CME CREDIT

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Thrombocytosis: When is an incidental finding serious?

■ ABSTRACT

For most patients, elevated platelet counts are benign and require no treatment, but for some, severe complications or death may ensue. This article discusses how to classify thrombocytosis and identify which patients require treatment, describes the characteristic complications that may arise, and provides an algorithm for management.

■ KEY POINTS

Most elevated platelet counts (normal range 150–450 × 10^9/L, varying somewhat by laboratory) that are found incidentally are due to a transient process. A repeat platelet count should be obtained a few weeks later before any further evaluation.

In most cases, high platelet counts are a reaction to a process such as inflammation, infection, or less likely, malignancy. Evaluation should be targeted on the basis of the presentation.

Thrombocytosis can also be caused by chronic myeloproliferative diseases (eg, essential thrombocythemia and polycythemia vera), which are clonal disorders of hematopoietic stem cells. Characteristic complications are bleeding and thrombotic events.

Essential thrombocythemia and polycythemia vera generally have an indolent course and do not shorten life, and only selected patients need treatment.

WHAT DO YOU DO if you order a complete blood count for some unrelated reason and, unexpectedly, the platelet count is high?

Most of the time, thrombocytosis (increased numbers of platelets in the blood) that is found incidentally is harmless and resolves spontaneously, being due to a transient underlying condition that may not be clinically obvious. But what if the count does not come down with time? Is the patient at risk of thrombosis or paradoxical bleeding? Platelet-lowering therapy is available but fraught with problems. And what if the thrombocytosis is due to undiagnosed cancer?

This article describes the common causes of thrombocytosis, how to distinguish between them, and the major complications that tend to develop. An algorithm to guide management is provided. Recent advances regarding the molecular basis of essential thrombocythemia and other myeloproliferative disorders are also discussed.

■ THREE PATHS TO THROMBOCYTOSIS

Thrombocytosis can be categorized as reactive (secondary), familial, or clonal. To understand these categories, we should first review how platelet production is regulated.

Thrombopoietin drives platelet production

Thrombopoietin is the key hormone that regulates the differentiation and proliferation of megakaryocytes—the precursors of platelets—in bone marrow. The cytokines interleukin-6 and interleukin-11 play an accessory role. Thrombopoietin is primarily synthesized in the liver, but some is made in the kidney as well.

Under normal circumstances, thrombopoietin helps keep platelets in the normal range. In the circulation, thrombopoietin binds to c-Mpl receptors on platelets. If platelets are few, the high concentration of free thrombopoietin that makes its way into the bone marrow binds to megakaryocytes and stimulates their proliferation, increasing platelet production. On the other hand, when the platelet count is elevated, increased binding of thrombopoietin leaves less free circulating thrombopoietin available to stimulate megakaryocytes.

Reactive thrombocytosis

In reactive thrombocytosis, thrombopoietin is increased because of an underlying condition that either directly produces thrombopoietin or stimulates its production via acute-phase reactants such as interleukin-6. The thrombopoietin-driven reactive thrombocytosis may be either transient or sustained, depending on the underlying condition.

Transient reactive thrombocytosis can occur after acute blood loss, infection, or inflammation. It can also occur after recovery from a transient thrombocytopenic state, such as myelosuppression from chemotherapy or after treatment of thrombocytopenia in a severe megaloblastic state. It can also be an acute response to exercise, a phenomenon believed to be mediated by catecholamine surges that trigger release of platelets from the spleen.

Most cases of thrombocytosis that are found incidentally are transient. Ruggeri et al[1] obtained platelet counts in 10,000 apparently healthy adults in an Italian city and found that 100 (1%) had a count of more than 400 × 10⁹/L. Of these, one already had been diagnosed with essential thrombocythemia. The other 99 had a follow-up platelet count a few weeks later, and of those, only 8 still had an elevated count, of whom 3 were found at that time to have essential thrombocythemia. The remaining 5 people were followed 5 years later: 1 additional patient was found to have essential thrombocythemia.

Sustained reactive thrombocytosis can be due to iron deficiency, chronic hemolytic anemia, asplenia, chronic inflammatory or infectious diseases, certain medications

(rarely), or cancer.

By far, most thrombocytosis is reactive. Griesshammer et al[2] reviewed the medical records of 732 patients with a platelet count of at least 500 × 10⁹/L and found that 643 (88%) had reactive thrombocytosis, with the most frequent causes being tissue damage (42%), infection (24%), malignancy (13%), and chronic inflammation (10%).

Traditional thinking held that an extremely high platelet count is likely to reflect clonal thrombocytosis, but in fact, it is not a good indicator. Buss et al[3] evaluated 280 patients with a platelet count of at least 1,000 × 10⁹/L and found that 231 (82%) had reactive thrombocytosis. An underlying inflammatory condition such as inflammatory bowel disease is one cause of extremely high platelet counts.

Familial thrombocytosis

Familial thrombocytosis is rare. It was initially described as an autosomal-dominant disease caused by gain-of-function mutations in the gene for thrombopoietin. The mutations markedly increase the plasma levels of thrombopoietin, increasing the platelet count.

But other abnormalities, some of which do not involve elevated levels of thrombopoietin, are now also known to cause familial thrombocytosis, which is now recognized as being genetically heterogeneous. Its prevalence is probably underestimated because it is not often sought.

Clonal thrombocytosis

A third group of disorders of elevated platelets is clonal, ie, involving a defect of hematopoietic stem cells, the common precursors of red blood cells, white blood cells, and platelets. Examples of these disorders are essential thrombocythemia, polycythemia vera, chronic myelogenous leukemia, and other chronic myeloproliferative disorders.

Each of the chronic myeloproliferative disorders begins with a single abnormal multipotent hematopoietic stem cell in the bone marrow that becomes dominant over nontransformed progenitors. Most patients have hypercellularity of the bone marrow with apparently unstimulated overproduction of one or more of the formed elements of blood.

Most cases of incidentally discovered thrombocytosis resolve spontaneously

Thrombopoietin levels are increased, but for a different reason than in reactive or familial thrombocytosis: loss of functional thrombopoietin receptors on the abnormal platelets and megakaryocytes leads to reduced binding of thrombopoietin and elevated plasma levels of free thrombopoietin. Paradoxically, the few remaining receptors on the megakaryocytes are hypersensitive to thrombopoietin, resulting in increased megakaryocyte proliferation and platelet production.

The myeloproliferative disorders tend to convert to one another. All are preleukemic states that can spontaneously transform to acute leukemia. Chronic myelogenous leukemia is the ultimate preleukemic state: most patients die of an acute leukemic transformation known as a "blast crisis."

■ THROMBOSIS *AND* BLEEDING IN CLONAL DISORDERS

The myeloproliferative disorders share clinical features, including, paradoxically, an increased risk of both thrombosis and bleeding, which are major causes of morbidity and mortality. The bleeding is "platelet-type," ie, spontaneous and from the mucosa, such as in gastrointestinal bleeding, genitourinary bleeding, hemoptysis, or epistaxis.

Counterintuitively, patients with extreme thrombocytosis ($> 1,500 \times 10^9$/L) are at increased risk for bleeding. Bleeding risk is also higher in patients who take aspirin or other antiplatelet agents.

Thrombotic and vascular complications

Venous thrombosis. The thrombotic and vascular complications of essential thrombocythemia are often venous: deep vein thrombosis and pulmonary embolism are the most common.

Intra-abdominal thrombotic manifestations are also characteristic, particularly in younger patients. Anatomical factors may play a role in their development. Patients with essential thrombocythemia and polycythemia vera tend to develop hepatic vein thrombosis (Budd-Chiari syndrome) or thrombosis in the portal, splenic, or mesenteric veins. Although other conditions can cause Budd-Chiari syndrome (eg, tumors) and portal vein thrombosis

(eg, cirrhosis, tumors), myeloproliferative disorders are most commonly the culprit. Many patients who present with "idiopathic" Budd-Chiari syndrome actually have a subclinical, latent myeloproliferative disorder, despite having apparently normal blood profiles.

Arterial thrombosis is even more common than venous thrombosis as a complication of essential thrombocythemia, and often involves large arteries or the cerebrovascular system. The incidence of nonbacterial thrombotic endocarditis may also be increased in myeloproliferative disorders.[4]

Placental ischemia caused by multiple infarctions of the placenta tends to occur in women with essential thrombocythemia; one of the major causes of repeated spontaneous miscarriages is a myeloproliferative disorder.

Wright and Tefferi[5] retrospectively studied 43 pregnancies in women with essential thrombocythemia and found that 21 (49%) ended in miscarriage, typically during the first trimester. Pregnancy success was independent of the preconception platelet count and the use of aspirin during pregnancy.

Digital ischemia is a microvascular thrombotic manifestation of essential thrombocythemia. A characteristic form known as erythromelalgia was first described in 1878. Symptoms are burning and often throbbing, intense pain in a patchy distribution on the palms of the hands and the soles of the feet. The painful areas are often red and warm, indicating that an inflammatory process is also occurring. Peripheral pulses are often intact, indicative of digital ischemia's microvascular nature.

Aspirin, in even low doses, can reverse the pain and physical findings within hours. But the underlying condition must be treated with antiplatelet agents, or erythromelalgia can progress to frank ischemic complications, including gangrene.

Why do bleeding and thrombosis occur?

Much research has centered around trying to discern the causes of bleeding and thrombosis in essential thrombocythemia, but no fully satisfactory explanation has yet emerged.

The elevated platelet count by itself does not fully explain the thrombotic tendency: patients with reactive thrombocytosis do not

Thrombosis and bleeding are major causes of complications and death in clonal thrombocytosis

Clinical features that may distinguish between reactive and clonal thrombocytosis

FEATURE	REACTIVE	CLONAL
Underlying systemic disease	Often clinically apparent	No
Digital or cerebrovascular ischemia	No	Characteristic
Large-vessel arterial or venous thrombosis	No	Increased risk
Bleeding complications	No	Increased risk
Splenomegaly	No	In about 40% of patients
Peripheral blood smear	Normal platelets	Giant platelets
Platelet function	Normal	May be abnormal
Bone marrow megakaryocytes		
Number	Increased	Increased
Morphologic features	Normal	Giant, dysplastic forms with increased ploidy; associated with large masses of platelet debris

No feature definitively distinguishes reactive from clonal thrombocytosis

tend to develop thrombosis (unless the underlying condition happens to be prothrombotic).

On the other hand, elevated platelets probably play some role: prospective, controlled trials of high-risk patients with essential thrombocythemia have found that reducing platelet counts to normal levels and maintaining them there lowers the incidence of thrombotic events.

Thrombosis and bleeding may occur because platelets function abnormally. Because myeloproliferative disorders are clonal disorders of the hematopoietic stem cell in the bone marrow, it is likely that functional defects occur in all the formed elements: red cells, white cells, and platelets. Peripheral blood smears of patients may contain platelet aggregates, megakaryocyte fragments (nucleated platelet precursors), and large hypogranular platelets,[6] and some patients develop acquired von Willebrand syndrome. A number of metabolic abnormalities in platelets have been found in patients with essential thrombocythemia and other myeloproliferative disorders, but none has conclusively been

linked to either thrombotic or bleeding manifestations.

Other unknown mechanisms are also likely to cause thrombosis and bleeding. The role of leukocytes is not well understood, but they are also affected by the clonal abnormality of these conditions and may participate in the pathogenesis of the vascular ischemic syndromes.

Defects in vascular endothelial cells—which arise from the same common stem cell precursor as red cells, white cells, and platelets—may also play an important role in bleeding and thrombotic complications. Normally, a mesodermal precursor gives rise to a primitive hemangioblast in the bone marrow, which differentiates into either angioblasts (endothelial cell precursors) or multipotent hematopoietic stem cells (which give rise to the formed elements in blood). Circulating stem-cell-derived endothelial progenitors home into areas of vascular injury or ischemia and repopulate intimal surfaces of the vessel wall. If these endothelial cells are defective, they may be important contributors

to bleeding and thrombotic complications.

DISTINGUISHING BETWEEN CLONAL AND REACTIVE THROMBOCYTOSIS

Clonal and reactive thrombocytosis can be distinguished by their clinical features (**TABLE 1**), although none of the features establishes a definitive diagnosis.[6] In addition, peripheral blood smears in essential thrombocythemia may demonstrate giant platelets, and bone marrow examination shows markedly increased numbers of megakaryocytes, which may actually appear in sheets.[6]

Until recently, no definitive diagnostic tests existed for essential thrombocythemia and other myeloproliferative disorders. In the past, the following diagnostic criteria for essential thrombocythemia were used for clinical trials:

- Platelet count > 600 × 10⁹/L
- Hemoglobin ≤ 13 g/dL or normal red cell mass, ruling out polycythemia vera
- Stainable iron in bone marrow or failure of a trial of iron therapy, ruling out iron deficiency as a reactive cause of thrombocytosis
- No Philadelphia chromosome, ruling out chronic myelogenous leukemia
- No marked collagen fibrosis of marrow, ruling out myelofibrosis
- No known cause for reactive thrombocytosis.

These criteria are too restrictive for clinical purposes: many patients with essential thrombocythemia have only mildly elevated platelet counts.

Other ancillary tests to help diagnose clonal thrombocytosis have mostly been used in research laboratories:

Clonality assays, which analyze X-chromosome inactivation patterns, have drawbacks for clinical use. There is normal age-dependent unbalanced X-chromosome skewing, making the test less accurate in older patients. Also, the test can be used only in women, and some patients with apparently classic essential thrombocythemia actually have a polyclonal disorder.

A number of biological and epigenetic markers have been identified, but they occur only variably in essential thrombocythemia.

Spontaneous in vitro erythroid colony growth occurs in polycythemia vera and essential thrombocythemia. The test is performed by culturing bone marrow: normally, exogenous erythropoietin must be added for red cell proliferation and differentiation to occur, but in polycythemia vera and essential thrombocythemia, red cell colonies grow spontaneously. Spontaneous megakaryocyte colony growth can also occur in these diseases.

Other variably occurring markers include qualitative platelet abnormalities, overexpression of the PRV-1 gene, and reduced megakaryocyte c-Mpl expression.

Mutation in tyrosine kinase

New discoveries in the molecular basis of clonal thrombocytosis will likely soon allow us to make a definitive diagnosis in many patients who present with elevated platelet counts. Advances in molecular genetics can be expected to change the general approach to classifying the entire spectrum of myeloproliferative disorders, as well as drive the design of targeted treatments.

The most important recent breakthrough has been the recognition of a specific molecular marker for the classic myeloproliferative disorders: a mutation in the tyrosine kinase known as the Janus kinase 2 (JAK2). In 2005, at least six series were published demonstrating a single somatic mutation in the JAK2 gene that occurs in almost 80% of the patients studied with polycythemia vera and up to half of patients with essential thrombocythemia and myeloid metaplasia, with or without myelofibrosis.[7–12]

The mutation is a single guanine-to-thymine mutation at nucleotide 1849, leading to a valine-to-phenylalanine substitution. The mutation, which is not known to be a polymorphism, is found in red cells, white cells, and platelets, but not in T cells (which have a different hematopoietic lineage) or buccal-swabbed DNA, indicating its hematopoietic clonal nature. In the future, testing for the JAK2 mutation will likely become part of the routine initial diagnostic evaluation of patients with thrombocytosis.

Other tyrosine kinase gene mutations involving sites other than JAK2 have also

Testing for the JAK2 mutation will likely become part of the routine evaluation of thrombocytosis

been found in chronic myelogenous leukemia and systemic mast cell disease.

■ TREATMENTS ARE NOT IDEAL

The first step in approaching a patient with thrombocytosis is to rule out causes of reactive thrombocytosis; patients in whom thrombocytosis is secondary to an underlying cause should not have specific treatment to lower the platelet count.

Once a patient is diagnosed with a clonal form of thrombocythemia, the major question is whether treatment is necessary. These disorders tend to be indolent, and only a minority of patients—those with potentially fatal thrombotic and bleeding complications—need treatment.

Passamonti et al[13] followed 435 patients with essential thrombocythemia and 396 patients with polycythemia vera for up to 15 years and found that the mortality rate was only 1.6 times higher with polycythemia vera and not higher with essential thrombocythemia compared with the general population.

Reducing platelet levels

For patients who require platelet reduction, several methods are available.

Plateletpheresis is reserved for patients with essential thrombocythemia who are having acute or unstable vascular ischemia, cerebral vascular ischemia, or digital ischemia. Plateletpheresis offers only a very transient benefit, and the platelet count often rebounds afterwards to even higher levels than before.

Alkylating agents were once standard treatment but are now known to be associated with leukemia and so are no longer used except in older patients who cannot tolerate other treatments.

Hydroxyurea reduces platelet counts by suppressing megakaryocytes. It is generally safe, although it sometimes causes ischemic leg ulceration, which reverses after discontinuing therapy.[14]

Cortelazzo et al[15] randomly assigned 114 patients with essential thrombocythemia at high risk of thrombosis to treatment with hydroxyurea or no myelosuppressive therapy for a median of 27 months. Significantly fewer patients in the treatment group (3.6%) had

thrombotic events vs patients in the control group (24%). A follow-up study that extended observation to a median of more than 6 years found a sustained benefit of hydroxyurea in controlling platelet counts and preventing thrombosis.[16]

Anagrelide also inhibits the proliferation and differentiation of megakaryocytes in the bone marrow, but it has numerous adverse effects attributed mainly to its vasodilatory and inotropic actions. Short-term side effects include fluid retention, palpitations, arrhythmias, heart failure, headaches, and gastrointestinal effects such as pain, nausea, and diarrhea. Mild to moderate anemia can occur in the long term.

Harrison et al[17] recently randomized 809 patients with essential thrombocythemia at high risk for vascular events to treatment with either hydroxyurea or anagrelide. All patients also received low-dose aspirin. Equivalent long-term control of platelet counts was achieved in both groups. Outcomes, however, differed significantly: after a median follow-up of 39 months, patients taking anagrelide were more likely to reach the composite primary end point of thromboembolic events, with increased rates of arterial thrombosis, serious hemorrhage, and transformation to myelofibrosis, but those taking hydroxyurea had a higher rate of venous thromboembolism. Patients taking anagrelide were also more likely to withdraw from treatment because of drug intolerance.
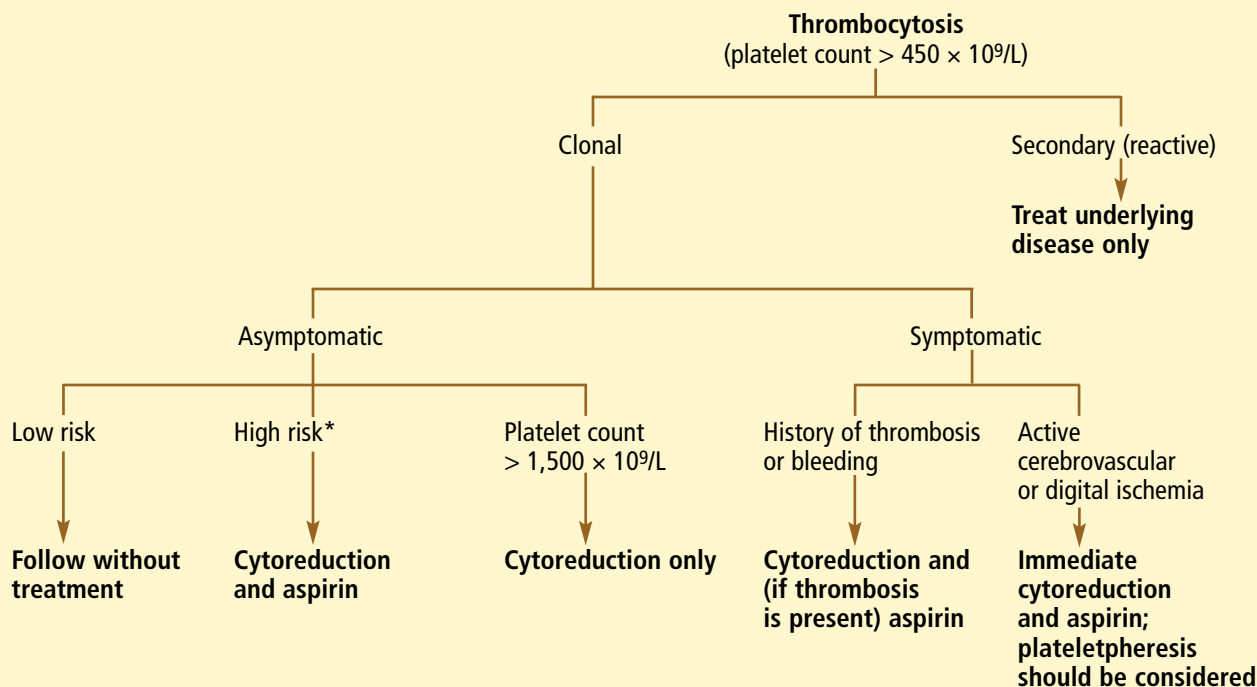
Based on this study, patients with essential thrombocythemia who are at high risk for a vascular event should be managed as follows:
- Hydroxyurea is the first-line therapy.
- Anagrelide is an appropriate second-line agent, but patients should be followed for the development of myelofibrosis.
- Whether aspirin should be used concurrently depends on the relative risk of bleeding vs arterial thrombosis.

Interferon is also very effective in reducing platelet counts in essential thrombocythemia, but it has an even worse side effect profile than anagrelide. About 20% of patients who start interferon quit because of severe flu-like symptoms. Other side effects may include altered mental status, depression, and exacerbation or even development

After pheresis, platelet counts often rebound higher than before

Approach to thrombocytosis

Thrombocytosis
(platelet count > 450 × 10⁹/L)

- Clonal
  - Asymptomatic
    - **Low risk** → **Follow without treatment**
    - **High risk*** → **Cytoreduction and aspirin**
    - **Platelet count > 1,500 × 10⁹/L** → **Cytoreduction only**
  - Symptomatic
    - **History of thrombosis or bleeding** → **Cytoreduction and (if thrombosis is present) aspirin**
    - **Active cerebrovascular or digital ischemia** → **Immediate cytoreduction and aspirin; plateletpheresis should be considered**
- Secondary (reactive) → **Treat underlying disease only**

*"High-risk" patients are those over age 60, with or without conventional cardiovascular risk factors, and with or without previous symptomatic thrombotic, vascular, or bleeding problems.

FIGURE 1

of autoimmune disorders. Nevertheless, because of its lack of potential teratogenic effects, interferon may be the preferred drug to control platelet counts when indicated in pregnant women.

Aspirin. The role of aspirin as antiplatelet therapy in the myeloproliferative disorders is controversial. However, Landolfi et al[18] randomized 518 patients with polycythemia vera to receive either aspirin 100 mg/day or placebo. At a mean of about 3 years, those taking aspirin had a significantly lower risk of the combined end point of nonfatal myocardial infarction, nonfatal stroke, pulmonary embolism, major venous thrombosis, or death from cardiovascular causes ($P = .03$), although overall mortality and cardiovascular mortality were not significantly reduced. The incidence of bleeding was higher in the aspirin group, but the difference was not statistically significant, and most of the episodes were minor. Whether this study is relevant to patients with essential thrombocythemia is uncertain.

Stem cell transplantation

Stem cell transplantation is a theoretically attractive way to treat chronic myeloproliferative disorders. Because these diseases tend to be indolent with a generally good prognosis, stem cell transplantation is used only for younger patients with advanced, complicated disease, including those whose disease has converted to myelofibrosis or acute leukemia.[19,20]

Targeted therapy

With the greater understanding of the mutations involved in polycythemia vera and essential thrombocythemia, future therapy will probably be directed at finding small-molecule inhibitors of JAK2, other JAKs, or other tyrosine kinases.

■ A PRACTICAL APPROACH TO THROMBOCYTOSIS

First, rule out a reactive process. A patient who presents with a platelet count of over 450×10^9/L should first have the test repeated a few weeks later before being evaluated further. For patients believed to have a reactive process, a high platelet count should not be treated, but the underlying disease should be identified and treated if possible (**FIGURE 1**). If no other cause is apparent, cancer should be looked for, but how exhaustive a workup to do is not clear. I recommend a thorough physical examination, stool for occult blood, chest radiography, and further testing as indicated by signs and symptoms.[6]

No symptoms, low risk of complications. If thrombocytosis is due to a clonal disorder and the patient has had no symptoms and is at low risk for bleeding and thrombotic complications (see below), he or she should be followed without treatment.

No symptoms, high risk of complications. Patients without symptoms but who are at higher risk for bleeding or thrombosis (ie, with a history of these events, with associated cardiovascular risk factors, or older than 60 years) should be treated with platelet cytoreduction. Hydroxyurea should be used as the first-line agent along with aspirin if there are no contraindications to using aspirin.

Extremely elevated platelets. For patients with extremely high platelet counts ($> 1,500 \times 10^9$/L), platelet counts should be reduced to normal levels. Aspirin should not be used or only used very cautiously because of the increased risk of bleeding complications in patients with essential thrombocythemia who have extreme thrombocytosis.

Patients with symptoms. For patients with essential thrombocythemia or other myeloproliferative disorders who have symptoms or who have had thrombotic or bleeding problems in the past, the platelet count should be reduced to a normal level. Aspirin should be added if the predominant problems in the past were thrombotic.

For those with active cerebrovascular or digital ischemia, immediate aspirin therapy and cytoreduction are indicated, possibly with plateletpheresis.

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