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Essential Thrombocythemia

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Background

Thrombocytosis, defined as a platelet count of ≥ 450 x 10^9/L, is common in clinical practice and can be related to primary or secondary causes. Essential thrombocythemia (ET), a primary cause, is a Philadelphia-negative classical myeloproliferative neoplasm (MPN) defined by clonal thrombocytosis[1]. Similar to other classical MPNs, mutually exclusive driver mutations including JAK2, CALR and MPL are responsible for the pathogenesis of ET with the most frequent mutation JAK2V617F found in 55% of ET, 15-30% having CALR and 4-8% having MPL, while 10-20% lack a driver mutation and are referred to as "triple negative"[2]. ET is complicated by thrombosis and bleeding risk with potential of transformation to myelofibrosis or alternative aggressive myeloid neoplasm. This guideline is to provide information regarding the diagnosis and management of ET based on our current standards.

Guideline Questions

1. What diagnostic and baseline investigations are recommended for adult patients with suspected or confirmed ET?
2. What are the recommended treatment options for ET?
3. How do you manage extreme thrombocytosis?
4. How do you treat thrombosis in the setting of ET and other MPNs?
5. What is the current peri-operative and peripartum management strategies for ET/MPN patients?

Search Strategy

This guideline was generated using systematic literature searches of PubMed and MEDLINE databases, ASCO, EHA abstracts and proceedings, and ASH abstracts and proceedings. The search included practice guidelines, systematic reviews, meta-analyses, randomized controlled trials and clinical trials. The guidelines were also adapted from the NCCN, AJH and BJH guidelines.

Target Population

Patients who are ≥18 years of age who are suspected of, or diagnosed with essential thrombocythemia.

Recommendations

1. In patients with persistent thrombocytosis with platelet count ≥ 450 x 10^9/L diagnostic evaluation for ET is suggested once secondary causes of thrombocytosis are ruled out.
2. Diagnosis of ET requires a bone marrow biopsy and is based on recent 2016 WHO criteria.
3. The risk of thrombosis is based on the IPSET thrombosis score (Link).
4. Low-dose ASA therapy (81 mg PO once daily) is suggested for all patients with the exception of those with very low risk disease (younger than 60yrs, CALR mutated, without cardiovascular risk factors). ASA should be avoided in those with extreme thrombocytosis (plts ≥1500 x 10^9/L)

who may have acquired vWD (see point #9) or have alternative bleeding diathesis. In the setting of patients already on a form of anticoagulation or antiplatelet therapy for other comorbidities, addition of low dose ASA is not indicated.

5. Treatment with cytoreduction is suggested for: high risk disease (ET patients ≥60 yrs and/or history of prior arterial/venous thrombosis).
6. First line cytoreductive therapy is hydroxyurea or IFN/PEG-IFN/ROPEG.
7. Second line therapy can include an alternative first line cytoreductive agent, anagrelide or consider combination therapy.
8. The goal of cytoreduction is to normalize the platelet count ideally < 450 x10^9/L. This is to be achieved without development of alternative severe cytopenias and/or side effects.
9. Extreme thrombocytosis (plts ≥ 1 million/L or >1000 x 10^9/L) results in higher risk of bleeding due to potential for acquired VWD and may require holding ASA therapy if the platelet count is ≥1500 x 10^9/L, if clinical evidence of bleeding and/or VWF activity levels < 30%
10. The treatment of thrombosis in ET is based on standard thrombosis guidelines. Current practice guidelines suggest primary anticoagulation use of LMWH and VKA therapy. The use of DOACs for treatment of venous thrombosis in MPNs is limited. Discuss cases with local thrombosis experts and manage on a case by case basis. Recurrence of thrombosis is higher among MPN patients with the majority of patients benefiting from lifelong anticoagulation in the setting of unprovoked thrombosis. Lifelong anticoagulation is also suggested for atypical thrombosis particularly in the setting of splanchnic vein and/or cerebral vein thrombosis. (Thrombosis Canada Link)
11. ET patients have higher rates of pregnancy related complications. ASA therapy is suggested during all MPN pregnancies to improve live birth rates. Prophylactic LMWH is suggested for 6 weeks postpartum. Cytoreduction using IFN, is suggested for high risk pregnancies with prior indication for cytoreduction and those with a high risk pregnancy.

Pathogenesis

ET is a clonal stem cell disorder resulting in excessive platelet production with increased platelet counts in the peripheral blood. Approximately 90 percent of cases have a somatically acquired driver mutation such as JAK2, CALR, or MPL that results in the upregulation of JAK-STAT pathway and pathogenesis of ET [3]. JAK2V617 is the most frequent driver mutation in ET occurring in ~50-65% of cases followed by 15-30% CALR mutated and 4-8% MPL mutated and 10-20% lack all three mutations and are known at triple negative [4]. The majority of cases of ET are sporadic, although families with an increased incidence of ET have been described, with affected members having the same or different MPN type [5] [6]. It is suspected that this is due to a genetic predisposition to acquire somatic mutations and subsequently develop an MPN, rather than a direct inheritance of germline mutations.

Epidemiology

ET represents one-third of cases of BCR-ABL-negative myeloproliferative neoplasms in the developed world[7] . The incidence rate for ET is 1 to 2.5 new cases/100,000 population per year and varies based on age, sex and race with female to male ratio of 2:1 [7,8] The prevalence is higher and estimated to be 9-24 cases per 100,000 population [9-11]. Median age at diagnosis is 60 years, although up to 20 percent are < 40 years of age[3]. More recent reports suggest younger median age (56 years compared to 60 years)[12]. Extreme thrombocytosis (platelet count ≥ 1 million/L) occurs in less than 2 % of population[13].

Clinical Manifestations

Patients present with sustained and progressive thrombocytosis which often can be found incidentally associated with no symptoms. A variable proportion of patients have mild splenomegaly and leukocytosis[14,15] . Up to 40% of patients report being variably symptomatic for fatigue, early satiety, inactivity, concentration issues, and abdominal discomfort, with a consequent decrease in quality of life[16,17 18].

In addition, patients, may experience arterial and/or venous thrombotic complications with a history of thrombosis occurring at or before diagnosis in ~20% of patients. [3] The overall median thrombotic risk is 1–3%/patients-year[19] with reports of risk of non-fatal arterial and venous thrombosis being 1.2% and 0.6%/patients-year, respectively [20].

Patient age and history of thrombosis have been considered the main risk factors for vascular complications in MPNs based on ELN classification whereby patients are defined as high risk (HR) if they are at least 60 years and/or have a history of thrombosis, versus low risk (LR) if they do not have either factor [21]. Risk of thrombosis among LR patients is not significantly higher from that of the general population [22]. A more integrated and accurate clinical molecular prognostic score for thrombosis risk in ET, named IPSET-t (*International Prognostic Score of thrombosis in Essential Thrombocythemia*) has been developed.[23] (IPSET Calculator: Link). It was subsequently, re-analyzed, and validated, with the inclusion of an additional risk group ('very low', VLR) in a revised IPSET-t (Link). Of note, *CALR* mutations have been associated with lower thrombotic risk compared with *JAK2* [2,24] .

In contrast, risk of bleeding events in ET can occur although less frequently and varies from 5% to 30% [25,26]. The most frequent sites are gastrointestinal and urogenital, but intracranial bleeding may also occur[25]. Extreme thrombocytosis (platelet count > 1000–1500*10^9/L) is the biggest predictive factor for bleeding as it can be associated with acquired von Willebrand disease (AVWD)[27,28] . This arises due to adsorption of large VW factor multimers by the platelet membrane in the setting of high platelet counts [29]. In cases of extreme thrombocytosis in particular if bleeding has occurred, measure the ristocetin activity and VW factor antigen level. If VWF activity levels are < 30%, antiplatelet therapy should be discontinued. Concomitant use of antiplatelet therapy and prior hemorrhagic event

increase risk of hemorrhage while other potential factors may include: leukocytosis [30] and *JAK2* mutation.[31]

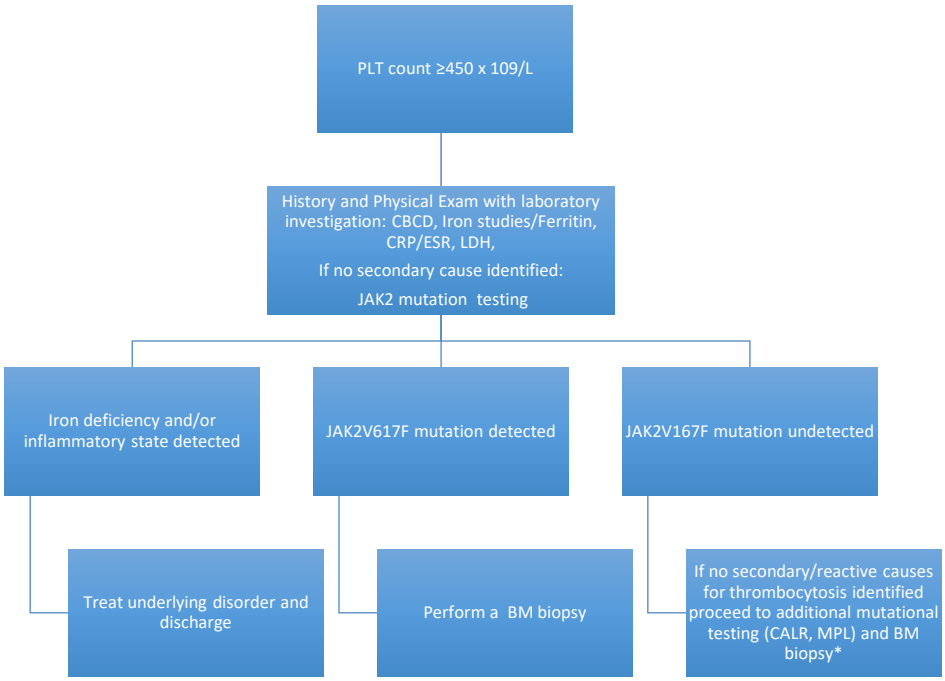
Diagnostic Evaluation

Thrombocytosis defined as a platelet count ≥ 450 x 109/L has a prevalence of approximately 2% among ambulatory patients ≥ 65 years of age [32]. There are primary and secondary causes for thrombocytosis[33]. The most common causes of secondary or reactive thrombocytosis are: infection, inflammation and/or trauma, and iron deficiency. Initial assessment of patients is necessary to carefully rule out secondary causes.

All patients require a complete history and physical examination. Review diseases and/or conditions associated with thrombocytosis: iron deficiency, malignancy, inflammatory bowel disease, rheumatological disorders, trauma, splenectomy, bleeding. A careful review of thrombotic history including both venous thrombosis and arterial thrombosis and a history of hemorrhagic complications is important. In addition, inquire about microcirculatory/vasomotor symptoms, such as headaches, dizziness, visual disturbances, burning dysesthesia of the palms and soles (erythromelalgia), paresthesia, acrocyanosis as well as constitutional symptoms (night sweats, fevers, weight loss) and signs/symptoms of splenomegaly.

Assess for cardiovascular risk factors, including hypertension, diabetes mellitus, active tobacco use, and hyperlipidemia (considered within IPSET-t score).
Review patient's family history of myeloproliferative and thrombosis disease.

Figure 1. Diagnostic Algorithm



*BM biopsy is needed in addition to confirmed driver mutation diagnosis based on WHO diagnostic criteria. Driver mutation detection can be attained via PB testing (PCR) or alternative via BM aspirate (NGS)

The diagnosis of ET requires a sustained thrombocytosis of ≥ 450 x 109/L with exclusion of reactive causes. A diagnostic algorithm is shown in Figure 1. A bone marrow examination (aspirate and trephine biopsy) is required based on recent WHO 2016 Criteria[1]. The World Health Organization (WHO) diagnosis of ET (Table 1) requires a platelet count of ≥450 x $10^{9/}$L, presence of a driver mutation and/or exclusion of an alternative cause of thrombocytosis along with bone marrow morphological consistent pathology[1]. Differential diagnosis of primary (clonal) thrombocytosis includes: primary myelofibrosis (prefibrotic or fibrotic), polycythemia, MPN-U, or variants of MDS. Most patients with MDS/MPN-RS-T carry a SF3B1 mutation[34,35].

In ET, the bone marrow is normocellular or mildly hypercellular with megakaryocytes increased in number with occasional small loose clusters. Large or giant megakaryocytes with hyperlobation are referred to as “staghorn”, nuclei may be prominent. Reticulin is not increased with grade 0/3 expected, Recently WHO classification has defined prefibrotic MF as a separate entity from both ET and overt myelofibrosis (see Table 1).[1]

Table 1. WHO 2016 Criteria for Essential Thrombocythemia in comparison to pre-fibrotic Primary Myelofibosis[1]

ESSENTIAL THROMBOCYTHEMIA Defined as: ALL Major Criteria OR 3 Major + 1 Minor	PRE-FIBROTIC PMF Defined as: ALL 3 Major + 1 Minor
Major Criteria: 1. Plts ≥ 450 x 109/L 2. BM biopsy: proliferation of MK lineage with enlarged mature MK and hyperlobulated nuclei without increase or left shift in neutrophil granulopoesis or erythropoiesis and minor (grade1) reticulin fibers 3. Not meeting WHO criteria for CML, PV, PMF, MDS or other myeloid neoplasm, 4. Presence of JAK2, CALR or MPL	**Major Criteria:** 1. MK proliferation and atypia WITHOUT reticulin fibrosis >1 with increased BM cellularity, gran proliferation, and decreased erythropoiesis 2. Not meeting WHO criteria: PV, CML, MDS or other myeloid neoplasm 3. JAK2, CALR, MPL or in absence another clonal marker or absence of reactive fibrosis
Minor Criteria: 1. Leukoerythroblastosis 2. Increased LDH 3. Anemia 4. Palpable splenomegaly	**Minor Criteria:** 1. Anemia 2. WBC ≥ 11 x 109/L 3. Palpable splenomegaly 4. Increased LDH

Lastly, genetic driver mutations are identified in over 90% of ET cases and can be tested via Polymerase Chain Reaction (PCR) and/or Next Generation Sequencing (NGS). Peripheral blood JAK2V617F mutational analysis should be performed and reflexive testing for additional driver mutations (CALR, MPL) will be ordered by hematopathology via PCR or NGS testing pending availability at individual academic centers. BCR-ABL1 gene rearrangement testing is suggested if evidence of basophilia or neutrophilia with left shift which is atypical in ET and in the cases of rearrangement this is diagnostic of CML and excludes ET[1]. One quarter of ET patients carry an additional non-driver somatic mutation and the significance in ET is unclear but it portends a poorer prognosis in MPN patients in prior studies.[36]

On exam, assess spleen and liver for organomegaly and if any associated features of portal hypertension although splenomegaly is rare in ET compared to alternative MPNs. Likewise, it is important to look for findings' suggestion of thrombosis and/or clinical signs of bleeding/bruising.

Laboratory studies, including a complete blood count with differential and review of the peripheral smear, and chemistries with liver and renal function and electrolytes in addition to iron studies including transferrin saturation and ferritin should be performed. CRP level can be performed to

assess for inflammatory status. If causes of reactive thrombocytosis are ruled out, then additional testing can be performed to rule in an MPN. Peripheral blood testing for JAK2V617F mutation can be done initially and if negative, reflexive testing for mutations of CALR exon 9, and MPL exon 10 can be obtained at some centers by peripheral blood PCR testing (Edmonton) or alternatively will be tested from a bone marrow aspirate sampling (via NGS). The detection of a driver mutation confirms the diagnosis of a myeloid neoplasm but a BM aspirate/biopsy is still required and the absence of a driver mutation does not rule out the diagnosis given cases of triple negative disease [37,38]. Ultimately if an MPN is suspected based on current standards, a bone marrow aspirate and biopsy is required and mutational testing can be obtained from the aspirate if PB sampling not possible. For patients with clinical evidence of bleeding or platelet counts >1000 x 10^9/L we suggest hemostasis testing (VWF antigen and activity levels) for possible acquired von Willebrand syndrome.

MDS/MPN with ringed sideroblasts and thrombocytosis (MDS/MPN-RS-t) can mimic ET with patients presenting with mild anemia and thrombocytosis. However, these patients often have a combination of the SF3B1 mutation driver as well as JAK, CALR or MPL (sub clone) but it should be considered as 1/3 of patients will have SF3B1 wildtype[36]. A bone marrow aspirate and biopsy should be performed to differentiate this from ET. In ET, the bone marrow is normocellular for age or mildly hypercellular. Megakaryocytes are increased in number with occasional loose clusters of enlarged megakaryocytes with mature cytoplasm and multilobulated nuclei. Erythropoiesis and granulopoesis is normal with lack of dysplastic morphology and reticulin is not increased grade 0/3.[1]

Recommendations

1. Diagnosis of ET requires comprehensive review of secondary/reactive causes and diagnosis of ET requires a bone marrow examination to diagnose primary causes**.**
2. Driver mutations are mutually exclusive with majority of ET patients possessing one of three driver mutations JAK2, CALR or MPL

Prognosis

The median estimate of survival among ET patients is 20 years. However, depending on age of presentation, this varies and as a result median survival of patients younger than 60 years of age approaches 33 years [39]. The most common cause of morbidity and mortality is thrombosis which occurs among 20% of ET patients compared to bleeding complications in 10% of this population [3,8]. The IPSET score was developed in order to better stratify prognosis of patients at time of diagnosis. Patients are determined as low, intermediate or high risk with median survival of: not reached among low risk patients, 24 years and 14 years among intermediate and high risk patients, respectively[40](Link). Moreover, recent observations suggest that women with ET live longer than male patients and that gender may supersede history of thrombosis as a risk variable for overall survival.[41] Thrombosis and hemorrhage represent two of the main causes of morbidity and mortality in patients with ET. In a study of 891 ET patients, after a median follow-up of 6.2 years, 109 (12%) patients

experienced arterial (*n* = 79) or venous (*n* = 37) thrombosis. Predictors of arterial thrombosis were: age > 60 years, prior thrombosis, cardiovascular (CV) risk factors (including tobacco use, hypertension, or diabetes mellitus), leukocytosis (> 11 × 10^9/L), and *JAK2*V617F mutation[12]. In contrast, predictors of venous thrombosis were only male gender. Elevated platelet count > 1000 × 10^9/L was associated with a lower risk of arterial thrombosis. Mutant *CALR* (vs *JAK2*) was associated with lower incidence of thrombotic events.[42] Current thrombosis risk can be calculated using a revised IPSET-thrombosis prognostic score based on 1019 WHO defined ET patients which takes into account: age, prior thrombosis, JAK mutation status and additional cardiovascular risk factors to further categorize patients into: "very low", low, intermediate and high risk[43,44] (Link) (Table 2) illustrate how each risk factor can influence thrombosis risk. Likewise, pre-PMF can be accurately stratified using similar score as developed for ET.[45]

Table 2. IPSET Thrombosis Score. [23,43]

IPSET-T Risk factors			**Revised IPSET Risk Factors**	
Age >60 yrs	1 point		Age >60	
Previous thrombosis	2 points		Previous thrombosis	
Cardiovascular risk factors	1 point		JAK2V617F	
JAK2V617F	2 points			
Annual thrombosis risk:			**Annual thrombosis Risk: (require all criteria)**	Rate of thrombosis per year
Low risk (<2points)	1.03% /year		Very Low: No thrombosis Age ≤ 60yrs JAK2V671F wildtype With additional cardiovascular RFS	0.44%/yr 1.05%/yr
Int risk (2 points)	2.35% /year		Low: No thrombosis Age ≤ 60yrs JAK2V671F Mutated With additional cardiovascular RFs	1.59 %/yr 2.57%/yr
High risk (>2 points)	3.56% /year		Intermediate: No thrombosis Age > 60yrs JAK2V671F wildtype With additional cardiovascular RFs	1.44 %/yr 1.64%/yr
			High: Prior thrombosis OR Age > 60yrs JAK2V671F mutated With additional cardiovascular RFs	2.36%/y 4.17%/yr

Based on the recent distinction of WHO defined ET and pre-fibrotic MF, the incidence of arterial and venous thrombosis prior to diagnosis is not significantly different[46] (23% vs 20 and 9 vs 8%) and thrombotic complications were also similar during the follow-up[47,48]. However, the overall prognosis varies between ET and prefibrotic MF whereby 10-year survival was found to be 89% vs 76%, with leukemic transformation of 0.7% vs 5.8% and MF transformation 0.8% vs. 12.3%, respectively, in large studies[48].

Transformation

The range of transformation risk to post-ET MF has been found to be 0.8-4.9% at 10 years and 4-11% at 15 years. This compares to post-ET AML occurring in 0.7-3% of ET patients at 10 years and 2.1-5.3% at 15 years. Diagnosis of transformation to post ET Myelofibrosis (PET-MF) requires fulfilling the criteria developed, through consensus by the IWG-MRT[49] as outlined in **Table 3**. Risk factors for progression to PET-MF include pre-PMF morphology, advanced age, and anemia, whereas the presence of JAK2V617F was associated with a lower risk of fibrotic progression[50].

Risk factors for post-ET AML include: advanced age, leukocytosis, anemia, extreme thrombocytosis, thrombosis, reticulin fibrosis, TP53 or RUNX1 mutations [51]. In a study of over 1100 patients with ET or pre-fibrotic PMF, risk factors for leukemia-free survival were pre-fibrotic PMF, BM morphology, thrombosis, and extreme thrombocytosis (platelets > 1000 × 10^9 /L)[48]. Mutation enhanced prognostic scores have been published[52] whereby spliceosome mutations enhance survival prediction in ET and PV and identify patients at risk for fibrotic progression while TP53 mutations predict leukemic transformation in ET.

Ultimately, transformation of all MPNs leads to poor outcomes and management remains challenging. Further understanding of the molecular events leading to disease transformation are currently being investigated.

Suspicion for MF transformation may be based on development of new onset or worsening cytopenias, progressive splenomegaly and/or constitutional symptoms and peripheral blood findings of leukoerythroblastic changes. Suspicion should prompt a repeat bone marrow examination and the diagnosis based on WHO criteria.

Prognosis of post ET MF is based on the Myelofibrosis Secondary to PV and ET-Prognostic Model (MYSEC-PM) score which differs from the current MF prognosis scores. It was developed as an integrated clinical-molecular prognostic model uniquely developed for secondary MF displaying superior accuracy over IPSS. This model was based on the analyses of 685 secondary MF patients (333 PET MF, 352 PPV MF) with phenotype driver mutations available. Four risk categories were developed with different survival (P<0.0001): low (median survival NR; 133 patients), intermediate-1 (9.3 years, 95% CI: 8.1-NR; 245 patients), intermediate-2 (4.4 years, 95% CI: 3.2–7.9; 126 patients), and high risk (2 years, 95% CI: 1.7–3.9; 75 patients). [53] The survival for secondary MF differs than

that in primary MF and can be calculated using this MYSEC-PM score: (Link). The Treatment of post ET MF is managed similarly based on current AHS Myelofibrosis guidelines (Link).

Transformation of essential thrombocythemia (ET) to myelodysplastic syndromes or acute myeloid leukemia is rare again comprising 1–5% of cases but confers dismal clinical outcome [54]. Post ET AML is defined as ≥ 20% blasts in peripheral blood and/or bone marrow and is prognostically worse and those fit for allogeneic SCT should receive induction chemotherapy and be referred for allogeneic SCT.

EXELS, was the largest prospective study of high-risk essential thrombocythemia (ET) patients, 3460 patients exposed to hydroxyurea (HU), anagrelide (ANA), or both, with an observation time of 5 years. EXELS found higher event rates of acute leukemia transformation in patients treated with HU although this was statistically inconclusive, with more than 90% of the patients having been treated with either ANA or HC. Sixty-seven cases of AML and 19 cases of MDS were recorded. Overall, 39 of 67 AML cases were found in the HU group (8970 person-years of treatment) and another 20 AML patients were found in the group that switched from HC to ANA (2934 person-years of treatment) while three cases were found in the group switching from ANA to HC during the study. Acute leukemia being a known complication of ET occurs in the absence of treatment and based on all available studies one cannot conclude whether or not hydroxyurea or anagrelide are truly leukemogenic [55].

Table 3. IWG-MRT Diagnostic Criteria for Post-Essential Thrombocythemia Myelofibrosis (PET-MF):[49,56]

IWG-MRT Criteria for Post Essential Thromboythemia myelofibrosis.
Required criteria • Documentation of a previous diagnosis of essential thrombocythemia as defined by the WHO criteria. • Bone marrow fibrosis grade 2-3 (on 0-3 scale). **Additional criteria (two are required)** • Anemia and a >20g/L decrease from baseline hemoglobin level. • A leukoerythroblastic peripheral blood picture. • Increasing splenomegaly defined as either an increase in palpable splenomegaly of > 5cm or the appearance of a newly palpable splenomegaly. • Increased LDH (above reference level) • Development of >1 of three constitutional symptoms: >10% weight loss in 6 months, night sweats, unexplained fever (>37.5°C)

Abnormal karyotype is infrequent in ET and its prognostic relevance uncertain [57]. A study of 906 molecularly-annotated patients (416 Mayo Clinic; 490 University of Florence, Italy), including 502 ET and 404 PV, were recruited with multivariable analysis that identified spliceosome mutations to adversely affect overall (SF3B1, SRSF2 in ET and SRSF2 in PV) and myelofibrosis-free (U2AF1,

SF3B1 in ET) survival; TP53 mutations predicted leukemic transformation in ET. Overall “adverse” mutations occurred in 51 (10%) of ET patients. Hazard-ratio-based risk point allocation led to the development of the three-tiered mutation-enhanced international prognostic systems (MIPSS) which was validated in both cohorts and performance was shown to be superior to conventional scoring systems. Adverse mutations leading to inferior overall, leukemia-free or fibrosis-free survival, included: SH2B3, SF3B1, U2AF1, TP53, IDH 2, and EZH 2; the effect was independent of conventional prognostic models[52]. Patients with ET and type 1/type1-like CALR mutations may have a higher risk of post ET MF but these patients have lower risk of thrombosis.[58]

Current medical therapy has not been shown to modify the natural history of ET, thus will not prevent leukemic or fibrotic progression or prolong survival. Current available therapy is indicated to prevent thrombotic complications. ET is classified as “high risk” based on conventional IWG risk factors of age equal to or older than 60 yrs and/or history of thrombosis[21].

Recommendations

1. Risk stratification is based on thrombosis risk with traditional categorization of “low” and “high” risk based on age and previous thrombosis

2. More detailed distinction of risk of thrombosis is based on the IPSET-t score.

3. Transformation to post ET myelofibrosis (PET MF) is diagnosed with a bone marrow aspirate and biopsy.

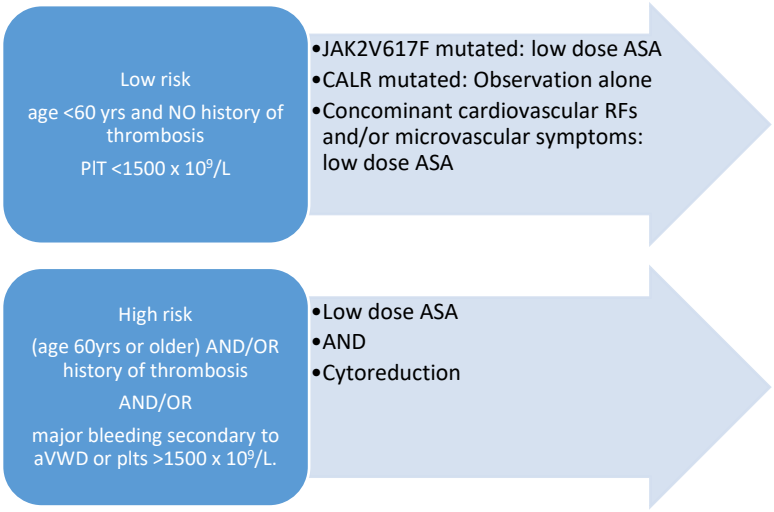
4. The MYSEC-PM score is used for prognostication of PET-MF with management on the basis of standard MF guidelines.

5. Leukemic transformation is poor prognosis and managed via standard leukemia guidelines.

Treatment

The main goal of therapy is to prevent thrombotic complications, particularly in high risk patients. Treatment is suggested based on risk adapted prognostic models with “high” risk patients being those older than 60yrs and/or with previous thrombosis (arterial and/or venous) The current IPSET scores[43,59] **(Table 2)** provides prognostic information and was not directly developed for treatment decisions but provides insight on risk stratification.

Figure 2. Risk adapted treatment for ET patients



Low dose ASA therapy showed benefit for secondary thrombotic prevention as shown in PV based on the ECLAP study and has been extrapolated to use for ET patients[60]. Low dose ASA (81-100 mg PO daily) has been suggested in all ET patients with exception of "very low" risk (Table 4) and/or those with extreme thrombocytosis (≥1500 x 10^9/L/1.5 million/L)) and/or bleeding complications[21 61]. Clopidogrel can be used as alternative agent if ASA allergy. Antiplatelet therapy reduces risks of venous thrombosis in JAK+ ET and lowers arterial thrombosis in ET patients with cardiovascular risk factors however may be ineffective for remaining low risk ET patients. In contrast, CALR-mutated patients have not had thrombosis risk reduction with antiplatelet therapy but rather an increased incidence of bleeding. CALR, MPL and triple negative patients have lower thromboembolic risk in comparison to JAK2 mutated patients[62]. Therefore, we suggest ASA therapy for all high-risk ET patients based on Figure 2. Use low dose ASA in low risk patients if JAK mutated, presence of additional cardiovascular risk factors, and microvascular symptoms with low bleeding risk profile. Testing for aVWD can be considered if platelets counts are equal to or greater than 1 million/L or in setting of clinical bleeding. ASA therapy is not suggested in the event of VWF levels of less than 30% or if patient is deemed to be at high risk of bleeding based on past or current clinical status. The benefits of ASA antiplatelet therapy have been inferred from polycythemia[60] studies and retrospective studies in ET[62-66]. In addition, use of twice daily ASA has been suggested among patients with additional cardiovascular risk factors however this has not been formally evaluated.

Patients may be on anticoagulation for alternative comorbidities such as atrial fibrillation and/or prior thrombosis and in this setting it is not suggested that this be replaced by low dose ASA nor do patients require low dose ASA in addition to their baseline anticoagulant or alternative antiplatelet agent (ie. clopidogrel).

Cytoreduction

Patients found to have conventional high risk disease (age >60yrs or history of thrombosis) or "intermediate" or "high risk" based on IPSET-thrombosis model should receive cytoreduction. In addition, in the setting of extreme thrombocytosis it is suggested to minimize risks of bleeding. Often a threshold of plts $\geq$1500 x 10^9/L is selected as time for starting cytoreduction. The target platelet count is variable among various studies and generally one attempts to achieve normalization of platelet count. Experts often suggest a platelet count between 450 x 10^9/L to 600 x 10^9/L as acceptable with attempts to achieve control while minimizes additional cytopenias and side effects of treatment. Many studies indicate risk of thrombosis is associated with high leukocyte count rather than actual platelet count[12,67-70].

First line cytoreduction is hydroxyurea and/or interferon-alfa 2a (IFN). In those with high risk disease, use of hydroxyurea (HU) has been shown to reduce thrombotic events compared to no cytoreduction 3.6% vs 24% (p=0.003)[71]. Starting dose is often 1000mg PO daily or 10-15mg/kg/day and can be titrated upwards with maximal dose being 2.5g/day. The ELN recommends hydroxyurea as first-line cytoreduction for any age although caution should be considered in patients younger than 40 years whereby hydroxyurea is teratogenic and should be avoided in those of child-bearing age[21]. Overall hydroxyurea is more widely used based on findings of the PT-1 trial assessing 809 high risk ET patients with findings of hydroxyurea being superior to anagrelide in terms of reducing atrial thrombosis, serious hemorrhage and myelofibrotic progression [72]. An open-label RCT (n=382) showed no benefit to Hydroxyurea plus ASA therapy in ET patients 40-59 yrs lacking high risk features (thrombosis, hemorrhage, ischemia, plts >1500 x 10^9/L) therefore cytoreduction is being restricted to higher risk disease [73].

Hydroxyurea is an antimetabolite that inhibits ribonucleoside diphosphate-reductase slowing down DNA synthesis and repair. Side effects of hydroxyurea are often self-limited and/or reversible and include bone marrow suppression, anorexia/nausea/diarrhea and skin alterations such as alopecia, rash, leg ulcers and increased risk of nonmelanomatous skin cancer. Rarer complications are fever, pneumonitis, liver injury, azoospermia and it is considered teratogenic[72]. Its risk for leukemogenic is controversial and not well supported in long term studies[74-76].

Currently we follow ELN criteria for clinicohematological response [77] (See appendix A).

Patients require optimal follow up and may require monthly lab work in the setting of cytoreductive therapies with clinical assessments on a 6-12 month basis. In the event of suspected myelofibrotic or leukemic transformation a repeat bone marrow aspirate/biopsy and/or abdominal ultrasound can be additionally performed. Baseline ultrasound and abdominal diagnostic imaging are not routinely performed.

Hydroxyurea resistance/intolerance

Hydroxyurea resistance and/or intolerance has been defined by ELN [78-80] (**Table 4).**

Inadequate control of platelet count can occur for which options may include: relaxing platelet target (i.e. to less than 600 x 10^9/L) or switch to second line therapy or consider combination therapy (i.e. HU and anagrelide)[81]. Relaxed plt targets were studied by Cortelazzo et al [71] whereby there was no significant increased incidence of thrombosis compared to more stringent plt control of 400 x 10^9/L among the PT-1 study[72]. Patents with a history of thrombosis should receive the most optimal cytoreduction that can be attained. In a retrospective series of 166 patients treated with hydroxyurea for a median of 4.5 years, 70% were able to achieve CR at 1 year. The best discriminating factor for resistance was detection of anemia. Twenty percent of this population met ELN criteria for resistance/intolerance and this resulted in poorer survival with 6 fold higher risks of death and median subsequent survival from onset of anemia was only 2.4 years. There was a lack of correlation between CR status and lower thrombosis incidence suggesting a particular platelet threshold is not the only factor resulting in thrombosis to consider[82].

Table 4. Criteria for Hydroxyurea (HU) Intolerance and Resistance[76-78].

Definition of resistance/intolerance to HU in patients with ET
• Platelet count > 600 x 10^9/ L after 3 months of at least 2 g/day of HU (2.5 g/day in patients with a body weight >80kg) • Platelet count > 400 x 10^9/Land WBC I< 2.5 x 10^9/L at any dose of HU • Platelet count > 400 x 10^9/L and Hb less than 100g/L at any dose of HU • Presence of leg ulcers or other unacceptable mucocutaneous manifestations at any dose of HU • HU-related fever

Anagrelide is a second-line option for cytoreduction if hydroxyurea resistance/intolerance occurs as discovered in the ANAHYDRET trial (n=259) to be non-inferior to hydroxyurea in preventing vascular events[83]. Alternative studies have illustrated superiority of hydroxyurea in combination with low dose ASA compared to anagrelide and low dose ASA for high risk ET patients in the ability of reducing vascular events. Thus, anagrelide remains a second line option and also poses concerning side effects particularly its potential cardiotoxicity[72]. Common side effects include: palpitations, headaches, GI upset but serious tachyarrhythmias can occur and a baseline ECG is suggested and consider further cardiac evaluation prior to use. Anagrelide has been associated with renal insufficiency, cardiac complications, arrhythmias and cardiomyopathy[84-87]. Anagrelide has been associated with higher risk for myelofibrosis transformation so consider this risk especially among younger patients. The starting dose of anagrelide is 0.5mg PO OD BID and it can be titrated to maximum 10 mg per day. Alternative agents to anagrelide such as busulfan are leukemogenic and in practice have not been used at our local site recently.

Interferon (IFN)

Interferon (IFN) is a second-line option for those with hydroxyurea resistance/intolerance and a front-line option in patients who are younger (particularly <40yrs). There is preference to utilize interferon given teratogenic effects of hydroxyurea and long term mutagenic potential has been of concern although observational studies have not shown an increased leukemic transformation rate[75]. Interferon is an immunomodulatory agent that suppresses pluripotent and lineage committed hematopoietic progenitors and directly inhibitors thrombopoietin induced megakaryocytic growth[88]. IFN side effects include depression, fatigue, hepatitis and pneumonitis with approximately one third of patients discontinuing therapy secondary to intolerance[89]. Prior to initiation of treatment assess thyroid and liver function and rule out presence of autoimmune disorder and/or psychiatric history. Generally, it is initiated at 3 x 10^6 /million units three times a week with titration. Given the anticipated flu-like symptoms, consider prophylactic treatment with acetaminophen.

The benefits of interferon consist of high hematologic and molecular remissions, with the latter suggesting potential for disease modification[90,91]. Newer formulations that are PEGylated (PEG) allow for weekly administration with the aim of reducing the side effect profile and ameliorating use and compliance including both PEG-IFNa-2B and PEG-IFN-2a. PEGylated interferon-2a has been shown to induce hematologic and complete molecular response in a subset of JAK mutated ET patients that may be sustained after drug discontinuation [91,92,93.] Therapy can be initiated at 45ug and titrated up to 180ug SC weekly as tolerated. In a recent systemic review and meta-analysis of IFN therapy in ET (730 ET patients) treated with various formulations of IFN over a period of more than three decades, the ORR was reported by all 30 ET studies and was 80.6% (95% CI 76.6–84.1%) Here, the complete hematologic remission/complete remission (CHR/CR) rate was 59.0% (95% CI 51.5–66.1%) with significant heterogeneity among the studies. The CHR/CR rate was not statistically significantly different ($p = 0.23$) between peg-IFN compared to non-peg-IFN and adverse events and discontinuation rates were reported as very similar [94].

Similarly, the Phase III DALIAH trial randomized 205 previously untreated MPN patients to interferon alfa-2a, interferon alfa-2b, or hydroxyurea (HU). Patients ≤ 60 years were assigned to INF-α-2a vs 2b only (1:1 randomization), whereas patients > 60 years were randomized (1:1:1) to all three agents to include the standard of HU. The interim analysis observed a 49% ORR in ET, PV, and pre-MF patients treated with interferon alfa which was lower than the 75% response rate seen with HU. Drug-related discontinuation was higher in the r-IFNα group (34–45% vs 13% for HU), with grade ≥ 3 adverse events (AEs) was similar in all groups. [95] The Myeloproliferative Disorders Research Consortium (MPD-RC)-111 study was an investigator-initiated, international, multicenter, phase 2 trial evaluating the ability of PEG therapy in high-risk ET or PV who were either refractory or intolerant to HU. The study included 65 patients with ET and 50 patients with PV. The overall response rates (ORRs; CR/PR) at 12 months were 69.2% (43.1% and 26.2%) in ET patients and 60% (22% and 38%). CR rates were higher in CALR-mutated ET patients (56.5% vs 28.0%; P = .01), compared with those in subjects lacking a CALR mutation. PEG discontinuation related to AEs occurred in only 13.9% of subjects. [96] The MPN-RC-112 was a randomized, open label, phase 3 clinical trial

comparing HU and PEG in pts with high risk ET/PV. After a median follow-up of 89.9 weeks (in patients treated > 24 months), PEG-IFN provided non-significantly higher rate of ORR (60% vs 41% for HU, $p = 0.22$). Interestingly, treatment with HU was associated with a higher rate of bone marrow best response (33% vs 17% PEG-IFN, $p = 0.05$). Six pts randomized to HU never received treatment due to study withdrawal prior to initiation of treatment. A higher incidence of grade ≥ 3 AE occurred for those on PEG-IFN (46.3% vs 27.5% for HU). [97]

Newer formulations such as Ropegintereferon alfa 2b (Ropeg, *Besremi*®) are available. These show promise with the ease of weekly or q2weekly subcutaneous injections being preferred and infers less injection related toxicity with newer IFN formulations being favored among patients and physicians. Ropeg was compared against HU in the phase 3, randomized, multicenter PROUD-PV study (continuing after 12 months as CONTINUATION-PV) in PV patients, who were either treatment naïve or who had already been treated with HU for <3 years and were neither intolerant nor complete responders. In 2019, Ropeg (*Besremi*®) received approval via European Medicines agency as a monotherapy in PV patients without symptomatic splenomegaly, independent of previous HU exposure. Future studies are pending in ET.

JAK inhibitors

JAK1/2 Inhibitor, Ruxolitinib, is approved in Canada as second line treatment for PV patients resistant or intolerant to hydroxyurea based on its superiority shown in RESPONSE and RESPONSE-2 studies [99],[100]. However, Ruxolitinib is not currently approved for ET. The MAJIC-ET study did not find any advantage to the use of Ruxolitinib compared to best available treatment (BAT) among ET patients with hydroxyurea resistance/intolerance (n=110). At 1 year CHR rates were 46.6% for ruxolitinib treated compared to 44.2% for BAT treated patients (p=0.40) with no difference in thrombosis, hemorrhage or transformation rates at 2 years. Improvement in disease related symptoms was noted among ruxolitinib treated arm[101]. It should be acknowledged that symptom burden is often high among MPN patients and consideration should be made into alternative therapies in order to address ongoing symptom management and improving QOL among ET patients [102]. The comparison of anagrelide to ruxolitinib is currently under evaluation (NCT031235888).

Recommendations

1. Low-dose ASA therapy (81 mg PO once daily) is suggested for all patients with the exception of those with very low risk disease (younger than 60yrs, CALR mutated, without cardiovascular risk factors). ASA should be avoided in those with extreme thrombocytosis (plts >1500 x 10^9/L) who may have acquired vWD (see point #9) or have alternative bleeding diathesis. In the setting of patients already on a form of anticoagulation or antiplatelet therapy for other comorbidities, addition of low dose ASA is not indicated.
2. Treatment with cytoreduction is suggested for: high risk disease (ET patients ≥60 yrs and/or history of prior arterial/venous thrombosis)
3. First line cytoreductive therapy is hydroxyurea or IFN/PEG-IFN/ROPEG

4. Second line therapy can include an alternative first line cytoreductive agent, anagrelide or consider combination therapy.
5. The goal of cytoreduction is to normalize the platelet count ideally <450 x10^9/L. This is to be achieved without development of alternative severe cytopenias and/or side effects.

Special Considerations in ET

Extreme Thrombocytosis:

Extreme thrombocytosis is defined as platelet count >1000 x 10^9/L. Although thrombosis is the most commonly feared complication related to ET, bleeding is in fact the complication of extreme thrombocytosis. This risk arises as a result of functional von Willebrand factor deficiency due to more platelet binding to large VWF multimers resulting in their increased clearance from the plasma[28,103]. Consideration for testing for acquired VWD via ristocetin cofactor activity level is suggested if using aspirin in setting of extreme thrombocytosis. Likewise, the use of antiplatelet agents in patients with low-risk ET and extreme thrombocytosis is associated with increased risk of bleeding[62].

Cytoreduction should be initiated to reduce platelet counts in the setting of bleeding while also discontinuing antiplatelet and/or anticoagulants in the setting of bleeding relating to aVWD. MPN-associated acquired von Willebrand's disease will resolves once platelet counts normalize. Desmopressin and tranexamic acid may also be used in cases of severe acute bleeding, while platelet transfusions, von Willebrand factor-containing concentrates, or other factor concentrates are restricted to more severe or life-threatening bleeding[104].

Not every patient with extreme thrombocytosis requires cytoreduction and the threshold to initiate cytoreduction is variable. Particularly, in asymptomatic patients with low risk disease medical monitoring may be considered. In a cohort of 445 ET patients with 99 being young (age <60years) with extreme thrombocytosis plt >1000 x 10^9/L, 75 received cytoreduction therapy with either hydroxyurea or anagrelide compared to 24 patients who had treatment deferred until occurrence of a vascular event. The incidence of post diagnosis major thrombosis was 33% vs 18% (p=0.17) revealing no difference in the prevalence of thrombotic nor hemorrhagic complications and this included when using a cut-off age of 40 years or when excluding those with microvascular symptoms from the overall analysis[105]. Further data is needed in this area including the best platelet threshold to initiate cytoreduction and the goal platelet target among these asymptomatic low risk patients.

Thrombosis:

Thrombosis and bleeding are major causes of death in ET, with case-fatality rates of 33% to 51% and 1% to 10% [20,59]. Based on a Canadian systematic review, 21 ET studies (15 comparative and 6 single-group) examined thrombosis. They found a median thrombosis risk of 19.9 events per 1000 patient-years without antiplatelet therapy and a modest relative risk reduction (26%) with use of

antiplatelet therapy. Median estimates of the risk for bleeding among ET patients without antithrombotic medications were 7.8 and 8.5 events per 1000 patient-years for any bleeding and 5.9 and 6.4 events per 1000 patient-years for major bleeding. Antiplatelet agents were associated with a median increased risk for bleeding (median increase in major bleeding 30%). Evidence on the potential effects of antiplatelet agents on mortality and disease transformation was insufficient to draw a formal conclusion.

This confirms that ET patients are at high thrombotic risk. Particularly a risk for cardiovascular events of 10 to 20 events per 1000 patient-years (10% to 20% 10-year risk). The use of antiplatelet therapy results in 26% risk reduction which is consistent with that in the general population (12% to 18%) but thrombotic risk in ET remains high despite the use of antiplatelet therapy[106].

In the event of a thrombotic event, acute thrombosis management is based on standard arterial and venous thrombosis guidelines. (Add thrombosis Canada link: https://thrombosiscanada.ca/clinicalguides/) Individual arterial and venous thrombosis risk factors need to be aggressively managed and controlled. Optimization of platelet count is important to avoid recurrent thrombosis. MPNs typically present with unusual or atypical thrombosis including splanchnic vein thrombosis. Thrombosis can occur in context of normal peripheral blood findings and many be a presenting feature of MPN.

The rate of recurrent VTE in the general population is 5–7% pt-years. Post-discontinuation of anticoagulation in the general population leads to a recurrence rate of 30% at 5 years after an unprovoked VTE, respectively, and 15% after provoked VTE [111-113]. The rate of recurrent thrombosis in Ph-neg MPN patients is 7.6% pt-years [20] 3.4 % on VKAs and 9.4% off VKAs, respectively ($p = 0.016$)[114] After stopping VKAs, the recurrence rate was 42.3% at 5 years; this being higher than the 29.1% rate observed at 5 years in the non-MPN patients[66].

Atypical thrombosis is more prone to recurrences and are generally seen more commonly among MPN patients. The efficacy of hydroxyurea in preventing thrombosis is significant for arterial thrombosis but limited for venous thrombosis[115]. Likewise, one must consider bleeding risk of Ph-neg MPN patients, with the incidence of major bleeding being 0.9–2.4% pt-years on VKAs and 0.7–1.5 off VKAs and up to 2.8% pt-years when combining VKAs and aspirin[66,114,116].

Overall there is heterogeneity in treatment practices for thrombosis in MPN patients with the recent consensus statements suggesting a prolongation of anticoagulation after unprovoked VTE, a life-threatening VTE or a VTE recurrence but there are no controlled studies that provide evidence directing our management [107,117-119].

Recommendations:

1. The treatment of thrombosis in ET is based on standard thrombosis guidelines.
2. Current practice guidelines suggest primary anticoagulation use of LMWH and VKA therapy.
3. The use of DOACs for treatment of venous thrombosis in MPNs is limited. Discuss cases with local thrombosis experts and manage on a case by case basis.
4. Recurrence of thrombosis is higher among MPN patients with the majority of patients benefiting from lifelong anticoagulation in the setting of unprovoked thrombosis. Lifelong anticoagulation is also suggested for atypical thrombosis particularly in the setting of splanchnic vein and/or cerebral vein thrombosis.

Pregnancy and hormone therapy:

Approximately 20% of patients with essential thrombocythemia are younger than 40 years at diagnosis[120] and of child bearing age. Pregnant MPN patients should ideally be under joint care of a consultant obstetrician experienced in the care of patients with high-risk pregnancies and a hematologist. Historically, platelet counts decline during pregnancy but do increase postpartum [121] and careful monitoring of MPN patients is required. Many expert opinions and guidelines have been published regarding best management practices. [122-124]

Essential thrombocythemia is associated with complications of eclampsia, placental abruption, intrauterine growth retardation and still birth[125]. Spontaneous abortion rates are reported in 25-50% of cases of ET pregnancy mainly in first trimester[126] Of note the overall risk rate of spontaneous abortion (≤20th week) in normal pregnancies is 11% and is accounting for 80% of all fetal losses [127]. The overall risk of stillbirth (intrauterine death >20th week and infant born showing no signs of life) in normal pregnancies is observed in 0.43%[127]. The rate of premature delivery is about 9% [128] and rates of miscarriage rate range between 10–15%[129].

In report by Griesshammer et al of 793 pregnancies in 492 women with ET a successful birth rate was achieved in 68.5% (543 live births in 793 pregnancies) with a miscarriage rate of 31.5% (250 miscarriages in 793 pregnancies). First trimester abortion (≤20th week) was the most frequent complication in 26.5% (210 spontaneous abortions in 793 pregnancies). Stillbirth, defined as fetal loss >20th week, occurred in 4.8%, which is more than 10 times higher than the overall risk of stillbirth in non-MPN pregnancies. Preterm delivery (birth <37th week) was found in 8.6% (43 of 502 evaluable pregnancies) and appears comparable to the rate in normal pregnancy with 9%. [122]

Aspirin has been used for prevention of uteroplacental insufficiency in high-risk groups because aspirin inhibits platelet aggregation and results in a reduction of oxidative stress and inflammation[130]. In a meta-analysis, aspirin reduced the risk of preterm birth in high-risk pregnancies by 14% (relative risk, 0.86; CI, 0.76-0.98), intrauterine growth restriction by 20% (RR, 0.80; CI, 0.65-0.99), and preeclampsia by 24% (relative risk, 0.76; 95% CI, 0.62-0.95)[131]. The Aspirin *versus* Placebo in

Pregnancies at High Risk for Preterm Preeclampsia study (ASPRE) [132] illustrates the benefits of aspirin once daily for MPN pregnancy. Generally, aspirin (81 mg PO OD) use should be considered early in all MPN pregnancy and continued throughout pregnancy. If prior pregnancy was associated with preterm pre-eclampsia women can be offered 160 mg aspirin once daily.[124]

Aspirin use in ET pregnant patients was not associated with increases in bleeding events when used alone or with heparin. Skeith et al report a systematic review and metanalysis of 191 ET based pregnancies, whereby bleeding occurred in 4.3% of women using aspirin compared with 4.9% among 129 pregnancies without aspirin use (95% CI, 2.0%-9.0%).There were no antepartum bleeding events in 71 pregnancies using a combination of LMWH and aspirin (95% CI, 0.0%-6.2%). [133]

A more recent systematic review and meta-analysis by Maze et al [134] evaluated whether treatment with aspirin, heparin, interferon, or combinations thereof affected live birth rate and adverse maternal outcomes in pregnant MPN patients. They report 22 studies on 767 women with a total of 1210 pregnancies, 15 studies including ET patients. The pooled rate of any adverse events was 9.6%. The most common adverse maternal event was preeclampsia, with an incidence of 3.1% (95% CI, 1.7%-4.5%). The overall live birth rate was 71.3% (95% CI, 65.1%-77.6%), which is lower than the expected live birth rate of approximately 80% (excluding elective terminations) in the general population. Successful pregnancies occurred more frequently in patients with essential thrombocythemia (71.1%) compared to polycythemia vera (66.7%). Use of aspirin (11 studies, 227 patients; unadjusted odds ratio, 8.6; 95% CI, 4.0-18.1) and interferon (6 studies, 90 patients; unadjusted odds ratio, 9.7; 95% CI, 2.3-41.0) were associated with 9 to 10-fold higher odds of live births. However, the addition of low doses of LMWH or unfractionated heparin to aspirin was not associated with significantly different odds of live birth (6 studies, 96 pregnancies; unadjusted OR, 2.1 for aspirin with heparin vs aspirin alone; 95% CI, 0.5-9.0; I 2 = 0%). The administration of LMWH alone was not associated with significantly different odds of live birth (unadjusted OR, 6.0; 95% CI, 0.40- 90.1; I 2 = 0%). [134]

Low molecular weight heparin is safe and effective for treating and preventing thrombosis in pregnancy[135]. Whether or not LMWH is beneficial in maternal VTE risk reduction for ET patients was studied in 756 ET pregnancies in which antepartum and postpartum VTE risk was identified as 2.5% vs 4.4% respectively, with a defined threshold of 3% at which LMWH prophylaxis is recommended.[133] The analysis led to recommendations that LMWH prophylaxis should be considered based on the presence of additional risk factors and a preference and values-based discussion, given a modest absolute risk of VTE. For women with ET during the post-partum period, use of LMWH prophylaxis to prevent thrombosis is suggested.

In particular “high risk” MPN pregnancies may benefit from adding prophylactic low dose molecular weight heparin (dalteparin 5000 IU or enoxaparin 40 mg once daily) to low-dose aspirin throughout pregnancy and for 6 weeks postpartum. [21]

A “high-risk” MPN pregnancy is considered, if any of the following factors is present: [21,122]

1. Prior thrombosis or severe hemorrhage in MPN patient.
2. Previous pregnancy complication like spontaneous abortion, intrauterine death or stillbirth, preeclampsia necessitating preterm delivery 45–50%.
3. Marked sustained increase in platelet count to greater than 1,500 × 10^9/L.

The local approach is to offer antenatal LMWH thromboprophylaxis in the presence of prior thrombosis or in the presence of one additional “high risk” factor. All women are offered six weeks post-partum thromboprophylaxis with LMWH. These recommendations are independent of aspirin, which should be continued concurrently.

If cytoreduction is needed which also applies to “high risk” MPN pregnancies, interferon alpha (IFN) based therapy is the drug of choice. Pegylated interferon alpha should be preferred due to better tolerability and efficacy. Griesshammer *et al.* summarized the literature regarding IFN over 90 MPN pregnancies. [122]

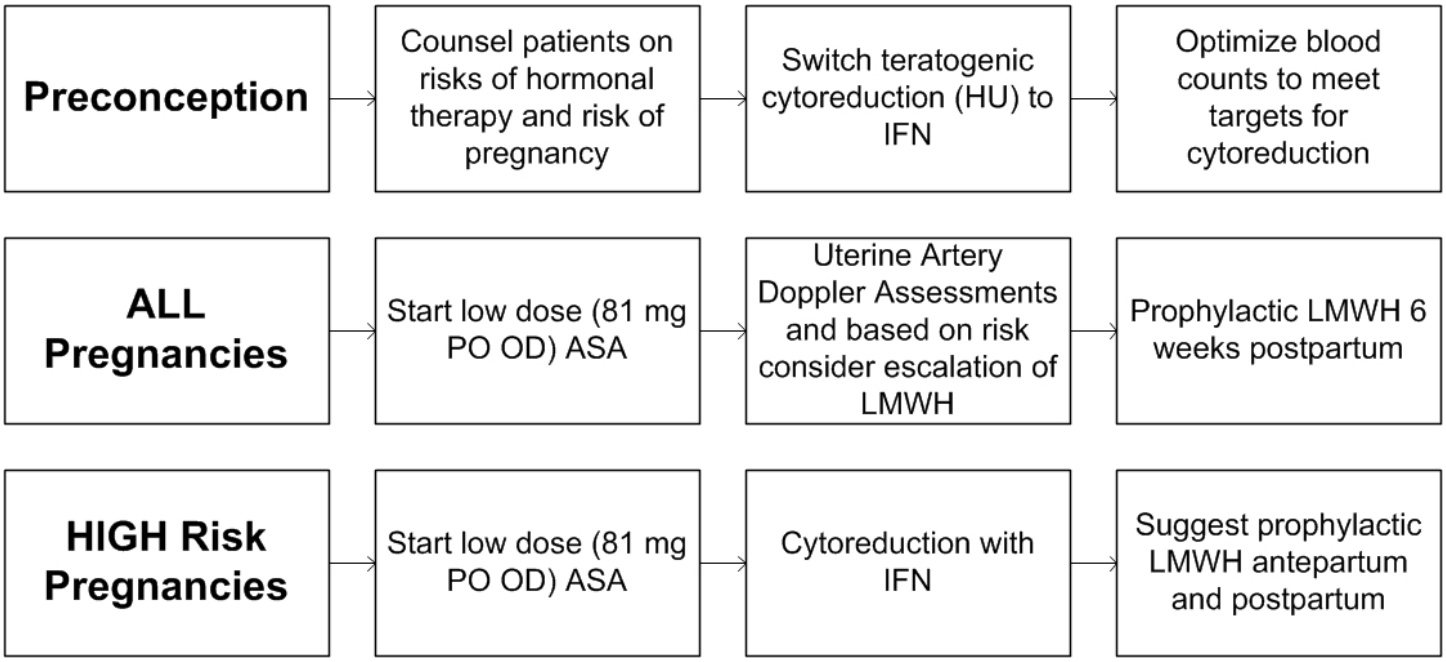
Importantly, in the event of planning pregnancy, preconception recommendations are to discontinue the use of possible teratogenic drugs such as hydroxyurea with a 3–6 months washout period being advised. Both men and women who are considering family growth should attempt this 3-6 month wash out period under the consultation of their physician. Alternative cytoreduction should be considered such as IFN based therapy if indicated based on ET risk status or begin administration if high-risk pregnancy with complications (as above). Platelet counts should not exceed 1500 × 10^9/lL due to an acquired von Willebrand’s syndrome and risk of peripartum bleeding.[122]

Uterine artery Doppler is a predictive test for the development of pregnancy complications such as pre-eclampsia, intra-uterine growth restriction, abruption and fetal death and should be performed between 18 and 24 weeks in all MPN pregnancies. A systematic review and meta-analysis have shown that an increased pulsatility index (PI) was the best predictor of pre-eclampsia (positive likelihood ratio 21·0 among high-risk patients and 7·5 among low-risk patients). It was also the best predictor of overall (positive likelihood ratio 9·1) and severe (positive likelihood ratio 14·6) intra-uterine growth restriction among low-risk patients [136]. In women with a positive test (i.e. mean uterine artery PI > 1·4) consider escalating anticoagulant therapy and enhancing screening with serial growth scans. [124]

With respect to breastfeeding, heparins are not excreted in breast milk and may be used safely when breast feeding. Aspirin and LMWH are not contraindicated in a breast-feeding woman.[124] Hydroxyurea, and possibly anagrelide are excreted in breast milk. Interferon α is variably excreted in breast milk and may be active orally; however, there is an absence of safety data rather than evidence of harm to the neonate. The recent HELPS trial[137] Hydroxyurea Exposure in Lactation: a Pharmacokinetics (PK) Study, illustrated that breastfeeding mothers will transfer only a small amount

of hydroxyurea to their infants, so lactation during hydroxyurea treatment should not be contraindicated.

Figure 3. Suggestions for MPN peripartum management[125].



A "high-risk" MPN pregnancy is considered, if any of the following factors is present: 21,122

(1) Prior thrombosis or severe hemorrhage in MPN patient.

(2) Previous pregnancy complication like spontaneous abortion, intrauterine death or stillbirth, preeclampsia necessitating preterm delivery 45–50%.

(3) Marked sustained increase in platelet count to greater than 1,500 × 109/L.

Recommendations

1. Use low dose Aspirin throughout MPN pregnancy

2. Treat all MPN pregnant patients with standard LMWH thromboprophylaxis postpartum x 6 weeks (e.g. dalteparin 5000 units sc o.d., enoxaparin 40 mg sc o.d)

3. Consider treatment with standard LMWH thromboprophylaxis antenatally in setting of "high risk" MPN pregnancy

3. Cytoreduction with IFN based therapy is suggested as first line if patient has prior indication for cytoreduction or any "high risk" MPN pregnancy risks. Note hydroxyurea is a teratogenic.

Hormones:

There is currently insufficient data available to evaluate the effects of combined OCP, hormonal replacement or ovarian stimulation in ET. In a series of 305 female patients with ET, the use of estrogen-containing hormone therapy was not associated with an increase in venous or arterial thrombotic events. However, the use of oral contraceptives was associated with a threefold increased risk of venous thrombosis (23 versus 7 percent) and a fivefold increased risk of splanchnic

thrombosis (15 versus 3 percent).[138] Overall it is suggested hormonal therapy be avoided in MPN patients.

Surgery:

Generally, MPNs are associated with higher odds of any surgery-related complications (OR, 1.37; P = .0099). [139] ET patients have a 5-6-fold higher risk of thrombosis perioperative[140]. Controlling of platelet count preoperatively with ideal normalization of count is suggested preoperatively. Of note, complications of blood loss and postoperative infection may result in reactive thrombocytosis and should be considered if reinitiating of cytoreduction postoperatively, Likewise, hydroxyurea can impair would healing so this needs to be reviewed and considered if delays in post-operative recovery are noted. Postoperative thromboprophylaxis is suggested although not necessary to extend beyond normal postoperative recommendations and/or hospitalization on the basis of MPN existence.

References

1. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;127(20):2391-2405.
2. Rumi E, Pietra D, Ferretti V, et al. JAK2 or CALR mutation status defines subtypes of essential thrombocythemia with substantially different clinical course and outcomes. *Blood*. 2014;123(10):1544-1551.
3. Tefferi A, Barbui T. Polycythemia vera and essential thrombocythemia: 2019 update on diagnosis, risk-stratification and management. *Am J Hematol*. 2019;94(1):133-143.
4. Tefferi A, Pardanani A. Myeloproliferative Neoplasms: A Contemporary Review. *JAMA Oncol*. 2015;1(1):97-105.
5. Rumi E, Passamonti F, Della Porta MG, et al. Familial chronic myeloproliferative disorders: clinical phenotype and evidence of disease anticipation. *J Clin Oncol*. 2007;25(35):5630-5635.
6. Rumi E, Harutyunyan AS, Pietra D, et al. CALR exon 9 mutations are somatically acquired events in familial cases of essential thrombocythemia or primary myelofibrosis. *Blood*. 2014;123(15):2416-2419.
7. Srour SA, Devesa SS, Morton LM, et al. Incidence and patient survival of myeloproliferative neoplasms and myelodysplastic/myeloproliferative neoplasms in the United States, 2001-12. *Br J Haematol*. 2016;174(3):382-396.
8. Meier B, Burton JH. Myeloproliferative Disorders. *Hematol Oncol Clin North Am*. 2017;31(6):1029-1044.
9. Mesa RA, Silverstein MN, Jacobsen SJ, Wollan PC, Tefferi A. Population-based incidence and survival figures in essential thrombocythemia and agnogenic myeloid metaplasia: an Olmsted County Study, 1976-1995. *Am J Hematol*. 1999;61(1):10-15.
10. Ma X, Vanasse G, Cartmel B, Wang Y, Selinger HA. Prevalence of polycythemia vera and essential thrombocythemia. *Am J Hematol*. 2008;83(5):359-362.
11. Roaldsnes C, Holst R, Frederiksen H, Ghanima W. Myeloproliferative neoplasms: trends in incidence, prevalence and survival in Norway. *Eur J Haematol*. 2017;98(1):85-93.
12. Carobbio A, Thiele J, Passamonti F, et al. Risk factors for arterial and venous thrombosis in WHO-defined essential thrombocythemia: an international study of 891 patients. *Blood*. 2011;117(22):5857-5859.
13. Hsieh RW, Ravindran A, Hook CC, et al. Etiologies of Extreme Thrombocytosis: A Contemporary Series. *Mayo Clin Proc*. 2019;94(8):1542-1550.
14. Picardi M, Martinelli V, Ciancia R, et al. Measurement of spleen volume by ultrasound scanning in patients with thrombocytosis: a prospective study. *Blood*. 2002;99(11):4228-4230.
15. Tefferi A, Barbui T. Polycythemia vera and essential thrombocythemia: 2017 update on diagnosis, risk-stratification, and management. *Am J Hematol*. 2017;92(1):94-108.
16. Johansson P, Mesa R, Scherber R, et al. Association between quality of life and clinical parameters in patients with myeloproliferative neoplasms. *Leuk Lymphoma*. 2012;53(3):441-444.
17. Wolanskyj AP, Schwager SM, McClure RF, Larson DR, Tefferi A. Essential Thrombocythemia Beyond the First Decade: Life Expectancy, Long-term Complication Rates, and Prognostic Factors. *Mayo Clinic Proceedings*. 2006;81(2):159-166.
18. Geyer HL, Mesa RA. Therapy for myeloproliferative neoplasms: when, which agent, and how? *Blood*. 2014;124(24):3529-3537.
19. Vannucchi AM, Antonioli E, Guglielmelli P, et al. Clinical profile of homozygous JAK2 617V>F mutation in patients with polycythemia vera or essential thrombocythemia. *Blood*. 2007;110(3):840-846.
20. Passamonti F, Rumi E, Pungolino E, et al. Life expectancy and prognostic factors for survival in patients with polycythemia vera and essential thrombocythemia. *The American Journal of Medicine*. 2004;117(10):755-761.
21. Barbui T, Barosi G, Birgegard G, et al. Philadelphia-negative classical myeloproliferative neoplasms: critical concepts and management recommendations from European LeukemiaNet. *J Clin Oncol*. 2011;29(6):761-770.
22. Ruggeri M, Finazzi G, Tosetto A, Riva S, Rodeghiero F, Barbui T. No treatment for low-risk thrombocythaemia: results from a prospective study. *Br J Haematol*. 1998;103(3):772-777.
23. Barbui T, Finazzi G, Carobbio A, et al. Development and validation of an International Prognostic Score of thrombosis in World Health Organization-essential thrombocythemia (IPSET-thrombosis). *Blood*. 2012;120(26):5128-5133; quiz 5252.
24. Rotunno G, Mannarelli C, Guglielmelli P, et al. Impact of calreticulin mutations on clinical and hematological phenotype and outcome in essential thrombocythemia. *Blood*. 2014;123(10):1552-1555.
25. Finazzi G, Carobbio A, Thiele J, et al. Incidence and risk factors for bleeding in 1104 patients with essential thrombocythemia or prefibrotic myelofibrosis diagnosed according to the 2008 WHO criteria. *Leukemia*. 2012;26(4):716-719.

26. Casini A, Fontana P, Lecompte TP. Thrombotic complications of myeloproliferative neoplasms: risk assessment and risk-guided management. *J Thromb Haemost*. 2013;11(7):1215-1227.
27. Elliott MA, Tefferi A. Thrombosis and haemorrhage in polycythaemia vera and essential thrombocythaemia. *Br J Haematol*. 2005;128(3):275-290.
28. Budde U, van Genderen PJ. Acquired von Willebrand disease in patients with high platelet counts. *Semin Thromb Hemost*. 1997;23(5):425-431.
29. Federici AB, Rand JH, Bucciarelli P, et al. Acquired von Willebrand syndrome: data from an international registry. *Thromb Haemost*. 2000;84(2):345-349.
30. Lim Y, Lee JO, Kim SH, et al. Prediction of thrombotic and hemorrhagic events during polycythemia vera or essential thrombocythemia based on leukocyte burden. *Thromb Res*. 2015;135(5):846-851.
31. Torregrosa JM, Ferrer-Marín F, Lozano ML, et al. Impaired leucocyte activation is underlining the lower thrombotic risk of essential thrombocythaemia patients with CALR mutations as compared with those with the JAK2 mutation. *Br J Haematol*. 2016;172(5):813-815.
32. Msaouel P, Lam AP, Gundabolu K, et al. Abnormal platelet count is an independent predictor of mortality in the elderly and is influenced by ethnicity. *Haematologica*. 2014;99(5):930-936.
33. Harrison CN, Bareford D, Butt N, et al. Guideline for investigation and management of adults and children presenting with a thrombocytosis. *Br J Haematol*. 2010;149(3):352-375.
34. Malcovati L, Della Porta MG, Pietra D, et al. Molecular and clinical features of refractory anemia with ringed sideroblasts associated with marked thrombocytosis. *Blood*. 2009;114(17):3538-3545.
35. Patnaik MM, Tefferi A. Refractory anemia with ring sideroblasts and RARS with thrombocytosis. *Am J Hematol*. 2015;90(6):549-559.
36. Lundberg P, Karow A, Nienhold R, et al. Clonal evolution and clinical correlates of somatic mutations in myeloproliferative neoplasms. *Blood*. 2014;123(14):2220-2228.
37. Milosevic Feenstra JD, Nivarthi H, Gisslinger H, et al. Whole-exome sequencing identifies novel MPL and JAK2 mutations in triple-negative myeloproliferative neoplasms. *Blood*. 2016;127(3):325-332.
38. Cabagnols X, Favale F, Pasquier F, et al. Presence of atypical thrombopoietin receptor (MPL) mutations in triple-negative essential thrombocythemia patients. *Blood*. 2016;127(3):333-342.
39. Tefferi A, Guglielmelli P, Larson DR, et al. Long-term survival and blast transformation in molecularly annotated essential thrombocythemia, polycythemia vera, and myelofibrosis. *Blood*. 2014;124(16):2507-2513.
40. Passamonti F, Thiele J, Girodon F, et al. A prognostic model to predict survival in 867 World Health Organization-defined essential thrombocythemia at diagnosis: a study by the International Working Group on Myelofibrosis Research and Treatment. *Blood*. 2012;120(6):1197-1201.
41. Tefferi A, Betti S, Barraco D, et al. Gender and survival in essential thrombocythemia: A two-center study of 1,494 patients. *Am J Hematol*. 2017;92(11):1193-1197.
42. Finazzi G, Carobbio A, Guglielmelli P, et al. Calreticulin mutation does not modify the IPSET score for predicting the risk of thrombosis among 1150 patients with essential thrombocythemia. Blood. Vol. 124. United States; 2014:2611-2612.
43. Barbui T, Vannucchi AM, Buxhofer-Ausch V, et al. Practice-relevant revision of IPSET-thrombosis based on 1019 patients with WHO-defined essential thrombocythemia. Blood Cancer J. Vol. 5; 2015:e369.
44. Haider M, Gangat N, Lasho T, et al. Validation of the revised International Prognostic Score of Thrombosis for Essential Thrombocythemia (IPSET-thrombosis) in 585 Mayo Clinic patients. *Am J Hematol*. 2016;91(4):390-394.
45. Guglielmelli P, Carobbio A, Rumi E, et al. Validation of the IPSET score for thrombosis in patients with prefibrotic myelofibrosis. *Blood Cancer J*. 2020;10(2):21.
46. Buxhofer-Ausch V, Gisslinger B, Schalling M, et al. Impact of white blood cell counts at diagnosis and during follow-up in patients with essential thrombocythaemia and prefibrotic primary myelofibrosis. *Br J Haematol*. 2017;179(1):166-169.
47. Rumi E, Boveri E, Bellini M, et al. Clinical course and outcome of essential thrombocythemia and prefibrotic myelofibrosis according to the revised WHO 2016 diagnostic criteria. *Oncotarget*. 2017;8(60):101735-101744.
48. Barbui T, Thiele J, Passamonti F, et al. Survival and disease progression in essential thrombocythemia are significantly influenced by accurate morphologic diagnosis: an international study. *J Clin Oncol*. 2011;29(23):3179-3184.
49. Barosi G, Mesa RA, Thiele J, et al. Proposed criteria for the diagnosis of post-polycythemia vera and post-essential thrombocythemia myelofibrosis: a consensus statement from the International Working Group for Myelofibrosis Research and Treatment. Leukemia. Vol. 22. England; 2008:437-438.
50. Vardiman JW, Thiele J, Arber DA, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. *Blood*. 2009;114(5):937-951.

51. Cerquozzi S, Tefferi A. Blast transformation and fibrotic progression in polycythemia vera and essential thrombocythemia: a literature review of incidence and risk factors. *Blood Cancer J*. 2015;5(11):e366.
52. Tefferi A, Guglielmelli P, Lasho TL, et al. Mutation-enhanced international prognostic systems for essential thrombocythaemia and polycythaemia vera. *Br J Haematol*. 2020;189(2):291-302.
53. Passamonti F, Giorgino T, Mora B, et al. A clinical-molecular prognostic model to predict survival in patients with post polycythemia vera and post essential thrombocythemia myelofibrosis. *Leukemia*. 2017;31(12):2726-2731.
54. Suleiman Y, Dalia S, Liu JJ, et al. Clinical prognostic factors and outcomes of essential thrombocythemia when transformed to myelodysplastic syndromes and acute myeloid leukemia. *Leukemia Research*. 2016;42:52-58.
55. Birgegård G, Folkvaljon F, Garmo H, et al. Leukemic transformation and second cancers in 3649 patients with high-risk essential thrombocythemia in the EXELS study. *Leuk Res*. 2018;74:105-109.
56. Mesa RA, Verstovsek S, Cervantes F, et al. Primary myelofibrosis (PMF), post polycythemia vera myelofibrosis (post-PV MF), post essential thrombocythemia myelofibrosis (post-ET MF), blast phase PMF (PMF-BP): Consensus on terminology by the international working group for myelofibrosis research and treatment (IWG-MRT). *Leuk Res*. 2007;31(6):737-740.
57. Gangat N, Tefferi A, Thanarajasingam G, et al. Cytogenetic abnormalities in essential thrombocythemia: prevalence and prognostic significance. *Eur J Haematol*. 2009;83(1):17-21.
58. Pietra D, Rumi E, Ferretti VV, et al. Differential clinical effects of different mutation subtypes in CALR-mutant myeloproliferative neoplasms. *Leukemia*. 2016;30(2):431-438.
59. Barbui T, Finazzi G, Carobbio A, et al. Development and validation of an International Prognostic Score of thrombosis in World Health Organization–essential thrombocythemia (IPSET-thrombosis). *Blood*. 2012;120(26):5128-5133.
60. Landolfi R, Marchioli R, Kutti J, et al. Efficacy and safety of low-dose aspirin in polycythemia vera. *N Engl J Med*. 2004;350(2):114-124.
61. Mesa RA, Jamieson C, Bhatia R, et al. NCCN Guidelines Insights: Myeloproliferative Neoplasms, Version 2.2018. *J Natl Compr Canc Netw*. 2017;15(10):1193-1207.
62. Alvarez-Larrán A, Pereira A, Guglielmelli P, et al. Antiplatelet therapy versus observation in low-risk essential thrombocythemia with a CALR mutation. *Haematologica*. 2016;101(8):926-931.
63. Alvarez-Larrán A, Cervantes F, Pereira A, et al. Observation versus antiplatelet therapy as primary prophylaxis for thrombosis in low-risk essential thrombocythemia. *Blood*. 2010;116(8):1205-1210; quiz 1387.
64. Randi ML, Rossi C, Fabris F, Menapace L, Girolami A. Aspirin seems as effective as myelosuppressive agents in the prevention of rethrombosis in essential thrombocythemia. *Clin Appl Thromb Hemost*. 1999;5(2):131-135.
65. van Genderen PJ, Mulder PG, Waleboer M, van de Moesdijk D, Michiels JJ. Prevention and treatment of thrombotic complications in essential thrombocythaemia: efficacy and safety of aspirin. *Br J Haematol*. 1997;97(1):179-184.
66. De Stefano V, Za T, Rossi E, et al. Recurrent thrombosis in patients with polycythemia vera and essential thrombocythemia: incidence, risk factors, and effect of treatments. *Haematologica*. 2008;93(3):372-380.
67. Carobbio A, Antonioli E, Guglielmelli P, et al. Leukocytosis and risk stratification assessment in essential thrombocythemia. *J Clin Oncol*. 2008;26(16):2732-2736.
68. Carobbio A, Finazzi G, Antonioli E, et al. Thrombocytosis and leukocytosis interaction in vascular complications of essential thrombocythemia. *Blood*. 2008;112(8):3135-3137.
69. Carobbio A, Finazzi G, Antonioli E, et al. Hydroxyurea in essential thrombocythemia: rate and clinical relevance of responses by European LeukemiaNet criteria. *Blood*. 2010;116(7):1051-1055.
70. Carobbio A, Ferrari A, Masciulli A, Ghirardi A, Barosi G, Barbui T. Leukocytosis and thrombosis in essential thrombocythemia and polycythemia vera: a systematic review and meta-analysis. *Blood Adv*. 2019;3(11):1729-1737.
71. Cortelazzo S, Finazzi G, Ruggeri M, et al. Hydroxyurea for patients with essential thrombocythemia and a high risk of thrombosis. *N Engl J Med*. 1995;332(17):1132-1136.
72. Harrison CN, Campbell PJ, Buck G, et al. Hydroxyurea compared with anagrelide in high-risk essential thrombocythemia. *N Engl J Med*. 2005;353(1):33-45.
73. Godfrey AL, Campbell PJ, MacLean C, et al. Hydroxycarbamide Plus Aspirin Versus Aspirin Alone in Patients With Essential Thrombocythemia Age 40 to 59 Years Without High-Risk Features. *J Clin Oncol*. 2018;36(34):3361-3369.
74. Kiladjian JJ, Chevret S, Dosquet C, Chomienne C, Rain JD. Treatment of polycythemia vera with hydroxyurea and pipobroman: final results of a randomized trial initiated in 1980. *J Clin Oncol*. 2011;29(29):3907-3913.
75. Björkholm M, Derolf AR, Hultcrantz M, et al. Treatment-related risk factors for transformation to acute myeloid leukemia and myelodysplastic syndromes in myeloproliferative neoplasms. *J Clin Oncol*. 2011;29(17):2410-2415.
76. Björkholm M, Hultcrantz M, Derolf Å R. Leukemic transformation in myeloproliferative neoplasms: therapy-related or unrelated? *Best Pract Res Clin Haematol*. 2014;27(2):141-153.

77. Barosi G, Mesa R, Finazzi G, et al. Revised response criteria for polycythemia vera and essential thrombocythemia: an ELN and IWG-MRT consensus project. *Blood*. 2013;121(23):4778-4781.
78. Barosi G. New consensus: a unified definition of clinical resistance and/or intolerance to hydroxyurea in essential thrombocythaemia. *Eur J Haematol Suppl*. 2007(68):24-26.
79. Barosi G, Besses C, Birgegard G, et al. A unified definition of clinical resistance/intolerance to hydroxyurea in essential thrombocythemia: results of a consensus process by an international working group. *Leukemia*. 2007;21(2):277-280.
80. Barosi G, Birgegard G, Finazzi G, et al. A unified definition of clinical resistance and intolerance to hydroxycarbamide in polycythaemia vera and primary myelofibrosis: results of a European LeukemiaNet (ELN) consensus process. Br J Haematol. Vol. 148. England; 2010:961-963.
81. D'Adda M, Micheletti M, Drera M, Ferrari S, Rossi G. The combined use of hydroxyurea and anagrelide allows satisfactory hematologic control in patients with chronic myeloproliferative disorders and thrombocytosis: a report on 13 patients with poor tolerance to hydroxyurea monotherapy. Leuk Lymphoma. Vol. 49. United States; 2008:2216-2218.
82. Hernández-Boluda JC, Alvarez-Larrán A, Gómez M, et al. Clinical evaluation of the European LeukaemiaNet criteria for clinicohaematological response and resistance/intolerance to hydroxycarbamide in essential thrombocythaemia. *Br J Haematol*. 2011;152(1):81-88.
83. Gisslinger H, Gotic M, Holowiecki J, et al. Anagrelide compared with hydroxyurea in WHO-classified essential thrombocythemia: the ANAHYDRET Study, a randomized controlled trial. *Blood*. 2013;121(10):1720-1728.
84. Engel PJ, Johnson H, Baughman RP, Richards AI. High-output heart failure associated with anagrelide therapy for essential thrombocytosis. Ann Intern Med. Vol. 143. United States; 2005:311-313.
85. Jurgens DJ, Moreno-Aspitia A, Tefferi A. Anagrelide-associated cardiomyopathy in polycythemia vera and essential thrombocythemia. *Haematologica*. 2004;89(11):1394-1395.
86. Mazzucconi MG, Redi R, Bernasconi S, et al. A long-term study of young patients with essential thrombocythemia treated with anagrelide. *Haematologica*. 2004;89(11):1306-1313.
87. Mela Osorio MJ, Ferrari L, Goette NP, et al. Long-term follow-up of essential thrombocythemia patients treated with anagrelide: subgroup analysis according to JAK2/CALR/MPL mutational status. *Eur J Haematol*. 2016;96(4):435-442.
88. Lengfelder E, Griesshammer M, Hehlmann R. Interferon-alpha in the Treatment of Essential Thrombocythemia. *Leukemia & Lymphoma*. 1996;22(sup1):135-142.
89. Masarova L, Patel KP, Newberry KJ, et al. Pegylated interferon alfa-2a in patients with essential thrombocythaemia or polycythaemia vera: a post-hoc, median 83 month follow-up of an open-label, phase 2 trial. *Lancet Haematol*. 2017;4(4):e165-e175.
90. Kiladjian JJ, Cassinat B, Chevret S, et al. Pegylated interferon-alfa-2a induces complete hematologic and molecular responses with low toxicity in polycythemia vera. *Blood*. 2008;112(8):3065-3072.
91. Quintás-Cardama A, Kantarjian H, Manshouri T, et al. Pegylated interferon alfa-2a yields high rates of hematologic and molecular response in patients with advanced essential thrombocythemia and polycythemia vera. *J Clin Oncol*. 2009;27(32):5418-5424.
92. Quintás-Cardama A, Abdel-Wahab O, Manshouri T, et al. Molecular analysis of patients with polycythemia vera or essential thrombocythemia receiving pegylated interferon α-2a. *Blood*. 2013;122(6):893-901.
93. Kiladjian JJ, Giraudier S, Cassinat B. Interferon-alpha for the therapy of myeloproliferative neoplasms: targeting the malignant clone. *Leukemia*. 2016;30(4):776-781.
94. Bewersdorf JP, Giri S, Wang R, et al. Interferon alpha therapy in essential thrombocythemia and polycythemia vera-a systematic review and meta-analysis. *Leukemia*. 2020.
95. Knudsen TA, Hansen DL, Ocias LF, et al. Long-Term Efficacy and Safety of Recombinant Interferon Alpha-2 Vs. Hydroxyurea in Polycythemia Vera: Preliminary Results from the Three-Year Analysis of the Daliah Trial - a Randomized Controlled Phase III Clinical Trial. *Blood*. 2018;132(Supplement 1):580-580.
96. Yacoub A, Mascarenhas J, Kosiorek H, et al. Pegylated interferon alfa-2a for polycythemia vera or essential thrombocythemia resistant or intolerant to hydroxyurea. *Blood*. 2019;134(18):1498-1509.
97. Mascarenhas J, Kosiorek HE, Prchal JT, et al. Results of the Myeloproliferative Neoplasms - Research Consortium (MPN-RC) 112 Randomized Trial of Pegylated Interferon Alfa-2a (PEG) Versus Hydroxyurea (HU) Therapy for the Treatment of High Risk Polycythemia Vera (PV) and High Risk Essential Thrombocythemia (ET). *Blood*. 2018;132(Supplement 1):577-577.
98. Gisslinger H, Klade C, Georgiev P, et al. Ropeginterferon alfa-2b versus standard therapy for polycythaemia vera (PROUD-PV and CONTINUATION-PV): a randomised, non-inferiority, phase 3 trial and its extension study. *Lancet Haematol*. 2020;7(3):e196-e208.

99. Vannucchi AM, Kiladjian JJ, Griesshammer M, et al. Ruxolitinib versus standard therapy for the treatment of polycythemia vera. *N Engl J Med*. 2015;372(5):426-435.
100. Passamonti F, Griesshammer M, Palandri F, et al. Ruxolitinib for the treatment of inadequately controlled polycythaemia vera without splenomegaly (RESPONSE-2): a randomised, open-label, phase 3b study. *Lancet Oncol*. 2017;18(1):88-99.
101. Harrison CN, Mead AJ, Panchal A, et al. Ruxolitinib vs best available therapy for ET intolerant or resistant to hydroxycarbamide. *Blood*. 2017;130(17):1889-1897.
102. Harrison CN, Koschmieder S, Foltz L, et al. The impact of myeloproliferative neoplasms (MPNs) on patient quality of life and productivity: results from the international MPN Landmark survey. *Ann Hematol*. 2017;96(10):1653-1665.
103. van Genderen PJ, Budde U, Michiels JJ, van Strik R, van Vliet HH. The reduction of large von Willebrand factor multimers in plasma in essential thrombocythaemia is related to the platelet count. *Br J Haematol*. 1996;93(4):962-965.
104. Appelmann I, Kreher S, Parmentier S, et al. Diagnosis, prevention, and management of bleeding episodes in Philadelphia-negative myeloproliferative neoplasms: recommendations by the Hemostasis Working Party of the German Society of Hematology and Medical Oncology (DGHO) and the Society of Thrombosis and Hemostasis Research (GTH). *Ann Hematol*. 2016;95(5):707-718.
105. Tefferi A, Gangat N, Wolanskyj AP. Management of extreme thrombocytosis in otherwise low-risk essential thrombocythemia; does number matter? *Blood*. 2006;108(7):2493-2494.
106. Chu DK, Hillis CM, Leong DP, Anand SS, Siegal DM. Benefits and Risks of Antithrombotic Therapy in Essential Thrombocythemia. *Annals of Internal Medicine*. 2017;167(3):170-180.
107. Barbui T, De Stefano V, Falanga A, et al. Addressing and proposing solutions for unmet clinical needs in the management of myeloproliferative neoplasm-associated thrombosis: A consensus-based position paper. *Blood Cancer J*. 2019;9(8):61.
108. Young AM, Marshall A, Thirlwall J, et al. Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight Heparin in Patients With Cancer With Venous Thromboembolism: Results of a Randomized Trial (SELECT-D). *Journal of Clinical Oncology*. 2018;36(20):2017-2023.
109. Raskob GE, van Es N, Verhamme P, et al. Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism. *New England Journal of Medicine*. 2017;378(7):615-624.
110. Ianotto J-C, Couturier M-A, Galinat H, et al. Administration of direct oral anticoagulants in patients with myeloproliferative neoplasms. *International Journal of Hematology*. 2017;106(4):517-521.
111. Cushman M. Epidemiology and risk factors for venous thrombosis. (0037-1963 (Print)).
112. Kearon C, Iorio A, Palareti G, On Behalf Of The Subcommittee On Control Of Anticoagulation Of The Ssc Of The I. Risk of recurrent venous thromboembolism after stopping treatment in cohort studies: recommendation for acceptable rates and standardized reporting. *Journal of Thrombosis and Haemostasis*. 2010;8(10):2313-2315.
113. Baglin TaBKaDJaBHaSAaJG. Duration of anticoagulant therapy after a first episode of an unprovoked pulmonary embolus or deep vein thrombosis: guidance from the SSC of the ISTH. *Journal of Thrombosis and Haemostasis*. 2012;10(4):698-702.
114. Hernández-Boluda JC, Arellano-Rodrigo E, Cervantes F, et al. Oral anticoagulation to prevent thrombosis recurrence in polycythemia vera and essential thrombocythemia. *Ann Hematol*. 2015;94(6):911-918.
115. De Stefano V, Rossi E, Carobbio A, et al. Hydroxyurea prevents arterial and late venous thrombotic recurrences in patients with myeloproliferative neoplasms but fails in the splanchnic venous district. Pooled analysis of 1500 cases. *Blood Cancer J*. 2018;8(11):112.
116. De Stefano V, Ruggeri M, Cervantes F, et al. High rate of recurrent venous thromboembolism in patients with myeloproliferative neoplasms and effect of prophylaxis with vitamin K antagonists. *Leukemia*. 2016;30(10):2032-2038.
117. Barbui T, De Stefano V. Management of venous thromboembolism in myeloproliferative neoplasms. *Curr Opin Hematol*. 2017;24(2):108-114.
118. De Stefano V, Finazzi G, Barbui T. Antithrombotic therapy for venous thromboembolism in myeloproliferative neoplasms. *Blood Cancer Journal*. 2018;8(7):65.
119. Kreher S, Ochsenreither S, Trappe RU, et al. Prophylaxis and management of venous thromboembolism in patients with myeloproliferative neoplasms: consensus statement of the Haemostasis Working Party of the German Society of Hematology and Oncology (DGHO), the Austrian Society of Hematology and Oncology (ÖGHO) and Society of Thrombosis and Haemostasis Research (GTH e.V.). *Ann Hematol*. 2014;93(12):1953-1963.
120. Srour SA, Devesa SS, Morton LM, et al. Incidence and patient survival of myeloproliferative neoplasms and myelodysplastic/myeloproliferative neoplasms in the United States, 2001–12. *British Journal of Haematology*. 2016;174(3):382-396.

121. Reese JA, Peck JD, McIntosh JJ, Vesely SK, George JN. Platelet counts in women with normal pregnancies: A systematic review. *Am J Hematol*. 2017;92(11):1224-1232.
122. Griesshammer M, Sadjadian P, Wille K. Contemporary management of patients with BCR-ABL1-negative myeloproliferative neoplasms during pregnancy. *Expert Rev Hematol*. 2018;11(9):697-706.
123. Gangat N, Tefferi A. Myeloproliferative neoplasms and pregnancy: Overview and practice recommendations. *Am J Hematol*. 2021;96(3):354-366.
124. Robinson SE, Harrison CN. How we manage Philadelphia-negative myeloproliferative neoplasms in pregnancy. *Br J Haematol*. 2020;189(4):625-634.
125. Passamonti F, Randi ML, Rumi E, et al. Increased risk of pregnancy complications in patients with essential thrombocythemia carrying the JAK2 (617V>F) mutation. *Blood*. 2007;110(2):485-489.
126. Harrison C. Pregnancy and its management in the Philadelphia negative myeloproliferative diseases. *Br J Haematol*. 2005;129(3):293-306.
127. Andersen A-MN, Wohlfahrt J, Christens P, Olsen J, Melbye M. Maternal age and fetal loss: population based register linkage study. *BMJ*. 2000;320(7251):1708.
128. Schleußner E. The prevention, diagnosis and treatment of premature labor. *Dtsch Arztebl Int*. 2013;110(13):227-235; quiz 236.
129. Green L, Knight M, Seeney FM, et al. The epidemiology and outcomes of women with postpartum haemorrhage requiring massive transfusion with eight or more units of red cells: a national cross-sectional study. *BJOG: An International Journal of Obstetrics & Gynaecology*. 2016;123(13):2164-2170.
130. Groom KM, David AL. The role of aspirin, heparin, and other interventions in the prevention and treatment of fetal growth restriction. *American Journal of Obstetrics and Gynecology*. 2018;218(2, Supplement):S829-S840.
131. Henderson JT, Whitlock EP, O'Connor E, Senger CA, Thompson JH, Rowland MG. Low-Dose Aspirin for Prevention of Morbidity and Mortality From Preeclampsia: A Systematic Evidence Review for the U.S. Preventive Services Task Force. *Annals of Internal Medicine*. 2014;160(10):695-703.
132. Rolnik DL, Wright D, Poon LC, et al. Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia. *New England Journal of Medicine*. 2017;377(7):613-622.
133. Skeith L, Carrier M, Robinson SE, Alimam S, Rodger MA. Risk of venous thromboembolism in pregnant women with essential thrombocythemia: a systematic review and meta-analysis. *Blood*. 2017;129(8):934-939.
134. Maze D, Kazi S, Gupta V, et al. Association of Treatments for Myeloproliferative Neoplasms During Pregnancy With Birth Rates and Maternal Outcomes: A Systematic Review and Meta-analysis. *JAMA Netw Open*. 2019;2(10):e1912666.
135. Greer IA, Nelson-Piercy C. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. *Blood*. 2005;106(2):401-407.
136. Cnossen JS, Morris RK, ter Riet G, et al. Use of uterine artery Doppler ultrasonography to predict pre-eclampsia and intrauterine growth restriction: a systematic review and bivariable meta-analysis. *Cmaj*. 2008;178(6):701-711.
137. Ware RE, Marahatta A, Ware JL, McElhinney KL, Dong M, Vinks AA. Hydroxyurea Exposure in Lactation—a Pharmacokinetics Study (HELPS). *Blood*. 2018;132(Supplement 1):3677-3677.
138. Gangat N, Wolanskyj AP, Schwager SM, Mesa RA, Tefferi A. Estrogen-based hormone therapy and thrombosis risk in women with essential thrombocythemia. *Cancer*. 2006;106(11):2406-2411.
139. Newman JM, George J, North WT, et al. Hematologic Malignancies Are Associated With Adverse Perioperative Outcomes After Total Hip Arthroplasty. *The Journal of Arthroplasty*. 2017;32(8):2436-2443.e2431.
140. Ruggeri M, Rodeghiero F, Tosetto A, et al. Postsurgery outcomes in patients with polycythemia vera and essential thrombocythemia: a retrospective survey. *Blood*. 2008;111(2):666-671.

Appendix A: ELN criteria for response[21,75]

Type of response	Criteria
Complete remission	-Durable (at least 12 weeks) resolution of disease-related signs including palpable hepatosplenomegaly, large symptoms improvement AND -Durable peripheral blood count remission (platelet count ≤400 x 10^9/L, leukocyte count <10x10^9/L, absence of leukoerythroblastosis) AND -No signs of progressive disease, absence of any hemorrhagic or thrombotic events AND -Bone marrow histological remission defined as disappearance of megakaryocyte hyperplasia and absence of > grade 1 reticulin fibrosis
Partial remission	-Durable resolution of disease-related signs including palpable hepatosplenomegaly, large symptoms improvement AND -Durable peripheral blood count remission (platelet count ≤400 x 10^9/L, leukocyte count <10x10^9/L, absence of leukoerythroblastosis) AND - No signs of progressive disease, absence of any hemorrhagic or thrombotic events AND -No marrow histological remission defined as the persistence of megakaryocyte hyperplasia
No response	Any response that does not satisfy partial remission
Progressive disease	Transformation into PV, PET MF, MDS or s-AML

Development and Revision History

This guideline was reviewed and endorsed by the Alberta Provincial Hematology Tumour Team. Members include surgical oncologists, radiation oncologists, medical oncologists, hematologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Hematology Tumour Team, external participants identified by the Working Group Lead, and a methodologist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in 2021.

Maintenance

A formal review of the guideline will be conducted in 2022. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

AHS, Alberta Health Services; CCA, Cancer Care Alberta ET, Essential Thrombocythemia; HU, Hydroxyurea; IFN, Interferon; MDS, Myelodysplastic Syndromes; MK, Megakaryocytes; MPN, Myeloproliferative Neoplasm; PET MF, Post Essential THrombocythemia Myelofibrosis; PV, Polycythemia Vera; s-AML, Secondary Acute Myeloid Leukemia; SMF, Secondary Myelofibrosis; WHO, World Health Organization;

Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial Hematology Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

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Conflict of Interest Statements

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