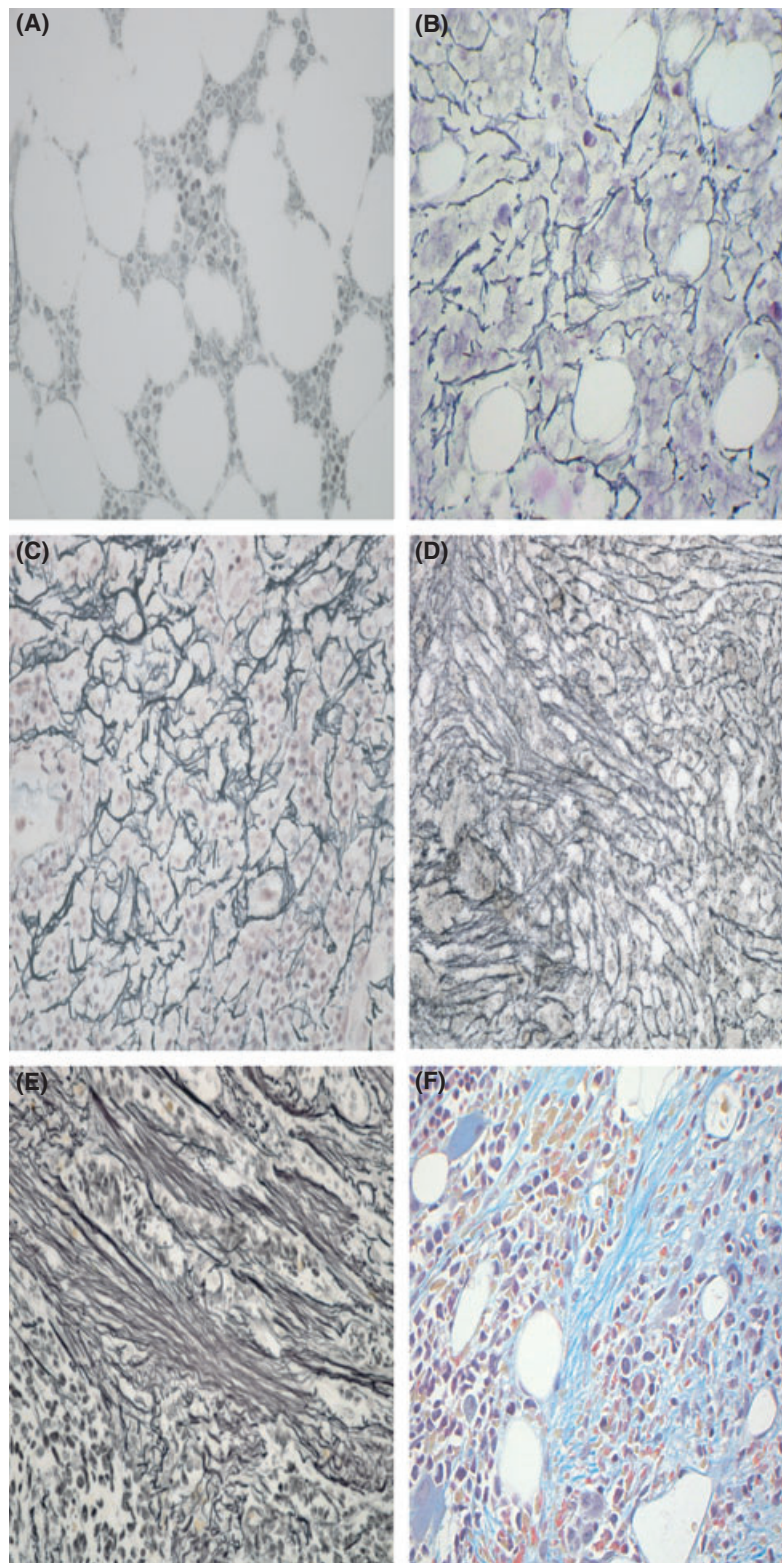


Fig 2. Reticulin grading: examples of reticulin stains. A. Grade 0/3 scattered linear reticulin with no intersections (cross-overs) corresponding to normal one marrow; B. Grade 1/3 loose network of reticulin with many intersections, especially in perivascular areas; C. Grade 2/3 widespread and dense increase in reticulin with extensive intersections; D. Grade 3/3 diffuse and dense increase in reticulin with extensive intersections; E. Grade 3/3 coarse bundles of collagen demonstrated; F. Collagen demonstrated using MSB trichrome stain (martius yellow, brilliant crystal scarlet 6R, and soluble blue). All panels original magnification $\times 40$.

Table IV. WHO grading of bone marrow fibrosis (Swerdlow, 2008).

| Grading | Description* |
|---------|---|
| MF-0 | Scattered linear reticulin with no intersections (cross-overs) corresponding to normal BM |
| MF-1 | Loose network of reticulin with many intersections, especially in perivascular areas |
| MF-2 | Diffuse and dense increase in reticulin with extensive intersections, occasionally with focal bundles of collagen and/or focal osteosclerosis |
| MF-3 | Diffuse and dense increase in reticulin with extensive intersections and coarse bundles of collagen, often associated with osteosclerosis |

*Fibre density should be assessed in areas showing active haematopoiesis

Megakaryocytes may form dense and often large clusters, sometimes forming sheets and have atypical morphology, with the majority being large and having distorted elongated and angular shapes. They have a high nuclear:cytoplasmic ratio and their nuclei are commonly enlarged, hyperchromatic and poorly lobated. Reticulin fibrosis is increased (grade 2/4, grade 1/3 or above) and may be accompanied by overt collagen and/or new bone formation. At its most extreme, there may be markedly reduced haemopoietic cellularity and osteosclerosis. As for ET, the diagnosis of primary myelofibrosis requires the demonstration of a clonal marker (e.g. *JAK2* V617F which is present in 50–60% of cases or *MPL* mutations in 10% (Pardanani *et al*, 2006; Pikman *et al*, 2006; Lasho *et al*, 2006) and the exclusion of PV, chronic myeloid leukaemia (CML) and MDS. Although the 2008 WHO classification includes ‘pre-fibrotic/early stage myelofibrosis’, there is contradictory evidence as to whether this is a distinct entity which requires distinction from ET (Thiele & Kvasnicka, 2003; Gianelli *et al*, 2006; Wilkins *et al*, 2008). In the new WHO classification (Swerdlow, 2008) a diagnosis of PMF, whatever the grade, requires the presence of other features, such as splenomegaly, a leucoerythroblastic blood film and constitutional symptoms. This new classification has resolved some uncertainty regarding the classification of patients with thrombocytosis who have increased reticulin fibrosis in the marrow but no other features of PMF – provided such patients have other features consistent with ET they should be managed according to protocols for this condition.

Myelodysplastic/myeloproliferative overlap syndromes

The existence of diseases that can demonstrate the clinical and laboratory features of both MDS and a chronic MPN, have been recognized within the WHO Classification of Tumours (Swerdlow, 2008). These entities have been termed the myelodysplastic syndromes/myeloproliferative neoplasms (MDS/MPN). Care should be taken to ensure that those patients who have a clear history of a preceding myeloprolif-

erative disorder with evidence of subsequent dysplastic transformation, are not included in this group, as the evidence base for their clinical management is different.

The MDS/MPN overlap category has been divided into four separate sub-groups: chronic myelomonocytic leukaemia (CMML); atypical CML (aCML); juvenile myelomonocytic leukaemia (JMML); and MDS/MPN, unclassifiable (MDS/MPN-U). Within the latter designation, there has been recognition of the provisional entity of refractory anaemia with ringed sideroblasts associated with marked thrombocytosis (RARS-T).

With the exception of RARS-T, where the presence of thrombocytosis is a diagnostic criterion, the other MDS/MPN entities are more commonly associated with thrombocytopenia. JMML is a rare leukaemic disorder of young children, and will not be discussed further in these guidelines. Chromosomal anomalies involving the 3q21–26 locus may be associated with thrombocytosis and should be categorized as MDS unless the blast count is >20%, when the disease is classed as AML (Swerdlow, 2008).

Myelodysplastic/myeloproliferative neoplasm; provisional entity – refractory anaemia with ring sideroblasts associated with marked thrombocytosis (RARS-T). This is a provisional entity which has features of both ET and refractory anaemia with ring sideroblasts. Platelet morphology is normal. Red cells are dimorphic and although the majority of cells are normochromic and normocytic, there are small numbers of hypochromic and markedly microcytic cells. The bone marrow (aspirate and trephine biopsy) is hypercellular and shows increased megakaryocytes with morphological features similar to those seen in ET or PMF. Megakaryocyte clustering can be present. There is also increased erythropoiesis with dyserythropoiesis and ring sideroblasts accounting for more than 15% of late normoblasts. Reticulin varies, from normal to moderately increased. The *JAK2* V617F mutation is present in more than 50% of patients (Boissinot *et al*, 2006; Szpurka *et al*, 2006).

Myelodysplastic Syndrome associated with isolated del(5q). Myelodysplastic syndrome with isolated del(5q) is commonly associated with thrombocytosis (30–50% of patients) and macrocytic anaemia. The platelet morphology is unremarkable whilst the red cells are macrocytic, with mild poikilocytosis and minimal polychromasia. The bone marrow is normocellular, or mildly hypercellular, with dyserythropoiesis. Megakaryocytes are increased in number and are present in the marrow interstitium; they are small or of normal size and have monolobed, or hypolobated nuclei that are characteristically eccentrically placed. Cytogenetic demonstration of del(5q), with loss of bands q31–q33 and without additional complex cytogenetic abnormalities, is required to make the diagnosis. A small number of patients may also have the *JAK2* V617F mutation (Ingram *et al*, 2006).

Recommendations: Diagnostic process

- **Thrombocytosis is a common finding with a wide range of primary and secondary causes as well as false or 'spurious' conditions mimicking thrombocytosis, evaluation of these patients therefore requires a comprehensive approach involving clinical and laboratory parameters**
- **The guideline group also developed a diagnostic algorithm to synthesize practice in undertaking the investigation of thrombocytosis (Fig 1).**

Essential thrombocythaemia*Prognosis and risk stratification*

Limitation of life expectancy is a major concern for many patients with ET, especially at the time of diagnosis and unfortunately data on this is scarce and sometimes conflicting (Rozman *et al*, 1991; Jensen *et al*, 2000; Passamonti *et al*, 2004; Wolanskyj *et al*, 2006). Life expectancy for the first 10 years after a diagnosis of ET is not affected, beyond 10 years the data is less clear. For example, a study from the Mayo clinic involving 322 ET patients followed for a median of 13.6 years, suggested that survival became significantly worse after the first decade (Wolanskyj *et al*, 2006). However, this evidence from the Mayo clinic study is likely to be influenced by limited knowledge regarding appropriate treatment at that time with use of agents known to increase the risk of leukaemic transformation (Campbell & Green, 2006). In the study by Passamonti *et al* (2004), ET patients at all ages had a standardized mortality ratio of 1, which was no different from an age- and sex-matched normal population. However, other authors suggest that young patients, who have a longer duration of disease, will accumulate more risk of transformation to myelofibrosis or AML (Passamonti *et al*, 2004; varez-Larran *et al*, 2007). Emerging evidence suggests that some patients with ET have a familial component to their disease, although they still appear to have the same risk of vascular complications and evolution to myelofibrosis and AML as classical ET (Rumi *et al*, 2007).

The proposal that various factors may influence prognosis is attractive as this facilitates identification of patients who might be suitable for more aggressive therapies. The major disease-related events that impact upon survival and quality of life for patients with ET are the occurrence of thrombosis, and transformation to leukaemia or myelofibrosis. Fatigue and other constitutional symptoms can also impact upon quality of life and there is data to suggest that these symptoms may be relatively common amongst the MPN patient population (Mesa *et al*, 2007a), and are therefore worthy of further study. The most frequent complication of ET is thrombosis. For example, in the study reported by Passamonti *et al* (2004), the rates of thrombosis for ET patients were 12 per 1000 patients years, compared with 1.6 and 1.2 per 1000 patient years for PMF and AML, respectively. Consequently, risk stratification

based upon the estimated chance of thrombotic events, has been a useful tool to guide the management of ET.

Thrombotic risk assessment

Current risk stratification for thrombosis in ET includes an assessment of age, history of thrombosis, concurrent medical conditions and the platelet count. Some studies suggest that patients aged <60 years and with no prior thrombosis do not show an increased incidence of thrombosis compared to age-matched healthy controls (Ruggeri *et al*, 1998), in contrast to the findings of other groups (Pearson *et al*, 1999). Clinical studies suggested that cytoreductive therapy reduced the incidence of thrombosis, which led to the interpretation that this was secondary to a reduction in the platelet count (Cortelazzo *et al*, 1995; Storen & Tefferi, 2001; Harrison *et al*, 2005). Paradoxically however, platelet count does not directly correlate with the incidence of thrombosis (Carobbio *et al*, 2008a) and, furthermore, the difference in the occurrence of thrombotic events in the two arms of the PT-1 trial, despite equivalent control of the platelet counts, suggests that additional factors, such as reduction of haematocrit, leucocyte count or endothelial factors, such as nitric oxide production, are important in the pathogenesis of thrombosis (Harrison *et al*, 2005).

The impact of conventional risk factors for atherosclerosis, including hyperlipidaemia and hypertension, have been assessed in MPN with variable results (Cortelazzo *et al*, 1990; Besses *et al*, 1999). Limited work has been specifically performed in ET. Recent recommendations for the management of atherosclerosis suggest that this patient group may benefit from aggressive risk management with the use of antihypertensives and a statin, where appropriate.

The utility of routine thrombophilia screening in patients with VTE but without an MPN has been challenged, as it does not usually alter management (Baglin *et al*, 2003). A single report suggests that *F5* R506Q (Factor V Leiden) may be more common in MPN patients with recurrent VTE (Ruggeri *et al*, 2002), although more studies are needed as *F5* R506Q is not a risk factor for recurrence even in patients without an MPN. Furthermore, even if this finding is true, the presence of a genetic thrombophilia is unlikely to alter clinical management of VTE in this context. An increased prevalence of antiphospholipid syndrome (aPL) has been described in ET and is variably associated with an increased risk of both arterial and venous thrombosis (Harrison *et al*, 2002; Bidot *et al*, 2005; Robertson *et al*, 2007). However routine screening for antiphospholipid antibodies is not presently indicated. Patients with persistent antiphospholipid antibodies, or aPL, should be managed according to guidelines for this condition (Greaves *et al*, 2000).

The identification of risk markers for thrombosis is an evolving field and may help to further define risk groups by which to stratify treatment. However any such novel markers should be robust and easily measurable. Some emerging data is discussed below.

White blood cell count. In a retrospective study of 143 patients, a normal white blood cell count at presentation (compared to a high count) was associated with a positive influence on symptom-free survival ($P = 0.02$) in univariate, but not multivariate analysis (Lengfelder *et al*, 1998). Two recent studies identified that a white blood cell count above $15 \times 10^9/l$ was associated with thrombotic complications (Wolanskyj *et al*, 2006; Carobbio *et al*, 2008b). In latter study, the association of leucocytosis and thrombosis was more evident in the untreated low-risk group, defined as age <60 years with no prior thrombotic event ($P = 0.01$) (Carobbio *et al*, 2008b). The potential of the leucocyte count to identify 'at risk' patients is attractive but requires a large prospective study.

JAK2 V617F. A large number of studies have assessed the impact of the JAK2 V617F mutation upon the clinical phenotype of ET patients. These studies variably identified that JAK2 V617F-positive ET patients had a higher risk of thrombosis. A recent meta-analysis suggests that there was a significant increase in the odds ratio (OR) for thrombosis [OR = 1.83 (95% confidence interval [CI], 1.32–2.53), $P < 0.0001$], and transformation to PV [OR = 7.67 (95% CI, 2.04–28.87), $P = 0.0009$] in JAK2 V617F-positive ET patients (Dahabreh *et al*, 2008), a conclusion confirmed in a second analysis (Lussana *et al*, 2009).

In a study of 260 ET patients, Vannucchi *et al* (2007) showed that splenomegaly and microvascular symptoms were significantly more common among the small number of ET patients with $>50\%$ and 25% JAK2 V617F allele burden, respectively. Increasing mutant allele load also correlated with a higher frequency of arterial thrombosis at diagnosis and this was confirmed in multivariate analysis with a relative risk of 3.0 (95% CI 1.3–6.8; $P = 0.01$) in patients having a $>25\%$ mutant allele burden. However, other groups have not identified this trend, and robust quantitative assays that could corroborate this observation have yet to be validated.

MPL mutations. In the PT-1 study, patients with MPL W515 mutations had an increased risk of venous thromboembolism when compared to JAK2 wild-type patients ($P = 0.02$), although this difference disappeared on multivariate analysis (Beer *et al*, 2008). In a subsequent study (Vannucchi *et al*, 2008) the presence of MPL mutations was weakly associated with microvascular disturbance, but not with other thrombotic manifestations. At present, it appears that MPL mutations, which are relatively uncommon in ET, do not add information with regard to prognostic or thrombotic risk.

Recommendations: risk stratification

- **Patients should be stratified according to their risk of thrombotic complications (Evidence level IIa Grade B). The most widely accepted risk stratification is as follows:**

HIGH RISK Patients who are either >60 years of age OR have had an ET-related thrombotic or haemorrhagic event OR who have a platelet count of $>1500 \times 10^9/l$.

For patients who have no high risk features. This group may be further subdivided by age into:

LOW RISK patients <40 years of age with no high risk features, and

INTERMEDIATE RISK patients aged 40–60 years with no high risk features

- Microvascular symptoms are not generally regarded as thrombotic events for the purpose of risk classification but if they are severe or not responding to aspirin the patient could be reclassified as 'high risk' (Evidence level IV Grade C).
- Platelet count per se does not correlate well with thrombotic risk, however, a platelet count $>1500 \times 10^9/l$ has been used as an indicator for cytoreductive therapy in view of the increased haemorrhagic risk (Evidence level III Grade B).
- In young patients (<40 years) it may be reasonable to use a higher platelet threshold for risk classification in the absence of symptoms. (Evidence level IIa Grade B).
- The impact of cardiovascular risk factors on thrombotic risk assessment in otherwise low or intermediate risk patients (<60 years and no thrombotic events) remains uncertain. (Evidence level III Grade B).
- Emerging risk factors include the leucocyte count and JAK2 allele burden, both of which require prospective validation with robust techniques. (Evidence level III Grade C).

Clinical trials

Two prospective randomized studies that assessed potential treatment strategies for patients with ET have been published. An Italian study randomized 114 high-risk patients (age >60 years or prior thrombosis) between treatment with HC (hydroxyurea) and no cytoreductive agent (Cortelazzo *et al*, 1995). With a median follow up duration of 27 months, patients on HC suffered statistically fewer thrombotic events. This important study demonstrated that for high-risk patients with ET, cytoreductive therapy with HC reduces vascular complications.

The second randomized study is the Medical Research Council (MRC) primary thrombocythemia-1 (PT-1) trial (Harrison *et al*, 2005). In this study, 809 high-risk patients (prior thrombosis, or age >60 years, or hypertension, or diabetes, or platelet count $>1000 \times 10^9/l$), diagnosed with ET according to the Polycythaemia Vera Study Group (PVSG) criteria (Murphy *et al*, 1997), were randomized to receive HC plus aspirin or anagrelide plus aspirin. Compared to HC plus aspirin, patients treated with anagrelide plus aspirin suffered higher rates of arterial thrombosis, major haemorrhage and

myelofibrotic transformation, but a decreased rate of VTE. These differences occurred despite equivalent control of the platelet count from 6 months after trial entry. These results can be compared with the Italian randomized study. The rate of first thrombosis at 2 years was 4% for those receiving HC in both studies, suggesting the two cohorts of patients were broadly comparable. For the non-HC arms however, the rates of first thrombosis at 2 years were 8% and 26% for patients receiving anagrelide plus aspirin (PT-1) or no cytoreductive therapy (Italian study), respectively. Although such comparisons across studies have their limitations, these data suggest that, for high risk patients, anagrelide plus aspirin provides at least partial protection against arterial thrombosis, but this is not as much as HC plus aspirin for high-risk patients.

Two currently running randomized trials will further inform the management of ET. The first is the National Cancer Research Institute study for intermediate risk patients (age 40–60 years; no high risk features) (<http://www.ctsu.ox.ac.uk/projects/leuk/pt1>). This is a randomized comparison of HC plus aspirin with aspirin alone. It is expected to report in 2011. Until the results of this study are known, treatment guidelines for this intermediate risk group of patients remain poorly evidence-based. The second trial is the ANAHYDRET (ANAgrelde versus HYDRoxyurea in ET) study (<http://www.anahydret.at/>), which has now reached its target recruitment. This study is powered as a non-inferiority comparison between HC and anagrelide in high-risk patients with ET diagnosed according to the WHO criteria (Vardiman *et al*, 2002). The study had not reported at the time of the literature review.

Two randomized studies of PV also have ramifications for the management of ET. The first is the PVSG-01 trial, a three-arm study comparing phlebotomy alone, chlorambucil and radioactive phosphorus (P32) in PV (Berk *et al*, 1986). There was a statistically significant difference in overall survival between the three arms. Median survival was best for the phlebotomy arm (13.9 years), intermediate for P32 (11.8 years) and worst for chlorambucil (8.9 years). The lower survival in the chlorambucil and P32 arms compared to phlebotomy was mainly due to an increased rate of AML and non-haematological malignancy. The other PV trial is the ECLAP (European Collaboration on Low-Dose Aspirin in Polycythaemia Vera) study (Landolfi *et al*, 2004), a randomized comparison of aspirin with no antiplatelet therapy in PV patients at low or intermediate risk of vascular events. This demonstrated a significantly reduced risk of vascular events in patients randomized to receive aspirin, with 3.2% of patients in the aspirin arm and 7.9% in the placebo arm suffering a primary end-point event over an average follow-up of approximately 3 years. The benefits of aspirin came at no increased risk of major haemorrhage.

Pharmacological therapy

Aspirin. Low-dose aspirin has clear benefit in the secondary prevention of myocardial infarction and stroke in cases where there is atherosclerosis in haematologically normal patients.

However, its role in preventing similar complications for patients with MPN has been controversial. The ECLAP study, as discussed above (Landolfi *et al*, 2004), supports the safety and utility of aspirin in the prevention of non-fatal thrombotic events in PV and has been used to support the use of aspirin in ET. Aspirin should be used with caution in patients with a history of bleeding and in those with extreme thrombocytosis (platelet count in excess of $1000\text{--}1500 \times 10^9/l$) especially in the context of a bone marrow biopsy (Bain, 2005). In haematologically normal patients biochemical aspirin resistance is associated with an increased risk of death and acute coronary syndrome in patients with cardiovascular disease (Krasopoulos *et al*, 2008). There is no reason to suggest aspirin resistance does not occur in MPN, indeed the frequency may be higher and is worthy of further investigation.

Thienopyridines-clopidogrel and prasugrel. Whether a thienopyridine, such as clopidogrel, can be used as an alternative to aspirin is uncertain (Zimmermann & Hohlfeld, 2008). In patients with symptoms of established atherosclerosis who do not have MPN, the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) study showed that aspirin and clopidogrel therapy in combination produced a 20% relative risk reduction of cardiovascular events and death, but this was associated with a relative increased risk of major bleeding events of 38% (Yusuf *et al*, 2001), which must be of concern in the MPN patient population. For MPN patients with ongoing thrombotic events despite optimal control of blood counts and other risk factors, consideration of the combination of aspirin and clopidogrel may be helpful, as in patients with atherosclerosis without MPN, but the efficacy and safety of this approach has not been evaluated in patients with MPNs where increased bleeding risk may be a particular concern. Clopidogrel may be useful as a single antiplatelet agent for patients with peptic ulcer disease or aspirin allergy.

Oral vitamin K antagonists. Unlike antiplatelet agents, current risk benefit analyses would suggest no role for oral vitamin K antagonists, such as warfarin, in the primary prevention of arterial atherothrombosis. For secondary prevention of VTE, it remains unclear whether it is better to give a short course (standard practice) or to continue with long-term warfarinization. The only clear indication for long-term anticoagulation is for ET patients who also have a thrombosis due to aPL (Ruiz-Irastorza *et al*, 2007) and those who have had recurrent VTE or a single life-threatening VTE episode, such as splanchnic vein thrombosis. The issue of duration of anticoagulation after a first thrombosis is currently being revisited by many groups; therefore contemporary guidance should be consulted.

Hydroxycarbamide (HC). HC is an antimetabolite that primarily acts on cells in S-phase. It acts by slowing DNA synthesis and repair through its action on ribonucleoside diphosphate-reductase, an enzyme that catalyses the reduction

of ribonucleotides (Young *et al*, 1967). Side effects are uncommon, most are mild and reversible and include bone marrow suppression, gastrointestinal tract abnormalities (anorexia, nausea, vomiting and diarrhoea) and skin changes (rashes, leg ulceration and alopecia). Rarer complications include fever, pneumonitis, azoospermia and acute elevations in liver function tests, while prolonged therapy may lead to a range of skin toxicity, such as actinic keratosis, squamous cell carcinoma, and nail changes, such as onychodystrophy and melanonychia. The evidence for teratogenicity is weak, although conception while on therapy should be avoided (Harrison, 2005a; Liebelt *et al*, 2007).

The important issue of whether HC can enhance leukaemogenesis remains unresolved. Despite many published studies there is little evidence to support a clear leukaemogenic risk for HC. For example, the risk of leukaemia for patients receiving single agent HC does not appear to differ from that seen in untreated patients (Finazzi & Barbui, 2001), at least in the short term. A study that quantified acquired mutations following drug therapy concluded that the mutagenic and carcinogenic potential of *in vivo* HC therapy is low (Hanft *et al*, 2000). However, follow up data from a French study of 108 ET patients, treated with HC alone with a median follow up of 22.3 years, suggests that the actuarial risks of AML is 12% at 10 years, 15% at 15 years and 20% at 20 years. Factors associated with poor survival were age over 60 years, male gender and raised neutrophil count (Kiladjian *et al*, 2006a). Furthermore, a recent systematic review of HC therapy in sickle cell disease, commissioned by the National Institutes of Health (NIH), concluded that there was no increased risk of leukaemia (Lanzkron *et al*, 2008) with HC use in this patient group. It is important to note that lack of comparison groups within studies limits assessment of causality. Importantly it is clear that where HC is used concurrently, or consecutively, with another drug with leukaemogenic potential, the risk of leukaemia is significantly increased to 20–30% (Sterkers *et al*, 1998; Finazzi *et al*, 2003, 2004).

A number of patients may either fail to achieve an adequate response or become refractory to or intolerant of initial HC therapy. Definitions of such criteria have been published by an international group of experts (Barosi *et al*, 2007) and include inadequate control of platelet count without causing anaemia or leucopenia. For these patients a number of options exist, for example, to relax the platelet target to $600 \times 10^9/l$, to switch therapy, or to use combination therapy. Relaxing the target platelet count to $600 \times 10^9/l$ could be justified as this was the therapeutic target in the study of Cortelazzo *et al* (1995) and the incidence of thrombosis in this study was not significantly different from the HC and aspirin arm of the PT-1 study (Harrison *et al*, 2005) where the treatment target was $400 \times 10^9/l$. However this would not be a recommended strategy for those patients with recurrent thrombotic events. For most patients, first line therapy will be HC and thus concern about leukaemogenesis with successive use of another agent with leukaemogenic potential suggests that therapy

should ideally be switched to an agent with no, or minimal, leukaemogenic capability, i.e. anagrelide or interferon. There is emerging experience with the combination of anagrelide and HC which suggests benefit in this group of patients (Christoforidou *et al*, 2008; D'adda *et al*, 2008).

Interferon alpha. Interferon alpha (IFNa) suppresses the proliferation of pluripotent and lineage-committed haematopoietic progenitors. IFNa directly inhibits thrombopoietin (TPO)-induced megakaryocytic growth by suppressing TPO-induced signalling through the induction of SOCS-1. Early studies showed that IFNa in ET patients can result in a reduction of platelet count to $<600 \times 10^9/l$ within 3 months with an average dose of 3 million IU daily (Lengfelder *et al*, 1996). IFNa has a broad spectrum of side effects including depression, fatigue, hepatitis, and pneumonitis. At least 20% of patients fail to tolerate this drug in the long term.

The use of pegylated (PEG) forms of IFN allows weekly administration and a possibly improved side effect profile, which may benefit compliance. There are two different formulations of this drug, which provisional data suggests may have varying benefits in treating patients with ET or PV. Results of a Phase II study (Jabbour *et al*, 2007) showed that PEG-IFNa-2B (Schering-Plough) was equal with respect to tolerability and efficacy when compared to IFNa in a cohort of patients with *BCR-ABL1* negative MPN. A multicentre phase II trial of PEG-IFN-2a (Roche), in 40 PRV patients (Kiladjian *et al*, 2008), confirmed a discontinuation rate of 8% due to side effects. Importantly, in this study 94.6% of patients had a complete haematological response. Molecular responses (by sequential quantitation of *JAK 2V617F* allele burden) were assessed in 29 patients, demonstrating a complete molecular remission in seven patients lasting from 6 to 18 months, and this molecular response persisted in five patients after cessation of pegylated IFN. No vascular events were noted.

Anagrelide. Anagrelide hydrochloride is an orally active quinazolinone derivative that was originally developed as a novel antiplatelet drug. The drug also inhibits cyclic nucleotide phosphodiesterase III and phospholipase A2, which is thought to cause the side effects of vasodilation, positive inotropism, reduced platelet aggregation and probably diarrhoea. There have been six phase II, or III, studies of anagrelide including MRC-PT-1 (as discussed earlier), and ANAHYDRET, which has not reported at the time of preparation of these guidelines but which was powered only to demonstrate equivalence of HC and anagrelide. A further randomized study and a long-term safety study are ongoing. Anagrelide is licensed in Europe as second-line therapy for those high-risk ET patients refractory or intolerant to first line therapy and by the US Federal Drug Administration (FDA) for treatment of thrombocytosis in MPN.

Clinical studies demonstrated that anagrelide has a relatively specific action in reducing platelet count in at least 80% of patients, although anaemia may occur in 10% of patients (Harrison, 2005b). The PT-1 study raised concerns about

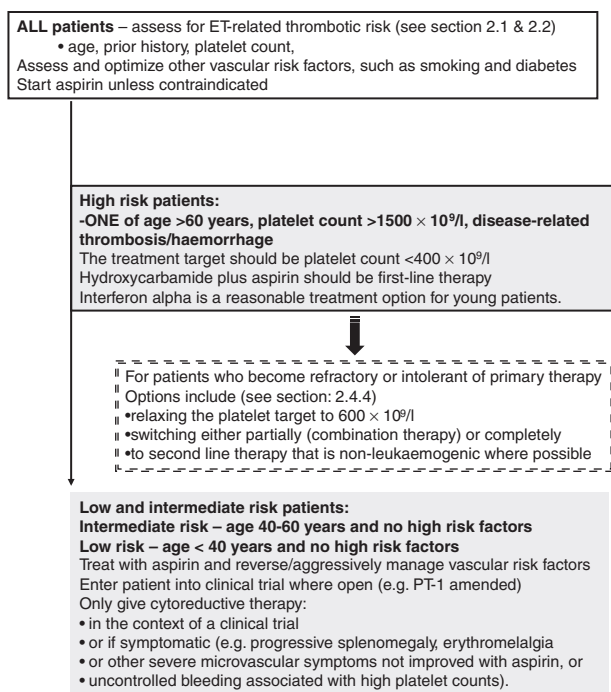


Fig 3. Recommended management of essential thrombocythaemia (ET).

anagrelide and the development of increased reticulin fibrosis in the marrow and has demonstrated correlation between reticulin grade and progressive anaemia in anagrelide- but not HC-treated patients (Harrison *et al*, 2005; Campbell *et al*, 2009). A further recent study documented an increase in reticulin deposition after anagrelide therapy but not an increase in transformation to frank post-ET myelofibrosis, although patient numbers and duration of follow up were low (19 over 2 years) (Hultdin *et al*, 2007). In the PT-1 patient cohort serial trephine specimens in patients randomly assigned to anagrelide showed significantly greater increases in reticulin grade compared with those allocated to HC ($P = 0.0003$). Interestingly, four patients who developed increased bone marrow reticulin on anagrelide showed regression of fibrosis when switched to HC (Campbell *et al*, 2009) For this reason, the guideline group recommends regular evaluation at 3 yearly intervals to monitor for evidence of myelofibrotic transformation in patients treated with anagrelide.

2.4.7. Busulfan. Busulfan, an alkylating agent, has had reported efficacy in controlling the platelet count in a number of case reports. In a series of patients followed for 25 years, vascular occlusive symptoms resolved but haemorrhagic symptoms did not (Van de Pette *et al*, 1986). This study however, demonstrated no apparent increase in leukaemia, although in other circumstances busulfan has been associated with leukaemogenesis. Busulfan is associated with pulmonary toxicity, which has distinct pathological and radiographic features (bronchopulmonary dysplasia and pulmonary fibrosis). The total dose for pulmonary toxicity has ranged

between 500 and 5700 mg, with a mean of 3000 mg. Risk factors for this complication include thoracic irradiation. The onset may be 8 months to 10 years after the last dose of busulfan, with a mean onset after 4 years of treatment. The course can be rapid with progression to pulmonary insufficiency and death, although treatment with 50–100 mg of prednisone may be of benefit.

Busulfan can be administered in a variety of dosing regimes, for example 60 µg/kg (maximum 4mg) orally continuously until the platelet count is reduced to <400 × 10⁹/l. The dose must then be interrupted until the platelet count rises above this level as continued dosing may lead to prolonged cytopenia. Alternatively, intermittent courses i.e. g per day for 7–14 d once every 4–6 weeks can be given until the platelet count is below 400 × 10⁹/l with repeat dosing when the count rises above this target. Finally, it may be useful to give a single dose of busulfan of, for example, 20–25 mg at intervals of 4–6 weeks.

Pipobroman. Pipobroman, a bromide derivative of piperazine, that acts as a metabolic competitor of pyrimidine bases and is an alkylating agent, is not available in the UK, but can be obtained on a named patient basis. It has been used in the treatment of ET for over 30 years. It is efficacious at controlling blood counts and in the two largest studies the rate of transformation to AML was low, with a 10-year cumulative risk of 3% and 5.5% (Passamonti *et al*, 2002; De Sanctis *et al*, 2003; Passamonti & Lazzarino, 2003) and transformation to myelofibrosis was 2% (Passamonti *et al*, 2002). However, longer term follow up of a French study comparing pipobroman with HC in patients with PV, suggests a greater risk of AML with pipobroman. In patients treated only with HC the rates of transformation to AML were 7.3%, 10.7% and 16.6% after 10, 15 and 20 years and for pipobroman-only treated patients they were 14.6%, 34% and 49.4% (Kiladjian *et al*, 2006a). This data suggests that pipobroman should be used with caution.

Radioactive phosphorus (P32). P32 has been used for treatment of MPN since the 1930s. The isotope has a half- life of 14.3 d, is a pure beta emitter and has a maximum range in tissues of 8 mm. It is effective in controlling blood counts with few acute side effects and no haematological complications (Randi *et al*, 1990). The usual dose is 150–300 MBq. This dose can be repeated after 3 months, when the erythrocyte or platelet counts have normalized in most people, until the platelet count is below 400 × 10⁹/l and the regime used again when this threshold is subsequently exceeded. The repeat administrations are normally kept as wide as possible. There is extensive evidence that P32 therapy is leukaemogenic and as a result this treatment is usually reserved for the elderly.

Miscellaneous chemotherapeutic agents. The alkylating agents CCNU (1-(2-chlorethyl)-cyclohexyl-nitrosourea) (Leoni *et al*, 1983) MCNU (Methyl-6[3-(2-chlorethyl)-3-nitrosoureido]-6-deoxy- Δ -glucopyranoside) (Murakami *et al*, 1993), uracil

Table V. Criteria for post-essential thrombocythaemia myelofibrosis (Mesa *et al*, 2007b).

| |
|--|
| Required criteria (both are required) |
| 1 Documentation of a previous diagnosis of ET as defined by the WHO criteria |
| 2 Bone marrow fibrosis grade 2–3 (on 0–3 scale) or grade 3–4 (on 0–4 scale) |
| Additional criteria (two are required) |
| 1 Anaemia and a 20 g/l decrease from the baseline haemoglobin level |
| 2 A leucoerythroblastic blood film |
| 3 Increasing splenomegaly defined as either an increase in palpable splenomegaly of 5 cm; or the appearance of a newly palpable splenomegaly |
| 4 Elevated lactate dehydrogenase LEVEL |
| 5 Development of at least one of three constitutional symptoms: >10% weight loss in 6 months, night sweats, unexplained fever (>37.5°C) |

mustard (Toh *et al*, 1988), thiotepa and chlorambucil in combination (Case, 1984) and carboquone (Higuchi *et al*, 1995) have all been shown to be efficacious in controlling the platelet count in small series of patients with ET. Most studies were too small to ascertain the incidence of leukaemic transformation, but an incidence of 31% was reported in carboquone-treated ET patients (Higuchi *et al*, 1995). Pyrimethamine, a dihydrofolate reductase inhibitor, was also shown in one series also to be effective in controlling the platelets count in ET (Bowcock *et al*, 1987). None of these agents have been assessed in large enough trials to fully determine the incidence of complications in the long term.

JAK2 inhibitors. The discovery of the *JAK2* V617F mutation revolutionized the diagnostic criteria for ET and also offered a potential therapeutic target. A number of *JAK2* inhibitors are in clinical trial at the time of preparation of these guidelines. Most of these studies have involved patients with intermediate, or high risk, myelofibrosis and no data has yet been published.

Summary of management recommendations for ET (see Fig 3)

General:

- Patients should be screened for hypertension, hyperlipidaemia, diabetes and a smoking history should be taken. Any cardiovascular risk factors should be aggressively managed (Evidence level IV Grade C).
- Aspirin should be given to all ET patients, unless contraindicated. (Evidence level IIb Grade B).

High risk patients:

- The treatment target should be to return the platelet count into the normal range (Evidence level Ib, Grade A).
- The results of the PT-1 trial suggest that HC plus aspirin should be first-line therapy for patients with high risk ET (Evidence level Ib Grade A).

- Although inferior to HC and aspirin, the PT-1 data suggest that anagrelide and aspirin is reasonable second-line therapy (Evidence level Ib Grade A).
- Due to the risks of myelofibrotic transformation in anagrelide-treated patients, regular monitoring (3-yearly) for early signs of progression is recommended (Evidence level Ib Grade A).
- Patients treated with anagrelide who demonstrate progression to post-ET MF should be switched to an alternative agent (Evidence level III Grade B).
- In young patients and those contemplating pregnancy, IFNa is a reasonable treatment option (Evidence level III Grade B).

Treatment specific recommendations:

- For refractory disease, options include relaxing the platelet target or to switching either partially (combination therapy) or completely to second-line therapy that is non-leukaemogenic where possible (Evidence level III Grade B).
- For patients with intolerance of HC, second-line therapy should be non-leukaemogenic where possible (Evidence level III, Grade B).
- IFNa is a useful agent for treatment of ET but is associated with a high incidence of side effects (Evidence level III, Grade B).
- Pegylated interferon is an emerging treatment for ET but randomized clinical trials are required to demonstrate its utility in comparison with HC (Evidence level III Grade B).
- Busulfan is an efficacious agent in the control of the platelet count in ET with a recognized side effect profile. It is not suitable for treatment of young patients and should be used with caution in those patients who have already received HC (Evidence level III Grade B).
- Pipobroman has utility in the treatment of ET, although recent evidence suggests that long-term use is associated with a significant risk of AML (Evidence level III Grade B).
- P32 is an easy-to-administer, effective treatment in the elderly where the increased longer term risks of AML may be acceptable (Evidence level III Grade B).

Low and intermediate risk patients:

- Until the results of the intermediate risk PT-1 study are known, it is recommended that patients under the age of 60 years with no high risk factors only receive cytoreductive therapy in the context of a clinical trial or if the ET is symptomatic (for example progressive splenomegaly, erythromelalgia or other severe microvascular symptoms not improved with aspirin, or uncontrolled bleeding associated with high platelet counts) (Evidence level III Grade B).

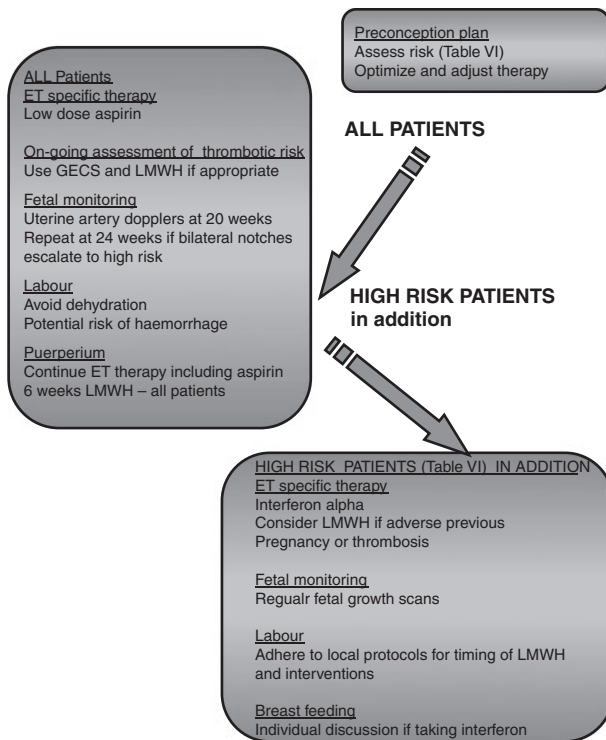


Fig 4. Algorithm for the management of essential thrombocythaemia in pregnancy. ET, essential thrombocythaemia; GECS, graded elastic compression stockings; LMWH, low molecular weight heparin.

Table VI. Risk factors for complications in pregnancy (please refer also to Fig 3).

| |
|---|
| Previous venous or arterial thrombosis in mother (whether pregnant or not); |
| Previous haemorrhage attributed to ET (whether pregnant or not); |
| Previous pregnancy complication that may have been caused by ET; e.g. |
| Unexplained recurrent first trimester loss (three unexplained first trimester losses) |
| Intrauterine growth restriction (birthweight <5th centile for gestation) |
| Intrauterine death or still birth (with no obvious other cause, evidence of placental dysfunction and growth restricted fetus); |
| Severe pre-eclampsia (necessitating preterm delivery <34 weeks) or development of any such complication in the index pregnancy; |
| Placental abruption |
| Significant ante- or postpartum haemorrhage (requiring red cell transfusion); |
| Marked sustained rise in platelet count rising to above $1500 \times 10^9/l$. |

Management of specific circumstances

Post-ET myelofibrosis. Criteria for the diagnosis of post-ET MF have been proposed by an international panel of experts (Table V) (Mesa *et al*, 2007b). Transformation to post-ET MF occurs in a proportion of patients and the dominant risk factor appears to be disease duration. In addition, the results of clinical trials (Najean & Rain, 1997; Harrison *et al*, 2005; Kiladjian *et al*,

2006a) in both ET and PV suggest that cytoreductive therapy may influence the rate or risk of progression to myelofibrosis, but this data is not conclusive. There is no data with regard to either prognosis or prognostic markers for patients with post-ET MF. Currently post-ET MF is managed in a similar manner to PMF.

Recommendations: post-ET myelofibrosis

- The diagnosis of post-ET MF should be made using standard criteria.
- Post-ET MF should be managed as primary myelofibrosis (Evidence Level IV grade C).

Blast phase/Leukaemic transformation of ET. In a study of 91 MPN patients (PMF [$n = 49$], ET [$n = 20$], PV [$n = 22$]) who developed leukaemic transformation it was demonstrated that almost 98% died, after a median of 3 months, regardless of therapeutic strategy, with no patients achieving complete remission from standard induction chemotherapy (Mesa *et al*, 2005). However, a recent publication of 74 patients (only seven with a prior diagnosis of ET) with leukaemic transformation of MPN (as defined by a sustained blast count in blood or bone marrow of >20%) suggests that a small subgroup of patients may survive beyond 12 months (Tam *et al*, 2008). In this series the initial treatment was as follows: induction chemotherapy (55%), low-intensity therapy (16%), stem cell transplantation (3%), or supportive care (26%). Median survival from the date of blastic transformation was 5 months, but only 6 weeks for those receiving supportive therapy. Overall, 46% of patients receiving induction chemotherapy achieved a remission, but these were not durable, with a median progression-free survival of only 5 months. Eight patients received a stem cell transplant, either as first therapy or after response to initial therapy. These patients had a markedly superior survival, with 73% being alive after a median follow-up of 31 months and represented the only 'long term' survivors. Whilst this data shows promise, the survival of these patients is superior to those patients undergoing allogeneic transplant for PMF, or secondary MF, and must therefore be viewed with caution.

Recommendations: leukaemic transformation of ET

- Leukaemic transformation is diagnosed when 20% blasts are consistently present either in blood or bone marrow.
- Most patients with leukaemic transformation have a poor overall survival. However, for a small subgroup, stem cell transplantation may result in superior survival. (Evidence Level III Grade B).

Pregnancy and ET. ET is the commonest MPN in women of childbearing age and a significant number of pregnancies have been described in the literature, but these data do not enable confident management guidelines to be drawn up. A summary and suggested algorithm for pregnancy management in ET

is shown in Fig 4. Recent studies suggest that the presence of *JAK2* V617F may increase the risk of pregnancy loss (Passamonti *et al*, 2007). However the strength of the association between *JAK2* V617F and fetal loss is not sufficient to recommend adjusting management strategy on this basis.

Therapeutic strategies for ET in pregnancy are influenced by the patients' disease status and prior obstetric history. A pregnancy is likely to be at high risk of maternal or fetal complications if one or more of a number of factors are present, or develop (Table VI). Cyto-reductive therapy and LMWH should be considered for patients with any such factors at the outset or during pregnancy. If treatment is deemed necessary (see Table VI), IFN- α is the drug of choice. There have been no reports of teratogenic effects in animals or adverse effects in the small numbers of reported pregnancies exposed to this drug. However, IFN- α may decrease fertility (Griesshammer *et al*, 1998) and so may be better avoided in women who have difficulty conceiving. A few pregnancies have been reported in patients treated with HC (Harrison, 2005a; Liebelt *et al*, 2007), most without fetal complications. However, HC is probably contraindicated at the time of conception (this also applies to male patients) and during pregnancy due to the risk of teratogenicity. Anagrelide is not recommended because there is insufficient documentation regarding its use in pregnancy and the molecule is small enough to cross the placenta. Thus HC and/or anagrelide should ideally be gradually withdrawn 3–6 months prior to conception and substituted by IFN- α if necessary. Low dose aspirin is safe in pregnancy and seems advantageous in ET (Gangat *et al*, 2009). We recommend that, in the absence of clear contraindications, all patients should receive aspirin 75 mg throughout pregnancy.

LMWH is safe in pregnancy; heparin-induced thrombocytopenia has not been described with LMWH in pregnancy and the risk of osteopenia is extremely low (Greer & Nelson-Piercy, 2005). It has been used anecdotally in women with ET and previous thrombosis and/or fetal morbidity, where an empirical dose of LMWH, e.g., enoxaparin 40 mg, has been used throughout pregnancy. If the patient has had a previous venous or arterial thromboembolism, thromboprophylaxis is indicated during pregnancy with unmonitored intermediate dose LMWH being widely used (e.g. for venous thromboprophylaxis enoxaparin 40 mg o.d. initially increasing to 40 mg twice daily from 16 weeks, and dropping to 40 mg/d for 6 weeks postpartum). The recent Royal College of Obstetricians and Gynaecologists (RCOG) guidelines for thromboprophylaxis in pregnancy (Royal College of Obstetricians and Gynaecologists, 2009) recommends constant reassessment of the venous thrombotic risk during pregnancy and that all women with previous VTE should be encouraged to wear graded elastic compression stocking (GECS) throughout pregnancy and for 6–12 weeks after delivery (Walker *et al*, 2001). The use of GECS is also recommended for pregnant women travelling by air (Kelman *et al*, 2003) while patients with two additional risk factors (one of which would be ET) should receive one dose of LMWH prior to the flight.

Regular maternal and fetal monitoring is imperative during pregnancy. It is important to discuss the implications of the use of thromboprophylaxis with the obstetrician and obstetric anaesthetist and plan for eventualities including instrumental delivery, caesarean section and epidural or spinal anaesthesia. During labour, dehydration should be avoided and attention should be given to the timing of the LMWH dose. In the puerperium, we recommend thromboprophylaxis with 6 weeks LMWH for all mothers with ET. Breast feeding is safe with heparin and warfarin (providing baby receives adequate vitamin K), but is traditionally contra-indicated with the cyto-reductive agents (IFN α , anagrelide and HC). However the recommendation to avoid breastfeeding during maternal IFN α therapy is based on reports that IFN α is variably excreted in breast milk and may be active orally (Bayley *et al*, 1995; Kumar *et al*, 2000). In essence, this represents an absence of evidence of safety, rather than any evidence of harm to the neonate. The substantial benefits of breastfeeding are well described and include a reduced risk of infection and gastroenteritis. Therefore, any decision about breast feeding should be made on an individual basis, after explanation of the possible risks and benefits. The first 6 weeks postpartum are a high-risk time for VTE and platelet counts may rise rapidly, so regular post-partum haematological monitoring is important.

Recommendations: management of pregnancy in ET (summarized in Fig 4)

- **Patients should be managed by a multidisciplinary team**
- **Therapeutic options, including aspirin, LMWH and IFN α , should be offered according to risk stratification.**
- **Uterine artery Doppler scans at 20–24 weeks are a useful tool to help predict late pregnancy complications.**
- **Patients should receive 6 weeks of LMWH post partum All (Evidence level IV Grade C).**

The use of combined oral contraceptive, hormone replacement therapy and ovulation induction therapy in ET. There is currently insufficient evidence to either support or refute an association between oestrogen-based hormone treatment and thrombosis risk in ET. A retrospective review of thrombotic events for a total of 305 women with ET and followed for a median of 133 months suggested that oestrogen-based hormone therapy may be safe in ET outside the setting of combined oral contraceptive pill use, which might be associated with an increased risk of deep vein thrombosis (Gangat *et al*, 2006). There is no data with regard to ovarian-stimulated therapy.

Recommendation: oestrogen-based therapy in ET

- **Combined oral contraceptive pill should be discouraged for women with ET.**

- **Hormone replacement therapy may pose a minor increase in VTE risk; thus this should only be used in patients without additional risk factors for VTE and without a personal history of thrombosis.**
- **Ovarian stimulation therapy is associated with a risk of thrombosis and each case should be individually assessed and offered thromboprophylaxis where appropriate (All evidence level IV, Grade C).**

Management of essential thrombocythaemia in children. Even if all causes of a reactive thrombocytosis have been excluded or resolved (for example after an acute infectious or surgical episode) some children still have a persistent thrombocytosis which does not appear to be due to an underlying MPN (Dame & Sutor, 2005). The reasons for this are uncertain and it may be that these children have either 'recalibrated' their platelet count at a higher level, or they may be at risk of developing an MPN and should therefore be kept under review.

ET is rare in children and there is no robust data for evidence-based guidance. A UK childhood registry for MPN patients and for children with a persistent thrombocytosis exists and ideally details of all appropriate patients should be entered. The literature suggests that some children with ET have symptoms and may have thrombotic events without an excessively high platelet count. Progression to PV, post-ET MF, or AML has been reported but the absolute risk is unknown. Furthermore, it is not certain that the risk stratification used to guide treatment decisions in adults is appropriate for children and in particular whether the same somewhat arbitrary platelet thresholds for considering therapy or indeed therapeutic targets should be used.

There is very little safety or efficacy data regarding individual cytotoxic agents in children and each drug has significant potential for long term side effects. Therefore, the selection of agent is probably best made after discussion with the child and parents and reviewed with regard to tolerance. HC (starting dose of 15 mg/kg per day) is well tolerated and a good agent to use in the short term to bring the platelet count down and control symptoms. Anagrelide, starting dose of 0.5 mg once daily incrementing as side effects allow, or an IFN α , starting dose of 3 MU/m² weekly, increasing as tolerance allows, are also suitable.

Aspirin (2–3 mg/kg, maximum 75 mg) should be used cautiously in children due to the risks of Reye's syndrome. This risk is greatest in younger children (<15 years), and those on high doses of aspirin (>20–45 mg/kg) (Belay *et al*, 1999). Some believe that there is no safe dose of aspirin, although few cases have been reported in children on doses <10 mg/kg per day (Pinsky *et al*, 1988). Reye's syndrome presents often in children who are febrile with influenza, or varicella zoster, with deranged liver function and effortless vomiting. If suspected, ammonia levels should be checked and aspirin stopped. However in children with MPN the

risk of Reye's syndrome associated with the use of very low dose aspirin must be weighed against that of possible thrombosis.

Before making a diagnosis of ET, other causes of a thrombocytosis should be rigorously excluded and screening for *JAK2* or *MPL* mutations may be useful but in some cases expert review of bone marrow histology may also prove necessary. If there is clear evidence of ET and the patient is asymptomatic with a platelet count of <1500 $\times 10^9/l$, treatment with aspirin alone, or a watch and wait policy, may suffice. When symptoms develop, or the platelet count rises to above 1500–2000 $\times 10^9/l$, cytoreductive therapy should probably be commenced; although there is no clear evidence upon which to base treatment recommendations. Regular review for development of late complications of disease and treatment is important.

Recommendations: management of children with ET

- **Causes of a reactive thrombocytosis should be rigorously excluded and the diagnosis of ET made only in the presence of definitive diagnostic features (Evidence level IV, Grade C).**
- **There is insufficient evidence to guide management of ET in children but a conservative approach should be used where possible (Evidence level IV, Grade C).**
- **Risk stratification used to guide therapeutic decisions in adults is not validated for use in children with ET (Evidence level IV, Grade C).**
- **Data regarding ET in children should be prospectively collected.**

Management of an acute thrombotic or haemorrhagic event. Acute thrombotic events should be managed according to current guidelines, individual risk factors should be re-examined and control of the platelet count optimized. Haemorrhage is both an infrequent and generally less severe clinical complication of ET than thrombosis and is most often reported in association with high platelet counts, acquired von Willebrand disease (Budde *et al*, 1984) and high doses of anti-platelet therapy (Tartaglia *et al*, 1986). It is not clear however that the presence of acquired von Willebrand disease predicts the risk of bleeding events but it would suggest that aspirin should only be used with caution. Clinically significant bleeding may paradoxically require platelet transfusion. Though the utility of recombinant activated Factor VII (VIIa) has been reported in MPN patients with uncontrolled life-threatening bleeding (Cervera *et al*, 2005) its safety and efficacy is uncertain. Other measures to consider in the better control of hemorrhagic events include plateletpheresis in the event of acute severe haemorrhage and optimum control of blood counts with the adjustment of any concomitant anti-platelet and/or anti-coagulant therapy.

Splanchnic vein thrombosis. It is increasingly recognized that haematological disorders, particularly, MPN, are the most common aetiological factor in splanchnic vein thrombosis (Menon *et al*, 2004). However, MPN may not be recognized in this context due to the absence of the typical peripheral blood features as a consequence of hypersplenism, gastrointestinal bleeding and/or haemodilution masking typical laboratory features. The discovery of *JAK2* V617F, exon 12 and *MPL* mutations has improved screening for MPN in this context. *JAK2* V617F is detected in up to 60% of patients with splanchnic vein thrombosis (Kiladjian *et al*, 2006b; Patel *et al*, 2006). A retrospective analysis of 241 patients with splanchnic vein thrombosis reported *JAK2* V617F in 45% of patients with Budd Chiari Syndrome and 34% of patients with portal vein thrombosis (Kiladjian *et al*, 2006b). This cohort confirmed previously recognized characteristics of patients with Budd Chiari Syndrome in the context of MPN: younger age, female preponderance and predominantly normal blood counts at presentation. The baseline Budd Chiari Syndrome prognostic score was worse for patients with an underlying MPN, though the overall 5-year survival was no different to those without an underlying MPN.

There is a paucity of good evidence to guide the management of patients with splanchnic vein thrombosis in the context of an MPN. A multidisciplinary approach to patient care, involving a hepatologist, regional liver transplant unit, haematologist, interventional radiologist and surgeon should be encouraged and long-term anticoagulation considered.

Recommendations: Splanchnic vein thrombosis

- A multidisciplinary approach to patient care is appropriate (Evidence level IV Grade C).
- All patients with unexplained splanchnic vein thrombosis should be evaluated for the presence of MPN even if their blood count is normal (Evidence level IV Grade C).

Surgery. Risks of venous and arterial thrombosis in ET patients may be amplified 5-fold by surgery (Ruggeri *et al*, 2008). Disease phenotype, individual patient variables and surgery-specific factors including choice of anaesthesia contribute to the personal risk of post-operative thrombosis in ET. For patients with ET arterial events are increased post-operatively at around 3.8% but there is also a 10.5% bleeding risk with surgery (Ruggeri *et al*, 2008), which is thought to be caused by a combination of disease-related primary platelet abnormalities, anti-platelet agents and anticoagulant therapy. For this reason, careful pre-operative review is required with consideration given to temporary control of the platelet count for procedures where there is a significant risk if bleeding occurs or when patients are at increased risk of bleeding or thrombosis as a consequence of the procedure. The use of anti-platelet agents should be adjusted according

to local policy. Post-operative thromboprophylaxis with LMWH is recommended; though it is not necessary to extend beyond the normal period of post-operative thromboprophylaxis after hospital discharge simply because of an MPN diagnosis.

Splenectomy is rarely undertaken in patients with ET even though a proportion of patients with ET have splenomegaly, this is not often painful and cytopenias due to hypersplenism are not often reported in ET. Splenic irradiation is an alternative to splenectomy but is not necessarily safer (Mesa & Tefferi, 2005).

Recommendations: Surgery in patients with ET

- Individual risk assessment for VTE, appropriate use of GECS and pharmacological agents should be attained for all patients including disease, patient and procedure specific risks.
- Standard protocols should be followed with regard to management of antiplatelet agents, warfarin and post-operative thromboprophylaxis (Evidence level Ib Grade A).
- Controlling platelet counts pre-operatively to a target of $<400 \times 10^9/l$ should be considered in ET patients undergoing surgery where bleeding is a risk or thromboprophylaxis would normally be prescribed (Evidence level IV Grade C).
- Surgical blood loss and post-operative infection may result in worsening thrombocytosis and should be managed according to the root cause (Evidence level III Grade C).

Recommendation: Splenectomy in ET

- Where splenectomy is performed, standard prophylactic measures should be applied and post-operative exacerbation of thrombocytosis should be anticipated (Evidence level IV Grade C).

Management of thrombocytosis in MDS/MPN disorders

The evidence base for controlling thrombocytosis and the use of anti-platelet agents in the MDS/MPN group of disorders is far from clear. Thrombotic complications, which are occasionally fatal, have been reported, but are uncommon. A recent case-controlled retrospective study demonstrated that those with a thrombocytosis had a lower probability of progression to a higher grade of MDS ($P = 0.03$), an equivalent risk of AML transformation, plus a statistically non-significant trend towards longer overall survival (Kodali *et al*, 2007). The choice of myelosuppressive therapy in these conditions is influenced by the known or potential risk of treatment-related leukaemogenicity.

Chronic myelomonocytic leukaemia

Only occasional CMML patients with platelet counts up to $1000 \times 10^9/l$ or so are seen, but thrombocytopenia is much more common. There is also no published evidence to suggest that thrombosis is a significant feature of uncomplicated CMML, nor is there any to suggest that cytoreductive therapy for CMML patients with thrombocytosis confers any benefit. Hence introduction of such treatment should be based on clinical grounds e.g symptomatic thrombocytosis, high white blood cell count or hypercatabolic symptoms.

Atypical CML and chronic neutrophilic leukaemia

Atypical CML (aCML) is a rare, poorly characterized disorder that is *JAK2* V617F mutation negative and lacks recurring cytogenetic abnormalities. In a recent case series only a few patients exhibited thrombocytosis (Breccia *et al*, 2006; Fend *et al*, 2008). Transformation to AML occurred in up to 40% of patients at a median of 18 months from diagnosis (Breccia *et al*, 2006). Recently the *JAK2* V617F mutation has been reported in association with chronic neutrophilic leukaemia (CNL) (Steensma *et al*, 2005). Although one patient has been described as having survived for over 8 years with *JAK2* V617F mutation-positive CNL ((Mc Lornan *et al*, 2005), there has been another mutation-positive case in which an aggressive disease course has been described (Kako *et al*, 2007). There is no published data with regard to treatment of thrombocytosis for these patients, which should probably be based upon the broad principles outlined above.

Abnormalities of the long arm of chromosome 3

Acquired anomalies of the long arm of chromosome 3 have been reported in 2% of patients with AML (Mitelman & Heim, 1992), myelodysplasia (Rubin *et al*, 1990), and in blast crisis of CML (Rubin *et al*, 1987). Overall, 20 patients (83%) had megakaryocytic dysplasia, but only 4 patients (16%) had an absolute thrombocytosis (platelet count $>500 \times 10^9/l$) (Grigg *et al*, 1993). A single case report has been published of sideroblastic anaemia with thrombocytosis in the setting of an *ins(3;3)(q26;q21q26)* mutation, leading to recurrent thromboembolic phenomena that proved fatal (Carroll *et al*, 1986). This demonstrated a rare but potentially important link between 3q anomalies and an RARS-T phenotype (see below), plus the possible prothrombotic consequences of a raised platelet count in the MDS/MPN setting.

Del 5q-syndrome

It is almost a quarter of a century since the first recognition of a specific haematological disorder in association with a deletion of the long arm of chromosome 5 (van den Berghe *et al*, 1974). This entity is categorized as a distinct myelodysplastic disorder within the WHO Classification of Tumours

(Swerdlow, 2008). The crucial gene is most likely to be that for RPS14; a ribosomal subunit protein. When there is partial loss of function of the latter, there is selective erythroid apoptosis with preservation of the megakaryocytes (Ebert *et al*, 2008).

Lenalidomide, a 4-amino-glutaramide derivative of thalidomide, can substantially reduce the transfusion requirements in the majority of these patients (Giagounidis *et al*, 2008). Cytogenetic responses would suggest that lenalidomide exerts an effect that is specific to the abnormal marrow clone associated with the del 5q abnormality. Indeed, the observation that, in these responding patients, there is also normalization of the platelet count, supports this hypothesis (Kelaidi *et al*, 2008). However there are concerns regarding increased risk of leukaemic transformation following lenalidomide and therefore its use is not currently recommended. It should also be noted that there is a single case report of bortezomib (Velcade) being used successively in one patient with del 5q- syndrome, producing a major erythroid response and resolution of the initial thrombocytosis (Terpos *et al*, 2007).

Refractory anaemia with ringed sideroblasts associated with marked thrombocytosis

In a previous review article, it was recognized that amongst MDS patients, an elevated platelet count was most commonly associated with the RARS subtype (Gupta *et al*, 1999). It was suggested that RARS-T was seemingly associated with a relatively good prognosis, none of that patient sub-group having died of disease-related progression during the time of study; however, one patient died of a cerebrovascular accident when the platelet count was around $450 \times 10^9/l$ (Shaw, 2005). It is not clear how this patient's platelet count had been managed, but 13 of the 16 RARS-T patients had received platelet lowering therapy, of whom 8 received HC, 2 received anagrelide and 1 patient received both (Shaw, 2005).

Further insights into this condition have come from *JAK2* mutation analysis, *MPL* mutation data, and an unexpected association with haemochromatosis-associated alleles. Recent work has suggested that RARS-T patients with the *JAK2* V617F mutation may have a more favourable prognosis (relative risk of death 79% lower than *JAK2* wild type group) than those with wild type *JAK2* (Schmitt-Graeff *et al*, 2008a). There have also been recent case reports of an *MPL* W515 mutation in a patient with features of both ET and RARS-T (Schnittger *et al*, 2009), and a *JAK2* V617F-negative RARS-T patient (Schmitt-Graeff *et al*, 2008a).

Recommendations: Management of thrombocytosis in the context of MDS/MPN

- **Patients who have a history of thrombosis, are symptomatic, or who are at high thrombotic risk should be considered candidates for cytoreductive and anti-platelet therapy where no contraindications are apparent (Evidence level IV Grade C).**

Management of reactive thrombocytosis

Platelet counts well above $1000 \times 10^9/l$ can occur in reactive thrombocytosis. (Buss *et al*, 1994). Despite high platelet counts these patients rarely have symptoms. (Buss *et al*, 1985; Randi *et al*, 1991). Usually the thrombocytosis resolves once the underlying reactive state has been treated although sometimes this may not occur concurrently. There is no concordance with regard to management and consideration should be given to the use of aspirin 75 mg although there is no published data to support this practice.

Key recommendations

Diagnostic process

- Thrombocytosis is a common finding with a wide range of primary and secondary causes as well as false or 'spurious' conditions mimicking thrombocytosis. Evaluation of these patients therefore requires a comprehensive approach involving clinical and laboratory parameters.
- The guideline group also developed a diagnostic algorithm to synthesize practice in undertaking the investigation of thrombocytosis (Fig 1).

Risk stratification

- Patients should be stratified according to their risk of thrombotic complications (Evidence level IIa Grade B).
- Microvascular symptoms are not generally regarded as thrombotic events for the purpose of risk classification but if they are severe or not responding to aspirin the patient could be re-classed as 'high risk' (Evidence level IV Grade C).
- Platelet count per se does not correlate well with thrombotic risk; however, a platelet count $>1500 \times 10^9/l$ has been used as an indicator for cytoreductive therapy in view of the increased haemorrhagic risk (Evidence level III Grade B).
- In young patients (<40 years) it may be reasonable to use a higher platelet threshold for risk classification in the absence of symptoms (Evidence level IIa Grade B).
- The impact of cardiovascular risk factors on thrombotic risk assessment in otherwise low or intermediate risk patients (<60 years and no thrombotic events) remains uncertain (Evidence level III Grade B).
- Emerging risk factors include the white blood cell (WBC) and JAK2 allele burden, both of which require prospective validation with robust techniques. (Evidence level III Grade C).

Management recommendations for essential thrombocythaemia (ET) General:

- Patients should be screened for hypertension, hyperlipidaemia, diabetes and a smoking history should be taken. Any cardiovascular risk factors should be aggressively managed (Evidence level IV Grade C).

- Aspirin should be given to all ET patients, unless contraindicated; a platelet count of over $1000 \times 10^9/l$ is a relative contraindication (Evidence level IIb Grade B).

High risk patients:

- The treatment target should be to return the platelet count into the normal range (Evidence level Ib, Grade A).
- The results of the primary thrombocythaemia-1 (PT-1) trial suggest that hydroxycarbamide (HC) plus aspirin should be first-line therapy for patients with high risk ET (Evidence level Ib Grade A).
- Although inferior to HC and aspirin, the PT-1 data suggest that anagrelide and aspirin is reasonable second-line therapy (Evidence level Ib Grade A).
- Due to the risk of myelofibrotic transformation in anagrelide-treated patients, regular monitoring (three yearly) for early signs of progression is recommended (Evidence level Ib Grade A).
- Patients treated with anagrelide who demonstrate progression to post-ET MF should be switched to an alternative agent (Evidence level III Grade B).
- In young patients and those contemplating pregnancy, interferon alpha (IFNa) is a reasonable treatment option (Evidence level III Grade B).

Treatment specific recommendations

- Options for refractory disease include relaxing the platelet target or to switching either partially (combination therapy) or completely to second-line therapy that is non-leukaemogenic where possible (Evidence level III Grade B).
- For patients with intolerance of HC, second-line therapy should be non-leukaemogenic where possible (Evidence level III, Grade B).
- IFNa is a useful agent for treatment of ET but is associated with a high incidence of side effects (Evidence level III, Grade B).
- Pegylated interferon is an emerging treatment for ET but randomized clinical trials are required to demonstrate its utility in comparison with HC (Evidence level III Grade B).
- Busulfan is an efficacious agent in the control of the platelet count in ET with a recognized side effect profile. It is not suitable for the treatment of young patients and should be used with caution in those patients who have already received HC (Evidence level III Grade B).
- Pipobroman has utility in the treatment of ET, although recent evidence suggests that long term use is associated with a significant risk of acute myeloid leukaemia (AML) (Evidence level III Grade B).
- Radioactive phosphorus (P32) is easy to administer, effective treatment in the elderly where the increased longer term risks of AML may be acceptable (Evidence level III Grade B).

Low and intermediate risk patients:

- Until the results of the intermediate risk PT-1 study are known, it is recommended that patients under the age of 60 years with no high risk factors only receive cytoreductive therapy in the context of a clinical trial or if the ET is symptomatic, for example progressive splenomegaly, erythromelalgia or other severe microvascular symptoms not improved with aspirin, or uncontrolled bleeding associated with high platelet counts. (Evidence level III Grade B).

Post-ET myelofibrosis (MF)

- The diagnosis of post-ET MF should be made using standard criteria.
- Post-ET MF should be managed as primary myelofibrosis (Evidence Level IV grade C).

Leukaemic transformation of ET

- Leukaemic transformation is diagnosed when 20% blasts are consistently present either in blood or bone marrow.
- Most patients with leukaemic transformation have a poor overall survival. However for a small subgroup stem cell transplantation may result in superior survival. (Evidence Level III Grade B).

Management of pregnancy in ET

- Patients should be managed by a multidisciplinary team.
- Therapeutic options including aspirin, low molecular weight heparin (LMWH) and IFNa should be offered according to risk stratification.
- Uterine artery dopplers at 20–24 weeks are a useful tool to help predict late pregnancy complications.
- Patients should receive 6 weeks of LMWH post partum.
- (All level IV Grade C).

Oestrogen-based therapy in ET

- The combined oral contraceptive pill should be discouraged for women with ET.
- Hormone replacement therapy may pose a minor increase in venous thromboembolism (VTE) risk; thus this should only be used in patients without additional risk factors for VTE and without a personal history of thrombosis.
- Ovarian stimulation therapy is associated with a risk of thrombosis and each case should be individually assessed and offered thromboprophylaxis where appropriate (Evidence level IV, Grade C).

Management of children with ET

- Causes of a reactive thrombocytosis should be rigorously excluded and the diagnosis of ET made only in the presence of definitive diagnostic features (Evidence level IV, Grade C).

- There is insufficient evidence to guide management of ET in children but a conservative approach should be used where possible (Evidence level IV, Grade C).
- Risk stratification used to guide therapeutic decisions in adults is not validated for use in children with ET (Evidence level IV, Grade C).
- Data regarding ET in children should be prospectively collected.

Splanchnic vein thrombosis

- A multidisciplinary approach to patient care is appropriate (Evidence level IV Grade C).
- All patients with unexplained splanchnic vein thrombosis should be evaluated for the presence of myeloproliferative neoplasms (MPN) even if their blood count is normal (Evidence level IV Grade C).

Surgery in patients with ET

- Individual risk assessment for VTE; appropriate use of anti-embolic stockings and pharmacological agents should be attained for all patients including disease, patient and procedure specific risks.
- Standard protocols should be followed with regard to management of antiplatelet agents, warfarin and post-operative thromboprophylaxis (Evidence level Ib Grade A).
- Controlling platelet counts pre-operatively to a target of $<400 \times 10^9/l$ should be considered in ET patients undergoing surgery where bleeding is a risk or thromboprophylaxis would normally be prescribed (Evidence level IV Grade C).
- Surgical blood loss and post-operative infection may result in worsening thrombocytosis and should be managed according to the root cause (Evidence level III Grade C).

Splenectomy in ET

- Standard prophylactic measures should be applied and post-operative exacerbation of thrombocytosis should be anticipated. (Evidence level IV Grade C).

Management of thrombocytosis in the context of myelodysplastic syndrome (MDS)/MPN

- Patients who have a history of thrombosis, are symptomatic, or who are at high thrombotic risk should be considered candidates for cytoreductive and anti-platelet therapy where no contraindications are apparent. (Evidence level IV Grade C).

Disclaimer

While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the British Society for Haematology nor the publishers accept any legal responsibility for the content of these guidelines.

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Suggested topics for audit

- The use of diagnostic criteria
- The management of cardiovascular risk factors
- Achievement of therapeutic targets
- Cutaneous side effects of hydroxycarbamide

Conflicts of interest

None of the authors have declared a conflict of interest (or other statement as agreed between the writing group and the Task Force Chair).

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