Why Does My Patient Have Thrombocytopenia?

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KEYWORDS

• Thrombocytopenia • Immune thrombocytopenic purpura • Platelet destruction
• Drug-induced thrombocytopenia

Thrombocytopenia, usually defined as a platelet count of less than 150,000/μL, is a common reason for a hematology consult in both the inpatient and outpatient setting. In most patients, the cause of the thrombocytopenia can be identified and treated. This article reviews the clinical approach to the patient with thrombocytopenia, the mechanisms that underlie it, and the laboratory tests available to investigate it. A practical approach to the investigation and management of thrombocytopenia in the clinical settings commonly encountered by the hematology consultant is then described.

PERTINENT HISTORY IN THE PATIENT WITH THROMBOCYTOPENIA

Thrombocytopenia classically causes mucosal-type bleeding, and patients should be asked about epistaxis, gingival bleeding, and menorrhagia in women. Other bleeding manifestations may include petechiae, bruising, hematochezia, and melenic stools. A history of bleeding associated with past hemostatic challenges must be obtained, including surgeries, dental procedures, trauma, and child birth. The patient's past and present alcohol use should be documented, and the patient should be asked about a history of liver disease, cirrhosis, jaundice, and risk factors for human immunodeficiency virus (HIV) and hepatitis infections. The medication history must also include questions about over-the-counter medications, herbal supplements, and the consumption of tonic water, which contains quinine, a cause of immune thrombocytopenia. Specific questions about the presence of a family history of bleeding are important, as congenital thrombocytopenia and Von Willebrand disease (VWD) can be diagnosed in young adults (reviewed in Ref.[1]) (**Table 1**).

PHYSICAL EXAMINATION

The physical examination in a patient with thrombocytopenia must establish first and foremost if there is evidence of bleeding associated with the thrombocytopenia, and

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Table 1
Pertinent items in history taking and physical examination in a patient with thrombocytopenia

History	Bleeding symptoms
	Epistaxis
	Gingival bleeding
	Menorrhagia
	Petechiae
	Bruising
	Hematochezia
	Melena
	Hemostatic challenges
	Surgeries
	Dental
	Trauma
	Childbirth
	Alcohol use
	Liver disease, hepatitis
	HIV risk factors
	Medication history
	Platelet function inhibitors
	Over-the counter medications/herbal supplements
	Tonic water (quinine)
	Family history of bleeding
Physical examination	General
	Pallor
	Tachycardia
	Skin
	Petechiae
	Purpura
	Splinter hemorrhages
	Ecchymosis
	Mucous membranes
	Blood blisters
	Lymphadenopathy
	Splenomegaly
	Heart murmur

Abbreviation: HIV, human immunodeficiency virus.

whether the bleeding is in proportion to the degree of thrombocytopenia. Patients with platelet counts greater than 50,000/μL do not exhibit spontaneous bleeding unless a coagulopathy is also present, the platelets are dysfunctional, and/or the patient is on a platelet inhibitor. The first sign of spontaneous bleeding from thrombocytopenia is usually petechiae on dependent areas such as the lower legs, or in areas of pressure (eg, at the site of a blood pressure cuff). Other signs of bleeding associated with more severe thrombocytopenia include ecchymosis and blood-filled blisters on the oral mucosa. The physical examination may also establish the underlying condition causing the thrombocytopenia, such as enlarged lymph nodes and spleen in lymphoma, and splenomegaly, telangiectasias, palmar erythema, jaundice, and other stigmata of chronic liver disease in patients with cirrhosis (reviewed in Ref.[1]; see **Table 1**).

ANCILLARY TESTS

A complete blood count with a white blood cell differential is the first step in the workup of thrombocytopenia, and establishes whether the patient has other cytopenias and/or

abnormal circulating cells. A review of the peripheral blood smear is essential, as it will rule out pseudothrombocytopenia (see later discussion), and enable the evaluation of all 3 cell lines for morphologic abnormalities. More specialized tests are ordered based on the initial clinical and laboratory evaluations, and are listed in **Table 2**. Platelet-associated antibodies and reticulated platelet counts, although widely available, lack standardization and, in the authors' opinion, are rarely helpful in establishing the cause of the thrombocytopenia.

Table 2
Ancillary tests for the workup of patients with thrombocytopenia

Test	Use
Complete blood count	Establish presence of other cytopenias Establish presence of lymphocytosis
Peripheral blood smear	Rule out pseudothrombocytopenia Morphology of platelets (large platelets suggest ITP, giant platelets suggest congenital disorders) Red blood cell fragments suggest microangiopathic process Toxic granulation suggests sepsis Abnormal lymphocytes suggest viral infection or lymphoproliferative disorder Neutrophil inclusions (Döhle bodies) suggest congenital thrombocytopenias Malaria, ehrlichiosis, and babesiosis can be diagnosed by demonstrating intracellular organisms on peripheral blood/buffy coat
PT and PTT Fibrinogen, D-dimer	Disseminated intravascular coagulation Evidence for Von Willebrand disease
Reticulated platelet count and antiplatelet antibodies	Lack standardization, usually not useful
Heparin-associated antiplatelet factor 4 and serotonin release assay	Heparin-induced thrombocytopenia
HIV and hepatitis C serology	Common causes for ITP
ANA, anti–double-stranded DNA	Systemic lupus erythematosus
Anticardiolipin antibody, lupus anticoagulant, anti-β2 glycoprotein 1	Antiphospholipid antibody syndrome
Drug-associated increase in antiplatelet IgG	Drug-induced ITP
Flow cytometry of peripheral blood	Lymphoproliferative disorders
Serum protein electrophoresis	Myeloma, lymphoma
Bone marrow aspirate and biopsy	Myelophthisic processes Hematologic malignancies Storage disease (eg, Gaucher disease)
Ultrasonogram of liver and spleen	Establish spleen size when not palpable Evaluate liver for cirrhosis
Liver/spleen scan	Establish spleen size Determine presence of accessory spleen Colloid shift indicates portal hypertension

Abbreviations: ANA, antineutrophil antibody; HIV, human immunodeficiency virus; IgG, immunoglobulin G; ITP, immune thrombocytopenic purpura; PT, prothrombin time; PTT, partial thromboplastin time.

MECHANISMS OF THROMBOCYTOPENIA

Platelets are produced from proplatelets, which are long, branching processes that extend from the cytoplasm of mature megakaryocytes. Their production is regulated by cytokines, especially thrombopoietin (TPO), and by close interactions with the bone marrow stroma. Approximately 4 to 7 days are required for the megakaryocyte progenitor cell to mature, at which point it produces 1000 to 3000 platelets before its residual nuclear material is engulfed by macrophages. Platelets normally circulate for approximately 10 days, although this life span is decreased to 5 to 7 days in patients with thrombocytopenia.[2,3] Disruption of any part of this process, when severe enough, can lead to thrombocytopenia.

When evaluating a patient with thrombocytopenia, the first step is to rule out pseudothrombocytopenia, a laboratory artifact with no clinical significance. True thrombocytopenia can be secondary to increased destruction of platelets, decreased production, sequestration (usually in the spleen), and hemodilution (**Table 3**). Although in most clinical situations a predominant mechanism can be identified, in many patients more than one pathway contributes to the thrombocytopenia.

Table 3
Mechanisms of thrombocytopenia

Mechanism	Examples
Increased destruction (immune mediated)	Primary ITP Secondary ITP Infections (HIV, hepatitis C, *Helicobacter pylori*) Lymphoproliferative disorders Medications (eg, quinine, quinidine, gold) Medications: nonclassic ITP (eg, heparin, glycoprotein IIb/IIIa inhibitors) Posttransfusion thrombocytopenia
Increased destruction (non–immune mediated)	DIC Thrombotic microangiopathies (TTP, HUS, disseminated cancer, eclampsia, HELLP syndrome) Cardiopulmonary bypass, intra-aortic balloon pump, ventricular assist devices Abnormal vascular surfaces (aneurysms, heart valves, Merritt-Kasabach syndrome) Hemophagocytosis
Decreased production	Congenital B_{12} and folate deficiency Medications (valproic acid, chemotherapy) Radiation Toxins (alcohol) Infections (parvovirus, CMV, erlichiosis) Liver disease (TPO deficiency) Primary marrow disorders (myelodysplasia, myelofibrosis, acute and chronic leukemias, lymphoproliferative disorders) Marrow replaced by solid tumors Granulomatous diseases of the marrow
Sequestration	Splenomegaly
Dilutional	Massive transfusion

Abbreviations: CMV, cytomegalovirus; DIC, disseminated intravascular coagulation; HIV, human immunodeficiency virus; HELLP, hemolysis, elevated liver enzymes, low platelets; HUS, hemolytic uremic syndrome; ITP, immune thrombocytopenic purpura; TTP, thrombotic thrombocytopenic purpura; TPO, thrombopoietin.

Pseudothrombocytopenia

Pseudothrombocytopenia, also called spurious thrombocytopenia, is an ex vivo phenomenon occurring in 0.09% to 0.29% of the population, in which platelets clump when blood is anticoagulated with a calcium chelator such as ethylenediaminetetraacetic acid (EDTA). Automated counters do not correctly identify the clumps as platelets, and as a result the platelet count is reported as low. Furthermore, the platelet clumps are sometimes misrecognized as neutrophils, causing pseudoleukocytosis. Review of a peripheral blood smear (**Fig. 1**) demonstrates the clumps, and the automated platelet count is usually higher when blood is collected into an alternative anticoagulant such as citrate or heparin. Pseudothrombocytopenia is caused by circulating antiplatelet antibodies against platelet membrane glycoproteins that are modified by the exposure to anticoagulants.[4–6] Platelet satellitism is a less common form of pseudothrombocytopenia in which EDTA causes antibodies against glycoprotein (GP) IIb/IIIa to attach platelets to neutrophils and monocytes via the leukocyte Fcγ receptor III. The peripheral blood smear (**Fig. 2**) demonstrates platelets forming rosettes around the neutrophils and/or monocytes.[7]

There are no known pathologic effects of the presence of the antiplatelet antibodies associated with pseudothrombocytopenia, and it is important to establish and document the diagnosis so that patients are not subjected to unnecessary testing and treatment.

Thrombocytopenia from Increased Platelet Destruction

The normal platelet life span of 7 to 10 days can be shortened by both immune-mediated and non–immune-mediated processes, and, when the destructive process overwhelms the bone marrow's ability to increase platelet production, the result will be thrombocytopenia.

Immune Destruction of Platelets

In patients with immune-mediated thrombocytopenia, antibodies attach to platelets and promote their destruction by the reticuloendothelial system. These antibodies can be either autoantibodies or alloantibodies. The most common cause of autoimmune platelet destruction is immune thrombocytopenic purpura (ITP), which is usually caused by antibodies of the immunoglobulin G subtype directed against platelet membrane glycoproteins.[8] In heparin-induced immune platelet destruction, autoantibodies target a heparin-platelet factor 4 complex and cause thrombocytopenia by binding to the membrane Fc receptor and activating the platelets (see **Table 3**).

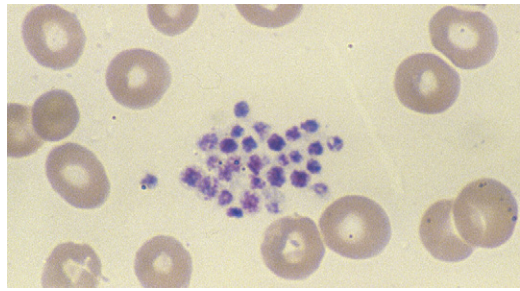

Fig. 1. Peripheral blood smear showing platelet clumping. (*Courtesy of* Dr Henry M. Rinder, Yale School of Medicine.)

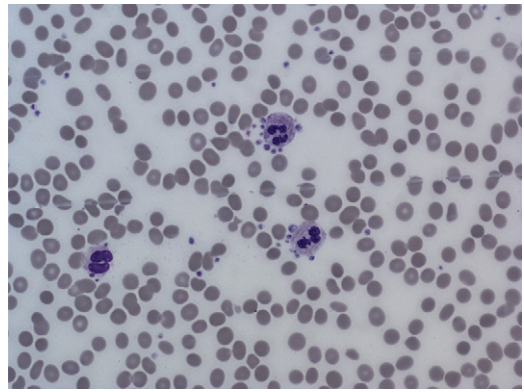

Fig. 2. Peripheral blood smear showing platelet satellitism. (*Courtesy of* Dr Richard Torres, VA Connecticut and Yale School of Medicine.)

Alloimmune destruction is a rare but severe cause of thrombocytopenia, in which platelets are destroyed by alloantibodies usually targeting the platelet antigen HPA-1a (PlA1) that have been transmitted through a transfusion (see discussion of post-transfusion purpura).

Nonimmune Destruction of Platelets

Nonimmune destruction of platelets occurs in patients with thrombotic microangiopathies such as thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, and the elevated liver enzymes, low-platelet (HELLP) syndrome of pregnancy. In these patients thrombocytopenia results from the shearing of platelets in a damaged microvasculature filled with thrombi. Microangiopathic hemolytic anemia is also present, and coagulation parameters are normal or near normal (see **Table 3**).

Disseminated intravascular coagulation (DIC) is a common cause of thrombocytopenia in acutely ill patients, and here the platelet destruction is secondary to their activation by thrombin and proinflammatory cytokines (see **Table 3**). Patients who have undergone cardiopulmonary bypass, insertion of an intra-aortic balloon pump, or insertion of a ventricular assist device develop thrombocytopenia as a result of the activation and destruction of platelets exposed to the artificial surfaces (see later discussion). Patients with a severely abnormal endovascular surface such as a damaged, malfunctioning heart valve, aortic aneurysm, or a vascular malformation may also develop thrombocytopenia secondary to activation of platelets on the abnormal surface.

Decreased Production of Platelets

Multiple processes affecting megakaryocyte maturation and differentiation, either directly or through a more global effect on hematopoiesis, may result in thrombocytopenia, often accompanied by anemia and/or leukopenia (see **Table 3**).

Sequestration of Platelets

Hypersplenism is defined as anemia, leukopenia, and/or thrombocytopenia that are caused by abnormal splenic-mediated destruction often associated with splenomegaly. Normally, approximately 30% of the platelet mass resides in the spleen. This percentage increases with increased spleen size, and most patients with

splenomegaly will have thrombocytopenia. When the cause of the thrombocytopenia is hypersplenism, the platelet count will rarely drop below 20,000/μL, and the low platelet count is not usually associated with bleeding unless other hemostatic abnormalities are present (see also **Table 1**).[9,10] Thrombocytopenia is usually the first manifestation of hypersplenism in patients with liver disease, and the hematologist sometimes establishes the diagnosis of otherwise clinically occult cirrhosis during the workup of a low platelet count.[11]

Dilutional Thrombocytopenia

Thrombocytopenia develops in patients receiving infusions of large amounts of non–platelet-containing fluids. A rapid transfusion of 10 to 12 units of packed red blood cells will result in a platelet drop of approximately 50%.[12,13]

THROMBOCYTOPENIA IN THE INTERNAL MEDICINE PATIENT

This section focuses on the different causes of thrombocytopenia that the clinician may encounter in either the outpatient or inpatient medical setting.

Nutritional Deficiencies

Vitamin B_{12} and folate deficiency cause megaloblastosis and pancytopenia through inhibition of purine synthesis. Thrombocytopenia may be the predominant cytopenia, and can be severe (reviewed in Ref.[14]). Because these are common, readily treatable conditions, all patients with thrombocytopenia should have documentation of normal levels of vitamin B_{12} and folic acid as part of their workup. Repletion of the deficient vitamin will rapidly correct the thrombocytopenia, and it is the authors' practice to offer repletion to all patients with low or borderline levels. Folate deficiency is commonly associated with ethanol abuse, and the etiology of thrombocytopenia may be multifactorial in these patients (see later discussion).

Iron Deficiency

Iron deficiency is usually associated with thrombocytosis. In rare cases, however, thrombocytopenia may be present,[15] and in these patients both increased and decreased numbers of megakaryocytes in the bone marrow have been reported. Although the exact mechanism remains unclear, the observation of increased megakaryocytes in the marrow accompanied by a rapid increase in platelets after iron administration suggests the involvement of iron in late-stage thrombopoiesis.[16]

Alcohol Abuse and Thrombocytopenia

Thrombocytopenia is the most common hematologic abnormality in patients who abuse alcohol.[17] Alcohol ingestion may lead to acute thrombocytopenia, and a common scenario is a falling platelet count in a patient admitted after binge drinking. With alcohol cessation and adequate folate and vitamin B_{12} repletion, recovery of platelet counts occurs within 1 to 2 weeks and may even be associated with a rebound thrombocytosis.

Heavy alcohol consumption has direct toxic effects on the bone marrow and causes a reversible suppression of platelet production.[18] Peripheral blood smear examination reveals thrombocytopenia, and may also show macrocytosis and stomatocytes. Marrow examination usually reveals a normal megakaryocyte count, but their number can also be significantly reduced.[19] Because alcohol inhibits heme biosynthesis, ringed sideroblasts are common.[18,20]

Liver Disease and Thrombocytopenia

Thrombocytopenia in patients with liver disease is multifactorial. Chronic thrombocytopenia in a patient with liver cirrhosis is usually a result of portal hypertension and splenomegaly, leading to splenic sequestration. Splenomegaly can be associated with any combination of cytopenia(s), including isolated thrombocytopenia.[20] There may also be direct marrow-suppressive effects from the cause of the liver damage, whether from alcoholism or viral or immune hepatitis. Hepatitis C and autoimmune hepatitis are associated with immune-mediated thrombocytopenia.[21,22] Chronic liver disease can also lead to deficiency of thrombopoietin, the hematopoietic growth factor responsible for platelet production.[23] In addition, DIC leading to platelet consumption is seen in severe liver disease.[24] Indeed, the combined hematologic effects of ongoing alcohol abuse in patients with cirrhosis who have pancytopenia and coagulopathy are particularly severe, with bleeding complications often necessitating significant transfusion support.

The Congenital Thrombocytopenias

Although congenital thrombocytopenias are rare, this is an essential diagnosis to establish, because patients are often misdiagnosed as having ITP, and subjected to unnecessary and potentially harmful treatments.[25] Some important considerations for diagnosing congenital thrombocytopenias are the age of onset and chronicity of symptoms.[26] Patients with inherited conditions associated with severe thrombocytopenia are generally recognized shortly after birth. Patients with milder forms of thrombocytopenia may present later in life, particularly during times of hemostatic challenge (eg, onset of menses, childbirth, trauma, surgery). Many other patients with mild to moderate thrombocytopenia, however, may be clinically asymptomatic and present only after routine blood tests.

If congenital thrombocytopenia is suspected, further evaluation is guided by platelet size. When a male patient presents with small platelets, an X-linked thrombocytopenia such as Wiskott-Aldrich syndrome should be considered. For patients presenting with normal-sized platelets, the differential includes neonatal conditions such as congenital amegakaryocytic thrombocytopenia, thrombocytopenia with absent radii, and a familial platelet disorder with predisposition to acute myeloid leukemia. Large platelets are seen in several inherited disorders of platelets including VWD 2B, MYH9-related diseases such as the May-Hegglin anomaly, Bernard-Soulier syndrome, and the gray platelet syndrome.

Von Willebrand Disease 2B

VWD 2B, also known as platelet-type VWD, deserves special mention as patients may present for the first time in adulthood. This rare autosomal dominant disorder is characterized by the presence of ultralarge multimers of Von Willebrand factor (VWF), which bind preferentially to platelets, leading to clumping and mild, fluctuating thrombocytopenia. VWD 2B, like other forms of VWD, presents clinically with excessive mucous membrane, menstrual, and/or postpartum hemorrhage.

Review of a peripheral blood smear may show pseudothrombocytopenia (see earlier discussion), and the platelet size is normal or large. Laboratory tests show a disproportionate reduction in VWF activity assays relative to VWF antigen, and absence of high molecular weight multimers. Desmopressin should be avoided, as it may lead to worsening thrombocytopenia caused by the increase in VWF multimers and increased platelet agglutination and clearance.

MYH9-related diseases

The MYH9-related diseases are associated with macrothrombocytopenia and involve myosin IIA mutations. The May-Hegglin anomaly is the most common form. The peripheral smear shows giant platelets and Döhle-like bodies in neutrophils (**Fig. 3**). Associated features include cataracts, hearing loss, and renal failure. Automated counters often underestimate the true platelet count because of limitations from preset size restrictions. Although the platelet count is variable and sometimes less than 20,000/μL, platelet function is normal and patients are usually asymptomatic.

Bernard-Soulier syndrome

Bernard-Soulier syndrome, caused by an absent GP Ib-V-IX complex on the platelet surface, leads to bleeding out of proportion to the platelet count. Similar to the MYH9-related diseases, the peripheral smear demonstrates giant platelets. In homozygous patients the diagnosis is made by platelet aggregation studies showing lack of aggregation to ristocetin and a negative VWD workup. Flow cytometry to quantify platelet glycoproteins is particularly helpful in identifying heterozygote patients.

DRUG-INDUCED THROMBOCYTOPENIA

Drug-induced thrombocytopenia (DITP) is an important entity to consider in all patients presenting with thrombocytopenia, and included in this discussion is thrombocytopenia caused by over-the-counter supplements and food items. The onset may be sudden and severe (platelet count nadirs are often <20,000/μL), leading to significant morbidity and even mortality[27,28] if the offending agent is not promptly removed. DITP can be misdiagnosed as idiopathic ITP, and the underlying etiology may be missed if patients are not specifically asked about foods, beverages, and/or herbal supplements.

DITP can be caused by nonimmune (eg, valproic acid or chemotherapy resulting in myelosuppression) or, more commonly, immune-mediated processes.[28,29] The immunologic mechanisms include autoantibody production (eg, gold [Ridaura; Solganal, others]), drug glycoprotein complex(es) (eg, quinine [Quinamm; Quindan, others]), ligand-induced binding (eg, eptifibatide [Integrilin]), and hapten-dependent binding (eg, penicillin) (reviewed in Ref.[30]). The mechanism for heparin-induced thrombocytopenia (HIT) is unique, as antibodies against platelet factor 4–heparin complexes cause platelet activation, thrombocytopenia, and thrombosis, rather than bleeding (see **Table 3**).

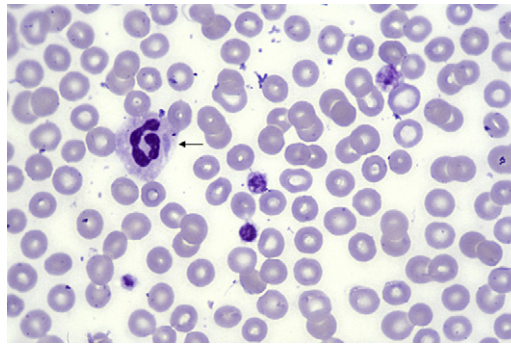

Fig. 3. Peripheral blood smear in a patient with the May-Hegglin anomaly. Giant platelets are present along with a Döhle body in a granulocyte (*arrow*). (*Courtesy of* Dr Henry M. Rinder, Yale School of Medicine.)

Drug-dependent antiplatelet antibodies usually occur within 1 to 2 weeks of exposure to the offending drug, but in some instances may develop after chronic, intermittent exposure (reviewed in Refs.[27,28]). On rare occasions acute immune-mediated thrombocytopenia may develop within several hours of exposure, as in the case of GP IIb/IIIa inhibitors used in cardiac procedures (see the section on thrombocytopenia in the cardiac care unit).[31] Regardless of the specific mechanism, DITP occurs only in the presence of the offending agent, and removal of the drug should lead to improvement within 1 to 2 days, with resolution of the platelet count within 1 to 2 weeks. Indefinite avoidance of the offending agent is recommended. If ITP was initially suspected and corticosteroids were initiated, therapy may be stopped once the offending agent has been removed and the platelet count normalizes.

DITP should be suspected when a patient presents with severe thrombocytopenia of unclear etiology, particularly in patients with repeated episodes and prompt resolution. In a cohort of 343 patients diagnosed as ITP, 8% were subsequently diagnosed with DITP, with quinine (including tonic water) being the most common cause.[32] The 2 most common causes of thrombocytopenia in one case-controlled study were trimethoprim/sulfamethoxazole (Bactrim; Septra) and quinine, in 38 and 26 cases/10^6 users/week, respectively.[33]

A systematic review of all published reports of DITP as of October 2010 is available online at www.ouhsc.edu/platelets. A causal relationship between a drug and thrombocytopenia is defined in that database if there is a single report with definite evidence or at least 2 reports with probable evidence.[34] A modified list of the most common drugs causing thrombocytopenia is also provided in **Table 4**. There is currently no published comprehensive list of foods or herbal remedies associated with thrombocytopenia, but convincing case reports suggest that tahini (pulped sesame seeds),[35] *Lupinus termis* beans,[36] *Jui* Chinese herbal tea,[37] cow's milk,[38] and cranberry juice[39] can cause thrombocytopenia.

The diagnosis of DITP is usually made clinically by identifying potential offending agents and withholding them to see whether thrombocytopenia resolves. The Blood Center of Wisconsin offers drug-dependent platelet-reactive antibody testing (http://www.bcw.edu/bcw.) If a drug is confirmed as the cause of a patient's thrombocytopenia, the authors recommend the clinician alert the Food and Drug Administration Adverse Event Reporting System via www.fda.gov/medwatch/. A case report should be published if available literature is lacking.

Primary Immune Thrombocytopenia

ITP is a relatively common clinical entity encountered in hematology practice. ITP is characterized by autoimmune-mediated platelet destruction and suppression of megakaryocyte platelet production, leading to an increased risk of bleeding.[40,41] The exact etiology of autoantibody production leading to ITP remains unclear.

ITP is a diagnosis of exclusion. The definition of primary ITP by the International Working Group is a platelet count less than 100,000/μL without other reasons to explain the thrombocytopenia.[42] The goal of the history taking and physical examination in these patients is to identify evidence of bleeding and to exclude other causes of thrombocytopenia. Laboratory investigation should include a complete blood count and peripheral blood smear review. Abnormalities in the peripheral smear other than isolated thrombocytopenia should lead to further investigation, for example, schistocytes in thrombotic microangiopathies, significantly increased giant or small platelets suggesting an inherited thrombocytopenia, and pseudothrombocytopenia resulting from EDTA-dependent platelet agglutination. All patients should be offered HIV and hepatitis C serologic testing, and *Helicobacter pylori* testing can be considered (see

Table 4
Drugs commonly associated with thrombocytopenia

Drug	Number of Reports (Definite or Probable)	Antibody Testing
Quinidine (Quinaglute; Cardioquin, others)	58	Yes
Quinine (Quinamm; Quindan, others)	24	Yes
Trimethoprim/sulfamethoxazole (Bactrim; Septra)	15	Yes
Abciximab (ReoPro)	13	Yes
Gold (Ridaura; Solganal, others)	11	Yes
Rifampin (Rifadin; Rimactane)	10	Yes
Carbamazepine (Tegretol)	10	Yes
Eptifibatide (Integrilin)	9	Yes
Tirofiban (Aggrestat)	8	Yes
Vancomycin (Vancoled)	7	Yes
Acetaminophen (Tylenol; Panadol, others)	7	Yes
Danazol (Danocrine)	7	No
Interferon-α (Roferon-A; Intron A)	7	No
Methyldopa (Aldomet)	6	Yes
Cimetidine (Tagamet)	6	Yes
Nalidixic acid (NegGram)	6	No
Efalizumab (Raptiva)	6	No
Diclofenac (Cataflam; Voltaren)	5	Yes
Hydrochlorthiazide (Aquazide-H; Esidrex, others)	5	Yes
Ranitidine (Zantac)	5	Yes
Chlorpropamide (Diabinese)	5	Yes

Each listed drug is associated with 5 or more published reports (individual and/or group data) with definite or probable evidence for drug-induced thrombocytopenia. The reference database is from www.ouhsc.edu/platelets. Specific antibody testing is available from the Blood Center of Wisconsin.

later discussion). A routine bone marrow evaluation is not necessary unless the initial workup points to a marrow disorder (see also the American Society of Hematology 2011 evidence-based practice guidelines for immune thrombocytopenia).[43]

Treatment of ITP is generally recommended when the platelet count falls below 30,000/μL. The standard first-line therapy is corticosteroids, and immunoglobulins are used when a more rapid response is needed or when steroids are contraindicated. Splenectomy, rituximab (Rituxan),[44] and the thrombopoietin receptor agonists romiplostim (Nplate)[45] and eltrombopag (Promacta)[46,47] are used in refractory or relapsing patients.

Secondary Immune Thrombocytopenic Purpura (ITP)

Systemic lupus erythematosus

Secondary immune-mediated thrombocytopenia may occur in many rheumatologic conditions, but is by far the most common in systemic lupus erythematosus (SLE). Most patients with SLE will exhibit a chronic thrombocytopenia, and acute, severe thrombocytopenia in the setting of a multiorgan lupus flare[48] is also common. A bleeding tendency out of proportion to the thrombocytopenia because of platelet dysfunction has been described in these patients.[49]

Treatment of the thrombocytopenia associated with SLE is analogous to that of ITP,[49] and corticosteroids remain the standard first-line therapy. An area of ongoing controversy is whether splenectomy is effective for refractory patients.[50]

Antiphospholipid antibody syndrome

Thrombocytopenia is seen in up to 50% of patients with antiphospholipid antibody syndrome, and tends to be mild and sporadic.[51,52] Similar to ITP, the mechanism is thought to be due, at least in part, to platelet glycoprotein-reactive autoantibodies.[53] However, in contrast to ITP, these patients are at increased risk for thrombosis, and therapy for the thrombocytopenia is usually not necessary.

Thrombocytopenia and HIV infection

Thrombocytopenia is the first sign of HIV infection in 10% of patients, is found in about 40% of patients overall, and correlates with a shorter survival.[54,55] Risk factors for thrombocytopenia include uncontrolled HIV replication, concurrent hepatitis C virus (HCV) infection, and cirrhosis.[56]

The most common cause of thrombocytopenia in HIV-infected patients is immune destruction through molecular mimicry between glycoproteins on the platelet surface and the outer membrane of the HIV. The antibody-coated platelets are then destroyed by splenic macrophages and by complement-mediated mechanisms. HIV also causes decreased platelet production by direct infection of megakaryocytes, as these cells can bind and internalize the virus through their CD4 receptor.[57,58] Other causes of thrombocytopenia in an HIV-infected patient include bone marrow infiltration by malignancy, opportunistic infections, side effects of drugs (eg, trimethoprim/sulfamethoxazole), and HIV-related thrombocytic microangiopathy. For patients found to have ITP secondary to HIV, initial management is antiviral therapy, which results in improvement of the thrombocytopenia in more than 75% of patients.[59]

Hepatitis C and Immune Thrombocytopenic Purpura (ITP)

Thrombocytopenia is reported in as many as 45% of patients with HCV infection, and it usually improves when the infection responds to interferon and ribavirin.[59] However, because interferon is a common cause of thrombocytopenia, it is relatively contraindicated in patients with platelet counts of less than 75,000/μL. An acute drop in platelet count in a patient with HCV usually indicates ITP, and should be treated with steroids and/or high-dose immunoglobulins.[60,61] A trial investigating the use of the TPO mimetic eltrombopag in HCV-associated thrombocytopenia was terminated early, however, because of increased rates of portal venous thrombosis.

Helicobacter pylori and Immune Thrombocytopenic Purpura (ITP)

H pylori has been reported to be associated with ITP, and the detection of an infection by urea breath test, stool antigen test, or endoscopic biopsy should prompt treatment for eradication when associated with otherwise unexplained thrombocytopenia.[43,62] However, the data showing improvement in platelet count after *H pylori* eradication have been variable. One meta-analysis showed an overall response rate (platelet count at least 30,000/μL and doubling of baseline) in 50% of patients after *H pylori* treatment.[62]

POSTTRANSFUSION PURPURA

Posttransfusion purpura (PTP) is a rare thrombocytopenia that should be suspected if a patient presents with an acute drop in platelet count 1 to 14 days after a transfusion. The classic presentation is an older, multiparous woman who presents with bleeding and severe thrombocytopenia 1 week after receiving a blood product containing

platelets.[63] Rarely, thrombocytopenia may develop within hours of exposure.[63,64] The diagnosis is made by the demonstration of platelet-specific alloantibodies targeting antigens not found on the patient's platelets. Despite the fact that the patient's platelets do not display the targeted antigen, they are destroyed as "innocent bystanders" by a poorly understood mechanism, resulting in severe thrombocytopenia that is relatively refractory to platelet transfusions.[65] Most alloantibodies are HPA-1a, with HPA-1b, HPA-5/5b, and other platelet antigens much less common.[63]

Treatment with high-dose immunoglobulins should begin as soon as PTP is suspected, and response within 2 to 3 days occurs in more than 90% of patients.[63,65–67] If left untreated, patients may have a protracted course with severe bleeding lasting a mean of 10 days, and mortality of up to 10%.[63]

THROMBOCYTOPENIA ASSOCIATED WITH INFECTIONS

Thrombocytopenia is commonly associated with both acute and chronic infections, and can be caused by multiple mechanisms (**Table 5**).[71] Unexplained thrombocytopenia in a patient with fever and other infectious symptoms should prompt a search for pathogens with a review of the peripheral blood smear for intracellular organisms, blood and other cultures, and appropriate serologic and molecular tests.

THROMBOCYTOPENIA IN THE INTENSIVE CARE UNIT

Thrombocytopenia is very common in patients admitted to the intensive care unit (ICU).[72–75] In a review of 24 studies that included 6894 patients from medical, surgical, mixed, and trauma ICUs, thrombocytopenia on admission was found in 8% to 68% of patients, and thrombocytopenia developed during the ICU stay in 13% to 44% of patients.[72] Many of the studies demonstrated that high illness severity, sepsis, and organ dysfunction correlated with thrombocytopenia. Most studies have found that thrombocytopenia in the ICU is associated with an increased risk of death.[72,74,75]

The main causes of thrombocytopenia in the ICU include sepsis and DIC, dilution secondary to massive fluid and/or transfusion resuscitation, and/or medications (**Table 6**).

Heparin-Induced Thrombocytopenia in the ICU

HIT deserves special mention, as most ICU patients are exposed to heparin, and those who develop HIT suffer high rates of morbidity and mortality.[76,77] However, the clinical diagnosis of HIT in the ICU is difficult to make, as thrombocytopenia and thrombosis are common in these patients and most have alternative explanations for their thrombocytopenia. There are limited data on the utility of the 4 Ts scoring system, a clinical tool that classifies patients into low, moderate, and high pretest probability for HIT (see **Table 3**), in critically ill patients.[78,79] Furthermore, whereas in all comers approximately 50% of patients with a positive platelet factor 4–dependent enzyme-linked immunosorbent assay will have a positive serotonin release assay and likely HIT, in the ICU setting that percentage is only 10% to 20%.[80]

Sakr and colleagues[76] reviewed records of 13,948 patients admitted to a surgical ICU in a German hospital, and found that the incidence of HIT was only 0.63%. Thus, the consultant should bear in mind that HIT explains fewer than 1% of cases of thrombocytopenia in the ICU (reviewed in Ref.[81]), and overdiagnosis of HIT results in the unnecessary use of more expensive anticoagulants, which have an increased bleeding risk, especially in critically ill patients.[82,83]

Table 5
Infectious causes of thrombocytopenia

Pathogen Group	Specific Organism and Proposed Mechanisms
All	DIC
	SIRS
	Marrow suppression
	Medication effect
	Hemophagocytosis
	Splenomegaly
Viruses	HIV
	ITP
	Medications (SMZ/TMP)
	Opportunistic infections (CMV, MAI)
	Marrow suppression (megakaryocyte infection)
	Thrombotic microangiopathies
	Acute EBV
	Hemophagocytosis
	Splenomegaly
	Hepatitis C
	ITP
	Splenomegaly/portal hypertension
	Medications (interferon)
	CMV
	Marrow suppression
	Medications (ganciclovir)
	Parvovirus B19
	Marrow suppression
Bacteria	*H pylori*
	ITP
	E coli (Shiga toxin producing)
	HUS
Parasites	*Babesia* species[68]
	DIC?
	Ehrlichia species[69]
	DIC
	Hemophagocytosis
	Marrow granulomas
	Malaria[70]
	DIC
	Hypersplenism

Abbreviations: CMV, cytomegalovirus; DIC, disseminated intravascular coagulation; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; HUS, hemolytic uremic syndrome; ITP, immune thrombocytopenic purpura; MAI, mycobacterium avium intracellulare; SIRS, systemic inflammatory response syndrome; SMZ/TMP, sulfamethoxazole/trimethoprim.

Thrombocytopenia in the Cardiac Care Unit

Rapid development of severe thrombocytopenia after treatment with anti-GP IIb/IIIa inhibitors such as abciximab, eptifibatide, and tirofiban occurs in 0.4% to 2% of patients, with the highest incident reported with abciximab.[84] Thrombocytopenia is usually severe, with platelet counts dropping to around 5000 to 10,000/μL, and is often associated with bleeding because most patients are also on other antiplatelet agents. The pathogenesis is thought to be immune mediated, and the incidence is higher among patients previously exposed to GP IIb/IIIa inhibitors. The incidence of

Table 6
Thrombocytopenia in the intensive care unit (ICU)

Unit	Etiology
All ICUs	Dilution (massive fluid or blood resuscitation) Sepsis Heparin Other medications
Surgical ICU	Post–cardiopulmonary bypass Ventricular assist devices Heparin
Cardiac ICU	Glycoprotein IIb/IIIa inhibitors Intra-aortic balloon pump Heparin Thrombotic microangiopathy (clopidogrel)

pseudothrombocytopenia with these drugs is also high, so the diagnosis of thrombocytopenia must be confirmed with smear review. Bleeding patients should receive urgent platelet transfusions. Delayed-onset thrombocytopenia (48 hours to 2 weeks after administration) has also been reported with GP IIb/IIIa inhibitors.

Rapid-onset HIT must also be considered in these patients if they have been exposed recently to heparin.[85] The intra-aortic balloon pump causes thrombocytopenia in approximately 50% of patients, with a nadir 3 days after placement. The thrombocytopenia is usually in the range of 50% from baseline, and a drop below this level should prompt further workup for alternative causes.[84]

Thrombocytopenia and cardiopulmonary bypass

Both thrombocytopenia and significant prolongation of the bleeding time occur in all patients undergoing cardiopulmonary bypass, with severities that are in proportion to the period of time that the patient is exposed to the extracorporeal oxygenator. The causes of the platelet abnormalities are dilution by the priming solution, and the activation and destruction of platelets on the membrane. The abnormal platelet function normalizes within an hour after the exposure to the membrane ends. The platelet count drops by approximately 50% and usually recovers by the fourth postoperative day.[86]

One of the more challenging consults in the surgical ICU is the post–bypass surgery patient with prolonged thrombocytopenia, because the vast majority of these patients are exposed to heparin and the available assays for HIT are unreliable in this setting. In the first 10 days after cardiac surgery, 25% to 70% of patients develop a positive immunoassay for antiplatelet factor 4–heparin antibodies, and 4% to 20% have an abnormal serotonin release assay.[87] Pouplard and colleagues[88] described 2 patterns of thrombocytopenia in these patients: profile 1, in which the platelet count recovers and then drops again between postoperative days 5 and 10; and profile 2, in which thrombocytopenia does not resolve after surgery and persists beyond day 5. In a prospective study of 581 cardiac surgery patients, HIT was found only in 3 (0.5%), but all 3 patients had a profile-1 thrombocytopenia.[89]

Thrombocytopenia is almost universal in patients after ventricular assist device implantation, and is caused by the preceding cardiopulmonary bypass use, infections, and exposure to heparin. The incidence of clinical HIT is estimated at 10% with a high risk of cerebrovascular infarcts, leading some experts to recommend alternative anticoagulation in these patients.[90]

THROMBOCYTOPENIA IN THE PATIENT WITH A HEMATOLOGIC MALIGNANCY

ITP is often associated with lymphoproliferative disorders, with the highest incidence seen in chronic lymphocytic leukemia[91] (incidence 2%–5%). Patients with other types of lymphoma have a 0.2% to 1% incidence of ITP.[92,93] In all these patients the differential diagnosis must include marrow infiltration, splenomegaly, and/or chemotherapy and biological therapy. In approximately 50% of patients with ITP associated with non-Hodgkin lymphoma, the diagnosis of ITP precedes the lymphoma diagnosis, whereas ITP associated with Hodgkin lymphoma usually occurs after the lymphoma has been diagnosed. ITP associated with active lymphoproliferative disease usually responds to antilymphoma therapy. Patients with large granular lymphocyte disorders often have mild thrombocytopenia, but in approximately 1% of patients platelets are severely reduced secondary to suppression of megakaryocytes by the malignant T cells.[92]

Virtually all patients with acute leukemia have thrombocytopenia at diagnosis. Patients with promyelocytic leukemia usually present dramatically with bleeding, thrombocytopenia, and coagulopathy, which reverse rapidly with all-*trans* retinoic acid and/or arsenic trioxide.

THROMBOCYTOPENIA IN THE SOLID TUMOR PATIENT

In most patients with solid tumors, thrombocytopenia can be explained by chemotherapy and/or radiation therapy. The incidence of chemotherapy-induced thrombocytopenia (platelet count <100,000/μL) is 21.8%, with the highest frequency seen in patients receiving carboplatin alone or in combination.[94] Drug-induced immune-mediated thrombocytopenia is also associated with chemotherapy agents, and has been described most commonly with oxaliplatin, fludarabine, and rituximab.[95,96]

In patients with advanced bone marrow metastasis, thrombocytopenia as part of the pancytopenia of a myelophthisic process can be readily diagnosed by demonstrating a leukoerythroblastic picture in the peripheral blood. However, less common causes of thrombocytopenia should not be overlooked. Patients may have thrombocytopenia as part of a consumptive coagulopathy (especially common in patients with widespread adenocarcinoma of the prostate, stomach, lung, and breast), which may also be associated with venous or arterial thrombosis and a Trousseau syndrome. In these patients low fibrinogen and other markers of DIC will be present, and they may respond to heparin therapy.

Thrombotic microangiopathy (TMA) mimicking thrombotic thrombocytopenic purpura or hemolytic uremic syndrome is an uncommon but well described complication of solid tumors, especially gastric and breast cancer, and other mucin-producing adenocarcinomas. Patients usually have widely disseminated cancer and do not respond to plasmapheresis.[97] Chemotherapy agents, mainly mitomycin (incidence 2%–15%) and gemcitabine (incidence 0.25%–0.4%), cause TMA likely through direct endothelial cell damage.[98] Data are now emerging that some of the newer, targeted antineoplastic agents are also associated with TMA, especially bevacizumab and sunitinib, drugs that target the vascular endothelial growth factor pathway.[99]

ITP is rare and potentially treatable complication of solid tumors, and should be suspected when the platelet count is lower than what would be expected by the antineoplastic therapy or the myelophthisic processes alone. In these patients a high index of suspicion is required and, as in other ITP patients, the diagnosis can often only be confirmed when response to treatment with steroids and/or immunoglobulins is demonstrated.[100]

THROMBOCYTOPENIA IN THE STEM CELL AND SOLID ORGAN TRANSPLANT PATIENT

Thrombocytopenia in the patient who has undergone a stem cell or organ transplant has a broad differential and is often a poor prognostic feature. Posttransplant TMA occurs in 9% to 15% of allogeneic stem cell transplants and in 5% of renal transplants. It is associated with the calcineurin inhibitors tacrolimus and cyclosporine, infections (*Aspergillus*, cytomegalovirus, adenovirus), and acute graft-versus-host disease. Renal damage is prominent, and overall prognosis is poor.[101,102] Other causes of thrombocytopenia in these patients include medications (methotrexate, ganciclovir, trimethoprim/sulfamethoxazole), ITP, splenomegaly, and infections, especially cytomegalovirus, which is associated with both stem cell graft failure and isolated thrombocytopenia.

SUMMARY

Thrombocytopenia is a common laboratory finding and is a frequent reason for a hematology consult. Once pseudothrombocytopenia has been ruled out, the differential diagnosis of thrombocytopenia includes platelet destruction, reduced platelet production, splenic sequestration, and hemodilution. The causes, severity, and acuity of thrombocytopenia vary widely depending on the clinical scenario. Infection, hemodilution, and DIC are common causes in the ICU. ITP and congenital causes are usually encountered in the outpatient setting. Alcohol consumption and medications are common causes in both the outpatient and inpatient setting. A thorough history, physical examination, and examination of the peripheral blood smear will reveal the cause in most patients. This review describes the mechanisms causing thrombocytopenia, and discusses the causes and management of a low platelet count in the different clinical settings likely encountered by the hematologist.

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