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Congenital or acquired hematologic disorders often present with life-threatening hemorrhage that requires immediate assessment and intervention. In some cases, patients will present to the emergency department (ED) with a confirmed diagnosis of platelet or bleeding disorder, and in other cases, hemorrhagic manifestations are the first indication of underlying disease.

Having strategies for distinguishing between platelet- and clotting factor-linked bleeding disorders is one of the primary challenges for the emergency physician, and a division along these broad categories provides a convenient scheme for patient assessment. Fortunately, most acute bleeding episodes that result from these conditions can be successfully managed with a combination of prompt blood replacement, when indicated, and platelet and/or factor replacement.

The first part of this two-part series focuses on platelet-related disorders, including diseases characterized by deficient platelet production, as well as increased platelet destruction. Such conditions as drug-induced thrombocytopenia, idiopathic thrombocytopenic purpura (ITP), disseminated intravascular coagulation (DIC), and thrombotic thrombocytopenic purpura (TTP) are discussed in detail, and accompanied by specific evaluative techniques for confirming the diagnosis and management strategies that will reduce the risk of hemorrhage-related complications and improve patient outcomes.

— The Editor

Hematologic Emergencies and Life-Threatening Bleeding Disorders: Differential Diagnosis, Evaluation, and Management

Part I: Platelet-Related Disorders

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Evaluation of the Bleeding Patient

As a rule, most bleeding episodes that present to the ED will occur in patients with normal hemostasis. In this group the clinician can expect to be able to control all but the most severe and difficult bleeding episodes. Patients with bleeding disorders may present to the ED in need of treatment for a known bleeding disorder, or they may present for the first time with an unusually severe bleeding episode.

The emergency medicine physician must be able to manage a range of bleeding disorders and also must be familiar with the presentation of patients with coagulopathies. One should be suspicious of the patient who has delayed or spontaneous bleeding episodes. Usually, severe and deep hematomas or hemarthrosis in the presence of little to no trauma should make the emergency medicine physician sus-

picious of an underlying bleeding disorder.

Hemostasis and Its Regulation. The blood clot formation process is a series of well-coordinated responses to blood vessel injury. For this complex process to occur properly, there must be cooperation between platelets, the clotting cascade, blood flow, endothelial cells, and fibrinolysis.

Platelet Function. The platelet activation process has four distinct steps: adhesion, aggregation, secretion, and procoagulant activity. Platelet adhesion primarily is mediated by the binding of a platelet surface receptor glycoprotein complex to the adhesive protein von Willebrand factor in the subendothelial matrix. This binding acts to deposit platelets on the subendothelial matrix.[1] Platelet aggregation involves the binding of fibrinogen to the platelet fibrinogen receptor. This binding only takes place on activated platelets. The fibrinogen acts as a bridge between activated platelets. Protein secretion from platelet granules occurs once platelets are activated. The activated platelets release granules of ADP (adenosine 5'-diphosphate) and serotonin that then act to stimulate and recruit additional platelets, as well as other adhesive proteins. Together, the proteins and additional activated platelets stabilize and reinforce the platelet aggregates. Additional proteins are released that act in the coagulation pathway and aid in vessel constriction. The final step is platelet procoagulation. This involves the production of clotting cascade enzyme complexes on the surface of the platelet.

Clotting Cascade. Most physicians are familiar with the clotting cascade. The central concept is the sequential activation of a series of proenzymes to enzymes that eventually result in fibrin. The fibrin then acts to reinforce the platelet "plug." Classically, it is taught that the clotting cascade has an intrinsic and extrinsic pathway. The intrinsic pathway is initiated by the exposure of blood to a negatively charged surface, while the extrinsic pathway is activated by tissue factor or thromboplastin. Both pathways converge at the activation of factor X. All of the procoagulants are synthesized in the liver except von Willebrand factor.

More recent work has found that the initiation portion of the intrinsic pathway is not important in vivo. For example, people who are severely deficient in factor XII do not have clinically significant bleeding. It is now clear that generation of tissue factor at the wound site is the primary physiologic event that initiates clotting.[2]

Platelets and the Clotting Cascade. When platelets become activated, factor V is released onto the platelet surface. Here, it is activated to factor Va and acts as an assembly site for factor Xa and prothrombin, known as the prothrombinase complex. This complex is an efficient generator of thrombin and the resulting-platelet helps keep the thrombin localized.

Control Mechanisms. Once initiated, the events leading to coagulation and clot formation must be brought back into check. Coagulation is modified via several mechanisms. These include dilution of procoagulants due to blood flow, removal of activated factors through the reticuloendothelial system, and control by natural antithrombotic pathways. Antithrombin III, protein C, protein S, and tumor factor pathway inhibitor regulate the clotting cascade; prostacyclin and nitric oxide modulate vascular and platelet activity; and fibrin clots are removed by fibrinolysis.

Hemorrhagic Disorders

Clinical Evaluation. Many patients will be able to relate a history of bleeding disorder. However, some patients will not know that they have a problem, and others may have an acquired abnormality that was not present previously. With this in mind, the physician must be able to acquire appropriate historical information to help identify an apparent bleeding disorder and determine whether it is part of a systemic problem; a congenital or acquired problem; or a vascular, platelet, or coagulation factor disorder.

Systemic disorders may be suspected in those patients who present with particularly severe bleeding or with bleeding that is atraumatic and spontaneous in onset. Bleeding or bruising over

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Table 1. Diseases Related to Abnormal Bleeding Times or Platelet Function/Count

LABORATORY TESTING	DISEASE OR CAUSE
Prolonged aPTT/normal PT	Hemophilias A and B, moderate to severe von Willebrand's disease, heparin therapy
Prolonged PT/normal aPTT	Factor VII deficiency, mild liver disease, initial coumadin therapy, vitamin K deficiency
Prolonged PT and aPTT	Severe liver disease, heparin and coumadin use, DIC, afibrinogenemia
Decreased platelet count	Decreased platelet production, increased platelet destruction, splenic sequestration
Abnormal bleeding time	Thrombocytopenia, von Willebrand's disease, aspirin use, nonsteroidal use, uremia, liver disease, cancer, other drugs

multiple areas also should raise concern that a bleeding problem may exist. In these cases, a family history should be obtained, but it is important to recall that hemophilia may occur from a spontaneous mutation. In these instances, a family history of a prior bleeding problem does not exist. Medications are responsible for some acquired bleeding disorders; therefore, the patient's current and recent medications should be evaluated. Certain underlying systemic disorders may account for the development of unusual bleeding, as well.

Specific characteristics of the bleeding pattern may point to a possible cause of the bleeding. For example, those patients with easy bruising, gingival bleeding, epistaxis, hematuria, gastrointestinal bleeding, and/or heavy menses are more likely to have a deficiency or dysfunction of the platelets. On the other hand, those patients who have spontaneous development of deep bruises, hemarthrosis, or intracranial bleeding are more likely to have a factor deficiency. In these patients, when bleeding is associated with trauma, it may present in a delayed fashion. This is presumed to be caused by the instability of the initial platelet thrombus that is not adequately stabilized by fibrin clot formation. Interestingly, those patients with von Willebrand's disease, severe liver disease, or DIC may present with features of both platelet and clotting factor problems.

The initial laboratory tests include a complete blood count (CBC) with platelets, an activated partial thromboplastin time (aPTT), and a prothrombin time (PT). Platelet counts normally are greater than 100,000/uL. When patients have counts below this level, they are considered thrombocytopenic. When levels fall below 10-20,000/uL, spontaneous bleeding may occur. The PT will detect abnormalities of the extrinsic and common pathways. It is prolonged when there are deficiencies in any of the following factors: I (fibrinogen), II (fibrin), V, VII, and X. The presence of a lupus anticoagulant may interfere with the PT. The PT also will be increased in patients taking coumadin. At this time, coumadin is monitored using the international normalized ratio (INR) rather than the PT because it more accurately reflects the degree of anticoagulation. The aPTT detects abnormalities of both the intrinsic pathway, and like the PT, the common pathway. Prolongation occurs with deficiencies of kininogen; prekallikrein; and factors I, II, V, VII, IX, X, XI, and XII. Fibrinogen degradation products, as well as heparin or coumadin, also may increase the aPTT.

More extensive testing is available when the exact cause of bleeding remains unclear, but these tests may be difficult to obtain in an urgent manner in the ED. Some of the available tests are discussed in this section. Thrombin time (TT) tests for abnormalities of the conversion of fibrinogen to fibrin. The TT may be prolonged because of hypofibrinogenemia or abnormal fibrinogen or if inhibitors are present. Prolonged TT most commonly is seen with DIC or severe liver disease. Other markers of DIC include tests like D-dimer and fibrin-fibrinogen degradation products. These products result from plasmin degradation of fibrinogen and fibrin clot. These markers are elevated in DIC. Individual factor levels can be measured if the situation warrants, but the results will not be available quickly. More common tests of platelet function include evaluation of the peripheral blood smear, as well as bleeding time. The peripheral smear will yield rapid information about the platelet count. It also will show platelet granularity and whether megathrombocytes are present. The bleeding time primarily measures platelet function. The bleeding time generally will be normal at platelet levels about 100,000/uL. If the bleeding time is elevated in the face of a normal platelet count, it suggests there is a problem with platelet function. Several of these tests and the information they yield are listed in Table 1.

Thrombocytopenia

Thrombocytopenia can result from accelerated platelet destruction, decreased platelet production, or a combination of the two. Decreased platelet count commonly is manifested by the presence of petechiae. These are most common in the lower extremities due to increased intravascular pressure. They also occur in areas where blood flow is restricted, such as around the tops of tight socks or around bra straps. The petechiae that occur due to low platelet counts are generally non-palpable. Other findings that are typical of thrombocytopenia include: purpura, mucosal bleeding, hemoptysis, hematuria, and hematochezia. Deep tissue bleeding is less common.

When platelet levels decrease to below 20,000/uL, the risk of spontaneous bleeding begins to be of concern, particularly in elderly patients who may have comorbid illnesses. The exact cause of the platelet deficiency also may change the risk of bleeding. For instance, at a given platelet level, those patients with idiopathic thrombocytopenic purpura bleed less than patients with aplastic anemia. This is thought to be related to the fact that the younger platelets present with idiopathic thrombocytopenic pur-

Table 2a. Production Deficits Leading to Thrombocytopenia

TYPE	ACQUIRED/CONGENITAL	DISORDER	CAUSE
Platelet Production Deficit	Congenital	Fanconi's syndrome Alport's syndrome Neonatal rubella/CMV Maternal thiazides	
	Acquired	Marrow aplasia or hypoplasia	Radiation, cytotoxic drugs, idiopathic, renal failure
	Acquired	Marrow infiltration, pancytopenia	Leukemia, lymphoma, marrow fibrosis
	Acquired	Impairment of platelet line production	Multiple medications, infections
	Acquired	Inadequate megakaryopoiesis	Nutritional deficiency (vitamin B_{12}, folic acid), alcohol abuse, myelodysplastic syndrome

pura are more effective in hemostasis because of their increased metabolic activity.

Initial Evaluation. If a patient complains of unusual bleeding or bruising or if he or she seems to have unusual problems bleeding when presenting to the ED, a complete history and physical examination, along with directed laboratory testing, may help limit the very extensive differential. As discussed previously, a family history is important, as are recent illness, current complaints, and recent medications. The physical examination should evaluate for additional bleeding sites and assess the size of the spleen.

A CBC count will establish whether a low platelet count is present. The CBC also will determine whether all cell lines are affected, or if the low platelet count is occurring in isolation. Platelet clumping may occur in some individuals, yielding a falsely low platelet count. This easily can be determined by looking at the peripheral smear, which will show clumps of platelets. In vitro platelet clumping results from cold-dependent or ethylenediaminetetraacetic acid-dependent agglutinins. A correct platelet count can be obtained by collecting the blood in a citrated or heparin anticoagulated blood sample.[3] If the low platelet count is thought to be real, a peripheral smear should be completed to evaluate the morphology of the platelets, as well as the other cell lines.

Differential Diagnosis. The potential causes of a low platelet count are numerous. While it is helpful to try to classify the causes of thrombocytopenia into increased removal or destruction, there are several subcategories for each of these headings. The differential is listed in Tables 2a and 2b.

Thrombocytopenia Due to Decreased Platelet Production. The congenital causes of poor platelet production generally have other developmental abnormalities that allow for diagnosis shortly after birth. These disorders are uncommon, and it is an unlikely ED diagnosis. Neonatal infections such as cytomegalovirus (CMV) or rubella may cause thrombocytopenia, but there generally are many other issues that need to be addressed in these infants. More commonly, an older child or adult will be found to have a low platelet count and the physician's evaluation will need to determine whether single or multiple cell lines have been affected. If multiple cell lines are involved, the patient may have aplastic anemia. Additional causes include marrow infiltration from lymphoma, leukemia, tuberculosis, or myelofibrosis. A drug history is critical in these instances, as many medications have been implicated. As well, chemotherapeutic drugs commonly will affect one or all cell lines. Chronic alcohol use is a common cause of thrombocytopenia and generally will resolve if the patient can stop drinking. Ultimately, a complete history and physical frequently can determine the most likely source of thrombocytopenia. While medications may be suspected as the likely culprit of a patient's problem, at times, a bone marrow biopsy is required to clarify the exact cause of either a lone platelet cell line problem or the involvement of more than one cell line. As this is not an ED procedure, consultation is appropriate to determine follow-up plans and if there is a need for admission.

Thrombocytopenia Due to Increased Platelet Removal. *Immune Causes of Platelet Destruction.* When accelerated platelet removal appears to be the cause of thrombocytopenia, consideration of the differential diagnosis should be made. The patient's age, medical history, concurrent symptoms, and type of bleeding should help clarify the potential causes of thrombocytopenia. Extensive work-up is not always necessary; the details will be discussed in this section.

Drug-Related Causes of Thrombocytopenia. Multiple medications have been implicated in immune-mediated destruction of platelets. While the exact cause has not been determined, certain medications appear to bind to the platelet membrane and cause a structural change that then stimulates an immune response.[4] The presentation may be identical to that of ITP, except the history should find that the patient is on a medication known to cause a potential immune response. Implicated medications are listed in Table 3.

Idiopathic Thrombocytopenic Purpura. ITP is an acquired autoimmune disease that results in the rapid destruction of platelets. It is characterized by thrombocytopenia, the presence of pupura or petechia, a normal bone marrow, and no other identifiable cause for the thrombocytopenia. The disease may be acute or chronic.

The normal half-life of a platelet is approximately four days. In autoimmune disorders, that half-life may be reduced to as little as 30-60 minutes. This destruction is mediated by the production of antibodies to the patient's own platelets. The antibody-

Table 2b. Causes of Increased Platelet Destruction Leading to Thrombocytopenia

TYPE	DISORDER	ETIOLOGY
Increased platelet destruction or removal	Increased destruction by immune mechanism	Idiopathic thrombocytopenic purpura Post-transfusion Systemic lupus erythematosis Graves' disease Medication-related antibody production (i.e., heparin, quinine, glycoprotein IIb-IIIa antagonists) Infections
	Increased destruction by nonimmune mechanism	Sepsis/DIC/infection Snake envenomation Extensive burn Preeclampsia and HELLP syndrome Vasculitis Thrombotic thrombocytopenic purpura Hemolytic-uremic syndrome Massive transfusion Aortic valve disease Fat embolism von Willebrand's disease (type IIB and platelet T-type) Giant hemangioma
	Other causes	Hypersplenism, heat stroke, hypothermia, HIV

coated platelets are then removed by the reticuloendothelial system (particularly the spleen). Generally, the bone marrow will respond to this destruction by increasing platelet production. However, in some cases the same antibodies that bind to the platelets also will bind to the megakaryocytes. This may result in a suboptimal response by the bone marrow to the low platelet counts. Despite these problems of production, the platelets produced in ITP are generally large and function properly. This accounts for the fact that many people with ITP may not have significant bleeding, despite very low platelet counts.

ITP is seen in all age groups and is one of the most common acquired bleeding disorders encountered by pediatricians. Acute ITP is more common among children younger than age 10 and affects males and females equally. It typically resolves in 1-2 months. Chronic ITP is more common in older children and adults and has a female predilection. Additionally, those people with chronic ITP are more likely to exhibit an underlying autoimmune disorder. Because of the differences in clinical and epidemiologic features of the two forms of ITP, there is some thought that acute and chronic ITP may have different pathophysiologic mechanisms. This may explain why the treatments for acute ITP are not as effective for chronic ITP. Chronic ITP rarely remits on its own.

Clinical Features. The diagnosis of ITP primarily is based on the history, physical, CBC count, and peripheral smear. Assuming that the evaluation supports the diagnosis of ITP and that there are no atypical findings that suggest a different disease, additional testing is not required. This includes tests such as the platelet survival study, chest radiograph, coagulation studies, serum complement levels, bleeding time, thyroid functions, and others.

A common presentation is one of an otherwise healthy child who presents with new and unusual bruising and a purpuric or petechial rash. Petechiae are more common on the lower extremities. Bleeding also may be seen at mucosal surfaces. More significant bleeding may be noted within the gastrointestinal or urinary systems, but is less common. Women of child-bearing age may notice the onset of unusually heavy menses. Onset of symptoms may be preceded by a viral illness; other predisposing illnesses include infectious mononucleosis, Graves' disease, and Hashimoto's thyroiditis.[5] The patient with ITP should have a completely normal physical examination except for bruising and, in some cases, bleeding. Important physical findings include lymphadenopathy, hepatosplenomegaly, and pallor. Hyperbilirubinemia should suggest other diseases such as leukemia, lymphoma, systemic lupus erythematosis, infectious mononucleosis, human immunodeficiency virus (HIV), and hemolytic anemia.

Other etiologies are uncommon; in one study in which children with suspected ITP had bone marrow biopsy, only 4% had another cause identified. All had abnormal physical exams.[6]

The presentation of chronic ITP may be similar to acute ITP. Ultimately, it is the length of symptoms that distinguishes this disorder, and the emergency medicine physician is unlikely to make this diagnosis from the presenting visit.

Laboratory Findings. As has already been alluded to, the laboratory evaluation of the patient with thrombocytopenia is driven, to a great extent, by historical and physical features that might suggest a disease process other than ITP. The mandatory evaluation of ITP is very limited. In both children and adults, if the evaluation suggests that the patient has ITP the key laboratory tests include a CBC with platelets and a peripheral blood smear. The CBC should be normal in all lines except the

Table 3. Drugs Causing Immune-Mediated Thrombocytopenia

- Quinine
- Quinidine
- Gold salts
- Sulfonamides
- Digitoxin
- Heparin
- Indomethacin
- Rifampin
- Glycoprotein IIb-IIIa receptor antagonists
- Aspirin
- Furosemide
- Procainamide
- Ranitidine
- Cocaine
- Amidarone
- Valproic acid
- Heroin

platelets. In some patients a mild anemia may be present as a result of bleeding, but the other red cell indices should be normal. The peripheral blood smear will help exclude a diagnosis of pseudothrombocytopenia, which is an in vitro artifact caused by the clumping of platelets in blood tubes. Additionally, the red cell morphology may help detect a concomitant hemolytic process. White blood cells also can be assessed for an abnormality suggesting an underlying bone marrow disease.

Additional testing should be directed by suspicious findings from the history and physical. For example, a patient with risk factors for HIV should be referred for testing. A patient noted to have an enlarged spleen should have a computed tomograph (CT) of the abdomen. Similarly, if abnormalities exist in the CBC other testing may be necessary. If the disease lingers, it may be appropriate to evaluate the bone marrow or to complete thyroid testing.[7]

Treatment. In children, acute ITP is a relatively benign disease, with most cases resolving spontaneously. The exact clinical course is difficult to describe due to limited data. The best data for children come from two series. Of untreated children, 0.9% had fatal bleeding events and 87% had complete remission.[8,9] The prognosis of children with chronic ITP is less clear. Up to one-third may still have a spontaneous remission from months to years after onset.[10]

ITP in adults is much more likely to be a chronic disease, and fatal hemorrhage is more likely (up to 5%).[7] The rate of hemorrhage may have improved in recent years because of the onset of platelet transfusions and use of intravenous immunoglobulin (IVIg). However, the disease itself tends to be chronic even with treatment.

Children. Studies yielding clear evidence for the best treatment plan for ITP in children is lacking. However, recommendations from the American Society of Hematology will be discussed.[7] In life-threatening bleeding episodes, the usual stabilization measures should be instituted. This includes local measures to treat mucosal bleeding, and may include hormonal therapy for an adolescent with severe menstrual bleeding. In addition, children should receive platelet transfusions and high-dose steroids (30 mg/kg methylprednisolone daily for 3 days). Along with the steroid therapy, use of IVIg (0.8-1.0 g/kg initial dose) may be initiated. Discussion with a pediatric hematologist would be prudent at this point, as there are no studies that have shown one method of therapy to be superior to another. If platelets are used, single-donor platelets should be chosen when possible. In children, one unit of platelets should increase the counts by 20,000/20 kg. However, platelet transfusions usually are of only transient value. For ongoing, severe bleeding, plasmapheresis may be an option.

Hospitalization is required when children have significant bleeding. However, other than these obvious indications, the necessity for hospitalization is less clear because many children will not have bleeding complications even with very low platelet counts. At counts below 20,000, hospitalization may be prudent for children in whom medical care is difficult to access or in whom compliance is in doubt. Again, this can be discussed with a hematologist. Hospitalization is generally not required for asymptomatic children with counts of 20,000-30,000. As well, when the platelet counts are greater than 30,000 and the child has only mild purpura, hospitalization is generally not required.

The recommended therapy for asymptomatic children is controversial. Since the course is relatively benign, not every physician feels that therapy is required. If a treatment decision is made, several options are available. IVIg may be used at the dose previously listed. This will increase the platelet count in up to 85% of patients, usually within 24-36 hours. A common side effect of this therapy is headache, which may increase concern that the child has an intracranial bleed. An alternative therapy is the use of oral steroids for 4-8 weeks at a dose of 2 mg/kg/d of prednisone. Again, prior to starting this regimen consultation is recommended because some clinicians believe that bone marrow aspiration should be done prior to the initiation of steroids. A recently developed therapy for ITP is the administration of antibody directed against the D-antigen of red blood cells (WinRho). These antibody-coated red blood cells are then sacrificed in the reticuloendothelial system rather than the antibody coated platelets. This therapy can be given over minutes rather than hours and is less likely to cause headache. The onset of action is usually slightly delayed compared to IVIg.[11] Side effects include mild to moderate hemolysis, and this therapy is only effective in Rh-positive patients.

Adults. As stated, ITP in adults is more typically a chronic disease. As with children, if life-threatening bleeding exists, stabilization and control of local bleeding should be implemented. In addition, initiation of high-dose steroid therapy (methylprednisolone 1gm IV for 3 days) is recommended. IVIg may be given in combination with steroids or as single therapy. Platelet transfusions also may be appropriate, with an expected increase in counts of 5000-10,000 for each unit of platelets. Again, this increase is transient. Recommendations for hospitalization are similar to those noted for children.

Treatment for the adult with no symptoms varies, and there are limited data on the optimal course. Available therapeutic measures are similar to those offered for children. The decision about treatment alternatives should not be made by the emergency medicine physician alone, but rather should be considered in conjunction with a hematologist. In chronic cases, splenectomy eventually may be recommended. With this in mind, all

Table 4. Manifestations of Thrombotic Thrombocytopenic Purpura

HEMOLYTIC ANEMIA	Microangiopathic hemolytic anemia manifesting with high LDH and a blood smear with helmet cells and schistoctes.
THROMBOCYTOPENIA	Moderate to severe thrombocytopenia with increased marrow megakaryocytes. Patients may have mucosal bleeding, petechiae, and purpura.
FEVER	Varies in elevation, but may be very high.
CNS SIGNS AND SYMPTOMS	Transient agitation, headache, and disorientation rapidly may progress to: aphasia, seizures, hemiparesis, focal deficits, coma, death.
RENAL DISEASE	Moderate elevation of creatinine and urine protein. Hematuria may be present.

adults with a history of ITP should be questioned about whether they have had their spleens removed.

Disposition. In many cases, both children and adults may be discharged with a diagnosis of ITP. Indications for admission have been discussed. If the patient is discharged, close follow-up must be arranged with a hematologist. In addition, precautions about activity must be discussed. Patients also should avoid medications that increase the risk of bleeding, such as aspirin and non-steroidal medications.

Non-immune Causes of Platelet Destruction. Several mechanisms may result in increased platelet destruction that are not immune-mediated. Severe infection with DIC is a well-described cause of platelet destruction,[12] as is the syndrome of hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome) that is associated with preeclampsia. Certain bacterial, rickettsial, and viral infections may cause direct toxic effects on platelets. Platelet destruction also can be noted in severe burns, certain snake envenomations, and in children with giant cavernous hemangiomas.

Thrombotic Thrombocytopenic Purpura (TTP)

Although sometimes thought of as a single disease entity, TTP actually encompasses a group of clinical syndromes in which an initial inciting event causes damage to the endothelia of small vessels that leads to platelet and fibrin deposition in small arterial vessels. While the age groups affected are widespread, women more commonly are affected than men.[13]

Presentation and Diagnosis. Five manifestations of this disease are commonly taught and are as follows: hemolytic anemia, thrombocytopenia, fever, CNS manifestations, and renal disease. Details of these manifestation are discussed in Table 4. The full pentad of symptoms is present in only 40% of patients.[14] The exact cause of this disorder remains unclear.

TTP occurs spontaneously, but also is associated with a variety of medications, pregnancy, infections, autoimmune diseases, bone marrow transplantation, and some cancers. In the pregnant patient, TTP may be difficult to differentiate from preeclampsia. Medications that have been implicated as causes of TTP include certain chemotherapeutic and immunosuppressive agents, ticlopidine, oral contraceptives, and quinine. Infections such as HIV,[15] *Mycoplasma pneumoniae,* dog bites, and subacute bacterial endocarditis all have been implicated in the development of TTP. In these cases, both the TTP and the underlying infection require treatment.[16]

When considering the diagnosis of TTP, other diseases should be ruled out. Hemolytic-uremic syndrome (HUS) in adults is thought to be a similar condition to TTP, and the treatment is the same. Differentiation between the two may not be possible. However, HUS in children is a distinct entity from the HUS seen in adults and typically has a more benign course. An exception to this is HUS which is a toxin-mediated disease caused by *Escherichia coli* (usually serotype 0157). This presents with bloody diarrhea, acute renal failure, hemorrhagic colitis, and thrombocytopenia. Laboratory studies typically show a microangiopathic hemolytic anemia, mild to moderate thrombocytopenia, red cell casts in the urine, and normal coagulation parameters.[17] TTP and adult HUS also need to be differentiated from systemic lupus, sepsis, Evan's syndrome (ITP and autoimmune hemolytic anemia), and DIC. TTP typically will have a microangiopathic hemolysis, thrombocytopenia, elevated direct bilirubin, normal coagulation profile, elevated lactic dehydrogenase (LDH), and a negative Coombs' test. Evidence of renal damage may be present. DIC is eliminated due to the normal coagulation profile, Evan's syndrome has a positive Coombs' test, and sepsis does not typically have a hemolytic anemia. Bone marrow biopsy is not usually required for diagnosis.

Treatment. When TTP is suspected, early consultation with a hematologist is recommended because treatment generally requires plasmapharesis.[18] Since this procedure may be available at a limited number of institutions, the use of fresh frozen plasma may be a temporizing measure while trying to either transfer a patient or arrange for plasmapheresis. The initial dose of fresh frozen plasma is 30 cc/kg. Other treatment regimens, such as steroids, aspirin, and dypyridamole, have not been proven in prospective randomized testing. Although these patients may be severely thrombocytopenic, the use of platelet transfusions should be avoided by the emergency medicine physician because there is some evidence that the transfusion may worsen the disease.[17] With this in mind, the decision to use platelets should be left to the hematologist. The concern of platelet transfusions does not hold with blood transfusion. Therefore, if the patient requires blood, it is appropriate to give it.

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Physician CME Questions

17. Spontaneous bleeding may occur when platelet levels fall below which of the following levels?
    A. 5,000/uL
    B. 10-20,000/uL
    C. 2,500/uL
    D. 1,000/uL

18. The prothrombin time (PT) will detect which of the following pathways?
    A. Common
    B. Extrinsic
    C. Intrinsic
    D. Both A and B

19. Which of the following is a common finding that is associated with thrombocytopenia?
    A. Deep tissue bleeding
    B. Palpable petechiae
    C. Hemarthrosis
    D. Mucosal bleeding

20. Findings that are typical of thrombocytopenia include which of the following?
    A. Pupura
    B. Hematuria
    C. Mucosal bleeding
    D. Hemoptysis
    E. All of the above

21. Which of the following diseases is associated with decreased platelet production?
    A. Tuberculosis
    B. Aplastic anemia
    C. Bone marrow infiltration from lymphoma
    D. Myelofibrosis
    E. All of the above

22. In thrombocytopenia caused by decreased platelet production, if multiple cell lines are involved the patient may have which of the following?
    A. Aplastic anemia
    B. Marrow infiltration from lymphoma
    C. Leukemia
    D. All of the above

23. Idiopathic thrombocytopenic purpura (ITP) is characterized by which of the following?
    A. Purpura or petechia
    B. A normal bone marrow
    C. Thrombocytopenia
    D. All of the above

24. The classic pentad of symptoms is present in what percentage of patients with TTP?
    A. 5%
    B. 20%
    C. 40%
    D. 50%
    E. 90%

In Future Issues: Hematologic Emergencies: Part II