INTRODUCTION

It is crucial that clinicians who provide care to surgical patients understand the dynamic interplay between the coagulation and fibrinolytic systems. An appreciation for the relevant underlying biologic mechanisms is central to the diagnosis and appropriate management of patients who present with bleeding diatheses in both the operative and the postoperative setting. Surgery provides the most significant challenge to the integrity of the hemostatic system, and the fidelity of the coagulation system serves as the homeostatic defense mechanism that abrogates the proclivity for bleeding in this context. Moreover, with the emergence of novel anticoagulants approved for the ongoing ambulatory management of atrial fibrillation, deep venous thrombosis, and pulmonary embolism in an ever aging population, comes the stipulation for an improved understanding of how these pharmacologic agents complicate the care of the bleeding patient.

PATHOPHYSIOLOGY

It is essential to differentiate between the inherited (primary) coagulation disorders, which are associated with a history of bleeding diatheses, from the more commonly acquired (secondary) coagulation disorders, which are the consequence of pathologic conditions and numerous medications (1–3). This nomenclature (primary vs. secondary) is distinct from, and should not be confused with, the traditional nomenclature used to describe the hemostatic process itself. In the formation of a stable clot, the hemostatic process was classically described as comprising two phases, a primary phase (also called primary hemostasis) and a secondary phase (also called secondary hemostasis). The primary phase of hemostasis involves vascular or tissue injury, initiating platelet adhesion and aggregation to form the platelet plug. The secondary phase involves the activation of the plasmatic coagulation protein cascade (both the extrinsic and the intrinsic systems), which results in formation of the stable fibrin clot. Disorders involving platelet number or function, or vascular interactions, are classified as disorders of primary hemostasis, and disorders involving the plasma coagulation factors are classified as disorders of secondary hemostasis. This serves the purpose of an operational definition, since in vivo these events are highly integrated, not separate processes.

Hemostatic disorders, whether primary (inherited) or secondary (acquired), can both be manifest by diffuse bleeding from the operative site, puncture wounds, vascular access sites, or traumatized tissue outside of the operative field. Surgical and postsurgical bleeding may therefore result from either quantitative (thrombocytopenia) or qualitative (abnormal function) platelet disorders.

Thrombocytopenia, defined as a platelet count less than 140 × 10^9/L, results from decreased production (aplastic anemia, hypoplastic bone marrow, chemotherapy, space-occupying lesions of the bone marrow as seen with malignancy), ineffective thrombopoiesis (vitamin B12 or folic acid deficiency states), sequestration particularly in the spleen (primary or secondary hypersplenism), increased destruction or consumption (microangiopathic processes such as thrombotic thrombocytopenic purpura [TTP], disseminated intravascular coagulation [DIC], or the hemolytic-uremic syndrome [HUS]; immune destruction due to antiplatelet antibodies, such as in posttransfusion purpura or idiopathic thrombocytopenic purpura), and dilution of circulating platelets associated with massive blood transfusion (1,2,4–15). Petechiae, purpura, and mucosal oozing are characteristics of thrombocytopenic states, although these findings may also be observed in qualitative platelet disorders and in conditions associated with increased vascular fragility. Platelet counts of 50 × 10^9/L or higher are generally considered adequate for surgical hemostasis in the absence of an associated qualitative functional defect, but below 20 × 10^9/L there is increased risk for spontaneous hemorrhages (1–3,6). Particularly lethal in this regard are those involving the central nervous system.

Cytotoxic chemotherapy and radiation therapy (total body) produce thrombocytopenia by suppression of bone marrow megakaryocytes, the progenitor cell for platelets. Together these are the most common causes of bleeding in patients undergoing therapy for malignancies. Marrow aplasia, hypoplasia, and space-occupying diseases of the bone marrow (e.g., metastatic carcinoma, leukemias, lymphomas) also result in decreased production of platelets. Certain drugs, including alcohol, have been associated with decreased production of platelets via a direct toxic effect on megakaryocytes. Ineffective thrombopoiesis is a characteristic trait of megaloblastic anemia resulting from either vitamin B12 or folate deficiency. Although there is an increase in the megakaryocytic mass, platelet production is impaired. Notwithstanding, hemorrhagic diatheses manifest in a few of these individuals (16).

The most frequent cause of thrombocytopenia resulting from increased destruction of circulating platelets is postoperative infection (2,9–12,17). Significantly, thrombocytopenia may be the first presenting sign of an occult infection and may herald impending sepsis. Consequently, in the postoperative setting, thrombocytopenia of unclear cause must promptly direct attention toward uncovering a potential source of occult sepsis.

Thrombocytopenia caused by increased destruction of platelets is also observed in microangiopathic hemolytic states, such as in TTP and HUS (2,18–20). Mechanical injury occurs when platelets traverse the small capillary beds in the peripheral circulation. TTP is characterized by fever, fluctuating neurologic symptoms (headaches, confusion, seizures, or coma), and acute renal failure, in addition to a microangiopathic hemolytic anemia and thrombocytopenia. HUS manifests similarly to TTP,
with the notable exceptions that the pediatric population is more commonly affected, neurologic manifestations are minimal, but the renal impairment is more pronounced. Central to the treatment of both these entities is supportive care, with particular attention given to management of the renal dysfunction (18,19). Plasma exchange is often efficacious in treating these diseases, and hemodialysis may also be required in some instances for support of renal failure.

Immune-mediated destruction of platelets is observed in several clinical conditions. Alloimmune antibodies are believed to account for posttransfusion purpura observed primarily in women, who may have been previously immunized by fetal-derived platelets because there is a significant association with a prior history of pregnancy (2,21). Immunizations to a number of candidate alloantigens have been reported in the literature, the most common being the PL^A^1 antigen. The antibodies induced are generally of the IgG class and therefore are also able to cross the placenta, as a described cause of neonatal thrombocytopenia. The purpura becomes apparent approximately 7 to 10 days after blood transfusion, presumably attributed to an anamnestic response, and can last several months. The population at risk has been estimated to be approximately 1% to 3%, and the condition tends to be self-limiting and responds to intravenous immune globulin. Idiopathic thrombocytopenic purpura is one of the more common examples of immune-mediated platelet destruction (2,14,20–23).

It tends to occur in otherwise healthy individuals, and both an acute and a chronic form have been described. Mechanistically, platelets coated with autoantibodies are removed by the reticuloendothelial cells in the spleen (and to an extent in the liver). The diagnosis is one of exclusion after other causes of thrombocytopenia have been ruled out. A similar mechanism may account for the thrombocytopenia associated with collagen vascular diseases, such as systemic lupus erythematosus, lymphoreticular diseases, and in some infectious diseases, such as infectious mononucleosis or human immunodeficiency virus infections. It is noteworthy in this regard that the acute form, often observed in the pediatric population, is often preceded by a viral syndrome. Splenectomy is required in a third of patients if immune globulin, corticosteroids, or plasmapheresis is unable to control the condition (2,14,22,23). In this condition, significant bleeding may not occur until platelet counts decrease as low as 10 × 10^9/L because most of the circulating platelet pool consists of younger, more functionally active platelets. The significance of this impact on the operative approach traditionally adopted during splenectomy. During splenectomy, platelets are hung by the anesthesiologist but not administered until the splenic artery is clamped or splenectomy completed. There is by and large minimal bleeding encountered despite the pronounced degree of thrombocytopenia, and if platelets are infused prior to control of the splenic arterial inflow, the infused platelets will merely be consumed by the spleen and not available for the hemostatic process. Immune-mediated destruction of platelets can also be caused by several drugs that can induce antibodies to platelets via hapten-mediated, or by immune complex-mediated, “innocent bystander” mechanisms. Quinine, amidarone, sulfa drugs, cimetidine, ranitidine, phenytoin, and semisynthetic penicillins are some examples that may be encountered in the critical care environment (2).

Heparin-induced thrombocytopenia is an unusual example of drug-induced thrombocytopenia in this context because a hypercoagulable condition is actually created characterized by thrombotic complications with the manifestation of the “white clot syndrome” (24). This syndrome typically becomes apparent after 1 week of therapy but may present within a few hours after implementing heparin therapy in already sensitized patients. Discontinuation of the offending agent is the appropriate treatment approach central to all causes of drug-induced, immune-mediated thrombocytopenia.

Contrary wise, the qualitative platelet disorders, generally manifesting normal platelet counts with impairment of function, may be inherited (Bernard–Soulier syndrome, abnormal release mechanism, Glanzmann thrombasthenia, storage pool disease, or von Willebrand disease) or acquired. Acquired disorders are the leading cause of qualitative platelet function abnormalities in the critically ill patient. It is vital to be aware that qualitative bleeding disorders are not measured by the standard battery of coagulation tests described below, with the exception of the template bleeding time.

Ingestion of numerous drugs has been associated with inhibition of platelet function (2,13,25). Among these, aspirin is the most well described and best characterized. Aspirin interferes with cyclo-oxygenase-mediated prostaglandin and thromboxane synthesis and has profound effects at multiple steps in the formation of the hemostatic platelet plug. It decreases the platelet response to aggregation in response to collagen, inhibits the second phase of aggregation in response to adenosine diphosphate (ADP) and epinephrine, and irreversibly injures platelets for the duration of their lifespan.

Another common cause of acquired qualitative defects in platelet function is hypothermia (26–28). Massive blood transfusions or crystalloid infusions without attention to use of blood warmers, lack of attention to maintaining a warm ambient environment in the operating room, especially during long procedures and for individuals at the extremes of age, and prolonged extractions and exposure time in the field in the patient with multiple traumatic injuries are all too familiar causes of hypothermia.

Renal failure is not uncommon in the critical care setting. In its acute form, bleeding is a common manifestation, most often from the gastrointestinal tract. The underlying mechanism is probably multifactorial, as there clearly is a qualitative platelet function defect related to the degree of uremia, in combination with abnormalities in the plasmatic coagulation system (29–31). The presence of acidosis also contributes to both the platelet and coagulation factor dysfunction.

Disorders involving plasmatic coagulation factors are generally caused by either a decrease in production of clotting factors (liver failure, vitamin K deficiency [oral antibiotic usage, which depresses gut flora in the setting of nutritional deficiency; malabsorption syndromes, such as celiac sprue or chronic diarrheal conditions; or obstructive jaundice]), and use of warfarin [Coumadin)] (2,15,32) or by an increase in consumption of circulating coagulation factors (such as in DIC) (2,7–12,15,26–28,32).

The most common cause of increased destruction of plasmatic coagulation factors has been variously termed DIC, defibrination syndrome, or consumptive coagulopathy (2,7–12,20,26–28). This syndrome is characterized by a hemorrhagic diathesis with unrestrained clotting and fibrinolysis in the vascular microcirculation, initiated by activation of the intrinsic or the extrinsic system, or both (2,7–12,20,26–28). Release of tissue thromboplastin, from injured tissue or from
leukocytes, activates the extrinsic system, whereas damage to vascular endothelium (in addition to releasing tissue thromboplastin) results in activation of the intrinsic system via collagen exposure (7–12). Exposed collagen initiates platelet aggregation with release of platelet factor III and also activates factor XII directly. The net result is deposition of fibrin in the microvasculature. This results in a microangiopathic hemolytic anemia with fragmentation of red blood cells as they traverse these vascular beds. These fragmented red blood cells, or schistocytes, seen on the peripheral blood smear are a classic finding in this syndrome. Additionally, microthrombi cause stasis and ischemia in a number of capillary beds, manifesting as renal insufficiency or failure with kidney involvement, pulmonary insufficiency with lung involvement, mental status changes with brain involvement, or dermal necrosis with skin involvement. Stasis itself can result in further activation of clotting factors. Fibrin deposition and endothelial wall damage both bring about the release of plasminogen activator, which catalyzes the conversion of circulating plasminogen to plasmin. Plasmin proteolytically hydrolyzes both fibrinogen and fibrin (secondary fibrinolysis), resulting in fibrinogen and fibrin degradation (or “split”) products. These degradation products then interfere with fibrin polymerization through the formation of complexes, further contributing to the hemorrhagic state. Additionally, these degradation products also interfere with platelet function, impairing both adhesion and aggregation. In the postoperative patient in the ICU, infection is the principle cause for DIC (9–12). Several causative organisms have been implicated, including gram-negative bacteria, such as the Enterobacteriaceae as well as the nonlactose fermenters; gram-positive bacteria; rickettsial organisms (Rocky Mountain spotted fever); mycotic infections, such as disseminated aspergillosis; parasitic agents, such as malaria; and viruses. The underlying pathophysiologic has been best elucidated with gram-negative infections, with endotoxin (cell wall lipopolysaccharide) triggering the intrinsic system by activation of factor XII directly and by factor XII exposure to subendothelial collagen, as a result of endotoxin-mediated damage to vascular endothelium. Endotoxin may also trigger the coagulation cascade by inducing expression of procoagulant activity in circulating leukocytes, hepatic macrophages, and endothelial cells, and by activating the extrinsic system mediated by the release of tissue thromboplastin from damaged leukocytes and vascular endothelium (33–35).

Traumatic injuries (particularly involving brain, bone, or liver), thermal injuries, and severe crush injuries, as well as surgical procedures may produce a consumptive coagulopathy (7–12, 26–28, 36–38). Secondary infection and hemorrhagic shock further serve to aggravate the coagulopathy, especially if acidosis, hyperthermia, or tissue ischemia and necrosis develop.

Acute pancreatitis, arising from various causes, may be associated with DIC due to release of enzymes that may directly activate a number of coagulation factors (39). In many instances, there is associated multiorgan dysfunction involving cardiopulmonary, renal, and hepatic function. In addition, pyogenic sequelae, such as the development of infected pancreatic necrosis or abscess formation, may result in DIC attributable to sepsis. Treatment is primarily supportive, with aggressive resuscitation, replacement of deficient coagulation factors if there is associated bleeding, appropriate use of broad-spectrum antibiotics, and surgical debridement and drainage for control of infectious complications.

Obstetric complications can result in some of the most profound and challenging instances of DIC. Well-recognized examples include amniotic fluid embolism, abruptio placentae, retained dead fetus, and eclampsia (9–11). In these circumstances, the culprit is massive systemic release of tissue thromboplastin that generates a fulminant course characterized by bilateral renal cortical necrosis to frank cardiopulmonary collapse, shock, multiorgan failure, and, at times, death even if aggressive attempts are made to treat these individuals. Both acute and chronic forms of DIC have been identified. In the acute form patients are critically ill, whereas in the chronic form the natural history is more indolent and protracted, and thrombotic complications may be the predominant feature.

Notwithstanding, coagulopathy manifested in the critically ill patient is often a result of a combination of both platelet and plasmatic coagulation factor defects. Well-known examples include obstructive biliary tract disease or chronic liver disease, which results in diminished production of coagulation factors given that the liver is the major site of synthesis of all coagulation factors with the exception of factor VIII. Hepatic parenchymal and biliary obstructive disease results in diverse manifestations of hemostatic abnormalities (15). Extrahepatic biliary obstruction results in diminished absorption of vitamin K due to lack of bile salts necessary for gastrointestinal absorption of lipid soluble vitamins. Decreased synthesis of the vitamin K–dependent factors II, VII, IX, and X occurs with abnormal prolongation of the prothrombin time (PT) and eventually the partial thromboplastin time (PTT). Parenchymal diseases such as cirrhosis, chronic active hepatitis, fulminant hepatic failure, or metastatic carcinoma impact on the hemostatic system in a heterogeneous manner. Most coagulation factors, naturally occurring anticoagulants (such as anti-thrombin III), fibrinolysin precursors (plasminogen), and inhibitors of the fibrinolytic system (antiplasmins) are synthesized by the liver. In severe liver disease, acquired dysfibrinogenemia has also been reported (15, 40). This impairs polymerization of soluble fibrin monomers and is suggested by a prolonged thrombin time (TT) on purified fibrinogen, which is generally done in a research laboratory. The liver also removes activated coagulation factors from the circulation, but it is speculative to conclude that this results in a coagulopathy by itself, despite the fact that this increased consumption of activated factors by the liver lowers coagulation factors already depressed by decreased production in a diseased liver. Clearance of fibrinogen/fibrin degradation products is reduced in chronic liver disease. These breakdown products inhibit both fibrin polymerization and platelet function and thus contribute to a defective hemostatic system, as discussed earlier. Thrombocytopenia occurs secondary to hypersplenism, potentially exacerbated by vitamin deficiencies associated with decreased thrombopoiesis. Additionally, alcohol has a direct toxic effect on megakaryocytes, which contributes to prevailing vitamin deficiencies and decreased bone marrow production of platelets. Massive trauma often results in decreases of both platelets and coagulation factors as a result of consumption secondary to ongoing bleeding or hemorrhage (2, 7–11, 26–28, 37, 38). If shock and acidosis develop, there is further decrease in coagulation factor synthesis due to impairment in liver function that results from low perfusion, in addition to impairment of both coagulation factor and platelet function from the acidemic state (26–28, 40, 41). Additionally,
a well-described sequela of massive blood transfusion, often associated with multiple trauma and hemorrhagic shock, is the development of a coagulopathy. Major trauma, major orthopedic (spine, hip, or pelvis) or hepatic procedures (major hepatic resections, liver transplantation), or other causes of potentially life-threatening, exsanguinating hemorrhage are often associated with the need for what has been termed massive blood transfusion. This term has been variously defined but generally refers to administering the equivalent of one total blood volume or more to a patient in less than a 24-hour period. Due to consumption of coagulation factors and platelets, release of inflammatory mediators, dilation of elements necessary for the optimal function of the coagulation cascade, hypocalcemia, hypothermia, fibrinolysis, and alterations in acid–base homeostasis, a coagulopathy often develops in this scenario (2,5–8,26–28,42–44). Banked blood is a negligible source of viable platelets, which rapidly deteriorate under conditions of cold storage (4–6). Additionally, depending on the age of the unit, plasmatic coagulation factors may also be diminished in activity. The derangement in clotting represents nonlocalized, nonsurgical bleeding that is characterized by sanguineous oozing from all raw surfaces, including any wounds, mucosal or peritoneal surfaces, and percutaneous entry sites. Numerous risk factors for the development of this condition (particularly in the setting of trauma) include high injury severity score, acidosis, hypothermia, and hypotension (7,8,10,26–28,41–43). Last, transient platelet dysfunction, responsive to desmopressin (DDAVP, 1-desamino-8-d-arginine vasopressin), is a well-recognized phenomenon in patients after cardiopulmonary bypass (45–49). To this end, postoperative bleeding is a frequent impediment of cardiopulmonary bypass. Numerous mechanisms are apparently involved, which include contact factor (factors XII and XI) activation, elevations of tissue plasminogen activator level and tissue thromboplastin, dilution of plasmatic coagulation factors, residual effects of systemic heparinization, hypothermia, platelet function defects, and failure of surgical hemostasis (45–50). Some investigations have demonstrated a 30% to 50% decrement in platelet count attributable to the shearing forces that are encountered in the bypass apparatus. The routine use of antiplatelet agents in patients with cardiac disease, such as aspirin and thienopyridine derivatives, also contributes to the increased risk for bleeding. The combined effects of aspirin and a thienopyridine derivative, such as clopidogrel, on bleeding complications are synergistic and not additive. In approximately 4% to 5% of patients, surgical re-exploration of the mediastinum is necessary, which varies based on the original procedure performed (45–50). Several criteria for re-exploration have been proposed that have in common the rate of blood loss from mediastinal or chest tubes. Criteria vary widely and include blood loss from chest or mediastinal tubes of 300 mL/hr within the first 3 hours; total blood loss of 1,000 mL after 4 hours; a sudden increase in bleeding (>300 mL/hr) in a patient who previously had minimal drainage; or evidence of cardiac tamponade. A coagulopathy must never be presumed to be the cause of bleeding postoperatively unless surgical causes of bleeding have first been excluded. A site of localized bleeding (surgical failure) is identified in more than 50% of patients re-explored based on these types of criteria (45–50). Despite multiple contributing factors to the bleeding that occurs in these patients, the prime offender is collectively believed to be secondary to qualitative platelet function defects (1,2,45–50). The bypass circuitry results in platelet activation with degradation and aggregation. Although this functional deficit is transient, increased time on bypass, hypothermia, and antiplatelet medications significantly exacerbates this condition. Laboratory analysis reveals a prolongation of the bleeding time with impaired adhesion and aggregation, particularly in the presence of ADP and ristocetin. This latter finding is believed to be linked to low levels of von Willebrand factor (vWf) found in plasma after cardiopulmonary bypass. Hence, some investigators have proposed use of desmopressin in this circumstance (and in patients with a history of preoperative use of aspirin), to increase levels of vWF by stimulating release from endothelial cells, increasing the glycoprotein receptors on platelets, and increasing the level of factor VIII and tissue plasminogen activator. However, others believe that this practice increases the risk of graft thrombosis and coronary occlusion (48–50). Additionally, peer-reviewed, reported outcome data in this circumstance are indeterminate (45–49). Usually the acquired qualitative platelet function defect resolves within 4 hours of completion of cardiopulmonary bypass without any intervention. In instances where there is prolonged nonsurgical postoperative bleeding, platelet transfusions are often beneficial (4,6,49).

Normal physiologic processes (fibrinolytic system) exist to control for unremitting clot formation and are described in several reviews (1,50–52). Impaired function of the coagulation cascade may be the result of various disorders that are characterized by the genesis of circulating anticoagulants, abnormal protein products, or accumulation of proteinaceous breakdown products that affect the normal function of coagulation proteins. Collagen vascular diseases, such as systemic lupus erythematosus, is one example (53,54). In these patients an antibody is produced (lupus anticoagulant) that affects the coagulation cascade at the juncture of the intrinsic and extrinsic systems, resulting in prolongation of both the PT and PTT in vitro. Paradoxically, these patients tend to be hypercoagulable, and if clinically significant bleeding is noted, it is attributable to associated thrombocytopenia and increased vascular fragility. When there are elevated titers of either the lupus anticoagulant or anticoagulant inhibitors, or both, these patients may present with manifestation of the antiphospholipid antibody syndrome with generalized microvascular thrombosis, thrombocytopenia, gangrene of the extremities, multiorgan failure, and death. Plasmapheresis, anticoagulation, and immunosuppressive therapy serve as the foundation of treatment (53,54). Other commonly acquired inhibitors or circulating anticoagulants include factor VIII inhibitors and factor IX inhibitors, related primarily to prior frequency of transfusion with plasma-derived blood concentrates and alloimmunization (55–57). Exogenously administered heparin, the prototype for anticoagulation therapy, binds to circulating antithrombin III and catalyzes its ability to neutralize the action of a number of coagulation factors. The end result is interference with the normal coagulation cascade. Disorders characterized by the production of abnormal globulins, often referred to collectively as the paraproteinemias (associated with multiple myeloma and Waldenstrom macroglobulinemia), also result in interference with coagulation proteins and inhibition of fibrin polymerization. Treatment of the coagulopathy associated with all of these conditions consists of replacement of deficient coagulation factors when bleeding is dominant and definitive treatment directed at the underlying disease process.
DIAGNOSIS

A detailed history and physical examination is the most important preliminary step in elucidating the cause of surgical bleeding and should be done simultaneously with resuscitative efforts (1,2,5,6,8). Collateral history from family members and previous medical records is a helpful adjunct to determine if a primary, congenital defect in the coagulation system is present. A history of easy bruising, excessive gingival bleeding after brushing of teeth, bleeding diathesis with dental extractions, hypermenorrhagia, frequent spontaneous epistaxis, melena stools or spontaneous hematuria, petechiae or purpura, hemarthroses, and a family history of bleeding disorders may indicate a congenital or familial coagulation disorder, such as hemophilia A or B or von Willebrand disease. The family pedigree may provide important clues as to the presumptive disease process based on the pattern of inheritance, whether autosomal or sex linked, dominant or recessive. Suspicion for a congenital disorder of coagulation is further raised by a history of blood transfusions required for common ambulatory procedures such as dental extractions, circumcisions, tonsillectomies, or biopsies. Due to differences in gene penetration, not all individuals afflicted with inherited coagulation disorders are diagnosed at an early age, and clinically latent, attenuated bleeding disorders may be unmasked when confronted by a major surgical procedure or trauma. A past history of liver disease or heavy ethanol consumption should alert the clinician to the possibility of acquired plasmatic factor deficiencies, in addition to thrombocytopenia resulting from secondary hypersplenism with platelet sequestration.

A thorough medication history is essential (including soliciting information on the use of dietary supplements or herbal tonics, and over-the-counter medications), to determine if the patient has been on any medication that interferes with hemostasis (common examples include aspirin, other nonsteroidal anti-inflammatory agents, ticlopidine, clopidogrel, semisynthetic penicillins, and more recently, newer classes of oral anticoagulants such as rivaroxaban, apixaban, and dabigatran (2–6,13). Popular supplements that may aggravate bleeding are ginkgo, garlic, ginger, ginseng, feverfew, and vitamin E. A history of anticoagulation therapy is equally important in this regard (2,3,32,58). Nutritional assessment is paramount, and careful evaluation for the presence of a vitamin K deficiency is obligatory, as this may occur in patients on parenteral nutrition or with cancer cachexia in those with malignancies. Other variables that may affect the integrity of the coagulation system include previous irradiation, renal failure, and sepsis, which affect the coagulation cascade at multiple points.

Physical examination often provides an index of the severity and the extent of the disease and may provide additional clues that assist in distinguishing localized surgical bleeding from systemic bleeding resulting from a coagulopathy. For example, the presence of petechiae, purpura, and mucosal bleeding is often indicative of thrombocytopenia, a qualitative functional disorder of platelets, or increased vascular fragility. Ecchymoses or spontaneous, nontraumatic hemarthrosis is consistent with plasmatic coagulation factor abnormalities or deficiencies such as hemophilia. Both platelet and plasmatic coagulation disorders are associated with hematomas. Hepatic insufficiency or failure can be presumptively identified by recognizing jaundice, ascites, angiomata, palmar erythema, asterixis, congestive splenomegaly, and testicular atrophy. Splenomegaly itself may also be associated with hematologic dyscrasias and malignancies associated with hemostatic abnormalities (lymphomas and leukemias). Connective tissue or collagen vascular disorders that result in increased vascular fragility may manifest with petechiae, joint abnormalities, and a history of delayed wound healing. These conditions focus attention on the increased risk for a perioperative bleeding complication, which underscores the need for vigilance both intraoperatively and postoperatively. Last, the possibility of sepsis as an underlying cause for the development of a coagulopathy must always be entertained in the postoperative, critically ill patient (12).

The establishment of a definitive diagnosis of a coagulation disorder rests on selective use of a limited battery of laboratory tests guided by information derived from the history and physical examination. These assays are selected to broadly screen the hemostatic system. These tests are, for the most part, automated (except for the bleeding time), readily available, and amenable to point-of-care testing methodology. The tests most commonly used include the template bleeding time, quantitative platelet count, PT, activated PTT, fibrinogen level, and thrombin time (TT). The template bleeding time is the only test that screens for qualitative platelet function abnormalities, a frequent cause of abnormal bleeding. This test is not commonly used, given that it does not lend itself to automation and still requires the laboratory technologist to remain at the patient’s bedside. Furthermore, this test has been attended by poor reproducibility, particularly in conditions associated with significant peripheral edema. Nevertheless, when a qualitative platelet function abnormality is suspected, the bleeding time is an appropriate first screening test to guide discriminate use of additional testing to further elucidate the underlying cause. This test also evaluates platelet number and vascular fragility, demonstrating abnormal prolongation in thrombocytopenic states and in conditions associated with increased vascular fragility (examples include connective tissue disorders such as senile purpura, Ehlers–Danlos syndrome, steroid-induced purpura, or Marfan syndrome; scurvy; amyloidosis; or hereditary hemorrhagic telangiectasia/Osler–Weber–Rendu disease). Therefore, if both the platelet count and the template bleeding time are normal, the presumptive differential diagnosis is directed toward a plasmatic coagulation factor abnormality. Measurement of both the PT and PTT will serve to further define the abnormality, given that each test is more sensitive to changes in procoagulants in the initial phases of the extrinsic and intrinsic pathways, respectively. The PTT provides a global measure of the activity of factors XII, XI, IX, and VIII in addition to the common pathway factors shared by the extrinsic system (factors X, V, II, and I) and, therefore, identifies many of the inherited disorders of bleeding, typically a deficiency of factor VIII (hemophilia A), IX (hemophilia B), or vWF (von Willebrand disease). It is worth noting that factor XII deficiency is not associated with any significant bleeding tendency despite abnormal prolongation of the PTT. Enzymatically active vWF is a necessary cofactor for optimum functioning of the factor VIII procoagulant protein. The PT exclusively evaluates factor VII, which is one of the vitamin K–dependent factors (in addition to factors II, IX, and X). Therefore, the PT is prolonged in individuals on warfarin (Coumadin) therapy, and this test is used to measure therapeutic efficacy of this form of oral anticoagulation therapy. Liver disease is another common cause for a prolonged
roxaban, and apixaban, have been Food and Drug Adminis-
worthy of comment. These agents, such as dabigatran, riva-
lysis time). Finally, the diagnostic dilemma associated with the
strongly positive (euglobulin clot lysis time, whole blood clot
not seen, and tests for increased levels of plasmin activity are
uble fibrin monomers are not present (measured by the plasma
fractionation test), schistocytes (red cell fragments) are
ubrination test), fibrinogen/fibrin degradation products are ele-
son the severity of the disease process, fibrinogen may not be
all prolonged, and the platelet count is decreased. Depending
lished with routinely available tests. The PT, PTT, and TT are
ratory results. The TT is a qualitative measure of fibrinogen
exted by the physiologic stress resulting from a surgical procedure.
latent, congenital coagulation disorders may be unmasked
bly, and plasmatic coagulation factors, and hypothermia are major
on of intravascular volume status may be obtained using both
cessful resuscitation is paramount to avert the disastrous
consequences of an unrecognized and inappropriately triaged
patient with ongoing, potentially life-threatening hemorrhage.
Second, there should be immediate dialogue with indi-
ividuals involved in the intraoperative management of the
atient. This may provide pertinent information regarding the
traoperative course of the patient, specifically regarding any observed characteristics of bleeding that may suggest an
underlying coagulation disorder. A generalized slow oozing of
of raw surfaces (often termed nonsurgical bleeding) is often a manifestation of a systemic disorder of hemostasis.
On the other hand, bleeding related to technical factors that
can be associated with the conduct of any surgical procedure (often termed surgical bleeding) is localized and is the most
common cause of postoperative bleeding. Although signs of
expanding hematoma or saturated dressings are indicative of localized bleeding, there is considerable overlap, and coagu-
ution system defects may present in a similar fashion post-
operationally. Dialogue with the surgical team should include
sideration for re-exploration. The evolving coagulopa-
ay proceed swiftly in critically ill patients. Qualitative
ormalities of platelet function, depletion of both platelets and plasmatic coagulation factors, and hypothermia are major
actors to the underlying pathophysiology responsible for the coagulopathy that manifests in the critical care setting. Moreover, previously undiagnosed, rare, at times clinically latent, congenital coagulation disorders may be unmasked by the physiologic stress resulting from a surgical procedure.
Familial coagulation defects that may be encountered in a
bleeding postoperative patient include von Willebrand disease, factor VIII deficiency (hemophilia A or classic hemophilia), and factor IX deficiency (hemophilia B or Christmas disease) (4,20,40,55,59,61,64).

**TREATMENT**

To expeditiously manage a critically ill patient experienc-
ing life-threatening hemorrhage, it is crucial that a defined approach for prompt recognition of the underlying cause is
used. First, attention is directed toward stabilizing the patient.
This includes securing an adequate airway, ventilation, vas-
cular access, and restoring intravascular volume. Early rec-
ognition of the clinical symptoms and signs attributable to
hypovolemia (restlessness, anxiety, shortness of breath, pallor,
tachycardia, and oliguria) is compulsory. Adjunctive estimates of intravascular volume status may be obtained using both noninvasive and invasive monitoring, as is common in the
critical care setting, described elsewhere in this textbook. Sys-
temic hypotension is a late sign of significant hypovolemia, and expeditious resuscitation is paramount to avert the disastrous
consequences of an unrecognized and inappropriately triaged
patient with ongoing, potentially life-threatening hemorrhage.

Second, there should be immediate dialogue with indi-
viduals involved in the intraoperative management of the
patient. This may provide pertinent information regarding the
traoperative course of the patient, specifically regarding any observed characteristics of bleeding that may suggest an
underlying coagulation disorder. A generalized slow oozing of
of raw surfaces (often termed nonsurgical bleeding) is often a manifestation of a systemic disorder of hemostasis.
On the other hand, bleeding related to technical factors that
can be associated with the conduct of any surgical procedure (often termed surgical bleeding) is localized and is the most
common cause of postoperative bleeding. Although signs of
expanding hematoma or saturated dressings are indicative of localized bleeding, there is considerable overlap, and coagu-
ution system defects may present in a similar fashion post-
operationally. Dialogue with the surgical team should include
sideration for re-exploration. The evolving coagulopa-
ay proceed swiftly in critically ill patients. Qualitative
ormalities of platelet function, depletion of both platelets and plasmatic coagulation factors, and hypothermia are major
actors to the underlying pathophysiology responsible for the coagulopathy that manifests in the critical care setting. Moreover, previously undiagnosed, rare, at times clinically latent, congenital coagulation disorders may be unmasked by the physiologic stress resulting from a surgical procedure.
Familial coagulation defects that may be encountered in a
bleeding postoperative patient include von Willebrand disease, factor VIII deficiency (hemophilia A or classic hemophilia), and factor IX deficiency (hemophilia B or Christmas disease) (4,20,40,55,59,61,64).

The therapeutic approach to hemostatic abnormalities
must be reasonably guided by the patient's clinical condition
and the outcome of appropriately selected laboratory tests (4–6). An important concept is not to fall behind in factor replacement. Due to the lag time in receiving laboratory values, in clinical conditions where the patient is actively bleeding, initiation of fresh-frozen plasma (FFP) and platelets should be started early with red cell transfusion. In patients with known warfarin use and a small bleed in an uncompromising area (skull), FFP should be used before patients develop increasing intracranial hemorrhage. In general, FFP is the most commonly used blood component for plasmatic coagulation abnormalities because it provides all necessary coagulation factors in concentrations that approach those found in normal plasma (2–6,40,55–58,60). Despite plasmatic coagulation factor activity deteriorating with storage, dilution of these factors below levels required for adequate hemostasis is rare. Therefore, routine administration of FFP after an arbitrary number of units of banked blood has been transfused is not supported by stringent investigations (5–8,10,26–28,60,62–66). If there is bleeding due to a coagulopathy with concomitant prolongation of the PT and PTT of more than 1.5 times normal, FFP should be infused (to normalize the PTT and achieve a PT international normalized ratio [INR] 1.5). There is emphasis on early correction because timely replacement of coagulation products will lead to more bleeding and being more coagulopathic, leading to a vicious cycle. Cryoprecipitate should be considered if the fibrinogen level is less than 0.8 g/dL.

Cryoprecipitate, a component made from thawing FFP in the cold under specialized conditions, is rich in factors XIII, VIII, I, vWF, and fibrinectin. It has been used in factor VIII-deficient states (hemophilia A) if virally inactivated plasma-derived or recombinant factor VIII concentrates are not readily available; in von Willebrand disease rectal/abdominal to desmopressin and if virally inactivated plasma-derived factor VIII concentrate rich in vWF is not readily available; in hypofibrinogenemic or dysfibrinogenemic conditions; in hemorrhage associated with massive blood transfusions; in DIC; in factor XIII deficiency (FFP is also used); in bleeding uremic patients with qualitative platelet function defects unresponsive to desmopressin therapy; or as a topically applied surgical sealant (“fibrin glue”) (67). It should be further highlighted that the number of disorders associated with DIC is substantial, but the unifying approach to management is supportive therapy with replacement of coagulation factors and platelets with attention focused on treating the underlying disease process. In DIC, FFP and platelet concentrates are the two most common blood products used as a temporizing measure (4–6,9–12,60). Stored or banked whole blood is a reasonable source of most clotting factors if the units are less than 24 hours old (4–6,43,60). The biologic half-life of factors V, VII, VIII, and IX are on the order of 24 hours or less; hence whole blood stored for longer than 24 hours may not provide adequate amounts of these coagulation factors. Heparin had been used in the past in a theoretical attempt to abrogate the clotting cascade, but its contemporaneous use for this purpose is at best controversial, may be contraindicated in the perioperative period, and is not supported by evidence-based data (9–12,68). Recombinant activated factor VIIa had demonstrated promise in significantly reducing bleeding and blood transfusion requirements in patients with traumatic injuries, or surgical procedures attended by significant hemorrhage, in addition to liver transplantation. However, a clear survival benefit has not been demonstrated in randomized controlled trials (69–75).

For specific coagulation disorders, such as hemophilia A, hemophilia B (deficiencies of factors VIII and IX, respectively), and von Willebrand disease, virally inactivated plasma-derived factor concentrates are commercially available, as are recombinant products, and these are the blood components of choice if available for use. These concentrates (and the recombinant product) also have a lower risk for virally transmitted disease because of a processing procedure that results in viral inactivation. For deficiencies of the vitamin K-dependent factors (II, VII, IX, X), prothrombin complex concentrates are also commercially available, as is recombinant factor VII for isolated factor VII deficiency states. In these situations, therapy is acutely centered on replacement of coagulation factors, most commonly with use of FFP. Vitamin K can be administered parenterally in patients with deficient states or to reverse the effects of Coumadin, but appreciable effects on coagulation factor synthesis (in the presence of normal hepatic synthetic function) is not generally seen for 24 to 36 hours after administration of parenteral vitamin K (32,58). Treatment of bleeding in liver failure with vitamin K usually is not successful given the lack of hepatic synthetic function. Whole blood both corrects the red blood cell deficit and is as effective as FFP in correcting coagulation factor deficits if the units of blood have not been banked for an extended period of time (4–6,43,60). Platelet transfusions should be judiciously used to raise the platelet count to above 100 × 10^9/L if bleeding is encountered in this setting, and FFP should be provided to correct deficits in plasmatic coagulation factors (4–6,60). For those patients who have recently (within the prior 24 hours) taken oral activated factor X or thrombin inhibitors, there are no known antidotes in the setting of acute hemorrhage (3). Furthermore, there are no evidence-based guidelines applicable to the use of hemostatic agents. Recombinant activated factor VIIa, and activated and nonactivated prothrombin complex concentrate have all been used clinically, but no outcome-based studies exist to guide management. Studies are underway to evaluate antidote prototypes for this newer class of oral anticoagulants.

Platelet concentrates are used for both quantitative (thrombocytopenias) and qualitative platelet disorders associated with significant bleeding (2,4–6,31). It is generally recommended for patients taking antiplatelet medications, such as aspirin or clopidogrel, that these agents are discontinued approximately 7 to 10 days prior to surgery. For nonsteroidal anti-inflammatory agents other than aspirin, ticlopidine, or clopidogrel, some investigators advocate 2 days of abstinence. It is important to recognize, again, that many over-the-counter medications contain aspirin (e.g., Aspirin, Ecotrin, Anacin) and many patients are not aware of this, so it is imperative to obtain a comprehensive drug history, specifically querying for use of aspirin-containing products. Discontinuing the antiplatelet drug combined with use of desmopressin and platelet transfusions have been beneficial in treating bleeding encountered in these situations (2,4–6,13). Prophylactic administration of platelets during massive blood transfusion in an attempt to prevent the development of a coagulopathy has been advocated by many centers, but the efficacy of this policy is unproven. Studies have failed to demonstrate conclusively a benefit to this approach (4–6,42,43,62,76,77). It is reasonable, however, to administer platelets to a bleeding patient or one with DIC if the platelet count is less than 50 × 10^9/L. For those patients with
rapid bleeding or with multiple traumatic injuries undergoing surgery or other high-risk procedures, a goal of at least 100 $\times 10^9$/L has been recommended, albeit in the absence of high-level evidence-based data. One unit of platelet concentrate typically raises the platelet count by $5 \times 10^9$/L, whereas one apheresis concentrate raises the platelet count by 20 to 25 $\times 10^9$/L in an average 70-kg adult.

The fundamental approach to therapy for patients with renal failure attended by qualitative platelet dysfunction centers on dialysis, which results in abatement of the bleeding diathesis. Use of desmopressin and cryoprecipitate, as temporizing measures to transiently stop the bleeding while awaiting institution of dialysis, have been reported to be successful (29–31). Conjugated estrogens have also been used with some success, albeit the effects are not as rapid but more durable, but any positive outcomes are balanced by undesirable consequences of hormonal side effects. In its chronic form, renal failure is still attended by a mild qualitative platelet function defect, but significant impact on hemostatic homeostasis is usually not seen (29–31).

It should be highlighted that patients transfused with any blood component, whether FFP, cryoprecipitate, plasma-derived factor concentrates, or platelet concentrates, incur similar risks of complications attributed to all types of blood component therapy such as febrile and allergic reactions, transmission of blood-borne pathogens (human immunodeficiency virus, hepatitis B and C), immunosuppression, transfusion-related pulmonary injury, and hemolytic transfusion reactions if a substantial volume of ABO-incompatible units are transfused. In the setting of massive blood transfusion, numerous points are warranted. Hemolytic transfusion reactions may occur as a result of ABO incompatibility between the actual units of blood transfused, or potentially because of clerical error, magnified by the volume of units required in a relatively short period of time. Red blood cells are a rich source of tissue thromboplastin, and hemolysis results in a massive release of this extrinsic system activator. This manifests as a generalized oozing from all raw surfaces, similar to the coagulopathy seen with massive blood transfusions, rendering this a difficult diagnosis to make. Hemoglobinuria may be observed due to filtration of plasmafree hemoglobin into the urine. Consistent with other types of transfusion reactions, the coagulation abnormality corrects rapidly once the offending transfusion is terminated. Treatment must be directed toward prevention of hemoglobin casts precipitating in the acidic environment of the collecting tubules, resulting in acute tubular necrosis and acute renal failure. Appropriate fluid resuscitation to maintain intravascular volume and to initiate a diuresis is paramount. Mannitol, an osmotic diuretic and free radical scavenger, may be administered intravenously as an adjunct to maintain urine flow, and intravenous sodium bicarbonate may be considered to alkalinize the urine to avoid further precipitation of hemoglobin in the renal tubules. In essence, judicious use of blood component therapy must always be adhered to.

A few comments on the effects of hypothermia is of merit here. It is important to bear in mind that all enzymatic processes in biologic systems are governed to an extent by the necessity to function in an optimal, typically narrow, temperature range. The coagulation factors are enzymes, and therefore function best under normothermic conditions. Platelets, too, function optimally under normothermic conditions. The implication of this is that the clinician must always remain alert to the effects of hypothermia as the origin of a coagulopathy, particularly in the critical care environment. Reliance solely on the values of the PT, PTT, or TT can be misleading, understanding that these assays are performed by both manual and automated laboratory methods at 37°C and results may thus fall within the reference range in vitro, despite ongoing coagulopathy clinically. External warming measures should include blankets generating heated air, warming of all fluid infusions, heated humidifier in ventilated patients, and warming the ambient environment. In extreme conditions, Gentiliello et al. (78) reported that continuous arteriovenous rewarming, which does not require heparinization of the patient and hence does not exacerbate the coagulopathy, improves hemostasis more rapidly than any other method with the exception of cardiopulmonary bypass.

In parallel with the ongoing resuscitation of the bleeding patient, attention must be directed toward expeditiously determining the need for surgical re-exploration. There are certain circumstances where operative re-exploration is obligatory, despite the fact that the bleeding may be self-limiting. Certain surgical procedures are not associated with exsanguinating hemorrhage or hypotension but can nonetheless be life threatening. Prototypic examples include neck operations for endocrine diseases (thyroid, parathyroid surgery), lymphadenectomies (radical neck dissections), major composite resections for tumors of the neck, and carotid surgery. From a pathophysiologic perspective, an expanding neck hematoma results in airway obstruction from both mechanical compression and from mural edema caused by lymphatic obstruction. The cause is frequently venous bleeding, compounded by hypertension and liberal preoperative use of antplatelet medications in those undergoing carotid surgery. Acutely reopening the incision and evacuating the hematoma is often lifesaving, although endotracheal intubation or cricothyroidotomy may be required as a temporizing measure until the airway edema resolves. In contrast, the natural history of a contained perioperative vascular Anastomatic dehiscence is characterized by the evolution of a false aneurysm. In this setting, immediate re-exploration with operative repair is indicated to avert the potentially catastrophic consequence of free rupture and death from exsanguinating hemorrhage. Therefore, nearly all patients who develop neck hematomas require operative re-exploration. It is common practice to place drains in the operative field at the time of surgery prior to closure, and surgical procedural anthologies are replete with instructions substantiating this approach. Caution must be exercised in interpreting drain output as an accurate index of early perioperative bleeding, and it is correspondingly crucial to recognize that placement of a drain is not an appropriate substitute for ensuring meticulous surgical hemostasis (79).

Notwithstanding, all bleeding patients must be considered candidates for reoperation. Postoperative bleeding, often termed local hemostatic failure or surgical bleeding, is a known potential complication of any surgical procedure. When associated with evolving hypovolemia, mental status changes, restlessness, anxiety, tachycardia, dyspnea, and oliguria are commonly associated manifestations. Hypotension is a late finding, and aggressive attempts must be made to avert this serious consequence with expeditious concurrent resuscitation as identification of the source of bleeding is confirmed. The vast majority of patients affected typically present within the immediate perioperative period. Subtle signs may be evident in
the postanesthesia care unit, and generally become apparent within the first 8 hours after surgery. A high index of suspicion is necessary to render an early diagnosis of postoperative bleeding, and meticulous attention to look for any evidence of bleeding must be applied, given that many signs of evolving hypovolemia are nonspecific and may also be observed in nonbleeding patients after major thoracic or abdominal procedures (tachycardia associated with postoperative pain, anxiety and restlessness, mental status changes secondary to narcotic analgesic administration, or oliguria resulting from anticipated third-space fluid sequestration after major abdominal surgery). Blood in the peritoneal cavity ordinarily does not result in a significant inflammatory response unless associated with secondary bacterial contamination and therefore is not associated with obvious peritoneal signs. On occasion, localized symptoms may be elicited that are attributable to irritation caused by a collection of blood, exemplified by the Kehr sign. This is referred pain to the right shoulder ascribed to an accumulation of blood under the right hemidiaphragm. Serial hemoglobin and hematocrit levels may assist in determining the degree of bleeding, but isolated, single values can be difficult to interpret. It is difficult to quantitatively account for the effects of isotonic fluid sequestration (third-spacing) after major abdominal procedures that may result in hemococoncentration and elevated hemoglobin and hematocrit levels, or the effects of isotonic fluid administration in the perioperative period that may contribute to hemodilution and lower hemoglobin and hematocrit levels.

Taken collectively, there is no single criterion available to direct re-exploration for control of postoperative bleeding, and this decision is based on considering a number of variables. The timing of the active bleed relative to the operative procedure, its duration, its rate, the potential for additional morbidity, the patient’s age as a surrogate for physiologic reserve, and other comorbid diseases (such as underlying cardiac or pulmonary disease, renal disease, diabetes, or obesity) must all be taken into consideration when deciding on the need for reoperation. Timing of re-exploration is of significant concern in conditions associated with limited or poor physiologic reserve as these patients are often quite ill and require judicious resuscitation and expeditious definitive surgical intervention prior to the inception of irreversible shock. The most conservative treatment is to return to the operating room with early control of surgical bleeding. Occasionally the need to return emergently to the operating room is quite obvious, as in the case of exsanguinating hemorrhage resulting from a coronary artery bypass graft dehiscence attended by brisk bleeding from the mediastinal drain. However, there are two caveats for consideration. First, it is desirable to correct any coagulopathy prior to returning to the operating room, and in some instances with minimal or mild bleeding this may be all that is necessary. It is important to recognize, however, that situations characterized by exsanguinating hemorrhage from failure of local surgical hemostasis may not allow for correction of the coagulopathy because of rapid ongoing consumption of coagulation factors and platelets. In these instances, operative intervention is paramount, and the decision to reoperate must not be unduly delayed while awaiting normalization of coagulation parameters. Second, as stated earlier, some subscribe to the notion that drains placed at the time of surgery are a useful adjunct to alert the surgical team to early signs of postoperative bleeding and to gauge the amount and rate of bleeding when it does occur. Caution with this practice must be promulgated, as it is a well-accepted observation that the absence of blood in a drain is not conclusive evidence that bleeding is not occurring, because the drain tip may be dislodged or may have migrated from its original position and this may not be readily apparent externally, or the drain may be obstructed with clot.

Finally, the surgeon must also be cognizant of the fact that there are some instances where bleeding is optimally addressed without surgical intervention. The prototypic illustration is the severe pelvic fracture with signs of ongoing hemorrhage. In accordance with the Advanced Trauma Life Support protocol, associated injuries and additional sources of obvious bleeding must first be excluded. Once hemoperitoneum and hemotorax have been excluded, the pelvis is stabilized (generally by external fixation), followed by arteriography with embolization of any bleeding pelvic or retroperitoneal blood vessels.

Consequently, a comprehensive assessment must take into account the degree and the duration of active bleeding, the anatomic site of involvement, and the potential for additional morbidity or mortality (e.g., evolving acidosis, myocardial ischemia, diminished mental status, oliguria, or a progressive neck wound hematoma with impending acute airway obstruction). Physiologic reserve is also a compelling variable to consider, for patients with significant comorbidities, such as the elderly, pediatric, obese, and diabetic patients are attended by less reserve. Therefore, vigilant observation to recognize early postoperative bleeding is crucial, before hemodynamic instability and shock become manifest. In these patients, consideration for early operative intervention may be necessary because this cohort may not be able to readily tolerate even mild degrees of anemia, hypovolemia, and hypoperfusion. Consideration of other modalities of hemorrhage control (interventional radiology and embolization) may be entertained in appropriate situations.

It should also be noted that many pharmacologic agents have proven efficacy in the management of nonsurgical bleeding, particularly in the post–cardiopulmonary bypass setting. Desmopressin has already been described. Epsilon aminocaproic acid (EACA) and tranexamic acid are lysine analogs that inhibit binding of plasmin to fibrin (48,50,80,81). EACA appears to have the weakest antifibrinolytic effect compared to tranexamic acid, but nevertheless has been used in the cardiopulmonary bypass patient with some success. Tranexamic acid has met with considerable success in the reduction of postoperative blood loss and the reduced need for red blood cell transfusion in cardiac surgery, total knee arthroplasty, transurethral prostate surgery, and oral surgery procedures. Neither EACA nor tranexamic acid is associated with thrombotic complications or anaphylactic reactions. The most commonly reported adverse reactions include nausea, diarrhea, and orthostatic reactions (48,50,80).

In conclusion, surgical and postsurgical bleeding requires immediate recognition of early shock, resuscitation, and differentiation between surgical and nonsurgical bleeding. Prudent and meticulous evaluation of the patient, in order to identify primary or secondary coagulation disorders, is paramount. Knowledge of the complexities of the coagulation cascade is essential, in this regard, to ensure timely and precise diagnosis and management of these conditions, with appropriate replacement of blood and blood products, to effect the best patient outcomes.
CONTROVERSIES

Measurement of the viscoelastic properties of clotting blood as a tool to evaluate the integrity of the coagulation system was first described in 1948, prior to the development of the PTT and the activated clotting time (82). Thromboelastography, and thromboelastometry, assays first popularized in Europe, have been used to determine if there is a platelet function abnormality, a deficit in plasmatic coagulation factors, the presence of circulating anticoaguants, or fibrinolysis in patients undergoing cardiopulmonary bypass (6,13,82,83). Not at all surprisingly, in the quest for more enhanced, more dynamic coagulation assays (rather than the static, global measures of coagulation in common use currently), the use of this technology has expanded into the realm of liver transplantation, obstetrics, trauma, sepsis, and therapeutic monitoring of anticoagulation (6,13,82–87). These assays have been touted as having the potential to diagnose early coagulopathies, and subsequently judiciously guide treatment. This technique fundamentally evaluates whole clot formation and dissolution, and continually evaluates clot firmness in an integrated manner, reflecting in vivo hemostasis. Furthermore, it is amenable to point-of-care testing, with short turnaround times, hence its usefulness both intra- and postoperatively. No specific specimen processing is required, and whole blood is used for testing. This technology is rapidly gaining attention as a valuable adjunct to managing complex coagulation disorders (6,82–87). It has been efficacious in decreasing blood transfusion requirements during cardiac surgery and in liver transplantation (82,83). The effect of hypothermia on a patient’s coagulation profile can also be determined simply by adjusting the temperature of the apparatus to correspond with the patient’s core body temperature. Several automated analyzers are available commercially, now that technical improvements have resulted in improved standardization of the methodology. However, a major disadvantage of these assays is their lack of validation. Systematic reviews of the literature have shown highly variable, heterogeneous study designs, control groups, and reference standards; timing of measurements; and preselected endpoints, all contributing to methodological flaws that have made it challenging to draw conclusive inferences (82–87). Moreover, the predictive value of these assays has not been found to be consistently superior to the coagulation assays currently in use. Taken collectively, adequately powered, stringent randomized controlled trials are needed to validate this technology before it can attain widespread clinical use. Despite its promise, there are currently no universally accepted guidelines that espouse use of this technology (6,82–87).

Key Points

- A detailed history and physical examination is the most important preliminary step in elucidating the cause of surgical bleeding and should be done simultaneously with resuscitative efforts.
- Physical examination often provides an index of the severity and the extent of the disease and may provide additional clues that assist in distinguishing localized surgical bleeding from systemic bleeding resulting from a coagulopathy.
- The establishment of a definitive diagnosis of a coagulation disorder rests on selective use of a limited battery of laboratory tests guided by information derived from the history and physical examination.
- To expeditiously manage a critically ill patient experiencing life-threatening hemorrhage, it is crucial that a defined approach for prompt recognition of the underlying cause is used. First and foremost, attention is directed toward stabilizing the patient.
- The therapeutic approach to hemostatic abnormalities must be reasonably guided by the patient’s clinical condition and the outcome of appropriately selected laboratory tests. It is important not to fall behind in factor replacement.
- In parallel with the ongoing resuscitation of the bleeding patient, attention must be directed toward expeditiously determining the need for surgical re-exploration.

References


