

# Thrombocytopenia

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Thrombocytopenia is defined as a platelet count of less than  $150 \times 10^3$  per  $\mu\text{L}$ . It is often discovered incidentally when obtaining a complete blood count during an office visit. The etiology usually is not obvious, and additional investigation is required. Patients with platelet counts greater than  $50 \times 10^3$  per  $\mu\text{L}$  rarely have symptoms. A platelet count from 30 to  $50 \times 10^3$  per  $\mu\text{L}$  rarely manifests as purpura. A count from 10 to  $30 \times 10^3$  per  $\mu\text{L}$  may cause bleeding with minimal trauma. A platelet count less than  $5 \times 10^3$  per  $\mu\text{L}$  may cause spontaneous bleeding and constitutes a hematologic emergency. Patients who present with thrombocytopenia as part of a multisystem disorder usually are ill and require urgent evaluation and treatment. These patients most likely have an acute infection, heparin-induced thrombocytopenia, liver disease, thrombotic thrombocytopenic purpura/hemolytic uremic syndrome, disseminated intravascular coagulation, or a hematologic disorder. During pregnancy, preeclampsia and the HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome are associated with thrombocytopenia. Patients with isolated thrombocytopenia commonly have drug-induced thrombocytopenia, immune thrombocytopenic purpura, pseudothrombocytopenia, or if pregnant, gestational thrombocytopenia. A history, physical examination, and laboratory studies can differentiate patients who require immediate intervention from those who can be treated in the outpatient setting. Treatment is based on the etiology and, in some cases, treating the secondary cause results in normalization of platelet counts. Consultation with a hematologist should be considered if patients require hospitalization, if there is evidence of systemic disease, or if thrombocytopenia worsens despite initial treatment. (*Am Fam Physician*. 2012;85(6):612-622. Copyright © 2012 American Academy of Family Physicians.)

► **Patient information:**  
A handout on low platelet count, written by the authors of this article, is provided on page 623.

Family physicians often see patients who present with a low platelet count. Although further inquiry may elicit additional signs and symptoms of systemic disease, the etiology of thrombocytopenia usually is not immediately apparent. A low platelet count may be the only hematologic abnormality. In adults, thrombocytopenia is a platelet count less than  $150 \times 10^3$  per  $\mu\text{L}$  ( $150 \times 10^9$  per L). Cases are considered mild if counts are between 70 and  $150 \times 10^3$  per  $\mu\text{L}$  ( $70$  to  $150 \times 10^9$  per L) and severe if less than  $20 \times 10^3$  per  $\mu\text{L}$  ( $20 \times 10^9$  per L).<sup>1</sup> Patients with a platelet count greater than  $50 \times 10^3$  per  $\mu\text{L}$  ( $50 \times 10^9$  per L) often are asymptomatic. Patients with a count from 30 to  $50 \times 10^3$  per  $\mu\text{L}$  ( $30$  to  $50 \times 10^9$  per L) rarely present with purpura, although they may have excessive bleeding with trauma. However, counts from 10 to  $30 \times 10^3$  per  $\mu\text{L}$  ( $10$  to  $30 \times 10^9$  per L) may cause bleeding with minimal trauma, and counts less than  $10 \times 10^3$  per  $\mu\text{L}$  increase the risk of spontaneous bleeding, petechiae, and bruising. Spontaneous bleeding (i.e., mucosal, intracranial, gastrointestinal, and genitourinary bleeding) is more likely in patients with platelet counts less than  $5 \times 10^3$  per  $\mu\text{L}$

( $5 \times 10^9$  per L), and is considered a hematologic emergency.<sup>2</sup>

## Initial Evaluation

Thrombocytopenia can result from decreased platelet production, increased platelet consumption, or sequestration (*Table 1*<sup>3-6</sup>). Common etiologies with clinical findings and suggested treatment are listed in *Table 2*,<sup>7-14</sup> and clinical considerations to aid in diagnosis are listed in *Table 3*. A systematic approach should be used to evaluate incidental thrombocytopenia. During the patient history, physicians should inquire about easy bruising or petechiae, melena, rashes, fevers, and bleeding. They also should inquire about medication use, immunizations, recent travel, transfusion history, family history, and medical history. A history of acute and chronic alcohol use should be obtained. Any recent hospitalization or heparin exposure should raise the possibility of heparin-induced thrombocytopenia. Pregnant patients with visual symptoms, headaches, abdominal pain, or influenza-like symptoms may have preeclampsia or HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome.

**SORT: KEY RECOMMENDATION FOR PRACTICE**

<i>Clinical recommendation</i>	<i>Evidence rating</i>	<i>References</i>	<i>Comments</i>
Corticosteroids are first-line treatment for immune thrombocytopenic purpura.	C	2, 21	Treatment is rarely indicated in patients with platelet counts greater than $50 \times 10^3$ per $\mu\text{L}$ ( $50 \times 10^9$ per L).
Patients older than 60 years with thrombocytopenia should be evaluated for myelodysplastic syndrome or lymphoproliferative disorders.	C	2, 21	Patients with myelodysplastic syndrome usually will present with anemia and lymphoma with lymphadenopathy.
Pregnant patients with platelet counts greater than $115 \times 10^3$ per $\mu\text{L}$ ( $115 \times 10^9$ per L) and no evidence of preeclampsia or HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome do not require further evaluation.	C	9, 37	Gestational thrombocytopenia is common and does not pose a risk to the fetus or mother.
Patients with mild thrombocytopenia (i.e., platelet counts of 100 to $150 \times 10^3$ per $\mu\text{L}$ [ $100$ to $150 \times 10^9$ per L]) who are asymptomatic should have a platelet count repeated in two to four weeks.	C	16	Any change in clinical health or evidence of bleeding before repeat testing should prompt immediate reevaluation.
Patients with stable thrombocytopenia (platelet counts greater than $50 \times 10^3$ per $\mu\text{L}$ ) generally do not require activity restrictions and are able to tolerate most invasive procedures.	C	39, 41, 42	The information is based on long-term outcomes from patients with chronic immune thrombocytopenic purpura.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to <http://www.aafp.org/afpsort.xml>.

**Table 1. Etiologies of Thrombocytopenia****Decreased platelet production**

Bone marrow failure (e.g., aplastic anemia, paroxysmal nocturnal hemoglobinuria, Shwachman-Diamond syndrome)  
 Bone marrow suppression (e.g., from medication, chemotherapy, or irradiation)  
 Chronic alcohol abuse\*  
 Congenital macrothrombocytopenias (e.g., Alport syndrome, Bernard-Soulier syndrome, Fanconi anemia, platelet-type or pseudo-von Willebrand disease, Wiskott-Aldrich syndrome)  
 Infection† (e.g., cytomegalovirus, Epstein-Barr virus, hepatitis C virus, HIV, mumps, parvovirus B19, rickettsia, rubella, varicella-zoster virus)  
 Myelodysplastic syndrome  
 Neoplastic marrow infiltration  
 Nutritional deficiencies (vitamin B<sub>12</sub> and folate)

**Increased platelet consumption**

Alloimmune destruction (e.g., posttransfusion, neonatal, posttransplantation)  
 Autoimmune syndromes (e.g., antiphospholipid syndrome, systemic lupus erythematosus, sarcoidosis)  
 Disseminated intravascular coagulation\*/severe sepsis\*  
 Drug-induced thrombocytopenia

**Increased platelet consumption (continued)**

Heparin-induced thrombocytopenia  
 Immune thrombocytopenic purpura\*  
 Infection† (e.g., cytomegalovirus, Epstein-Barr virus, hepatitis C virus, HIV, mumps, parvovirus B19, rickettsia, rubella, varicella-zoster virus)  
 Mechanical destruction (e.g., aortic valve, mechanical valve, extracorporeal bypass)  
 Preeclampsia/HELLP syndrome  
 Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome

**Sequestration/other**

Chronic alcohol abuse\*  
 Dilutional thrombocytopenia (e.g., hemorrhage, excessive crystalloid infusion)  
 Gestational thrombocytopenia  
 Hypersplenism (e.g., distributional thrombocytopenia)  
 Liver disease (e.g., cirrhosis, fibrosis, portal hypertension)  
 Pseudothrombocytopenia  
 Pulmonary emboli  
 Pulmonary hypertension

HELLP = hemolysis, elevated liver enzymes, and low platelet count; HIV = human immunodeficiency virus.

\*—More than one mechanism of action.

†—Thrombocytopenia with infection is usually caused by bone marrow suppression. In some cases, the thrombocytopenia is also immune-mediated. Information from references 3 through 6.

**Table 2. Common Etiologies of Thrombocytopenia with Clinical Findings and Suggested Treatment**

<i>Etiology</i>	<i>Severity</i>	<i>Clinical presentation</i>
Bone marrow suppression by irradiation, chemotherapy, or neoplasia	Moderate to severe	History of exposure, comorbid preexisting disease, or malignancy Acute leukemias present with fatigue, weakness, bruising, hepatosplenomegaly
Chronic alcohol abuse	Mild to moderate	Findings range from normal to evidence of cirrhosis or hepatic failure
Chronic liver disease	Mild to severe	Symptoms are variable based on evidence of cirrhosis, liver dysfunction, gastrointestinal bleeding, ascites, hepatomegaly, and jaundice
Congenital thrombocytopenia	Mild to moderate	Long history of abnormal platelet count or family history of thrombocytopenia
Disseminated intravascular coagulation	Severe	Acute illness; bleeding, acute renal failure, hepatic and respiratory dysfunction, and shock are common clinical manifestations Secondary to other comorbid conditions, such as sepsis, trauma, burns, or malignancy
Drug-induced thrombocytopenia	Moderate to severe	Can range from asymptomatic to evidence of clinical bleeding
Gestational thrombocytopenia	Mild	Asymptomatic with platelet counts rarely $< 70 \times 10^3$ per $\mu\text{L}$ ( $70 \times 10^9$ per L)
Heparin-induced thrombocytopenia	Mild to moderate	Thrombocytopenia or a 50 percent reduction after exposure to heparin or low-molecular-weight heparin Arterial and venous thrombosis
Immune thrombocytopenic purpura	Moderate to severe	Often asymptomatic, although symptoms can range from petechiae and easy bruising to severe bleeding diathesis (rare) Secondary ITP may present in patients with autoimmune disorders, infections (e.g., cytomegalovirus, Epstein-Barr virus, <i>Helicobacter pylori</i> , hepatitis C virus, human immunodeficiency virus, varicella-zoster virus), and lymphoproliferative disorders
Infections (viral or rickettsial)	Mild to moderate	Viral: prodrome or asymptomatic; known viruses include cytomegalovirus, Epstein-Barr virus, hepatitis B and C viruses, human immunodeficiency virus, parvovirus B19, varicella-zoster virus Rickettsial: Lyme disease, Rocky Mountain spotted fever, ehrlichiosis; tick-borne illnesses present with fever, headache, malaise, arthralgias, and rash
Preeclampsia/HELLP syndrome	Mild to moderate	Elevated blood pressure, visual symptoms, headache, right upper quadrant abdominal pain, influenza-like symptoms
Pseudothrombocytopenia	Factitious	Asymptomatic; in vitro agglutination of platelets
Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome	Moderate to severe	Most common presentation is nonspecific and includes abdominal pain, nausea/vomiting, and weakness; patients with thrombotic thrombocytopenic purpura may have neurologic abnormalities at presentation

ALT = alanine transaminase; AST = aspartate transaminase; CBC = complete blood count; EDTA = ethylenediaminetetraacetic acid; ELISA = enzyme-linked immunosorbent assay; GGT =  $\gamma$ -glutamyltransferase; HELLP = hemolysis, elevated liver enzymes, and low platelet count; ITP = immune thrombocytopenic purpura; IVIG = intravenous immune globulin; LDH = lactate dehydrogenase; MMR = measles, mumps, and rubella.

Information from references 7 through 14.

<i>Evaluation</i>	<i>Treatment</i>	<i>Comments</i>
Directed by preexisting diagnosis, specific cancer markers Abnormal blood smear or bone marrow biopsy	Based on underlying etiology	Usually affects all cell lines
Positive screening questionnaire, abnormal liver function tests (AST/ALT > 2, GGT), macrocytosis, folate deficiency, hepatic imaging as clinically indicated	Cessation of alcohol use, vitamin and nutritional replacement	Cessation of alcohol use may lead to platelet rebound (> 500 × 10 <sup>3</sup> per µL [500 × 10 <sup>9</sup> per L]) at one to two weeks
Abnormal intrinsic liver function testing, imaging and liver biopsy as clinically indicated	Based on etiology; often supportive	Hypersplenism often is present contributing to thrombocytopenia
Many disorders associated with giant platelets, neutrophil inclusions, or other congenital anomalies	Varies depending on primary abnormality	Often asymptomatic when there is no bleeding diathesis
Prolonged coagulation activation, elevated fibrin markers, and accelerated fibrinolysis (low fibrinogen levels)	Supportive treatment with platelet and clotting factor replacement therapy	Mortality rates exceed 20 percent; prognosis is based on treating the underlying disorder
Detailed history of recent prescription medications, nutritional supplements, and over-the-counter agents	Removal of offending agent Serial platelet monitoring until normalization	May be initially indistinguishable from ITP Often resolves within seven to 14 days after agent is discontinued
Identified during initial prenatal CBC No associated fetal thrombocytopenia Spontaneous resolution after delivery	No treatment indicated Platelet counts approaching 50 × 10 <sup>3</sup> per µL (50 × 10 <sup>9</sup> per L) often are considered ITP and treated with corticosteroids or IVIG	Possible immunologic etiology May be difficult to distinguish from ITP before delivery Up to 15 percent of infants with thrombocytopenia are born to women with ITP
History of heparin use; erythema or necrosis at site of injection; thrombosis; ELISA test for presence of platelet factor 4 antibodies	Immediate withdrawal of heparin; treatment with nonheparin anticoagulant	Warfarin (Coumadin) monotherapy may induce thrombosis and is contraindicated in the acute setting
Remainder of CBC normal; normal peripheral blood smear; absence of clinically associated conditions Secondary ITP causes should be investigated as clinically indicated	Corticosteroids, IVIG, rituximab (Rituxan), splenectomy Treatment not indicated for platelet counts > 50 × 10 <sup>3</sup> per µL unless active bleeding Secondary ITP also requires treatment of underlying cause	Diagnosis of exclusion Patients older than 60 years should have bone marrow biopsy to rule out myelodysplastic syndrome or lymphoproliferative disorder MMR vaccination causes one case of ITP per 40,000 doses
Viral: diagnosis based on viral etiology; directed antiviral titer testing if available Rickettsial: ELISA testing may be useful	Viral: based on viral etiology; most self-limited viral infections are supportive Rickettsial: doxycycline is recommended in symptomatic tick-borne disease	Viral: varicella (live) and influenza A (H1N1) vaccinations have been reported to cause mild transient thrombocytopenia Rickettsial: ehrlichiosis causes more severe thrombocytopenia than Rocky Mountain spotted fever and Lyme disease
CBC, liver function test, urine protein level, increased uric acid level, increased LDH level, basic metabolic panel	Delivering the fetus; intravenous magnesium sulfate	Recovery usually is within three days of delivery If persistent beyond the third day after delivery, presume thrombotic thrombocytopenic purpura
Repeat CBC using non-EDTA anticoagulant	No treatment indicated	Peripheral blood smear will demonstrate clumping
Microangiopathic hemolytic anemia; impaired renal function; neurologic abnormalities; proteinuria; increased LDH, increased bilirubin, and decreased haptoglobin levels	Plasma exchange	10 to 30 percent mortality despite treatment; in children, hemolytic uremic syndrome presents with gastroenteritis (bloody diarrhea) and 60 percent will have thrombocytopenia

**Table 3. Clinical Considerations to Aid in Diagnosis of Thrombocytopenia**

<i>Clinical consideration</i>	<i>Possible diagnosis</i>
<b>Timing</b>	
Acute	Acute infection (primarily viral), acute leukemias, aplastic anemia, chemotherapy or irradiation, drug-induced thrombocytopenia, HELLP syndrome/preeclampsia, heparin-induced thrombocytopenia, ITP, malignancies with marrow infiltration, myelofibrosis, TTP/HUS
Chronic	Chronic alcohol abuse, congenital syndromes, ITP, liver disease, myelodysplastic syndrome
<b>History</b>	
Family history	Congenital thrombocytopenia
Liver disease	Chronic alcohol abuse, chronic liver disease
Pregnancy	Gestational thrombocytopenia, HELLP syndrome/preeclampsia
Recent change in medication	Drug-induced thrombocytopenia
Recent hospitalization	Heparin-induced thrombocytopenia
Recent immunization	MMR, varicella, influenza A (H1N1)
Recent transfusion or high-risk behavior	Alloimmune destruction, posttransfusion purpura, viral infection (HCV, HIV)
Recent travel	Dengue fever, malaria, rickettsial diseases
Recent valve replacement surgery	Mechanical destruction
<b>Symptoms</b>	
Abdominal pain	HELLP syndrome/preeclampsia, HUS, platelet sequestration
Recent fever	Viral infections (CMV, EBV, HIV, influenza A [H1N1], parvovirus B19), TTP, rickettsial diseases
Weight loss or night sweats	HIV, malignancies (acute leukemias, myelodysplastic syndrome)
<b>Physical examination</b>	
Acute rash	Rickettsial diseases, SLE, viral infections
Generalized lymphadenopathy	Viral infections (CMV, EBV, HIV), SLE, myeloproliferative disorders, lymphoproliferative disorders
Hepatomegaly	Chronic liver disease, acute leukemias, viral infections (CMV, EBV, HBV, HCV)
Neurologic	TTP
Splenomegaly*	Autoimmune (SLE, sarcoidosis), hypersplenism, viral infections

CMV = cytomegalovirus; EBV = Epstein-Barr virus; HBV = hepatitis B virus; HCV = hepatitis C virus; HELLP = hemolysis, elevated liver enzymes, and low platelet count; HIV = human immunodeficiency virus; HUS = hemolytic uremic syndrome; ITP = immune thrombocytopenic purpura; MMR = measles, mumps, and rubella; SLE = systemic lupus erythematosus; TTP = thrombotic thrombocytopenic purpura.

\*—Ultrasonography may be useful in patients who are obese.

management) or nonemergent (outpatient management). Some syndromes may fall in either category based on the severity of thrombocytopenia.

A peripheral blood smear can provide diagnostic information on a variety of white blood cell disorders, hemolytic anemias, and thrombocytopenia.<sup>15</sup> A blood smear should be obtained during the initial evaluation. *Table 4* lists common findings on peripheral blood smear and their associated diagnoses.

### Long-term Outcomes of Incidental Thrombocytopenia

The findings of isolated thrombocytopenia in an outpatient setting have prognostic implications. A prospective study evaluated the long-term outcomes of patients with incidental thrombocytopenia. The study followed 217 persons with platelet counts from 100 to 150 × 10<sup>3</sup> per μL (100 to 150 × 10<sup>9</sup> per L) over a 10-year period. In 64 percent of patients, platelet counts normalized or remained stable. The probability of developing immune thrombocytopenic purpura or an autoimmune disorder was approximately 7 and 12 percent, respectively. Four cases of myelodysplastic syndrome were diagnosed (2 percent), all of which were in older patients.<sup>16</sup>

### Factitious Thrombocytopenia

Pseudothrombocytopenia is secondary to platelet clumping and has no clinical significance. It occurs in one in 1,000 persons in the general population, and can be confirmed by a peripheral blood smear.<sup>3</sup> Causes include use of abciximab (Reopro) or ethylenediaminetetraacetic acid–dependent agglutinins.<sup>17,18</sup> The platelet count should be repeated by collecting blood in a tube with a non-ethylenediaminetetraacetic acid anticoagulant, such as heparin or sodium

citrate. If the complete blood count still shows thrombocytopenia, other causes should be investigated.

### Emergent Thrombocytopenia

#### IMMUNE (IDIOPATHIC) THROMBOCYTOPENIC PURPURA

Immune thrombocytopenic purpura is an acquired immune-mediated disorder characterized by isolated thrombocytopenia and the absence of other conditions

The physical examination should include the eyes (e.g., hemorrhage is suggestive of central nervous system bleeding), abdomen (e.g., splenomegaly, hepatomegaly), lymph nodes (e.g., lymphadenopathy), skin (e.g., petechiae, purpura, bruising), and neurologic system. Bleeding (e.g., epistaxis, mucosal, gastrointestinal, genitourinary) also should be assessed. Thrombocytopenia can be classified as emergent (usually requires inpatient

**Table 4. Common Peripheral Blood Smear Findings and Possible Diagnoses**

<i>Smear findings</i>	<i>Possible diagnosis</i>	<i>Comments</i>
Atypical lymphocytosis	Viral infection (e.g., Epstein-Barr virus, cytomegalovirus)	Abundant cytoplasm
Basophilic stippling	Thalassemia, chronic alcohol use, lead or metal poisoning	Ribosomal precipitate (appears as blue granules) throughout the cytoplasm of the red blood cell
Cryoglobulin	Cryoglobulinemia, mycoplasma pneumonia, multiple myeloma, some autoimmune disorders	Proteins that precipitate when blood is below normal body temperature
Giant platelets	Congenital thrombocytopenias, immune thrombocytopenic purpura	Caused by increased platelet turnover or release of immature forms into the circulation
Megakaryocyte fragments	Myelofibrosis	Presence of large platelets
Nucleated red blood cells	Severe hemolysis, myelofibrosis	Immature red blood cells secondary to accelerated erythropoiesis
Oval macrocytosis	Vitamin B <sub>12</sub> and folate deficiencies	Suggests impaired bone marrow synthesis
Platelet agglutination	Pseudothrombocytopenia	Clumping of platelets in patients with EDTA-activated antiplatelet antibodies
Platelet hypogranularity	Myelodysplastic syndrome, myelofibrosis	Suggests impaired bone marrow synthesis
Round macrocytosis	Myelodysplastic syndrome, myelofibrosis, chronic liver disease	Suggests impaired bone marrow synthesis
Schistocytosis	Thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, disseminated intravascular coagulation, defective prosthetic heart valve	Fragmented erythrocytes
Target cells	Chronic liver disease, hemoglobinopathies	Excess hemoglobin in the center of the red blood cell

EDTA = ethylenediaminetetraacetic acid.

or agents known to induce thrombocytopenia. The incidence is 100 cases per 1 million persons annually, and approximately 50 percent of cases occur in children.<sup>2</sup> Immune thrombocytopenic purpura in children often resolves spontaneously but tends to be more insidious and chronic in adults. The risk of bleeding correlates to the severity of thrombocytopenia. Patients may present without symptoms, with minimal bleeding, or with serious hemorrhage (e.g., mucosal, intracranial, gastrointestinal, genitourinary). Older patients, patients on antiplatelet therapy, and patients with comorbid conditions may have more severe bleeding manifestations.<sup>19</sup>

Secondary immune thrombocytopenic purpura is associated with other underlying conditions, such as autoimmune disorders (e.g., systemic lupus erythematosus, antiphospholipid syndrome, Graves disease, sarcoidosis), lymphoproliferative disorders, and infections (e.g., human immunodeficiency virus, Epstein-Barr virus, cytomegalovirus, varicella-zoster virus, hepatitis C virus, *Helicobacter pylori*). Testing to rule out other causes should be performed as clinically indicated. Forty percent of patients with immune thrombocytopenic purpura test positive for antinuclear or

antiphospholipid antibodies without having an underlying autoimmune syndrome.<sup>20</sup> Treatment is generally restricted to those with severe thrombocytopenia and is rarely indicated when platelet counts are greater than  $50 \times 10^3$  per  $\mu\text{L}$  unless there is evidence of active bleeding. Corticosteroids are considered first-line treatment and increase platelet counts usually within one week of initiation.<sup>2,21</sup> Intravenous immune globulin and rituximab (Rituxan) also have been used for initial treatment of immune thrombocytopenic purpura. Second-line treatment includes thrombopoietin-receptor agonists and splenectomy. Any patient older than 60 years presenting with isolated thrombocytopenia should be evaluated for myelodysplastic syndrome and lymphoproliferative disorders.<sup>2,21</sup>

#### HEPARIN-INDUCED THROMBOCYTOPENIA

Heparin-induced thrombocytopenia should be suspected in patients recently treated with heparin. Platelet counts decline within five to 10 days in patients with no previous exposure to heparin and may decline precipitously (within hours) in patients with recent heparin exposure. This life-threatening disorder is characterized

## Thrombocytopenia

by the presence of platelet-activating antibodies recognizing multimolecular complexes bound to unfractionated heparin or low-molecular-weight heparin. Patients with heparin-induced thrombocytopenia present with mild thrombocytopenia or a 50 percent decrease in platelet count from baseline.<sup>22</sup> The incidence is higher among surgical patients than medical patients. Thrombosis complications (termed heparin-induced thrombocytopenia with thrombosis) develop in 20 to 50 percent of patients and may affect arterial and venous systems, even after heparin is discontinued.<sup>23</sup>

Characteristic features are erythematous or necrotizing skin reactions at the site of injection or severe manifestations, such as deep venous thrombosis, pulmonary emboli, stroke, or myocardial infarction. The most widely available diagnostic test is an enzyme-linked immunosorbent assay with platelet factor 4/anion complex as the antigen. This test has a high sensitivity (greater than 97 percent) but a lower specificity (74 to 86 percent) because of the presence

**Drug-induced thrombocytopenia is one of the most common types of thrombocytopenia in the outpatient setting.**

of platelet factor 4 antibodies in patients without heparin-induced thrombocytopenia.<sup>22,24</sup> If the clinical diagnosis is suspected or confirmed by laboratory analysis, heparin should be stopped immediately and treatment should be changed to a nonheparin anticoagulant. One study showed that patients who developed heparin-induced thrombocytopenia had a 20 percent in-hospital mortality rate, regardless of thrombosis development.<sup>25</sup>

### THROMBOTIC THROMBOCYTOPENIC PURPURA

Patients presenting with thrombocytopenia and microangiopathic hemolytic anemia should be admitted to the hospital with a presumptive diagnosis of thrombotic thrombocytopenic purpura. Renal manifestations, neurologic changes, and fever also may be present. Severity is reflected by the extent of microvascular aggregation of platelets resulting in ischemia and necrosis of tissue cells. The incidence of thrombotic thrombocytopenic purpura is four to 11 patients per 1 million annually in the United States.<sup>7</sup> The condition often is caused by the absence or deficiency of a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13.<sup>7</sup> It is fatal without treatment; prompt initiation of plasma exchange is critical. Thrombotic thrombocytopenic purpura occurs primarily in adults. Hemolytic uremic syndrome is thrombotic thrombocytopenic purpura found in children presenting with acute renal failure, bloody

diarrhea, and/or abdominal pain. Shiga toxin-producing *Escherichia coli* is the most common causative organism in hemolytic uremic syndrome.<sup>26</sup>

### PREECLAMPSIA AND HELLP SYNDROME

Pregnant patients beyond 20 weeks' gestation with thrombocytopenia or signs and symptoms such as headache, visual disturbances, right upper quadrant abdominal pain, or elevated blood pressure should be evaluated for preeclampsia and HELLP syndrome. Laboratory abnormalities may include anemia, elevated liver enzymes, elevated lactate dehydrogenase, and proteinuria.<sup>27</sup> Treatment is intravenous magnesium sulfate and active management to deliver the fetus.<sup>28</sup> Pregnant patients also can present with other causes of thrombocytopenia, including disseminated intravascular coagulation (as seen with sepsis and placenta abruptio) and thrombotic thrombocytopenic purpura, which can mimic HELLP syndrome.

### OTHER CAUSES

Aplastic anemia, chemotherapy, irradiation, acute leukemias, and myelodysplastic disorders may result in severe or symptomatic thrombocytopenia. Paroxysmal nocturnal hemoglobinuria is associated with hemolysis, renal disease, and thrombosis complications. Hospitalized patients with comorbid conditions, such as sepsis, trauma, burns, or malignancy, can develop disseminated intravascular coagulation with resultant thrombocytopenia.

### Nonemergent Thrombocytopenia

#### DRUG-INDUCED THROMBOCYTOPENIA

One of the most common types of thrombocytopenia in the outpatient setting is drug-induced thrombocytopenia. An epidemiologic study from Europe and the United States showed an annual incidence of 10 cases per 1 million persons, but numbers could be higher in older persons and in hospitalized patients.<sup>29</sup> Drug-induced thrombocytopenia should be suspected in all patients presenting with an acute drop in platelet count. Most patients with drug-induced thrombocytopenia have moderate to severe thrombocytopenia reaching a nadir platelet count of  $20 \times 10^3$  per  $\mu\text{L}$ .<sup>8</sup> Physicians should ask specific questions about the use of any medications, including nutritional supplements and over-the-counter remedies. Quinine is a common cause of drug-induced thrombocytopenia and often is missed in the patient history.

*Table 5* lists common medications that may cause thrombocytopenia.<sup>8</sup> A comprehensive list of all case reports describing drug-induced thrombocytopenia is available at <http://www.ouhsc.edu/platelets>. Drug-induced thrombocytopenia typically occurs within five

**Table 5. Medications/Substances Commonly Associated with Drug-Induced Thrombocytopenia**

Medication/substance	Drug class	Proposed mechanism of action
Abciximab (Reopro)	Glycoprotein IIb/IIIa inhibitor	Drug-specific antibody
Alcohol	Ethanol	Suppression of megakaryocyte production
Carbamazepine (Tegretol)	Anticonvulsant	Unknown
Cephalosporins	Antibiotic	Hapten-dependent
Cimetidine (Tagamet)	Histamine H <sub>2</sub> blocker	Unknown
Eptifibatid (Integrilin)	Glycoprotein IIb/IIIa inhibitor	Drug-specific antibody
Gold salts	Antirheumatic	Autoantibody
Heparin	Anticoagulant	Platelet factor 4/heparin antibody
Hydrochlorothiazide	Antihypertensive	Suppression of megakaryocyte production
Interferon	Antiviral	Drug-specific antibody
Measles, mumps, and rubella vaccine	Vaccine	Vaccine-specific antibody
Phenytoin (Dilantin)	Anticonvulsant	Unknown
Procainamide	Antiarrhythmic	Autoantibody
Quinidine/quinine	Cinchona alkaloid	Drug-glycoprotein complex
Rifampin	Antibiotic	Autoantibody
Sulfasalazine (Azulfidine)	Anti-inflammatory	Drug-specific antibody
Trimethoprim/sulfamethoxazole (Bactrim, Septra)	Antibiotic	Drug-glycoprotein complex
Vancomycin	Antibiotic	Drug-specific antibody

Adapted with permission from Kenney B, Stack G. Drug-induced thrombocytopenia. *Arch Pathol Lab Med.* 2009;133(2):314. Copyright 2009. College of American Pathologists.

to seven days of exposure to the causative agent and usually resolves within seven to 14 days after discontinuation.<sup>30</sup> If drug-induced thrombocytopenia is suspected, the causative medication should be discontinued and the patient's platelet count should be repeated in one week.

### INFECTIONS

Infections may cause thrombocytopenia by direct bone marrow suppression or increased peripheral platelet consumption. Common viruses include hepatitis B and C, human immunodeficiency virus, Epstein-Barr, cytomegalovirus, parvovirus B19, varicella-zoster, rubella, and mumps. Recent studies found thrombocytopenia

in 14 percent of hospitalized patients with influenza A (H1N1) virus.<sup>31</sup> Platelet counts usually recover in patients with a self-limited viral infection. If the patient has a recent travel history, especially to South America or Mexico, dengue fever and malaria should be considered. Other travel-associated infections, such as typhoid fever, can cause thrombocytopenia.<sup>32</sup> Ehrlichiosis, Rocky Mountain spotted fever, and Lyme disease are common tick-borne illnesses that can cause transient thrombocytopenia.<sup>33</sup>

### LIVER DISEASE

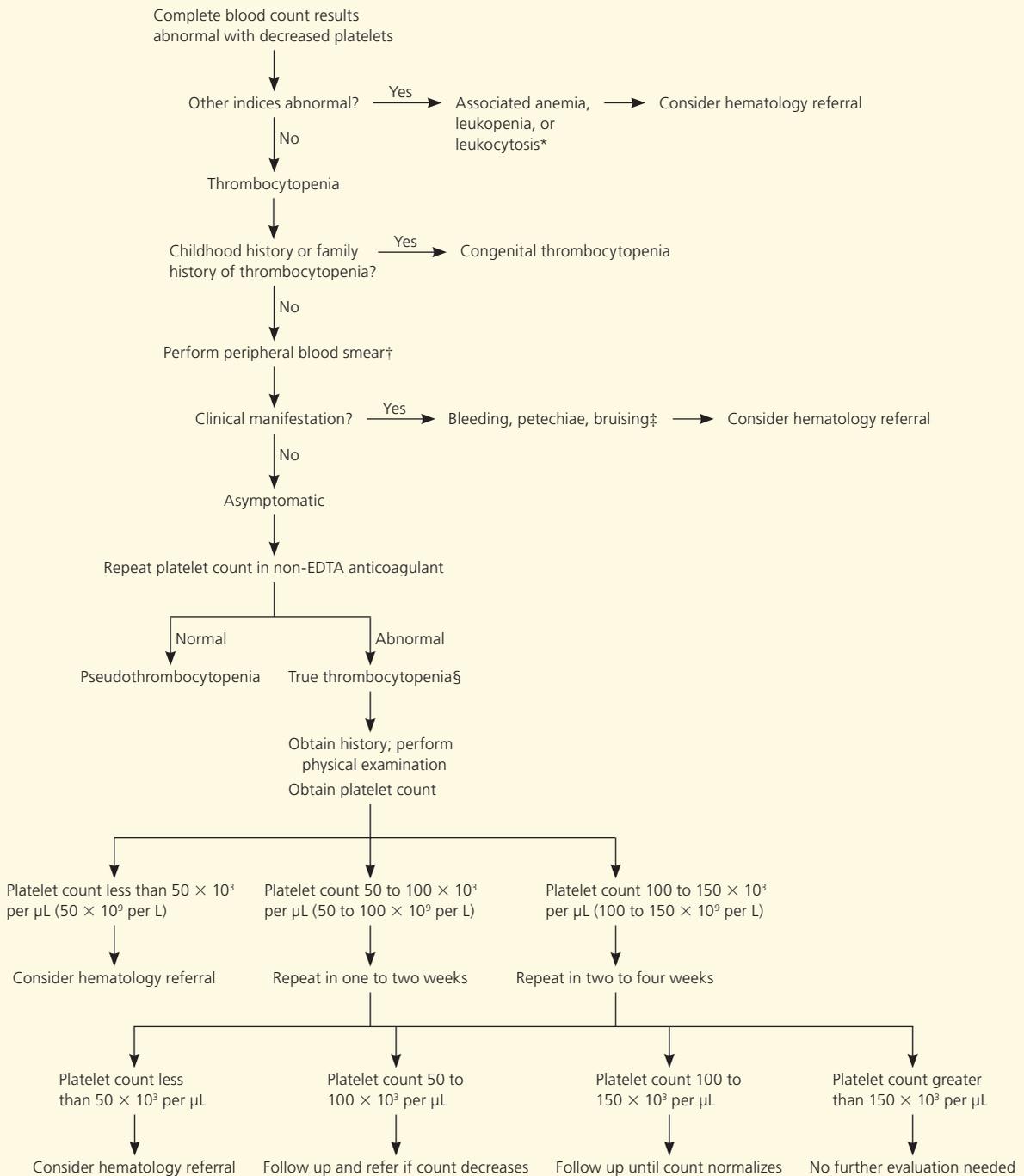
Chronic liver disease usually causes persistent thrombocytopenia, and manifests as cirrhosis, fibrosis, and portal hypertension. The most common cause is chronic alcohol abuse; however, other etiologies include infectious hepatitis, drug-induced liver disease, nonalcoholic liver disease, and metabolic disorders. Patients who consume excessive amounts of alcohol can present with varying degrees of liver impairment ranging from asymptomatic fatty liver to end-stage liver disease. Thrombocytopenia results from direct toxic marrow suppression and splenic sequestration. Folic acid deficiency (related to malnutrition) often coexists with alcohol abuse. Abstinence and nutritional replacement often lead to platelet normalization in three to four weeks in the absence of chronic liver disease.<sup>34</sup>

### GESTATIONAL THROMBOCYTOPENIA

Gestational thrombocytopenia is the most common diagnosis of thrombocytopenia in pregnancy, occurring in 8 percent of pregnancies.<sup>9,10</sup> Its etiology is thought to be hemodilution and accelerated platelet clearance. Gestational thrombocytopenia is characterized by mild thrombocytopenia, no history of thrombocytopenia, no association of fetal thrombocytopenia, and spontaneous resolution after delivery.<sup>35,36</sup> Gestational thrombocytopenia is a benign clinical condition not associated with maternal or neonatal morbidity or mortality.

Recommendations for the initial evaluation of thrombocytopenia in pregnancy include a complete blood count and peripheral blood smear.<sup>10</sup> Additional studies are determined on the basis of history and physical examination. Pregnant patients with platelet counts greater

## Management of Thrombocytopenia



\*—Bone marrow suppression, hematologic or infiltrative malignancy, TTP/HUS, liver disease, DIC, viral/rickettsial infection, nutritional deficiency, preeclampsia/HELLP syndrome (in pregnancy).

†—Giant platelets suggest congenital thrombocytopenia. Clumping is seen in pseudothrombocytopenia. Fragmented red blood cells suggest microangiopathic hemolytic anemia (TTP/HUS, DIC).

‡—ITP, TTP/HUS, heparin-induced thrombocytopenia if exposed, hypersplenism, viral/rickettsial infection, DIC, mechanical destruction, preeclampsia/HELLP syndrome (in pregnancy).

§—ITP, heparin-induced thrombocytopenia if exposed, drug-induced thrombocytopenia, hypersplenism, viral/rickettsial infection, mechanical destruction, gestational thrombocytopenia (in pregnancy).

**Figure 1.** Algorithm for the management of thrombocytopenia. (DIC = disseminated intravascular coagulation; EDTA = ethylenediaminetetraacetic acid; HELLP = hemolysis, elevated liver enzymes, and low platelet count; HUS = hemolytic uremic syndrome; ITP = immune thrombocytopenic purpura; TTP = thrombotic thrombocytopenic purpura.)

Information from reference 4.

than  $115 \times 10^3$  per  $\mu\text{L}$  ( $115 \times 10^9$  per L) and no evidence of preeclampsia or HELLP syndrome do not require further evaluation.<sup>9,37</sup>

Mild immune thrombocytopenic purpura and gestational thrombocytopenia often are indistinguishable and cannot be differentiated on the basis of antiplatelet antibody screening; however, 12 to 15 percent of neonates delivered to women with immune thrombocytopenic purpura will develop platelet counts of less than  $50 \times 10^3$  per  $\mu\text{L}$ .<sup>38</sup> The platelet count in infants should be monitored when immune thrombocytopenic purpura is suspected in the mother.

## Management

A suggested algorithm for the management of thrombocytopenia is shown in *Figure 1*.<sup>4</sup> Symptomatic patients require immediate evaluation. Patients with incidental thrombocytopenia (i.e., platelet counts of 50 to  $150 \times 10^3$  per  $\mu\text{L}$ ) who are asymptomatic should have a platelet count repeated in one to four weeks depending on the severity of thrombocytopenia.<sup>16</sup> Reassessment should be performed immediately if patients become symptomatic during the surveillance period. Additional laboratory evaluation should be performed as clinically indicated, and a trial of discontinuing agents known to decrease platelet counts is recommended. Patients with chronic alcohol abuse or known nutritional deficiencies with stable thrombocytopenia can be treated by a primary care physician. Rickettsial diseases and most viral infections causing transient thrombocytopenia also can be managed by a primary care physician. Patients with unexplained severe thrombocytopenia, decreasing platelet counts, additional hematologic abnormalities, or associated bleeding complications should be referred to a hematologist.

## Activity Participation and Invasive Procedures

General recommendations for activity participation have been based on historical data from patients with chronic severe thrombocytopenia.<sup>39,40</sup> A platelet count greater than  $50 \times 10^3$  per  $\mu\text{L}$  is adequate for hemostasis and is unlikely to be clinically recognized. Patients with a platelet count greater than this level can engage in most activities, but should use caution if participating in contact sports.<sup>16,40</sup> Patients with platelet counts less than  $10 \times 10^3$  per  $\mu\text{L}$  should be restricted from contact sports and other potentially traumatic activities. In one study, 42 percent of patients with platelet counts less than  $10 \times 10^3$  per  $\mu\text{L}$  had spontaneous bleeding requiring intervention (e.g., nasal packing) compared with 6 percent of patients with counts between 10 and  $30 \times 10^3$  per  $\mu\text{L}$ .<sup>39</sup>

Most surgical and invasive procedures can be performed safely in patients with platelet counts greater than  $50 \times 10^3$  per  $\mu\text{L}$ . Other procedures, such as bone marrow biopsy, bronchoscopy, and endoscopy, can be completed safely in patients with platelet counts greater than  $20 \times 10^3$  per  $\mu\text{L}$ , provided that no other bleeding abnormalities are noted.<sup>41,42</sup> The American College of Obstetricians and Gynecologists recommendations state that epidural anesthesia in pregnancy is safe in patients with platelet counts between 50 and  $100 \times 10^3$  per  $\mu\text{L}$ .<sup>10</sup>

**Data Sources:** The authors searched OvidSP, UpToDate, American Academy of Family Physicians, American College of Obstetricians and Gynecologists, American Society of Clinical Oncology Practice Guidelines, Hematology/Oncology Clinics or North America, Harrison's Principles of Internal Medicine (17th edition), Agency of Healthcare Research and Quality Evidence Reports, National Guidelines Clearinghouse, Cochrane Database of Systematic Reviews, and the Centre for Reviews and Dissemination. Key words included: thrombocytopenia, review, treatment, idiopathic (immune) thrombocytopenic purpura, thrombocytopenia in pregnancy, thrombotic thrombocytopenic purpura, heparin-induced thrombocytopenia, hemolytic uremic syndrome, preeclampsia, HELLP syndrome, gestational thrombocytopenia, pseudothrombocytopenia, myelodysplastic syndrome, microangiopathic hemoglobinopathies, drug-induced thrombocytopenia, platelet transfusion, inherited thrombocytopenias, antiphospholipid antibodies, and viral infections. Information published between 1996 and June 2010 was included. Original search dates: April 5 and June 16, 2010. Final search date: November 23, 2011.

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## REFERENCES

1. Buckley MF, James JW, Brown DE, et al. A novel approach to the assessment of variations in the human platelet count. *Thromb Haemost.* 2000; 83(3):480-484.
2. Cines DB, Blanchette VS. Immune thrombocytopenic purpura. *N Engl J Med.* 2002;346(13):995-1008.
3. Veneri D, Franchini M, Randon F, Nichele I, Pizzolo G, Ambrosetti A. Thrombocytopenias: a clinical point of view. *Blood Transfus.* 2009;7(2): 75-85.

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- Finnish Medical Society Duodecim. Thrombocytopenia. In: EBM Guidelines. Evidence-Based Medicine. Helsinki, Finland: Wiley Interscience. John Wiley & Sons; April 27, 2007. <http://www.guideline.gov/content.aspx?id=11048>. Accessed November 25, 2011.
- Landaw SA, George JN. Approach to the adult patient with thrombocytopenia [subscription required]. UpToDate. <http://www.uptodate.com/contents/approach-to-the-adult-patient-with-thrombocytopenia>. Accessed November 28, 2011
- Balduini CL, Cattaneo M, Fabris F, et al. Inherited thrombocytopenias: a proposed diagnostic algorithm from the Italian Gruppo di Studio delle Piastrine. *Haematologica*. 2003;88(5):582-592.
- George JN. Clinical practice. Thrombotic thrombocytopenic purpura. *N Engl J Med*. 2006;354(18):1927-1935.
- Kenney B, Stack G. Drug-induced thrombocytopenia. *Arch Pathol Lab Med*. 2009;133(2):309-314.
- Boehlen F, Hohlfeld P, Extermann P, et al. Platelet count at term pregnancy: a reappraisal of the threshold. *Obstet Gynecol*. 2000;95(1):29-33.
- ACOG practice bulletin: Thrombocytopenia in pregnancy. Number 6, September 1999. Clinical management guidelines for obstetrician-gynecologists. American College of Obstetricians and Gynecologists. *Int J Gynaecol Obstet*. 1999;67(2):117-128.
- France EK, Glanz J, Xu S, et al.; Vaccine Safety Datalink Team. Risk of immune thrombocytopenic purpura after measles-mumps-rubella immunization in children. *Pediatrics*. 2008;121(3):e687-e692.
- Bratton RL, Corey R. Tick-borne disease. *Am Fam Physician*. 2005;71(12):2323-2330.
- Levi M, Toh CH, Thachil J, Watson HG. Guidelines for the diagnosis and management of disseminated intravascular coagulation. British Committee for Standards in Haematology. *Br J Haematol*. 2009;145(1) 24-33.
- Boyce TG, Swerdlow DL, Griffin PM. *Escherichia coli* O157:H7 and the hemolytic-uremic syndrome. *N Engl J Med*. 1995;333(6):364-368.
- Bain BJ. Diagnosis from the blood smear. *N Engl J Med*. 2005;353(5):498-507.
- Stasi R, Amadori S, Osborn J, Newland AC, Provan D. Long-term outcome of otherwise healthy individuals with incidentally discovered borderline thrombocytopenia. *PLoS Med*. 2006;3(3):e24.
- Vicari A, Banfi G, Bonini PA. EDTA-dependent pseudothrombocytopenia: a 12-month epidemiological study. *Scand J Clin Lab Invest*. 1988;48(6):537-542.
- Sane DC, Damaraju LV, Topol EJ, et al. Occurrence and clinical significance of pseudothrombocytopenia during abciximab therapy. *J Am Coll Cardiol*. 2000;36(1):75-83.
- Cortelazzo S, Finazzi G, Buelli M, Molteni A, Viero P, Barbui T. High risk of severe bleeding in aged patients with chronic idiopathic thrombocytopenia purpura. *Blood*. 1991;77(1):31-33.
- Diz-Küçükkaya R, et al. Antiphospholipid antibodies and antiphospholipid syndrome in patients presenting with immune thrombocytopenic purpura: a prospective cohort study. *Blood*. 2001;98(6):1760-1764.
- Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. *Blood*. 2010;115(2):168-186.
- Arepally GM, Ortel TL. Clinical practice. Heparin-induced thrombocytopenia. *N Engl J Med*. 2006;355(8):809-817.
- Greinacher A, Farner B, Kroll H, Kohlmann T, Warkentin TE, Eichler P. Clinical features of heparin-induced thrombocytopenia including risk factors for thrombosis. A retrospective analysis of 408 patients. *Thromb Haemost*. 2005;94(1):132-135.
- Warkentin TE, Sheppard JA, Moore JC, Moore KM, Sigouin CS, Kelton JG. Laboratory testing for the antibodies that cause heparin-induced thrombocytopenia: how much class do we need? *J Lab Clin Med*. 2005;146(6):341-346.
- Baroletti S, Piovela C, Fanikos J, Labreche M, Lin J, Goldhaber SZ. Heparin-induced thrombocytopenia (HIT): clinical and economic outcomes. *Thromb Haemost*. 2008;100(6):1130-1135.
- Moake JL. Thrombotic microangiopathies. *N Engl J Med*. 2002;347(8):589-600.
- ACOG Committee on Practice Bulletins—Obstetrics. ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. *Obstet Gynecol*. 2002;99(1):159-167.
- Sibai BM. Diagnosis, controversies, and management of the syndrome of hemolysis, elevated liver enzymes, and low platelet count. *Obstet Gynecol*. 2004;103(5 pt 1):981-991.
- van den Bemt PM, Meyboom RH, Egberts AC. Drug-induced immune thrombocytopenia. *Drug Saf*. 2004;27(15):1243-1252.
- Aster RH, Bougie DW. Drug-induced immune thrombocytopenia. *N Engl J Med*. 2007;357(6):580-587.
- Jain S, Kamimoto L, Bramley AM, et al.; 2009 Pandemic Influenza A (H1N1) Virus Hospitalizations Investigation Team. Hospitalized patients with 2009 H1N1 influenza in the United States, April-June 2009. *N Engl J Med*. 2009;361(20):1935-1944.
- Ryan ET, Wilson ME, Kain KC. Illness after international travel. *N Engl J Med*. 2002;347(7):505-516.
- Chapman AS, Bakken JS, Folk SM, et al.; Tickborne Rickettsial Diseases Working Group; CDC. Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever, ehrlichioses, and anaplasmosis—United States: a practical guide for physicians and other health-care and public health professionals. *MMWR Recomm Rep*. 2006;55(RR-4):1-27.
- Girard DE, Kumar KL, McAfee JH. Hematologic effects of acute and chronic alcohol abuse. *Hematol Oncol Clin North Am*. 1987;1(2):321-334.
- Burrows RF, Kelton JG. Fetal thrombocytopenia and its relation to maternal thrombocytopenia. *N Engl J Med*. 1993;329(20):1463-1466.
- Burrows RF, Kelton JG. Low fetal risks in pregnancies associated with idiopathic thrombocytopenic purpura. *Am J Obstet Gynecol*. 1990;163(4 pt 1):1147-1150.
- Ruggeri M, Schiavotto C, Castaman G, Tosi A, Rodeghiero F. Gestational thrombocytopenia: a prospective study. *Haematologica*. 1997;82(3):341-342.
- Webert KE, Mittal R, Sigouin C, Heddle NM, Kelton JG. A retrospective 11-year analysis of obstetric patients with idiopathic thrombocytopenic purpura. *Blood*. 2003;102(13):4306-4311.
- Lacey JV, Penner JA. Management of idiopathic thrombocytopenic purpura in the adult. *Semin Thromb Hemost*. 1977;3(3):160-174.
- George JN. Evaluation and management of thrombocytopenia by primary care physicians [subscription required]. UpToDate. <http://www.uptodate.com/contents/evaluation-and-management-of-thrombocytopenia-by-primary-care-physicians>. Accessed October 18, 2011.
- Schiffert CA, Anderson KC, Bennett CL, et al. Platelet transfusion for patients with cancer: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol*. 2001;19(5):1519-1538.
- Slichter SJ. Evidence-based platelet transfusion guidelines. *Hematology Am Soc Hematol Educ Program*. 2007:172-178.