CLINICAL PRACTICE GUIDELINES

AUGUST 2004

MOH/P/PAK/85.04 (GU)

DIAGNOSIS AND MANAGEMENT OF CHRONIC MYELOPROLIFERATIVE DISORDERS

MINISTRY OF HEALTH MALAYSIA

ACADEMY OF MEDICINE MALAYSIA

MALAYSIAN SOCIETY OF HAEMATOLOGY

Statement of Intent

These guidelines are meant to be a guide for clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not necessarily ensure the best outcome in every case. Every health care provider is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and the management options available locally.

Review of the Guidelines

These guidelines were issued in August 2004 and will be reviewed in August 2006 or sooner if newer evidence becomes available.

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FOREWORD

Clinicians and general practitioners will encounter patients with a high white cell, red cell or platelet counts during their clinical practice. There are many causes for elevated cell counts and one of them is chronic myeloproliferative disorders (MPD). It is important not to miss the diagnosis of MPD because of the thrombotic and bleeding complications that are not uncommonly seen as well as the small risk of leukaemic transformation.

As the diagnosis of MPD is one of exclusion, a guideline is urgently needed to assist clinicians and haematologists alike in making a definitive diagnosis.

With the development of this guideline, we hope to create a better understanding of the MPDs among physicians such that appropriate management and referral to the haematologists are undertaken.

Jameela Sathar
President
Malaysian MPD Group

GUIDELINE DEVELOPMENT AND OBJECTIVES

Chronic Myeloproliferative Disorders (MPD) are a closely related group of haematologic disorders in which there is inappropriate proliferation of myeloid precursors in the bone marrow. The MPDs are further classified into four groups: Polycythaemia Rubra Vera(PRV), Essential Thrombocythaemia(ET), Myelofibrosis with Myeloid Metaplasia(MMM) and the unclassified MPDs.

There is no specific test to diagnose MPD; the diagnosis is one of exclusion. It is important not to miss the diagnosis as delay in treatment may lead to thrombotic complications with increased morbidity and mortality.

The clinical practice guideline on " Diagnosis & Management of Myeloproliferative Disorders in Malaysia" was prepared by a group of haematologists based on a systematic review of evidence and clinical practices. The Malaysian MPD group is affiliated to the Asia Pacific MPD Study Group comprising countries from Taiwan, Korea, Hong Kong, Singapore, Australia, Thailand and Indonesia.

Objectives

The aim of the guideline is to provide diagnostic criteria and proper management for patients with MPD.

Target Population

This guideline is targeted to patients with high cell counts where no obvious cause is found.

Target Group

This guideline is developed for clinicians and haematologists.

DESIGN AND METHODS.

- The Malaysian MPD Group consisting of Consultant Haematologists from both teaching and government institutions & hospitals systematically reviewed the published literature from 1980 to August 2002.

- From September 2002 to Dec 2004, four Consensus Discussion Group were held with the goal of solving residual disagreement on recommendations.

- The drafted guidelines were then sent to an expert panel consisting of senior Haematologists.

- Systematic review of clinical evidence: a list of clinical papers were made available to the expert panel for review and a consensus was reached by the panel of expert. A search was done for Myeloproliferative Diseases, Essential Thrombocythaemia, Thrombocythaemia, Thrombocytosis, Erythrocytosis, Polycythaemia Vera, Polycythaemia Rubra Vera, Polycythaemia, Myelofibrosis and Myeloid Metaplasia with Myelofibrosis in the following journals :

    - NEJM
    - PUB-Med
    - Blood
    - Annals of Haematology
    - European Journal of Haematology
    - American Journal of Haematology
    - British Medical Journal
    - Journal of Clinical Oncology
    - Leukemia
    - Cancer
    - LeukemiaLymphoma

Results. The Malaysian MPD Group provided recommendations on when to start platelet-lowering therapy, the most appropriate platelet-lowering agent, the use of anti-platelet therapy, and the management in women of childbearing age and pregnant women. The management includes risk stratification, therapy options, efficacy & side-effects of various drugs.

Conclusions. By using evidence and consensus, recommendations for the treatment of key problems in MPDs have been agreed upon. The guideline is then drafted according to the strength of the supporting evidence and uncertainty is explicitly declared.

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- **Dr Goh Ai Sim** who has also contributed her input to the guideline development.

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- **Dr Ong Tee Chuan** for providing input, designing the MPD registry format.

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INTRODUCTION

MYELOPROLIFERATIVE DISORDERS (MPD)

Myeloproliferative disorders (MPD) are chronic diseases caused by clonal proliferation of bone marrow stem cells leading to excess production of one or more haemopoietic lineages. The current classification of the MPD includes the following:

Polycythaemia rubra vera (PRV)
Essential thrombocythaemia (ET)
Myelofibrosis with myeloid metaplasia (MMM)
Unclassified

These four disorders are considered separate from chronic myeloid leukaemia (CML) and the myelodysplastic syndrome (MDS) with variable propensity to evolve into acute leukaemia. PRV and ET are associated with an increased risk of thrombosis.

Chronic myeloid leukaemia (CML) had been traditionally considered as part of chronic myeloproliferative disorder. As the emphasis on Philadelphia Chromosome became more prominent, CML evolved into its own entity defined by the translocation t(9:22) whereas the remaining disorders not associated with the translocation remain as part of MPD.

The combined overall incidence of MPD is 100-150 cases/year/million population in Europe. The respective incidences of PRV, ET, MMM are approximately 2.3, 2.5 and 1.3 per 100,000 population[1]. Median age at diagnosis is similar among the MPD, about 60 years. There is a slight preponderance of males in PRV and MMM and of females in ET.

POLYCYTHAEMIA RUBRA VERA (PRV)[2]

Definition

Polycythaemia (erythrocytosis) is defined as an increase in haemoglobin concentration above normal i.e.[raised packed cell volume (PCV) in male>0.51 and female>0.48]. True polycythaemia exists when the total red cell mass(RCM), measured by dilutional method with radio-isotopic red cells, is increased above normal. Spurious or relative (pseudo or stress) polycythaemia exists when an elevated haemoglobin concentration is caused by a reduction in plasma volume as measured by dilutional method with radio-isotopically labeled albumin (Figure below).

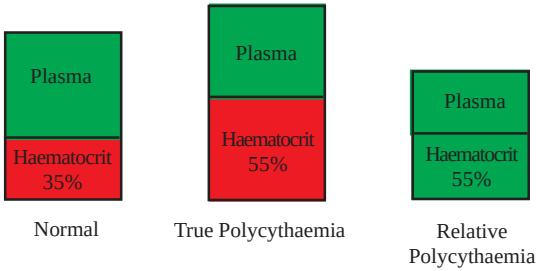


Fig. showing graphic representation of various types of polycythaemia

Table 1. Causes of polycythaemia

True polycythaemia

Primary

Polycythaemia rubra vera (PRV)
Congenital truncation of erythropoietin receptor

Secondary

Erythropoietin appropriately increased
- High altitude
- Cyanotic congenital heart disease
- Chronic lung disease
- Haemoglobin variant with increased oxygen affinity

Erythropoietin inappropriately increased
- Renal disease: hypernephroma, renal cyst, hydronephrosis
- Uterine myoma
- Other tumours, e.g. hepatocellular carcinoma, bronchial carcinoma

Idiopathic erythrocytosis

Relative (spurious) polycythaemia
Plasma volume depletion
Stress ('pseudo- polycythaemia')
Dehydration
Diuretic therapy

Pathogenesis
Based on X chromosome-associated enzyme and DNA analysis, PRV have shown clonal myeloproliferation involving multiple lineages. Erythrocytosis is independent of erythropoietin (EPO) with presence of the intact structure and function of EPO. EPO-independent erythroid viability in PRV may be facilitated by an abnormal expression of apoptosis-inhibiting oncoproteins or augmented stimulatory signal transduction as evidence by hypersensitivity of some erythroid progenitors to a variety of cytokines, including insulin-like and myeloid growth factors (stem cell factors, granulocyte-monocyte colony stimulating factor, interleukin-3).

Diagnosis
Causes of secondary erythrocytosis should be considered prior to making the diagnosis of PRV.

Criteria for the diagnosis of PRV[3]

A1	Raised red cell mass (>25% above mean normal predicted value) or PCV >0.60 in males and >0.56 in females
A2	Absence of causes of secondary erythrocytosis* (*Normal arterial O_2 saturation >92%) (*Leucocyte alkaline phophatase >100; no fever or infection)
A3	Palpable splenomegaly
A4	Clonality marker, i.e acquired abnormal marrow karyotype
A5	Endogenous erythroid colony formation
B1	Thrombocytosis (platelet count >400 $x10^9$/L)
B2	Neutrophil leucocytosis (neutrophil count >10 x 10^9/L; >12.5 x 10^9/L in smokers)
B3	Splenomegaly demonstrated on ultrasound or isotope scanning
B4	Low serum erythropoeitin

Required Diagnostic Criteria

A1 + **A2** plus any other **A** establishes PRV
A1 + **A2** + two of **B** establishes PRV

Clinical features

The major symptoms are related to hyperviscosity caused by the increased red cell mass. In nearly 25% of patients, an episode of venous or arterial thrombosis, such as deep vein thrombosis, myocardial ischaemia or stroke, is the first manifestation. Mesenteric and portal or splenic vein thrombosis should always lead to consideration of PRV as a possible cause, and may even precede the onset of an overt polycythaemic stage. Vasomotor symptoms such as headache, dizziness, visual disturbances and paresthesias are also major complaints. Other findings may include pruritus, erythromelalgia and gout. Haemorrhage, particularly from the gastrointestinal tract, may also occur.

Physical findings include phlethora in 70% of patients, palpable splenomegaly in 70%, and hepatomegaly in 40%.

Prognosis[4]

Age and the history of previous thrombosis are the most powerful predictors of recurrent thrombosis. Patients with PRV and ET may be stratified into defined risk groups that are managed differently. (Table 2)

Table 2. Risk stratification in PRV

Low risk

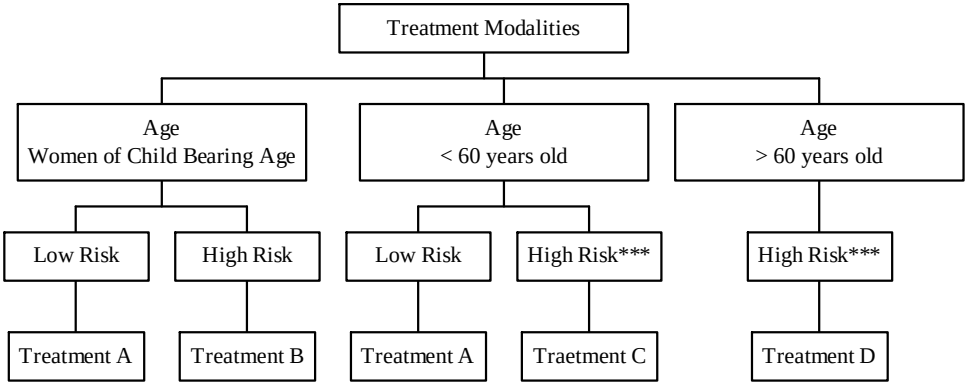
Age < 60 years, and
No history of thrombosis, and / or vasomotor symptoms
Platelet count < 600 x 10^9/L and
No cardiovascular risk factors (smoking, obesity)

High risk

Age > 60 years, or
A previous history of thrombosis, and or vasomotor symptoms

Treatment modalities ***(Level of Evidence III or B)***

Thrombosis is the main cause of morbidity and mortality. Its incidence can be reduced by maintaining the PCV <0.45 in men and <0.42 in women as well as keeping the platelets <600x10^9/L. The beneficial role of low-dose aspirin in PRV was shown in a large prospective European Collaboration on Low-dose Aspirin in Polycythaemia Vera(ECLAP) study in significantly reducing the number of cardiovascular death and major thrombosis with minimal bleeding complications.[5] Table 3 shows a treatment algorithm for PRV according to risk groups.



Treatment A	Phlebotomy* + Low Dose Aspirin**
Treatment B	Phlebotomy + Interferon-a [8,9,10,11] + Low Dose Aspirin
Treatment C	Phlebotomy + Hydroxyurea [6, 7] + /or Interferon-a + Low Dose Aspirin
Treatment D	Phlebotomy + Hydroxyurea + Low Dose Aspirin

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* Phlebotomy : First line management of an erythrocythemic individual. Ideal PCV (< 0.45 for men and < 0.42 for women.)
Phlebotomy (400mls red cells) is performed every other day for the first week, twice weekly for the second week and weekly thereafter until the ideal PCV is achieved. Each venesection is replaced with 500ml of normal saline. For patients who are not able to comply with the venesection or there is failure to achieve ideal PCV by the third week, cytoreduction with hydroxyurea or interferon-a is started for the low risk group.

** Low-dose aspirin: 75-100mg daily
***Consider anagrelide for control of symptomatic thrombocytosis.

ESSENTIAL THROMBOCYTHAEMIA (ET)

Definition
ET is a chronic non-reactive thrombocythaemic state that is not accounted for by another chronic myeloid disorder.

Pathogenesis
X-linked enzyme and genetic analysis have shown that patients with ET have clonal haematopoeisis that originates in stem cells. Serum thrombopoeitin (TPO) levels are usually elevated or normal despite an increased megakaryocyte mass and this has been attributed to ineffective TPO clearance because of the markedly reduced TPO-receptor (c-Mpl) expression in platelets and megakaryocytes, rather than an overproduction of TPO.[12]

Diagnosis
A diagnosis of ET is made by excluding both reactive thrombocytosis and thrombocytosis associated with another myeloid disorder (Table 4) & (Table 5). All cases of thrombocytosis from automated counter should be counter checked by blood smear to exclude pseudothrombocytosis secondary to cellular fragments.

Table 4. Causes of thrombocytosis[13, 14]

I. Non-clonal

- Iron deficiency
- Splenectomy
- Haemolysis or bleeding
- Infection or inflammation (connective tissue disease, vasculitis)
- Tissue damage (surgery, myocardial infarction, pancreatitis, trauma)
- Malignancy

II. Clonal

- Essential Thrombocythaemia
- Polycythaemia Vera
- Myelofibrosis
- Chronic myeloid leukaemia
- Myelodysplastic syndrome

Table 5. Diagnostic Criteria for ET[13,14]

A	**Diagnostic criteria**
A1	Platelet count in excess of 400 $x10^9$/L and no known cause of reactive thrombocytosis

A2 Increase and clustering of enlarged and mature megakaryocytes with hyperploid nuclei in marrow biopsy material

B **Confirmative criteria**

B1 Normal or elevated leukocyte alkaline phosphatase score, normal ESR, and no fever or infection

B2 Normal or increased cellularity of the bone marrow with or without the presence of reticulin fibers in biopsy material

B3 Splenomegaly on palpation, isotope or ultrasound scan, or computer tomogram

B4 No Philadelphia chromosome or bcr-abl rearrangement

Required Diagnostic Criteria

A1 + **A2** establishes ET

A1 + **B1** plus any one of **B2** to **B4** establishes ET

Clinical Features [15]

Approximately 25% of patients with ET are asymptomatic at presentation. The rest may present with:

1. vasomotor symptoms (incidence 40%)
    a. headaches
    b. transient neurologic or ocular symptoms
    c. distal paraesthesias
    d. erythromelalgia (burning pain of the hands or feet associated with erythema and warmth)

2. thrombosis (incidence 18%)
    a. strokes
    b. transient ischaemic attacks
    c. retinal artery or venous occlusion
    d. myocardial infarction
    e. pulmonary embolism
    f. hepatic or portal vein thrombosis
    g. deep vein thrombosis
    h. digital ischaemia

3. bleeding (incidence 26%)
    a. gastrointestinal haemorrhage mainly associated with the use of nonsteroidal anti-inflammatory drugs
    b. mucocutaneous bleeding

Four different studies have failed to define a relationship between the frequency of thrombotic complications and platelet numbers. Instead, thrombotic events occurred at a wide range of platelet counts.[16,17,18,19] In two studies, patients with extreme thrombocytosis (>1000x10^9/L) were reported to have a much higher incidence of haemorrhagic events. This may be due to the acquired von Willebrand syndrome.

Leukaemic transformation occurs in less than 5% of all patients with ET. Among 74 young women with ET observed for up to 26 years, only 1 developed acute leukaemia and 3 developed post-thrombocythaemic myelofibrosis.[20]

Spontaneous first trimester abortions occur in up to 45% of pregnancies in ET. [21]

Prognostic Factors

Age and a history of previous thrombosis are the most powerful predictors of recurrent thrombosis in ET. In one study, the estimated annual risk of thrombosis was 30% for patients with a history of thrombosis and only 3% for those without. Similarly, the annual thrombotic risk was 15% in patients older than 60 years but less than 2% among patients younger than 40 years.[18]

Risk Stratification[22]

Patients with ET may be categorized into different risk groups similar to PRV with different treatment strategies (Table 6).

Table 6. Risk stratification in ET

Low risk

Age < 60 years, and
No history of thrombosis, and or vasomotor symptoms
Platelet count < 600 x 10^9/L and
No cardiovascular risk factors (smoking, obesity)

High risk

Age > 60 years, or
A previous history of thrombosis, and or vasomotor symptoms

Treatment Strategies *(Level of Evidence III or B)*

The benefit of treatment for high risk ET patients was demonstrated by Cortelazzo et al.[23] in a study of 114 high-risk patients. After a median follow-up of 27 months, 24% of the untreated group had experienced a thrombotic event, in contrast to only 3.6% of the treated group. Maintenance of the platelet count under 400x10^9/L may be associated with further reduction in thrombotic risk.[24]

The issue of treatment for low risk patients has been more controversial. Although the study by Ruggeri et al [25] concluded that low-risk ET patients do not require treatment, aspirin use was not controlled in this study. The use of low-dose aspirin in this patient group can be extrapolated from the ECLAP study.[5]

A. General measures
    i. Stop smoking
    ii. Avoid NSAIDs
    iii. Avoid OCPs, HRTs or Hormonal Therapy

B. Specific measures
    a. Platelet-lowering agents
        i. Hydroxyurea
        ii. Anagrelide
        iii. Interferon alpha
        iv. Others (busulphan)

    b. Anti-Platelet agents (i.e. Aspirin)

    c. Plateletpharesis in the acute setting where life-threatening complications are present

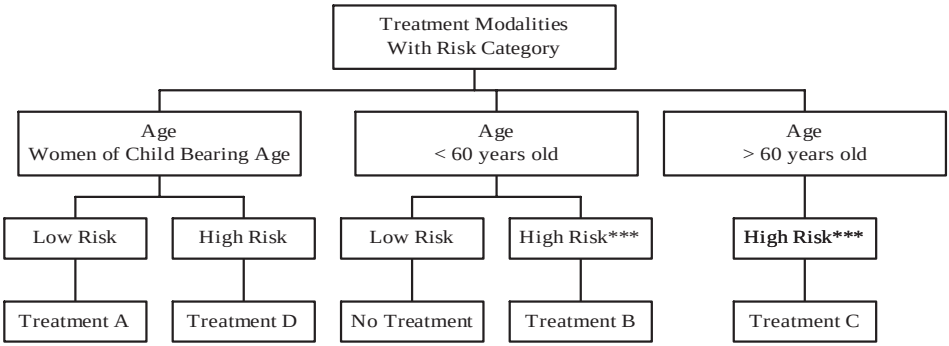
In a randomized study, the use of hydroxyurea reduced the risk of thrombosis in high-risk patients with ET from 24% to <4% compared with no treatment[23]. To date, there is no randomized study that directly implicates hydroxyurea as being more leukemogenic. Some long term studies found that a proportion of ET patients treated with hydroxyurea developed acute leukaemia.[26,27] In other studies, this drug was not associated with an increase risk of leukaemic transformation.[28,29] As the leukaemogenecity of hydroxyurea is still being debated, it is recommended that this drug is reserved for the elderly (>60 years). Initial starting dose is 15-20 mg/kg/day or 500mg daily or bd. Side effects are neutropenia, anaemia, oral ulcers, hyperpigmentation, rash and nail changes.

Anagrelide is an oral imidazoquinazoline derivative that has a platelet lowering effect. It can control thrombocytosis in > 80% of patients regardless of previous treatments[30,31]. The drug may interfere with megakaryocyte maturation, resulting in the underproduction of platelets. The mode of action is unclear but it could be that anagrelide blocks the c-mpl receptor on the surface of the megakaryocyte, thereby interfering with the action of thrombopoeitin on the cell. As there is no risk of leukaemogenecity with the use of anagrelide, this drug is preferred for younger patients. Initial dose is 0.5mg three to four times a day (maximum tolerable daily dose is 8 mg). Side effects are headache, forceful heart beats, palpitations, diarrhoea and fluid retention. It is contraindicated in patients with congestive heart failure and pregnancy.

Interferon alpha controls the thrombocytosis associated with any myeloproliferative disorder including ET. An overview of the literature indicates that treatment with 3 to 5 million units subcutaneously three times a week give an 86% haematologic response rate and a 32% reduction in spleen size. However, 20% of patients did not tolerate the treatment because of side effects.[32] The common side effects are flu-like symptoms, fatigue, anorexia, weight loss, alopecia and depression. The use of interferon alpha is restricted to high-risk women of childbearing age and to those who are pregnant.

Thromboxane is a potent stimulator of platelet aggregation leading to thrombosis. Thromboxane synthesis is increased in patients with ET and can be suppressed with low dose aspirin (75-150 mg/day). Low dose aspirin is used to control vasomotor symptoms in the absence of bleeding or when the platelet counts have been brought to below $1000x10^9$/L.

Treatment algorithm in ET



Treatment A	#Low dose Aspirin
Treatment B	Anagrelide (1st Choice) or Hydroxyurea + Low Dose Aspirin
Treatment C	Hydroxyurea (1st Choice) or Anagrelide (2nd Choice) + Low Dose Aspirin
Treatment D	Interferon Alpha + Low Dose Aspirin

- Target platelet count < $400x10^9$/L
- Aspirin started only when platelet counts reduced to < $1000x10^9$/L to prevent bleeding complications
- # If no contraindication. Regular life-long follow-up.

MYELOFIBROSIS WITH MYELOID METAPLASIA (MMM)

Definition

Myelofibrosis with myeloid metaplasia (idiopathic myelofibrosis, agnogenic myeloid metaplasia) is characterized by progressive anaemia, marked splenomegaly, extramedullary haemopoiesis and prominent bone marrow stromal reaction including collagen fibrosis, neo-angiogenesis and osteosclerosis.

Pathogenesis

Primary defect is within the haemopoietic stem cell with trilineage myeloproliferation as evident by analysis of X chromosome inactivation patterns at both the enzyme and the DNA levels. There is also increased stromal reaction including collagen fibrosis, neo-angiogenesis, and osteosclerosis which was thought to be a reactive process mediated by fibrogenic and angiogenic cytokines that may be abnormally secreted by clonal megakaryocytes or monocytes. One third of patients have a preceding history of PRV or ET.

Diagnosis

The diagnosis of MMM is suspected if the peripheral blood film shows teardrop-shaped red blood cells and leukoerythroblastic picture. The bone marrow aspiration is usually dry and trephine biopsy shows marrow fibrosis associated with atypical megakaryocytic hyperplasia and thickening with distortion of the bony trabeculae (osteosclerosis). The diagnosis is made after ruling out other causes of marrow fibrosis (Table 7).

Table 7 : Causes of bone marrow fibrosis

Myeloid disorders
Chronic myeloproliferative diseases
Myelodysplastic syndrome
Acute myeloid leukaemia
Mast cell disease
Malignant histiocytosis

Lymphoid disorders
Lymphoma
Hairy cell leukaemia
Multiple myeloma

Nonhaematologic disorders
Metastatic cancer
Connective tissue disease
Infections e.g. tuberculosis
Vitamin D deficiency / rickets
Renal osteodystrophy

Diagnostic criteria for MMM[33]

Necessary criteria

1. Diffuse bone marrow fibrosis
2. Absence of Philadelphia chromosome or bcr-abl in peripheral blood

Optional criteria

1. Splenomegaly of any grade
2. Anisopoikilocytosis with teardrop erythrocytes
3. Presence of circulating immature myeloid cells
4. Presence of circulating erythroblasts
5. Presence of clusters of megakaryocytes and anomalous megakaryocytes in bone marrow biopsy sections
6. Myeloid metaplasia

Required Diagnostic Criteria

1. **Two** *necessary criteria* plus **two** *optional criteria* when splenomegaly is **present;**
2. **Two** *necessary criteria* plus any **four** *optional criteria* when splenomegaly is **absent**

Clinical features

20% of patients are asymptomatic and detected incidentally with splenomegaly or from routine blood smear. The rest may present with:

1. Hypercatabolic symptoms
   - Severe fatigue
   - Low grade fever
   - Night sweats
   - Weight loss

2. Extramedullary haemopoeisis
   - Hepatomegaly
   - Splenomegaly with left hypochondrium pain
   - Lymphadenopathy
   - Ascites
   - Pleural effusion
   - Cord compression secondary to paraspinal and epidural masses

3. Portal hypertension
4. Bone pains

Prognosis

The overall prognosis of MMM is poor with the median survival between 3 to 5 years. The prognostic factors and risk stratification are summarized in Table 8.[34,35,36] Low-risk patients may expect a median survival of 8 to 10 years whereas the high-risk group may survive less than 3 years.

Table 8:
Independent prognostic factors and risk stratification in myelofibrosis with myeloid metaplasia[33]

Adverse prognostic features in MMM*

- Age > 60 years
- Haemoglobin < 10 g/dL
- Presence of hypercatabolic symptoms (eg. weight loss, profound fatigue, night sweat, low grade fever)
- White blood cell count > 30,000/uL
- White blood cell count < 4,000/uL
- Circulating blasts > 1%
- Presence of +8 or 12p-

Risk Stratification for MMM[33]

*Number of Adverse Prognostic factors **	*Risk Group*
0	Low
1	Intermediate
2	High

Treatment strategies *(Level of Evidence IV or C)*
Low Risk Patients
Low-risk patients with MMM may not benefit from currently available specific therapy.

Intermediate & High Risk Patients
High-risk patients should be offered haematopoietic stem cell transplantation (HSCT) if the service is available. Myeloablative allogeneic haematopoietic stem cell transplantation is the treatment of choice for young patients who are less than 45 years old.[37,38] For patients older than 45 years, alternative transplant options including non-myeloablative allogeneic and autologous haematopoietic stem cell transplantation can be considered.[39,40]

The management in a center with no transplant option mainly focus in symptomatic relief for anaemia, cytoreduction for thrombocytosis and leukocytosis as well as alleviation of splenomegaly-associated complications such as mechanical discomfort, refractory anaemia, hypercatabolic symptoms and portal hypertension.

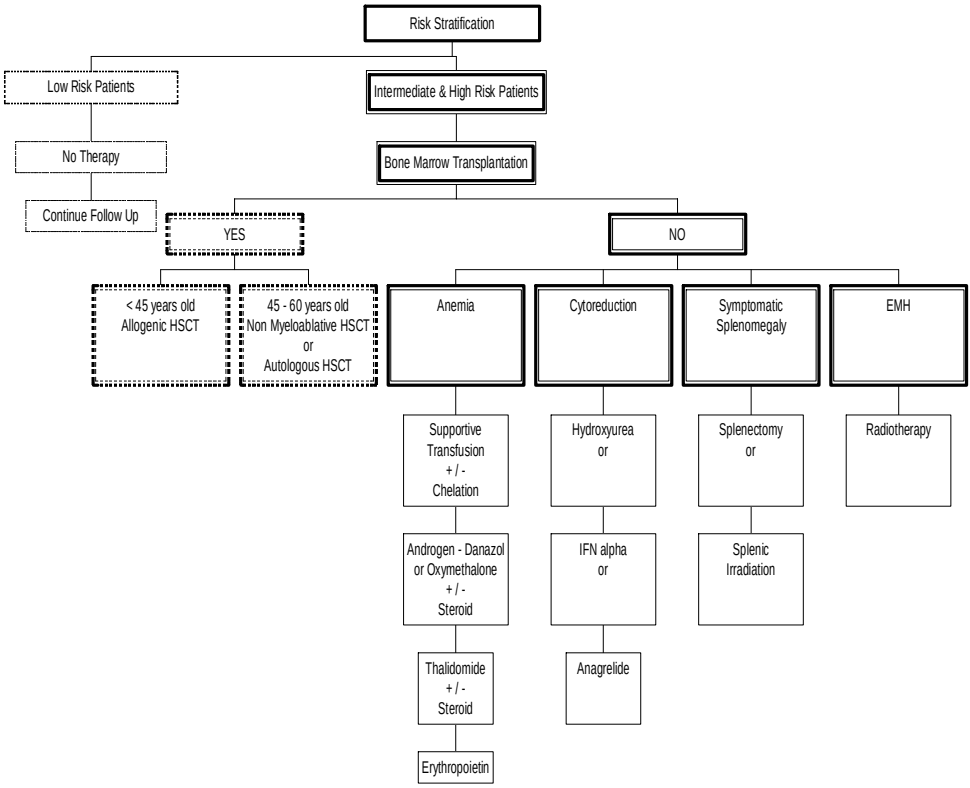
Anaemia is the most frequent reason for treatment among patients with MMM. Many patients become transfusion-dependent and iron chelation may be needed. Only a small proportion of patients respond to drug therapy including androgen preparations as a single agent like Oxymethalone (2mg/kg/day) or Danazol (600 to 800 mg/day). All patients treated with androgen preparations should have liver functions monitored periodically.[41,42] Recently, combination therapy with low dose Thalidomide (50 mg/day) and a tapering dose of prednisolone (0.5 mg/kg/day) has been associated with higher response in anaemia (62%).[43,44,45] Erythropoietin (r/c EPO 40,000 U/wk) has been proven for a subset of patients with endogenous EPO level <100 mU/mL.[46]

Hydroxyurea (starting dose 500 mg orally twice a day) is the drug of choice for cytoreduction and controlling splenomegaly.[47] However, anaemia may worsen and some authors advocate combination therapy with Erythropoietin. Interferon-alfa has been used in the similar setting with favorable results reported.[48] Lately, Anagrelide may be used for cases with problematic thrombocytosis.

Splenectomy is the option for patients who are drug-refractory to alleviate splenomegaly-associated complications. Operative mortality was about 9% with a post operative median survival of 27 months. Post surgical complications include intra-abdominal haemorrhage, subphrenic abscess, sepsis, large-vessel thrombosis, extreme thrombocytosis and progressive hepatomegaly.[49]

The role of radiotherapy is mainly for nonhepatosplenic extramedullary haemopoiesis (EMH). This includes paraspinal/ epidural mass (1,000 cGy in 5 to 10 fractions), pleural and peritoneal effusions (100 to 500 cGy in 5 to 10 fractions), and pulmonary hypertension from diffuse pulmonary EMH (100 cGy in a single-fraction to the whole lung). In poor risk patients for splenectomy, splenic irradiation (200-300 cGy in 10 to 15 fractions) may provide transient symptomatic relief for 3-6 months.[50,51]

Treatment Algorithm in MMM



UNCLASSIFIED

This category applies to cases with an overlap of clinical, laboratory and morphologic features that support a diagnosis of a myeloproliferative disease (MPD), but do not meet the criteria for any of the other specific entities. The treatment modalities follow as for the specific MPD entities depending on which are the more prominent features.

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APENDIX 1

GRADES OF RECOMMENDATIONS

A Requires at least one randomized controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation

B Requires the availability of well conducted clinical studies but no randomized clinical trials on the topic of recommendation

C Requires evidence obtained from expert committee reports or opinions and /or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality.

Levels of evidence

Ia Evidence obtained from meta-analysis of randomized controlled trials

Ib Evidence obtained from at least one randomized controlled trial

IIa Evidence obtained from at least one wel-designed, non-randomized study, including phase II trials and case-controlled studies.

IIb Evidence obtained from at least one other type of well-designed, quasi-experimental study, i.e. studies without planned intervention, including observational studies.

III Evidence obtained from well-designed, non-experimental descriptive studies. Evidence obtained from meta-analysis or randomized controlled trials or phase II studies that is published only in abstrct form.

IV Evidence obtained from expert committee reports or opinions and / or clinical experience of respected authorities.