Acquired Coagulation Disorders

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Introduction

Hemostasis is a complex, regulated sequence of interactions involving platelets, the blood vessel endothelium, and coagulation factors. Primary hemostasis involves platelet activation and culminates in the formation of the platelet plug. Secondary hemostasis follows with the activation of the coagulation cascade on the surface of platelets, leading to the formation of a stable fibrin clot. Under physiologic conditions, an equilibrium exists between the formation of a clot and its degradation. Fibrinolysis is a series of reactions that limit the extent of thrombosis. Our understanding of the normal coagulation cascade has changed substantially over the last two decades and is focused on thrombin generation, which is initiated by the activation of factor VII by tissue factor and is amplified at multiple steps (Fig. 8.1) [1]. However, in a conceptual sense, one can still divide the cascade into the intrinsic and extrinsic pathways as it helps interpret the commonly used tests – prothrombin time (PT) and activated partial thromboplastin time (aPTT) (Fig. 8.2). The initiation of the intrinsic pathway involves activation of factor XII by the serine protease prekallikrein, which leads to the subsequent activation of factors XI and IX. The extrinsic pathway is activated when tissue factor is exposed and activates factor VII at the site of endothelial damage. Both intrinsic and extrinsic pathways converge onto the common pathway with the activation of factor X and factor V, culminating in the generation of thrombin and subsequent fibrin formation.

Abnormal bleeding can occur when the normal equilibrium no longer exists and can result from disorders of the coagulation system, platelets, or blood vessels. Disorders of the coagulation system can be acquired or hereditary, the former resulting from nutritional deficiencies, systemic diseases, formation of factor inhibitors, and drugs [2]. This chapter will address the most common and clinically relevant acquired coagulation disorders including vitamin K deficiency, liver dysfunction, factor deficiencies, and inhibitors. We will conclude with a discussion of the antiphospholipid antibody (APLA) syndrome, which is primarily a prothrombotic state and rarely causes bleeding.

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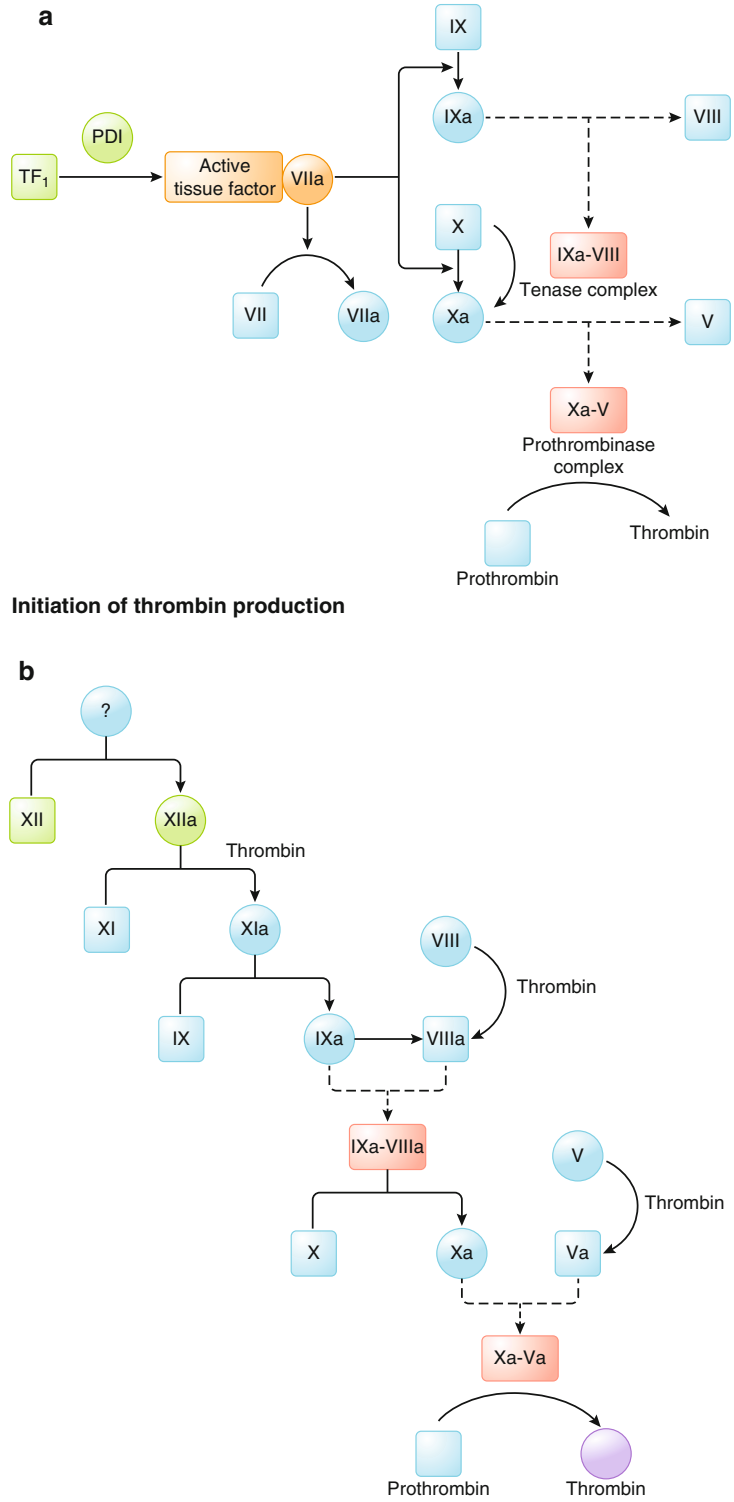

Fig. 8.1 Modern view of coagulation pathways. (**a**) Initiation phase in which a small amount of thrombin is generated. (**b**) Amplification phase in which thrombin generation is significantly increased (Furie B, et al. New Eng J Med 2008)

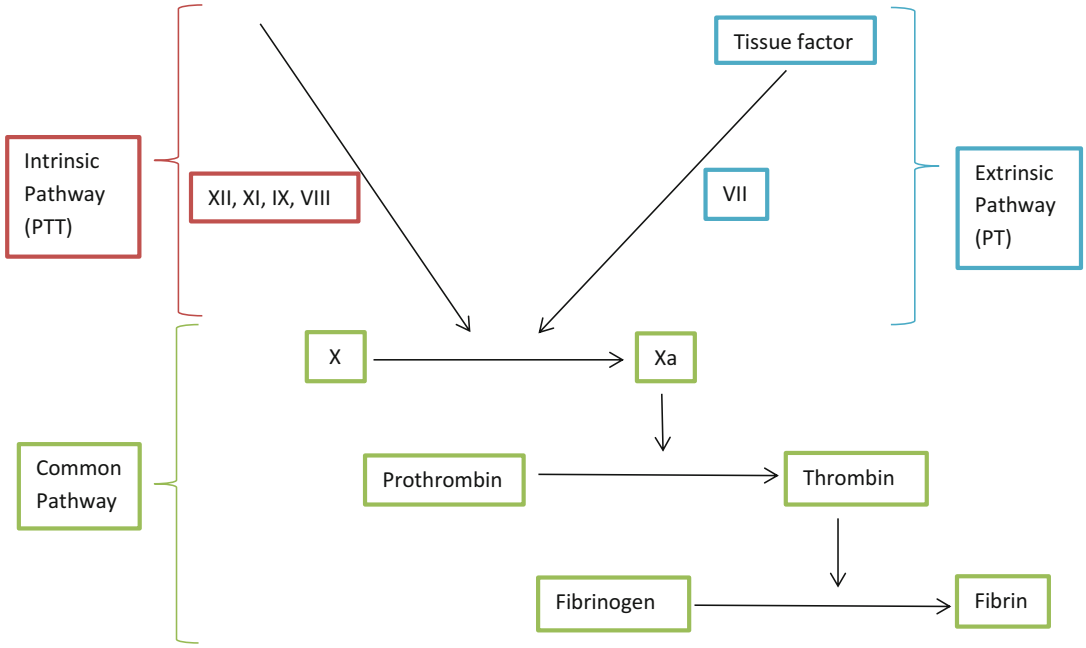

Fig. 8.2 Coagulation cascade

Vitamin K Disorders

Disorders of vitamin K can result from multiple etiologies including the use of vitamin K antagonists such as warfarin, inadequate dietary intake, malabsorption syndromes, or the chronic use of antibiotics. Vitamin K is a cofactor required for the activity of several key proteins containing carboxyglutamic acid residues important in the coagulation cascade. Hepatocytes contain carboxylase enzymes, which are necessary for the activation of coagulation factors II, VII, IX, and X. These residues facilitate the binding of coagulation factors to calcium ions on the negatively charged phospholipids [3]. Therefore, vitamin K deficiency can lead to decreased synthesis of these coagulation factors and render them ineffective, leading to coagulation abnormalities [4, 5].

The term "vitamin K" was first coined more than 50 years ago. Henrik Dam of Denmark reported the "anticlotting" factor that had the capability of reversing dietary-induced bleeding disorders in chicks. In fact, the name comes from the German/Danish word *koagulationsvitamin* (clotting vitamin) [5]. Doisy and colleagues first isolated vitamin K from alfalfa sprouts [4, 6]. There are multiple sources of vitamin K. Dietary vitamin K1 (i.e., phylloquinone or phytonadione), which is fat soluble, is mostly found in green leafy vegetables such as spinach and broccoli [7]. Its absorption requires intact pancreatobiliary function and fat absorptive mechanisms. Vitamin K2 is synthesized by microflora colonizing the GI tract, i.e., colon and terminal ileum [8]. Vitamin K, a lipophilic molecule, is protein-bound in the bloodstream and therefore requires proteolytic enzymes to liberate the active vitamin K component within the small intestines. Bile salts then solubilize vitamin K into micelles, which are absorbed into enterocytes, incorporated into chylomicrons, and then absorbed into the intestinal lymphatic system and portal circulation for transportation to the liver [9].

The normal physiologic requirement of vitamin K is 0.5 μg/kg/day [10]. Inadequate intake may deplete vitamin K stores in the body in as little as 7 days. Clinical signs and symptoms of vitamin K deficiency are characterized by easy bruising and mucosal bleeding. A prolonged PT

that corrects with mixing study is a characteristic of vitamin K deficiency. When the deficiency is mild, only the PT is prolonged, but in severe cases, both the PT and aPTT may be affected. Repletion of vitamin K can be provided by oral, subcutaneous, and intravenous routes. Intravenous vitamin K carries a small risk of anaphylaxis. The PT begins to improve within 12 h and should completely normalize in 24–48 h.

Antibiotic Use and Malabsorption

Acquired vitamin K deficiency can occur secondary to the use of drugs such as antibiotics or in patients receiving total parenteral nutrition (TPN). Chronic antibiotic use can lead to alteration of the normal gut flora responsible for the synthesis of vitamin K2. In addition, antibiotics can directly affect the activation of vitamin K in the liver. Prolonged starvation or the fasting state can also decrease vitamin K levels. Since vitamin K is a fat-soluble vitamin, dysregulation in the fat absorption pathway can result in vitamin K deficiency. Disorders of bile or pancreatic enzyme secretion, including cystic fibrosis, primary biliary cirrhosis, primary sclerosing cholangitis, biliary atresia, familial intrahepatic cholestasis, and inherited disorders associated with cholestasis, as well as intestinal diseases such as celiac disease, inflammatory bowel disease, and short bowel syndrome, can result in vitamin K deficiency. Any prior history of intestinal resection, especially at the terminal ileum which is responsible for fat absorption, can result in vitamin K deficiency.

Liver Dysfunction

The liver produces most of the procoagulants, natural anticoagulants, and fibrinolytic proteins [11]. In fact, all coagulation factors are synthesized in the liver, except von Willebrand factor and factor VIII. Thus, liver dysfunction can lead to coagulation abnormalities secondary to decreased synthesis of coagulation factors, decreased clearance of activated factors, dysregulation of fibrinolysis, and production of abnormal fibrinogen [11]. Reduction of factor V distinguishes liver disease from vitamin K deficiency [10]. The degree of coagulopathy is proportional to the extent of liver parenchymal cell damage. For instance, mild to moderate liver dysfunction is associated with slightly prolonged PT, which is caused by a decrease in factor VII since it has the shortest circulating half-life. More advanced liver disease is characterized by additional factor deficiencies, including factors II, IX, and X, fibrinogen, and factor V. Factor VIII is often preserved in severe liver disease due to extrahepatic synthesis.

Acute liver injury is usually not associated with bleeding as loss of coagulation factors is compensated by a similar loss of anticoagulant proteins [12]. Even though disseminated intravascular coagulation (DIC) is seen in a small number of patients with acute hepatic necrosis and shock liver, it is not clear that hepatic injury is directly responsible for disseminated intravascular coagulopathy. Fulminant hepatic failure is characterized by activated fibrinolysis and impaired clot formation due to increasing levels of tissue plasminogen activator (t-PA) and urokinase plasminogen activator [11]. In patients with chronic liver failure, the clinical picture is frequently complicated by splenomegaly and thrombocytopenia. In both acute and chronic liver failure, patients have a risk of bleeding as well as thrombosis [13].

Vitamin K Antagonists

Vitamin K antagonists (VKAs) are often used on a long-term basis in patients with prosthetic heart valves, high-risk atrial fibrillation, venous thromboembolism, or others at high risk of thrombotic or embolic events including stroke. VKAs such as warfarin, which has a similar structure to vitamin K, block the synthesis of factors II, VII, IX, and X and anticoagulant proteins C, S, and Z (a cofactor for the inhibition of activated factor X). In particular, it interrupts the cycling of vitamin K between its oxidized and reduced state, thus preventing the gamma-carboxylation of glutamic acid residues on vitamin K-dependent proteins [11, 13]. Treatment with a VKA results in decreased

synthesis and thus reduced activity of such proteins. After ingestion, warfarin is rapidly absorbed from the GI tract and reaches maximal concentration in the blood in approximately 90 min. It then accumulates in the liver where it is metabolized by P450 cytochromes CYP2C9, CYP1A2, and CYP3A4. Its half-life is roughly 36–42 h. It has a narrow therapeutic index and thus can be challenging to monitor. In addition, there are multiple food-drug and drug-drug interactions. Various patient factors affect the anticoagulant response, including age, body weight, dietary habits, gender, ethnicity, and genetic polymorphisms [3]. Its anticoagulant effect is monitored by the international normalized ratio (INR). The annual incidence of any warfarin-associated major bleeding is 0–16 %, whereas the annual incidence of warfarin-associated fatal bleed is 0–2.9 % [14]. A significantly elevated INR predicts a high risk of major bleeding. For example, Hylek et al. prospectively reported that the risk of bleeding doubles for each single point of increase in the INR above 3.0, with major bleeding occurring at a rate of 2.4–8 % per patient-year [15]. The most devastating bleeding complication is intracranial hemorrhage (ICH), which is estimated to occur at a rate of nearly 1 % per patient-year. ICH carries an estimated mortality rate of 60 %. Published guidelines to date on management of ICH are largely based on expert opinion rather than randomized clinical trials [8].

Management of VKA-Associated Coagulopathy

Treatment of VKA-associated bleeding depends on the degree of anticoagulation, clinical manifestations, and urgency at which reversal is required. Reversal agents include vitamin K, fresh frozen plasma (FFP), or prothrombin complex concentrate (PCC). Intravenous vitamin K carries a small risk of anaphylaxis, especially if formulations contain polyethoxylated castor oil, which is used to maintain vitamin K in solution [8]. The estimated risk of anaphylaxis according to one study is approximately 3 per 10,000. Several randomized controlled trials have demonstrated that low doses of oral vitamin K are effective in reducing an elevated INR in this setting. No studies have directly compared the efficacy of different doses of oral vitamin K to reverse VKA-associated coagulopathy.

In the case of a non-bleeding patient with a moderately elevated INR (less than 5), a potential management strategy includes withholding the VKA and allowing the INR to drift down. It is also reasonable to withhold the VKA and administer low-dose oral vitamin K. It is not recommended to administer FFP or coagulation factor concentrates in this setting. A number of studies have demonstrated that the incidence of 30-day major bleeding in patients with an INR greater than 9 was high (9.6 %) compared to only 1 % with INR over 5–6 [8]. If the INR is greater than 9 without associated bleeding, it is generally accepted to hold warfarin and give oral vitamin K at a dose of 2–5 mg, which can reduce the INR within 24–48 h. If the INR is between 5 and 9 and the patient is not bleeding, warfarin should be held and the administration of low-dose vitamin K is optional.

The urgency of anticoagulation reversal in the setting of VKA-associated bleeding complications depends on the severity, bleeding site, and degree of INR elevation. The VKA should be withheld and intravenous vitamin K and/or coagulation factor replacement administered in cases of VKA-associated major bleeding. With intact hepatic function, the INR generally starts to improve within 8–12 h of vitamin K administration and reaches the normal range within 24 h in most patients. The management of acute major life-threatening bleeding includes the administration of intravenous vitamin K, FFP, and PCC.

FFP is obtained from either whole blood donations or automated plasmapheresis techniques. It is widely available but provides only partial reversal of coagulopathy through replacement of factors II, VII, IX, and X. It contains all the natural pro- and anticoagulant factors at concentration of 1 U/ml. Thus, it is administered at a dose of 15 ml/kg, which usually requires infusion of volumes over 1 L. A lower dose of 5–8 ml/kg may be appropriate in cases of urgent reversal. There are advantages and disadvantages to its use [9, 14].

PCCs are pooled human plasma-derived products containing factors II, IX, and X with variable amounts of factor VII, proteins C and S, and antithrombin. It is supplied as a powder and diluent, which are reconstituted prior to administration. Products must be warmed to room temperature if previously refrigerated [3]. There are two types: a nonactivated and an activated form. Nonactivated PCCs can be classified as three factor (3F-PCC) or four factor (4F-PCC). The former contains factors II, IX, and X with a small amount of VII concentrate. The latter contains sufficient levels of all vitamin K-dependent factors. Thus, 3-F PCC and 4-F PCC differ by amount of FVII. In the United States, 4F-PCC (Kcentra) was approved in April 2013 for reversal of acquired coagulopathy due to vitamin K antagonists. However, this product has been used in Canada and Europe for many years [14]. PCC provides a rapid and effective method for replacing deficient clotting factors and correcting the INR. In a randomized clinical trial, 18 over-anticoagulated patients were randomized to receive PCC or intravenous vitamin K [16]. The authors concluded that patients who received PCC had a more rapid INR correction compared those treated with vitamin K. In another study comparing the use of PCC versus FFP, Makris et al. reported that complete correction of the INR occurred within 15 min in 28 out of 29 patients treated with PCC, compared to none of the 12 patients treated with FFP [17]. The optimal dose of PCC is not established. The dose of PCC can be adjusted based on weight, initial INR, and target INR. The effect of PCC lasts only 12–24 h. Thus, vitamin K should be coadministered with PCC as the INR may rebound due to the persistent effects of warfarin. PCC therapy is generally safe. A systematic review of 14 studies involving 460 patients demonstrated only 7 total thrombotic complications (3 strokes, 2 myocardial infarctions, 2 deep vein thromboses) after the use of PCC [8].

Fresh Frozen Plasma Versus Prothrombin Complex Concentrates

PCCs do not require ABO compatibility or thawing. The volume of PCC necessary for reversal is smaller than FFP since PCCs contain 25 times the concentration of vitamin K-dependent factors relative to an equal volume of plasma. At present, it is recommended that PCCs should be given for reversal of VKA-associated major bleeding based on the ability of PCCs to rapidly correct a supratherapeutic INR. However, it is unclear if rapid reversal of the INR translates to improved patient outcomes. A prospective, randomized controlled trial comparing the efficacy and safety of 4F-PCC to FFP demonstrated the following conclusions: 4F-PCC is non-inferior, achieves rapid reduction in INR (62.2 % vs. 9.6 %), requires a shorter infusion time, results in a lower incidence of fluid overload (5 % vs. 13.2 %), and has a similar safety profile [18]. Doses reported in the literature range from 8 to 50 U/kg. Risk of thrombotic complications and high cost are potential barriers to use of 4F-PCC by clinicians [9]. In contrast to the use of PCCs, FFP requires thawing for approximately 30 min at 30–37 °C and ABO typing prior to administration; in addition, it carries a small risk of transmissible infections and has the potential for causing volume overload [8, 9, 14]. Although more costly, PCC can normalize INR faster (15 min vs. 1–2 h), reduces the need for PRBC transfusions, requires a smaller infusion volume, and does not increase adverse events in comparison to FFP [3, 19]. In addition, PCCs undergo a viral inactivation process to reduce transmission of infective agents.

In cases of major or life-threatening bleeding associated with VKA use, intravenous vitamin K and coagulation factor replacement are recommended [8].

Recombinant Factor VIIa

Recombinant factor VIIa (rFVIIa) can reverse VKA-associated coagulopathy in patients with serious bleeding complications. It is currently approved for treatment of bleeding complications in patients with hemophilia who develop antibodies to factor VIII or IX. Its primary mechanisms of action include activation of tissue factor at the site of endothelial injury to activate factor X and the reversal of platelet defects. There are a paucity of data to support its clinical efficacy in patients with vitamin K deficiency or antagonism. The use of rFVIIa is associated with the

development of arterial thrombosis. Since the therapeutic effect of rFVIIa lasts only about 12–24 h, vitamin K must be administered as well.

US and European guidelines, including the American College of Chest Physicians, recommend PCCs as primary treatment for anticoagulation reversal in life-threatening bleeding and increased INR, with rFVIIa as a possible alternative. The VKA should be discontinued and intravenous vitamin K should be concomitantly administered.

Perioperative Management of Patients Receiving Vitamin K Antagonists

The management of patients receiving a VKA who require surgical procedures can be challenging. There is an increased risk of thromboembolism when anticoagulation is interrupted for a surgical procedure. However, invasive surgeries are associated with inherent bleeding risk, which is magnified in patients who are on anticoagulation. Thus for each patient, a balance between reducing risk of thromboembolism and preventing excess bleeding must be reached at the time of surgery. One should take into account the estimated thromboembolic risk, the bleeding risk inherent to the procedure, the timing of VKA interruption, and whether or not bridging anticoagulation is indicated. Most published guidelines are based on expert opinion since data from randomized clinical trials in this setting are lacking [3, 18, 20–22].

For an elective procedure, the VKA should be discontinued about 6 days prior to planned surgery. PT/INR should be obtained 1 day prior to surgery. If procedure is planned after 24 h, vitamin K administration is reasonable. Subcutaneous vitamin K can be given if the INR remains greater than 1.5 despite receiving oral vitamin K. The INR should be in the normal range in patients undergoing procedures associated with a high bleeding risk, i.e., intracranial, spinal, or urologic surgeries, and/or any procedure requiring neuroaxial anesthesia. Discontinuation of the VKA for several days will result in subtherapeutic anticoagulation. Bridging with a subcutaneous or intravenous short-acting agent, i.e., low molecular weight heparin or unfractionated heparin for approximately 2–3 days prior to surgery in patients deemed at high or very high risk of thromboembolism, may be indicated. For urgent procedures requiring rapid INR normalization, additional reversal agents can be utilized. The appropriate reversal agent for VKA-induced coagulopathy depends on the degree of anticoagulation, urgency of the procedure, and bleeding risk. For semi-urgent reversal, which is often defined as within 1–2 days, the VKA should be withheld and vitamin K (either oral or IV) can be given. In contrast, when immediate reversal is desired (i.e., active major bleeding and/or emergent surgery), PCC or FFP along with vitamin K is recommended [3, 18, 20–22].

Acquired Factor Deficiencies and Inhibitors

Acquired Factor X Deficiency

Factor X is a vitamin K-dependent coagulation factor which may be deficient in a variety of clinical scenarios, including patients with liver disease or vitamin K deficiency. Acquired factor X deficiency has been described in patients with certain malignancies, such as spindle cell thymoma, renal or adrenal carcinoma, gastric carcinoma, and acute leukemia. *Mycoplasma pneumoniae* infection may cause a transient decrease in factor X levels [23]. Acquired factor X deficiency is well-described in patients with AL amyloidosis.

Factor X Deficiency in AL Amyloidosis

AL amyloidosis is a plasma cell disorder in which abnormal protein fibrils deposit in tissues, resulting in organ failure. AL refers to the amyloid light chain-derived subtype of amyloidosis, which occurs in 8 per million people per year [24]. It is more common in men and occurs most commonly in the sixth or seventh decade of life. In most patients, a monoclonal protein will be detected by serum or urine immunofixation and free light chain assays. Common sites of amyloid fibril deposition include the liver, heart, soft tissues, kidneys, and nerves. This entity is diagnosed by

tissue biopsy of an involved organ or tissue with positivity by Congo red staining, showing apple-green birefringence under polarized light. Patients may present with fatigue, weight loss, macroglossia, neuropathy, heart failure symptoms, hepatomegaly, or nephrotic range proteinuria. AL amyloid may occur in isolation or in association with another B-cell disorder, such as multiple myeloma or non-Hodgkin lymphoma. Other common subtypes of amyloidosis include AA amyloidosis, which is associated with chronic inflammatory diseases, hereditary amyloidosis, and age-related "senile" systemic amyloidosis, the detailed discussion of which is outside the scope of this chapter.

Acquired deficiency of factor X is the most common coagulation factor deficiency seen in patients with AL amyloidosis [25]. However, less than 5 % of patients with AL amyloidosis present with factor X deficiency [26]. The mechanism involves increased clearance of factor X from circulation due to adherence to amyloid fibrils [27]. This is likely independent of proteinuria and liver dysfunction [25]. Bleeding in this scenario can be life-threatening and can present a therapeutic challenge. Factor X is rapidly removed from circulation in this disease, and therefore factor replacement with products such as fresh frozen plasma or prothrombin complex concentrates is often ineffective [28]. Patients with amyloidosis can also have bleeding due to other mechanisms, including fragile blood vessels, hyperfibrinolysis, platelet dysfunction, and other less common factor deficiencies (II, VII, IX, V) [25, 29, 30]. Severe bleeding is generally seen in patients with plasma factor X levels below 25 % of normal [25]. Moderate to severe bleeding can occur in patients with factor X levels 25–50 % of normal [25]. Patients with acquired factor X deficiency may have a prolonged PT or PTT, with a mixing study which corrects with the addition of normal plasma.

Extensive binding of factor X to amyloid fibrils can occur in the spleen. If the patient has significant splenic involvement by amyloidosis, splenectomy may improve the coagulopathy by removal of amyloid deposits [31]. RFVIIa has been used perioperatively for splenectomy or other surgical procedures to reduce bleeding risk [28, 32, 33]. However, the benefits of rFVIIa must be balanced with the risk of thrombosis. Ultimately, treatment of the underlying AL amyloidosis is necessary to reverse the coagulopathy. The preferred therapy is high-dose melphalan followed by autologous stem cell transplantation (ASCT). If not eligible for ASCT, patients may receive chemotherapy with agents such as bortezomib, melphalan, alkylating, or immunomodulatory agents.

Acquired Factor XIII Deficiency

Factor XIII is a tetramer which plays an important role in the formation of the fibrin clot. It consists of two active A subunits and two B subunits, which protect the A subunits in circulation. In addition to congenital factor XIII deficiency (see Chap. 7), a variety of medical conditions can result in an acquired deficiency of factor XIII, such as major surgery, sepsis, DIC, pulmonary embolism, malignancy, stroke, cirrhosis, or an autoimmune disorder. Severe factor XIII deficiency is defined as a factor XIII level less than 5 %, with moderate 5–10 %, and mild greater than 10 %. Patients with factor XIII deficiency will have a normal PT, PTT, and thrombin time; the test of choice to evaluate for this condition is a factor XIII activity assay. In general, patients with acquired factor XIII deficiency do not reach levels less than 30 % and therefore do not require replacement therapy. If necessary, factor XIII concentrate is the preferred treatment for this disorder, with fresh frozen plasma an alternative option. Patients with autoantibodies against factor XIII should be considered for plasma exchange and/or immunosuppressive medications [34].

Acquired von Willebrand Syndrome (Factor VIII Deficiency)

Von Willebrand disease (VWD) is an inherited bleeding disorder in which patients may experience mucosal or skin bleeding, as well as hemostatic dysfunction perioperatively. This condition occurs when there is dysfunctional or deficient von Willebrand factor (VWF), a plasma protein which facilitates the binding of platelets to each

other and to sites of tissue injury. VWF also acts as a carrier for coagulation factor VIII. Therefore, the bleeding diathesis seen in patients with VWD occurs due to a reduction in factor VIII levels and impaired adhesion of platelets to sites of tissue injury. See Chap. 7 for a detailed discussion of the evaluation and management of patients with inherited von Willebrand disease.

Acquired von Willebrand syndrome (AVWS) occurs when there is a deficiency or defect in the function of von Willebrand factor as a consequence of another medical condition. This disorder is relatively rare and is usually associated with an underlying lymphoproliferative or myeloproliferative disorder. It can also be seen in patients with other malignancies, cardiovascular conditions, those with autoimmune diseases, or as a result of certain medications. Its prevalence may be increasing due to a greater use of left ventricular assist devices (LVADs). It is more common in elderly patients [35]. There are three mechanisms which lead to AVWS: destruction of VWF from shear stress, autoimmune destruction or inhibition of VWF, or increased binding of VWF to platelets or other surfaces [36]. Patients with this syndrome as a result of cardiac valvular disease or another vascular condition may have a decrease in VWF multimers due to destruction from shear stress. Patients may present with mucocutaneous bleeding and usually will not have a past or family history of bleeding. Diagnostic evaluation generally reveals a normal PT and a normal or prolonged PTT. Additional studies may show a decrease in factor VIII activity, VWF activity (ristocetin cofactor activity), and/or VWF antigen.

Treatment of AVWS is aimed at controlling acute bleeding, preventing perioperative bleeding, and treating the underlying disorder if possible. This can include desmopressin, which causes release of VWF stores into circulation, although not all patients will respond to this therapy. If possible, patients should have a therapeutic trial of desmopressin with measurement of plasma VWF activity and factor VIII levels prior to and at intervals following administration to ensure adequate response. The typical dose used is 0.3 μg/kg over 30 min once daily. Patients should be monitored for the common adverse effects of hyponatremia and volume overload [35]. Tachyphylaxis can occur and therefore desmopressin should not be used more than once per day for up to 3 days. If patients do not respond to desmopressin or if response is unknown, VWF/factor VIII concentrates can be effective, although these products can have a short half-life, especially in patients with inhibitors to VWF [35]. Intravenous immunoglobulin (IVIG) is another therapy which may provide benefit if patients do not respond to desmopressin or VWF/factor VIII concentrates [37]. In patients with immune-mediated AVWS, plasma exchange, steroids, or immunosuppression may be effective. Successful use of rFVIIa has been reported in patients with AVWS, although benefits must be balanced with the risk of thrombosis. Treatment of the underlying malignancy or surgical correction of the cardiac defect if possible may eliminate the coagulopathy. In patients with thrombocytosis and AVWS, correction of the thrombocytosis will often correct the coagulopathy. Patients with hypothyroidism may develop AVWS, which is treated with thyroid hormone replacement [36].

Acquired Hemophilia A (Factor VIII Inhibitor)

Hemophilia A is the congenital deficiency of coagulation factor VIII, which is active in the intrinsic pathway of the coagulation cascade. The acquisition of an inhibitor to factor VIII, or acquired hemophilia A, can be idiopathic, or secondary to various medical conditions, including autoimmune disorders, malignancy, the postpartum period, infections, or certain medications [38]. It occurs more commonly in elderly patients. Factor VIII inhibitors are rare, with an incidence of 1–4 per million people per year [38]. This condition causes severe and often life-threatening bleeding, with a high mortality rate (8–22 %) [38]. In contrast to patients with congenital hemophilia A, who often experience hemarthrosis, patients with an acquired factor VIII inhibitor may present with mucosal or subcutaneous bleeding, hematuria, or GI bleeding. Evaluation reveals a prolonged PTT which does not correct with the

addition of normal plasma by mixing study. Additional workup should include a factor VIII level and factor VIII inhibitor activity.

Treatment of a bleeding patient with a factor VIII inhibitor should include one of two strategies: raising the factor VIII level (generally only if a low titer factor VIII inhibitor is present, less than 5 Bethesda units (BU)) or bypassing factor VIII. Patients with a low titer inhibitor can be treated with human factor VIII concentrates, 20 IU/kg for each BU of inhibitor plus 40 IU/kg intravenously [38].

If the titer is greater than or equal to 5 BU, a bypassing agent should be used. RFVIIa is frequently used as a first-line agent, with a recommended dose of 90–120 μg/kg every 2–3 h, as the half-life is approximately 2.5 h [39, 40]. RFVIIa leads to the generation of thrombin. The benefit of this agent must be balanced against the risk of thrombosis, particularly in elderly patients. Activated prothrombin complex concentrate (aPCC) is an alternative bypassing agent, which provides the vitamin K-dependent clotting factors. The recommended dose range of aPCC is 50–100 IU/kg every 8–12 h [39, 40]. In order to eliminate the inhibitor, various immunosuppressive agents have been employed. Steroids alone or in combination with cyclophosphamide are frequently used for this indication. Intravenous immunoglobulin may also be effective when combined with immunosuppressive agents. Plasma exchange, immune tolerance protocols, cyclosporine, and rituximab have been used to eradicate factor VIII inhibitors as well. In patients with a minor bleeding episode, desmopressin can be considered. There is a high risk of infectious complications from immunosuppressive therapy. These therapies should be administered after consultation with a hematologist.

Antiphospholipid Antibody Syndrome

The antiphospholipid antibody syndrome (APS) is an acquired condition resulting in a prothrombotic state. APS can be a primary condition or can be associated with an underlying disorder such as a rheumatologic disease or malignancy. The syndrome requires the presence of both laboratory and clinical components for diagnosis, including an autoantibody in the plasma and either a venous or arterial thrombosis or recurrent obstetrical complications. In a surgical setting, it is important to identify a preexisting history of this syndrome as patients are prone to thrombosis and may require anticoagulant therapy. In some settings, preoperative workup may reveal a prolonged aPTT, which prompts further investigation with a mixing study and evaluation for circulating inhibitors. The APLAs implicated in this syndrome include anticardiolipin antibodies (aCL), anti-β_2-glycoprotein I antibodies (aβ_2GPI), and the lupus anticoagulant (LA). Perioperative management of patients with known APS includes holding warfarin prior to planned intervention and reversing warfarin if urgent surgery is required. Prophylactic doses of anticoagulation should be started as soon as possible postoperatively, and therapeutic anticoagulation should be reinitiated as soon as safe from a surgical standpoint. Here we will review the pathophysiology, laboratory diagnosis, clinical presentation, and treatment of APS. We will also include a brief discussion of catastrophic APS (CAPS).

Pathophysiology

APS is an autoimmune process associated with circulating autoantibodies to phospholipid protein complexes. Although these antibodies were first detected in patients with systemic lupus erythematosus (SLE), the disorder is not limited to those with SLE. Subtypes of the antiphospholipid antibodies include aCL, aβ_2GPI, and LA. Positivity for all three of these tests is associated with the highest risk for thrombosis and pregnancy loss. There are a number of proposed mechanisms for how the presence of these antibodies results in an increased risk of thrombosis, including the effects of antibodies on platelets, endothelial cells, monocytes, and trophoblasts and interference with complement activation. Cell signaling pathways such as the phosphatidyl-inositol 3-kinase (PI3K)/AKT pathway may also be involved in pathogenesis [41].

Antiphospholipid antibodies can be detected in a variety of clinical settings including healthy individuals, in the presence of autoimmune or rheumatologic diseases, with infections, medication related, or in the presence of malignancy. The most frequent rheumatologic condition associated with APS is SLE, and approximately 31 % of patients with SLE will have a LA. Although LA is the most prevalent antibody in the setting of SLE, aCL or aβ_2GPI antibody may also be identified. Bacterial, viral, and parasitic infections can be associated with APLA. Such infections include HIV, mononucleosis, rubella, hepatitis, syphilis, Lyme disease, tuberculosis, malaria, and toxoplasmosis, among others. Common medications associated with the development of APLA include procainamide, phenothiazines, phenytoin, hydralazine, quinidine, quinine, ethosuximide, alpha interferon, amoxicillin, chlorothiazide, oral contraceptives, and propranolol. Associations with malignancies including solid tumors, Hodgkin and non-Hodgkin lymphoma, leukemias, and myeloproliferative disorders have been reported [42].

Diagnosis

Diagnosis of APS requires the presence of clinical and laboratory findings. Diagnostic workup may be pursued in the setting of (1) more than one otherwise unexplained thrombosis or thromboembolic events, (2) more than one pregnancy-related complications, or (3) otherwise unexplained prolongation of the aPTT or thrombocytopenia. The following laboratory studies should be obtained: IgG and IgM aCL antibodies, IgG and IgM aβ_2GPI antibodies, and LA testing. The aCL and aβ_2GP I antibodies are evaluated by enzyme-linked immunosorbent assay (ELISA). The LA is evaluated with an initial dilute Russell viper venom time (dRVVT), and if positive, a confirmatory test should follow. If any of the initial laboratory tests are positive, they need to be repeated and confirmed a second time, 12 weeks later.

The Sapporo criteria, now referred to as the revised Sapporo criteria or the Sydney criteria, are used to make a diagnosis of definite APS. According to these criteria, definite APS can be considered if at least one of the following clinical and one of the following laboratory criteria are present. The clinical criteria include (1) vascular thrombosis or (2) pregnancy morbidity. Specifically the vascular thrombosis must be a venous, arterial, or small vessel thrombosis with unequivocal imaging or histologic evidence. This does not include the presence of superficial thrombosis. Pregnancy-related morbidity is defined as unexplained fetal death at $\geq$10 weeks gestation of a normal fetus or one or more premature births before 34 weeks because of eclampsia, preeclampsia, or placental insufficiency or three or more early (<10 weeks) pregnancy losses unexplained by other etiologies.

The laboratory findings that are required for the diagnosis of APS include the presence of one or more of the following: (1) IgG and/or IgM anticardiolipin antibodies in moderate or high titer (>40 GPL or MPL units or greater than the 99th percentile for the laboratory testing), (2) antibodies to beta2-glycoprotein I of IgG or IgM isotype at a titer greater than the 99th percentile for the testing laboratory when tested according to recommended procedures, or (3) lupus anticoagulant activity detected according to published guidelines [43]. As previously stated, if any of the above tests are positive, the finding must be confirmed a second time, 12 weeks later, to rule out a false-positive result. False-positive tests can be observed in the setting of oral anticoagulants, older patients, or only mildly positive lupus anticoagulant results. False-negative results also occur and are usually related to laboratory processing. Checking for APLA at the time of acute thrombosis is not recommended as they can decrease temporarily or may be transiently positive.

Clinical Presentation

Clinical presentation of APS includes manifestations of venous or arterial thrombosis and/or pregnancy complications or loss. On physical exam, findings may include livedo reticularis, digital ischemia, asymmetric lower extremity

edema from a deep venous thrombosis (DVT), or neurologic findings from stroke. Additional clinical manifestations may include thrombocytopenia, coronary artery disease, valvular heart disease, pulmonary hypertension, peripheral arterial disease, retinal disease, adrenal failure, and gastrointestinal manifestations. Venous thrombosis is more common than arterial thrombosis and the calf veins are the most common sites of DVT [44]. APS should be considered in young patients with history of stroke and no other risk factors for cerebrovascular disease or recurrent thrombotic events in the absence of other risk factors.

Additional hematologic manifestations may include thrombocytopenia, thrombotic microangiopathy, or bleeding. Thrombocytopenia is the most commonly seen hematologic manifestation and the usual platelet count ranges from 50,000 to 140,000/μl [45]. Thrombocytopenia does not preclude the development of thrombosis and should not preclude the use of anticoagulant therapy if the platelet count remains above 50,000.

Treatment

Once a diagnosis of APS has been reached and confirmed, timely treatment should be initiated. Treatment may include the use of anticoagulants such as heparin or warfarin and possibly antiplatelet agents such as aspirin. In the setting of an acute thrombosis associated with APS, the thrombosis should be treated in the same manner as thrombosis independent of APS. Heparin or low molecular weight heparin is frequently initiated with the simultaneous initiation of warfarin. The heparin product should be continued until the INR has been in the target therapeutic range for 48–72 h. Unfractionated heparin may be preferred in the setting of hemorrhagic complications as it can be rapidly reversed. The use of unfractionated heparin requires additional consideration when the aPTT is elevated at baseline. In this setting, the aPTT may not be a reliable measure of heparin levels and instead monitoring with anti-factor Xa levels may be more appropriate.

There must be consideration for long-term, possibly lifelong anticoagulation in the setting of unprovoked, spontaneous thromboembolism in the context of APS. There are no prospective data to support higher intensity anticoagulation therapy with an INR goal of 3.0–4.0 in APS. Clinical trials have demonstrated that there is no reduction in the rate of recurrent thrombosis with a higher INR goal as compared to a standard INR goal of 2.0–3.0 [46]. There are also no prospective data to support the use of direct factor Xa inhibitors or direct thrombin inhibitors in APS and thus these agents are not recommended.

In patients with a prolonged PT/INR at baseline, it may be necessary to confirm a therapeutic level of anticoagulation by monitoring factor II activity level or measuring chromogenic factor X assay. Whole blood point of care testing may be unreliable in the setting of APLA and therefore it should be correlated with a plasma INR from a peripheral blood draw prior to accepting point of care testing as an accurate measurement. Patients should be counseled regarding the potential medication and dietary interactions while on warfarin therapy. Home self-monitoring INR is a potential option in a carefully selected patient population.

The antiplatelet agents studied for therapeutic use in APS include aspirin and clopidogrel. There are some studies to suggest aspirin at a dose of 81 mg/day may decrease the risk of thrombosis in patients with APS; however, the routine use of aspirin should be driven primarily by the cardiovascular risk factors of the patient [47]. There are no data from randomized studies to support the routine use of clopidogrel in treatment of APS and this is not recommended [48]. There have been studies investigating the use of prophylactic aspirin in patients with positive APLA, but no history of thrombosis. However, these trials have failed to document a benefit from the addition of daily aspirin [49].

Catastrophic Antiphospholipid Antibody Syndrome

The catastrophic antiphospholipid antibody syndrome (CAPS) is a potentially life-threatening condition involving widespread thrombosis despite appropriate anticoagulation that results in

multiorgan failure. Mortality rates have been reported as high as 30 % in some studies [50]. Criteria for the diagnosis of this syndrome include (1) evidence of involvement of three or more organs, systems, and/or tissues; (2) development of manifestations simultaneously or within 1 week of each other; (3) confirmation by histopathology of small vessel occlusion in at least one organ tissue; and (4) laboratory confirmation of the presence of APLAs. The diagnosis of definite CAPS requires the presence of all four criteria. If less than all four criteria are present, the diagnosis of probable CAPS may be reached [51]. Treatment of CAPS is focused on treating the thrombotic events and also the underlying cytokine storm that ensues. Patients with CAPS may benefit from combined treatment with anticoagulants, glucocorticoids, plasma exchange, and/or intravenous immune globulin (IVIG). Rituximab has been studied in the setting of resistant CAPS and may provide some benefit [52].

A preexisting history of APS in the neurosurgical patient is important to identify, as careful attention to perioperative anticoagulation is required. The goal of treatment should be to safely resume anticoagulation as soon as safe from a surgical perspective as these patients are at high risk of thrombosis. At times, a new diagnosis of APS may be identified by a neurosurgical service with an appropriate level of suspicion based on clinical and laboratory findings. Consultation with a hematologist is appropriate in the setting of APS.

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