A Review of Essential Thrombocythemia and Its Complications

Rodrick Babakhanlou, MD, MSc, Lucia Masarova, MD, and Srdan Verstovsek, MD, PhD

Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, Texas

Corresponding author:
Rodrick Babakhanlou, MD, MSc
Department of Leukemia
The University of Texas
MD Anderson Cancer Center
1515 Holcombe Blvd
Houston, TX 77030
Email: rbabakhanlou@mdanderson.org

Abstract: Essential thrombocythemia (ET) is a chronic myeloproliferative neoplasm characterized by an increased platelet count in the peripheral blood and excessive megakaryopoiesis in the bone marrow. In one-third of cases, the disease remains benign and does not lead to complications. In the remaining cases, however, ET may present with thromboembolic and hemorrhagic complications and transform into more aggressive myeloid neoplasms, with a negative effect on morbidity and mortality. Despite extensive research and a better understanding of the pathogenesis and etiology of the complications associated with ET, limited data are available on the management of complications and emergencies. This article highlights the complications and emergencies associated with ET and discusses treatment options and the controversies associated with management.

Keywords
Emergencies, essential thrombocythemia, essential thrombocytosis, ET, MPN, myeloproliferative neoplasms, thrombosis

Introduction

Myeloproliferative neoplasms (MPNs) are a group of myeloid disorders characterized by stem cell–derived clonal myeloproliferation.[1,2] Polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF) are the classic Philadelphia chromosome–negative chronic MPNs.[2,3] The hallmark of PV and ET is an elevated cell count in the peripheral blood, resulting in increased blood viscosity and a variety of symptoms.[4] It is not uncommon for MPN to remain undiagnosed until acute complications develop, prompting the patient to seek urgent or emergent medical care. Hence, physicians should be familiar with the variety of clinical presentations of MPNs. This article provides a review of ET, including the clinical presentation, potential complications, and associated emergencies, followed by recommendations for management. PV, PMF, and the medical therapy of ET are beyond the scope of this review and are not discussed.

Essential Thrombocythemia

Thrombocytosis, which is defined as a platelet count of more than

Table 1. Causes of Secondary Thrombocytosis

• Iron deficiency
• Paraneoplastic syndromes
• Chronic inflammatory conditions
• Asplenic states
• Chronic infections
• Post-traumatic states
• Acute or chronic blood loss

Sources: Adams BD et al. *Emerg Med Clin North Am*. 2009;27(3):459-476; Grieshammer M et al. *Dtsch Arztebl*. 2007;104:2341-2346; Tefferi A, Pardanani A. *N Engl J Med*. 2019;381(22):2135-2144.[4-6]

Table 2. World Health Organization Classification of Essential Thrombocythemia

Major criteria[a]
• Platelet count >450,000/mm^3
• Bone marrow biopsy showing proliferation, mainly of the megakaryocytic lineage, with increased numbers of enlarged, mature megakaryocytes that have hyperlobulated nuclei; no substantial increase or left shift in neutrophil granulopoiesis or erythropoiesis
• Absence of criteria for BCR-ABL1–positive chronic myeloid leukemia, polycythemia vera, primary myelofibrosis, or other myeloid neoplasms
• *JAK2* V617F, *CALR*, or *MPL* mutation
Minor criterion[a]
• Presence of a clonal marker or evidence of reactive thrombocytosis

[a]A diagnosis requires the presence of all 4 major criteria or the first 3 major criteria plus the 1 minor criterion.

CALR, calreticulin gene; *JAK2*, Janus kinase 2 gene; *MPL*, myeloproliferative leukemia virus oncogene.

Source: Tefferi A, Barbui T. *Am J Hematol*. 2015;90(2):162-173.[10]

450,000/mm^3, is frequently encountered in clinical practice. It can be categorized as primary or secondary thrombocytosis.[4-6] Although primary thrombocytosis is the result of myeloproliferative disorders, secondary thrombocytosis can be related to various pathologies, as outlined in Table 1.[4-6]

ET is a chronic myeloproliferative disorder with an annual incidence of 1.2 to 3.0 per 100,000 population.[6,7] Although it is a disease of the elderly, usually affecting patients between the ages of 55 and 65 years, it also develops in adults younger than 40 years in 20% of cases.[8] Women are more often affected than men. Compared with other MPNs, ET has a relatively good prognosis.[7] The hallmark of ET is an elevated thrombocyte count in the peripheral blood, accompanied by excessive megakaryopoiesis in the bone marrow.[9] The World Health Organization (WHO) classification of ET is outlined in Table 2.[1]

Pathogenesis

The discovery of a mutation in the Janus kinase 2 gene (*JAK2* V617F) in 2005, the myeloproliferative leukemia virus oncogene (*MPL*) in 2006, and the calreticulin gene (*CALR*) in 2013 has improved our understanding of the pathogenesis of ET and enabled diagnostic capabilities.[7,10-12] The *JAK2* V617F mutation is the most frequently observed, occurring in 50% to 60% of patients with ET.[7,10-11] Mutations involving *CALR* are observed in 20% to 25% of patients with ET, and mutations involving *MPL*, also known as the thrombopoietin receptor gene, occur in 5% of cases.[7,12] Mutations in *CALR* occur almost exclusively in patients with thrombocytosis.[12] Although 90% of patients with ET will have 1 of these 3 mutations, no mutations are detected in 10%. The term "triple negative" is used to describe cases of ET without any of these 3 mutations.[7] The development of thrombosis is a major concern in ET, and the incidence of thrombosis in this patient population has been reported to be 6.6% per year, contributing to an increase in morbidity and mortality.[13-14] Interestingly, the risk of thrombotic events is lower in individuals with ET than in those with PV. In ET, microcirculatory events are more common than large-vessel events.[2,3] The mechanism of occlusion is multifactorial and not entirely understood. It is believed to be associated with dysfunctional platelets and their activation, involvement of leukocytes and endothelial cells that results in an inflammatory reaction and endothelial damage, and subsequently an activation of the coagulation system that leads to a hypercoagulable state.[3,14-17] Leukocytes contribute to platelet activation in ET and are a stronger predictor of thrombosis than the platelet count.[14,18] Therefore, it is important to note that the risk of thrombosis is not correlated with the platelet count per se.

Although thrombosis may develop in patients with slightly elevated platelet counts, it may not develop in others with platelet counts higher than 1000 × 10^9/L; moreover, these patients may be at higher risk for bleeding due to acquired von Willebrand syndrome (VWS).[6,18,19] Although patients with ET may be asymptomatic, their prothrombotic and inflammatory state puts them at an increased risk for thrombotic events.[16] Mutations have been reported to affect the risk of thrombus formation. Patients with *JAK2*-mutated ET tend to be older, have higher white blood cell counts and hemoglobin levels, and have lower platelet counts. Thrombosis is more likely to

Table 3. Risk Factors for Thrombosis Related to Essential Thrombocythemia

• Leukocytosis (white cell count >11 × 10^9/L)
• Previous thromboembolic events
• Age >60 years
• Cardiovascular risk factors Smoking Hypercholesterolemia Hypertension Diabetes mellitus
• Hereditary thrombophilia Factor V Leiden Hyperhomocysteinemia Antiphospholipid antibodies Prothrombin mutation
• Molecular marker *JAK2* mutation

develop in these patients.[7,20-21] On the other hand, patients with *CALR* mutations tend to have higher platelet counts, lower hemoglobin levels, and lower leukocyte counts. Men are more commonly affected by these mutations, and the risk of thrombosis is lower in this subgroup.[22-23]

The etiology of ET-related thrombosis is multifactorial, and risk factors include cardiovascular risk factors, a previous history of thrombosis, age older than 60 years, and hereditary thrombophilia. A summary of the risk factors is provided in Table 3.[2,6,8,9,24-25]

Clinical Presentation

The clinical course of ET is variable, and patients can present with a myriad of symptoms and signs.[9] Although one-third of patients may be asymptomatic and have a benign course of disease, the remaining two-thirds experience symptoms that may take the form of complications or emergencies resulting from microvascular and macrovascular occlusions or major hemorrhage.[2,7,9,24] In many cases, it is the acute onset of complications and emergencies that leads to a diagnosis of this condition.

Vascular complications are a common manifestation of ET and can develop in both the venous and arterial systems, although the arterial system is 3 times more likely to be affected.[4,19,24,26-27] Microcirculatory disturbances due to small-vessel occlusions can occur in any part of the body and negatively affect quality of life. Involvement of the central nervous system may lead to headaches, dizziness, transient visual disturbances, or even a complete loss of vision if the ophthalmic vessels are occluded. Occlusions in vessels of the peripheral limbs can result in erythromelalgia, digital ischemia, or peripheral paresthesia.[3,24,26-27] Erythromelalgia can affect the skin of both the lower and upper limbs and presents as red, painful hot spots. If it is untreated, acrocyanosis, necrosis, or gangrene of the toes and fingers can occur.[28]

Large-vessel occlusions, on the other hand, can have devastating effects on morbidity and mortality. They can occur in several locations. If the coronary arteries are occluded, angina or a myocardial infarction may develop.[15] Acute coronary syndrome occurs in 9% of patients with ET.[29] Coronary artery thrombosis is the main cause of acute myocardial infarction in patients with ET. The left anterior descending artery has been reported to be the most frequently affected vessel in patients with ET.[30] Also noted in patients with ET is a high incidence of cardiac arrhythmias, mostly atrial fibrillation, which itself increases the risk of thrombosis.[31]

The occlusion of important vessels supplying the brain can result in transient ischemic attacks or an ischemic stroke.[3,6,11,12,15,22] Although ET is a rare cause of ischemic stroke and accounts for fewer than 1% of cases, it is important to recognize this condition to prevent recurrences.[32] In a retrospective study assessing 102 patients with ET, a stroke developed in 11 patients. All were on antiplatelet therapy or had received cytoreductive therapy, and all had cardiovascular risk factors.[33] In another retrospective study, 14 patients who had ET with ischemic strokes were assessed.[33] Of these, 12 had atherosclerotic risk factors. Both studies highlighted that cardiovascular risk factors augment the risk of stroke in patients with preexisting ET.

Forms of venous thrombosis, such as deep vein thrombosis (DVT) and pulmonary embolism (PE), are more common in PV than in ET.[3] In ET, the cumulative rate of venous thrombosis ranges from 1.9% to 3% per patient-year, and the prevalence of thrombosis at the time of diagnosis ranges between 10% and 29%.[14,25] Age older than 60 years, previous history of thrombosis, the presence of a *JAK2* mutation, immobilization, surgery, pregnancy, and the use of oral contraceptive pills have been reported to be risk factors for the development of venous thrombosis.[34] Venous thrombosis can affect various sites in the body.

Common manifestations of venous thrombosis in patients with ET are the same as those in the general population and include DVT of the lower extremities. DVT can also affect the pulmonary arteries, resulting in PE.[14] Clinically, a patient with DVT can present with a swollen, painful limb, and acute shortness of breath can develop in a patient with PE. Another feature of ET is the occurrence of venous thrombosis in unusual locations, such as the splanchnic system, including the hepatic, portal, splenic, and mesenteric venous systems.[7,14,25] A study assessing 187 patients with ET reported that 60% of all venous events occurred either in an abdominal vein or

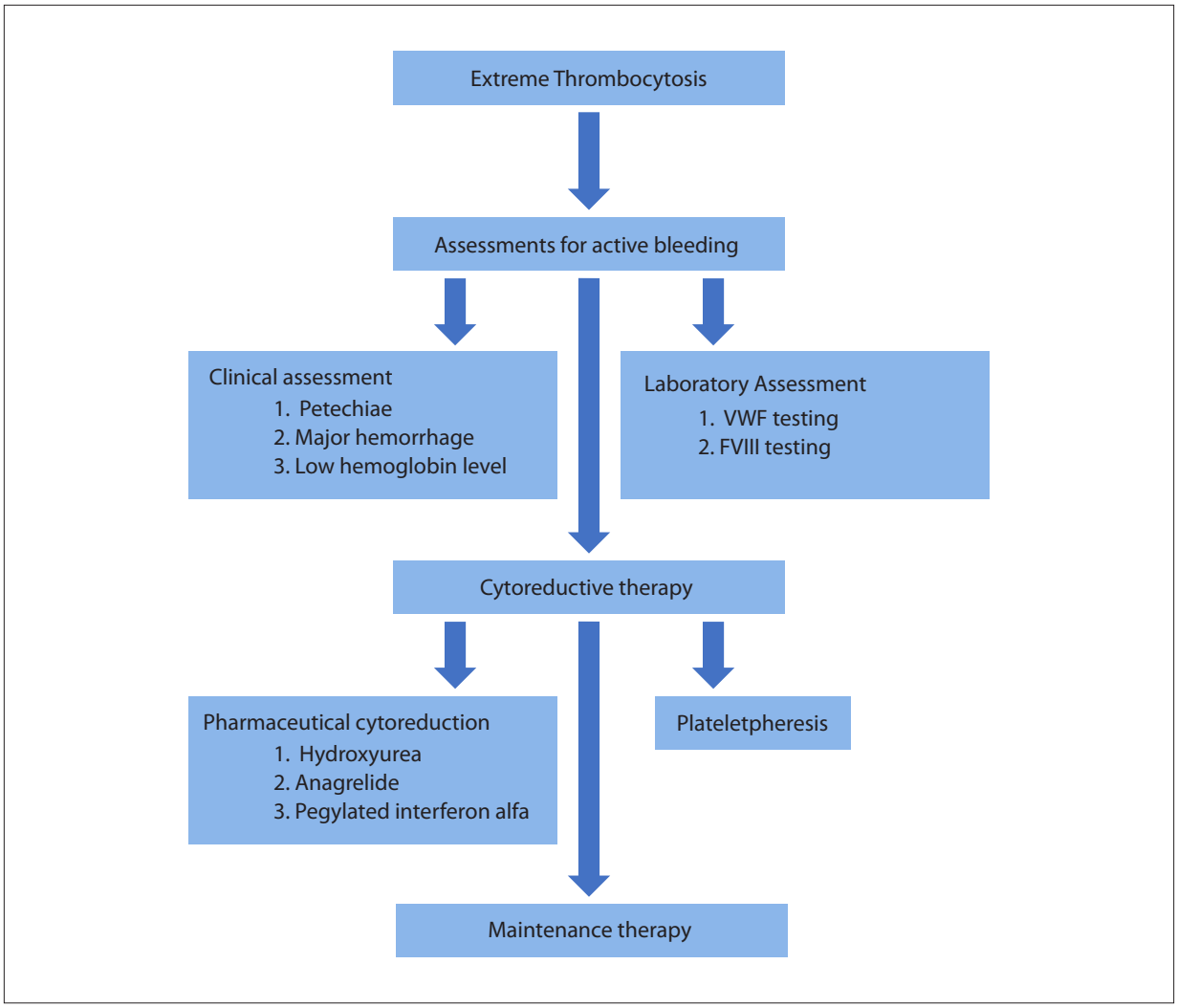

Figure. Approach to extreme thrombocytosis.

FVIII, factor VIII; VWF, von Willebrand factor.

in a cerebral sinus.[35] If the splanchnic venous system is involved, Budd-Chiari syndrome may develop and the patient may present with signs of portal hypertension (eg, ascites, esophageal varices, splenomegaly), which is associated with high rates of morbidity and mortality.[14,25,36] The presence of acute neurologic deficits, such as dizziness, visual problems, hemiparesis, headaches, and seizures, can indicate involvement of a cerebral venous sinus and should alert the assessing physician to involvement of the central nervous system.[34,37]

Hemorrhagic events are less common than thrombotic events in ET.[25] Bleeding in ET is typically due to acquired VWS and a selective loss of von Willebrand factor (VWF) multimers.[6,18,19] Acquired VWS should be suspected in patients who have ET with severe thrombocytosis and a platelet count higher than 1000 × 10^9/L, and who present with episodes of bleeding or hemorrhage.[37] VWF is a large multimeric glycoprotein with an important role in hemostasis, promoting the initial tethering and adhesion of platelets to sites of vascular injury and supporting platelet aggregation.[20] Acquired VWS in ET is believed to be due to increased binding of VWF to platelets and leukocytes, resulting in an increased consumption (and subsequently a depletion) of large multimers.[19] VWF function declines with increasing platelet counts.[22] Clinically, hemorrhagic events can range from minor bleeds to fatal major hemorrhage.[2] Minor bleeds can present in the form of petechiae, gingival bleeding, or other mucosal bleeding.[4] Although major hemorrhage is rare, it can be fatal.[2,4,6,7,38] The anatomic sites most commonly affected are the gastrointestinal tract and the urogenital tract, but intracranial bleeding has been

reported as well.[4,6-7,20,38] Patients at risk for major hemorrhage include those who have significant thrombocytosis, acquired VWS, or previous bleeding events and who concomitantly use aspirin.[15,38,39]

Another concerning complication of ET is transformation to acute myeloid leukemia (AML), myelodysplastic syndrome, or myelofibrosis (MF).[40] Leukemic transformation in ET is rare and has been estimated to occur in 0.7% of patients at 10 years and in 2.1% of patients at 15 years.[7] Risk factors for leukemic transformation have been reported to be anemia, increased age, platelet count higher than 1000 × 10^9/L, leukocytosis, and previous thrombosis.[7,40-42] MF, a more common complication of ET, is characterized by the development of anemia, progressive splenomegaly, and increasing marrow fibrosis.[21,43] The risk of the development of post-ET MF increases with time and is cumulative.[44] Risk factors for transformation to MF have been reported to be age, anemia, features of hypercellularity, and increased reticulin in bone marrow.[40-42,45,46] In some patients, PV may develop in the course of *JAK2*-mutated ET, characterized by a gradual increase in the hematocrit levels and symptoms typical of PV, such as aquagenic pruritus, vasomotor disturbances, and constitutional symptoms.[45]

Further frequently reported complications are constitutional symptoms that may occur in response to microvascular disorders affecting the central nervous system. The most common complaints include fatigue, numbness, vertigo, night sweats, headaches, bone pain, and abdominal pain.[47]

Diagnosis

The diagnosis of ET is based on the WHO 2016 criteria, displayed in Table 2. For a diagnosis of ET, either all 4 major criteria or the first 3 major criteria plus the 1 minor criterion must be fulfilled.[1,48] The initial approach to a patient who has ET and is presenting with complications or an emergency should start with a comprehensive medical history and a thorough clinical examination. The history should cover cardiovascular risk factors such as hypertension, diabetes, smoking, and hyperlipidemia.[49] A previous history of thromboembolic events and episodes of minor and major bleeding should be investigated.[49] In patients with ET, the next step should be a laboratory workup (repeated complete blood cell count; metabolic panel; measurement of inflammatory markers; iron studies; measurement of coagulation parameters, VWF, serum erythropoietin levels, and ristocetin cofactor activity), especially when the platelet count is higher than 1000 × 10^9/L.[5,49,50] Patients who have chest pain should be evaluated for a myocardial injury with an urgent electrocardiogram and measurement of cardiac enzymes. Imaging modalities, including computed tomography, are highly recommended for patients with neurologic deficits and shortness of breath to rule out central nervous system pathologies or PE. For patients with hepatomegaly and splenomegaly, abdominal ultrasonography or computed tomography can evaluate the size of the abdominal organs.[49] The differential diagnosis of ET includes secondary and reactive thrombocytosis, prefibrotic MDF, PV, and PMF, for which a bone marrow biopsy is helpful. Although the detection of *JAK2* V617F, *CALR*, or *MPL* mutations confirms the presence of MPN, their absence does not rule it out because 20% of ET cases can be triple-negative.[51] A fraction of patients with masked PV may present with increased thrombocyte counts, mimicking ET.[52] Therefore, a bone marrow examination is often necessary to make an accurate morphologic diagnosis of ET and distinguish it from prefibrotic PMF and PV.[51]

Table 4. The International Prognostic Score for Essential Thrombocytopenia (IPSET)

Clinical characteristics	Points
• Age >60 years	+1
• Prior thrombotic event	+2
• Cardiovascular risk factors (diabetes mellitus, hypertension, smoking)	+1
• *JAK2* mutation	+2
Risk category	**Score**
• Low	0-1
• Intermediate	2
• High	>3

JAK2, Janus kinase 2 gene.
Source: Barbui T et al. *Blood*. 2012;120(26):5128-5133.[55]

Therapy

ET is an indolent disease, and the life expectancy of patients with ET does not differ significantly from that of the general population.[7,53] Because the 15-year survival has been reported to be 80% and the 10-year risk of transformation to AML or MF is less than 1%, treating every patient with ET is not recommended.[1] Current treatment in ET aims to prevent thrombotic complications, which can occur in 10% to 20% of patients, and to prevent episodes of bleeding (Figure).[54] Hence, emphasis has been placed on identifying those patients who will benefit from treatment.[8] The International Prognostic Score for Essential Thrombocytopenia (IPSET) was developed to predict the risk of thrombosis, as shown in Table 4[47,54-58]; this scoring system was revised and updated in 2015.[57] The revision from 2015 (Revised-IPSET) currently recognizes 4 risk levels in ET: very low, low, intermediate, and high, as outlined in Table 5.[57]

Table 5. The Revised International Prognostic Score for Essential Thrombocytopenia (Revised IPSET)

Very low risk	No history of thrombosis, age <60 years, *JAK2/MPL* unmutated
Low risk	No history of thrombosis, age <60 years, *JAK2/MPL* mutated
Intermediate risk	No history of thrombosis, age >60 years, *JAK2/MPL* unmutated
High risk	History of thrombosis *or* Age >60 years, *JAK2/MPL* mutated

JAK2, Janus kinase 2 gene; *MPL*, myeloproliferative leukemia virus oncogene.
Source: Barbui T et al. *Blood Cancer* J. 2015;5(11):e369.[57]

Although treatment has focused on preventing complications to reduce morbidity and mortality, few data are available on the management of complications and emergencies and the risks vs the benefits of active therapy for ET.[59]

Management of Extreme Thrombocytosis

Extreme thrombocytosis has not been clearly defined, and platelet counts higher than 1000×10^9/L are used arbitrarily to define it.[60,61] Approximately 22% of patients who have ET present with extreme thrombocytosis, which is associated with an increased risk of bleeding.[60,61] Currently, no consensus has been reached regarding the management of patients who have ET with extreme thrombocytosis.

Management of Bleeding. The incidence of bleeding has been inconsistent in the literature. It has been reported that hemorrhage affects approximately 5% to 10% of patients with ET.[38,45] Although several risk factors for bleeding have been identified, they have not been solid enough to warrant treatment recommendations.[62] The paradoxical increase in the risk of hemorrhage associated with extreme thrombocytosis is linked to depletion of VWF. The management of major hemorrhage in patients with ET has not been evaluated in prospective trials, and few data are available to guide the physician. Therefore, patients who have ET with extreme thrombocytosis present a clinical dilemma. For patients with active bleeding, the primary approach involves hemodynamic stabilization. Antiplatelet medication and blood-thinning products should be stopped immediately. The choice and intensity of cytoreduction depend on the severity of the hemorrhagic event.[62] When time is not critical, pharmacologic cytoreduction may be a suitable option and can be achieved with hydroxyurea, anagrelide, or pegylated interferon alfa.[63,64] However, in patients with severe acute bleeding, time is critical, and immediate cytoreduction may be needed to prevent further hemorrhage. Measures include the use of desmopressin and tranexamic acid, or even the transfusion of VWF-containing concentrates in cases of life-threatening bleeding.[19,63] Plateletpheresis may be the only option for rapid platelet count reduction; it acts by reducing levels of prothrombotic factor VIII, fibrinogen, antithrombin, protein C, and protein S.[63,65] Because plateletpheresis offers only a short-term solution, the simultaneous administration of cytoreductive agents may be indicated.[63] Although plateletpheresis is an effective method to reduce platelet counts, complications are observed in 4% to 5% of cases. The most common complications include infections, hypocalcemia, mechanical hemolysis, and allergic reactions.[65] Life-threatening complications such as cardiac arrhythmias and fatal hemorrhages are rare, but patients should be monitored for these.[65] In patients with nonactive bleeding, the recommendations of the European LeukemiaNet and the British Committee for Standards in Haematology are similar.[50] Both recommend cytoreductive therapy for patients with platelet counts higher than 1500×10^9/L to reduce the risk of vascular events and bleeding.[50,62] Patients with platelet counts higher than 1000×10^9/L should avoid aspirin or antiplatelet agents to mitigate the risk of further bleeding.[62] Although the benefit of cytoreduction to prevent thrombosis in low-risk ET is debatable, extreme thrombocytosis in the entire risk spectrum of ET is a medical emergency and must be considered of the utmost clinical importance.[61] Other therapies that have been used in the past for refractory extreme thrombocytosis include chemotherapeutic agents such as busulfan.[66] However, their use is best restricted to those extreme situations in which the previously listed modalities fail to attain a significant reduction in platelet counts.

Management of Venous Thrombosis. Although most of the literature focuses on the prevention of arterial and venous thrombosis, little evidence is available on the acute management of venous thrombosis in ET.[14,50-52] The therapeutic approach to the management of venous thrombosis in patients with ET is consistent with recommendations for the management of venous thrombosis in patients without MPN.[25,67] In the acute setting, low-molecular-weight heparin is preferred over unfractionated heparin, mainly because of concerns regarding heparin-induced thrombocytopenia and a negative effect on patients with impaired kidney function.[25,67,68] Direct oral anticoagulants are potential alternatives and have been reported to be safe.[25,69-71]

Because of the paucity of data on the duration of treatment in patients with ET, recommendations have been extrapolated from the general population without MPN. The risk of recurrent thrombosis in patients with PV or ET has been reported to be approximately 7.6%.[72]

As a result, 3 to 6 months of either direct oral anticoagulants or vitamin K antagonists is recommended, overlapping with acute therapy, with a targeted international normalized ratio of 2.0 to 3.0. However, individual risk for complications of bleeding and recurrence of thrombotic events must be evaluated regularly.[25,67] Data on the management of splanchnic venous thrombosis (SVT) in patients with ET are scarce. The *JAK2* V617F mutation is a risk factor for the development of SVT.[35]

The complexity of management was demonstrated in an audit specifically regarding the strategy of anticoagulation, and a consensus regarding the treatment of SVT in MPN is lacking among hematologists.[35,71] Combination therapy with both anticoagulants and antiplatelet agents is considered to be associated with a high risk for bleeding.[35] Although long-term anticoagulation treatment is recommended in SVT because of the high risk of recurrence, an individualized risk assessment based on the location and extent of the thrombosis, the presence of varices and the risk of variceal hemorrhage, and the patient's prognosis is recommended.[67,72] Currently, no prospective trials have been conducted, and more data are needed to guide the management of SVT in patients with ET.

Management of Arterial Occlusions. ET is known to cause both microcirculatory and macrocirculatory occlusions. Occlusions of small arteries are more common.[13] Arterial occlusions can affect cerebral, coronary, and peripheral arteries.[13] These situations are emergencies and require immediate treatment.

The management of an acute myocardial infarction includes primary angioplasty, aspiration thrombectomy, and stent insertion.[29,30,72] Because the risk of stent thrombosis is elevated in patients with ET, drug-eluting stents are the preferred option.[29,72] Platelet function is altered in patients with ET, and the effects of aspirin may not be sufficient to prevent further thrombotic incidents because resistance to aspirin has been reported. Literature recommends double antiplatelet therapy: aspirin in combination with ticlopidine or clopidogrel.[29] However, double antiplatelet therapy also increases the risk of bleeding. Therefore, careful patient selection is needed to ensure that the benefits outweigh the risks.[73] The role of antithrombotic therapy needs to be further evaluated in this patient population.[29,30,72] In patients with high numbers of thrombocytes and an increased risk of VWS, cytoreduction with hydroxyurea is the preferred method of preventing further thrombotic incidents.[29,72,73] Although anagrelide is a possible alternative, it is less commonly used. Anagrelide is a phosphodiesterase 3 inhibitor with vasodilator and positive inotropic and chronotropic effects, which are less desired in the post–acute coronary syndrome setting.[29] The therapeutic approach should always be coordinated with the cardiologist. Atrial arrhythmias are commonly observed in elderly patients who have ET with coexisting cardiovascular risk factors, and they pose a high risk for thrombosis. No data address the management of cardiac arrhythmias in patients with ET. Recommendations for the management of cardiac arrhythmias in patients with ET were extrapolated from the ECLAP study of patients with PV, in whom low-dose aspirin was shown to reduce the risk of stroke, myocardial infarction, and death from cardiovascular factors.[31,74] The treatment should be chosen in collaboration with the cardiologist and based on the CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years [doubled], diabetes, stroke [doubled], vascular disease, age 65-74 years, and sex category [female]) score, but the risks vs the benefits of anticoagulation in the elderly population should also be considered.

The management of an ischemic stroke in patients with ET follows the same principles used for the general population, including general management of the acute stroke and secondary prevention. Additionally, cytoreduction may be indicated for patients with high-risk ET.[75] As long as the patient is within the revascularization time window, thrombolysis or thrombectomy should be considered.[75]

Currently recommended antiplatelet therapy after an ischemic stroke in patients who have ET with high-risk features, including age older than 60 years, *JAK2* mutation, and cardiovascular risk factors, includes twice-daily low-dose aspirin initiated within 24 to 48 hours after the onset of the stroke and continued for 3 weeks to 3 months.[75] Before antiplatelet therapy is started, VWS should be excluded. For the management of stroke due to cerebral venous thrombosis, the recommendations include low-dose aspirin once daily in combination with anticoagulation. However, the management decision is not straightforward because of the increased risk of bleeding, and risks vs benefits should always be considered.[75]

Because the risk of arterial thrombosis is increased in patients with metabolic syndrome, it is mandatory to address cardiovascular risk factors, such as hypertension, hyperlipidemia, and diabetes mellitus, to reduce the risk of further thromboembolic incidents.[49]

Conclusion

The clinical course of ET is variable. Complications and emergencies can present in the form of vascular occlusions or hemorrhage. Despite extensive research and a better understanding of the pathogenesis and etiology of the complications associated with ET, limited data are available on the management of the various complications and emergencies. Most recommendations have been extrapolated from studies of patients with PV or the general

population without MPNs. More research is needed to address the management of complications and emergencies in patients with ET, together with a consideration of the risks vs benefits of treatment to avoid harm.

Disclosures

Drs Babakhanlou, Masarova, and Verstovsek report no conflicts of interest.

References

1. Tefferi A, Barbui T. Polycythemia vera and essential thrombocythemia: 2015 update on diagnosis, risk-stratification and management. *Am J Hematol*. 2015;90(2):162-173.
2. Greenfield G, McMullin MF. A spotlight on the management of complications associated with myeloproliferative neoplasms: a clinician's perspective. *Expert Rev Hematol*. 2018;11(1):25-35.
3. Vannucchi AM. Insights into the pathogenesis and management of thrombosis in polycythemia vera and essential thrombocythemia. *Intern Emerg Med*. 2010;5(3):177-184.
4. Adams BD, Baker R, Lopez JA, Spencer S. Myeloproliferative disorders and the hyperviscosity syndrome. *Emerg Med Clin North Am*. 2009;27(3):459-476.
5. Grieshammer M, Lengfelder E, Doehner K, Kvasnicka HM, Thiele J, Heimpel H. Essentielle thrombozythaemie. *Dtsch Arztebl*. 2007;104:2341-2346.
6. Tefferi A, Pardanani A. Essential thrombocythemia. *N Engl J Med*. 2019;381(22):2135-2144.
7. Chuzi S, Stein BL. Essential thrombocythemia: a review of the clinical features, diagnostic challenges, and treatment modalities in the era of molecular discovery. *Leuk Lymphoma*. 2017;58(12):2786-2798.
8. Barbui T, Thiele J, Carobbio A, et al. Disease characteristics and clinical outcome in young adults with essential thrombocythemia versus early/prefibrotic primary myelofibrosis. *Blood*. 2012;120(3):569-571.
9. Griesshammer M. Risk factors for thrombosis and bleeding and their influence on therapeutic decisions in patients with essential thrombocythemia. *Semin Thromb Hemost*. 2006;32(4 Pt 2):372-380.
10. Baxter EJ, Scott LM, Campbell PJ, et al; Cancer Genome Project. Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders. *Lancet*. 2005;365(9464):1054-1061.
11. Levine RL, Wadleigh M, Cools J, et al. Activating mutation in the tyrosine kinase JAK2 in polycythemia vera, essential thrombocythemia, and myeloid metaplasia with myelofibrosis. *Cancer Cell*. 2005;7(4):387-397.
12. Klampfl T, Gisslinger H, Harutyunyan AS, et al. Somatic mutations of calreticulin in myeloproliferative neoplasms. *N Engl J Med*. 2013;369(25):2379-2390.
13. Jung SM, Jun H. Recurrent thrombosis of splanchnic and lower extremity arteries with essential thrombocythemia [published online September 27, 2019]. *SAGE Open Med Case Rep*. 7:X19880079.
14. Reikvam H, Tiu RV. Venous thromboembolism in patients with essential thrombocythemia and polycythemia vera. *Leukemia*. 2012;26(4):563-571.
15. Petrides PE, Siegel F. Thrombotic complications in essential thrombocythemia (ET): clinical facts and biochemical riddles. *Blood Cells Mol Dis*. 2006;36(3):379-384.
16. Vianello F, Cella G, Osto E, et al. Coronary microvascular dysfunction due to essential thrombocythemia and policythemia vera: the missing piece in the puzzle of their increased cardiovascular risk? *Am J Hematol*. 2015;90(2):109-113.
17. 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.
18. Carobbio A, Finazzi G, Antonioli E, et al. Thrombocytosis and leukocytosis interaction in vascular complications of essential thrombocythemia. *Blood*. 2008;112(8):3135-3137.
19. 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.
20. Wolanskyj AP, Lasho TL, Schwager SM, et al. JAK2 mutation in essential thrombocythaemia: clinical associations and long-term prognostic relevance. *Br J Haematol*. 2005;131(2):208-213.
21. Cheung B, Radia D, Pantelidis P, Yadegarfar G, Harrison C. The presence of the JAK2 V617F mutation is associated with a higher haemoglobin and increased risk of thrombosis in essential thrombocythaemia. *Br J Haematol*. 2006;132(2):244-245.
22. Rotunno G, Mannarelli C, Guglielmelli P, et al; Associazione Italiana per la Ricerca sul Cancro Gruppo Italiano Malattie Mieloproliferative Investigators. Impact of calreticulin mutations on clinical and hematological phenotype and outcome in essential thrombocythemia. *Blood*. 2014;123(10):1552-1555.
23. Rumi E, Pietra D, Ferretti V, et al; Associazione Italiana per la Ricerca sul Cancro Gruppo Italiano Malattie Mieloproliferative Investigators. JAK2 or CALR mutation status defines subtypes of essential thrombocythemia with substantially different clinical course and outcomes. *Blood*. 2014;123(10):1544-1551.
24. Besses C, Cervantes F, Pereira A, et al. Major vascular complications in essential thrombocythemia: a study of the predictive factors in a series of 148 patients. *Leukemia*. 1999;13(2):150-154.
25. Kreher S, Ochsenreither S, Trappe RU, et al; Haemostasis Working Party of the German Society of Hematology and Oncology; Austrian Society of Hematology and Oncology; Society of Thrombosis and Haemostasis Research. 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.
26. Meier B, Burton JH. Myeloproliferative Disorders. *Hematol Oncol Clin North Am*. 2017;31(6):1029-1044.
27. Elliott MA, Tefferi A. Thrombosis and haemorrhage in polycythaemia vera and essential thrombocythaemia. *Br J Haematol*. 2005;128(3):275-290.
28. Michiels JJ, Berneman Z, Schroyens W, et al. Platelet-mediated erythromelalgic, cerebral, ocular and coronary microvascular ischemic and thrombotic manifestations in patients with essential thrombocythemia and polycythemia vera: a distinct aspirin-responsive and coumadin-resistant arterial thrombophilia. *Platelets*. 2006;17(8):528-544.
29. Tortorella G, Calzolari M, Tieghi A, Muià N, Piccin A, Gugliotta L. Acute coronary syndrome (ACS) in patients with essential thrombocytemia (ET). What is the best treatment? *Int J Cardiol*. 2016;203:225-227.
30. Gao W, Shen W, Luo X, Shi H, Jiang X, Pan J. ST-segment elevation myocardial infarction in patient with essential thrombocythemia without associated risk. *Int J Cardiol*. 2015;180:223-225.
31. Mahé K, Delluc A, Chauveau A, et al. Incidence and impact of atrial arrhythmias on thrombotic events in MPNs. *Ann Hematol*. 2018;97(1):101-107.
32. Pósfai É, Marton I, Szőke A, et al. Stroke in essential thrombocythemia. *J Neurol Sci*. 2014;336(1-2):260-262.
33. Richard S, Perrin J, Baillot PA, Lacour JC, Ducrocq X. Ischaemic stroke and essential thrombocythemia: a series of 14 cases. *Eur J Neurol*. 2011;18(7):995-998.
34. Gangat N, Singh A, Szuber N, et al. Site-specific venous thrombosis in essential thrombocythemia: impact on subsequent vascular events and survival. *J Thromb Haemost*. 2022;20(10):2439-2443.
35. Bazzan M, Tamponi G, Schinco P, et al. Thrombosis-free survival and life expectancy in 187 consecutive patients with essential thrombocythemia. *Ann Hematol*. 1999;78(12):539-543.
36. Greenfield G, McMullin MF. Splanchnic venous thrombosis in *JAK2* V617F mutation positive myeloproliferative neoplasms - long term follow-up of a regional case series. *Thromb J*. 2018;16:33.
37. Chen WB, Wang XL. Cerebral venous sinus thrombosis as the first manifestation of JAK2 V617F-positive essential thrombocythemia. *Chin Med J (Engl)*. 2018;131(6):748-750.
38. 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.
39. Papadakis E, Hoffman R, Brenner B. Thrombohemorrhagic complications of myeloproliferative disorders. *Blood Rev*. 2010;24(6):227-232.
40. Chim CS, Kwong YL, Lie AK, et al. Long-term outcome of 231 patients with essential thrombocythemia: prognostic factors for thrombosis, bleeding, myelofibrosis, and leukemia. *Arch Intern Med*. 2005;165(22):2651-2658.
41. Gangat N, Wolanskyj AP, McClure RF, et al. Risk stratification for survival and leukemic transformation in essential thrombocythemia: a single institutional study of 605 patients. *Leukemia*. 2007;21(2):270-276.
42. Abdulkarim K, Ridell B, Johansson P, Kutti J, Safai-Kutti S, Andréasson B. The impact of peripheral blood values and bone marrow findings on prognosis for patients with essential thrombocythemia and polycythemia vera. *Eur J Haematol*.

2011;86(2):148-155.
43. Barosi G, Mesa RA, Thiele J, et al; International Working Group for Myelofibrosis Research and Treatment (IWG-MRT). 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*. 2008;22(2):437-438.
44. 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 Clin Proc*. 2006;81(2):159-166.
45. Alvarez-Larrán A, Cervantes F, Bellosillo B, et al. Essential thrombocythemia in young individuals: frequency and risk factors for vascular events and evolution to myelofibrosis in 126 patients. *Leukemia*. 2007;21(6):1218-1223.
46. Buxhofer-Ausch V, Heibl S, Sliwa T, et al. Austrian recommendations for the management of essential thrombocythemia. *Wien Klin Wochenschr*. 2021;133(1-2):52-61.
47. 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.
48. 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.
49. Harrison C, Barbui T. Aspirin in low-risk essential thrombocythemia, not so simple after all? *Leuk Res*. 2011;35(3):286-289.
50. Harrison CN, Bareford D, Butt N, et al; British Committee for Standards in Haematology. Guideline for investigation and management of adults and children presenting with a thrombocytosis. *Br J Haematol*. 2010;149(3):352-375.
51. Tefferi A, Barbui T. Polycythemia vera and essential thrombocythemia: 2021 update on diagnosis, risk-stratification and management. *Am J Hematol*. 2020;95(12):1599-1613.
52. Barbui T, Thiele J, Gisslinger H, et al. Masked polycythemia vera (mPV): results of an international study. *Am J Hematol*. 2014;89(1):52-54.
53. Passamonti F, Rumi E, Pungolino E, et al. Life expectancy and prognostic factors for survival in patients with polycythemia vera and essential thrombocythemia. *Am J Med*. 2004;117(10):755-761.
54. Tefferi A, Vannucchi AM, Barbui T. Essential thrombocythemia treatment algorithm 2018. *Blood Cancer J*. 2018;8(1):2.
55. 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.
56. Rumi E, Cazzola M. How I treat essential thrombocythemia. *Blood*. 2016;128(20):2403-2414.
57. 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*. 2015;5(11):e369.
58. Falchi L, Kantarjian HM, Verstovsek S. Assessing the thrombotic risk of patients with essential thrombocythemia in the genomic era. *Leukemia*. 2017;31(9):1845-1854.
59. Chu DK, Hillis CM, Leong DP, Anand SS, Siegal DM. Benefits and risk of antithrombotic therapy in essential thrombocythemia: a systematic review. *Ann Intern Med*. 2017;167(3):170-180.
60. Squizzato A, Romualdi E, Passamonti F, Middeldorp S. Antiplatelet drugs for polycythaemia vera and essential thrombocythaemia. *Cochrane Database Syst Rev*. 2013;30(4):CD006503.
61. Tefferi A, Szuber N, Pardanani A, et al. Extreme thrombocytosis in low-risk essential thrombocythemia: retrospective review of vascular events and treatment strategies. *Am J Hematol*. 2021;96(6):E182-E184.
62. Koren-Michowitz M, Lavi N, Ellis MH, Vannucchi AM, Mesa R, Harrison CN. Management of extreme thrombocytosis in myeloproliferative neoplasms: an international physician survey. *Ann Hematol*. 2017;96(1):87-92.
63. Falchi L, Bose P, Newberry KJ, Verstovsek S. Approach to patients with essential thrombocythaemia and very high platelet counts: what is the evidence for treatment? *Br J Haematol*. 2017;176(3):352-364.
64. Boddu P, Falchi L, Hosing C, Newberry K, Bose P, Verstovsek S. The role of thrombocytapheresis in the contemporary management of hyperthrombocytosis in myeloproliferative neoplasms: A case-based review. *Leuk Res*. 2017;58:14-22.
65. Elhassan AM, Alsaud A, Yassin MA, et al. Thrombocytapheresis in patient with essential thrombocythemia: a case report. *Case Rep Oncol*. 2020;13(2):675-679.
66. Yilmaz M, Dikmen T, Sonmez M, et al. Change of coagulation parameters after double plateletpheresis. *Transfus Apheresis Sci*. 2007;37(2):161-163.
67. Huenerbein K, Sadjadian P, Becker T, et al. Direct oral anticoagulants (DOAC) for prevention of recurrent arterial or venous thromboembolic events (ATE/VTE) in myeloproliferative neoplasms. *Ann Hematol*. 2021;100(8):2015-2022.
68. Castelli R, Gallipoli P, Schiavon R, Teatini T, Deliliers GL, Bergamaschini L. High prevalence of heparin induced thrombocytopenia with thrombosis among patients with essential thrombocytemia carrying V617F mutation. *J Thromb Thrombolysis*. 2018;45(1):106-113.
69. De Stefano V, Za T, Rossi E, et al; GIMEMA CMD-Working Party. Recurrent thrombosis in patients with polycythemia vera and essential thrombocythemia: incidence, risk factors, and effect of treatments. *Haematologica*. 2008;93(3):372-380.
70. Kreuziger LB, Ageno W, Lee A. Management of incidental splanchnic vein thrombosis in cancer patients. *Hematology (Am Soc Hematol Educ Program)*. 2014;2014(1):318-320.
71. Kikuchi S, Hibi K, Tamura K, Kimura K. The assessment of the platelet function during the acute phase of ST-segment elevation myocardial infarction in essential thrombocythemia. *Intern Med*. 2021;60(16):2639-2643.
72. Ellis MH, Lavi N, Vannucchi A, Harrison C. Treatment of thromboembolic events coincident with the diagnosis of myeloproliferative neoplasms: a physician survey. *Thromb Res*. 2014;134(2):251-254.
73. Kumagai N, Mitsutake R, Miura S, et al. Acute coronary syndrome associated with essential thrombocythemia. *J Cardiol*. 2009;54(3):485-489.
74. Landolfi R, Marchioli R, Kutti J, et al. European collaboration on low-dose aspirin in polycythemia vera. *N Engl J Med*. 2004;350:114-124.
75. Das S, Deb A, Pal T. Antithrombotic management in ischemic stroke with essential thrombocythemia: current evidence and dilemmas. *Med Princ Pract*. 2021;30(5):412-421.