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Section 3 Disorders of Hemostasis Barbara A. Konkle

Disorders of Platelets

and Vessel Wall Hemostasis is a dynamic process in which the platelet and the blood vessel wall play key roles. Platelets are activated upon adhesion to von Willebrand factor (VWF) and collagen in the exposed subendothelium after injury. Platelet activation is also mediated through shear forces imposed by blood flow itself, particularly in areas where the vessel wall is diseased, and is also affected by the inflammatory state of the endo thelium. The activated platelet surface provides the major physiologic site for coagulation factor activation, which results in further platelet activation and fibrin formation. Genetic and acquired influences on the platelet and vessel wall, as well as on the coagulation and fibrino lytic systems, determine whether normal hemostasis or bleeding or clotting symptoms will result. THE PLATELET Platelets are released from the megakaryocyte, likely under the influ ence of flow in the capillary sinuses. The normal blood platelet count is 150,000–450,000/μL. The major regulator of platelet production is the hormone thrombopoietin (TPO), which is synthesized in the liver and other organs. Synthesis is increased with inflammation and specifically by interleukin 6. TPO binds to its receptor on platelets and megakaryo cytes, by which it is removed from the circulation. Thus, a reduction in platelet and megakaryocyte mass increases the level of TPO, which then stimulates platelet production. Platelets circulate with an average life span of 7–10 days. Approximately one-third of the platelets reside in the spleen, and this number increases in proportion to splenic size, although the platelet count rarely decreases to <40,000/μL as the spleen enlarges. Platelets are physiologically very active, but are anucleate, and thus have limited capacity to synthesize new proteins. Normal vascular endothelium contributes to preventing thrombosis by inhibiting platelet function (Chap. 69). When vascular endothelium is injured, these inhibitory effects are overcome, and platelets adhere to the exposed intimal surface primarily through VWF, a large multi meric protein present in both plasma and in the extracellular matrix of the subendothelial vessel wall. Platelet adhesion results in the genera tion of intracellular signals that lead to activation of the platelet glyco protein (Gp) IIb/IIIa (αIIbβ3) receptor and resultant platelet aggregation. Activated platelets undergo release of their granule contents, which include nucleotides, adhesive proteins, growth factors, and procoagu lants that serve to promote platelet aggregation and blood clot forma tion and influence the environment of the forming clot. During platelet aggregation, additional platelets are recruited to the site of injury, leading to the formation of an occlusive platelet thrombus. The platelet plug is

stabilized by the fibrin mesh that develops simultaneously as the product of the coagulation cascade. THE VESSEL WALL Endothelial cells line the surface of the entire circulatory tree, totaling 1–6 × 1013 cells, enough to cover a surface area equivalent to about six tennis courts. The endothelium is physiologically active, control ling vascular permeability, flow of biologically active molecules and nutrients, blood cell interactions with the vessel wall, the inflammatory response, and angiogenesis. The endothelium normally presents an antithrombotic surface (Chap. 69) but rapidly becomes prothrombotic when stimulated, which promotes coagulation, inhibits fibrinolysis, and activates plate lets. In many cases, endothelium-derived vasodilators are also platelet inhibitors (e.g., nitric oxide), and conversely, endothelium-derived

vasoconstrictors (e.g., endothelin) can also be platelet activators. The net effect of vasodilation and inhibition of platelet function is to promote blood fluidity, whereas the net effect of vasoconstriction and platelet activation is to promote thrombosis. Thus, blood fluidity and hemostasis are regulated by the balance of antithrombotic/prothrom botic and vasodilatory/vasoconstrictor properties of endothelial cells.

DISORDERS OF PLATELETS ■ ■THROMBOCYTOPENIA Thrombocytopenia results from one or more of three processes: (1) decreased bone marrow production; (2) sequestration, usually in an enlarged spleen; and/or (3) increased platelet destruction. Disorders of production may be either inherited or acquired. In evaluating a patient with thrombocytopenia, a key step is to review the peripheral blood smear and to first rule out “pseudothrombocytopenia,” particularly in a patient without an apparent cause for the thrombocytopenia. Pseu dothrombocytopenia (Fig. 120-1B) is an in vitro artifact resulting from platelet agglutination via antibodies (usually IgG, but also IgM and IgA) when the calcium content is decreased by blood collection in eth ylenediamine tetraacetic (EDTA) (the anticoagulant present in tubes [purple top] used to collect blood for complete blood counts [CBCs]). If a low platelet count is obtained in EDTA-anticoagulated blood, a blood smear should be evaluated and a platelet count determined in blood collected into sodium citrate (blue top tube) or heparin (green top tube), or a smear of freshly obtained unanticoagulated blood, such as from a finger stick, can be examined. CHAPTER 120 Disorders of Platelets and Vessel Wall APPROACH TO THE PATIENT Thrombocytopenia The history and physical examination, results of the CBC, and review of the peripheral blood smear are all critical components in the initial evaluation of thrombocytopenic patients (Fig. 120-2). The overall health of the patient and whether they are receiving drug treatment will influence the differential diagnosis. A healthy young adult with thrombocytopenia will have a much more lim ited differential diagnosis than an ill hospitalized patient who is receiving multiple medications. Except in less common inherited disorders, decreased platelet production usually results from bone marrow disorders that also affect red blood cell (RBC) and/or white blood cell (WBC) production. Because myelodysplasia can present with isolated thrombocytopenia, the bone marrow should be exam ined in patients presenting with isolated thrombocytopenia who are older than 60 years of age or who do not respond to initial therapy. While inherited thrombocytopenia is uncommon, any prior platelet counts should be retrieved and a family history regarding thrombo cytopenia obtained. A careful history of drug ingestion should be obtained, including nonprescription and herbal remedies, because drugs are the most common cause of thrombocytopenia. The physical examination can document an enlarged spleen, evidence of chronic liver disease, and other underlying disorders. Mild to moderate splenomegaly may be difficult to appreciate in many individuals due to body habitus and/or obesity but can be eas ily assessed by abdominal ultrasound. A platelet count of approxi

mately 5000–10,000 is required to maintain vascular integrity in the microcirculation. When the count is markedly decreased, petechiae first appear in areas of increased venous pressure, the ankles and feet in an ambulatory patient. Petechiae are pinpoint, nonblanching hemorrhages and are usually a sign of a decreased platelet num ber and not platelet dysfunction. Wet purpura, blood blisters that form on the oral mucosa, are thought to denote an increased risk of life-threatening hemorrhage in the thrombocytopenic patient. Excessive bruising is seen in disorders of both platelet number and function. Infection-Induced Thrombocytopenia Many viral and bacte rial infections result in thrombocytopenia and are the most common

A PART 4 Oncology and Hematology B FIGURE 120-1 Photomicrographs of peripheral blood smears. A. Normal peripheral blood. B. Platelet clumping in pseudothrombocytopenia. C. Abnormal large platelet in autosomal dominant macrothrombocytopenia. D. Schistocytes and decreased platelets in microangiopathic hemolytic anemia. Platelet count <150,000/μL Hemoglobin and white blood count Normal Abnormal Bone marrow examination Peripheral blood smear Platelets clumped: redraw in sodium citrate or heparin Fragmented red blood cells Normal RBC morphology; platelets normal or increased in size Microangiopathic hemolytic anemias (e.g., DIC, TTP) Consider: Drug-induced thrombocytopenia Infection-induced thrombocytopenia Idiopathic immune thrombocytopenia Congenital thrombocytopenia FIGURE 120-2 Algorithm for evaluating the thrombocytopenic patient. DIC, disseminated intravascular coagulation; RBC, red blood cell; TTP, thrombotic thrombocytopenic purpura.

C D noniatrogenic cause of thrombocytopenia. This may or may not be associated with laboratory evidence of disseminated intravascular coagulation (DIC), which is most commonly seen in patients with systemic infections with gram-negative bacteria and is seen in patients ill with COVID-19. Infections can affect both platelet production and platelet survival. In addition, immune mechanisms can be at work, as in infectious mononucleosis and early HIV infection. Late in HIV infection, pancytopenia and decreased and dysplastic platelet produc tion are more common. Immune-mediated thrombocytopenia in children usually follows a viral infection and almost always resolves spontaneously. This association of infection with immune thrombocy topenic purpura is less clear in adults. Drug-Induced Thrombocytopenia Many drugs have been asso ciated with thrombocytopenia. A predictable decrease in platelet count occurs after treatment with many chemotherapeutic drugs due to bone marrow suppression (Chap. 78). Drugs that cause isolated thrombocy topenia and have been confirmed with positive laboratory testing are listed in Table 120-1, but all drugs should be suspect in a patient with thrombocytopenia without an apparent cause and should be stopped, or substituted, if possible. Although not as well studied, herbal and over-the-counter preparations may also result in thrombocytopenia and should be discontinued in patients who are thrombocytopenic. Classic drug-dependent antibodies are antibodies that react with specific platelet surface antigens and result in thrombocytopenia only when the drug is present. Many drugs are capable of inducing these antibodies, but for some reason, they are more common with quinine and sulfonamides. Drug-dependent antibody binding can be demon strated by laboratory assays, showing antibody binding in the presence

TABLE 120-1 Drugs Reported as Definitely or Probably Causing Isolated Thrombocytopeniaa Abciximab Acetaminophen Amiodarone Amlodipine Ampicillin Carbamazepine Ceftriaxone Cephamandole Ciprofloxacin Diazepam Eptifibatide Furosemide Gold Haloperidol Heparin Ibuprofen Lorazepam Mirtazapine Naproxen Oxaliplatin Penicillin Phenytoin Piperacillin Quinidine Quinine

Ranitidine Rosiglitazone Roxifiban Sulfisoxazole Suramin Tirofiban Tranilast Trimethoprim/sulfamethoxazole Vancomycin aBased on scoring requiring a compatible clinical picture and positive laboratory testing. Note, this is not inclusive of newer medications. Source: Adapted from DM Arnold et al: J Thromb Hemost 11:169, 2013. of, but not without, the drug present in the assay. The thrombocytope nia typically occurs after a period of initial exposure (median length 21 days), or upon reexposure, and usually resolves in 7–10 days after drug withdrawal. The thrombocytopenia caused by the platelet Gp IIb/ IIIa inhibitory drugs, such as abciximab, differs in that it may occur within 24 h of initial exposure. This appears to be due to the presence of naturally occurring antibodies that cross-react with the drug bound to the platelet. Heparin-Induced Thrombocytopenia Drug-induced throm bocytopenia due to heparin differs from that seen with other drugs in two major ways. (1) The thrombocytopenia is not usually severe, with nadir counts rarely <20,000/μL. (2) Heparin-induced thrombo cytopenia (HIT) is not associated with bleeding and, in fact, markedly increases the risk of thrombosis. The pathogenesis of HIT is complex. It results from antibody formation to a complex of the platelet-specific protein platelet factor 4 (PF4) and heparin or other glycosaminogly cans. The anti-heparin/PF4 antibody can activate platelets through the FcγRIIa receptor and also activate monocytes, endothelial cells, and coagulation proteins. Many patients exposed to heparin develop anti bodies to heparin/PF4 but do not appear to have adverse consequences. A fraction of those who develop antibodies will develop HIT, and a portion of those (up to 50%) will develop thrombosis (HITT). HIT can occur after exposure to low-molecular-weight heparin (LMWH) as well as unfractionated heparin (UFH), although it is more common with the latter. Most patients develop HIT after expo sure to heparin for 5–14 days (Fig. 120-3). It occurs before 5 days in those who were exposed to heparin in the prior few weeks or months HIT only if heparin in last ~100 days Risk of HIT Delayed-onset HIT occurs rarely

Days of heparin (UFH or LMWH) exposure FIGURE 120-3 Time course of heparin-induced thrombocytopenia (HIT) development after heparin exposure. The timing of development after heparin exposure is a critical factor in determining the likelihood of HIT in a patient. HIT occurs early after heparin exposure in the presence of preexisting heparin/platelet factor 4 (PF4) antibodies, which disappear from circulation by ~100 days following a prior exposure. Rarely, HIT may occur later after heparin exposure (termed delayedonset HIT). In this setting, heparin/PF4 antibody testing is usually markedly positive. HIT can occur after exposure to either unfractionated (UFH) or low-molecularweight heparin (LMWH).

(<~100 days) and have circulating anti-heparin/PF4 antibodies. Rarely, thrombocytopenia and thrombosis begin several days after all heparin has been stopped (termed delayed-onset HIT), and more rarely, spon taneous HIT, or autoimmune HIT syndrome, occurs where there is no history of heparin exposure. A syndrome similar to spontaneous HIT has been described rarely after COVID-19 vaccination with the adenovirus-based ChAdOx1-S/nCoV-19 vaccine and termed vaccineinduced immune thrombocytopenia and thrombosis (VITT). Even more rarely, a similar thrombotic syndrome can follow an adenovirus infec tion. then go to the 4Ts. The “4Ts” are recommended to be used in a diagnostic algorithm for HIT: thrombocytopenia, timing of platelet count drop, thrombosis and other sequelae such as localized skin reac tions, and other causes of thrombocytopenia not evident. Application of the 4T scoring system is very useful in excluding a diagnosis of HIT but will result in overdiagnosis of HIT in situations where thrombocy topenia and thrombosis due to other etiologies are common, such as in the intensive care unit.

LABORATORY TESTING FOR HIT Because of the prevalence of anti heparin antibodies without clinical disease, testing should be done in individuals who are at intermediate or high risk based on clinical pretest assessment. HIT (anti-heparin/PF4) antibodies can be detected using two types of assays. The most widely available are immunoassays usually with PF4/polyanion complex as the antigen. Because many patients develop antibodies but do not develop clinical HIT, the test has a low specificity for the diagnosis of HIT. This is especially true in patients who have undergone surgery requiring cardiopulmonary bypass, where approximately 50% of patients develop these antibod ies postoperatively. The other assay is a platelet activation assay, most commonly the serotonin release assay, which measures the ability of the patient's serum to activate platelets in the presence of heparin in a concentration-dependent manner. This test has lower sensitivity but higher specificity than the enzyme-linked immunosorbent assay (ELISA). However, HIT remains a clinical diagnosis. CHAPTER 120 Disorders of Platelets and Vessel Wall TREATMENT Heparin-Induced Thrombocytopenia Early recognition is key in treatment of HIT, with prompt discon tinuation of heparin and use of alternative anticoagulants if bleeding risk does not outweigh thrombotic risk. Thrombosis is a common complication of HIT, even after heparin discontinuation, and can occur in both the venous and arterial systems. In patients diagnosed with HIT, imaging studies to evaluate the patient for thrombosis (at least lower extremity duplex Doppler imaging) are recommended. Patients requiring anticoagulation should be switched from

heparin to an alternative anticoagulant. The direct thrombin inhibi tor (DTI) argatroban is effective in HITT. The DTI bivalirudin, the antithrombin-binding pentasaccharide fondaparinux, and direct oral anticoagulants (DOACs) appear to have efficacy, although none of these are approved by the U.S. Food and Drug Administra tion (FDA) for this indication. Of the DOACs, the most experience reported is with rivaroxaban. In general, an intravenous DTI should be used in acutely ill patients with transition to fondaparinux or a DOAC when they are more stable, which then allows outpatient treatment. HIT antibodies cross-react with LMWH, and these drugs should not be used in the treatment of HIT. Because of the high rate of thrombosis in patients with HIT, anti coagulation should be considered, even in the absence of thrombo sis. In patients with thrombosis, anticoagulation is continued for 3–6 months, but in patients without thrombosis, the duration of anticoagulation is less well defined, but should be continued at least until platelet recovery. An increased risk of thrombosis is present for at least 1 month after diagnosis; however, most thromboses occur early, and whether thrombosis occurs later if the patient is initially anticoagulated is unknown. Introduction of warfarin alone in the setting of HIT or HITT may precipitate thrombosis, particularly venous gangrene, presumably due to clotting activation and severely reduced levels of proteins C and S. Warfarin therapy,

if started, should be overlapped with a DTI, fondaparinux, or a DOAC and started after resolution of the thrombocytopenia and lessening of the prothrombotic state.

The rare VITT syndrome is characterized by high D-dimer levels and thrombosis in unusual sites like the cerebral venous sinuses. Fatal in about 20%, treatment is usually intravenous gamma globu lin (IVIgG) to block platelet activation through Fc receptors, the pathogenic effect of the anti–PF4-polyanion antibody, and a non heparin anticoagulant. Immune Thrombocytopenic Purpura Immune thrombocyto penic purpura (ITP; also termed idiopathic thrombocytopenic purpura) is an acquired disorder in which there is immune-mediated destruction of platelets and possibly inhibition of platelet release from the mega karyocyte. In children, it is usually an acute disease,

most commonly following an infection, and with a self-limited course. In adults, it is a more chronic disease, although in some adults, spontaneous remission occurs, usually within months of diagnosis. ITP is termed secondary if it is associated with an underlying disorder; autoimmune disorders, particularly systemic lupus erythematosus (SLE), and infections, such as HIV and hepatitis C, are common causes. The association of ITP with Helicobacter pylori infection is unclear but appears to have a geo graphic distribution. PART 4 Oncology and Hematology ITP is characterized by mucocutaneous bleeding and a low, often very low, platelet count, with an otherwise normal peripheral blood cells and smear. Patients usually present either with ecchymoses and petechiae or with thrombocytopenia incidentally found on a routine CBC. Mucocutaneous bleeding, such as oral mucosa, gastrointestinal, or heavy menstrual bleeding, may be present. Rarely, life-threatening, including central nervous system, bleeding can occur. Wet purpura (blood blisters in the mouth) and retinal hemorrhages may herald lifethreatening bleeding. LABORATORY TESTING IN ITP Laboratory testing for antibodies (sero logic testing) is usually not helpful due to the low sensitivity and specificity of the current tests. Bone marrow examination can be reserved for those who have other signs or laboratory abnormalities not explained by ITP or in patients who do not respond to initial therapy. The peripheral blood smear may show large platelets, with otherwise normal morphology. Depending on the bleeding history, iron-deficiency anemia may be present. Laboratory testing is performed to evaluate for secondary causes of ITP and should include testing for HIV infection and hepatitis C (and other infections if indicated). Serologic testing for SLE, serum protein electrophoresis, immunoglobulin levels to potentially detect hypogam maglobulinemia, selective testing for IgA deficiency or monoclonal gammopathies, and testing for H. pylori infection should be consid ered, depending on the clinical circumstance. If anemia is present, direct antiglobulin testing (Coombs' test) should be performed to rule out combined autoimmune hemolytic anemia with ITP (Evans' syndrome). TREATMENT Immune Thrombocytopenic Purpura The treatment of ITP uses drugs that decrease reticuloendothelial uptake of the antibody-bound platelet, decrease antibody produc tion, and/or increase platelet production. The diagnosis of ITP does not necessarily mean that treatment must be instituted. Patients with platelet counts >30,000/μL appear not to have increased mor tality related to the thrombocytopenia. Initial treatment in patients without significant bleeding symp toms, severe thrombocytopenia (<5000/μL), or signs of impending bleeding (e.g., retinal hemorrhage or large oral mucosal hemor rhages) can be instituted as an outpatient using single agents. Tra ditionally, this has been prednisone at 1 mg/kg or a 4-day course of dexamethasone, 40 mg/d, although Rh0(D) immune globulin therapy, at 50–75 μg/kg, is also being used in this setting. Rh0(D) immune globulin must be used only in Rh-positive patients because

the mechanism of action is production of limited hemolysis, with antibody-coated cells "saturating" the Fc receptors, inhibiting Fc receptor function. Monitoring patients for 8 h after infusion is now advised by the FDA because of the rare complication of severe intravascular hemolysis. IVIgG, which is pooled, primarily IgG antibodies, also blocks the Fc receptor system, but appears to work primarily through different mechanism(s). IVIgG has more efficacy than anti-Rh0(D) in postsplenectomized patients. IVIgG is dosed at 1–2 g/kg total, given over 1–5 days. Side effects are usually related to the volume of infusion and infrequently include aseptic meningitis and renal failure. All immunoglobulin preparations are derived from human plasma and undergo treatment for viral inactivation. Rituximab, an anti-CD20 (B-cell) antibody, has shown efficacy in the treatment of refractory ITP, although long-lasting remission only occurs in approximately 30% of patients. TPO receptor ago nists (TPO-RA), administered subcutaneously (romiplostim) or orally

(eltrombopag, avatrombopag), are effective in raising platelet counts in patients with chronic ITP. For patients with severe ITP and/or symptoms of bleeding, hospital admission is required, and combined-modality therapy is given using high-dose glucocorticoids with IVIgG or anti-Rh0(D) therapy and, as needed, additional immunosuppressive agents. For chronic ITP, broad immune therapy and splenectomy are now generally used less frequently compared to TPO-RAs due to unfavorable side effects and a negative impact on quality of life. Newer drugs are under study. In individuals who achieve a complete response to a TPO-RA, many will maintain a sustained response off therapy. In patients who are to undergo splenectomy, vaccination against encapsulated organisms (especially pneumococcus, but also menin gococcus and Haemophilus influenzae, depending on patient age and potential exposure) is recommended. Accessory spleens are a very rare cause of relapse. Inherited Thrombocytopenia Thrombocytopenia is rarely inherited, either as an isolated finding or as part of a syndrome, and may be inherited in an autosomal dominant, autosomal recessive, or X-linked pattern. Multiple genetic variants have now been identified in individuals with isolated thrombocytopenia and cytopenic syndromes, some of which carry an increased risk of hematologic malignancy. Many forms of autosomal dominant macrothrombocytopenia are now known to be associated with variants in the nonmuscle myosin heavy chain MYH9 gene. These include the May-Hegglin anomaly, and Sebastian, Epstein's, and Fechtner syndromes, all of which have distinct distinguishing features. A common feature of these disorders is large platelets (Fig. 120-1C). It is important that family history be explored in any individual with unexplained thrombocytopenia. ■ ■THROMBOTIC THROMBOCYTOPENIC PURPURA AND HEMOLYTIC-UREMIC SYNDROME Thrombotic thrombocytopenic microangiopathies are a group of dis orders characterized by microangiopathic hemolytic anemia (MAHA) defined by thrombocytopenia and fragmented RBCs (Fig. 120-1D) on peripheral blood smear, laboratory evidence of hemolysis (elevated lac tate dehydrogenase [LDH] and unconjugated bilirubin and decreased haptoglobin), and microvascular thrombosis. They include thrombotic thrombocytopenic purpura (TTP) and hemolytic-uremic syndrome (HUS), as well as syndromes complicating bone marrow transplanta tion, certain medications and infections, pregnancy, and vasculitis. In DIC, although thrombocytopenia and microangiopathy are seen, a coagulopathy predominates, with consumption of clotting factors and fibrinogen resulting in an elevated prothrombin time (PT) and often activated partial thromboplastin time (aPTT). The PT and aPTT are characteristically normal in TTP or HUS. Thrombotic Thrombocytopenic Purpura TTP was first described in 1924 by Eli Moschcowitz and characterized by a pentad of findings that include microangiopathic hemolytic anemia, thrombo cytopenia, renal failure, neurologic findings, and fever. The full-blown

VWF and Platelet Adhesion Blood flow Protease No protease "Ultralarge" multimers Normal multimers TTP? FIGURE 120-4 Pathogenesis of thrombotic thrombocytopenic purpura (TTP). Normally the ultra-high-molecular-weight multimers of von Willebrand factor (VWF) produced by the endothelial cells are processed into smaller multimers by a plasma metalloproteinase called ADAMTS13. In TTP, the activity of the protease is inhibited, and the ultra-high-molecular-weight multimers of VWF initiate platelet aggregation and thrombosis. syndrome is less commonly seen now, probably due to earlier diag nosis. The introduction of treatment with plasma exchange markedly improved the prognosis in patients, with a decrease in mortality from 85–100% to 10–30%. The pathogenesis of inherited (Upshaw-Schulman syndrome) and idiopathic TTP (ITTP) is related to a deficiency of, or antibodies to, the metalloprotease ADAMTS13, which cleaves VWF. VWF is normally secreted as ultra-large multimers, which are then cleaved by ADAMTS13. The persistence of ultra-large VWF molecules is thought to contribute to pathogenic platelet adhesion

and aggregation (Fig. 120-4). This defect alone, however, is not sufficient to result in TTP because individuals with a congenital absence of ADAMTS13 develop TTP only episodically, including during first pregnancy. The level of ADAMTS13 activity, as well as antibodies to ADAMTS13, can be detected by laboratory assays, which play a critical role in the dif ferential diagnosis of MAHA. ADAMTS13 activity levels of <10% are diagnostic of TTP. Idiopathic TTP appears to be more common in women than in men. No geographic or racial distribution has been defined. TTP is more common in patients with HIV infection and in pregnant women. Medication-related MAHA may be secondary to antibody formation (ticlopidine and possibly clopidogrel) or direct endothelial toxicity (cyclosporine, gemcitabine, mitomycin C, tacrolimus), although this is not always so clear, and fear of withholding treatment, as well as lack of other treatment alternatives, may result in initial application of plasma exchange. However, withdrawal, or reduction in dose, of endothelial toxic agents usually decreases the microangiopathy. TREATMENT Thrombotic Thrombocytopenic Purpura TTP is a devastating disease if not diagnosed and treated promptly. In patients presenting with new thrombocytopenia, with or without evidence of renal insufficiency and other elements of classic TTP,

laboratory data (PT, aPTT, CBC with platelet count and peripheral smear, ADAMTS13 activity, LDH, bilirubin, haptoglobin, direct antiglobulin assay) should be obtained to rule out DIC and to evalu ate for evidence of MAHA.

Therapeutic plasma exchange (TPE) remains the mainstay of treatment of TTP. TPE is continued until the platelet count is normal and signs of hemolysis are resolved for at least 2 days. Although never evaluated in clinical trials, the use of glucocorti coids seems a reasonable approach but should only be used as an adjunct to plasma exchange. The addition of rituximab to initial therapy decreases the risk of relapse. Caplacizumab, an anti-VWF nanobody, decreases mortality and burden of care when used in patients with ADAMTS13 <10% or with high clinical probability of disease. Guidelines from the International Society of Thrombosis and Hemostasis recommend starting caplacizumab and rituximab only in individuals with diagnostic ADAMTS13 levels (usually <10%) and, additionally for rituximab, in patients with evidence of an inhibitor, given potential side effects and costs. Patients with persistently low ADAMTS13 have a greater risk of ongoing sequelae including stroke. There is a significant relapse rate; in patients treated with TPE, 25–45% of patients relapse within 30 days of initial “remission,” and 12–40% of patients have late relapses. Relapses are more frequent in patients with severe ADAMTS13 deficiency at presentation. Treatment of patients with TTP relapses should be initiated before confirmatory laboratory assays are available. CHAPTER 120 Hemolytic-Uremic Syndrome HUS is a syndrome character ized by acute renal failure, microangiopathic hemolytic anemia, and thrombocytopenia. It is seen preceded by an episode of diarrhea, often hemorrhagic in nature, predominantly in children. Escherichia coli O157:H7 is the most frequent, although not only, etiologic serotype. HUS not associated with diarrhea is more heterogeneous in presenta tion and course. Atypical HUS (aHUS) is usually due to genetic defects in complement genes or antibodies directed against complementary regulatory proteins that result in chronic complement activation. Laboratory testing for DNA variants in complement regulatory genes is available, although assigning pathogenicity to variants remains chal lenging. Currently, a commercially available functional assay is not available that is diagnostic of the disease. Disorders of Platelets and Vessel Wall TREATMENT Hemolytic-Uremic Syndrome Treatment of HUS is primarily supportive. In HUS associated with diarrhea, many (~40%) children require at least some period of support with dialysis; however, the overall mortality is <5%. In HUS

not associated with diarrhea, the mortality is higher, approximately 26%. Plasma infusion or plasma exchange has not been shown to alter the overall course in HUS or aHUS, except in patients with antibodies to factor H. ADAMTS13 levels are generally reported to be normal in HUS, although occasionally they have been reported to be decreased. In patients with aHUS, anticomplement therapy has efficacy in resolution of aHUS and improving or preserving renal function. Patients with aHUS may initially be treated with plasma exchange, until the ADAMTS13 level is returned and the diagnosis is more clear, since aHUS remains a diagnosis of exclu sion. However, plasma exchange has not been shown to affect clini cal outcomes in aHUS. ■ ■THROMBOCYTOSIS Thrombocytosis is almost always due to (1) iron deficiency; (2) inflammation, cancer, or infection (reactive thrombocytosis); or (3) an underlying myeloproliferative process (essential thrombocythemia or polycythemia vera) (Chap. 108) or, rarely, the 5q– myelodysplastic process (Chap. 107). Patients presenting with an elevated platelet count should be evaluated for underlying inflammation and malignancy, and iron deficiency should be ruled out. Thrombocytosis in response to

acute or chronic inflammation has not been clearly associated with an increased thrombotic risk. In fact, patients with markedly elevated platelet counts (>1.5 million), usually seen in the setting of a myelopro liferative disorder, have an increased risk of bleeding. This appears to be due, at least in part, to acquired von Willebrand disease (VWD) due to platelet-VWF binding and removal from the circulation.

■ ■QUALITATIVE DISORDERS OF PLATELET FUNCTION Inherited Disorders of Platelet Function Inherited platelet function disorders are thought to be relatively rare, although the preva lence of mild disorders of platelet function is unclear, in part because our testing for such disorders is suboptimal. Rare qualitative disorders include the autosomal recessive disorders Glanzmann’s thrombasthe nia (absence of the platelet Gp IIb/IIIa receptor) and Bernard-Soulier syndrome (absence of the platelet Gp Ib-IX-V receptor). Both are inherited in an autosomal recessive fashion and present with bleeding symptoms in childhood. Platelet storage pool disorder (SPD) is the classic autosomal domi nant qualitative platelet disorder. This results from abnormalities of platelet granule formation. It is also seen as a part of inherited disorders of granule formation, such as Hermansky-Pudlak syndrome. Bleeding symptoms in SPD are variable but often are mild. The most common inherited disorders of platelet function prevent normal secretion of granule content and are termed secretion defects. An increasing number of genetic variants are being found in patients with these disorders, although assigning pathogenicity remains challenging. PART 4 Oncology and Hematology TREATMENT Inherited Disorders of Platelet Dysfunction Bleeding symptoms or prevention of bleeding in patients with severe platelet dysfunction frequently requires platelet transfusion. Care must be taken to limit the risk of alloimmunization by limit ing exposure and using human leukocyte antigen–matched single donor platelets for transfusion when needed. Recombinant factor VIIa (rFVIIa) is FDA approved in Glanzmann’s thrombasthenia and Bernard Soulier syndrome where use can avoid platelet alloim munization and antireceptor antibody formation. Platelet disorders associated with milder bleeding symptoms frequently respond to desmopressin (1-deamino-8-d-arginine vasopressin [DDAVP]). DDAVP increases plasma VWF and factor VIII levels; it may also have a direct effect on platelet function. Particularly for mucosal bleeding symptoms, antifibrinolytic therapy (tranexamic acid or ε-aminocaproic acid) is used alone or in conjunction with DDAVP or platelet therapy. Acquired Disorders of Platelet Function Acquired platelet dysfunction is common, usually due to medications, either intention ally as with

antiplatelet therapy or unintentionally as with high-dose penicillins. Acquired platelet dysfunction occurs in uremia. This is likely multifactorial, but the resultant effect is defective adhesion and activation. The platelet defect is improved most by dialysis but may also be improved by increasing the hematocrit to 27–32%, giving DDAVP (0.3 μg/kg), or use of conjugated estrogens. Platelet dysfunction also occurs with cardiopulmonary bypass due to the effect of the artificial circuit on platelets, and bleeding symptoms respond to platelet transfu sion. Platelet dysfunction seen with underlying hematologic disorders can result from nonspecific interference by circulating paraproteins or intrinsic platelet defects in myeloproliferative and myelodysplastic syndromes. ■ ■VON WILLEBRAND DISEASE VWD is the most common inherited bleeding disorder, with preva lence of symptomatic disease of 1 in 1000 to 1 in 10,000 individuals. VWF serves two roles: (1) as the major adhesion molecule that tethers the platelet to the exposed subendothelium; and (2) as the binding

TABLE 120-2 Laboratory Diagnosis of von Willebrand Disease (VWD) VWF ANTIGEN VWF ACTIVITY FVIII ACTIVITY MULTIMER TYPE aPTT

Nl or ↑ ↓ ↓ ↓ Normal distribution, decreased in quantity 2A Nl or ↑ ↓ ↓ ↓ ↓ Loss of high- and intermediate-MW multimers 2Ba Nl or ↑ ↓ ↓ ↓ ↓ Loss of high-MW multimers 2M Nl or ↑ ↓ ↓ ↓ ↓ Normal distribution, decreased in quantity 2N ↑↑ Nl or ↓b Nl or ↓b ↓↓ Normal distribution

↑↑ ↓↓ ↓↓ ↓↓ Absent aUsually also decreased platelet count. bFor type 2N, in the homozygous state, factor VIII is very low; in the heterozygous state, it is only seen in conjunction with type 1 VWD. Abbreviations: aPTT, activated partial thromboplastin time; F, factor; MW, molecular weight; Nl, normal; VWF, von Willebrand factor. protein for factor VIII (FVIII), resulting in significant prolongation of the FVIII half-life in circulation. The platelet-adhesive function of VWF is critically dependent on the presence of large VWF multim ers, whereas FVIII binding is not. Most of the symptoms of VWD are “platelet-like” except in more severe VWD when the FVIII is low enough to produce symptoms similar to those found in FVIII defi ciency (hemophilia A). VWD has been classified into three major types, with four subtypes of type 2 (Table 120-2). By far, the most common type of VWD is type 1 disease, with a parallel decrease in VWF protein, VWF function, and FVIII levels, accounting for at least 80% of cases. Type 1C is a subtype associated with increased VWF clearance. In type 1 VWD, patients have predominantly mucosal bleeding symptoms, although procedurerelated and other bleeding is also seen. Bleeding symptoms are uncom mon in infancy and usually manifest later in childhood with excessive bruising and epistaxis. Because these symptoms occur commonly in childhood, the clinician should particularly note bruising at sites unlikely to be traumatized and/or prolonged epistaxis requiring medi cal attention. Heavy menstrual bleeding is a common manifestation of VWD. Menstrual bleeding resulting in anemia should warrant an evaluation for VWD and, if negative, functional platelet disorders and other bleeding disorders. Type 1 VWD may first manifest with dental extractions, particularly wisdom tooth extraction, or tonsillectomy. Not all patients with low VWF levels have bleeding symptoms. Whether patients bleed or not will depend on the overall hemostatic balance they have inherited, along with environmental influences and the type of hemostatic challenges they experience. Although the inheritance of VWD is autosomal, many factors modulate both VWF levels and bleeding symptoms. These have not all been defined, but include blood type, thyroid hormone status, race, stress, exercise, hor monal (both endogenous and exogenous) influences, and modulators of VWF clearance. Patients with type O blood have VWF protein levels of approximately

one-half those of patients with AB blood type, and in fact, the normal range for patients with type O blood overlaps that which has been considered diagnostic for VWD. Patients with mildly decreased VWF levels should be diagnosed with VWD only in the set ting of bleeding symptoms and/or a family history of VWD. Patients with type 2 VWD have functional defects; thus, the VWF antigen measurement is significantly higher than the test of function. For types 2A, 2B, and 2M VWD, platelet-binding and/or collagen-binding VWF activity is decreased. In type 2A VWD, the impaired function is due either to increased susceptibility to cleavage by ADAMTS13, result ing in loss of intermediate- and high-molecular-weight multimers, or to decreased production of these multimers by the cell. Type 2B VWD results from gain-of-function DNA variants that result in increased binding of VWF to platelets in circulation with subsequent increased ADAMTS13 cleavage and clearance. The resulting VWF in the patients'

plasma lacks the highest molecular-weight multimers, and the platelet count is usually modestly reduced, but not uniformly. Type 2M occurs as a consequence of DNA variants that result in a dysfunctional protein not affecting multimer structure. Type 2N VWD is due to variants in the VWF gene that affect bind ing of FVIII. As FVIII is stabilized by binding to VWF, the FVIII in patients with type 2N VWD has a very short half-life, and the FVIII level is markedly decreased. This is sometimes termed autosomal hemophilia. Type 3 VWD, or severe VWD, describes patients with virtually no VWF protein and usually FVIII levels <10%. Patients experience mucosal and joint bleeding, surgery-related bleeding, and other bleeding symptoms. Some patients with type 3 VWD, particu larly those with large VWF gene deletions, are at risk of developing antibodies to infused VWF. Acquired VWD or von Willebrand syndrome can be seen in patients with underlying lymphoproliferative disorders, including monoclonal gammopathies of underdetermined significance (MGUS), multiple myeloma, and Waldenström's macroglobulinemia. It is seen most com monly in the setting of MGUS and should be suspected in patients, particularly elderly patients, with a new onset of severe mucosal bleeding symptoms. Laboratory evidence of acquired VWD is found in patients with cardiac valvular disease. Heyde's syndrome (aortic stenosis with gastrointestinal bleeding) is attributed to the presence of angiodysplasia of the gastrointestinal tract in patients with aortic stenosis. The shear stress on blood passing through the stenotic aortic valve appears to unfold VWF, making it susceptible to proteolysis. Consequently, large multimer forms are lost, leading to an acquired type 2 VWD, but return when the stenotic valve is replaced. TREATMENT Von Willebrand Disease The mainstay of treatment for type 1 VWD is DDAVP (desmopres sin), which results in release of VWF and FVIII from endothelial stores. DDAVP can be given intravenously, by high-concentration intranasal spray (1.5 mg/mL), or when a concentrated form is available, by subcutaneous injection. The peak activity when given intravenously is approximately 30 min, whereas it is 2 h when given intranasally. The usual dose is 0.3 μg/kg intravenously or two squirts (one in each nostril) for patients >50 kg (one squirt for those <50 kg). It is recommended that patients with VWD be tested with DDAVP to assess their response before using it. In patients who respond well (increase in laboratory values greater than twofold with levels >50% for at least 4 h), it can be used for procedures with minor to moderate risk of bleeding. Depending on the procedure, additional doses may be needed; it is usually given every 12–24 h. Less frequent dosing may result in less tachyphylaxis, which occurs when synthesis cannot compensate for the released stores. The major side effect of DDAVP is hyponatremia due to decreased free water clearance. This occurs most commonly in the very young and the very old, but fluid restriction should be advised for all patients for the 24 h following each dose. Some patients with type 2A VWD respond to DDAVP such that it can be used for minor procedures. For

the other subtypes, for type 3 disease, and for major procedures requiring longer periods of normal hemostasis, VWF replacement can be given. Virally inac tivated VWF-plasma-derived and recombinant factor concentrates are safer than cryoprecipitate as the replacement product. Antifibrinolytic therapy using either tranexamic acid (TXA) or ε-aminocaproic acid is an important therapy, either alone or in an adjunctive capacity, particularly for the prevention or treatment of mucosal bleeding. These agents are particularly useful in treat ment of heavy menstrual bleeding (TXA 1300 mg every 8 h) and postpartum hemorrhage, as prophylaxis for dental procedures, and with DDAVP or factor concentrate for dental extractions, tonsillec tomies, and prostate procedures. Antifibrinolytic agents are contra indicated in the setting of upper urinary tract bleeding due to the risk of ureteral obstruction.

■ ■DISORDERS OF THE VESSEL WALL The vessel wall is an integral part of hemostasis, and separation of a fluid phase is artificial, particularly in disorders such as TTP or HIT that clearly involve the endothelium as well. Inflammation localized to the vessel wall, such as vasculitis, and inherited connective tissue disorders are abnormalities inherent to the vessel wall.

Metabolic and Inflammatory Disorders Acute febrile illnesses may result in vascular damage. This can result from immune com plexes containing viral antigens or the viruses themselves. Certain pathogens, such as the rickettsiae causing Rocky Mountain spotted fever, replicate in endothelial cells and damage them. SARS-CoV-2 also infects endothelial cells, resulting in activation and damage con tributing to COVID-19 pathogenicity. Vascular purpura may occur in patients with polyclonal gammopathies but more commonly occurs in those with monoclonal gammopathies, including Waldenström’s mac roglobulinemia, multiple myeloma, and cryoglobulinemia. Patients with mixed cryoglobulinemia develop a more extensive maculopapular rash due to immune complex–mediated damage to the vessel wall. Patients with scurvy (vitamin C deficiency) develop painful epi sodes of perifollicular skin bleeding as well as more systemic bleed ing symptoms. Vitamin C is needed to synthesize hydroxyproline, an essential constituent of collagen. Patients with Cushing’s syndrome or on chronic glucocorticoid therapy develop skin bleeding and easy bruising due to atrophy of supporting connective tissue. A similar phenomenon is seen with aging, where following minor trauma, blood spreads superficially under the epidermis. This has been termed senile purpura. It is most common on skin that has been previously damaged by sun exposure. CHAPTER 120 Disorders of Platelets and Vessel Wall Immunoglobulin A vasculitis, formerly called Henoch-Schönlein purpura, is a distinct, self-limited type of vasculitis that occurs in chil dren and young adults. Patients have an acute inflammatory reaction with IgA and complement components in capillaries, mesangial tissues, and small arterioles leading to increased vascular permeability and localized hemorrhage. The syndrome is often preceded by an upper respiratory infection, commonly with streptococcal pharyngitis, or is triggered by drug or food allergies. Patients develop a purpuric rash on the extensor surfaces of the arms and legs, usually accompanied by polyarthralgias or arthritis, abdominal pain, and hematuria from focal glomerulonephritis. All coagulation tests are normal, but renal impair ment may occur. Glucocorticoids can provide symptomatic relief but do not alter the course of the illness. Inherited Disorders of the Vessel Wall Patients with inherited disorders of the connective tissue matrix, such as Marfan’s syndrome, Ehlers-Danlos syndrome, and pseudoxanthoma elasticum, frequently report easy bruising. Inherited vascular abnormalities can result in increased bleeding. This is notably seen in hereditary hemorrhagic telangiectasia (HHT, or Osler-Weber-Rendu disease), a disorder where abnormal telangiectatic capillaries result in frequent bleeding episodes, primarily from the nose and gastrointestinal tract. Arteriovenous malformation (AVM) in the lung, brain, and liver may

also occur in HHT. The telangiectasia can often be visualized on the oral and nasal mucosa. Signs and symptoms develop over time. Epistaxis begins, on average, at the age of 12 and occurs in >95% of affected individuals by middle age. Approximately 25% have gastrointestinal bleeding usu ally beginning after the age of 50. HHT is caused by pathogenic DNA variants in a number of genes involved in the TGFβ/BMP signaling cascade. ■ ■FURTHER READING Boender J et al: A diagnostic approach to mild bleeding disorders. J Thromb Haemost 14:1507, 2016. Cines DB, Greinacher A: Vaccine-induced immune thrombotic thrombocytopenia. Blood 141:1659, 2023. Connell NT: ASH ISTH NHF WFH 2021 guidelines on the manage ment of von Willebrand disease. Blood Adv 5:301, 2021. Cuker A et al: American Society of Hematology 2018 guidelines for management of venous thromboembolism: Heparin-induced throm bocytopenia. Blood Adv 2:23360, 2018.

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