

# Thrombocytopenia

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**ABBREVIATIONS:** DIC = disseminated intravascular coagulation; HELLP syndrome = microangiopathic hemolysis, elevated liver enzymes, and a low platelet count; HIT = heparin-induced thrombocytopenia; HUS = hemolytic-uremic syndrome; HUS = hemolytic-uremic syndrome; ITP = immune thrombocytopenic purpura; PF4 = platelet factor 4; TAR = thrombocytopenia with absent radii; TTP = thrombotic thrombocytopenic purpura; ULVWF = unusually large von Willebrand factor; VWF = von Willebrand factor.

**INDEX TERMS:** platelets; immune thrombocytopenic purpura; thrombocytopenia.

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## LEARNING OBJECTIVES

Upon completion of this article, the reader will be able to:

1. list the inherited forms of thrombocytopenia and distinguish disorders of production from disorders of consumption.
2. recall the hallmark laboratory findings of chronic and acute immune thrombocytopenia purpura.

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3. test for heparin-induced thrombocytopenia with thrombosis.
4. distinguish thrombocytopenia-induced mucocutaneous bleeding from anatomic bleeding.
5. describe the mechanism of drug-induced thrombocytopenia and the means for its detection and cure.
6. distinguish between thrombotic thrombocytopenic purpura and hemolytic-uremic syndrome.

Thrombocytopenia is a decrease in circulating platelet count. The typical reference range is approximately 150,000 to 450,000/ $\mu$ L. Thrombocytopenia (platelet count  $<150,000/\mu$ L) is the most common cause of mucocutaneous bleeding, characterized by petechiae, purpura, ecchymoses, epistaxis, hematemesis, and menorrhagia. The primary pathophysiologic processes in thrombocytopenia are decreased platelet production, accelerated platelet destruction, and abnormal platelet distribution or sequestration (Table 1).

It is unusual for bleeding to occur when the platelet count is greater than 50,000/ $\mu$ L, and patients with platelet counts of 20,000/ $\mu$ L may have few bleeding symptoms. Patients with platelet counts less than 10,000/ $\mu$ L are at high risk for a serious spontaneous hemorrhagic episode.

## IMPAIRED PLATELET PRODUCTION

### Congenital megakaryocytic hypoplasia

Megakaryocytic hypoplasia (decrease in bone marrow megakaryocytes) is seen in thrombocytopenia with absent radii (TAR), Wiskott-Aldrich syndrome, Bernard-Soulier syndrome, and May-Hegglin anomaly. Although thrombocytopenia is a feature of Bernard-Soulier syndrome and Wiskott-Aldrich syndrome, the primary abnormality is qualitative so these are discussed separately.

May-Hegglin anomaly is a rare autosomal dominant disorder whose exact frequency is unknown. Platelets are 20  $\mu$ m in diameter and Döhle bodies are present in neutrophils (Figure 1). Other than their increased diameter, platelet morphology is normal. Thrombocytopenia is present in about one third to one half of patients. Platelet function in response to platelet activating agents is normal. In some patients, megakaryocytes are increased in number and have abnormal

**Table 1.** Thrombocytopenia classification

**Impaired or decreased platelet production**

**Congenital**

May-Hegglin anomaly  
Bernard-Soulier syndrome  
Fechtner syndrome  
Sebastian syndrome  
Epstein syndrome  
Montreal platelet syndrome  
Fanconi anemia  
Wiskott-Aldrich syndrome  
thrombocytopenia with absent radii (TAR)  
congenital amegakaryocytic thrombocytopenia  
autosomal dominant and X-linked  
thrombocytopenia

**Neonatal**

**Viral**

**Drug-induced**

**Acquired**

**Platelet destruction**

**Immune**

acute and chronic autoimmune thrombocytopenic  
purpura (ITP)  
drug-induced: immunologic  
heparin induced thrombocytopenia with  
thrombosis (HIT)  
neonatal alloimmune thrombocytopenia (NAIT)  
neonatal autoimmune thrombocytopenia  
post-transfusion purpura  
secondary autoimmune thrombocytopenia

**Nonimmune**

thrombocytopenia in pregnancy and pre-eclampsia  
human immunodeficiency virus-1 (HIV-1)  
hemolytic disease of the newborn (HDN)  
thrombotic thrombocytopenic purpura (TTP)  
hemolytic-uremic syndrome (HUS)  
disseminated intravascular coagulation (DIC)  
drugs: non-immune mechanisms of platelet  
destruction

**Disorders related to distribution or dilution**

**Splenic sequestration**

**Kasabach-Merritt syndrome**

**Hypothermia**

Loss of platelets: massive blood transfusions, extracorporeal circulation

ultrastructure. A mutation in the MYH9 gene that encodes for non-muscle myosin heavy chain, a cytoskeletal protein in platelets, may be responsible for the abnormal platelet diameter.<sup>1-3</sup> Most May-Hegglin patients have no bleeding, unless severe thrombocytopenia is present.

TAR syndrome is a rare autosomal recessive disorder characterized by neonatal thrombocytopenia and hypoplasia of the radial bones of the forearms with absent, short, or malformed ulnae. There is impaired DNA repair that results from a fetal injury at about eight weeks' gestation. Because exposure to radiation causes cellular DNA damage, TAR is also a radiation sensitivity syndrome.<sup>4</sup> Patients have a 90% incidence of leukemoid reactions with white blood cell counts sometimes exceeding 100,000/ $\mu$ L.<sup>5</sup> Platelet counts are 10,000 to 30,000/ $\mu$ L.

**Congenital amegakaryocytic thrombocytopenia**

Congenital amegakaryocytic thrombocytopenia is an autosomal recessive disorder reflecting bone marrow failure.<sup>6</sup> Affected infants have platelet counts less than 20,000/ $\mu$ L at birth with evidence of bleeding and physical anomalies. About half develop aplastic anemia in the first year of life, and there are reports of myelodysplasia and leukemia later in childhood. Stem cell transplantation is curative for infants with clinically severe disease or aplasia.<sup>7</sup> This disorder is caused by a *c-mpl* gene mutation with complete loss of thrombopoietin receptor function. This results in reduced megakaryocyte progenitors and high thrombopoietin levels.<sup>8</sup>

**Acquired neonatal hypoplasia**

Neonatal megakaryocytic hypoplasia is caused by infection with cytomegalovirus (CMV), *Toxoplasma*, rubella, and human immunodeficiency virus (HIV) and *in utero* exposure to chlorothiazide diuretics and the oral hypoglycemic tolbutamide. CMV is the most common infectious agent causing congenital thrombocytopenia at an overall incidence of 0.5% to 1% of all births,<sup>9</sup> but only 10% to 15% of infected infants have symptomatic disease,<sup>10</sup> so that the incidence of significant neonatal thrombocytopenia caused by CMV is about one in 1000 infants. CMV probably inhibits megakaryocytes, resulting in impaired platelet production.<sup>11</sup>

One in 1000 to one in 3000 infants are affected by congenital toxoplasmosis, and 40% develop thrombocytopenia.<sup>12</sup> Congenital rubella is now rare in countries with organized immunization programs,<sup>13,14</sup> persistent thrombocytopenia is a prominent feature of infants with congenital rubella syndrome. Thrombocytopenia also is a feature of maternal

transmission of HIV to the neonate and is a sign of intermediate-to-severe disease.<sup>15</sup>

Maternal ingestion of chlorothiazide diuretics or tolbutamide can have a direct cytotoxic effect on the fetal marrow megakaryocytes. Thrombocytopenia may be severe, with platelet counts 70,000/ $\mu$ L and sometimes lower. Bone marrow examination reveals a marked decrease or absence of megakaryocytes. Recovery usually occurs within a few weeks after birth.<sup>16,17</sup>

#### Adult acquired hypoplasia: drugs

A wide array of chemotherapeutic agents used for the treatment of malignancies suppress bone marrow megakaryocyte production. Examples include the commonly used agents methotrexate, busulfan, cytosine arabinoside, cyclophosphamide, and cisplatin. The resulting thrombocytopenia may lead to hemorrhage, and the platelet count should be monitored closely. Drug-induced thrombocytopenia is often the dose-limiting factor for many chemotherapeutic agents. Recombinant interleukin-11 has been approved for treatment of chemotherapy-induced thrombocytopenia.<sup>18-20</sup> Zidovudine used for the treatment of HIV infection also is known to cause myelotoxicity and severe thrombocytopenia.<sup>21</sup>

Although its mechanism is unknown, anagrelide affects megakaryocytopoiesis without significantly affecting other marrow elements. This makes anagrelide useful for treating

the thrombocytosis of patients with essential thrombocythemia and other myeloproliferative disorders.<sup>22</sup>

Mild thrombocytopenia is a common finding in alcoholic patients in whom other causes, such as portal hypertension, splenomegaly, and folic acid deficiency, have been excluded. The platelet count usually returns to normal within a few weeks of alcohol withdrawal, but may persist. A transient, rebound thrombocytosis may develop when alcohol ingestion is stopped.<sup>10</sup> Chronic ethanol ingestion may cause persistent severe thrombocytopenia. Although the mechanism is unknown, alcohol may inhibit megakaryocytopoiesis.

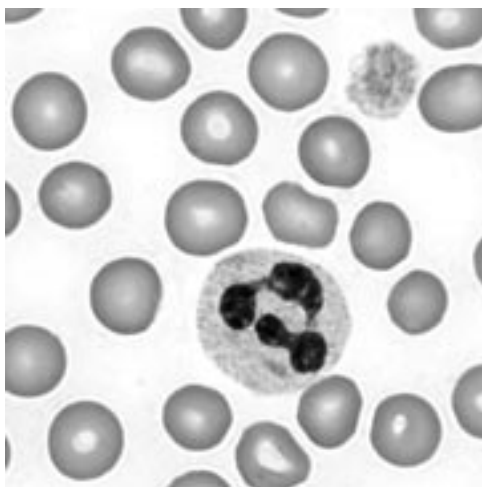
Interferon may cause mild-to-moderate, and occasionally life-threatening thrombocytopenia. Interferon- $\alpha$  and interferon- $\gamma$  inhibit stem cell differentiation and proliferation in the bone marrow.<sup>23</sup>

Thrombocytopenia also has been reported to follow the administration of large doses of estrogen or estrogenic drugs such as diethylstilbestrol. Other drugs, such as chloramphenicol, tranquilizers, and anticonvulsants, have been associated with thrombocytopenia caused by bone marrow suppression.<sup>24-26</sup>

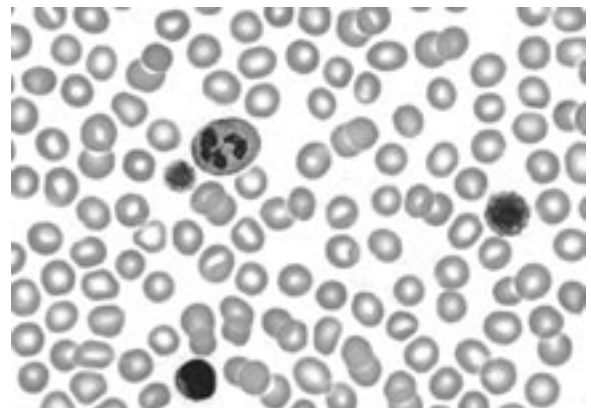
#### Ineffective thrombopoiesis

Thrombocytopenia is a feature of the megaloblastic anemias of folic acid and vitamin B<sub>12</sub> deficiency. Similar to eryth-

**Figure 1.** Döhle body in polymorphonuclear neutrophil and giant platelets associated with May-Hegglin anomaly



**Figure 2.** Typical peripheral blood cell morphology in ITP



Note scarce platelets and increased platelet size, but normal RBC and leukocyte morphology

rocyte production, platelet production is ineffective. The bone marrow may contain an increase in the number of megakaryocytes, however the number of platelets released is decreased. Because of impaired DNA synthesis, the bone marrow may contain numerous megakaryocytes with deformed, dumbbell-shaped nuclei. Blood films reveal large platelets with decreased survival that may have abnormal function. Patients typically respond to vitamin replacement within one to two weeks.<sup>27-29</sup>

## PLATELET DESTRUCTION

Platelet destruction thrombocytopenia occurs by immunologic or mechanical platelet destruction. Increased production is required to maintain a normal platelet count, and the patient becomes thrombocytopenic only when production capacity is no longer able to compensate.

### Acute immune thrombocytopenic purpura (ITP)

Acute ITP is primarily a disorder of children. There is abrupt onset of bruising, petechiae, and mucosal bleeding such as epistaxis in a previously healthy child. The primary hematologic feature is thrombocytopenia, which frequently occurs one to three weeks after a viral infection or live virus vaccination.<sup>30</sup> The incidence is four per 100,000 children, with a peak frequency between two years and five years. There is no sex predilection. In 10% to 15% of cases, thrombocytopenia persists beyond six months. These children are reclassified as having chronic ITP.<sup>31</sup> The observation that acute ITP often follows a viral illness suggests that antibodies and immune complexes are produced; and that platelet destruction may result from their binding the platelet surface.

The diagnosis of acute ITP can be made without bone marrow examination. If the child has sudden onset of bleeding, thrombocytopenia with normal red blood cell and white blood cell parameters, and a normal physical examination except for signs of bleeding there is a high likelihood of acute ITP. There is no test that separates acute from chronic ITP.

Three percent to four percent of acute ITP cases are severe with generalized purpura, gastrointestinal bleeding, hematuria, mucous membrane bleeding, and retinal hemorrhage. Of the severe cases, 25% to 50% are at risk for intracranial hemorrhage, the complication that contributes to the overall 1% to 2% mortality rate. Most patients with life-threatening hemorrhage have a platelet count of less than 4000/ $\mu$ L.<sup>32</sup> Hemorrhage is rarely experienced by patients whose platelet counts exceed 10,000/ $\mu$ L.

Most patients with acute ITP recover in three weeks with or without treatment. In a few children, recurrent episodes of acute ITP are seen after complete recovery from the first episode.<sup>33</sup> The most severe cases are treated with intravenous immunoglobulin, platelet transfusions, and splenectomy.<sup>34</sup>

### Chronic ITP

Chronic ITP occurs mostly in patients 20 years to 50 years old and females outnumber males 2:1 to 3:1. The incidence of chronic ITP ranges from 3.2 to 6.6/100,000/yr. Chronic ITP begins insidiously, with platelet counts variably normal or decreased. Presenting symptoms are those of mucocutaneous bleeding, with menorrhagia, recurrent epistaxis, or ecchymoses most common.

Chronic ITP is autoimmune. The offending autoantibodies attach to platelets which are then removed by reticuloendothelial cells and cytotoxic T cell-mediated lysis.<sup>35</sup> Platelet life span is shortened to a few hours, proportional to the thrombocytopenia. Epitopes on platelet glycoproteins (GP) IIb and IIIa ( $\alpha$ IIb/ $\beta_3$ ) are most often the target, although epitopes on GP Ib also have been identified.<sup>36,37</sup> Because megakaryocytes also express GP IIb/IIIa and GP Ib/IX/V, they are targets; consequently turnover studies may show impaired platelet production in ITP.<sup>38</sup>

Platelets number between 30,000/ $\mu$ L and 80,000/ $\mu$ L. Patients with ITP undergo periods of remission and exacerbation, and their platelet counts may range from near-normal to less than 20,000/ $\mu$ L (Figure 2). Platelets appear normal, although larger in diameter, reflected in an increased mean platelet volume as measured by electronic cell counters. Megakaryocytes are increased in diameter, although young forms with a single nucleus, smooth contour, and diminished cytoplasm are commonly seen. Although platelet-associated IgG levels are increased, no method of testing for platelet antibodies is specific for ITP.<sup>39</sup>

ITP patients with a platelet count greater than 30,000/ $\mu$ L who require no treatment may anticipate a mortality rate equal to the general population. If additional risk factors such as old age, coagulation defects, recent surgery, trauma, or uncontrolled hypertension exist, the platelet count should be maintained at 50,000/ $\mu$ L or higher.<sup>40</sup> The initial treatment consists principally of prednisone. About 70% to 90% of patients respond with an increase in platelet count and about 50% have a long-term beneficial effect. If the response is inadequate, steroid therapy can be supplemented with intravenous immunoglobulin (IVIg) or anti-D immunoglobulin.<sup>41</sup>



For patients in whom prednisone becomes ineffective, splenectomy is necessary. Splenectomy eliminates the primary site of platelet removal, and also removes an organ containing autoantibody-producing lymphocytes. Splenectomy is the most effective treatment for adult chronic ITP with 88% of patients showing improvement and 66% having a complete and lasting response.<sup>42</sup> In the most severe cases, chemotherapeutic agents such as azathioprine may be necessary. In such patients, platelet transfusions may be of transient benefit in treating severe hemorrhagic episodes, but are not given routinely.<sup>39</sup>

### Immunologic drug-induced thrombocytopenia

As Table 2 shows, many drugs can induce acute thrombocytopenia through immune mechanisms. In most cases, an IgG alloantibody or autoantibody arises in response to the drug or a drug-platelet protein complex. The Fab portion of the antibody binds a membrane constituent, usually GP Ib/V/IX or GP IIb/IIIa, in the presence of drug.<sup>43,44</sup> The antibody may activate the platelet or mediate extravascular sequestration by the reticuloendothelial system. The number of bone marrow megakaryocytes is usually normal to elevated.<sup>43</sup> Once antibody production has begun, the platelet count falls rapidly, often to 10,000/ $\mu$ L, and the patient may have abrupt onset of bleeding symptoms. If drug-induced thrombocytopenia develops in a pregnant woman, she and her fetus may both be affected. Timely recognition and swift termination of the drug reverses the thrombocytopenia.

### Heparin-induced thrombocytopenia

In heparin-induced thrombocytopenia (HIT), unfractionated standard heparin binds platelet factor 4 (PF4), a heparin-neutralizing protein synthesized by megakaryocytes and stored in platelets. Binding causes a conformational change of PF4, exposing neoepitopes. This leads to the production of an antibody within seven days to 14 days, or one day to three days following previous exposure. In HIT, heparin and PF4 form a complex on the platelet surface to which the Fab portion binds. This leaves the Fc portion of the IgG free to bind with the platelet Fc $\gamma$ R receptor, causing platelet activation with potential thrombosis.<sup>45,46</sup>

One percent to five percent of patients develop HIT during unfractionated heparin administration. Patients with HIT may not have significant risk of bleeding because their platelet count remains above 40,000/ $\mu$ L, however, 10% to 30% of patients with HIT develop venous or arterial thrombosis. Because the platelet count may fall sharply in one day, patients receiving unfractionated heparin therapy must have daily platelet counts.

Patients who develop HIT should be removed from heparin therapy as soon as the diagnosis is made as continued therapy may lead to significant morbidity and mortality, including gangrene of the extremities, amputation, and death. After discontinuation of heparin, the platelet count begins to increase and should return to normal within a few days.<sup>47</sup> Heparin treatment is replaced with a non-heparin anticoagulant such as the direct thrombin inhibitors argatroban or lepirudin.<sup>48</sup>

Three laboratory methods for HIT depend on heparin-induced antiplatelet antibodies in the patient's serum or plasma. In platelet aggregation, serum from the patient is added to platelet-rich plasma from normal donors, heparin is added to the mixture, and platelet aggregation is monitored. Several simultaneous controls are necessary, and although the specificity is nearly 100%, the sensitivity is quite low, typically about 50%.<sup>49,50</sup>

Platelets have an active mechanism for rapid uptake of serotonin with storage in dense granules. This property is employed in the *serotonin release assay*, a standard test for HIT in which normal platelets are incubated with radioactive serotonin.<sup>51</sup> The serotonin is taken up and stored in the dense granules of the donor platelets, which are washed and resuspended. In the presence of therapeutic-level heparin and heparin-dependent antiplatelet antibody, the donor platelets release the radioactive serotonin. Detection of radioactive serotonin in the fluid phase indicates the presence of a heparin-dependent antiplatelet antibody.

An enzyme immunoassay employs a PF4-heparinoid complex as the solid-phase target antigen for the heparin-dependent antiplatelet antibody. In this assay, PF4 and a heparin surrogate are coated on microplate wells. Serum or plasma from the patient is added, and if the antibody is present, it adheres to the complex and is detected in the colorimetric marker phase of the assay.<sup>52</sup> This assay is more sensitive than aggregometry and has similar sensitivity to the serotonin release assay, but is less specific than either.

### Nonimmune mechanisms of platelet destruction

Nonimmune platelet destruction may result from exposure to nonendothelial surfaces, coagulation activation, or platelet consumption by endovascular injury without measurable depletion of coagulation factors.

### Thrombocytopenia in pregnancy and preeclampsia

Incidental gestational thrombocytopenia appears in five

**Table 2.** Common drugs causing immune thrombocytopenia

**Analgesics**

salicylates  
acetaminophen  
phenylbutazone

**Antibiotics**

cephalothin  
penicillin  
streptomycin  
aminosalicylic acid  
rifampin  
novobiocin

**Various sulfa drugs (chlorthalidone, furosemide)**

**Alkaloids**

**Quinidine**

**Quinine**

**Sedatives, anticonvulsants**

methoin  
troxidone  
chlorpromazine  
diphenylhydantoin  
meprobamate  
phenobarbital  
carbamazepine

**Oral hypoglycemics**

chlorpropamide  
tolbutamide

**Heavy metals**

gold  
mercury  
bismuth  
organic arsenicals

**Miscellaneous**

chloroquine  
chlorothiazide  
insecticides

percent of healthy pregnant women with counts of 100,000-150,000/ $\mu$ L. The women have no history of thrombocytopenia, and there is no apparent risk of maternal or fetal bleeding. Maternal platelet counts return to normal within several weeks of delivery, and the fetus does not exhibit thrombocytopenia. There is recurrence in subsequent pregnancies.<sup>53</sup>

Approximately 20% of thrombocytopenia cases in pregnancy are associated with hypertensive disorders, including preeclampsia, preeclampsia-eclampsia, or preeclampsia with chronic hypertension, chronic hypertension, and gestational hypertension. Preeclampsia complicates about five percent of all pregnancies and occurs at about 20 weeks' gestation. The disorder is characterized by the onset of hypertension and proteinuria and may include abdominal pain, headache, blurred vision, or mental function disturbances.<sup>54</sup> Thrombocytopenia occurs in 15% to 20% of patients with preeclampsia, and about 40% to 50% of patients progress to eclampsia with hypertension, proteinuria, and seizures.<sup>55,56</sup>

Some patients with preeclampsia also have microangiopathic hemolysis, elevated liver enzymes, and a low platelet count (HELLP syndrome). HELLP syndrome affects an estimated four percent to 12% of patients with severe preeclampsia,<sup>57,58</sup> and it seems to be associated with higher rates of maternal and fetal complications. This disorder may be difficult to differentiate from thrombotic thrombocytopenic purpura (TTP), hemolytic-uremic syndrome (HUS), and disseminated intravascular coagulation (DIC).

HELLP associates with increased platelet destruction, though the mechanism is unclear. Elevated D-dimer suggests these patients have an underlying low-grade DIC.<sup>59</sup> Elevated platelet-associated immunoglobulin is commonly found, suggesting immune involvement.<sup>60</sup> Early reports suggested there may be a platelet activation component because low-dose aspirin appeared to prevent preeclampsia in high-risk patients.<sup>90,91</sup> When aspirin is used to prevent preeclampsia, however, there is only a 15% reduction in risk.

In preeclampsia, the physician delivers the infant as early as possible. Thrombocytopenia usually resolves a few days later. If the infant would be too premature, bed rest and aggressive treatment of the hypertension with magnesium sulfate may help to raise the platelet count.

**Thrombotic thrombocytopenic purpura (TTP)**

TTP, sometimes referred to as Moschowitz syndrome, is characterized by the triad of microangiopathic hemolytic

anemia, thrombocytopenia, and neurologic abnormalities.<sup>63</sup> In addition, fever and renal dysfunction (the pentad) are often present. Additional symptoms at diagnosis include diarrhea, anorexia, nausea, weakness, and fatigue. TTP is uncommon, but not rare, and its incidence may be increasing. About twice as many women as men are affected, and it is most common in women 30 to 40 years old.<sup>64</sup> About half the patients have a history of a viral-like illness several days before onset.

Hyaline thrombi are found in end arterioles and capillaries. These thrombi are composed of platelets and von Willebrand factor (VWF), but contain little fibrin or fibrinogen. As platelet-VWF thrombi are deposited, thrombocytopenia develops. RBCs flowing under arterial pressure may fragment when they encounter the strands of these thrombi.

Hemolysis is severe, and most patients have less than 10 g/dL hemoglobin at diagnosis. Examination of the peripheral blood film reveals a marked decrease in platelets, polychromic RBCs, and RBC fragmentation with microspherocytes, schistocytes, and keratocytes characteristic of microangiopathic hemolytic anemias. Standard coagulation tests are usually normal and may differentiate TTP from DIC.

The development of TTP seems to be directly related to the plasma accumulation of unusually large von Willebrand factor (ULVWF) multimers.<sup>65</sup> ULVWF multimers are secreted by megakaryocytes and endothelial cells. They are cleaved into typical VWF multimers by a plasma VWF-cleaving metalloprotease, also called "*a disintegrin-like and metalloprotease domain with thrombospondin type I motifs*" (ADAMTS 13).

Familial chronic relapsing TTP is characterized by recurrent episodes of thrombocytopenia. In this type of TTP, VWF-cleaving metalloprotease is absent. The more common non-familial form of TTP does not tend to recur, but patients also are deficient in the metalloprotease. In this form, the metalloprotease is removed by an autoantibody that disappears in remission.<sup>66,67</sup> An assay to measure VWF-cleaving metalloprotease is available from reference laboratories and may help diagnose TTP.<sup>68</sup>

The most effective treatment for TTP is plasma exchange using fresh frozen plasma or cryoprecipitate-poor plasma, which lacks fibrinogen and VWF.<sup>69,70</sup> Exchange may produce dramatic effects within a few hours. If plasmapheresis is not available, the patient should be given corticosteroids and infusions of fresh frozen plasma immediately and plasma exchange should be arranged as quickly as possible.

Before 1990, TTP was fatal in more than 80% of patients. With rapid diagnosis and the advent of exchange plasmapheresis, 80% of patients now survive. Because patients are known to relapse, however, the platelet count should be monitored on a regular basis until they are in remission. The detection of ULVWF multimers in patient samples after complete remission has predicted relapse accurately in 90% of the patients tested, this may prove to be useful in the long-term management of TTP.<sup>68</sup>

### Hemolytic-uremic syndrome (HUS)

Clinically, HUS resembles TTP except that it is found predominately in children six months to four years old and is self-limiting. Approximately 90% of cases are caused by *Shigella dysenteriae* serotypes or enterohemorrhagic *Escherichia coli* O157:H7.<sup>71</sup> The bloody diarrhea of childhood HUS is caused by colonization of the large intestine with the offending organism, which causes erosive damage to the colon. *S. dysenteriae* produces Shiga toxin, and the enterohemorrhagic *E. coli* produce either Shiga-like toxin-1 (SLT-1) or SLT-2, which are detected in fecal samples from patients with HUS. The toxins enter the bloodstream and attach to renal glomerular capillary endothelial cells, which become damaged and swollen and release ULVWF multimers.<sup>72</sup> This process leads to hyaline thrombi in the renal vasculature and the development of renal failure, thrombocytopenia, and microangiopathic hemolytic anemia, although the RBC fragmentation is usually not as severe as in TTP. The extent of renal involvement correlates with the rate of recovery. In more severely affected children, renal dialysis may be needed. The mortality rate associated with HUS in children is lower than in TTP, but there is often residual renal dysfunction that may lead to renal hypertension and severe renal failure. Because HUS in children is an infectious disorder, it affects boys and girls equally and is often found in geographic clusters. The rare adult form of HUS is associated with immunosuppressive or chemotherapeutic agents, but it may occur during the postpartum period.

The cardinal signs of HUS are hemolytic anemia, renal failure, and thrombocytopenia. The thrombocytopenia is usually mild to moderate in severity. Renal failure is reflected in elevated blood urea nitrogen and creatinine levels. The urine nearly always contains RBCs, protein, and casts. The hemolytic process is shown by a hemoglobin level of less than 10 g/dL, elevated reticulocyte count, and the presence of schistocytes in the peripheral blood.

### Disseminated intravascular coagulation (DIC)

A common cause of thrombocytopenia is activation of the co-

agulation cascade by a variety of agents or conditions, resulting in intravascular coagulation that entraps platelets in fibrin clots. DIC has many similarities to TTP, including microangiopathic hemolytic anemia and thrombi deposition in the arterial circulation of most organs. In DIC, however, the thrombi are composed of platelets and fibrinogen, not VWF.

Acute DIC consumes platelets rapidly and results in severe thrombocytopenia. The test for D-dimer, a breakdown product of stabilized fibrin, is grossly elevated. Acute DIC is life-threatening and must be treated immediately.

Chronic DIC is an ongoing, low-grade coagulopathy. Clotting factors may be normal or slightly reduced, and compensatory thrombocytopoiesis results in a moderately low to normal platelet count. D-dimer is moderately increased. Chronic DIC is seldom life-threatening, and treatment is not urgent. Chronic DIC should be followed carefully, because it can transition to the life-threatening acute form.

## DISORDERS RELATED TO DISTRIBUTION OR DILUTION

Abnormal platelet distribution also may cause thrombocytopenia. The normal spleen sequesters approximately one third of the total platelet mass, but mild thrombocytopenia may be present in any of the "big spleen" syndromes. The total body platelet mass is normal, but numerous platelets are sequestered in the enlarged spleen, consequently the platelet count is low. Disorders such as Gaucher disease, Hodgkin disease, sarcoidosis, lymphomas, cirrhosis of the liver, and portal hypertension may result in splenomegaly and lead to thrombocytopenia.

Lowering the body temperature to less than 25°C, as is routinely done in cardiovascular surgery, results in a transient but mild thrombocytopenia secondary to platelet sequestration in the spleen and liver. An associated transient defect in function also occurs with hypothermia. Platelet count and function return to baseline values on return to normal body temperature.

Finally, thrombocytopenia often follows surgery involving extracorporeal circulatory devices, as a consequence of damage and partial activation of platelets in the pump. In a few cases, severe thrombocytopenia, marked impairment of platelet function, and activation of fibrinolysis and intravascular coagulation may develop.

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