Instructions

1. Review the stated learning objectives at the beginning of the CME article and determine if these objectives match your individual learning needs.
2. Read the article carefully. Do not neglect the tables and other illustrative materials, as they have been selected to enhance your knowledge and understanding.
3. The following quiz questions have been designed to provide a useful link between the CME article in the issue and your everyday practice. Read each question, choose the correct answer, and record your answer on the CME Registration Form at the end of the quiz.
4. Type or print your full name and address and your date of birth in the space provided on the CME Registration Form.
5. Indicate the total time spent on the activity (reading article and completing quiz). Forms and quizzes cannot be processed if this section is incomplete. All participants are required by the accreditation agency to attest to the time spent completing the activity.

6. Complete the Evaluation portion of the CME Registration Form. Forms and quizzes cannot be processed if the Evaluation portion is incomplete. The Evaluation portion of the CME Registration Form will be separated from the quiz upon receipt at ORTHOPEDICS. Your evaluation of this activity will in no way affect the scoring of your quiz.

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educational objectives

As a result of reading this article, physicians should be able to:

1. Possess a basic understanding of commonly encountered disorders of primary and secondary hemostasis.
2. Identify the clinical presentation of patients with bleeding disorders.
3. Understand the importance of the diagnoses, treatments, and potential complications associated with commonly encountered bleeding disorders in orthopedic surgery.
4. Understand the preoperative management of antiplatelet and anticoagulant therapeutic agents.

ABSTRACT
With increasing recognition of the complications related to coagulopathies, it is of paramount importance for all orthopedic surgeons to possess a basic knowledge of common bleeding disorders. The evaluation of the coagulopathic patient requires a careful history, physical examination, and laboratory evaluation. Bleeding disorders commonly include quantitative and qualitative platelet and coagulation factor disorders and coagulation inhibitors. The management of these coagulopathies that can be encountered in elective and non-elective practice is often ignored. With appropriate knowledge and a multidisciplinary approach with hematologists and cardiologists, surgeons can perform minor and major orthopedic procedures safely and effectively.

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Bleeding Disorders in Orthopedic Surgery

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Thrombotic and bleeding complications occur in 5.8% and 5.4%, respectively, of patients undergoing orthopedic surgery of the hip, knee, and spine. The management of acquired deep venous thrombosis and pulmonary embolism in orthopedic surgery is a controversial issue. However, the management of other coagulopathies (bleeding events) that one may encounter in elective and non-elective practice is often ignored. Orthopedic surgery in patients with these coagulopathies achieves pain relief, corrects contractures and angular deformities, and controls recurrent bleeds into the joint, thus contributing significantly to the functional ability of the patients. However, they are not without significant economic costs. With the increasing incidence of complications related to bleeding disorders, it is critical for orthopedic surgeons to possess a basic understanding of their diagnoses, treatments, and potential postoperative complications.

Bleeding disorders are characterized by defects in primary and secondary hemostasis. Primary hemostasis involves the adherence of platelets to the injured blood vessel via the von Willebrand factor anchor, creating a platelet plug. Secondary hemostasis is the fibrin clot formation process by way of tissue factor triggering the coagulation cascade. The initial platelet plug is strengthened by the fibrin clot, which serves as a matrix for fibroblasts as they migrate to repair the damaged vessel.

**APPRAOCH TO THE PATIENT**

The clinical evaluation of a patient with a bleeding disorder begins with a thorough history assessment and can usually establish whether the disorder is inherited or acquired. Although an important part of the preoperative evaluation, the bleeding history can have false-negative results and should serve only as a screening guide to the selection of lab tests. An inherited bleeding disorder is commonly associated with the onset of bleeding symptoms in infancy or childhood and a positive family history. Given the variability in patients’ perceptions of bleeding, as well as their documentation in medical records, a comprehensive dialogue must ensue between the patient and the physician.

Patients with a suspected bleeding disorder should also be questioned about past bleeding problems (eg, epistaxis, oral injuries, dental extractions, menorrhagia, or parturition), a history of medical conditions affecting hemostasis (eg, uremia, hepatic cirrhosis, cancer, or collagen vascular disorders), previous operations and the occurrence of prolonged bleeding or unusual postoperative bruising, history of transfusions, family history of bleeding disorders, and dietary habits or antibiotic use that might predispose to vitamin K deficiency. Disclosure of medication use is also important, including prescribed medications, over-the-counter medications, and herbal products.

The physical examination may also yield clues to the origin of the bleeding. A mucocutaneous bleeding pattern is the hallmark of primary hemostasis. Unexplained or extensive bruising, epistaxis, oral cavity bleeding, easy bruising, and menorrhagia are characteristic. Because the initial platelet plug has not yet formed, persistent bleeding occurs. Large-vessel bleeding associated with factor deficiencies as characterized by bleeding into muscles and joints is the result of secondary hemostasis. Delayed bleeding occurs because the platelet plug gradually succumbs to the pressures of blood flow without reinforcement of fibrin strands to strengthen the hemostatic plug.

Preoperative laboratory screening for coagulation disorders is only necessary when the history and physical examination are suggestive of a bleeding disorder or the patient is undergoing a moderate-to-high-risk procedure, such as elective orthopedic surgery. In these situations, a complete blood count with the platelet count, prothrombin time (PT), and activated partial thromboplastin time (aPTT) are the screening assays warranted. The aPTT evaluates the ability of coagulation factors II, V, VIII, IX, X, and XI, whereas the PT assesses the ability of factors II, V, VII, and X to form a fibrin clot. Although once part of the initial evaluation, the bleeding time test has recently been omitted due to its non-specificity in the general clinical setting.

**DISORDERS OF PRIMARY HEMOSTASIS**

The disorders of primary hemostasis comprise quantitative and qualitative abnormalities of platelets or the vascular endothelium. Dysfunction of platelet adherence occurs in von Willebrand disease and Bernard-Soulier syndrome. Platelet activation can be limited secondary to drugs, such as aspirin, clopidogrel, nonsteroidal anti-inflammatory drugs (NSAIDs), and certain herbals, or in uremia caused by kidney failure.

Primary immune thrombocytopenia, formerly known as idiopathic immune thrombocytopenia, is an acquired disease of isolated thrombocytopenia, defined as a peripheral blood platelet count less than 100,000 cells/µL with no clear initiating or underlying cause of the low platelet count. The pathogenesis is now thought to be due to autoantibodies that lead to premature destruction of platelets mediated by impaired platelet production and T-cell-mediated effects. In addition to increased platelet destruction, decreased platelet production by megakaryocytes in the bone marrow has recently been proven. According to international consensus, treatment is rarely indicated in patients with platelet counts greater than 50,000 cells/µL in the absence of bleeding due to platelet dysfunction or other hemostatic defect, trauma, or surgery. However, for patients undergoing major surgery, platelet counts should remain greater than 80,000 cells/µL.

The treatment of idiopathic immune thrombocytopenia has focused on preventing platelet destruction by using corticosteroids in 1 of 2 ways: prednisone (1 to 2 mg/kg per day until a response is seen) or pulse dexamethasone (40 mg per day for...
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4 days) as first-line therapy. For patients with low platelet counts and the presence of bleeding, immunoglobulins such as intravenous immune globulin (0.5 to 2.0 g/kg over 2 to 5 days) and Anti-Rho(D) (50 to 75 µg/kg intravenously over 2 to 5 minutes) have been proposed; however, much of the morbidity and mortality is associated with the side effects rather than the bleeding. Second-line therapy includes immunosuppressive agents and splenectomy.

Although all other treatments act by decreasing platelet destruction, the recently approved thrombopoietin receptor agonists increase platelet production. However, they are not without side effects, such as rebound thrombocytopenia, bone marrow fibrosis, thrombosis, hepatotoxicity and even progression of hematologic malignancies.17

Von Willebrand Disease

With a prevalence of 1% to 3% in the general population, von Willebrand disease (vWD) is the most common inherited bleeding disorder.18 Most cases are transmitted as an autosomal dominant trait affecting men and women equally.18 Clinically, patients may experience mild to moderate bleeding evidenced by nose bleeds, heavy menstrual flow, gingival bleeding, easy bruising, and bleeding associated with surgery or trauma. Von Willebrand disease is classified based on severity: type I is the mildest form and presents as atraumatic bruising or frequent bleeding from the gums or nostrils; type II presents with increasing severity of these symptoms; and type III is the most severe and presents similarly to severe hemophilia with recurrent hemarthroses.

Because the pathophysiology of vWD is similar to that of hemophilia, joint bleeding is treated in the same manner. Von Willebrand factor (vWF) plays a vital role in primary hemostasis by enabling platelets to adhere to the sites of vascular injury and then form platelet aggregates.19 It also contributes to fibrin clot formation by acting as a carrier protein by binding to and stabilizing factor VIII, which has a greatly shortened half-life and an abnormally low concentration unless it is bound to vWF.20 Secondary hemostatic dysfunction can occur due to low factor VIII levels in vWD and is important to understand for treatment purposes. Initial laboratory screenings show an elevated bleeding time, and diagnosis is confirmed with vWF antigen level (Ag) (vWF:Ag<30 IU/dL), vWF ristocetin cofactor activity level (RCO) (vWF:RCO<30 IU/dL), and factor VIII (normal or decreased).

Of note, despite the comparatively high prevalence of vWD, studies have not shown value in preoperative screening. A study of patients undergoing surgery found that, although the prevalence of vWD was 0.6%, most could be predicted from clinical evaluation, and those who were not had no difference in severe bleeding risk.21 Desmopressin releases stored vWF from the endothelium and is the first line of therapy. For patients with mild bleeding or undergoing minor surgery, intravenous desmopressin can be administered as 0.3 µg/kg infused slowly over 15 to 30 minutes at 12-hour intervals to achieve vWF:RCO of at least 30 IU/dL. Two to 4 repeat doses may be required, but tachyphylaxis may occur.22-24

For major surgical procedures, the vWF:RCO and factor VIII should increase above 80 IU/dL and maintain more than 50 IU/dL until hemostasis is confirmed. Factor VIII should also remain more than 50 IU/dL until wound healing is achieved.25 It is strongly recommended that patients with major bleeding or undergoing major surgery be hospitalized at a facility with expertise in managing vWD and laboratory monitoring of vWF levels.

Bernard-Soulier Disease

Bernard-Soulier Disease (BSD) is a qualitative defect of platelet binding to collagen, as demonstrated by the absent aggregation on exposure to ristocetin.23 These platelets’ defect is in the platelet membrane glycoprotein GPIb-IX-V complex, resulting in the inability to adhere to

### Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Aspirin</th>
<th>NSAIDs</th>
<th>ADP Receptor Antagonists</th>
<th>GP IIb-IIIa Receptor Antagonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Action</td>
<td>Inhibits platelet function via irreversible acetylation of platelet COX-1, indirectly inhibits TXA2 synthesis</td>
<td>Inhibits platelet function via reversible acetylation of platelet COX-1, indirectly inhibits TXA2 synthesis</td>
<td>Inhibits platelet activation</td>
<td>Inhibits platelet aggregation</td>
</tr>
<tr>
<td>Cessation</td>
<td>7-10 d</td>
<td>24-48 h</td>
<td>7-10 d (clopidogrel, prasugrel); 14 d (ticlopidine)</td>
<td>24-48 h (abciximab); 10 h (eptifibatide); 2-4 h (tiropiban)</td>
</tr>
</tbody>
</table>

Abbreviations: ADP, adenosine diphosphate; COX-1, cyclooxygenase-1; GP, glycoproteins; NSAIDs, nonsteroidal anti-inflammatory drugs; TXA2, thromboxane A2.
vWF. However, this complex site is not associated with a platelet-specific antigen site; therefore, repeated transfusion with platelet concentrate will not result in the acquisition of specific antibodies. First-line treatment for any platelet disorder in a patient undergoing major surgery consists of either 8 U of platelet concentrate or 90 µg/kg intravenously of recombinant activated factor VII (rFVIIa) followed by 2 or more injections every 2 hours as needed.

**THERAPEUTIC ANTIPLATELET AGENTS**

The most common clinical circumstances leading to disordered platelet function include a desired therapeutic effect or an adverse medication effect. With the expanding use of anticoagulants and platelet inhibitor drugs, a substantial amount of the population is at risk for abnormal bleeding (Table 1).

### Aspirin and Nonsteroidal Anti-inflammatory Drugs

Aspirin is the most common and most extensively studied of the antiplatelet drugs due to its role in prevention of thrombotic cardiovascular events. Aspirin inhibits platelet function via irreversible acetylation of platelet cyclooxygenase-1 (COX-1) and the resulting inhibition of thromboxane A2 (TXA2) synthesis. A 5% to 10% incidence of minor bleeding and a 1% to 2% incidence of major bleeding exist following aspirin ingestion. An associated increased rate of bleeding at gastrointestinal and other sites is observed with the combined use of aspirin and clopidogrel or of aspirin and warfarin. The effects of aspirin on platelets remain for the lifespan of the platelet, which is 8 to 10 days. Therefore, patients taking aspirin alone are advised to stop the medicine 7 to 10 days preoperatively to allow for reversal of the effect. In contrast to aspirin, NSAIDs reversibly inhibit COX-1, generally to a lesser degree than aspirin, and platelet function is restored within 24 to 48 hours after discontinuation of the drug.

### Antagonize Adenosine Diphosphote Receptor Antagonists

Clopidogrel, ticlodipine, and prasugrel are thienopyridines that selectively and irreversibly antagonize adenosine diphosphate (ADP) stimulation. Platelets subjected to clopidogrel are normally affected for 5 to 7 days, but recent studies have shown no serious complications or increased transfusion requirements in patients undergoing nonelective orthopedic surgery who are taking clopidogrel. However, to reverse the anticoagulant effects, clopidogrel and prasugrel should be discontinued 7 to 10 days preoperatively. Ticlodipine is longer acting and requires 14 days.

### Glycoprotein Iib-IIIa Receptor Antagonists

The final common pathway of platelet aggregation leading to coronary thrombosis involves cross-linking of platelet receptor glycoprotein (GP) Iib-IIIa by adhesive plasma proteins, primarily fibrinogen. Abciximab, eptifibatide, and tirofiban block this final common pathway and are considered the most powerful platelet inhibitors. Time to normal platelet aggregation is 24 to 48 hours after administration of abciximab, and eptifibatide and tirofiban require 4 to 8 hours. Eptifibatide and tirofiban interrupted 10 hours preoperatively should not allow for restoration of platelet function. According to a recent study evaluating the use of tirofiban in patients undergoing urgent or emergent coronary artery bypass grafting, no delay in treatment is necessary; the authors concluded that discontinuation of the GP IIb-IIIa inhibitor within 2 to 4 hours of elective surgery appears sufficient to ensure a safe surgical procedure.

### Herbal Preparations

Important herbal preparations that can interfere with blood clotting include garlic, ginkgo biloba, and ginseng. All of these agents affect platelet function. Therefore, garlic and ginseng should be stopped at least 7 days preoperatively, whereas ginkgo biloba should be stopped 36 hours preoperatively. Other medications affecting normal clotting function include feverfew, ginger, kava kava, clove, and white willow bark and should be discontinued 2 weeks preoperatively. Other supplements that pose a concern are fish oil and vitamins A and E. These dietary supplements may perturb the effects of anticoagulants and antiplatelets (Table 2).

### Table 2

**Herbal Medications**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Garlic</th>
<th>Ginger</th>
<th>Ginseng</th>
<th>Ginkgo Biloba</th>
<th>Kava Kava</th>
<th>Fish Oil</th>
<th>Vitamin E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Action</td>
<td>Dose-dependent irreversible inhibition of platelet aggregation</td>
<td>Prolonged bleeding time</td>
<td>Inhibits in vitro platelet aggregation and prolongs coagulation times</td>
<td>May inhibit platelet-activating factor and alter platelet function</td>
<td>Platelet dysfunction; hepatotoxicity</td>
<td>Increased bleeding risk at high doses</td>
<td>Antioxidant; may increase effects of anticoagulants and antiplatelets</td>
</tr>
<tr>
<td>Cessation preoperatively</td>
<td>7 d</td>
<td>2 wk</td>
<td>7 d</td>
<td>36 h</td>
<td>2 wk</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
DISORDERS OF SECONDARY HEMOSTASIS

Deficiencies of coagulation factors either inherited or acquired characterize the disorders of secondary hemostasis. These include inherited thrombophilias, liver disease, vitamin K deficiency, and antibodies. Medications such as warfarin, heparin, low-molecular-weight heparin, and direct thrombin inhibitors also interfere with secondary hemostasis.

The Hemophilias

Factor VIII (hemophilia A) and factor IX (hemophilia B) deficiency are X-linked recessive disorders with clinical manifestations seen exclusively in men. These X-linked disorders represent the majority of inherited deficiencies of clotting factors, occurring in approximately 1 per 5000 and 1 per 50,000 male births, respectively, with no racial predilection.41-43 The hemophilias are classified by the baseline level of percentage of clotting factor activity as mild (more than 5%), moderate (1%-5%), or severe (less than 1%). This classification directly reflects the severity of clinical symptoms. The bleeding diathesis of the mild form may only present during surgeries, dental extractions, and injuries, whereas spontaneous joint and muscle bleeds are largely confined to patients with severe hemophilia. The knee, ankle, and elbow account for approximately 80% of the involved joints.44 Although a consensus has not been reached on the exact mechanism of blood-induced joint damage, it has been postulated that hemosiderin deposition in the joint cavity leads to a visco-pathological cycle of synovial inflammation and cartilage degeneration, ultimately resulting in the destruction of cartilage and bone. With recurrent hemarthroses, iron deposits elucidate synovial hypertrophy characterized by villous sinuses, neovascularization, and infiltration of lymphocytes.45 A multifactorial process then ensues, occurring in parallel and sequentially leading to chronic arthropathy and arthrofibrosis.

Replacement of the deficient factor is the mainstay of treatment for bleeding episodes, according to the type and severity of bleeds and until complete resolution of bleeding or surgical wound healing.46 Although resolution of bleeding is accomplished, progressive joint destruction is undeterred. Once thought to be the hallmark of hemophilia, recent data on the use of prophylactic clotting factor replacement has been shown to slow the natural course of hemophilic arthropathy.

In a recent prospective, randomized study, continuous prophylactic clotting factor replacement of 25 to 40 units/kg of factor VIII 3 times weekly or factor IX 2 to 3 times weekly in patients with hemophilia A and B, respectively, was shown to slow the natural course of hemophilic arthropathy.47,48 Significant reductions in severity and frequency of spontaneous bleeds and arthropathy, hospitalizations, missed school or work days lost, and overall higher levels of quality of life have led to the consensus of prophylaxis.46

Primary prophylaxis is defined as the infusion of concentrates started after the first joint bleed or before age 2 years and is now the first line of treatment in children with severe hemophilia.49 Secondary prophylaxis aims to delay the progression of joint damage and occurs after age 2 years or after 2 or more joint bleeds.49 Before undergoing elective surgery, the patient’s clotting factor level is brought to 100% of normal activity and confirmed by factor assay. A continuous infusion of factor to maintain more than 60% is continued intraoperatively and maintained until discharge from the hospital. A level of 30% to 60% is recommended for at least 2 weeks postoperatively.50

If prophylaxis is not a possibility, due in part to high costs or intravenous access, the prevention of hemophilic arthropathy begins with the successful management of joint bleeds. Arthrocentesis, regular replacement of factor concentrate to 50% every 48 hours, splinting of the involved joint for 48 hours, physical therapy to maintain adequate range of motion, and strengthening exercises are all first-line treatment options to prevent the progression of chronic synovitis.51 Radiosynovectomy remains the preferred initial treatment option for chronic hemophilic synovitis, with success rates of approximately 80%. However, skin burns have been reported if the material is injected outside the joint,51 and 2 case reports exist of acute lymphoblastic leukemia.52,53 After 3 unsuccessful attempts to prevent progression, an arthroscopic synovectomy is indicated.

During the second and fourth decades, progression to advanced arthropathy is commonly encountered. Possible treatment options include realignment osteotomies, joint fusion, and joint arthroplasty. With repeated episodes of hemarthroses, leg-length discrepancies and angular deformities may occur during childhood as a result of the increased vascularity leading to asymmetrical hypertrophy of the epiphyseal growth plates.45 Realignment osteotomies provide a solution to the varus or valgus strain imparted on the knee joint and thus prevent the progression of joint destruction. Arthrodesis has proven to be a reliable procedure in the shoulder, hip, and ankle; however, it is contraindicated in the knee joint. Because of the systemic pathology of hemophilia, it is common for patients to present with involvement of the hip or ankle. A double fusion leads to significant problems with ambulating and activities of daily living. Total knee arthroplasty has been proven to restore function and relief of pain but can be technically challenging due to arthrofibrosis, joint surface erosions, and bony synovial cysts. Current recommendations are for a posterior-stabilized cemented design.51 Total hip arthroplasty with a press-fit uncemented design remains an option; however, a high rate of loosening of the acetabular and femoral components has been reported in the literature.51,54

To ensure a prompt recovery from orthopedic surgery, rehabilitation is of vital importance. A strong focus on increasing range of motion and muscle strengthening around the joint should be the main goal of each session.
Intramuscular bleeds occur less frequently than joint bleeding in hemophiliacs but can be associated with complications such as infection, compartment syndrome, and pseudotumors. An iliopsoas hematoma is a common and serious complication of muscular bleeds that can imitate an acute appendicitis. Hemophilic pseudotumors consist of a hematoma encased in a fibrous calcific capsule that will invade and destroy the surrounding soft tissue, bone, and neurovascular structures. With a mortality rate of approximately 20%, surgical removal should only be performed in specialized hemophilic treatment centers.

Acquired Inhibitors of Anticoagulation

The most common and serious complication of replacement therapy in patients with hemophilia is the development of an inhibitor against factor VIII or factor IX. This acquired autoantibody inactivates the specific factor concentrate, resulting in complete preclusion of therapy. Approximately 30% of patients with hemophilia A and 5% of patients with hemophilia B generate antibodies during the first 20 to 50 days of exposure. Inhibitor detection is quantified using Bethesda units (BU), where 1 unit is associated with the inactivation of 50% of factor concentrate. Because high-dose replacement therapy for major surgical procedures is generally only appropriate for the treatment of patients with titer at or below 1 to 2 BU/mL, these patients have been denied all but essential surgery due to the fear of inadequacy with obtaining and maintaining hemostasis. Furthermore, an anamnestic rise in inhibitor titer associated with high-dose replacement therapy in as little as 1 to 2 days has been reported in the literature. Recent studies have shown greater morbidity and mortality and poorer quality of life in regard to orthopedic status partially due to the increased lifespan of inhibitor patients with the accompanying degenerative, age-associated orthopedic conditions.

With the introduction of bypassing agents, rFVIIa, and activated prothrombin complex concentrates, major elective orthopedic surgery in hemophilia patients with inhibitors has now become a reality. Preoperatively, a bolus dose of 90 µg/kg rFVIIa should be given every 2 hours for at least 48 hours and may be increased based on response, whereas activated prothrombin complex concentrates should be administered at 50 to 75 units/kg per hour and every 6 to 8 hours thereafter, not to exceed 200 units/kg per day. These bypassing agents are recommended to be given at least 10 to 14 days postoperatively, with prophylactic consideration during the patient’s rehabilitative course.

Rehabilitation management of hemophilia patients with or without inhibitors follows a near equivocal path, with a few specific and important details. Careful monitoring and daily assessment by the physical therapist with a gradual progression of activity is crucial in preventing postoperative bleeding into the affected joint or other sites. Any associated limitation in active range of motion accompanied with increased swelling or pain should warrant a short period of rest, elevation, and ice, with resumption of activity at a lower level at allow adequate healing. Other common causes of acquired inhibitors include the use of fibrin sealants during surgical procedures, antiphospholipid antibodies, antibiotics, pregnancy, and lymphoid malignancies.

Since the mid-1980s, topical hemostatic agents, such as topical thrombin, have been commonly used to control surgical bleeding by promoting the formation of a stable fibrin clot. First reported in 1989, bovine thrombin has been associated with considerable safety concerns regarding the development of autoimmune iatrogenic coagulopathies. This acquired coagulopathy results from the formation of antibodies directed against bovine thrombin and coagulation factors, mainly factor V. The diagnosis should always be suspected in postoperative patients who present with simultaneously abnormal PT and aPTT, particularly if these parameters do not correct with the administration of vitamin K or fresh-frozen plasma. Failure to correct with a plasma mixing study suggests the diagnosis of an inhibitor present.

With the recent availability of human thrombin products, the incidence of bleeding related to the use of bovine thrombin is expected to decline. A recent phase 3, randomized, double-blind comparative study of recombinant thrombin vs bovine-derived thrombin demonstrated human thrombin-based products possess equivalent efficacy and safety, with an improved immunogenicity profile. Forty-three (21.5%) patients exposed to the bovine-derived thrombin product developed antithrombin thrombin antibodies, compared with 3 (1.5%) patients exposed to recombinant human thrombin who developed antithrombin thrombin antibodies.

Liver Disease

With the exceptions vWF and tissue plasminogen activator, the liver is the production site for almost all of the coagulation factors. The PT is a sensitive indicator of hepatic synthetic function due to the short half-life (6 hours) of factor VII, which the failing liver cannot maintain. Both the PT and aPTT tests are prolonged with more severe hepatic synthetic dysfunction. Ten to 15 mL/kg of fresh-frozen plasma intermittently replaces all coagulation factors but is short lived and may predispose the patient to volume overload. Desmopressin (0.3 µg/kg) may help by improving platelet function, and vitamin K administration (1 to 25 mg) excludes concurrent vitamin K deficiency.

Vitamin K Deficiency

Clotting factors II, VII, IX, and X, as well as proteins C and S, require vitamin K–dependent gamma carboxylation for full activity. Dietary forms are obtained primarily from the intake of dark green vegetables and modified by gut flora to the active form. Interruption of bile flow will prevent absorption. Antibiotic-related
elimination of enteric bacteria limits intestinal sources of vitamin K, whereas warfarin directly antagonizes its activity. Prothrombin time is first to prolong, but the aPTT will also increase with further factor deficiencies. In adults with normal hepatic function, oral or subcutaneous vitamin K usually corrects within 24 hours; however, if a patient is already receiving warfarin, doses of vitamin K should be minimized to prevent refractoriness to further anticoagulation.

**PARENTERAL ANTICOAGULANTS**

Knowledge of the risks associated with particular drugs and combinations of them, their advantages, and the complications associated with the interruption of drug use for interventional procedures are essential for the orthopedic surgeon to reduce the incidence of iatrogenic bleeding (Table 3).

**Factor Xa Inhibitors**

Factor Xa inhibitors block factor Xa either directly or indirectly. Fondaparinux inhibits thrombin formation indirectly by selectively binding to antithrombin III, thus neutralizing factor Xa. Rivaroxaban and apixaban act via direct inhibition and bind directly to the active binding site of factor Xa blocking the interaction with substrates. No clinical trials have evaluated the length of time required for preoperative discontinuation; however, based on time of elimination from the body, they should be stopped at least 2 days preoperatively for patients without a high risk of bleeding and 4 days preoperatively in patients with a high risk of bleeding. If truly warranted, recombinant factor VIIa can partially reverse the anticoagulant effects of these inhibitors.

**Heparin**

Unfractionated heparin (UFH) indirectly inactivates thrombin and factors VIIa, IXa, Xa, and Xla. The anticoagulant response to UFH is most frequently monitored through the aPTT. The last preoperative dose of UFH should be no later than 6 hours preoperatively. If urgent reversal of the effect of UFH is required, slow intravenous protamine sulfate infusion will normalize the aPTT. The neutralization effect is achieved with a dose of 1 mg protamine sulfate per 100 units of heparin. Protamine administration may also lead to allergic reactions and anaphylaxis.

Heparin-induced thrombocytopenia may result from the administration of UFH from the induction of heparin-platelet antibodies. A 5% incidence of heparin-induced thrombocytopenia has been demonstrated in the literature for orthopedic surgery patients who received UFH for more than 2 weeks. A 50% decrease in the baseline platelet count or thrombocytopenia less than 100,000 µL constitutes the diagnosis of heparin-induced thrombocytopenia. Although several antibody detection tests have been proposed, the diagnosis is made clinically. Immediate cessation of heparin with the addition of danaparoid or lepirudin is recommended as parenteral therapy when beginning warfarin.

**Low-molecular-weight Heparin**

Low-molecular-weight heparin, such as enoxaparin, inactivates factor Xa but has a lesser effect on thrombin and does not prolong the aPTT. If monitoring is required, antifactor Xa assays can be used. These should be stopped at least 12 to 24 hours preoperatively. Unlike its efficacy with UFH, protamine does not completely eradicate the anti-Xa activity of low-molecular-weight heparin. However, for patients who experience bleeding while receiving low-molecular-weight heparin, protamine sulfate (1 mg/100 anti-Xa units of low-molecular-weight heparin) may reduce clinical bleeding.

**Warfarin**

Warfarin’s effects are mediated through inhibition of the vitamin K–dependent gamma-carboxylation of procoagulant factors II, VII, IX, X and anticoagulant proteins C and S. The major clinical effect is through the suppression of thrombin generation from the nonfunctional prothrombin and factor X. Normal monitoring takes place by following the

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**Table 3**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Factor Xa Inhibitors</th>
<th>Unfractionated Heparin</th>
<th>LMWH</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Action</td>
<td>Directly inhibits (rivaroxaban, apixaban); indirectly inhibits via binding to antithrombin III (fondaparinux)</td>
<td>Binds antithrombin III; indirectly inhibits thrombin and factors VIIa, IXa, Xa, and Xla</td>
<td>Inactivates factor Xa; less effect on thrombin</td>
<td>Inhibits vitamin K–dependent γ-carboxylation of procoagulant factors II, VII, IX, X and anticoagulant proteins C and S</td>
</tr>
<tr>
<td>Cessation preoperatively</td>
<td>2-4 d&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6 h</td>
<td>12 h</td>
<td>Approximately 5 d to achieve target INR of 1.5</td>
</tr>
</tbody>
</table>

<sup>a</sup>Anticoagulant effect can persist for 2 to 4 days, depending on renal and hepatic function.

Abbreviations: INR, international normalized ratio; LMWH, low-molecular-weight heparin.
PT/international normalized ratio level. For fully elective surgery in patients with an international normalized ratio of 2 to 3, simple cessation of warfarin for approximately 5 days is enough time to allow the international normalized ratio to drop to 1.5 or less. Once surgical hemostasis has been achieved, warfarin therapy may be resumed 12 to 24 hours postoperatively. If more rapid reversal is required over 1 to 2 days, warfarin should be stopped and 1.0 to 2.0 mg of intravenous vitamin K should be administered.

For significant or life-threatening bleeding requiring emergent surgery, rapid reversal of anticoagulation should consist of stopping warfarin and beginning low-dose intravenous or oral vitamin K (2.5 to 5.0 mg) over slow intravenous infusion. For immediate reversal, 50 units/kg of activated prothrombin complex concentrates or fresh-frozen plasma in addition to vitamin K can be used. Activated prothrombin complex concentrate is a combination of factors II, VII, IX, X and proteins C and S and is preferred to fresh-frozen plasma because it has been shown to contain insufficient concentrations of the vitamin K factors. An alternate result can be achieved with factor VIIa.

**Conclusion**

Despite all of the advances made to decrease perioperative complications, blood loss continues to be a major problem. With increasing recognition of complications related to coagulopathies, it is of paramount importance for every orthopedic surgeon to possess a basic knowledge of the diagnoses, treatment, and potential postoperative complications of common bleeding disorders. Evaluation of the coagulopathic patient requires a careful history, physical examination, and laboratory screening. Commonly encountered bleeding disorders are both inherited and acquired.

The management of other bleeding events that one may encounter in both elective and nonelective practice is often ignored. With appropriate knowledge and a multidisciplinary approach with hematologists and cardiologists, patients can undergo minor and major orthopedic procedures safely and effectively.

**References**


28. Delaney JA, Optarmy L, Brophy JM, Suisa S. Drug drug interactions between antithrom-


