
Pan-London Haemato-Oncology Clinical Guidelines

Acute Leukaemias and Myeloid Neoplasms
Part 4: Myeloproliferative Neoplasms

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Disclaimer

These guidelines should be read in conjunction with the latest NICE guidance, and all applicable national/international guidance. The prescribing information in these guidelines is for health professionals only. It is not intended to replace consultation with the Haematology Consultant at the patient's specialist centre. For information on cautions, contra-indications and side effects, refer to the up-to-date prescribing information. While great care has been taken to see that the information in these guidelines is accurate, the user is advised to check the doses and regimens carefully and if there is any uncertainty about the guidance provided, you should discuss your queries with a Haematology Consultant or Senior Pharmacist. No set of guidelines can cover all variations required for specific patient circumstances. It is the responsibility of the healthcare practitioners using them to adapt them for safe use within their institutions and for the individual needs of patients.

Contact us

The writing cycle for the guidelines will be from May-July each year. If you wish to be part of the writing group, please contact us through the following link: [Pan London Blood Cancer](#) (or via uclh.panlondonbloodcancer@nhs.net).

If you wish to report errors or omissions that require urgent attention please contact us via the same email addresses.

1 Introduction

Myeloproliferative neoplasms (MPN) conditions include essential thrombocythaemia (ET), polycythaemia vera (PV) and primary myelofibrosis (PMF). They are all closely related and have an intrinsic tendency to evolve into acute myeloid leukaemia (AML), confirming their classification as haemato-oncological disorders.

MPNs are perhaps the orphan diseases of haemato-oncology, but these patients, if managed judiciously, have prolonged survival, with a median survival greater than 10–15 years for ET and PV. However, available treatments have significant side-effect profiles and need to be chosen with care, particularly in young patients. The last decade has seen the publication of a considerable body of clinical data informing clinical decisions. Many therapeutic options, however, remain unlicensed.

The following sections contain current management protocols for ET, PV and MF (including MF in patients with an antecedent history of ET and PV and pre-fibrotic MF).

Other entities within the MPN group – MPNU, chronic eosinophilia, chronic neutrophilic leukaemia and mast cell disorders – are not covered in these guidelines.

These conditions listed in the World Health Organization (WHO) criteria for MPN 2016 (WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. IARC, Lyon 2016) are:

Myeloproliferative neoplasms

- Chronic myeloid leukemia (CML), BCR-ABL1⁺
- Chronic neutrophilic leukemia (CNL)
- Polycythemia vera (PV)
- Primary myelofibrosis (PMF)
 - PMF, prefibrotic/early stage
 - PMF, overt fibrotic stage
- Essential thrombocythemia (ET)
- Chronic eosinophilic leukemia, not otherwise specified (NOS)
- MPN, unclassifiable
- Mastocytosis

Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of

- PDGFRA, PDGFRB, or FGFR1, or with PCM1-JAK2
- Myeloid/lymphoid neoplasms with PDGFRA rearrangement
- Myeloid/lymphoid neoplasms with PDGFRB rearrangement
- Myeloid/lymphoid neoplasms with FGFR1 rearrangement
- Provisional entity: Myeloid/lymphoid neoplasms with PCM1-JAK2

Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)

- Chronic myelomonocytic leukemia (CMML)
- Atypical chronic myeloid leukemia (aCML), BCR-ABL1-
- Juvenile myelomonocytic leukemia (JMML)
- MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)
- MDS/MPN, unclassifiable

2 Clinical Features

2.1 Essential thrombocythaemia (ET)

ET is characterised by a persistent thrombocytosis. The previously accepted platelet count threshold $>600 \times 10^9/L$ has been revised to $>450 \times 10^9/L$. Short-term complications of ET include thrombosis and, less frequently, haemorrhage. In common with PV, long-term problems include MF and acute leukaemia, although these are less frequent in ET.

Thrombotic events affect the arterial and venous macro and microvasculature, as well as the placental circulation. Microvascular events predominate in ET typically causing erythromelalgia (asymmetric erythema, congestion and burning pain in the hands and feet), which may progress to ischaemia and gangrene, migraine-like headaches and transient ischaemic attacks (TIAs).

Approximately 30–50% of patients are symptomatic at presentation.

2.2 Polycythaemia vera (PV)

PV is characterised by an erythrocytosis (packed cell volume (PCV) >0.52 in men and >0.48 in women, 2008 criteria; $>49\%$ in men and $>48\%$ in women, 2016 criteria) and sometimes thrombocytosis and neutrophilia according to the BCSH. Recent WHO criteria are shown below. The median age at presentation is 55–60 years.

Vascular thromboses, especially arterial events and more rarely bleeding, are major short-term events. In the longer term (10–15 years), MF or ‘spent phase’ occurs and AML (partially treatment related) in 5–10% of patients.

Aquagenic pruritus, gout and splenomegaly are also classical clinical features, but only occur in a few patients.

2.3 Primary myelofibrosis (PMF) including Prefibrotic-MF (Pre-MF)

Chronic idiopathic myelofibrosis, also known as agnogenic myeloid metaplasia, PMF may arise *de novo* or as a late phase of ET, and particularly PV known as post-PV (PPV)-MF and post-ET (PET)-MF. Fibrosis is thought to arise from an interaction between diseased megakaryocytes, releasing mitogens such as platelet-derived growth factor (PDGF) and transforming growth factor that directly increase fibroblast proliferation.

PMF has a median age of presentation of 50–60 years. Symptoms relate to bone marrow failure (anaemia, infection, bleeding) or progressive splenomegaly (pain, weight loss, sweating). Progression to acute leukaemia occurs in up to 25% of patients (more than PV or ET) and may be associated with extramedullary collections of myeloid progenitors (chloromas). Accelerated phase of MF with BM blasts $<20\%$ can be associated with increasing circulating blasts, bone marrow failure and splenomegaly.

Pre-MF is a relatively recently described entity. Like ET, pre-MF is characterised by a chronic thrombocytosis, but it differs from ET in terms of bone marrow morphology and prognosis (Thiele, *et al.*, 2011). The bone marrow in pre-MF is markedly hypercellular, with pronounced granulocytic hyperplasia, erythroid hypoplasia, and distinctive megakaryocytic morphology, distinguishing it from ET. However, there is no significant increase in reticulin fibres in pre-MF, distinguishing it from PMF. The life expectancy in pre-MF is probably intermediate between ET and PMF, but the natural history of pre-MF is unknown and studies are on-going. This is something we could usefully contribute to across London, i.e. defining natural history and outcome.

3 Referral Pathways

Patients with a high WBC, haemoglobin/haematocrit or platelet count and/or suspected MPN by other means (e.g. splenomegaly, unprovoked and unusual site for a thrombotic episode) should be referred to a haematologist for assessment, via a 2 week wait pathway.

All new patients should be referred to the MDT for confirmation of diagnosis, prognosis and management plan, taking into account their performance status, needs and co-morbidities. A joint approach with elderly care physicians and palliative care teams may be appropriate, depending on the performance status of the patient and the phase of disease.

The following patients should be referred to the MDT:

- All new patients with MPN in order to confirm the diagnosis and treatment plan
- All patients where a new line of therapy needs to be considered
- All patients with a restaging assessment
- All patients in whom an allogeneic stem cell transplant is a consideration.

Information to be captured and documented prior to, or during, the MDT includes:

- Demographic information
- Referring physician and/or GP
- Performance status
- An indicator of co-morbidities (e.g. co-morbidity score)
- Any relevant history
- Pertinent positive and negative findings on physical examination (splenomegaly, rashes, etc.)
- Spleen size (by ultrasound)
- FBC, haematinics, LFTs, U&E, LDH, urate, reticulocyte count, DAT, AIS, SPEP, serum erythropoietin, transfusion dependency
- Bone marrow aspirate and trephine histology (where available)
- Bone marrow aspirate immunophenotyping, if relevant
- Cytogenetic status, if relevant
- Mutational status (in most cases this will include the driver mutations JAK2/CALR/MPL but in patients with atypical features, triple negative MF and patients where SCT is considered a wider mutational panel should be considered).
- Specific diagnosis/category of MPN and prognostic risk score (we recommend recording which diagnostic criteria were used, i.e. WHO or BCSH)
- Other relevant imaging
- Availability of a clinical trial/research study and whether the patient is eligible
- Management and treatment plan
- Key worker/clinical nurse specialist
- Named consultant or team (as per local work patterns).

The MDT outcome form should be sent to the GP (by email, or preferably by fax) within 24 working hours of the MDT discussion.

Patients with PV, ET and MF may be managed at facilities with at least BSCH Level 1 designation. Complex patients may be referred to centres with specific expertise or which have available trials.

Management protocols for patients with therapy intolerance, for adults contemplating parenthood or for women during pregnancy are more complex and individualised. These patients should be discussed with a consultant haematologist who is experienced in such cases, and the patient may be referred to a sub-specialist centre if needed, e.g. for obstetric care or for patients with difficult-to-manage mastocytosis.

Patients who are being considered for an allogeneic stem cell transplant should be referred to a JACIE-accredited centre. Young patients with MF eligible for a transplant option should be referred for an opinion early.

3.1 Children

Children below the age of 16 years with a diagnosis of MPN must be referred to the paediatric oncology team at the principal treatment centre (PTC) and must not be managed exclusively by adult site-specific teams. However adult input in this specialty which is extremely rare in the paediatric setting is critical.

- The joint PTC for children aged below 16 years for South Thames is The Royal Marsden (Sutton)/St George's Hospital.
- The PTC for North Thames (including North West London) is Great Ormond Street Hospital/ University College London Hospitals.
- All patients <1 year from both North and South Thames should be referred to Great Ormond Street Hospital.

3.2 Teenagers and young adults

Teenagers aged 16–18 should be managed at a PTC for teenage and young adult (TYA) cancers. Young adults aged 19–24 should be given the choice of being managed at a PTC or TYA-designated hospital.

- The PTC for TYA for South Thames is The Royal Marsden (Sutton)/Guy's Hospital
- The PTC for North Thames (including North West London) is University College London Hospitals.

All patients within this age range, regardless of place of care, should be referred to the TYA MDT at the relevant PTC.

4 Investigation and Diagnosis

A thorough clinical history and examination should be performed, focusing upon exclusion of secondary causes.

For patients with unprovoked blood clots (in particular of the splanchnic or cerebral venous circulation, or other unusual sites), check JAK2 and CALR mutational status even if blood counts are normal.

Diagnostic criteria: in this document we present both BCSH and WHO diagnostic criteria; we recommend consistent use of one of these options.

4.1 Essential thrombocythaemia (ET)

There is no diagnostic hallmark for ET. The diagnosis is made by excluding other MPNs, and a reactive or secondary thrombocytosis. Causes of a reactive thrombocytosis include iron deficiency anaemia, chronic inflammation (e.g. rheumatoid arthritis, inflammatory bowel disease), splenectomy, acute haemorrhage, and malignant disease. In an otherwise well patient, the diagnosis is generally uncomplicated. However, where conditions co-exist which may cause a reactive thrombocytosis, this may make the diagnosis more difficult.

Historically, the diagnostic criteria for ET were those of the polycythaemia vera study group. Forty years on, continual development of the diagnostic criteria for MPNs set the stage for the World Health Organization (WHO) Diagnostic Criteria 2001, modified in 2008 and again in 2016. The revised WHO criteria (2016) require characteristic bone marrow morphology, a platelet threshold of $450 \times 10^9/L$ and molecular analysis for the JAK2 V617F mutation and other clonal markers. Modified BCSH (British Committee for Standards in Haematology, 2013) criteria or WHO criteria may be used.

4.1.1 WHO ET criteria (2016)

Major criteria

1. Platelet count $\geq 450 \times 10^9/L$
2. BM biopsy showing proliferation mainly of the megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei. No significant increase or left shift in neutrophil granulopoiesis or erythropoiesis and very rarely minor (grade 1) increase in reticulin fibres
3. Not meeting WHO criteria for BCR-ABL1 CML, PV, PMF, myelodysplastic syndromes, or other myeloid neoplasms
4. Presence of JAK2, CALR, or MPL mutation.

Minor criterion

Presence of a clonal marker or absence of evidence for reactive thrombocytosis.

Diagnosis of ET requires meeting all 4 major criteria or the first 3 major criteria and the minor criterion.

4.1.2 BCSH (2013) diagnostic criteria for ET

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 JAK2, CALR or MPL 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.

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

‡ Chronic myeloid leukaemia; excluded by absence of BCR-ABL1 fusion from bone marrow or peripheral blood.

§ Myelodysplastic syndrome; excluded by absence of dysplasia on examination of blood film and bone marrow aspirate.

Investigations to be performed on all patients include:

- FBC and blood film
- Haematinics
- Renal/liver profiles and CRP
- ANA and RhF
- Chest X-ray (most patients, all smokers).

Where there is a high index of suspicion on first appointment, otherwise at second visit:

- JAK2 V617F, CALR and MPLW515L/K screen
- Abdominal ultrasound scan
- Bone marrow aspirate and trephine (BMAT), cytogenetics in all patients <60 years, JAK2/MPL/CALR mutation negative patients and patients where there is a suspicion of MDS, pre-MF or MF, regardless of mutation status
- PB/BM samples sent for bcr-abl FISH to exclude a diagnosis of CML
- Consider testing for vWFAg and Ricof looking for acquired VWD in patients with platelets $>1000 \times 10^9/L$ and haemorrhagic symptoms

The decision to proceed to formal cytogenetic analysis on any sample received is made at the diagnostic multidisciplinary (MDT) meeting.

The recent WHO criteria (2016) for ET place greater emphasis upon bone marrow histology, in particular megakaryocyte morphology, and also emphasis is placed on discriminating PV from JAK2 positive ET. The other condition that must be excluded when diagnosing ET is myelodysplastic syndrome. This is usually associated with a low rather than high platelet count and is characterised by dysplastic features morphologically and particular chromosomal abnormalities.

Note that some patients with refractory anaemia with ring sideroblasts (RARS) or chromosome 5 abnormalities and MDS may also carry the JAK2 V617F mutation (see WHO classification for MDS-RARS-T).

4.2 Polycythaemia vera (PV)

An erythrocytosis is defined as an HCT >0.52 in men and >0.48 in women (*per* BCSH, 2007), although the WHO (2016) have a lower HCT threshold (0.49 for men; 0.47 for women) this has not yet been widely adopted. To determine whether there is an absolute erythrocytosis (increased red cell mass [RCM]) or an apparent/pseudo-erythrocytosis (normal RCM, reduced plasma volume), an RCM study may be performed where facilities are available. This has been largely superseded by testing for the presence of the JAK2 V617F mutation which indicates the presence of an MPN or an MDS. The JAK2 V617F mutation negative erythrocytosis cases may still be a PV case without a genetic marker or with a JAK2 exon12 mutation; alternatives include a pseudo/apparent, primary congenital, secondary congenital or acquired, or idiopathic erythrocytosis, all of which require definition.

Table 1: WHO (2016) diagnosis of PV

Diagnosis needs both major and one minor criteria OR major criterion no.1 with two minor criteria (after exclusion of secondary causes):

Major	<ol style="list-style-type: none"> 1. Hb >16.5 g/dL in men; >16.0 g/dL in women or hematocrit >49% in men; >48% in women or increased red cell mass (RCM)* 2. BM biopsy† showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size) 3. Presence of JAK2V617F or JAK2 exon 12 mutation
Minor	Subnormal serum erythropoietin level

Diagnosis of PV requires meeting either all 3 major criteria, or the first 2 major criteria and the minor criterion†.

*More than 25% above mean normal predicted value.

†Criterion number 2 (BM biopsy) may not be required in cases with sustained absolute erythrocytosis: Hb >18.5 g/dL in men (haematocrit > 55.5%) or >16.5 g/dL in women (haematocrit > 49.5%) if major criterion 3 and the minor criterion are present. However, initial myelofibrosis (present in up to 20% of patients) can only be detected by performing a BM biopsy; this finding may predict a more rapid progression to overt myelofibrosis (post-PV MF).

The current BCSH erythrocytosis guideline amendment suggests a three-stage approach to investigation, this is practically helpful in the wider context of erythrocytosis. The procedure outlined below is an adaptation of this guidance, based upon modified diagnostic criteria suggested by Campbell and Green (2006), simplifying the diagnosis and the need for investigation in JAK2-positive PV. Determination of a case of JAK2-negative PV or an alternative cause of erythrocytosis will require further investigation.

JAK2-positive PV (Diagnosis requires both to be present)

- A1 PCV >0.52 men, >0.48 in women or a raised RCM (>25% above predicted)
- A2 Mutation in JAK2

JAK2-negative PV (Diagnosis requires A1 + A2 + A3 + either another A or two B criteria)

- A1 Raised RCM (>25% above predicted) or a PCV >0.60 in men, >0.56 in women
- A2 Absence of mutation in JAK2
- A3 No cause of secondary erythrocytosis
- A4 Palpable splenomegaly
- A5 Presence of acquired genetic mutation (excluding BCR-ABL) in haemopoietic cells
- B1 Thrombocytosis: platelet count >450 x 10⁹/L
- B2 Neutrophil leukocytosis
- B3 Radiological evidence of splenomegaly
- B4 Endogenous erythroid colonies or low serum erythropoietin

The primary clinical assessment of an erythrocytosis case should include a thorough history and examination seeking out possible secondary causes, followed by Stage 1 investigations to confirm or refute a diagnosis of a JAK2 V617F-positive PV. The majority of patients (excluding borderline erythrocytosis) and all ex- and current smokers will require a chest X-ray. Urinalysis is a simple effective screen for renal disease, which should be performed in all patients at the initial visit. Patients may present with co-morbidity; thus, regardless of a diagnosis of PV, a review of secondary causes is pertinent. Additional investigation of possible secondary causes will vary according to symptoms or signs present.

PV Stage 1:

- FBC and blood film
- Haematinics
- Renal, liver profile and urate level
- JAK2 V617F
- Chest X-ray (smokers)
- Urinalysis
- Serum erythropoietin level
- Pulse oximetry and venous carboxyhaemoglobin

If the initial screening tests are negative for a JAK2 mutation and there is no obvious secondary cause, further investigations are indicated. An RCM may be required to define whether a case is a pseudo/apparent or an absolute erythrocytosis at this point and should be discussed with the consultant. A PCV of >0.60 and >0.56 in a man or woman, respectively, can be assumed to have an absolute erythrocytosis and an RCM would not be indicated. Cases confirmed as an absolute erythrocytosis require Stage 2 tests, as appropriate, with consultant guidance.

PV Stage 2:

- Strongly consider BMAT for JAK2 V617F-positive patients <60 (required if there is evidence or suspicion of MDS or MF) and JAK2 V617F-negative patients with a strong suspicion of PV (clinician choice if age >60)
- Cytogenetics (not mandatory but useful in JAK2-negative/atypical cases and young patients)
- Peripheral blood for JAK2 exon12 screen in a JAK2 V617F-negative patient with a strong suspicion of PV
- Abdominal ultrasound
- Erythroid burst-forming unit culture (BFU-E): if test available and considered appropriate, discuss with consultant (largely a research tool)
- RCM performed in nuclear medicine – discuss with consultant.

The serum erythropoietin level, JAK2 exon12 mutation screen, abdominal ultrasound and, in very specific cases, BFU-E culture will aid the diagnosis of JAK2 V617F-negative PV. Hypoxaemia causing a secondary erythrocytosis can be screened for by assessing oxygen saturation using pulse oximetry (92% is the arbitrary cut-off for significance) and the carboxyhaemoglobin level available from biochemistry. It is important to subtract the carboxyhaemoglobin level from the oxygen saturation to obtain the correct estimate of oxygen saturation. The abdominal ultrasound combined with urinalysis and GFR estimation enables a renal disease screen.

A BMAT should be performed in all cases of JAK2 V617F-negative absolute erythrocytosis where no cause of secondary erythrocytosis is found. Although the Green and Campbell criteria do not include histology as a diagnostic criterion, the presence of typical histology will support a diagnosis of JAK2-negative PV, whereas its absence will suggest an alternative cause. Recently, WHO has proposed new criteria, included below for comparison, which place significant emphasis on bone marrow histology and have yet to gain widespread credence. A baseline BMAT should also be obtained in all JAK2 V617F-positive patients who are under 60 for future reference regarding progression, although it is not essential to confirm a diagnosis. A BMA sample should be sent for cytogenetics – the decision whether to formally proceed to assess these samples is made in the diagnostic MDT meeting.

For those patients whose absolute erythrocytosis is still undefined, Stage 3, consisting of further specialised investigations, needs to be considered and discussed with a consultant. Symptoms, including snoring, daytime somnolence and a body habitus suggestive of sleep apnoea, may warrant referral for sleep studies. The Epworth score is a useful indicator for referring for sleep studies. A genetic screen including the erythropoietin receptor mutation, HIF-1alpha and proline dehydroxylase mutations can be sent to the haematology lab at Viapath at King's College Hospital, and may lead to a diagnosis of a primary congenital erythrocytosis. A p50 estimation/beta chain sequencing may demonstrate a high affinity haemoglobin causing a secondary congenital erythrocytosis.

PV Stage 3 (selected):

- Sleep studies
- P50
- Genetic screen for VHL, PHD and erythropoietin receptor mutations (EPOR) and EGLN1
- CT head
- Lung function studies
- RCM and BFU-E: if considered appropriate, discuss with consultant.

4.3 Prefibrotic myelofibrosis (pre-MF) and primary myelofibrosis (PMF)

For diagnosis of PMF, exclude other MPNs (PV, ET and CML) and disorders in which marrow fibrosis can develop as a secondary feature (e.g. metastatic carcinoma, lymphoma, irradiation, TB and leishmaniasis).

The following are generally necessary to confirm PMF:

- Splenomegaly
- Increased BM fibrosis. In later stages, new osteoid is formed (osteomyelofibrosis)
- Leucoerythroblastic blood film
- Absence of other MPN, including CML (perform FISH for bcr-abl)
- Exclude secondary causes of myelofibrosis (see above)
- It may be useful to obtain an LDH level and cytogenetics (consider from peripheral blood) periodically to monitor
- In patients with atypical features, triple negative MF and patients where SCT is considered a wider mutational panel should be considered.

The following tests should be performed:

- FBC and blood film, blast count
- Haematinics
- Renal, liver profile, LDH and urate level
- JAK2 V617F, CALR and MPL W515L/K screen
- Chest X-ray
- Abdominal ultrasound scan
- BMAT with samples sent for cytogenetics and FISH for bcr-abl.

Table 2: WHO diagnosis of pre-MF: need to meet all three major and at least one minor criterion

Major	<ol style="list-style-type: none"> 1. Megakaryocytic proliferation and atypia, without reticulin fibrosis grade 1*, accompanied by increased age-adjusted BM cellularity, granulocytic proliferation, and often decreased erythropoiesis 2. Not meeting the WHO criteria for BCR-ABL11 CML, PV, ET, myelodysplastic syndromes, or other myeloid neoplasms 3. Presence of JAK2, CALR, or MPL mutation or in the absence of these mutations, presence of another clonal marker,[†] or absence of minor reactive BM reticulin fibrosis[‡]
Minor	<p>Presence of at least 1 of the following, confirmed in 2 consecutive determinations:</p> <ol style="list-style-type: none"> a. Anaemia not attributed to a comorbid condition b. Leukocytosis $\geq 11 \times 10^9/L$ c. Palpable splenomegaly d. LDH increased to above upper normal limit of institutional reference range

Diagnosis of pre MF requires meeting all 3 major criteria, and at least 1 minor criterion.

*See [Table 5](#).

†In the absence of any of the 3 major clonal mutations, the search for the most frequent accompanying mutations (eg, ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, SF3B1) are of help in determining the clonal nature of the disease.

‡Minor (grade 1) reticulin fibrosis secondary to infection, autoimmune disorder or other chronic inflammatory conditions, hairy cell leukaemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies.

Table 3: WHO overt PMF criteria

Major	<ol style="list-style-type: none"> 1. Presence of megakaryocytic proliferation and atypia, accompanied by either reticulin and/or collagen fibrosis grades 2 or 3* 2. Not meeting WHO criteria for ET, PV, BCR-ABL11 CML, myelodysplastic syndromes, or other myeloid neoplasms 3. Presence of JAK2, CALR, or MPL mutation or in the absence of these mutations, presence of another clonal marker,[†] or absence of reactive myelofibrosis[‡]
Minor	<p>Presence of at least 1 of the following, confirmed in 2 consecutive determinations:</p> <ol style="list-style-type: none"> a. Anemia not attributed to a comorbid condition b. Leukocytosis $\geq 11 \times 10^9/L$ c. Palpable splenomegaly d. LDH increased to above upper normal limit of institutional reference range e. Leukoerythroblastosis

Diagnosis of overt PMF requires meeting all 3 major criteria, and at least 1 minor criterion

*See [Table 5](#).

†In the absence of any of the 3 major clonal mutations, the search for the most frequent accompanying mutations (eg, ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, SF3B1) are of help in determining the clonal nature of the disease.

‡BM fibrosis secondary to infection, autoimmune disorder, or other chronic inflammatory conditions, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies.

Table 4: BCSH diagnostic criteria***BCSH diagnostic criteria (2015) for PMF: requires A1 + A2 and any two B criteria***

- A1 Bone marrow fibrosis ≥ 3 (on 0–4 scale)
- A2 Pathogenetic mutation (e.g. in JAK2, CALR or MPL), or absence of both BCR-ABL1 and reactive causes of bone marrow fibrosis
- B1 Palpable splenomegaly
- B2 Unexplained anaemia
- B3 Leucoerythroblastic blood film
- B4 Tear-drop red cells
- B5 Constitutional symptoms¹
- B6 Histological evidence of extramedullary haematopoiesis.

BCSH diagnostic criteria for post-PV and post-ET MF: requires A1 + A2 and any two B criteria

- A1 Bone marrow fibrosis ≥ 3 (on 0–4 scale)
- A2 Previous diagnosis of ET or PV
- B1 New palpable splenomegaly or increase in spleen size of ≥ 5 cm
- B2 Unexplained anaemia with 2g/dL decrease from baseline haemoglobin
- B3 Leucoerythroblastic blood film
- B4 Tear-drop red cells
- B5 Constitutional symptoms*
- B6 Histological evidence of extramedullary haematopoiesis.

* Drenching night sweats, weight loss >10% over 6 months, unexplained fever (>37.5°C) or diffuse bone pains.

Table 5: Grading of myelofibrosis

Myelofibrosis grading	
MF-0	Scattered linear reticulin with no intersections (crossovers) 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 thick fibres mostly consistent with collagen, and/or focal osteosclerosis*
MF-3	Diffuse and dense increase in reticulin with extensive intersections and coarse bundles of thick fibres consistent with collagen, usually associated with osteosclerosis*

Semiquantitative grading of BM fibrosis (MF) with minor modifications concerning collagen and osteosclerosis. Fibre density should be assessed only in hematopoietic areas.

* In grades MF-2 or MF-3 an additional trichrome stain is recommended.

Source: Arber, *et al.* The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;127:2391–2405

4.4 Pathology

Careful attention must be paid to the labelling of forms and samples before sending to the Specialist Integrated Haematological Malignancy Diagnostic Service (SIHMDS). Samples are unlikely to be processed unless clearly and correctly labelled.

BMAT:

- Slides for morphology to SIHMDS lab
- 2–5ml in EDTA for immunophenotyping with a slide
- 2–5ml in EDTA for molecular genetics
- 2–5ml in heparin (PFH or lithium heparin) for cytogenetics/FISH
- Trepine for histopathology

4.5 Imaging

All patients should have an ultrasound of the abdomen performed at diagnosis to document spleen (and liver) size, and thereafter when clinically appropriate.

5 Risk Stratification

We recommend that all patients be risk stratified at diagnosis and yearly thereafter.

Risk stratification systems for ET and PV: please choose a system and stay with it.

Table 6: Risk stratification systems in MPN for vascular/thrombotic events

MPN Risk group	BCSH ET	IPSET ET	Firenze PV	Conventional PV
Low	Age <40 years No high-risk features	0	Age <60 and no past h/o thrombosis	0 features from list below
Intermediate	Age 40-60 years No high-risk features	1-2	CV risk factors	
High	Any feature from list below	≥3	Age >60 or past h/o thrombosis	Any feature from list below
<p>BCSH ET high-risk features to predict thrombosis:</p> <ul style="list-style-type: none"> – Age >60 years – Platelet count >1500 x 10⁹/L – Previous thrombosis, erythromelalgia (if refractory to aspirin) – Previous haemorrhage related to ET – Diabetes or hypertension requiring pharmacological therapy* – Pregnant patients with pregnancy-related complications in previous or current pregnancy – these patients revert to original risk group 6/52 post-partum <p>IPSET: Age ≥60 = 1; CV risk factors = 1; Previous thrombosis = 2; Jak2V617F = 2</p> <p>PV conventional: Predicts thrombosis but not tested prospectively</p> <ul style="list-style-type: none"> – Age >60 years – Previous thrombosis, erythromelalgia (if refractory to aspirin) – Platelets >1000 x 10⁹/L* – WBC >11 x 10⁹/L* – Diabetes or hypertension requiring pharmacological therapy* – Significant (i.e. >5cm below costal margin on palpation) or symptomatic (pain, early satiety) splenomegaly. NB this may be an indication for treatment rather than a risk factor <i>per se</i>* <p>* These risk factors are more controversial and have not been fully agreed.</p>				

5.1 Primary myelofibrosis (PMF)

The most widely adopted risk stratification was validated on 1,500 PMF patients: the International Prognostic Scoring System IPSS (Cervantes, 2008). But this applies to patients at diagnosis only. Subsequent studies have shown that the high-risk features of the IPSS can be applied in a dynamic manner to give useful prognostic information during follow-up of MF patients (DIPSS, Passamonti, 2010). The most recent scoring system is the DIPSS-Plus (Gangat, 2011), which takes into account transfusion dependence and thrombocytopenia.

None of these have been validated for post-ET or post-PV MF.

Table 7: IPSS, DIPSS and DIPSS-plus scoring for MF with prognostic chart

Variable	IPSS	DIPSS
Age >65 years	✓	✓
Constitutional symptoms	✓	✓
Haemoglobin <10g/dL	✓	✓
Leukocyte count >25 x 10 ⁹ /L	✓	✓
Circulating blasts ≥1%	✓	✓
	1 point each	1 point each but Hb=2

DIPSS-plus add one to the DIPSS score for each of:		
Platelet count <100 x 10 ⁹ /L		
RBC transfusion need		
Unfavourable karyotype +8,-7/7q-,i(17q),inv(3), -5/5q-,12p-, 11q23 rearr.		

Linking scores to prognosis:

Risk group	IPSS		DIPSS		DIPSS-plus	
	No. predictors	Median survival, years	No. predictors	Median survival, years	No. predictors	Median survival, years
Low	0	11.3	0	Not reached	0	15.4
Int-1	1	7.9	1 or 2	14.2	1	6.5
Int-2	2	4	3 or 4	4	2–3	2.9
High	>3	2.3	5 or 6	1.5	>4	1.3

6 Patient Information/Support

All patients must have access to a key worker. This is usually (but not always) the clinical nurse specialist.

The clinical nurse specialist/key worker should be present at diagnosis and at any significant discussion where treatment changes and outcomes are discussed. In the absence of the clinical nurse specialist, a senior nurse may deputise who must ensure that all conversations are documented in the patient's notes and on the electronic patient record. Where it is not possible for the clinical nurse specialist or a deputy to be present, patients should be given the clinical nurse specialist's contact numbers. The clinician leading the consultation should advise the clinical nurse specialist who should then arrange to make contact with the patient.

The clinical nurse specialist should ensure that all patients are offered a Holistic Needs Assessment (HNA) at key pathway points, including within 31 days of diagnosis; at the end of each treatment regime; and whenever a person requests one. Following each HNA, every patient should be offered a written care plan. This plan should be developed with the patient and communicated to all appropriate healthcare and allied healthcare professionals.

Written and verbal information is essential and the key worker/clinical nurse specialist plays a key role in ensuring that patients have access to appropriate and relevant written information about their condition.

Information booklets are available to download from the Bloodwise, Macmillan Cancer Support, and MPN Voice websites:

www.bloodwise.org.uk/info-support/myeloproliferative-neoplasms

www.macmillan.org.uk/Cancerinformation/Cancerinformation.aspx

www.mpnvoice.org.uk

7 Treatment

Formal written consent should be obtained for all patients before commencing any cytoreductive therapy (red cell-, white cell- or platelet-controlling drugs) including hydroxyurea (hydroxycarbamide/HU), anagrelide, interferon-alpha, ruxolitinib, busulfan or radioactive phosphorus.

- MPN related symptoms can have a major impact upon the quality of life of MPN patients and these should be documented formally and regularly reviewed using a validated tool such as the MPN- symptom assessment form (MPN-SAF) or MPN10.
- Cardiovascular risk factors should also be identified, discussed and regularly reviewed with all MPN patients.

7.1 Essential thrombocythaemia (ET)

7.1.1 Management and prognosis

Patients with ET, akin to those with PV, are predisposed to thrombosis, which is a major cause of morbidity and mortality. Haemorrhage occurs less frequently and is particularly associated with platelet counts in excess of $1500 \times 10^9/L$ and acquired von Willebrand disease.

Initial management should address lifestyle issues and risk factors associated with vascular events, including smoking, diabetes, hypertension and hyperlipidaemia. Most patients would benefit from 75mg aspirin daily or alternative anti-platelet drugs. The exceptions are those with active haemorrhage, aspirin intolerance, active or previous peptic ulcer disease, and, in aspirin, should be used with caution in those patients with platelets $>1000 \times 10^9/L$. There is some provisional data that low-risk CALR positive patients may not benefit from aspirin, but at the present time each case should be considered on its own merits.

An acquired von Willebrand disease should be considered in patients with a haemorrhagic phenotype by testing vWF:Ag and ristocetin cofactor activity.

The likelihood of thrombosis and haemorrhage is significantly reduced by therapy to control the platelet count to $<400 \times 10^9/L$. The current gold standard cytoreductive drug is hydroxyurea/hydroxycarbamide (HU). Alternatives include ^{32}P and busulfan, although these agents are more leukaemogenic. Interferon (IFN)- α controls the platelet count in a majority of patients but is poorly tolerated, with up to 30% being unable to continue treatment in the long term. IFN and anagrelide (ANA) have the advantage of being non-leukaemogenic and they preserve fertility. The MRC-PT1 study made a direct comparison between HU and ANA in patients with ET. The results of the high-risk arm suggest that HU + aspirin is a more effective first-line therapy than ANA + aspirin, which was associated with a higher rate of arterial thrombosis, haemorrhage and myelofibrotic transformation. A randomised trial to compare HU versus IFN would be of benefit to further evidence-based practice.

As survival in ET is long and cytoreductive agents have a poor side-effect profile, current practice would be to use these agents only in patients with a high risk of thrombosis. This would include patients aged over 60 or with any of the following risk factors: a prior thrombosis, diabetes, hypertension, vascular disease or a platelet count $>1500 \times 10^9/L$. For patients under 40 with none of these risk factors, aspirin alone is probably sufficient. For patients aged between 40 and 60 and lacking any of the risk factors, the management strategy is far from clear. Best practice would be to randomise such patients into an appropriate clinical trial, if available.

7.1.2 Aims of treatment

The aims of treatment are to reduce the incidence of thrombotic and haemorrhagic complications and potentially reduce long-term risk of transformation to myelofibrosis.

7.1.3 Evidence

- HU reduces the incidence of thrombotic episodes in high-risk patients according to a randomised controlled trial (Cortelazzo, *et al.*, 1995).
- IFN usage is based upon retrospective case series (Elliott and Tefferi, 1997; Reilly, 1996; Radin, 2003).
- ANA may be inferior to HU according to the results of the high-risk arm of the MRC-PT1 study (Harrison, 2005).
- There is no evidence on which to base a management strategy for intermediate- or low-risk patients (Harrison, 2002).
- There is evidence that HU reduces long-term risk of transformation to myelofibrosis in PV, although there is no direct evidence for ET (Najean, *et al.*, 1996).
- Patients who are resistant or intolerant to HU may have a worse prognosis (Hernandez-Boluda, 2015).

7.1.4 Treatment protocol

- Identify and aggressively manage all reversible risk factors for arterial disease including smoking, hypercholesterolaemia, hypertension and diabetes. Responsibility for this to be defined with primary care.
- Document MPN related symptoms.
- Aspirin for all in absence of contraindications as above. Consider screen for acquired von Willebrand disease in those with platelets $>1000 \times 10^9/L$. Consider clopidogrel if intolerant of aspirin.

Evidence grade level overall Ib-III

High-risk patients

First-line therapy is HU, pegylated IFN should be considered in younger patients.

Ensure counselling of all patients of reproductive age regarding teratogenicity. Uncertain effects upon fertility in long-term use and reiterate necessity for contraception (see above).

Evidence grade level Ib

Second-line therapy (in those patients who are refractory/intolerant to first-line therapy or developing PMF or progressive splenomegaly):

- Patients aged >70 years, consider busulfan or combination therapy with ANA and HU.
- Patients aged <70 years, consider either IFN or ANA or combination therapy with ANA and HU or consider pegylated interferon alpha 2A (see restrictions above).

*Evidence grade level III**Intermediate- and low-risk patients*

The MRC-PT1 trial (closed to recruitment) is currently evaluating treatment for these patient groups and best therapy is currently unclear. Intermediate-risk patients may receive either aspirin alone or aspirin and hydroxycarbamide. Low-risk patients may receive aspirin. **Discuss with consultant.** Consider recruiting into an appropriate clinical trial or research study.

Treatment Summary Box: Essential thrombocythaemia

- **ALL** patients – assess and manage cardiovascular risk factor; screen for disease-related symptoms
- **TREAT WITH** low dose aspirin (unless contraindicated)
- HIGH-RISK PATIENTS*
 - >60* years**
 - 1st line: hydroxycarbamide or pegylated IFN in selected cases
 - 2nd line: consider clinical trial or pegylated interferon**, anagrelide*** alone or in combination; if
 - >75 years busulfan or ³²P
 - <60* years**
 - 1st line: hydroxycarbamide or interferon**
 - 2nd line: consider clinical trial; pegylated interferon**, anagrelide*** alone or in combination.

* Treatment recommendations made for high-risk patients only, high-quality clear evidence for low or intermediate risk ET or PV management is unclear.

** Not currently licensed for this indication.

*** Current British guidelines recommend regular monitoring of patients treated with anagrelide for the development of fibrosis.⁹

Treatment options

Aggressively manage all reversible risk factors for arterial disease.

Patient leaflets are available for all treatment options from the MPN Voice (www.mpnvoice.org.uk) and the [Macmillan](#) websites.

Pre-chemotherapy counselling is available from the CNS/key worker. The counselling session should be followed up one week later with a telephone consultation.

Formal written consent should be obtained for all patients before commencing any cytoreductive therapy (red cell-, white cell- or platelet-controlling drugs) including hydroxycarbamide (hydroxyurea), anagrelide, interferon alpha, busulfan or radioactive phosphorus.

Aspirin

75mg per day for all patients without a clear contraindication (asthma, history of peptic ulceration, haemorrhage, platelet count in excess of 1000 x 10⁹/L). Clopidogrel 75 mg/day may be used if the patient is intolerant of aspirin.

Hydroxyurea/hydroxycarbamide

Refer to local or regional protocol. HC is the only treatment with demonstrated benefit in a randomised controlled trial; benefit for intermediate-risk patients is currently being assessed in the MRC-PT1 study. Limiting side effects include teratogenicity and the development of a refractory state in 10–15% of patients. There is no published evidence that HC monotherapy is leukaemogenic but HC may enhance the leukaemogenic effect of other cytoreductive agents such as busulfan and ³²phosphorus (risk of AML 15–30% if used in combination with alternative leukaemogenic agents (Murphy, *et al.*, 1997; Sterkers, *et al.*, 1998).

Prior to conception, a three-month wash-out period is required. Women should be reviewed, stop HC and discuss alternative treatment if necessary with IFN. Similarly, men wishing to father a child should discontinue HU three months prior to planned conception and discuss treatment if necessary with IFN. Young male patients should be offered sperm cryopreservation before starting this treatment.

Interferon

Use of pegylated interferon in specific clinical circumstances should be considered as standard of care across London hospitals. IFN reduces the risk of complications in high-risk patients; unfortunately, up to 30% of patients are not able to tolerate IFN due to the side effects. It is a suitable second-line agent and also the only treatment currently used in pregnancy (Harrison, 2002). Pegylated-IFN is better tolerated and is the formulation of choice for these patients.

The relative benefit of HU versus IFN first-line is yet to be determined.

For all interferons, it is important to screen twice yearly for liver and thyroid disease, as well as surveillance for depression.

Anagrelide

Refer to local or regional protocol. ANA is currently licensed for high-risk patients as a second-line agent for patients refractory or intolerant of first-line therapy. Limitations include cardiac toxicity and teratogenicity. Preliminary data from the MRC-PT1 study suggest ANA is not as effective as HU in preventing thrombotic and haemorrhagic complications, and is associated with greater risk of progression to myelofibrosis. **The risk of bleeding should be assessed and considered prior to the concomitant use of aspirin.**

ANA may be usefully given in combination with HU in some patients.

Prior to commencing ANA, all patients must have a chest x-ray and ECG. An echocardiogram should be performed in those with a previous cardiac history or abnormal ECG or increased cardiothoracic ratio on chest x-ray. Further evaluation is required if patients become symptomatic. Consider referral to a cardiologist if indicated.

Busulfan

Refer to local or regional protocol. Busulfan is a historical treatment associated with a higher incidence of leukaemic transformation than treatment with hydroxycarbamide. Other serious complications are idiopathic pulmonary fibrosis and aplasia. Use is limited in general to second line

in patients over 75 years of age due to the associated risk of leukaemia. **Discuss with consultant haematologist.**

³²Phosphorus

Phosphorus is a historical treatment which has an even higher incidence of leukaemic transformation than treatment with busulfan. Hence, it is reserved for the very elderly or patients in whom one cannot ensure compliance with medications. A medical consent generated by nuclear medicine should be completed by the haematology department. **Discuss with consultant haematologist.**

JAK inhibitors/HDACs

For refractory or intolerant patients, consider entry into a clinical trial for use of a novel agent.

7.1.5 Situations where alternative agents to HC may be needed

- i. **Inability to suppress platelet count to normal range without causing anaemia or neutropenia – i.e. HC-refractory (see [Annex 3, Table B](#))**

Consider relaxing platelet target to $<600 \times 10^9/L$ or switching to alternative agent (see below). Combining low-dose anagrelide with HC can be effective in this setting.

- ii. **Development of HC-related side-effects**

If mild gastrointestinal symptoms or rash, consider temporarily reducing the HC dose then slowly re-increasing as necessary, with appropriate symptom-management.

For more serious effects, including ankle ulceration, actinic keratosis, squamous cell carcinoma, and nail changes, HC should be stopped and an alternative agent started.

Patient concerns regarding leukaemogenicity of HC

Patients should be counselled that there is no available evidence that HC is associated with an increased risk of leukaemic transformation *per se*, despite extensive experience of the drug and a large Swedish registry-based study (Bjorkholm, *et al.*, 2011). If patients remain reluctant to take HC, they should be offered an alternative drug.

Patients who are pregnant or lactating, or planning to become pregnant or father children in the near future

HC should be stopped and patients offered interferon-alpha (IFN α) therapy. See [section 9.2](#) on 'ET in pregnancy'.

7.2 Polycythaemia vera (PV)

7.2.1 Management and prognosis

Thrombosis is the major cause of death in untreated patients whose median survival is only 18 months. Control of the elevated PCV is achieved by repeated venesection or cytoreductive therapy (especially if the platelet count is elevated). The target HCT is <0.45 (venesections should be timed to keep HCT <0.45 ; this target may be reduced in patients remaining symptomatic), and platelets $<400 \times 10^9/L$. Most patients would benefit from 75mg aspirin daily or alternative anti-

platelet drugs. The exceptions are those with active haemorrhage, aspirin intolerance, active or previous peptic ulcer disease, and, in aspirin should be used with caution in those patients with platelets $>1000 \times 10^9/L$.

An acquired von Willebrand disease should be considered in patients with a haemorrhagic phenotype by testing vWF:Ag and ristocetin cofactor activity.

HU is the standard cytoreductive drug used to treat PV and other MPNs. It is generally well tolerated but there is some anxiety that it might increase the risk of leukaemia. Historically ³²Phosphorus and busulfan were used, but their use is restricted because of their well-defined leukaemogenic potential. Emerging therapies include IFN α , pegylated-IFN and ANA, with the dual advantages of preserving fertility and being non-leukaemogenic.

Treated patients have a median survival of at least 8–15 years and are then at risk of transformation to myelofibrosis or ‘spent phase’. This phase of the disease is characterised by progressive splenomegaly and pancytopenia and is generally treated supportively; for a minority of patients bone marrow transplantation is an option. AML is a terminal feature of PV and is usually refractory to treatment. However, options include an AML protocol or cytarabine (unlicensed and unfunded indication) or, for example, ²⁵zacytidine (unlicensed and unfunded indication). Most patients, however, respond very poorly. A clinical trial with novel agents should be sought in the case of AML transformation.

7.2.2 Aims of treatment

The aim is to reduce the incidence of thrombotic and haemorrhagic complications and the long-term risk of transformation to myelofibrosis.

7.2.3 Evidence

- Control of haematocrit and thrombocytosis reduces thrombotic complications according to the PVSG trials (Berk, 1986; Najean, 1994).
- Retrospective case series support the use of IFN and ANA (Reilly, 1996; Radin, 2003; Anagrelide Study Group, 1992; Kiladjian, 2008).
- Cytoreductive therapy compared to venesection alone reduces the incidence of myelofibrosis (Najean, 1996).
- Patients with a high platelet count, high white cell count are at particular risk of MF (Najean, 1996).
- Patients with abnormal cytogenetics and high white cell count are at risk of developing AML (Tefferi, 2013).
- Patients who are resistant or intolerant to HU may have a worse prognosis (Alvarez-Larran, 2015).
- Target HCT is 0.45 (Barbui, *et al.*, 2013).
- White cell count >11 has an impact upon thrombotic risk (Barbui, 2016).
- Ruxolitinib may be of benefit for patients who are resistant/intolerant to HU (Vannucchi, 2015).

7.2.4 Treatment protocol

- Aggressively manage all reversible risk factors for cardiovascular disease.
- Aspirin should be considered in all cases in absence of contra-indications as above.

Evidence grade level Ib

High-risk patients

First-line therapy is HU, but pegylated interferon should be considered in young patients.

Ensure counselling of all patients of reproductive age regarding teratogenicity potential and long-term effects upon fertility and reiterate necessity for contraception.

Evidence grade level III

Second-line therapy (in those patients refractory/intolerant to first-line therapy or developing PMF or progressive splenomegaly on hydroxycarbamide):

- Patients aged >75 years – busulfan or consider combination therapy with HU and ANA or PEG-interferon, but see restrictions above.
- Patients aged <75 years – consider IFN or consider combination therapy with HU and ANA.
- Or treatment as for myelofibrosis.

Evidence grade level IV

Low-risk patients

First-line treatment is venesection alone. Monitor if repeat BM suggests development of myelofibrosis, or if spleen enlarges add cytoreductive therapy as for high-risk patients above.

*Evidence grade level IV***Treatment Summary Box: Polycythaemia vera**

- **ALL patients**
 - Assess for and manage cardiovascular risk factors
 - Screen for disease-related symptoms
 - Treat** with low dose aspirin (unless contraindicated)
- **Low-risk patients**
 - Venesect to target PCV <0.45
- **High-risk patients**
 - >60* years:
 - 1st line: HU or peg interferon
 - 2nd line: consider clinical trial or pegylated interferon**,
 - if >75 years busulfan or ³²P
 - <60* years:
 - 1st line: pegylated interferon or HU**
 - 2nd line: consider clinical trial or pegylated interferon, HU or anagrelide**,***

* Treatment recommendations made for high-risk patients only, high-quality clear evidence for low- or intermediate-risk ET or PV management is unclear.

** Not currently licensed for this indication.

*** Current British guidelines recommend regular monitoring of patients treated with anagrelide for the development of fibrosis.⁹

Treatment options

Patient leaflets are available for all treatment options from www.mpnvoice.org.uk or the [Macmillan](#) website.

Pre-chemotherapy counselling is available from the CNS/key worker. The counselling session should be followed up one week later with a telephone consultation.

Formal written consent should be obtained for all patients before commencing any cytoreductive therapy (red cell-, white cell- or platelet-controlling drugs) including hydroxyurea (hydroxycarbamide), anagrelide, interferon alpha, busulfan or radioactive phosphorus.

Venesection

To maintain PCV less than 0.45. Coulter counters underestimate PCV when patients have microcytic, hypochromic indices – a correction factor is available (discuss with a consultant). In patients with a platelet count >400 x 10⁹/L, there is a possible increased risk of complications and myelofibrosis if treated by venesection alone.

Aspirin

A dose of 75mg per day should be considered for all patients without clear contraindication (asthma, history of peptic ulceration, haemorrhage, platelet count in excess of 1000 x 10⁹/L). Clopidogrel is a suitable alternative.

Hydroxyurea/hydroxycarbamide (HU)

Refer to local chemotherapy protocol. The benefit of HU is demonstrated in the PVSG study (Berk, 1986, *GISP*). Limiting side effects include teratogenicity and the development of a refractory state in 10–15% of patients. There is no published evidence that HU monotherapy is leukaemogenic but HU may enhance the leukaemogenic effect of other cytoreductive agents such as busulfan and ³²phosphorus (risk of AML 15–30% if used in combination with alternative leukaemogenic agents) (Murphy, *et al.*, 1997; Sterkers, *et al.*, 1998).

Prior to conception, a three-month wash-out period is required. Women should be reviewed, stop HU and discuss alternative treatment if appropriate with IFN. Similarly, men wishing to father a child should discontinue HU three months prior to planned conception and discuss treatment if appropriate with IFN. Sperm banking should be considered for young males starting HU.

Interferon

Use of pegylated-interferon in specific clinical circumstances should be considered as standard of care across London hospitals. There is evidence of a reduction in the risk of complications (Reilly, 1996; Radin, 2003). Unfortunately, up to 30% of patients are not able to tolerate IFN due to the side effects. IFN is a suitable second-line agent and the sole agent currently used in pregnancy. Pegylated-IFN may have some benefit in patients not tolerating conventional IFN.

Pegylated-interferon

This agent has a similar utility to conventional interferon. It is currently approved for treatment of patients who are refractory or intolerant to first-line therapy, and there are some early data suggesting it is useful in this setting (Rea, *et al.*, 2009). Intolerance to therapy would include development of side effects that would lead to therapy introduction, and refractory disease is defined as inability to reach therapeutic targets without causing dose-limiting toxicity or unacceptable cytopenia. There are also provisional data suggesting it may induce molecular remissions in some patients with ET or PV (Kiladjian, *et al.*, 2008; Masarova, *et al.*, 2017) and also significant responses in patients with PMF (Iantotto, *et al.*, 2009; Silver, *et al.*, 2017). **This agent should ONLY be prescribed by a consultant haematologist and ONLY when funding has been approved.**

For all interferons, it is important to screen twice yearly for liver and thyroid disease, as well as surveillance for depression.

Anagrelide

Refer to the local chemotherapy protocol. There is evidence of a reduction of complications in high-risk ET patients in observational but not in comparative studies. The numbers of patients with PV in these studies is small (Anagrelide Study Group, 1992). See further comments under [section 7.1: Essential thrombocythaemia](#). **The risk of bleeding should be assessed and considered prior to the concomitant use of aspirin.**

ANA may be used in combination with HU in selected patients.

All patients must have a chest x-ray and ECG before commencing ANA. An echocardiogram should be performed in those with a previous cardiac history or abnormal ECG or increased cardiothoracic ratio on chest x-ray. Consider follow-up evaluation if patients become symptomatic. Consider referral to a cardiologist if indicated.

Busulfan

Refer to the local chemotherapy protocol. Busulfan is a historical treatment associated with a higher incidence of leukaemic transformation than treatment with hydroxycarbamide is. Other serious complications are idiopathic pulmonary fibrosis and aplasia. Its use is limited to patients over 65 due to the associated risk of leukaemia, in whom it is a second-line therapy in those patients refractory/intolerant to HU. **Discuss with consultant haematologist.**

³²Phosphorus

Phosphorus is a historical treatment which has an even higher incidence of leukaemic transformation than treatment with busulfan. Hence it is reserved for the very elderly or patients in whom one cannot ensure compliance with medications. Orders are via EPR; a medical consent generated by nuclear medicine should be completed by the haematology department. **Discuss with consultant haematologist.**

Ruxolitinib, a JAK1 and JAK2 inhibitor which is approved for MF, has also been approved but is not currently reimbursed for HU resistant/intolerant PV patients whose symptoms are severe and uncontrolled with standard therapy (NB not funded in UK). These patients should be discussed in an MDM and if the drug seems appropriate, an IFR or compassionate use application would be needed.

Primary (or secondary) myelofibrosis (PMF, PPV-MF, PET-MF).

7.2.5 Management and prognosis

Supportive therapy with red cell transfusions and treatment of infection is a mainstay with JAK2 inhibitor treatment, androgens or erythropoietin therapy for some. Chemotherapy, in particular with hydroxyurea/hydroxycarbamide, may be useful initially to reduce splenomegaly and slow/reduce fibrosis, although this may not affect prognosis. Thalidomide is of interest but is toxic and not beneficial for most; it may be best used as a low dose with steroids.

In advanced disease, splenectomy is an option but has significant morbidity rates and is not generally recommended; splenic irradiation may be useful. Allogeneic stem cell transplantation may cure a small number of patients but, due to high procedure-related mortality, it has only been performed in young patients with poor prognosis. Low intensity allogeneic transplants with reduced procedure-related mortality have been useful.

Use an IPSS, DIPSS or DIPSS-plus score for prognosis in PMF – these have not been validated in PET- or PPV-MF. Additional myeloid panel mutations may be of benefit in selected patients (see [section 5: Risk Stratification](#)).

7.2.6 Aims of treatment

- Control symptoms of disease (transfusions)
- Reduce incidence of thrombotic and haemorrhagic complications
- Reduce disease progression.

7.2.7 Treatment protocol

Intermediate- and high-risk patients

Tissue type and refer for stem cell transplant discussion if less than 65–70 years and sufficiently fit. Consider agents below as per specific indications.

Low-risk patients

Tissue type siblings if under 60 to inform future therapy.

If progress, treat as for high-risk patient.

If thrombocytosis or develop thrombotic or haemorrhagic complications treat with hydroxyurea.

Evidence grade level IV

7.2.8 Treatment options

Also see comments under [section 7.1: Essential thrombocythaemia](#).

Aggressively manage all reversible risk factors for arterial disease.

Patient leaflets are available for all treatment options from the [Macmillan](#) website.

Pre-chemotherapy counselling is available from the CNS/key worker.

Counselling session should be followed up one week later with a telephone consultation.

Formal written consent should be obtained for all patients before commencing any cytoreductive therapy (red cell-, white cell- or platelet-controlling drugs) including hydroxyurea (hydroxycarbamide), anagrelide, interferon alpha, busulfan or radioactive phosphorus.

Aspirin

75mg per day should be considered in all patients without clear contraindication (asthma, history of peptic ulceration, haemorrhage, laboratory evidence of acquired von Willebrand disease, or a platelet count in excess of 1000 or a platelet count $<50 \times 10^9/L$).

Ruxolitinib

The JAK2 inhibitor ruxolitinib is currently available for first- or second-line use in symptomatic MF patients for IPSS or DIPPS Intermediate 2 and above patients. Evidence from the COMFORT and COMFORT-2 studies indicates that ruxolitinib is effective in reducing spleen size and associated symptoms and improves overall quality of life as well as overall survival (Harrison, 2016; Verstovsek, 2017). Refer to the local chemotherapy protocol.

Hydroxyurea/hydroxycarbamide (HU)

Refer to the local chemotherapy protocol. Limiting side effects include teratogenicity and the development of a refractory state in 10–15% of patients. There is no published evidence that HU monotherapy is leukaemogenic but HU may enhance the leukaemogenic effect of other cytoreductive agents such as busulfan and ³²phosphorus (risk of AML 15–30% if used in combination with alternative leukaemogenic agents (Murphy, *et al.*, 1997; Sterkers, *et al.*, 1998).

Prior to conception, a three-month wash-out period is required. Women should be reviewed, stop HU and discuss alternative treatment if appropriate with IFN. Similarly, men wishing to father a child should discontinue HU three months prior to planned conception and discuss treatment if appropriate with IFN. Sperm banking should be considered for young males.

Thalidomide

Recent evidence suggests that low doses of thalidomide (50mg) in combination with a reducing dose of prednisolone commencing 1mg/kg may be beneficial and less toxic than doses used previously (Mesa, 2003; Giovanni, 2002). Some patients develop worsening thrombocytosis and extramedullary haemopoiesis. In patients with a previous history of thrombosis, low molecular weight heparin prophylaxis should be considered. All thalidomide is prescribed via the Pharmion risk management system by a registered prescriber. **This is an unlicensed indication for thalidomide and is not funded by NHS England.**

Interferon

Use of pegylated-interferon in specific clinical circumstances should be considered as standard of care across London hospitals. There is limited evidence of benefit in reducing disease progression; unfortunately, up to 30% of patients are not able to tolerate IFN due to the side effects. IFN is a suitable second-line agent and the only treatment currently used in pregnancy.

Pegylated-interferon

This agent has a similar utility to conventional interferon. It is currently approved for treatment of patients who are refractory or intolerant to first-line therapy. There are some early data suggesting it is useful in this setting (Rea, *et al.*, 2009). Intolerance to therapy would include development of side effects that would lead to therapy introduction, and refractory disease is defined as inability to reach therapeutic targets without causing dose-limiting toxicity or unacceptable cytopenia. There are also provisional data suggesting it may induce molecular remissions in some patients with ET or PV (Kiladjian, *et al.*, 2008; Masarova, *et al.*, 2017) and also significant responses in patients with PMF (Ilanotto, *et al.*, 2009; Silver, *et al.*, 2017). **This agent should ONLY be prescribed by a consultant haematologist and ONLY when funding has been approved.** Refer to the local chemotherapy protocol.

For all interferons, it is important to screen twice yearly for liver and thyroid disease, as well as surveillance for depression.

Busulfan

Refer to the local chemotherapy protocol. Busulfan is a historical treatment associated with a higher incidence of leukaemic transformation than treatment with hydroxycarbamide. Other serious

complications are idiopathic pulmonary fibrosis and aplasia. Its use is limited to patients over 65 due to the associated risk of leukaemia. It is a second-line therapy in those patients refractory/intolerant to HU. **Discuss with consultant haematologist.**

Erythropoietin

Erythropoietin is only of limited use (Cervantes, 2004). **Discuss with consultant haematologist and pharmacy.**

Haematopoietic stem cell transplantation (HSCT)

There is evidence that a limited number of patients may benefit from HSCT; most recently, reduced intensity transplants have shown provisional promising results (Hessling, 2002). Refer patients at diagnosis, if they are a suitable candidate, in line with BSBMT recommendations.

Investigational agents

Other JAK2 inhibitors are in clinical trials, as are combinations of JAK2 inhibitors and pan-deacetylase inhibitors. JAK2 inhibitors have thus far demonstrated significant and sustained improvement in splenomegaly, disease-related symptoms, functioning and quality of life. They have been well tolerated with minimal toxicities.

MF in accelerated or blast phase

Low-dose cytarabine

The dosing is as per the MRC AML14 trial 20mg given sc bd 14 days every 28 days. **Discuss with consultant haematologist.**

Azacitidine

Azacitidine has been used in some patients with accelerated or transformed MF with success – 75mg/m² for seven days (or 5-2-2 regimen) is a suitable starting dose. This should be discussed with a consultant haematologist. **This is an unlicensed indication for azacitidine and is not funded by NHS England.**

AML induction treatment followed by SCT.

7.3 Fertility

Management protocols for women in pregnancy and in the three months before conception are more complex and individualised. These cases should be discussed with a consultant haematologist experienced in such cases. FERTILITY INDUCTION MUST BE DISCUSSED WITH CONSULTANT AND TREATED AT SPECIALISED CENTRES

For young patients with MPN due to undergo AML induction-type chemotherapy and/or an HSCT, the options for fertility preservation should be discussed and the patient referred to a fertility specialist for preservation of sperm and ovarian tissue or fertilised embryos. This should also be considered for young patients starting HU.

Expert onco-fertility advice should be considered in line with guidance and recommendations for referral to fertility services.

8 Supportive Care

8.1 Anaemia

Red cell transfusions may be required in addition to dose-modification of cytoreductive medication(s) (see also [Table 8](#)). Threshold Hb needs to be individualised but in general a threshold of 80g/L is appropriate. Routine iron chelation is not recommended. If EPO levels less than 200u/L, rEPO or biosimilar may be commenced at 10,000 u three times a week (or darbepoietin 150ug/wk), double dose after 1-2 months in absence of response. Discontinue EPO if no response in 3-4 months.

If EPO levels elevated, danazol 200 mg/day escalating to 600-800 mg/day (800 mg/day for >80kg wt) over 6-8 weeks. Minimum 6 months treatment. Responding patients should receive a further 6 months of 400mg/day and then taper dose to minimum required to maintain response. Monthly LFT, ultrasound liver 6-12 monthly. Men must be screened for prostate cancer before and during therapy. Alternatively, thalidomide 50-100mg, sometimes with prednisolone, may be helpful.

8.2 Haemostasis and thrombosis

VTE: For thrombotic events, anticoagulate as per local protocols and ensure counts are well controlled to prevent future events. For secondary prophylaxis of VTE, use long-term anticoagulation. The role of primary prophylaxis in patients at high risk of VTE has to be considered on an individual basis. The use of DOACs, and combined use of VKA and aspirin, have not been studied.

Arterial thrombosis: For primary prophylaxis, see each specific disease entity. For secondary prophylaxis, use local cardiac or cerebrovascular protocols. Consider switching from aspirin to clopidogrel if arterial events are not prevented by aspirin. Good quality data on aspirin resistance are lacking and the use of dual anti-platelet therapy in MPN has not been studied.

Patients on clopidogrel require cessation of the drug for 5 days pre-procedures with moderate to high risk of bleeding. Patients on aspirin may continue the drug through minor procedures depending on bleeding versus thrombotic risk. Bridging of VKA is required if VTE is <3 months old.

8.3 Hyperviscosity syndrome

Urgent platelet apheresis or red cell apheresis can be undertaken if high counts are causing symptoms of hyperviscosity. Cytoreductive therapy must be initiated or optimised simultaneously.

8.4 Infection

Local protocols should be followed for treatment of infections and prophylaxis.

8.5 Pain management

For symptomatic splenomegaly, see [section 7: Treatment](#) for disease-specific treatment options (hydroxycarbamide versus surgery versus splenic irradiation versus ruxolitinib or other chemotherapy in MF).

People reporting pain should be considered for non-pharmacological intervention including, but not limited to, TENS (transcutaneous electrical nerve stimulation), complementary therapy and psychological intervention such as mindfulness.

8.6 Other symptom control

Table 8: Symptomatic therapy for MF

Clinical need	Drugs/Intervention	
Anaemia	Corticosteroids Danazol ESA if EPO level <200IU Transfusion	Thalidomide + steroids (unlicensed indication) Pomalidomide negative clinical trial (unlicensed indication)
Symptomatic splenomegaly	Ruxolitinib Hydroxycarbamide Cladribine, others	Splenectomy
Extramedullary haematopoiesis	Radiation therapy Ruxolitinib	
Risk of thrombosis or recurrence	Low-dose ASA	Hydroxyurea
Constitutional symptoms/QoL	Ruxolitinib and consider bisphosphonates for bone pain	
Risk of leukaemia transformation	None specifically directed	
Improved survival	Ruxolitinib Allogeneic HSCT	

8.7 Breathlessness

- Any inpatient showing signs of respiratory distress should be assessed by a physician with knowledge of treatment for patients with MPN and, if appropriate, referred for respiratory physiotherapy assessment in accordance with local on-call guidelines, unless of overt metabolic cause. Consider VTE and pulmonary hypertension.
- Ongoing breathlessness management strategies can be provided by occupational therapy or physiotherapy.

8.8 Weight loss

- A screening tool for the assessment of dietary issues should be completed weekly for inpatients and, if issues are identified, a referral should be made to a specialist dietitian.
- Referral for specialist dietetic input should be made in the following instances:
 - Any patient with neutropenia should be provided with information and education on the neutropenic diet and be referred to a specialist dietitian.
 - If artificial feeding is being considered, a referral to the specialist dietitian should be made.
 - Any patient with mucositis should be referred for dietetic assessment, as well as for specialist speech and language assessment.
- Weight loss/malnutrition should be identified through weekly screening of inpatients.

8.9 Cardiovascular risk assessment

All patients require a formal CV risk assessment at baseline and yearly. The following CV risk factors must be assessed: smoking, diabetes, hypertension, hyperlipidemia. Primary prophylaxis such as statins should be provided based on national recommendations.

Patients should have CV risk factors optimally controlled by primary care or CV specialists in secondary care.

Primary care should be specifically informed of CV risk posed by MPN to the patient.

8.10 Complex symptom management

- Discuss with specialist palliative care team for advice on symptom management, e.g. pain, mucositis when there is no/poor response to standard interventions. Patients with accelerated or transformed MF may benefit from palliative care support. Where appropriate, referral can be made to the specialist palliative care team.
- Irradiation therapy can be used for symptom control for bone pain, splenomegaly and rare for pulmonary hypertension.

9 Special circumstances

9.1 Splanchnic vein thrombosis

- Patients with splanchnic vein thrombosis should have a blood count and mutation analysis for MPN related mutations. If idiopathic, a bone marrow assessment should be considered and undertaken only when heparin or warfarin may be safely withheld.
- MPN may be masked in SVT patients due to haemodilution and splenomegaly associated with SVT.
- MPN with high blood counts should be treated with venesection/chemotherapy to control the blood counts in therapeutic range. Iron deficiency is frequent due to GI blood loss and tolerance to chemotherapy is affected by splenomegaly and baseline cytopenia.
- There is lack of evidence on the role of marrow modifying drugs in patients with JAK2 V617F mutation without MPN phenotype.
- All patients should be anticoagulated with heparin in the acute setting, followed by warfarin. Patients should be considered for long-term anticoagulation based on risk-benefit analysis.
- In patients with incidental detection of SVT anticoagulation in the long-term should be considered based on risk-benefit analysis.
- Patients should have access to tertiary level hepatologist and haematologist for shared care in the acute and chronic setting. See schema and protocol in [Annex 3, Flowchart 1](#).

9.2 Pregnancy

- Refer to specialist obstetrician, serial US monitoring, control counts with IFN if past h/o miscarriage or MPN-related maternal morbidity or high risk of thrombosis. Decide if the pregnancy is high- or low-risk and discuss with an experienced clinician. Antenatal aspirin +/- , post-natal LMWH 6 weeks for low-risk pregnancy. See [Annex 6](#) for further details regarding high-risk pregnancies.
- If bleeding phenotype, provide tranexamic acid post third stage.

10 Treatment Summary and Care Plan

Patients with MPN are followed for life or have supervised care by a haematologist experienced in such disorders. The MDT outcome form and clinic letters will serve to communicate new lines of treatment/change of treatment with the GP.

Treatment summaries should therefore be agreed when there are any significant changes in treatment and follow-up plans. HNAs should be offered through follow-up, with a care plan completed to document the plans to address the issues raised by the patient.

10.1 Treatment summary and care plan

There are two related but distinct documents which patients should be given when there are changes in treatment:

- A **treatment summary** provides a summary of the cancer treatments received by the end of the first treatment, planned follow-ups (including mechanisms for these), and signs and symptoms of which to be aware. Their aim is to provide information not only to the patient, but also to the GP about possible consequences of cancer and its treatment, signs of recurrence and other important information.
- A **care plan** is generated as a result of an HNA and is the agreed plan between the patient and healthcare professional about how the identified areas of concern will be addressed. This may cover provision of information (e.g. through an information prescription), onward referral for specialist assessment and intervention (e.g. breathlessness management), or things which the patient themselves can do (e.g. contact their HR department about graduated return to work options).

Recommendation:

An end of treatment consultation should be offered to every patient when there are any significant changes in treatment and follow-up arrangements. This should include an HNA and associated written care plan and should also include the discussion and provision of a comprehensive treatment summary.

11 Follow-up Arrangements

Monitoring of blood counts and renal and liver function should occur according to treatment regimen and patient risk factors by practitioners experienced with these drugs. Telephone and/or nurse-led clinics or prescribing with agreement of the GP (using formalised protocols) may also be used for those patients who are stable and reliable.

12 End-of-life Care

For older patients and in those with high-risk disease, discussions regarding prognosis and treatment options should also include discussions on end-of-life care. These are to facilitate transitions between active disease-modifying therapy and clinical trials, to supportive care only at the time of disease progression/non-response. Care may be required from specialist palliative care teams.

The named CNS/key worker, patient, family members and palliative care teams, as well as members of the inpatient ward team, may be involved. Clear documentation of the discussion with guidance to the treating teams is helpful in communicating these discussions and outputs to the wider team that may care for the individual.

13 Data Requirements

Accurate data collection is essential to monitor outcomes, and the collection of this information, particularly clinical data, remains the responsibility of the members of the multidisciplinary team with support from a data manager. Haematology services are required to submit data to nationally mandated datasets for all patients diagnosed with haematological cancer; further details on these datasets are available in [Annex 2](#)).

All patients should be listed on a local database with a basic dataset.

Dataset:

Name/demographics

Diagnosis

Mutation

VTE yes/no location year

Arterial thr yes/no location year

Treatment 1st line/2nd line/3rd line

Annual SAF score; CR/PR/NR

Alive/dead

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Annex 1: Nurse-led MPN Clinic SOP and Referral Guideline

[Polycythaemia vera (PV) and essential thrombocythaemia (ET)]

Background

The nurse-led MPN clinic is often established in response to a number of factors:

1. A growing number of patients in haematology clinics which can lead to lengthy waits.
2. To live with a chronic blood condition, patients require education and support, effectively provided by a clinical nurse specialist (CNS).
3. Nurse-led clinics are supported by recent government and nursing policy which encourages new collaborative ways of working across professional boundaries to make effective use of human and other resources (DH, 1999).

It is envisaged that the nurse-led clinic will enable consultant haematologists to see more complex patients, keeping clinics running in a more efficient and timely manner, and that patients will receive continuity of care and high-quality, multi-professional care.

Role of the haematology clinical nurse specialist

The role of the CNS in the clinic includes the following:

- Monitoring the patient's condition in order to maintain disease stability and control. This involves taking a full history, physical assessment, interpreting blood results, and prescribing and management of medication.
- Educating and empowering patients by explaining the illness to them, their carers and families, assisting them to identify signs of deterioration and how to take appropriate action, and promoting increased compliance with medication.
- Psychological and emotional support/holistic care including referral to allied healthcare professionals as appropriate.

Potential advantages

Development of this nursing role improves the quality of the service provided for haemato-oncology patients (Scope of Professional Practice, 2010) and reduces workload pressures on junior and senior doctors.

Improvements anticipated as a result of implementing this service include:

- Provision of a more flexible service for patients with regards to appointments
- Rapid access to services and reduced waiting times
- Patients increasingly able to deal more effectively with health problems
- Patients' holistic needs being met
- A more cost-effective service for the Trust
- CNS professional development.

The CNS has gained specialist experience in patients with MPNs through shadowing the doctors and running the clinic in parallel with the haematology consultant. CPD will be undertaken to increase CNS knowledge in the MPNs and other general haematology conditions and to develop clinical expertise. This will be achieved through the following:

- Attending relevant study days/courses/conferences
- Visits to/observation of specialist clinics at other centres
- Feedback to and from and discussion with medical and nursing colleagues
- Reflection
- Case studies and problem solving
- Professional portfolio
- Completing the extended nurse prescribing course.

Indemnity

Upon approval of this document and following competency assessment of the CNS by the consultant haematologist, the Trust will provide vicarious liability, providing practice is within written protocols. The Royal College of Nursing indemnity insurance will also cover the CNS.

Accountability

The haematology CNS will at all times adhere to the Nursing and Midwifery Council (NMC) Code of Professional Conduct (2010) and be professionally responsible and accountable for his/her own actions. The NMC makes it clear that the ultimate responsibility is upon the practitioner to determine his/her own individual competence and also to be prepared to refuse to undertake a task if he or she feels they are not competent to undertake it. The consultant haematologist will ultimately remain responsible for the medical management of the patient.

Mode of referral to MPN nurse-led clinic

Referral to the nurse-led clinic may be made by the consultant haematologist, associate specialist or specialist trainees working in haematology. The decision for referral to the clinic will be documented in the medical notes and an MPN nurse-led clinic referral form completed and given to the CNS. The haematology secretaries and administrative clerks are informed by the CNS or individual making the referral so that the patient's name is added to the CNS clinic list.

Criteria for patients to be included

- Patients with PV or ET who are stable and asymptomatic on treatment (venesection, hydroxycarbamide, anagrelide or interferon).
- Patients with MPN who require support to manage their disease effectively.
- Patients in whom the disease progresses or who become unstable and therefore require medical intervention will be referred back to the consultant haematology clinic. All patients will be reviewed annually by a doctor for a physical assessment and to assess for hepatosplenomegaly. This can be done jointly in the nurse-led clinic.

Workload

The CNS can independently see a maximum of 10 patients in one clinic session. Time should be given for administrative work. The CNS should also be available to accompany consultants or SpRs in consultations with new or follow-up patients. The CNS should also be able to refer patients to other members of the multidisciplinary team. Some patients will be able to be monitored through a CNS-led telephone clinic.

Location and frequency

The nurse-led MPN clinic is held in the outpatient department. Frequency of the clinic depends on the patient population and catchment/need, but it should be run in parallel with the consultant clinic so that there is a doctor available to provide advice or see the patient and/or to prescribe medication as needed.

Liaising with doctors

In the event that the CNS needs medical advice about a patient or for the prescribing of medication, he/she liaises with a doctor in haematology. If further investigations are needed, this would be done after discussing the patient with the doctor.

Patients will be seen annually by the doctors for a medical review. The CNS will discuss the patient with the consultant haematologist if he/she is concerned about the patient, for example splenomegaly (e.g. early satiety or abdominal distension) etc.

The CNS will discuss all patients after clinic with the consultant in order to provide medical oversight. The CNS dictates a letter to the patient's GP after each consultation and these letters are also co-signed by the patient's consultant.

Medicines management

Many of these patients will be taking some form of treatment such as hydroxycarbamide, interferon, anagrelide or busulfan to control blood counts or symptoms of disease. Dose adjustments may be required according to blood results and clinical history. When the FBC is stable, the interval between appointment times may be increased to a maximum of four months. In this case, a blood test should be done at two months and the results checked by the CNS. The CNS will then call the patient and inform them of any dose adjustments if needed. If the platelet count is less than 200 on two consecutive occasions the CNS can reduce the dose of hydroxycarbamide. If the platelets are above 400 on two or more consecutive occasions the CNS can increase the dose of hydroxycarbamide. These dose adjustments should be considered alongside other blood results such as haemoglobin and neutrophils, etc.

The CNS will give advice on medications only when he/she is confident that he/she can do so with the same competence as a doctor professing to have that skill (Bolan, 1957). Dose adjustments will be communicated to the patient's GP via a letter which will also be co-signed by the patient's consultant.

Venesection

If a venesection is indicated (to keep haematocrit below a specific target), the CNS will liaise with haematology day care.

Documentation

Patient assessments, blood counts and advice given are documented in the medical notes and the electronic patient record. Information is also entered onto a database detailing the patient's demographics and treatment details, which is constantly updated and modified. This is to help with future audits.

Sickness and annual leave cover

When the CNS is on annual leave or study leave, the clinic will be cancelled and patients will be rescheduled. In the event of sickness, the patients will be urgently accommodated into the consultant clinic.

Evaluation

Evaluation is the systemic, objective and critical assessment of the degree to which services fulfil their stated goals. It can be applied to the processes of care, the actual actions and behaviours of the staff giving the care, and the outcomes of care which refers to what is actually achieved in measurable terms. Evaluation of the nurse-led clinic will aim to establish its effectiveness and benefit both to patients and to the delivery and outcomes of care. Such information will inform future service developments and will add to the evidence base regarding nurse-led clinics in general. The following will be evaluated:

1. Patient satisfaction with aspects of care such as waiting times, continuity of care, history taking and assessment, perception of nurses' knowledge and information giving or advice sharing.
2. Impact on service delivery/organisation of services – sources of referral, number of patients seen, impact of waiting times, length of consultation and "what is it about the nursing that enhances care".
3. Impact on nursing such as identification of training needs, impact on other role functions, number of referrals to others, number of prescriptions required, etc.
4. Audit – systematic and critical analysis reviewed against explicit criteria, allowing practice to be modified where indicated:
 - a. Appropriate/inappropriate referrals
 - b. Accuracy of treatment advice/dose adjustments
 - c. DNA rates
 - d. Analysis of complaints

References

Department of Health (1999) Making a difference. Strengthening the nursing, midwifery and health visiting contribution to health and health care. DH London.

Nursing and Midwifery Council (2010) *Code of Professional Conduct*. NMC London.

Nursing and Midwifery Council (2010) *The Scope of Professional Practice*. UKCC London.

Referral Form for MPN (PV/ET) Nurse-led Clinic

N.B. Only refer if the patient is on a stable dose of medication and has controlled counts.
If the patient has active medical problems related to MPN, do not refer.

NAME (OR STICKER): _____

HOSPITAL NUMBER: _____

D.O.B: _____

TYPE OF MPN (Please circle): PV ET

DATE OF DIAGNOSIS: _____

HISTORY OF THROMBOTIC OR HAEMORRHAGIC EVENTS:

DIAGNOSTIC INVESTIGATIONS (Please give results):

PRESENTING FBC:	HB	G/L
	PCV	
	WBC	X 10 ⁹ /L
	PLTS	X 10 ⁹ /L

MUTATION STATUS:

ABDOMINAL EXAMINATION/ABDOMINAL USS (Give date):

RCM/PV: _____ DATE: _____

BONE MARROW ASPIRATE AND TREPINE (DATE):

OXYGEN SATURATIONS: _____ BLOOD PRESSURE: _____

OTHER INVESTIGATIONS:

TREATMENT (Circle): HYDROXYUREA ANAGRELIDE INTERFERON

STABLE DOSE:

OTHER ISSUES:

NAME AND SIGNATURE OF REFERRING DOCTOR: _____

DATE OF REFERRAL: _____

Annex 2: Data Requirements

Haematology oncology services are required to submit data to the following nationally mandated datasets for all patients diagnosed with haematological cancers.

The Cancer Outcomes and Services Dataset (COSD)

The core dataset for all tumour types including haematological cancers is mandated from January 2013, and the site-specific dataset is mandated from July 2013. Details of the dataset can be found on the National Cancer Intelligence Network website:

www.ncin.org.uk/collecting_and_using_data/data_collection/cosd.aspx

The local cancer registry will be collating this dataset using Trust data feeds which should include all these items. The feeds are:

- Trust PAS
- Trust pathology
- Trust radiology
- Trust multidisciplinary team (MDT) feed.

In line with the requirements set out in Provider Trust contracts, this data should be submitted within 25 working days of the end of the month in which the activity took place.

Three groups of haematological cancers are considered stageable by the Registry:

- Lymphomas, using Ann Arbor (or Murphoy St Jude for children)
- Myelomas, using ISS
- CLLs, using Rai and Binet

For the purposes of COSD, any other haematological cancers are not counted as stageable.

For CLL both Rai (0-IV) and Binet (A-C), stages need to be recorded and submitted to COSD to be considered “fully staged”.

MGUS does not need to be recorded and submitted as is not defined as an invasive tumour.

Systemic Anti-Cancer Therapy dataset (SACT)

Provider Trusts that provide chemotherapy to patients are required to submit data to the SACT dataset. Details of the audit and the dataset requirements are available on the dataset homepage: www.chemodataset.nhs.uk/home.aspx

Radiotherapy Dataset (RTDS)

Provider Trusts that provide radiotherapy to patients are required to submit data to the RTDS dataset. Details of the audit and the dataset requirements are available on the dataset homepage: www.ncin.org.uk/collecting_and_using_data/rtds.

Cancer Waiting Times dataset

Trusts are required to submit data to the Cancer Waiting Times dataset, which includes details of all patients who are referred as a 2 week wait (2ww) referral, and all patients who are treated for cancer. Trusts are required to submit this data within 25 working days of the month of either when the patient was first seen for the 2ww target, or when the patient was treated. The Cancer Waiting Times dataset can be found at:

www.datadictionary.nhs.uk/data_dictionary/messages/clinical_data_sets/data_sets/national_cancer_waiting_times_monitoring_data_set_fr.asp

Annex 3: Tables and Flowcharts

Table A: European LeukaemiaNet clinico-haematological response criteria in ET (Barosi, *et al.*, 2009)

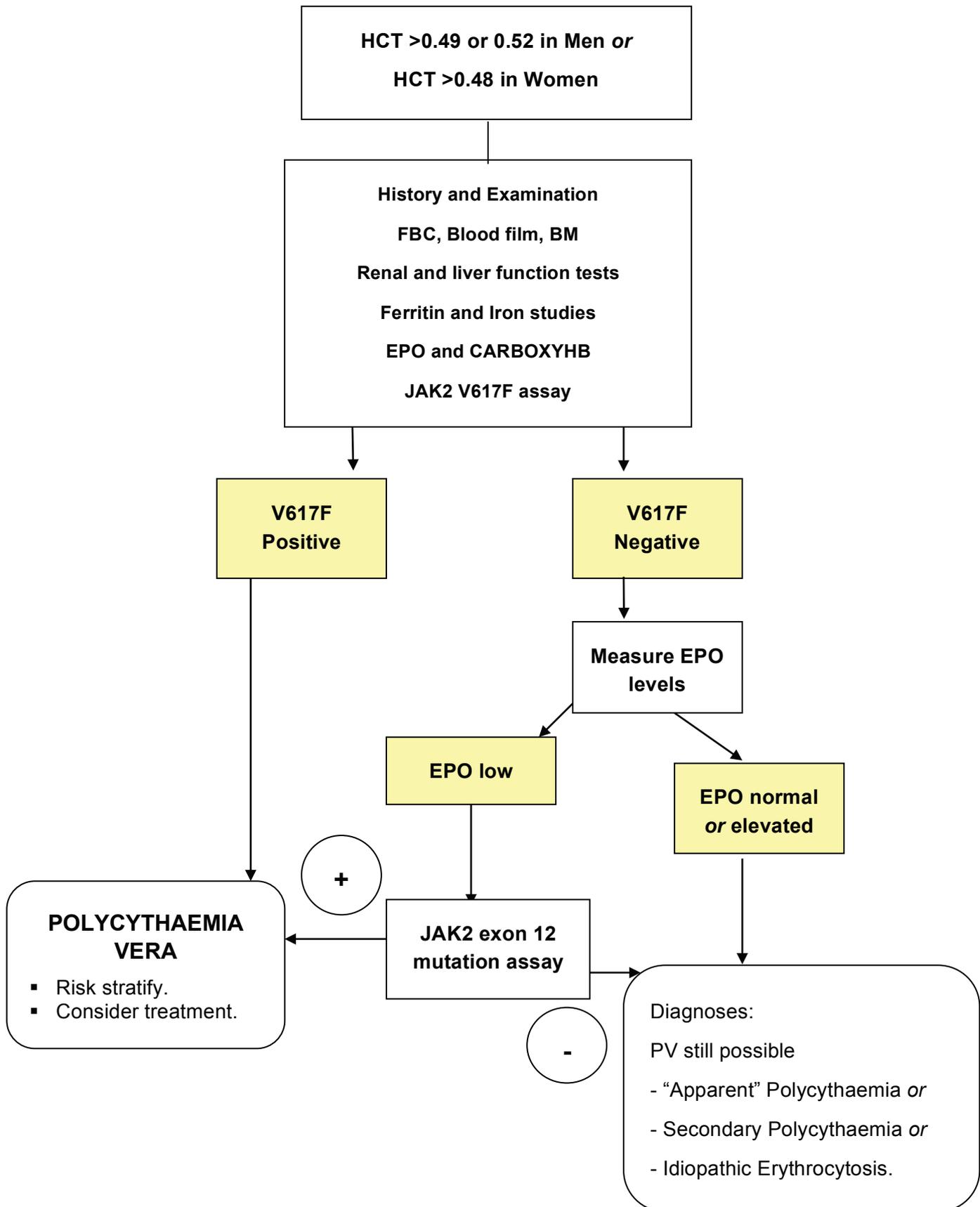
Response grade	Definition
Complete response	(1) Platelet count $\leq 400 \times 10^9/L$, AND
	(2) No disease-related symptoms, AND
	(3) Normal spleen size on imaging, AND
	(4) White blood cell count $\leq 10 \times 10^9/L$
Partial response	In patients who do not fulfil the criteria for complete response, platelet count $\leq 600 \times 10^9/L$ OR decrease $>50\%$ from baseline
No response	Any response that does not satisfy partial response

Table B: Definition of resistance/intolerance to HC in patients with ET (Barosi, *et al.*, 2007)

Any one of:

1	Platelet count $< 600 \times 10^9/L$ after 3 months of at least 2g/day of HC (2.5g/day in patients with a body weight >80 kg)
2	Platelet count $< 600 \times 10^9/L$ and WBC less than 2500/ml at any dose of HC
3	Platelet count $< 600 \times 10^9/L$ and Hb less than 10g/dl at any dose of HC
4	Presence of leg ulcers or other unacceptable muco-cutaneous manifestations at any dose of HC
5	HC-related fever

Flowchart 1: Primary investigations for patients presenting with erythrocytosis



Annex 4: Response Criteria and Definition of Resistance

Table A: Definition of clinicohaematological response in PV

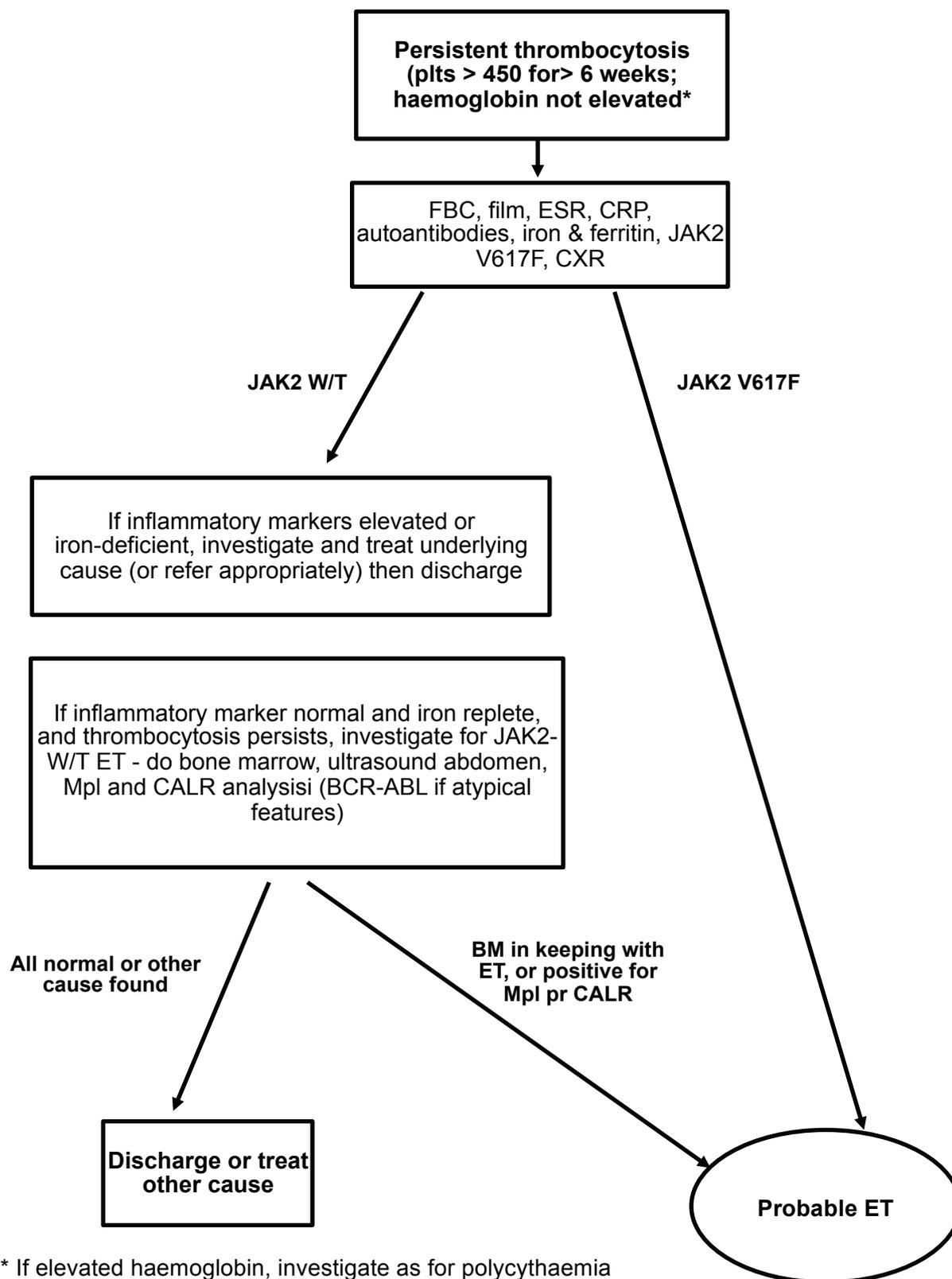
Complete Response (CR)	HCT <0.45 without venesection <i>and</i> Platelet count $\leq 400 \times 10^9/L$ <i>and</i> White count $\leq 10 \times 10^9/L$ <i>and</i> Normal spleen size on imaging <i>and</i> No disease-related symptoms
Partial Response (PR)	In patients who do not achieve CR, HCT <0.45 without venesection <i>or</i> A response in 3 or more of other criteria
No Response	Responses that do not satisfy criteria for PR

Table B: Definition of intolerance/resistance to hydroxycarbamide (HU) in PV

Any of the following:	
1	Need for venesections to keep HCT <0.45 after 3 months of at least 2gm/day of HU
2	Uncontrolled myeloproliferation, i.e. platelet count $>400 \times 10^9/L$ AND white cell count $>10 \times 10^9/L$ after 3 months of at least 2gm/day HU
3	Failure to reduce massive splenomegaly by more than 50% as measured by palpation, OR failure to completely relieve symptoms related to splenomegaly, after 3 months of at least 2gm/day HU
4	Absolute neutrophil count $<1.0 \times 10^9/L$ OR platelet count $<100 \times 10^9/L$ OR haemoglobin $<10\text{gm/dL}$ at the lowest dose of HU required to achieve a complete or partial clinicohaematological response
5	Presence of leg ulcers or other unacceptable HU-related non-haematological toxicities, such as mucocutaneous manifestations, gastrointestinal symptoms, pneumonitis or fever at any dose of HU.

Flowchart 1: Investigation of patients with persistent thrombocytosis

Patients should be investigated according to the following schema:



Algorithm for management of MPN related SVT

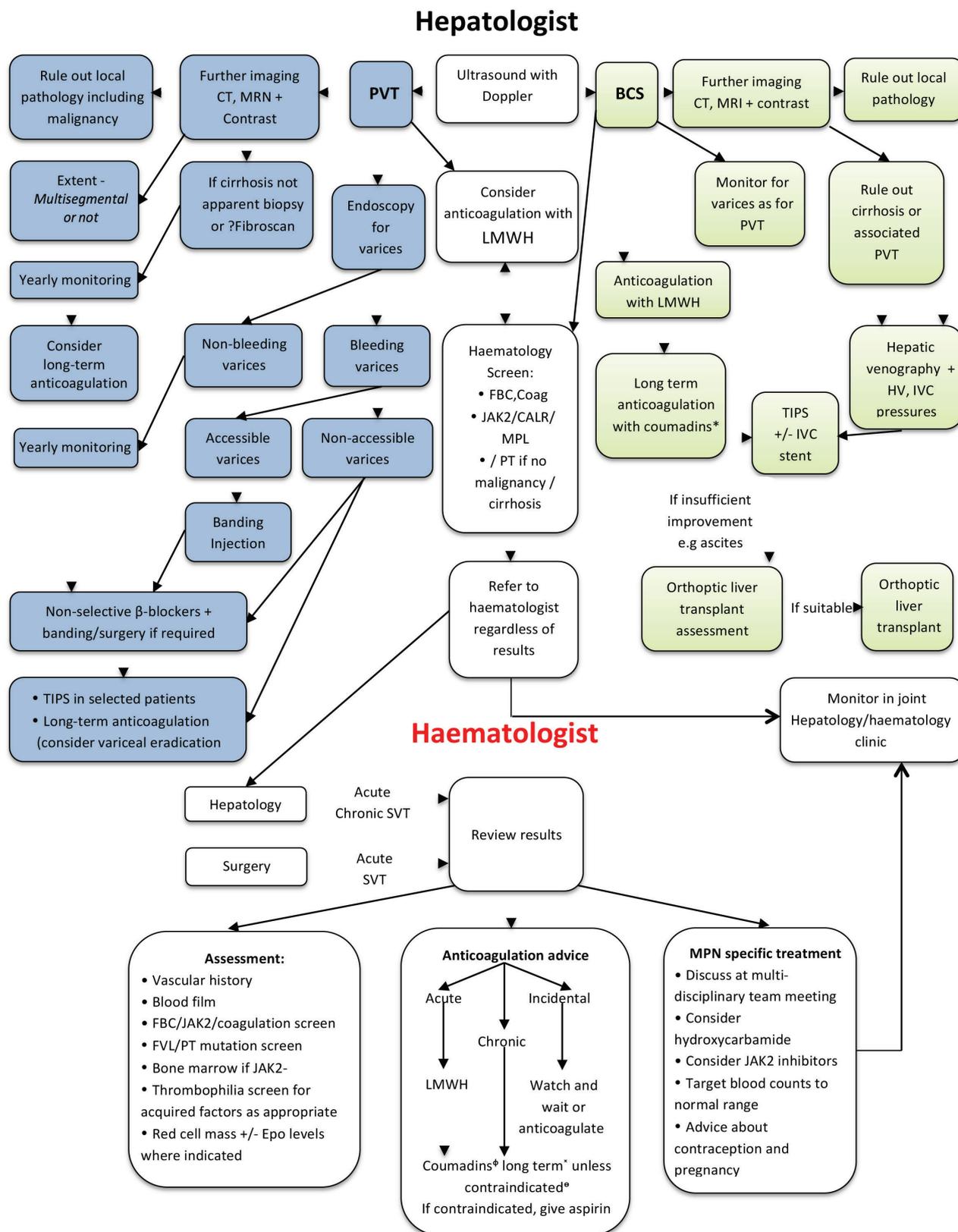


Figure 1 – Royal Free algorithm for management of PVT/BCS.

[†] Coumadin monitoring with INR in patients with liver disease may be problematic

^{*} If persistent risk of thrombosis

[‡] Presence of varices is not a contraindication

PVT-specific management

BCS-specific management

Annex 5: Guide on Dosing Cytoreductive Agents

Hydroxycarbamide (HC)

HC should be commenced at a dose of 500–1000mg daily, increased slowly with the aim of achieving a complete response (CR) or at least a partial response (PR) as defined in Appendix 2.

HC should be avoided in women who are pregnant or lactating, and in patients planning to become pregnant or father children in the near future.

IFN α (non-pegylated)

Usual starting dose 3 million IU once or twice-weekly subcutaneously, increasingly slowly to 3 million IU daily maximum. Response to the drug often takes several weeks or months and the timing of dose-adjustment should reflect this. Fatigue, myalgia, malaise and low mood are common side effects and 20–40% of patients cannot tolerate this therapy. Premedication with paracetamol may help. Avoid in patients with a history of severe psychiatric disorders unless absolutely necessary.

This is the standard therapy for PV patients needing cytoreductive treatment during lactation or pregnancy, or whilst planning to become pregnant or father children.

IFN α (pegylated) (e.g. Pegasys)

This is an alternative to non-pegylated IFN α : it benefits from once-weekly administration and a lower incidence of fatigue, myalgia, etc. As with the non-pegylated form, exercise caution in patients with a history of psychiatric disorders. Usual starting dose 45–90mcg weekly subcutaneously. Doses can be increased slowly up to 180mcg weekly. In some patients, doses less than 90mcg may be required. Prefilled syringes are available as 90mcg, 135mcg or 180mcg (which may be graduated to smaller doses such as 45mcg or 60mcg).

Busulfan

Various dosing regimens exist – see BCSH ET guidelines. Most common dosing regimen is intermittent high-dose busulfan (e.g. 25–40mg every 4–6 weeks).

Busulfan is generally considered to be leukaemogenic (and may cause pulmonary disease) so should be reserved for elderly patients who have failed first-line therapy.

Radioactive phosphorus (^{32}P)

Rarely used, primarily because of its leukaemogenic effect, ^{32}P may be useful for treating selected elderly patients.

Anagrelide

Rarely used in the UK for the management of PV as it is a relatively platelet-specific cytoreductive agent. However, it is known to induce anaemia in some patients and is not considered to be leukaemogenic. So, it may be useful in managing patients who are reluctant to take chemotherapeutic agents such as hydroxycarbamide or busulfan, and who are not adequately managed solely with venesections.

Usual starting dose 500–1000mcg daily, increased slowly to a maximum 10mg daily (max single dose = 2.5mg). Common side effects include palpitations, D&V, headaches, which usually settle after a few weeks. It can occasionally cause serious tachyarrhythmias – request ECG for all patients prior to starting anagrelide and use cautiously in patients with known cardiac disease.

Based on data from trials in ET, anagrelide is associated with a greater risk of progression to secondary myelofibrosis (MF) than is HC, so patients should be counselled appropriately and undergo bone marrow examination every 3 years (or sooner if their blood counts suddenly change). If there is evidence of MF, anagrelide should be stopped and a trial of HC (which may reverse early MF in some cases) considered.

Annex 6: High-risk Pregnancy

- **Previous venous or arterial thrombosis in mother (whether pregnant or not)**
- **Previous haemorrhage attributed to MPN (whether pregnant or not)***
- **Previous pregnancy complication that may have been caused by a MPN:**
 - Three or more unexplained consecutive spontaneous miscarriages before 10th week gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal abnormalities excluded
 - One or more unexplained deaths of morphologically normal fetus at or beyond 10 weeks gestation
 - One or more premature births of a morphologically normal fetus before 34 weeks gestation because of eclampsia, severe pre-eclampsia or recognized placental insufficiency**
 - A significant ante- or postpartum haemorrhage (requiring red cell transfusion)
- **Platelet count rising to $>1500 \times 10^9/L$ prior to pregnancy or during pregnancy***
- **Diabetes mellitus or hypertension requiring treatment**

* Indication for cytoreductive treatment but not LMWH.

** Generally accepted features of placental insufficiency include:

- (i) abnormal or non-reassuring fetal surveillance tests
- (ii) abnormal Doppler flow velocity wave forms analysis suggestive of fetal hypoxaemia
- (iii) oligohydramnios
- (iv) post-natal birth weight less than the 10th centile for gestational age

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