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It is suggested that if organ damage is HLH-triggered, lympholytic agents should be considered and a two-step approach is suggested: First, target the cytokine storm and T-cell proliferation with moder ately dosed etoposide (75–100 mg/m2), glucocorticoids, and possibly IVIG, and then target the neoplastic disease by specific treatment as soon as organ function has improved to an acceptable degree. Other HLH-directed immunomodulatory agents, such as anakinra, may also be valuable, but results of studies on such therapies are limited. ■ ■MACROPHAGE ACTIVATION SYNDROME Macrophage activation syndrome (MAS) is a life-threatening hyperin flammatory complication of rheumatic disease and other autoimmune diseases. It is characterized by an uncontrolled activation and prolif eration of T lymphocytes and macrophages and classified among the secondary, acquired forms of HLH because it shares many clinical and laboratory features with both primary and secondary HLH, hence the term MAS-HLH. MAS-HLH is the third most common form of HLH in adults and the second most common in children. In children, it occurs most fre quently in individuals with systemic juvenile idiopathic arthritis (sJIA), affecting 10% of these patients, and with systemic lupus erythematosus. In adults, systemic lupus erythematosus is the most common cause, followed by adult-onset Still’s disease, affecting about 5% and 10–15% of these patient groups, respectively. Other causes include systemic vasculitis and inflammatory bowel disease. Clinically, MAS-HLH manifests as fever, liver dysfunction, cytope nia, hyperferritinemia, coagulopathy, CNS abnormalities, and, more rarely, hemophagocytosis. Fibrinogen and platelet levels are often higher than in other forms of HLH, due to the inflammatory nature of sJIA. In 2016, MAS-HLH in sJIA patients was defined as a febrile patient with ferritin >684 µg/L and any two of the following: platelet count ≤181 × 109/L, aspartate aminotransferase >48 U/L, fasting tri glycerides >1.76 mmol/L (156 mg/dL), and fibrinogen ≤3.6 g/L. Most MAS-HLH flares are reported to be triggered by active disease, but about a third have an infectious trigger. The cytokine pattern in MAS-HLH is characterized by high serum levels of IL-18, distinguish ing it from other forms of HLH such as FHL. The mortality rate in MAS-HLH is about 5–10% in children and 10–15% in adults. CNS involvement is frequent and may lead to irre versible neurologic damage. Early diagnosis and treatment are therefore crucial. Patients with MAS-HLH may also develop severe pulmonary disease with a high fatality rate, reported to be about 50%, for which the best treatment and prevention still is unknown. The predominant pathology is pulmonary alveolar proteinosis and/or endogenous lipoid pneumonia, but the underlying cause is unknown. ■ ■TREATMENT A common first-line approach is glucocorticoids in high doses, such as intravenous pulse methylprednisolone 30 mg/kg per dose up to a maxi mum of 1000 mg/dose once daily for

3–5 days followed by high-dose oral or intravenous glucocorticoids. Cyclosporin A (2–7 mg/kg/d) can be added. IL-1–blocking therapy is also effective, such as with anakinra in a dose of 2–6 mg/kg up to 10 mg/kg per day in divided doses. Expe rience with other immunomodulating agents, including tocilizumab, emapalumab, and ruxolitinib, is increasing. In patients with severe disease or CNS involvement despite gluco corticoids, cyclosporin A, and/or anakinra, a moderate dose of etopo side (50–100 mg/m2 once weekly) can be very effective. ■ ■TRANSPLANT-RELATED AND CHIMERIC ANTIGEN RECEPTOR HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS Other causes of secondary HLH include transplantation, particularly kidney and hematologic transplantations, and novel drugs, such as chimeric antigen receptor (CAR) T cells, bispecific T-cell engagers, and checkpoint inhibitors. HLH with late onset (>30 days) after HSCT is often comparable to infection-associated HLH. Based on other forms of secondary HLH, it is reasonable to start treatment with corticosteroids. As second-line

treatment, favorable response after low-dose etoposide has been reported; one dose of 50–75 mg/m2 may be sufficient.

Increasing use of CAR T-cell therapy and other immune effector cell-based therapies has led to an increasing number of cases with a clinical picture resembling secondary HLH that is distinct from cyto kine release syndrome. This HLH-like complication is more frequent when using CD22 CAR T cells, affecting about a third of these patients. Data on treatment results are limited, but anakinra with or without glucocorticoids is suggested as first-line therapy. As second- and thirdline therapy, ruxolitinib, emapalumab, and low-dose etoposide have been suggested. Bleeding and Thrombosis CHAPTER 69 CONCLUSION The survival and biological understanding of primary and secondary HLH have increased dramatically over the past decade(s), but much remains to be learned. Despite being life-threatening and now also treatable, HLH is still markedly underdiagnosed. Numerous lives might be saved by increased awareness of HLH. ■ ■FURTHER READING Daver N et al: A consensus review on malignancy-associated hemo phagocytic lymphohistiocytosis in adults. Cancer 123:3229, 2017. Ehl S et al: Recommendations for the use of etoposide-based therapy and bone marrow transplantation for the treatment of HLH: Con sensus statements by the HLH Steering Committee of the Histiocyte Society. J Allergy Clin Immunol Pract 6:1508, 2018. Hines MR et al: Consensus-based guidelines for the recognition, diag nosis, and management of hemophagocytic lymphohistiocytosis in critically ill children and adults. Crit Care Med 50:860, 2022. La Rosée P et al: Recommendations for the management of hemo phagocytic lymphohistiocytosis in adults. Blood 133:2465, 2019. Ramos-Casals M et al: Adult haemophagocytic syndrome. Lancet 383:1503, 2014. Barbara A. Konkle

Bleeding and Thrombosis The human hemostatic system provides a natural balance between pro coagulant and anticoagulant forces. The procoagulant forces include platelet adhesion and aggregation and fibrin clot formation; anticoagu lant forces include the natural inhibitors of coagulation and fibrinoly sis. Under normal circumstances, hemostasis is regulated to promote blood flow; however, it is also prepared to clot blood rapidly to arrest blood flow and prevent exsanguination. After bleeding is successfully halted, the system remodels the damaged vessel to restore normal blood flow. The major components of the hemostatic system, which function in concert, are (1) platelets and other formed elements of blood, such as monocytes and red cells; (2) plasma proteins (the coagu lation and fibrinolytic factors and inhibitors); and (3) the vessel wall. STEPS OF NORMAL HEMOSTASIS ■ ■PLATELET PLUG FORMATION On vascular injury, platelets

adhere to the site of injury, usually the denuded vascular intimal surface. Platelet adhesion is mediated pri marily by von Willebrand factor (VWF), a large multimeric protein present in both plasma and the extracellular matrix of the subendothe lial vessel wall, which serves as the primary “molecular glue,” providing

sufficient strength to withstand the high levels of shear stress that would tend to detach them with the flow of blood. Platelet adhesion is also facilitated by direct binding to subendothelial collagen through specific platelet membrane collagen receptors.

Platelet adhesion results in subsequent platelet activation and aggre gation. This process is enhanced and amplified by humoral mediators in plasma (e.g., epinephrine, thrombin); mediators released from acti vated platelets (e.g., adenosine diphosphate, serotonin); and vessel wall extracellular matrix constituents that come in contact with adherent platelets (e.g., collagen, VWF). Activated platelets undergo the release reaction, during which they secrete contents that further promote aggregation and inhibit the naturally anticoagulant endothelial cell factors. During platelet aggregation (platelet-platelet interaction), addi tional platelets are recruited from the circulation to the site of vascular injury, leading to the formation of an occlusive platelet thrombus. The platelet plug is anchored and stabilized by the developing fibrin mesh. PART 2 Cardinal Manifestations and Presentation of Diseases The platelet glycoprotein (Gp) IIb/IIIa (αIIbβ3) complex is the most abundant receptor on the platelet surface. Platelet activation converts the normally inactive Gp IIb/IIIa receptor into an active receptor, enabling binding to fibrinogen and VWF. Because the surface of each platelet has about 50,000 Gp IIb/IIIa–binding sites, numerous acti vated platelets recruited to the site of vascular injury can rapidly form an occlusive aggregate by means of a dense network of intercellular fibrinogen bridges. ■ ■FIBRIN CLOT FORMATION Plasma coagulation proteins (clotting factors) normally circulate in plasma in their inactive forms. The sequence of coagulation protein reactions that culminate in the formation of fibrin was originally described as a waterfall or a cascade. Two pathways of blood coagulation have been described in the past: the so-called extrinsic, or tissue factor, pathway and the so-called intrinsic, or contact activation, pathway. We now know that coagulation is normally initiated through tissue factor (TF) exposure and activation through the classic extrinsic pathway but with critically important amplification through elements of the classic intrinsic pathway, as illustrated in Fig. 69-1. These reactions take place on phospholipid surfaces, usually the activated platelet surface. Coagu lation testing in the laboratory can reflect other influences due to the artificial nature of the in vitro systems used (see below). The immediate trigger for coagulation is vascular damage that exposes blood to TF that is constitutively expressed on the surfaces of subendothelial cellular components of the vessel wall, such as smooth Vessel injury IX TF VIIa IXa TFPI X Va Xa II (Prothrombin) Fibrinogen Fibrin FIGURE 69-1 Coagulation is initiated by tissue factor (TF) exposure, which, with factor (F) VIIa, activates FIX and FX, which in turn, with FVIII and FV as cofactors, respectively, results in thrombin formation and subsequent conversion of fibrinogen to fibrin. Thrombin activates FXI, FVIII, and FV, amplifying the coagulation signal. Once the TF/FVIIa/ FXa complex is formed, tissue factor pathway inhibitor (TFPI) inhibits the TF/FVIIa pathway, making coagulation dependent on the amplification loop through FIX/FVIII. Coagulation requires calcium (not shown) and takes place on phospholipid surfaces, usually the activated platelet membrane.

muscle cells and fibroblasts. TF is also present in circulating micropar ticles, presumably shed from cells including monocytes and platelets. TF binds the serine protease factor VIIa; the complex

activates factor X to factor Xa. Alternatively, the complex can indirectly activate factor X by initially converting factor IX to factor IXa, which then activates factor X. The participation of factor XI in hemostasis is not dependent on its activation by factor XIIa but rather on its positive feedback acti vation by thrombin. Thus, factor XIa functions in the propagation and amplification, rather than in the initiation, of the coagulation cascade. The role of factor XIIa in activation of factor XI is not fully elucidated, but studies suggest it may be a mechanism to promote thrombosis. Factor Xa can be formed through the actions of either the TF/factor VIIa complex or factor IXa (with factor VIIIa as a cofactor) and converts prothrombin to thrombin, the pivotal protease of the coagulation system. The essential cofactor for this reaction is factor Va, which is produced by thrombin-induced limited proteolysis of factor V. Thrombin is a multifunctional enzyme that converts soluble plasma fibrinogen to an insoluble fibrin matrix. Fibrin polymerization involves an orderly pro cess of intermolecular associations (Fig. 69-2). Thrombin also activates factor XIII (fibrin-stabilizing factor) to factor XIIIa, which covalently cross-links and thereby stabilizes the fibrin clot. The assembly of the clotting factors on activated cell membrane surfaces greatly accelerates their reaction rates and also serves to local ize blood clotting to sites of vascular injury. The critical cell membrane components, acidic phospholipids, are not normally exposed on rest ing cell membrane surfaces. However, when platelets, monocytes, and endothelial cells are activated by vascular injury or inflammatory stimuli, the procoagulant head groups of the membrane anionic phos pholipids become translocated to the surfaces of these cells or released as part of microparticles, making them available to support and pro mote the plasma coagulation reactions. ANTITHROMBOTIC MECHANISMS Several physiologic antithrombotic mechanisms act in concert to pre vent clotting under normal circumstances. These mechanisms operate to preserve blood fluidity and to limit blood clotting to specific focal sites of vascular injury. Endothelial cells have many antithrombotic effects. They produce prostacyclin, nitric oxide, and ectoADPase/ CD39, which act to inhibit platelet binding, secretion, and aggrega tion. Endothelial cells produce anticoagulant factors including heparan proteoglycans, TF pathway inhibitor, and thrombomodulin. They also activate fibrinolytic mechanisms through the production of tissue plas minogen activator, urokinase, plasmino gen activator inhibitors, and annexin-2. Antithrombin is the major plasma pro tease inhibitor of thrombin and other clot ting factors in coagulation. Antithrombin neutralizes thrombin and other activated coagulation factors by forming a complex between the active site of the enzyme and the reactive center of antithrombin. The rate of formation of these inactivating complexes increases by a factor of sev eral thousand in the presence of heparin. Antithrombin inactivation of thrombin and other activated clotting factors occurs physiologically on vascular surfaces, where glycosaminoglycans, including heparan sulfates, are present to catalyze these reactions. Inherited quantitative or qualitative deficiencies of antithrombin lead to a lifelong predisposition to venous thromboembolism (VTE). IX VIIIa XIa X XI Thrombin (IIa) Protein C is a plasma glycoprotein that becomes an anticoagulant when it is activated by thrombin. The thrombininduced activation of protein C occurs physiologically on thrombomodulin, a transmembrane proteoglycan-binding site

A D E D Thrombin Fibrin assembly D E D D E D D E D B D E D D E D D E D Fibrin cross-linking Factor XIIIa D E D D E D D E D C D E D D E D D E D Plasmin D D D E FIGURE 69-2 Fibrin formation and dissolution. (A) Fibrinogen is a trinodular structure consisting of two D domains and one E domain. Thrombin activation results in an ordered lateral assembly of protofibrils (B) with noncovalent associations. Factor XIIIa cross-links the D domains on adjacent molecules (C). Fibrin and fibrinogen (not shown) lysis by plasmin occurs at discrete sites and results in intermediary fibrin(ogen) degradation products (not shown). d-Dimers are the product of complete lysis of fibrin (D),

maintaining the cross-linked D domains. for thrombin on endothelial cell surfaces. The binding of protein C to its receptor on endothelial cells places it in proximity to the thrombinthrombomodulin complex, thereby enhancing its activation efficiency. (See Fig. 69-3.) Activated protein C acts as an anticoagulant by cleav ing and inactivating activated factors V and VIII. This reaction is accel erated by a cofactor, protein S, which, like protein C, is a glycoprotein that undergoes vitamin K–dependent posttranslational modification. Quantitative or qualitative deficiencies of protein C or protein S, or resistance to the action of activated protein C by a specific variant at Protein S Free protein S FVIIIa FVa C4 binding protein Thrombomodulin APC FVIIIi FVi Protein C IIa Endothelial protein C receptor Endothelial cell FIGURE 69-3 The activated protein C pathway in regulation of thrombosis. Thrombin generation results in protein C activation through interaction with thrombomodulin and protein C bound to the endothelial protein C receptor (EPCR). Activated protein C (APC) with free protein S converts activated factors (F) VIII and V to inactivate forms, thus in turn decreasing thrombin generation. C4BP, C4 binding protein; EC, endothelial cell; F, factor; IIa, thrombin; PC, protein C; PS, protein S; TM, thrombomodulin.

its target cleavage site in factor Va (factor V Leiden), lead to hyperco agulable states.

Tissue factor pathway inhibitor (TFPI) is a plasma protease inhibi tor that regulates the TF-induced extrinsic pathway of coagulation. TFPI inhibits the TF/factor VIIa/factor Xa complex, essentially turning off the TF/factor VIIa initiation of coagulation, which then becomes dependent on the “amplification loop” via factor XI and factor VIII activation by thrombin. TFPI is bound to lipoprotein and can also be released by heparin from endothelial cells, where it is bound to gly cosaminoglycans, and from platelets. The heparin-mediated release of TFPI may play a role in the anticoagulant effects of unfractionated and low-molecular-weight heparins. Bleeding and Thrombosis CHAPTER 69 ■ ■THE FIBRINOLYTIC SYSTEM Any thrombin that escapes the inhibitory effects of the physiologic anticoagulant systems is available to convert fibrinogen to fibrin. In response, the endogenous fibrinolytic system is then activated to dispose of intravascular fibrin and thereby maintain or reestablish the patency of the circulation. Just as thrombin is the key protease enzyme of the coagulation system, plasmin is the major protease enzyme of the fibrinolytic system, acting to digest fibrin to fibrin degradation products. The general scheme of fibrinolysis and its control is shown in Fig. 69-4. Clot lysis The plasminogen activators, tissue type plasminogen activator (tPA) and the urokinase-type plasminogen activator (uPA), cleave the Arg560-Val561 bond of plasminogen to generate the active enzyme plasmin. The lysine-binding sites of plasmin (and plasminogen) permit it to bind to fibrin, so that physiologic fibrinolysis is “fibrin specific.” Both plasminogen (through its lysine-binding sites) and tPA possess specific affinity for fibrin and thereby bind selectively to clots. The assembly of a ternary complex, consisting of fibrin, plasminogen, and tPA, promotes the localized interaction between plasminogen and tPA and greatly accelerates the rate of plasminogen activation to plasmin. Moreover, partial degradation of fibrin by plasmin exposes new plas minogen and tPA-binding sites in carboxy-terminus lysine residues of fibrin fragments to enhance these reactions further. This creates a highly efficient mechanism to generate plasmin locally on the fibrin clot, which then becomes plasmin’s substrate for digestion to fibrin degradation products. Plasmin cleaves fibrin at distinct sites of the fibrin molecule, leading to the generation of characteristic fibrin fragments during the pro cess of fibrinolysis (Fig. 69-2). The sites of plasmin cleavage of fibrin are the same as those in fibrinogen. However, when plasmin acts on covalently cross-linked fibrin, d-dimers are released; hence, d-dimers uPA Plasminogen tPA PAI Plasmin Thrombin α2PI-Plasmin FDPs FIGURE 69-4 A

schematic diagram of the fibrinolytic system. Tissue plasminogen activator (tPA) is released from endothelial cells, binds the fibrin clot, and activates plasminogen to plasmin. Release of plasminogen activator inhibitors (PAI-1 and PAI-2) inhibits tPA and urokinase (uPA). Excess fibrin is degraded by plasmin to distinct degradation products [FDPs (d-dimers)]. Any free plasmin is complexed with α2-antiplasmin (α2Pl). PAI, plasminogen activator inhibitor; uPA, urokinase-type plasminogen activator.

can be measured in plasma as a relatively specific test of fibrin (rather than fibrinogen) degradation. d-Dimer assays can be used as sensitive markers of blood clot formation and have been validated for clinical use to exclude the diagnosis of deep venous thrombosis (DVT) and pulmonary embolism in selected populations. d-Dimer levels increase with age. Use of an age-adjusted d-dimer threshold for risk stratifica tion results in less additional testing for VTE.

Physiologic regulation of fibrinolysis occurs primarily at three levels: (1) plasminogen activator inhibitors (PAIs), specifically PAI-1 and PAI-2, inhibit the physiologic plasminogen activators; (2) the thrombin-activatable fibrinolysis inhibitor (TAFI) limits fibrinolysis; and (3) α2-antiplasmin inhibits plasmin. PAI-1 is the primary inhibitor of tPA and uPA in plasma. TAFI cleaves the N-terminal lysine residues of fibrin, which aid in localization of plasmin activity. α2-Antiplasmin is the main inhibitor of plasmin in human plasma, inactivating any nonfibrin clot–associated plasmin. PART 2 Cardinal Manifestations and Presentation of Diseases APPROACH TO THE PATIENT Bleeding and Thrombosis CLINICAL PRESENTATION Disorders of hemostasis may be either inherited or acquired. A detailed personal and family history is key in determining the chronicity of symptoms and the likelihood of the disorder being inherited, as well as providing clues to underlying conditions that have contributed to the bleeding or thrombotic state. In addition, the history can give clues as to the etiology by determining (1) the bleeding (mucosal and/or joint) or thrombosis (arterial and/ or venous) site and (2) whether an underlying bleeding or clotting tendency was enhanced by another medical condition or the intro duction of medications or dietary supplements. History of Bleeding A history of bleeding is the most important predictor of bleeding risk. In evaluating a patient for a bleeding disorder, a history of at-risk situations, including the response to past surgeries, should be assessed. Does the patient have a history of spontaneous or trauma/surgery-induced bleeding? Spontaneous hemarthroses are a hallmark of moderate and severe factor VIII and IX deficiency and, in rare circumstances, of other clotting fac tor deficiencies. Mucosal bleeding symptoms are more suggestive of underlying platelet disorders or von Willebrand disease (VWD), termed disorders of primary hemostasis or platelet plug formation. Disorders affecting primary hemostasis are shown in Table 69-1. A bleeding score has been validated as a tool to predict patients more likely to have an inherited bleeding disorder, particularly type 1 VWD (International Society on Thrombosis and Haemo stasis Bleeding Assessment Tool [www.isth.org/resource/resmgr/ssc/

isth-ssc_bleeding_assessment.pdf]), and a self-administered form has been validated. This is the most useful tool in excluding the diagnosis of a bleeding disorder, thus avoiding unnecessary testing, and is recommended by 2021 guidelines for screening for VWD in primary care. Bleeding symptoms that are more common in patients with bleeding disorders include prolonged bleeding with surgery, dental procedures and extractions, and/or trauma; heavy menstrual bleeding or postpartum hemorrhage; and large bruises (often described with lumps). Easy bruising and heavy menstrual bleeding are common com plaints in patients with and without bleeding disorders. Easy bruis ing can also be a sign of medical conditions in which there is no identifiable coagulopathy;

instead, the conditions are caused by an abnormality of blood vessels or their supporting connective tissues. In Ehlers-Danlos syndrome, there may be posttraumatic bleed ing and a history of joint hyperextensibility. Cushing’s syndrome, chronic steroid use, and aging result in changes in skin and sub cutaneous tissue, and subcutaneous bleeding occurs in response to minor trauma. The latter has been termed senile purpura. Epistaxis is a common symptom, particularly in children and in dry climates, and may not reflect an underlying bleeding disorder.

TABLE 69-1 Primary Hemostatic (Platelet Plug) Disorders Defects of Platelet Adhesion von Willebrand disease Bernard-Soulier syndrome (absence or dysfunction of platelet Gp Ib-IX-V) Defects of Platelet Aggregation Glanzmann’s thrombasthenia (absence or dysfunction of platelet glycoprotein [Gp] IIb/IIIa) Afibrinogenemia Defects of Platelet Secretion Decreased cyclooxygenase activity Drug-induced (aspirin, nonsteroidal anti-inflammatory agents, thienopyridines) Inherited Granule storage pool defects Inherited Acquired Nonspecific inherited secretory defects Nonspecific drug effects Uremia Platelet coating (e.g., paraprotein, penicillin) Defect of Platelet Coagulant Activity Scott’s syndrome However, it is the most common symptom in hereditary hemor rhagic telangiectasia and in boys with VWD. Clues that epistaxis is a symptom of an underlying bleeding disorder include lack of seasonal variation and bleeding that requires medical evaluation or treatment, including cauterization. Bleeding with eruption of primary teeth is seen in children with more severe bleeding disorders, such as mod erate and severe hemophilia. It is uncommon in children with mild bleeding disorders. Patients with disorders of primary hemostasis (platelet adhesion) may have increased bleeding after dental clean ings and other procedures that involve gum manipulation. Heavy menstrual bleeding is defined quantitatively as a loss of >80 mL of blood per cycle, based on the quantity of blood loss required to produce iron-deficiency anemia. A complaint of heavy menses is subjective and has a poor correlation with excessive blood loss. Predictors of heavy menstrual bleeding include bleeding resulting in iron-deficiency anemia or a need for blood transfusion, passage of clots >1 inch in diameter, and changing a pad or tampon more than hourly. Heavy menstrual bleeding is a common symp tom in women with underlying bleeding disorders and is reported in the majority of women with VWD, factor XI deficiency, platelet function disorders, and hemophilia, including genetic carriers with borderline-normal factor levels. Women with underlying bleeding disorders are more likely to have other bleeding symptoms, includ ing bleeding after dental extractions and postoperative and postpar tum bleeding, and are much more likely to have heavy menstrual bleeding beginning at menarche than women with heavy menstrual bleeding due to other causes. Heavy menstrual bleeding may result in iron deficiency and is documented to have significant adverse effects on quality of life. Postpartum hemorrhage is a common symptom in women with underlying bleeding disorders. In women with type 1 VWD or hemophilia A in whom levels of VWF and factor VIII often nor malize during pregnancy, postpartum hemorrhage may be delayed. Women with a history of postpartum hemorrhage may have a higher risk of recurrence with subsequent pregnancies. Women with underlying bleeding disorders are at risk for other reproduc tive tract bleeding, including rupture of ovarian cysts with intraab dominal hemorrhage. Tonsillectomy is a major hemostatic challenge, because intact hemostatic mechanisms are essential to prevent excessive bleeding from the tonsillar bed. Bleeding may occur early after surgery or after approximately 7 days postoperatively, with loss of the eschar

at the operative site. Similar delayed bleeding is seen after colonic polyp resection. Gastrointestinal (GI) bleeding and hematuria are usually due to underlying pathology, and procedures to identify

and treat the bleeding site should be undertaken, even in patients with known bleeding disorders. VWD, particularly types 2 and 3, is associated with angiodysplasia of the bowel and GI bleeding. Hemarthroses and spontaneous muscle hematomas are char acteristic of moderate or severe congenital factor VIII or IX defi ciency. They can also be seen in moderate and severe deficiencies of fibrinogen, prothrombin, and factors V, VII, and X. Spontaneous hemarthroses occur rarely in other bleeding disorders except for severe VWD, with associated very low factor VIII levels. Muscle and soft tissue bleeds are also common in acquired factor VIII deficiency. Bleeding into a joint results in severe pain and swelling, as well as loss of function, but is rarely associated with discoloration from bruising around the joint. Life-threatening sites of bleeding include bleeding into the oropharynx, where bleeding can obstruct the air way, into the central nervous system, and into the retroperitoneum. Central nervous system bleeding is the major cause of bleedingrelated deaths in patients with severe congenital factor deficiencies. Prohemorrhagic Effects of Medications and Dietary Supple ments Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) that inhibit cyclooxygenase 1 impair primary hemostasis and may exacerbate bleeding from another cause or even unmask a previously occult mild bleeding disorder such as VWD. All NSAIDs, however, can precipitate GI bleeding, which may be more severe in patients with underlying bleeding disorders. The aspirin effect on platelet function lasts for the life of the platelet; however, in indi viduals with typical platelet turnover, the functional defect reverts to near-normal within 2–3 days after the last dose. The effect of other NSAIDs is shorter, as the inhibitor effect is reversed when the drug is removed. Inhibitors of the ADP P2Y12 receptor (clopidogrel, prasugrel, and ticagrelor) inhibit ADP-mediated platelet aggregation and, like NSAIDs, can precipitate or exacerbate bleeding symptoms. The risk of bleeding with these drugs is higher than with NSAIDs. Many herbal supplements can impair hemostatic function. Some are more convincingly associated with a bleeding risk than others. Fish oil or concentrated omega-3 fatty acid supplements impair platelet function. They alter platelet biochemistry to produce more PGI3, a more potent platelet inhibitor than prostacyclin (PGI2), and more thromboxane A3, a less potent platelet activator than throm boxane A2. In fact, diets naturally rich in omega-3 fatty acids can result in a prolonged bleeding time and abnormal platelet aggre gation studies, but the actual associated bleeding risk is unclear. Many supplements have been associated with increased bleeding with surgery and anticoagulant-related bleeding. In patients with unexplained bruising or bleeding, it is prudent to review any new medications or supplements and discontinue those that have been associated with bleeding. Underlying Systemic Diseases That Cause or Exacerbate a Bleeding Tendency Acquired bleeding disorders are commonly secondary to, or associated with, systemic disease. The clinical evaluation of a patient with a bleeding tendency must therefore include a thorough assessment for evidence of underlying disease. Bruising or mucosal bleeding may be the presenting complaint in liver disease, severe renal impairment, hypothyroidism, paraproteinemias or amyloidosis, and conditions causing bone marrow failure. All coagulation factors are synthesized in the liver, and hepatic failure results in combined factor deficiencies. This is often compounded by thrombocytopenia and portal hypertension. Coagulation factors II, VII, IX, and X and proteins C, S, and Z are dependent on vitamin K for posttranslational modification. Although vitamin K is required in both procoagulant and anticoagulant processes, the phenotype of vitamin K deficiency or the warfarin effect on coagulation is bleeding. The normal blood platelet count is 150,000–450,000/μL. Throm bocytopenia results from decreased production, increased destruc tion, and/or sequestration. Although the bleeding risk varies

TABLE 69-2 Some Risk Factors for Thrombosis VENOUS VENOUS AND ARTERIAL Inherited Factor V Leiden Prothrombin G20210A Antithrombin deficiency Protein C deficiency Protein S deficiency Acquired Age Previous thrombosis Immobilization Major surgery Pregnancy and puerperium Hospitalization Obesity Infection Smoking Inherited Homocystinuria Dysfibrinogenemia Acquired Malignancy Antiphospholipid antibody syndrome Hormonal therapy Polycythemia vera Essential thrombocythemia Paroxysmal nocturnal hemoglobinuria Thrombotic thrombocytopenic purpura Heparin-induced thrombocytopenia Disseminated intravascular coagulation Infection Unknowna Bleeding and Thrombosis CHAPTER 69 Elevated factor II, VIII, IX, XI Elevated TAFI levels Low levels of TFPI aUnknown whether risk is inherited or acquired. Abbreviations: APC, activated protein C; TAFI, thrombin-activatable fibrinolysis inhibitor; TFPI, tissue factor pathway inhibitor. somewhat by the reason for the thrombocytopenia, bleeding rarely occurs in isolated thrombocytopenia at counts >50,000/μL and usually not until <10,000–20,000/μL. Coexisting coagulopathies, as is seen in liver failure or disseminated coagulation; infection; platelet-inhibitory drugs; and underlying medical conditions can all increase the risk of bleeding in the thrombocytopenic patient. Most procedures can be performed in patients with a platelet count of 50,000/μL or greater. HISTORY OF THROMBOSIS The risk of thrombosis, like that of bleeding, is influenced by both genetic and environmental factors. The major risk factor for arte rial thrombosis is atherosclerosis, whereas for venous thrombosis, the risk factors are immobility, surgery, underlying medical condi tions such as malignancy, medications such as hormonal therapy, obesity, and genetic predispositions. Factors that increase risks for venous and for both venous and arterial thromboses are shown in Table 69-2. The most important point in a history related to venous throm bosis is determining whether the thrombotic event was idiopathic (meaning there was no clear precipitating factor) or was a precipi tated event. In patients without underlying malignancy, having an idiopathic event is the strongest predictor of recurrence of VTE. In patients who have a vague history of thrombosis, a history of being treated with warfarin or other anticoagulants suggests a past DVT. Age is an important risk factor for venous thrombosis—the risk of DVT increases per decade, with an approximate incidence of 1/100,000 per year in early childhood to 1/200 per year among octogenarians. Family history is helpful in determining if there is a genetic predisposition and how strong that predisposition appears to be. A genetic thrombophilia that confers a relatively small increased risk, such as being a heterozygote for the prothrombin G20210A or factor V Leiden mutation, is a minor determinant of risk in an elderly individual undergoing a high-risk surgical procedure. As illustrated in Fig. 69-5, a thrombotic event usually has more than one contributing factor. Predisposing factors must be carefully assessed to determine the risk of recurrent thrombosis and, with consideration of the patient’s bleeding risk, determine the length of anticoagulation. Testing for inherited thrombophilias in adults should be limited to instances where results would change clinical care. Such instances are rare.

OCP use Leg in cast HRT use Thrombotic risk DVT Thrombosis Surgery PART 2 Cardinal Manifestations and Presentation of Diseases Factor V Leiden Age FIGURE 69-5 Thrombotic risk over time. Shown schematically is an individual’s thrombotic risk over time. An underlying factor V Leiden variant provides a “theoretically” constant increased risk. The thrombotic risk increases with age and, intermittently, with oral contraceptive (OCP) or oral hormone replacement therapy (HRT) use; other events, like major surgery or illness, will increase the risk further. At some point, the cumulative risk may increase to the threshold for thrombosis and result in deep venous thrombosis (DVT). Note: The magnitude and duration of risk portrayed in the figure are meant for example only and may not precisely reflect the relative risk determined by clinical study. (Sources:

From BA Konkle, A Schafer, in DP Zipes et al [eds]: Braunwald’s Heart Disease, 7th ed. Philadelphia, Saunders, 2005; from FR Rosendaal: Venous thrombosis: A multicausal disease. Lancet 353:1167, 1999.) LABORATORY EVALUATION Careful history taking and clinical examination are essential com ponents in the assessment of bleeding and thrombotic risk. The use of laboratory tests of coagulation complements, but cannot substitute for, clinical assessment. No test exists that provides a global assessment of hemostasis. Thrombin generation assays have not generally provided reproducible results across laboratories. The bleeding time does not predict bleeding risk, and it is not recom mended for this indication. Thromboelastography can be useful in guiding intraoperative transfusion and is being explored in other settings but is not broadly applicable for the diagnosis of disorders of hemostasis and thrombosis. For routine preoperative and preprocedure testing, an abnormal prothrombin time (PT) may detect liver disease or vitamin K defi ciency that had not been previously appreciated. Studies have not confirmed the usefulness of an activated partial thromboplastin time (aPTT) in preoperative evaluations in patients with a negative bleeding history. The primary use of coagulation testing should be to confirm the presence and type of bleeding disorder in a patient with a suspicious clinical history. Because of the nature of coagulation assays, proper sample acquisition and handling is critical to obtaining valid results. In patients with abnormal coagulation assays who have no bleeding history, repeat studies with attention to these factors frequently results in normal values. Most coagulation assays are performed in sodium citrate anticoagulated plasma that is recalcified for the assay. Because the anticoagulant is in liquid solution and needs to be added to blood in proportion to the plasma volume, incorrectly filled or inadequately mixed blood collection tubes will give errone ous results. These vacutainer tubes should be filled to >90% of the recommended fill, which is usually denoted by a line on the tube. An elevated hematocrit (>55%) can result in a false value due to a decreased plasma-to-anticoagulant ratio. Screening Assays The most commonly used screening tests are the PT, aPTT, and platelet count. The PT assesses the factors I

aPTT HMWK PT PK FXII FVII FXI FIX FVIII FX FV Prothrombin (FII) Fibrinogen (FI) FIGURE 69-6 Coagulation factor activity tested in the activated partial thromboplastin time (aPTT) in red and prothrombin time (PT) in green, or both. F, factor; HMWK, high-molecular-weight kininogen; PK, prekallikrein. (fibrinogen), II (prothrombin), V, VII, and X (Fig. 69-6). The PT measures the time for clot formation of the citrated plasma after recalcification and addition of thromboplastin, a mixture of TF and phospholipids. The sensitivity of the assay varies by the source of thromboplastin. The relationship between defects in secondary hemostasis (fibrin formation) and coagulation test abnormalities is shown in Table 69-3. To adjust for this variability, the overall sensitivity of different thromboplastins to reduction of the vitamin K–dependent clotting factors II, VII, IX, and X in anticoagulation patients is expressed as the International Sensitivity Index (ISI). The international normalized ratio (INR) is determined based on the formula: INR = (PTpatient/PTnormal mean)ISI. The INR was developed to assess stable anticoagulation due to reduction of vitamin K–dependent coagulation factors; it is commonly used in the evaluation of patients with liver disease. Although it does allow comparison between laboratories, reagent sensitivity as used to determine the ISI is not the same in liver disease as with warfarin anticoagulation. In addition, progressive liver failure is associated with variable changes in coagulation fac tors; the degree of prolongation of either the PT or the INR only roughly predicts the bleeding risk. Thrombin generation has been shown to be normal in many patients with mild to moderate liver dysfunction. Because the PT only measures one aspect of hemosta sis affected by liver dysfunction, we likely overestimate the bleed ing risk of a mildly elevated INR in this setting. PT reagents have variable sensitivity to the direct Xa

inhibitors, and the PT is usually normal in patients on apixaban. The aPTT assesses the intrinsic and common coagulation path ways; factors XI, IX, VIII, X, V, and II; fibrinogen; prekallikrein; high-molecular-weight kininogen; and factor XII (Fig. 69-6). The aPTT reagent contains phospholipids derived from either animal or vegetable sources that function as a platelet substitute in the coagu lation pathways and includes an activator of the intrinsic coagula tion system, such as nonparticulate ellagic acid or the particulate activators kaolin, celite, or micronized silica. The phospholipid composition of aPTT reagents varies, which influences the sensitivity of individual reagents to clotting factor deficiencies and to inhibitors such as heparin and lupus anticoagu lants. Thus, aPTT results will vary from one laboratory to another, and the normal range in the laboratory where the testing occurs

TABLE 69-3 Hemostatic Disorders and Coagulation Test Abnormalities Prolonged Activated Partial Thromboplastin Time (aPTT) No clinical bleeding—↓ factor XII, high-molecular-weight kininogen, prekallikrein Variable, but usually mild, bleeding—↓ factor XI, mild ↓ factor VIII and factor IX Frequent, severe bleeding—severe deficiencies of factors VIII and IX Heparin and direct thrombin inhibitors Prolonged Prothrombin Time (PT) Factor VII deficiency Vitamin K deficiency—early Warfarin anticoagulation Direct Xa inhibitors (rivaroxaban, edoxaban, apixaban—note PT may be normal) Prolonged aPTT and PT Factor II, V, X, or fibrinogen deficiency Vitamin K deficiency—late Direct thrombin inhibitors Prolonged Thrombin Time Heparin or heparin-like inhibitors Direct thrombin inhibitors (e.g., dabigatran, argatroban, bivalirudin) Mild or no bleeding—dysfibrinogenemia Frequent, severe bleeding—afibrinogenemia Prolonged PT and/or aPTT Not Corrected with Mixing with Normal Plasma Bleeding—specific factor inhibitor No symptoms, or clotting and/or pregnancy loss—lupus anticoagulant Disseminated intravascular coagulation Heparin or direct thrombin inhibitor Abnormal Clot Solubility Factor XIII deficiency Inhibitors or defective cross-linking Rapid Clot Lysis Deficiency of α2-antiplasmin or plasminogen activator inhibitor 1 Treatment with fibrinolytic therapy should be used in the interpretation. Local laboratories can relate their aPTT values to the therapeutic heparin anticoagulation by correlating aPTT values with direct measurements of heparin activ ity (anti-Xa or protamine titration assays) in samples from heparin ized patients, although correlation between these assays is often poor. The aPTT reagent will vary in sensitivity to individual factor deficiencies and usually becomes prolonged with individual factor deficiencies of ≤30–50%. Mixing Studies Mixing studies are used to evaluate a prolonged aPTT or, less commonly, PT to distinguish between a factor defi ciency and an inhibitor. In this assay, normal plasma and patient plasma are mixed in a 1:1 ratio, and the aPTT or PT is determined immediately and after incubation at 37°C for varying times, typi cally 30, 60, and/or 120 min. With isolated factor deficiencies, the aPTT will correct with mixing and stay corrected with incubation. With aPTT prolongation due to a lupus anticoagulant, the mixing and incubation will show no correction. In acquired neutralizing factor antibodies, notably an acquired factor VIII inhibitor, the ini tial assay may or may not correct immediately after mixing but will prolong or remain prolonged with incubation at 37°C. Failure to correct with mixing can also be due to the presence of other inhibi tors or interfering substances such as heparin, fibrin split products, and paraproteins. Specific Factor Assays Decisions to proceed with specific clot ting factor assays will be influenced by the clinical situation and the results of coagulation screening tests. Precise diagnosis and effec tive management of inherited and acquired coagulation deficiencies

necessitate quantitation of the relevant factors. When bleeding is severe, specific assays are urgently required to guide appropriate therapy. Individual factor assays are usually performed as modi fications of the mixing study, where the patient’s plasma is mixed with plasma deficient in

the factor being studied. This will correct all factor deficiencies to >50%, thus making prolongation of clot formation due to a factor deficiency dependent on the factor miss ing from the added plasma. Chromogenic assays may also be used. Testing for Antiphospholipid Antibodies Antibodies to phos pholipids (cardiolipin) or phospholipid-binding proteins (β2-microglobulin and others) are detected by enzyme-linked immunosorbent assay (ELISA). When these antibodies interfere with phospholipid-dependent coagulation tests, they are termed lupus anticoagulants. The aPTT has variability sensitivity to lupus anticoagulants, depending in part on the aPTT reagents used. An assay using a sensitive reagent has been termed an LA-PTT. The dilute Russell viper venom test (dRVVT) is a modification of a standard test with the phospholipid reagent decreased, thus increasing the sensitivity to antibodies that interfere with the phos pholipid component. These tests, however, are not specific for lupus anticoagulants, because factor deficiencies or other inhibitors will also result in prolongation. Documentation of a lupus anticoagu lant requires not only prolongation of a phospholipid-dependent coagulation test but also lack of correction when mixed with nor mal plasma and correction with the addition of activated platelet membranes or certain phospholipids (e.g., hexagonal phase). Bleeding and Thrombosis CHAPTER 69 Other Coagulation Tests The thrombin time and the reptilase time measure fibrinogen conversion to fibrin and are prolonged when the fibrinogen level is low (usually <80–100 mg/dL) or quali tatively abnormal, as seen in inherited or acquired dysfibrinogen emias, or when fibrin/fibrinogen degradation products interfere. The thrombin time, but not the reptilase time, is prolonged in the presence of heparin. The thrombin time is markedly prolonged in the presence of the direct thrombin inhibitor, dabigatran; a dilute thrombin time is used to assess drug activity. Measurement of anti–factor Xa plasma inhibitory activity is a test frequently used to assess low-molecular-weight heparin (LMWH) levels, as a direct measurement of unfractionated heparin (UFH) activity, or to assess activity of the direct Xa inhibitors rivaroxaban, apixaban, and edox aban. Drug in the patient sample inhibits the enzymatic conversion of an Xa-specific chromogenic substrate to colored product by fac tor Xa. Standard curves are created using multiple concentrations of the specific drug and are used to calculate the concentration of anti-Xa activity in the patient plasma. Laboratory Testing for Thrombophilia Laboratory assays to detect thrombophilic states include molecular diagnostics and immuno logic and functional assays. These assays vary in their sensitivity and specificity for the condition being tested. Furthermore, acute thrombosis, acute illnesses, inflammatory conditions, pregnancy, and medications affect levels of many coagulation factors and their inhibitors. Antithrombin is decreased by heparin and in the set ting of acute thrombosis. Protein C and S levels may be increased in the setting of acute thrombosis and are decreased by warfarin. Antiphospholipid antibodies are frequently transiently positive in acute illness. Testing for genetic thrombophilias should, in general, only be performed when there is a strong family history of throm bosis and results would affect clinical decision-making. Because thrombophilia evaluations are usually performed to assess the need to extend anticoagulation, testing, if indicated, should be performed in a steady state, remote from the acute event. Functional assays, but not genetic assays, will be affected by anti coagulants including warfarin (for vitamin K–dependent proteins) and thrombin and Xa inhibitors and cannot be interpreted in patients on those drugs. In most instances, when discontinuation of anticoagulation is being considered, drugs can be stopped after the initial 3–6 months of treatment, and testing can be performed at least 3 weeks later.

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