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Bleeding and Clotting Disorders

Lauren L. Patton, DDS

Dental health care workers are increasingly called upon to provide quality dental care to individuals whose bleeding and clotting mechanisms have been altered by inherited or acquired diseases. This provides an opportunity for the dentist who is trained in the recognition of oral and systemic signs of altered hemostasis to assist in the diagnosis of the underlying condition. A number of dental procedures result in the risk of bleeding that can have serious consequences, such as severe hemorrhage or possibly death, for the patient with a bleeding disorder. Safe dental care may require consultation with the patient's physician, systemic management, and dental treatment modifications.

Of the inherited coagulopathies, von Willebrand's disease (vWD) is the most common. It results from deficiency of von Willebrand's factor (vWF) and affects about 0.8 to 1% of the population.[1] Hemophilia A, caused by coagulation factor (F) VIII deficiency, is the next most common, followed by hemophilia B, a F IX deficiency. The age-adjusted prevalence of hemophilia in six surveillance states in 1994 was 13.4 cases in 100,000 males (10.5 for hemophilia A and 2.9 for hemophilia B).[2] Application to the US population resulted in an estimated national prevalence of 13,320 cases of hemophilia A and 3,640 cases of hemophilia B, with an incidence rate of 1 per 5,032 live male births. Hemophilia A was predominant, accounting for 79% of all hemophiliacs, and prevalence of disease severity was 43% severe (< 1% F VIII), 26% moderate (1–5% F VIII), and 31% with mild (6–30% F VIII) disease.[2]

Acquired coagulation disorders can result from drug actions or side effects, or underlying systemic disease. A stratified household sample of 4,163 community residents aged 65 years or older living in a five-county area of North Carolina revealed 51.7% to be taking one or more medications (aspirin, warfarin, dipyridamole, nonsteroidal anti-inflammatory drugs

[NSAIDs], or heparin) with the potential to alter hemostasis.[3] The use of coumarin anticoagulants is increasing as a result of their demonstrated effectiveness in the treatment of atrial fibrillation and venous thromboembolism, and control of thrombosis in the presence of a mechanical heart valve.[4]

▼ PATHOPHYSIOLOGY

Basic Mechanisms of Hemostasis and Their Interactions

Interaction of several basic mechanisms produces normal hemostasis. For clarity and understanding, these are presented separately. Hemostasis can be divided into four general phases: the vascular phase; the platelet phase; the coagulation cascade phase, consisting of intrinsic, extrinsic, and common pathways; and the fibrinolytic phase. The first three phases are the principal mechanisms that stop the loss of blood following vascular injury. Briefly, when vessel integrity is disrupted, platelets are activated, adhere to the site of injury, and form a platelet plug that reduces or temporarily arrests blood loss.[5] The exposure of collagen and activation of platelets also initiates the coagulation cascade, which leads to fibrin formation and the generation of an insoluble fibrin clot that strengthens the platelet plug.[5] Fibrinolysis is the major means of disposing of fibrin after its hemostatic function has been fulfilled, and it can be considered the rate-limiting step in clotting. It leads to fibrin degradation by the proteolytic enzyme plasmin. As seen in Figure 17-1, multiple processes occur either simultaneously or in rapid sequence, such that, following almost immediate vascular contraction, platelets begin to aggregate at the wound site. The coagulation cascade is underway within 10 to 20 seconds of injury, an initial hemostatic plug is formed in 1 to 3 minutes, and fibrin has been generated and added to stabilize the clot by 5 to 10 minutes.

Vascular Phase

After tissue injury, there is an immediate reflex vasoconstriction that may alone be hemostatic in small vessels. Reactants such as serotonin, histamine, prostaglandins, and other materials are vasoactive and produce vasoconstriction of the microvascular bed in the area of the injury.

Platelet Phase

When circulating platelets are exposed to damaged vascular surfaces (in the presence of functionally normal vWF, endothelial cells, collagen or collagen-like materials, basement membrane, elastin, microfibrils, and other cellular debris), platelets are activated to experience physical and chemical changes.[6] These changes produce an environment that causes the platelets to undergo the aggregation-and-release phenomenon and form the primary vascular plug that reduces blood loss from small blood vessels and capillaries. These platelet plugs adhere to exposed basement membranes. As this reaction is occurring, the release reaction is underway, involving the intracellular release of active components for further platelet aggregation as well as promotion of the clotting mechanism. Adenosine diphosphate (ADP) is a potent nucleotide that activates and recruits other platelets in the area, immensely adding to the size of the plug. Platelet factor 3 (PF3) is the intracellular phospholipid that activates F X and subsequently results in the conversion of prothrombin to thrombin. Additionally, the platelet plug, intermixed with fibrin and cellular components such as red and white cells, contracts to further reduce blood loss and to seal the vascular bed.

Coagulation Phase

The generation of thrombin and fibrin the end product of the third phase of hemostasis, the coagulation phase. This process involves multiple proteins, many of which are synthesized by the liver (fibrinogen, prothrombin, Fs V, VII, IX, X, XI, XII, and XIII) and are vitamin K dependent (Fs II, VII, IX, and X). The process of coagulation essentially involves three separate pathways. It initially proceeds by two separate pathways (intrinsic and extrinsic) that converge by activating a third (common) pathway.

The blood clotting mechanism is the most studied unit; it was outlined originally in 1903 by Markowitz as the prothrombin-to-thrombin and fibrinogen-to-fibrin conversion system. In 1964, the "cascade" or "waterfall" theory was proposed.[7,8] It offered a useful device for understanding this complex system and its control, as well as the clinically important associated laboratory tests.

Figure 17-2 depicts the sequence of interactions between the various clotting factors following injury of tissue. The scheme of reaction is a bioamplification, in which a precursor is altered to an active form, which, in turn, activates the next precursor in the sequence. Beginning with an undetectable biochemical reaction, the coagulation mechanism results in a final explosive change of a liquid to a gel. The major steps involve the conversion of a precursor protein to an "activated" form, which activates another precursor protein, and so on down the cascade. The coagulation of blood also requires the presence of both calcium ions and phospholipid (or a phospholipid-containing membrane fragment derived from blood platelets).

The intrinsic pathway is initiated when F XII is activated by surface contact (eg, with collagen or subendothelium), and it involves the interaction of F XII and F XI. The next step of intrinsic coagulation, the activation of F IX to F XIa, requires a divalent cation.[9] Once activated, F IXa forms a complex with F VIII, in a reaction that requires the presence of both calcium ions and phospholipid, which, in turn, converts F X to an activated form— F Xa.

The extrinsic pathway is initiated by the release of tissue thromboplastin, also called tissue factor, and does not require contact activation. Tissue thromboplastin binds to F VII in the presence of calcium, and this complex is capable of activating Fs IX and X, linking the intrinsic and extrinsic pathways.

It is the activation of X that begins the common pathway. Once activated, F Xa converts prothrombin to thrombin in a reaction similar to the activation of F X by F IXa. The

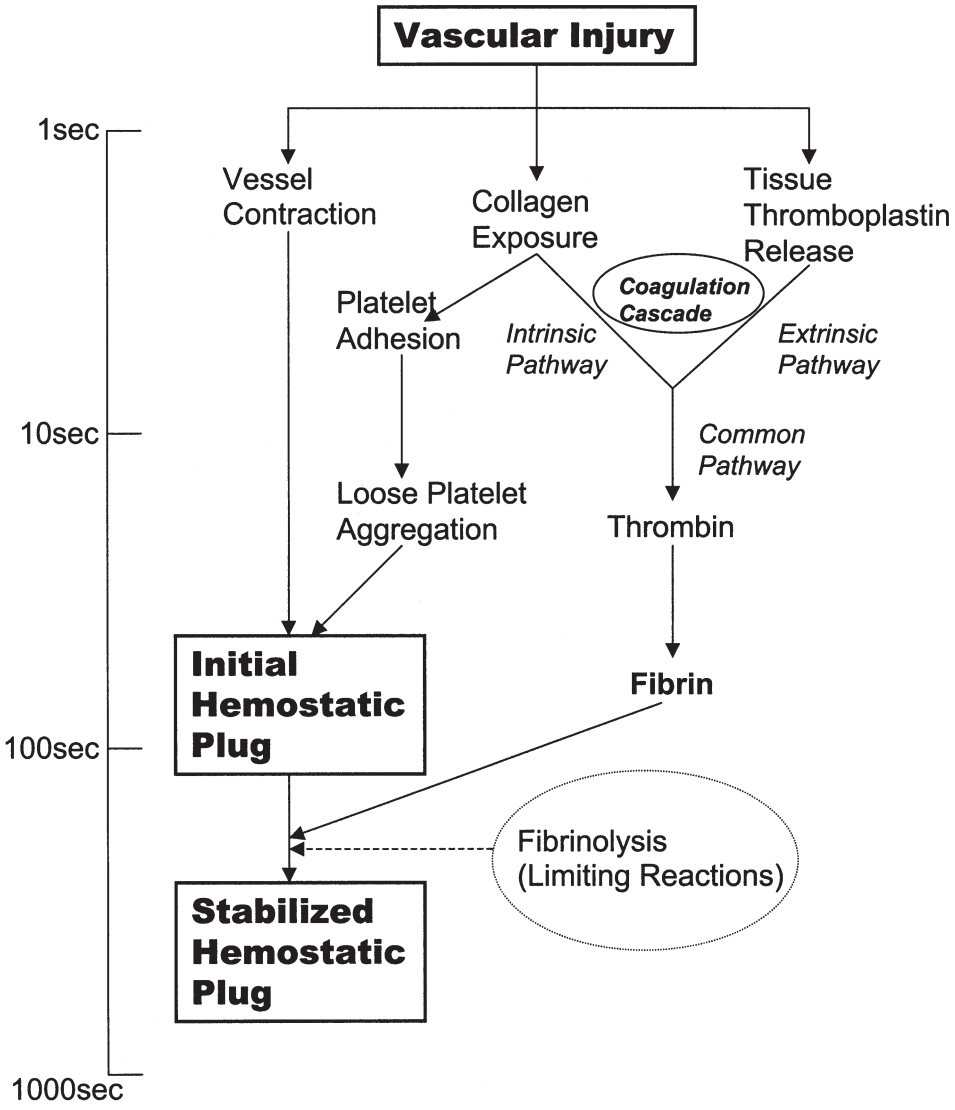


FIGURE 17-1 Mechanisms of hemostasis following vascular injury.

activation of prothrombin by F Xa requires the presence of calcium ions and phospholipid as well as F V, a plasma protein cofactor.[10] Once formed, thrombin converts fibrinogen, a soluble plasma protein, to insoluble fibrin. Fibrin polymerizes to form a gel, stabilizing the platelet plug. Finally, F XIII, which has been converted to an activated form by thrombin,[11] produces covalent cross-links between the fibrin molecules that strengthen the clot and make it more resistant to lysis by plasmin. Individuals deficient in this clotting factor experience poor wound healing.[12]

Fibrinolytic Phase

The fourth phase of hemostasis is fibrinolysis; this is considered the major means of disposing of fibrin after its hemostatic function has been fulfilled. Once the microvascular bed is sealed and primary hemostasis is complete, the secondary hemostasis pathway has already commenced in parallel. As the monomeric fibrin is cross-linked with the aid of F XIII (fibrin-stabilizing factor), the propagation of the formed clot is limited by several interactions.[12] One of these limiting systems is the fibrinolytic system (Figure 17-3). Kallikrein, which is an intrinsic activator of plasminogen, is generated when prekallikrein is bound to kininogen, thereby becoming a substrate for F XIIa. Tissue plasminogen activator (TPA) is released from the endothelial cells and converts plasminogen to plasmin that degrades fibrinogen and fibrin into fibrin degradation products (FDPs). TPA is a proteolytic enzyme that is nonspecific and also degrades Fs VIII and V. Regulation of this system is controlled tightly by plasminogen activator inhibitor that limits TPA, and by α_2-antiplasmin that restricts plasmin. TPA has been used with great success in therapeutic doses to lyse thrombi in individuals with thromboembolic disorders associated with myocardial infarction.[13] Effectiveness of this drug is limited to the first 6 hours post infarction.

Extended function of the fibrinolytic system is realized during wound healing. As the wound is revascularized and

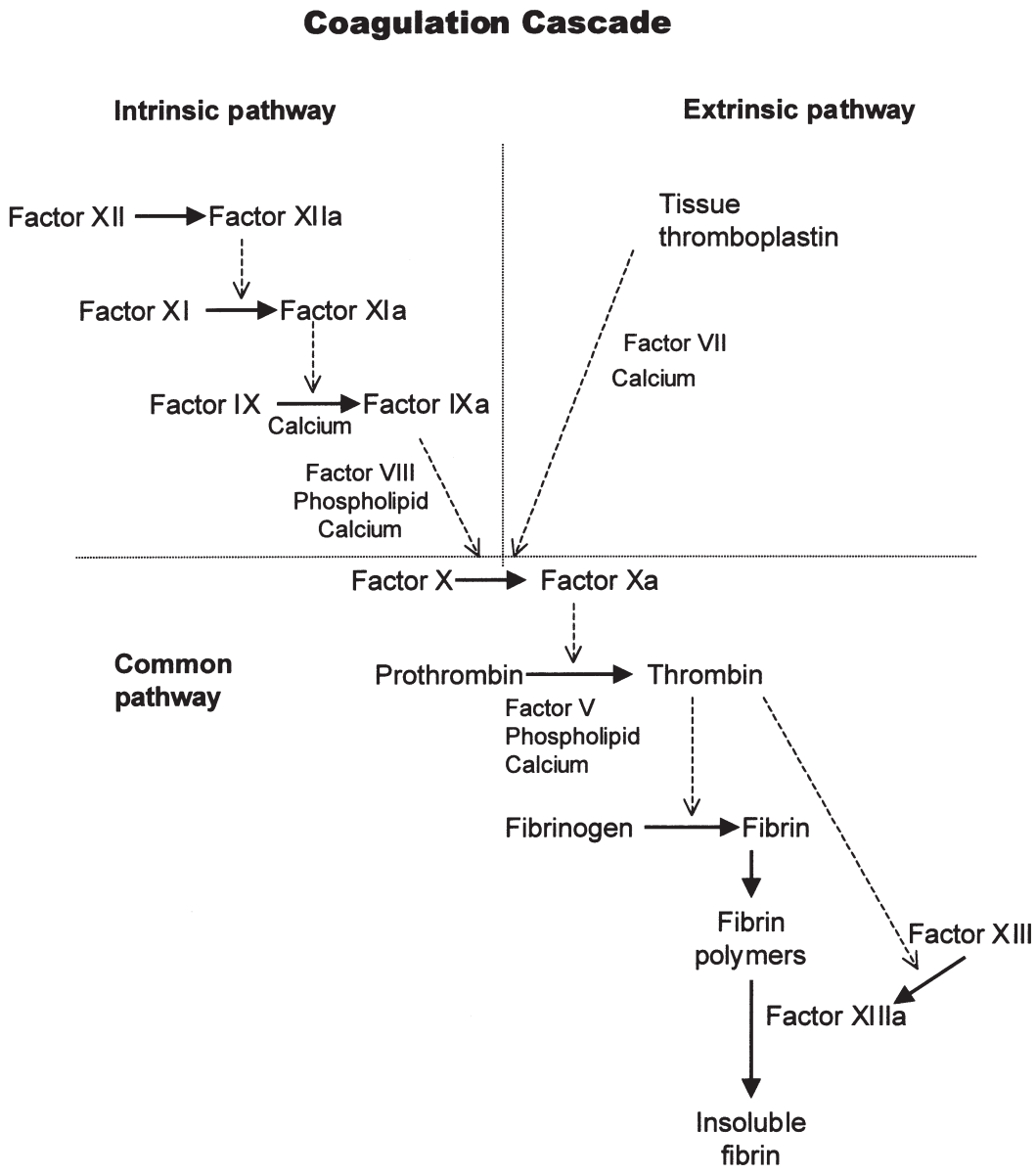


FIGURE 17-2 The coagulation cascade. *Solid arrow* (⟶) indicates conversion; *broken arrow* (- - ➤) indicates catalytic action.

the capillary beds extend into the fibrin clot, the way for plasmin to remove the cross-linked fibrin is paved by the release of TPA. Without this unique system, wound healing would be impossible. While the fibrinolytic system limits the coagulation process as described above, other systems function to limit the extent of the microvascular thrombosis in the area of injury. Antithrombin III is a potent inhibitor directed at thrombin.

▼CLINICAL AND LABORATORY FINDINGS

Clinical Manifestations

Clinical manifestations of bleeding disorders can involve various systems, depending on the extent and type of disease. Individuals with mild disease may present with no clinical signs, whereas individuals with severe coagulopathies may have definite stigmata. When skin and mucosa are involved, individuals may present with petechiae, ecchymoses, spider angiomas, hematomas, or jaundice. Deep dissecting hematomas and hemarthroses of major joints may affect severe hemophiliacs and result in disability or death. Disorders of platelet quantity may result in hepatosplenomegaly, spontaneous gingival bleeding, and risk of hemorrhagic stroke. Table 17-1 illustrates clinical features that distinguish coagulation disorders from platelet or vascular disorders.

Clinical Laboratory Tests

There are a variety of common and less common laboratory tests that help to identify deficiency of required elements or dys-

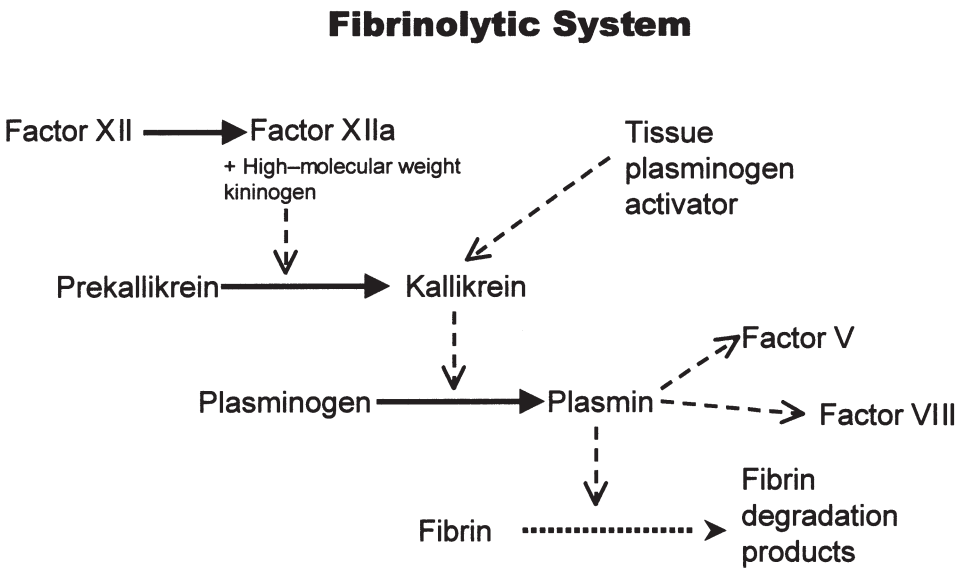


FIGURE 17-3 The fibrinolytic system. *Thin solid arrow* (⟶) indicates conversion; *broken arrow* (⇢) indicates catalytic actions; *dotted arrow* (⋯➤) indicates degradation.

function of the phases of coagulation (Tables 17-2 and 17-3). The two clinical tests used to evaluate primary hemostasis are the platelet count and bleeding time (BT). Normal platelet counts are 150,000 to 450,000/mm^3. Spontaneous clinical hemorrhage is usually not observed with platelet counts above 10,000 to 20,000/mm^3. Surgical or traumatic hemorrhage is more likely with platelet counts below 50,000/mm^3. BT is determined from a standardized incision on the forearm. BT is usually considered to be normal between 1 and 6 minutes (by modified Ivy's test) and is prolonged when greater than 15 minutes. The skin BT test, thought to identify qualitative or functional platelet defects, is a poor indicator of clinically significant bleeding at other sites, and its use as a predictive screening test for oral surgical procedures has been discouraged.[14]

Tests to evaluate the status of other aspects of hemostasis include prothrombin time (PT)/international normalized ratio (INR), activated partial thromboplastin time (aPTT), thrombin time (TT), FDPs, specific coagulation factor assays (especially Fs VII, VIII, and IX and fibrinogen), and coagulation factor inhibitor screening tests (blocking antibodies).

The normal range of PT is approximately 11 to 13 seconds. Because of individual laboratory reagent variability and the desire to be able to reliably compare the PT from one laboratory to that from another, the PT test is now commonly reported with its INR.[15,16] The INR, introduced by the World Health Organization in 1983, is the ratio of PT that adjusts for the sensitivity of the thromboplastin reagents, such that a normal coagulation profile is reported as an INR of 1.0.[17] This test evaluates the extrinsic coagulation system and measures the presence or absence of clotting Fs I, II, V, VII, and X. Its most common use is to measure the effects of coumarin anticoagulants and reduction of the vitamin K–dependent Fs II, VII, IX, and X. Since the extrinsic system uses only Fs I, II, VII, and X, it does not measure the reduction of Fs VIII or IX, which characterizes hemophilias A and B. Additionally, the PT is used to measure the metabolic aspects of protein synthesis in the liver.

TABLE 17-1 Clinical Features of Bleeding Disorders

Feature	Vascular or Platelet Disorders	Coagulation Disorders
Bleeding from superficial cuts and scratches	Persistent, often perfuse	Minimal
Delayed bleeding	Rare	Common
Spontaneous gingival bleeding	Characteristic	Rare
Petechiae	Characteristic	Rare
Ecchymoses	Characteristic, usually small and multiple	Characteristic, usually large and solitary
Epistaxis	Common	Common
Deep dissecting hematomas	Rare	Characteristic
Hemarthroses	Rare	Characteristic

TABLE 17-2 Laboratory Tests for Assessing Hemostasis

Test	Normal Range
Platelet count	150,000 to 450,000/mm^3
Bleeding time	< 7 min (by simplate); 1–6 min (modified Ivy's test)
Prothrombin time/international normalized ratio	Control ± 1 s (eg, PT: 11–13 s/INR 1.0)
Activated partial thromboplastin time	Comparable to control (eg, 15–35 s)
Thrombin time	Control ± 3 s (eg, 9–13 s)
Fibrin degradation products	< 10 µg/dL
Fibrinogen assay	200–400 mg/dL
von Willebrand's antigen	60–150% vWF activity
Coagulation factor assays (eg, F VIII assay)	60–100% F VIII activity
Coagulation factor inhibitor assays (eg, Bethesda inhibitor assay for F VIII)	0.0 Bethesda inhibitor units

F = factor; INR = international normalized ratio; PT = prothrombin time; vWF = von Willebrand's factor.

The aPTT is considered normal if the control aPTT and the test aPTT are within 10 seconds of each other. Control aPTT times are usually 15 to 35 seconds. Normal ranges depend on the manufacturer's limits; each supplier varies slightly. The unactivated PTT was originally described by Langdell and associates in 1953 as a simple one-stage assay for measuring F VIII.[18] Now it is used to evaluate the intrinsic cascade and measure the functional levels of Fs VIII, IX, XI, and XII. Since the addition of the activator (a rare earth), the test no longer measures Fs XI and XII. As a screening test, the aPTT is prolonged only when the factor levels in the intrinsic and common pathways are less than about 30%. It is altered in hemophilias A and B and with the use of the anticoagulant heparin.

The TT is used specifically to test the ability to form the initial clot from fibrinogen and is considered normal in the range of 9 to 13 seconds. Additionally, it is used to measure the presence of heparin, FDPs, or other paraproteins that inhibit conversion of fibrinogen to fibrin. Fibrinogen can also be specifically assayed and should be present at a level of 200 to 400 mg/dL.

FDPs are measured using a specific latex agglutination system to evaluate the presence of the D dimer of fibrinogen and/or fibrin above normal levels. Such presence indicates that intravascular lysis has taken place or is occurring. This state can result from primary fibrinolytic disorders or disseminated intravascular coagulation (DIC). DIC is a catastrophic state that may result from massive trauma, extensive and terminal metastatic cancer, or fulminant viral or bacterial infections. DIC is rarely seen in the practice of dentistry, but it can occur.

To further identify factor deficiencies and their level of severity, specific activity levels of factors can be measured. Normal factor activity is usually in the 60 to 150% range. Inhibitor screening tests are essential when sufficient factor concentrate to correct the factor deficiency under normal conditions fails to control bleeding. To identify the specific type of von Willebrand's disease (types I–III and platelet type), additional studies such as the ristocetin cofactor, ristocetin-induced platelet aggregation studies, and monomer studies are helpful.

The tourniquet test for capillary fragility, which assesses the Rumpel-Leede phenomenon, is useful for identifying disorders of vascular wall integrity or platelet disorders. Stasis is produced by inflating a sphygmomanometer cuff around the arm in the usual manner to a pressure halfway between systolic and diastolic levels. This moderate degree of stasis is maintained for 5 minutes. At 2 minutes following cuff deflation and removal, a 2.5 cm diameter region (size of a quarter) of skin on the volar surface of the arm at 4 cm distal to the antecubital fossa is observed for petechial hemorrhages. Normally petechiae in men do not exceed five, and in women and children they do not exceed 10.

TABLE 17-3 Results of Hemostatic Screening Tests for Selected Bleeding Disorders

	Screening Laboratory Test			
Bleeding Disorder	Platelet Count	PT/INR	aPTT	BT
Thrombocytopenia Leukemia	↓	N	N	↑
F VIII, IX, XI deficiency Heparin anticoagulation	N	N	↑	N
F II, V, X deficiency Vitamin K deficiency Intestinal malabsorption	N	↑	↑	N
F VII deficiency Coumarin anticoagulation Liver disease	N	↑	N	N
von Willebrand's disease	N, ↓	N	N,↑	↑
DIC Severe liver disease	↓	↑	↑	↑
F XIII deficiency	N	N	N	N
Vascular wall defect	N	N	N	↑

aPTT = activated partial thromboplastin time; BT = bleeding time; DIC = disseminated intravascular coagulation; INR = international normalized ratio; N = normal; PT = prothrombin time; ↑ = increased; ↓ = decreased.

▼CLASSIFICATION OF BLEEDING DISORDERS

Vessel Wall Disorders

Vessel wall disorders can result in hemorrhagic features. Bleeding is usually mild and confined to the skin, mucosa, and gingiva. Vascular purpura can result from damage to capillary endothelium, from abnormalities in the vascular subendothelial matrix or extravascular connective tissue bed, or from abnormal vessel formation. The pathogenesis of bleeding is not well defined in many conditions, and the capillary fragility test is the only test to demonstrate abnormal results.

Scurvy, resulting from dietary deficiency of water-soluble vitamin C, is found primarily in regions of urban poverty, among either infants on nonsupplemented processed milk formulas, elderly who cook for themselves, or adults with alcohol or drug dependencies.[19,20] Many of the hemorrhagic features of scurvy result from defects in collagen synthesis. Vitamin C is necessary for the synthesis of hydroxyproline, an essential constituent of collagen. One of the first clinical signs is petechial hemorrhages at the hair follicles and purpura on the back of the lower extremities that coalesce to form ecchymoses. Hemorrhage can occur in the muscles, joints, nail beds, and gingival tissues. Gingival involvement may include swelling, friability, bleeding, secondary infection, and loosening of teeth.[20] Scurvy results when dietary vitamin C falls below 10 mg/d. Implementation of a diet rich in vitamin C and administration of 1 g/d of vitamin C supplements provides rapid resolution.

Cushing's syndrome, resulting from excessive exogenous or endogenous corticosteroid intake or production, leads to general protein wasting and atrophy of supporting connective tissue around blood vessels. Patients may show skin bleeding or easy bruising. Aging causes similar perivascular connective-tissue atrophy and lack of skin mobility. Tears in small blood vessels can result in irregularly shaped purpuric areas on arms and hands, called purpura senilis. Other metabolic or inflammatory disorders resulting in purpura include Schönlein-Henoch or anaphylactoid purpura, hyperglobulinemic purpura, Waldenström's macroglobulinemia, multiple myeloma, amyloidosis, and cryoglobulinemia.

Ehlers-Danlos syndrome is an inherited disorder of connective-tissue matrix, generally resulting in fragile skin blood vessels and easy bruising. It is characterized by hyperelasticity of the skin and hypermobile joints. Eleven subtypes have been identified with unique biochemical defects and varying clinical features.[21] Type I is the classic form, with soft velvety hyperextensible skin, easy bruising and scarring, hypermobile joints, varicose veins, and prematurity. Type VIII has skin findings similar to those in type I, with easy bruising following minor trauma, and is characterized by early-onset periodontal disease with loss of permanent dentition.[22] Children with type VII syndrome may present with microdontia and collagen-related dentinal structural defects in primary teeth, in addition to bleeding after tooth brushing.[23] Other oral findings include fragility of the oral mucosa, gingiva, and teeth, as well as hypermobility of the temporomandibular joint, and stunted teeth and pulp stones on dental radiographs.[24,25]

Rendu-Osler-Weber syndrome, also called hereditary hemorrhagic telangiectasia, is a group of autosomal dominant disorders with abnormal telangiectatic capillaries, frequent episodes of nasal and gastrointestinal bleeding, and associated brain and pulmonary lesions.[26,27] Perioral and intraoral angiomatous nodules or telangiectases are common with progressive disease, involving areas of the lips, tongue, and palate that may bleed with manipulation during dental procedures.[28] Diagnosis is facilitated by the history and the observation of multiple nonpulsating vascular lesions, where arterioles connect to venules representing small arteriovenous malformations. These lesions blanch in response to applied pressure, unlike petechiae or ecchymoses. Mucocutaneous lesions may bleed profusely with minor trauma or, occasionally, spontaneously.[29] Persistently bleeding lesions may be treated with cryotherapy, laser ablation, electrocoagulation, or resection.[30] Blood replacement and iron therapy may be necessary following dental extractions in involved areas.[29]

Platelet Disorders

Platelet disorders may be divided into two categories by etiology—congential and acquired—and into two additional categories by type—thrombocytopenias and thrombocytopathies (Table 17-4). Thrombocytopenias occur when platelet quantity is reduced and are caused by one of three mechanisms: decreased production in the bone marrow, increased sequestration in the spleen, or accelerated destruction. Thrombocytopathies, or qualitative platelet disorders, may result from defects in any of the three critical platelet reactions: adhesion, aggregation, or granule release. Dysfunctional platelet mechanisms may occur in isolated disorders or in conjunction with dysfunctional coagulation mechanisms.

TABLE 17-4 Classification of Platelet Disorders

Congenital
Thrombocytopenic—quantitative platelet deficiency
May-Hegglin anomaly
Wiskott-Aldrich syndrome
Neonatal alloimmune thrombocytopenia
Nonthrombocytopenic—qualitative or functional platelet defect
Glanzmann's thrombasthenia
Platelet-type von Willebrand's disease
Bernard-Soulier syndrome
Acquired
Thrombocytopenic—quantitative platelet deficiency
Autoimmune or idiopathic thrombocytopenia purpura
Thrombotic thrombocytopenia purpura
Cytotoxic chemotherapy
Drug-induced (eg, quinine, quinidine, gold salts, trimethoprim/sulfamethoxazole, rifampin)
Leukemia
Aplastic anemia
Myelodysplasia
Systemic lupus erythematosus
Associated with infection: HIV, mononucleosis, malaria
Disseminated intravascular coagulation
Nonthrombocytopenic—qualitative or functional platelet defect
Drug-induced (eg, by aspirin, NSAIDs, penicillin, cephalosporins)
Uremia
Alcohol dependency
Liver disease
Myeloma, myeloproliferative disorders, macroglobulinemia
Acquired platelet-type von Willebrand's disease

HIV=human immunodeficiency virus; NSAIDs = nonsteroidal anti-inflammatory drugs.

CONGENITAL PLATELET DISORDERS

Congenital abnormalities of platelet function or production are rare. Glanzmann's thrombasthenia is a qualitative disorder characterized by a deficiency in the platelet membrane glycoproteins IIb and IIIa.[31–33] Clinical signs include bruising, epistaxis, gingival hemorrhage, and menorrhagia. Treatment of oral surgical bleeding involves platelet transfusion and use of antifibrinolytics and local hemostatic agents. Wiskott-Aldrich syndrome is characterized by cutaneous eczema (usually beginning on the face), thrombocytopenic purpura, and an increased susceptibility to infection due to an immunologic defect.[34] Oral manifestations include gingival bleeding and palatal petechiae. May-Hegglin anomaly is a rare hereditary condition characterized by the triad of thrombocytopenia, giant platelets, and inclusion bodies in leukocytes. Clinical features and the pathogenesis of bleeding in this disease are poorly defined.[35] Bernard-Soulier syndrome and platelet-type vWD also result from identified defects in platelet membrane glycoproteins.[36] Unlike the other types of vWD, the platelet type is rare and presents with less severe clinical bleeding.

ACQUIRED PLATELET DISORDERS

Two of the most commonly encountered platelet disorders, idiopathic or immune thrombocytopenia purpura (ITP) and thrombotic thrombocytopenia purpura (TTP), have clinical symptoms including petechiae and purpura over the chest, neck, and limbs—usually more severe on the lower extremities. Mucosal bleeding may occur in the oral cavity and gastrointestinal and genitourinary tracts.

ITP may be acute and self-limiting (2 to 6 weeks) in children. In adults, ITP is typically more indolent in its onset, and the course is persistent, often lasting many years, and may be characterized by recurrent exacerbations of disease. In severe cases of ITP, oral hematomas and hemorrhagic bullae may be the presenting clinical sign.[37,38] Most patients with chronic ITP are young women. Intracerebral hemorrhage, although rare, is the most common cause of death. ITP is assumed to be caused by accelerated antibody-mediated platelet consumption. The natural history and long-term prognosis of adults with chronic ITP remain incompletely defined.[39] ITP may be a component of other systemic diseases. Autoimmune thrombocytopenia associated with systemic lupus erythematosus is often of little consequence but may occasionally be severe and serious, requiring aggressive treatment.[40] Immune-mediated thrombocytopenia may occur in conjunction with HIV disease in approximately 15% of adults, being more common with advanced clinical disease and immune suppression, although less than 0.5% of patients have severe thrombocytopenia with platelet counts below 50,000/mm^3.[41]

TTP is an acute catastrophic disease that, until recently, was uniformly fatal. Causes include metastatic malignancy, pregnancy, mitomycin C, and high-dose chemotherapy. If untreated, it still carries a high mortality rate. In addition to thrombocytopenia, clinical presentation of TTP includes microangiopathic hemolytic anemia, fluctuating neurologic abnormalities, renal dysfunction, and occasional fever. Microvascular infarcts occur in gingival and other mucosal tissues in about 60% of the cases. These appear as platelet-rich thrombi. Serial studies of plasma samples from patients during episodes of TTP have often shown vWF multimer abnormalities.[42]

Thrombocytopenia may be a component of other hematologic disease such as myelodysplastic disorders,[43] aplastic anemia,[44] and leukemia.[45] Bone marrow suppression from cytotoxic chemotherapy can result in severe thrombocytopenia, requiring platelet transfusions for prevention of spontaneous hemorrhage. Thrombocytopenia and thrombocytopathy in liver disease are complicated by coagulation defects, as discussed below. Alcohol can, itself, induce thrombocytopenia.[46] The coagulopathy of renal disease consists of an acquired qualitative platelet defect resulting from uremia.[47]

Medications can also reduce absolute numbers of platelets or interfere with their function, resulting in postsurgical hemorrhage.[48–50] Drug-related platelet disorders are reversible within 7 to 10 days of discontinuation of the drug. Aspirin induces a functional defect in platelets detectable as prolongation of BT. It inactivates an enzyme called prostaglandin synthetase, resulting in inactivation of cyclo-oxygenase catalytic activity and decreasing biosynthesis of prostaglandin and thromboxanes that are needed to regulate interactions between platelets and the endothelium.[51] A single 100 mg dose of aspirin provides rapid complete inhibition of platelet cyclo-oxygenase activity and thromboxane production. Aspirin is commonly used as an inexpensive and effective antiplatelet therapy for thromboembolic protection. Antiplatelet therapy reduces the risk of death from cardiovascular causes by about one-sixth and the risk of nonfatal myocardial infarction and stroke by about one-third for patients with unstable angina or a history of myocardial infarction, transient ischemia, or stroke.[51] Most NSAIDs have similar, but less significant, antiplatelet effects compared with aspirin. The new NSAIDs that act as cyclo-oxygenase-2 inhibitors, rofecoxib (Vioxx, Merck and Co. Inc, Whitehouse Station, NJ) and celecoxib (Celebrex, Pfizer, New York, NY), generally do not inhibit platelet aggregation at indicated doses.

Coagulation Disorders

Coagulation disorders may be either congenital or acquired secondary to drugs or disease processes.

CONGENITAL COAGULOPATHIES

Inherited disorders of coagulation can result from deficiency of a number of factors (seen in Table 17-5) that are essential in the coagulation cascade or deficiency of vWF. Clinical bleeding can vary from mild to severe, depending on the specific clotting factor affected and the level of factor deficiency.

Hemophilia A. A deficiency of F VIII, the antihemophilic factor, is inherited as an X-linked recessive trait that affects males (hemizygous). The trait is carried in the female (heterozygous) without clinical evidence of the disease, although a few do manifest mild bleeding symptoms. Males with hemophilia transmit the affected gene to all their female

TABLE 17-5 Coagulation Factors

Factor (Name)	Coagulation Factor Affected		t½ (h)
	Intrinsic	Extrinsic	
XIII (fibrin-stabilizing factor)	*	*	336
XII (Hageman factor)	*		60
XI (plasma thromboplastin antecedent)	*		60
X (Stuart factor)	*	*	48
IX (Christmas factor)	*		18–24
VIII (antihemophilic factor)	*		8–12
VII (proconvertin)		*	4–6
V (proaccelerin)	*	*	32
IV (calcium)	*	*	—
III (tissue thromboplastin)		*	—
II (prothrombin)	*	*	72
I (fibrinogen)	*	*	96

t½ = half-life in hours

offspring, yet their sons are normal, and the effects skip a generation unless their wives were carriers and their daughters received the maternal affected X chromosome as well. Only 60 to 70% of families with newly diagnosed hemophiliacs report a family history of the disease, suggesting a high mutation rate. There is no racial predilection. Clinical symptoms and F VIII levels vary from pedigree to pedigree.[52] Severe clinical bleeding is seen when the F VIII level is less than 1% of normal. Severe hemorrhage leads to joint synovitis and hemophilic arthropathies, intramuscular bleeds, and pseudotumors (encapsulated hemorrhagic cyst). Retroperitoneal and central nervous system bleeds, occurring spontaneously or induced by minor trauma, can be life threatening. Moderate clinical bleeding is found when F VIII levels are 1 to 5% of normal. Only mild symptoms, such as prolonged bleeding following tooth extraction, surgical procedures, or severe trauma, occur if levels are between 6 and 50% of normal.

Hemophilia B. F IX (Christmas factor) deficiency is found in hemophilia B. The genetic background, factor levels, and clinical symptoms are similar to those in hemophilia A. The distinction was made only in the late 1940s between these two X-linked diseases. Concentrates used to treat F VIII and F IX deficiencies are specific for each state, and therefore a correct diagnosis must be made to ensure effective replacement therapy. Further discussion of the clinical management is presented later in this chapter. Circulating blocking antibodies or inhibitors to Fs VIII and IX may be seen in patients with these disorders. These inhibitors are specific for F VIII or F IX and render the patient refractory to the normal mode of treatment with concentrates. Catastrophic bleeding can occur, and only with supportive transfusions can the patient survive.

Factor XI Deficiency. Plasma thromboplastin antecedent deficiency is clinically a mild disorder seen in pedigrees of Jewish descent; it is transmitted as an autosomal dominant trait. Bleeding symptoms do occur but are usually mild. In the event of major surgery or trauma, hemorrhage can be controlled with infusions of fresh frozen plasma.

Factor XII Deficiency. Hageman factor deficiency is another rare disease that presents in the laboratory with prolonged PT and partial thromboplastin time (PTT). Clinical symptoms are nonexistent. Treatment is therefore contraindicated.

Factor X Deficiency. Stuart factor deficiency, also a rare bleeding diathesis, is inherited as an autosomal recessive trait. Clinical bleeding symptoms in the patient with levels less than 1% are similar to those seen in hemophilias A and B.

Factor V Deficiency. Proaccelerin deficiency, like F XI and F X deficiencies, is a rare autosomal recessive trait that presents with moderate to severe clinical symptoms. When compared with hemophilias A and B, this hemorrhagic diathesis is moderate, only occasionally resulting in soft-tissue hemorrhage, and only rarely presenting with hemarthrosis; it does not involve the devastating degenerative joint disease seen in severe hemophilias A and B.

Factors XIII and I Deficiencies. Fibrin-stabilizing deficiency and fibrinogen deficiency are very rare, and these diagnoses can be made only with extensive laboratory tests usually available only in tertiary-care medical centers. Both are autosomal recessive traits. Most dysfibrinogenemias result in no symptoms, others lead to moderate bleeding, and a few induce a hypercoagulable state. Factor XIII deficiency appears to have different forms of penetrance, and in some families appears only in the males.

Von Willebrand's Disease. vWD is a unique disorder that was described originally by Erik von Willebrand in 1926.[53] This disorder is usually transmitted as an autosomal dominant trait with varying penetrance. The defect is found in the F VIII protein complex. The clinical features of the disease are usually mild and include mucosal bleeding, soft tissue hemorrhage, menorrhagia in women, and rare hemarthrosis.[54] The common genetic profile suggests a heterozygous state, with both males and females affected. Normal plasma vWF level is 10 mg/L, with a half-life of 6 to 15 hours.

vWD is often classified into four basic types based on the separation of vWF multimers or subunits of varying molecular weights by electrophoresis.[55] Type I accounts for approximately 85% of occurrences, with all multimeric forms present in reduced concentrations. Type II is characterized by an absence of high-molecular-weight multimers and occurs in 10 to 15% of vWD patients. Rarely diagnosed is the homozygous individual with type III vWD (autosomal recessive inheritance), who has less than 1% F VIII, a long BT (> 15 minutes), and reduced levels (usually < 1%) of vWF. The

fourth type is called pseudo- or platelet-type vWD, and it is a primary platelet disorder that mimics vWD. The increased platelet affinity for large multimers of vWF results primarily in mucocutaneous bleeding. Due to familial genetic variants, wide variations occur in the patient's laboratory profile over time; therefore, diagnosis may be difficult.[56] The uncovering of all of the biochemical, physiologic, and clinical manifestations of vWD has held experts at bay for many years. As early as 1968, acquired vWD was noted to occur as a rare complication of autoimmune or neoplastic disease, associated mostly with lymphoid or plasma cell proliferative disorders and having clinical manifestations that are similar to congenital vWD.[57]

ANTICOAGULANT-RELATED COAGULOPATHIES

Heparin. Intentional anticoagulation is delivered acutely with heparin or as chronic oral therapy with coumarin drugs. Indications for heparin therapy include prophylaxis or treatment for venous thromboembolism, including prophylaxis in medical and surgical patients.[58] Heparin is a potent anticoagulant that binds with antithrombin III to dramatically inhibit activation of Fs IX, X, and XI, thereby reducing thrombin generation and fibrin formation. The major bleeding complications from heparin therapy are bleeding at surgical sites and bleeding into the retroperitoneum.

Heparin has a relatively short duration of action of 3 to 4 hours, so is typically used for acute anticoagulation, whereas chronic therapy is initiated with coumarin drugs. For acute anticoagulation, intravenous infusion of 1,000 units unfractionated heparin per hour, sometimes following a 5,000-unit bolus, is given to raise the aPTT to 1.5 to 2 times the pre-heparin aPTT. Alternatively, subcutaneous injections of 5,000 to 10,000 units of heparin are given every 12 hours. Newer biologically active low-molecular-weight heparins administered subcutaneously once or twice daily are less likely to result in thrombocytopenia and bleeding complications. Protamine sulfate can rapidly reverse the anticoagulant effects of heparin.

Coumarin. Coumarin anticoagulants, which include warfarin and dicumarol (Coumadin, DuPont Pharmaceuticals, Wilmington, DE), are used for anticoagulation to prevent recurrent thrombotic phenomena (pulmonary embolism, venous thrombosis, stroke, myocardial infarction), to treat atrial fibrillation, and in conjunction with prosthetic heart valves.[59] They slow thrombin production and clot formation by blocking the action of vitamin K. Levels of vitamin K–dependent Fs II, VI, IX, and X (prothrombin complex proteins) are reduced. The anticoagulant effect of coumarin drugs may be reversed rapidly by infusion of fresh frozen plasma, or over the course of 12 to 24 hours by administration of vitamin K. PT/INR is used to monitor anticoagulation levels. Therapeutic ranges, depending on the indication for anticoagulation, vary from a PT of 18 to 30 seconds (INR of 1.5 to 4.0). Doses of 2.5 to 7.5 mg coumarin daily typically are required to maintain adequate anticoagulation. Patients with paroxysmal atrial fibrillation and porcine heart valves require minimal anticoagulation (INR target 1.5–2.0), venous thrombosis is managed with intermediate-range coagulation (INR 2.0–3.0), whereas mechanical prosthetic heart valves and hypercoagulable states require more intense anticoagulation (INR target 3.0–4.0).

Coumarin therapy requires continual laboratory monitoring, typically every 2 to 8 weeks, as fluctuations can occur. It has a longer duration of action, with coagulant activity in blood decreased by 50% in 12 hours and 20% in 24 hours of therapy initiation. Coagulation returns to normal levels in approximately 2 to 4 days following discontinuation of coumarin drugs. Coumarin therapy can result in bleeding episodes that are sometimes fatal. Intramuscular injections are avoided in anticoagulated patients because of increased risk of intramuscular bleeding and hematoma formation. Coumarin drugs are particularly susceptible to drug interactions. Drugs that potentially increase coumarin potency (ie, elevate the INR) include metronidazole, penicillin, erythromycin, cephalosporins, tetracycline, fluconazole, ketoconazole, chloral hydrate, and propoxyphene; those that reduce its potency (ie, decrease the INR) include barbiturates, ascorbic acid, dicloxacillin, and nafcillin.[60] Additive hemostatic effect is seen when coumarin drugs are used in combination with aspirin or NSAIDs.

DISEASE-RELATED COAGULOPATHIES

Liver Disease. Patients with liver disease may have a wide spectrum of hemostatic defects depending upon the extent of liver damage.[61] Owing to impaired protein synthesis, important factors and inhibitors of the clotting and the fibrinolytic systems are markedly reduced. Additionally, abnormal vitamin K–dependent factor and fibrinogen molecules have been encountered. Thrombocytopenia and thrombocytopathy are also common in severe liver disease. Acute or chronic hepatocellular disease may display decreased vitamin K–dependent factor levels, especially Fs II, VII, IX, and X and protein C, with other factors still being normal.

Vitamin K Deficiency. Vitamin K is a fat-soluble vitamin that is absorbed in the small intestine and stored in the liver. It plays an important role in hemostasis. Vitamin K deficiency is associated with the production of poorly functioning vitamin K–dependent Fs II, VII, IX, and X.[62] Deficiency is rare but can result from inadequate dietary intake, intestinal malabsorption, or loss of storage sites due to hepatocellular disease. Biliary tract obstruction and long-term use of broad-spectrum antibiotics, particularly the cephalosporins, can cause vitamin K deficiency. Although there is a theoretic 30-day store of vitamin K in the liver, severe hemorrhage can result in acutely ill patients in 7 to 10 days. A rapid fall in F VII levels leads to an initial elevation in INR and a subsequent prolongation of aPTT. When vitamin K deficiency results in coagulopathy, supplemental vitamin K by injection restores the integrity of the clotting mechanism.

Disseminated Intravascular Coagulation. DIC is triggered by potent stimuli that activate both F XII and tissue factor to initially form microthrombi and emboli throughout the microvasculature.[63] Thrombosis results in rapid consumption of both coagulation factors and platelets, while also creating FDPs that have antihemostatic effects. The most frequent triggers for DIC are obstetric complications, metastatic cancer, massive trauma, and infection with sepsis. Clinical symptoms vary with disease stage and severity. Most patients have bleeding at skin and mucosal sites. Although it can be chronic and mild, acute DIC can produce massive hemorrhage and be life threatening.

Fibrinolytic Disorders

Disorders of the fibrinolytic system can lead to hemorrhage when clot breakdown is enhanced, or excessive clotting and thrombosis when clot breakdown mechanisms are retarded. Primary fibrinolysis typically results in bleeding and may be caused by a deficiency in α_2-plasmin inhibitor or plasminogen activator inhibitor. Laboratory coagulation tests are normal with the exception of decreased fibrinogen and increased FDP levels. Impaired clearance of TPA may contribute to prolonged bleeding in individuals with severe liver disease. As discussed above, deficiency of F XIII, a transglutaminase that stabilizes fibrin clots, is a rare inherited disorder that leads to hemorrhage. Patients with primary fibrinolysis are treated with fresh frozen plasma therapy and antifibrinolytics.

Differentiation must be made from the secondary fibrinolysis that accompanies DIC, a hypercoagulable state that predisposes individuals to thromboembolism. Dialysis patients with chronic renal failure show a fibrinolysis defect at the level of plasminogen activation.[64] Reduced fibrinolysis may be responsible, along with other factors, for the development of thrombosis, atherosclerosis, and their thrombotic complications. Activators of the fibrinolytic system (TPA, streptokinase, and urokinase) are frequently used to accelerate clot lysis in patients with acute thromboembolism, for example, to prevent continued tissue damage in myocardial infarction or treat thrombotic stroke.

▼ IDENTIFICATION OF THE DENTAL PATIENT WITH A BLEEDING DISORDER

Identification of the dental patient with or at risk for a bleeding disorder begins with a thorough review of the medical history.[65,66] Patient report of a family history of bleeding problems may help to identify inherited disorders of hemostasis. A patient's past history of bleeding following surgical procedures, including dental extractions, can help identify a risk. Surveying the patient for current medication use is important. Identification of medications with hemostatic effect, such as coumarin anticoagulants, heparin, aspirin, NSAIDs, and cytotoxic chemotherapy, is essential. Active medical conditions, including hepatitis or cirrhosis, renal disease, hematologic malignancy, and thrombocytopenia, may predispose to bleeding problems. Additionally, a history of heavy alcohol intake is a risk factor for bleeding consequences.

A review-of-systems approach to the patient interview can identify symptoms suggestive of disordered hemostasis (see Table 17-1). Although the majority of patients with underlying bleeding disorders of mild to moderate severity may exhibit no symptoms, symptoms are common when disease is severe. Symptoms of hemorrhagic diatheses reported by patients may include frequent epistaxis, spontaneous gingival or oral mucosal bleeding, easy bruising, prolonged bleeding from superficial cuts, excessive menstrual flow, and hematuria. When the history and the review of systems suggest increased bleeding propensity, laboratory studies are warranted.

▼ MANAGEMENT

Management of the patient with a hemorrhagic disorder is aimed at correction of the reversible defect(s), prevention of hemorrhagic episodes, prompt control of bleeding when it occurs, and management of the sequelae of the disease and its therapy.

Platelet Disorders

Treatment modalities for platelet disorders are determined by the type of defect. The thrombocytopenias are primarily managed acutely with transfusions of platelets to maintain the minimum level of 10,000 to 20,000/mm^3 necessary to prevent spontaneous hemorrhage. Corticosteroids are indicated for ITP, with titration governed by the severity of hemorrhagic symptoms.[37,38] Splenectomy may be necessary in chronic ITP to prevent antiplatelet antibody production and sequestration and removal of antibody-labeled platelets.[38] Plasma exchange therapy combined with aspirin/dipyridamole or corticosteroids has recently lowered the mortality rate for patients with TTP over that previously obtained by treatment with fresh frozen plasma (FFP) infusions.[67,68] The thrombocytopenia of Wiskott-Aldrich syndrome may be managed with platelet transfusions, splenectomy, or bone marrow transplantation.[34]

Treatment of bleeding episodes in the patient with the congenital qualitative platelet defect of Glanzmann's thrombasthenia is usually not warranted unless hemorrhage is life threatening. Therapy has included periodic random platelet transfusions, which carry the risk of development of antiplatelet isoantibodies. Human leukocyte antigen (HLA)–matched platelets may be required after antibody development, to reduce the number of platelet transfusions needed for hemostasis. In the absence of satisfactorily compatible platelets, blood volume and constituents can be maintained with low-antigenicity blood products. Plasmapheresis to remove circulating isoantibodies is held in reserve for cases of severe thrombasthenia and life-threatening bleeding.

Hemophilias A and B

Therapy for hemophilias A and B is dependent upon the severity of disease, type and site of hemorrhage, and presence or absence of inhibitors. Commercially prepared Fs VIII and IX

complex concentrates, desmopressin acetate, and, to a lesser extent, cryoprecipitate and FFP are replacement options (Tables 17-6 and 17-7). Since partially purified Fs VIII and IX complex concentrates prepared from pooled plasma were first used in the late 1960s and 1970s, multiple methods of manufacturing products with increased purity and reduced risk of viral transmission have been developed.[69,70] Current intermediate-purity products are prepared by heat or solvent/detergent treatment of the final product. In 1987, dry heat–treated concentrates constituted approximately 90% of the total F VIII concentrate consumption in the United States.[70]

High-purity F VIII products, manufactured using recombinant or monoclonal antibody purification techniques, are preferred today for their improved viral safety.[71] However, their cost of up to 10 times more than dry-heated concentrates can be financially restrictive for uninsured patients.[70] High-purity products generally cost over $1.00 (US) per unit. F VIII concentrates are dosed by units, with one unit of F VIII being equal to the amount present in 1 mL of pooled fresh normal plasma. The plasma level of F VIII is expressed as a percentage of normal. Since one unit of F VIII concentrate per kilogram of body weight raises the F VIII level by 2%, a 70 kg patient would require infusion of 3,500 units to raise his factor level from < 1% to 100%. A dose of 40 U/kg F VIII concentrate typically is used to raise the F VIII level to 80 to 100% for management of significant surgical or traumatic bleeding in a patient with severe hemophilia. Additional outpatient doses may be needed at 12-hour intervals, or continuous inpatient infusion may be established.

Highly purified recombinant and monoclonal F IX concentrates were developed in the late 1980s and early 1990s and are the treatment of choice for hemophilia B patients undergoing surgery.[72–74] F. IX complex concentrates (prothrombin complex concentrate [PCC]), which contain Fs II, VII, IX, and X, are also widely used at present for patients with hemophilia B. One unit of PCC or higher-purity F IX concentrates given by bolus per kilogram of body weight raises the F IX level by 1 to 1.5%. Thus, a dose of 60 U/kg of F IX concentrate typically is needed to raise the F IX level to 80 to 100% for management of severe bleeding episodes in a patient with a severe F IX deficiency. Repeat outpatient doses may be needed at 24-hour intervals. Properly supervised home therapy, in which patients self-treat with factor concentrates at the earliest evidence of bleeding, is a cost-effective method offered to educable and motivated patients by some medical centers.[75]

Currently, cryoprecipitate and FFP are rarely the treatment of choice for hemophilias A and B because of their disadvantages of potential viral transmission and the large volumes

TABLE 17-6 Principal Products for Systemic Management of Patients with Bleeding Disorders

Product	Description	Source	Common Indications
Platelets	"One pack" = 50 mL; raises count by 6,000	Blood bank	< 10,000 in nonbleeding individuals < 50,000 presurgical < 50,000 in actively bleeding individuals Nondestructive thrombocytopenia
Fresh frozen plasma	Unit = 150–250 mL 1 hour to thaw Contains Fs II, VII, IX, X, XI, XII, XIII and heat labile V and VII	Blood bank	Undiagnosed bleeding disorder with active bleeding Severe liver disease When transfusing > 10 units blood Immune globulin deficiency
Cryoprecipitate	Unit = 10–15 mL Contains Fs VIII, XIII, vWF and fibrinogen	Blood bank	Hemophilia A, von Willebrand's disease, when factor concentrates/DDAVP are unavailable Fibrinogen deficiency
F VIII concentrate (purified antihemophilic factor) *	Unit raises F VIII level by 2% Heat treated contains vWF Recombinant and monoclonal technologies are pure F VIII	Pharmacy	Hemophilia A, with active bleeding or presurgical; some cases of von Willebrand's disease
F IX concentrate (PCC)*	Unit raises F IX level by 1–1.5% Contains Fs II, VII, IX, and X Monoclonal F IX is only F IX	Pharmacy	Hemophilia B, with active bleeding or presurgical PCC used for hemophilia A with inhibitor
DDAVP	Synthetic analogue of antidiuretic hormone 0.3 µg/kg IV or SQ Intranasal application	Pharmacy	Active bleeding or presurgical for some patients with von Willebrand's disease, uremic bleeding, or liver disease
E-Aminocaproic acid	Antifibrinolytic 25% oral solution (250 mg/mL) Systemic: 75 mg/kg q6h	Pharmacy	Adjunct to support clot formation for any bleeding disorder
Tranexamic acid	Antifibrinolytic 4.8% mouth rinse—not available in US Systemic: 25 mg/kg q8h	Pharmacy	Adjunct to support clot formation for any bleeding disorder

F = factor; DDAVP = desmopressin acetate; PCC = prothrombin complex concentrate.

* see Table 17-7 for additional factor concentrate products.

TABLE 17-7 Coagulation Factor Concentrate Products

Product Category	Proprietary Name*	Manufacturer/ Distributor	Corporate Location
High purity F. VIII concentrates			
Monoclonal:	Hemofil-M	Baxter Healthcare Corp.	Deerfield, IL, USA
	Monoclate-P	Aventis-Behring	King of Prussia, PA, USA
Recombinant:	Kogenate	Bayer Corp.	Clayton, NC, USA
	Recombinate	Baxter Healthcare Corp.	Deerfield, IL, USA
	Helixate-FS	Aventis-Behring	King of Prussia, PA, USA
	Bioclate	Aventis-Behring	King of Prussia, PA, USA
	ReFacto	Wyeth Biopharma	Andover, MA, USA
Intermediate purity F. VIII concentrates			
Pasturized:	Humate-P	Aventis-Behring	King of Prussia, PA, USA
Solvent/Detergent:	Koate-DVI	Bayer Corp.	Clayton, NC, USA
	Alphanate	Alpha Therapeutic Corp.	Los Angeles, CA, USA
Porcine F. VIII concentrates	Hyate-C	Ipsen, Inc.	Milford, MA, USA
High purity F. IX concentrates			
Monoclonal:	AlphaNine-SD	Alpha Therapeutic Corp.	Los Angeles, CA, USA
	Mononine	Aventis-Behring	King of Prussia, PA, USA
Recombinant:	BeneFix	Wyeth Biopharma	Andover, MA, USA
Prothrombin complex concentrates (PCC)	Profilnine-SD	Alpha Therapeutic Corp.	Los Angeles, CA, USA
	Proplex-T	Baxter Healthcare Corp.	Deerfield, IL, USA
F. IX activated PCCs	FEIBA-VH	Baxter Healthcare Corp.	Deerfield, IL, USA
	Autoplex-T	Nabi	Boca Raton, FL, USA
F. VIIa concentrate			
Recombinant:	NovoSeven	Novo-Nordisk	Bagsvaerd, Denmark

F = factor; PCCs = prothrombin complex concentrates.

*Product availability changes periodically.

needed to raise factor levels adequately for hemostasis. Cryoprecipitate is the cold insoluble precipitate remaining after FFP is thawed at 4°C. A typical bag (1 unit) of cryoprecipitate contains about 80 units of F VIII and vWF, and 150 to 250 mg fibrinogen in a 10 to 15 mL volume. Cryoprecipitate has been used to treat selected patients with vWD and hemophilia A. FFP contains all coagulation factors in nearly normal concentrations and may aid hemorrhage control in a patient with mild hemophilia B. In the average-size patient, one unit of FFP raises F IX levels by 3%. Postoperative bleeding in mild to moderate F X deficiency can be managed with FFP, and PCCs may be held in reserve for severely deficient patients.[76]

Desmopressin acetate (DDAVP [1-deamino-8-D-arginine vasopressin]) provides adequate transient increases in coagulation factors in some patients with mild to moderate hemophilia A and type I vWD, avoiding the need for plasma concentrates.[77] This synthetic vasopressin analogue is now considered the treatment of choice for bleeding events in patients with these bleeding diatheses owing to its absence of viral risk and lower cost. DDAVP can be given at a dose of 0.3 μg/kg body weight by an intravenous or subcutaneous route prior to dental extractions or surgery, or to treat spontaneous or traumatic bleeding episodes.[78] It results in a mean increase of a two- to fivefold rise (range 1.5–20 times) in F VIII coagulant activity, vWF antigen, and ristocetin cofactor activity, with a plasma half-life of 5 to 8 hours for F VIII and 8 to 10 hours for vWF.[77] Intranasal spray application of DDAVP (Stimate, Aventis Behring, King of Prussia, PA) contains 1.5 mL of desmopressin per milliliter, with each 0.1 mL pump spray delivering a dose of 150 μg. Children require one nostril spray, and adults require two nostril sprays to achieve favorable response; correction of bleeding occurs in around 90% of patients with mild to moderate hemophilia A and type I vWD.[79] Time to peak levels is 30 to 60 minutes after intravenous injection and 90 to 120 minutes following subcutaneous or intranasal application.[77]

Unfortunately, DDAVP is ineffective in individuals with severe hemophilia A. A DDAVP trial or test dose response may be indicated prior to extensive surgery, to evaluate the level of drug effect on assayed F VIII activity in the individual patient. DDAVP, thought to stimulate endogenous release of F VIII and vWF from blood vessel endothelial cell storage sites, is hemostatically effective provided that adequate plasma concentrations are attained.[80] Prolonged use of DDAVP results in exhaustion of F VIII storage sites and diminished hemostatic effect; hence, antifibrinolytic agents are useful adjuncts to DDAVP therapy.

Complications of factor replacement therapy, in addition to allergic reactions, include viral disease transmission (hepatitis B and C, *Cytomegalovirus*, and human immunodeficiency virus [HIV]), thromboembolic disease, DIC, and development of

antibodies to factor concentrates. Hepatitis B and non-A/non-B have been major causes of morbidity and mortality in the hemophiliac population, resulting in chronic active hepatitis and cirrhosis in a number of patients.[52] More recently, hepatitis C and HIV infection have become the most common transfusion-related infections in hemophiliacs. By the end of 1986, some centers reported that 80 to 90% of hemophiliacs treated with F VIII concentrates and around 50% of those who had received F IX concentrates were HIV seropositive.[81] Since 1986, with viral screening of donated plasma, there have been few transfusion-related HIV seroconversions.

Use of factor IX complex concentrate can result in thrombotic complications, such as deep venous thromboses, myocardial infarctions, pulmonary emboli, and DIC. Concurrent use of systemic antifibrinolytics with these products may increase the risks. DIC is believed to occur as a consequence of high levels of activated clotting factors, such as Fs VIIa, IXa, and Xa, that cannot adequately be cleared by the liver.

Development of a F VIII or F IX inhibitor is a serious complication. These pathologic circulating antibodies of the IgG class, which specifically neutralize F VIII or F IX procoagulant activity, arise as alloantibodies in some patients with hemophilia.[82] Inhibitors develop in at least 10 to 15% of patients with severe hemophilia A and less commonly in patients with hemophilia B.[83,84] Development is related to exposure to factor products and genetic predisposition.[82,83] Inhibitor level is quantified by the Bethesda inhibitor assay and is reported as Bethesda units (BU).

The inhibitor titer and responsiveness to further factor infusion (responder-type) dictate which factor replacement therapy should be used. Patients with inhibitors are classified according to titer level—low (< 10 BU/mL) or high (> 10 BU/mL)—and also by responder type.[84] Low responders typically maintain low titers with repeated factor concentrate exposure, whereas high responders show a brisk elevation in titer due to the amnestic response and are the most challenging to manage.[84,85] Patients with low inhibitor titers are usually low responders, and those with high titers are often high responders. Seventy-five percent of hemophilia A patients with inhibitors are high responders, whereas only 25% are low responders.[84]

For hemorrhages, hemophilia A patients with low-level low-responding inhibitors are treated with F VIII concentrates in doses sufficient to raise plasma F VIII levels to the therapeutic range. Critical hemorrhages in patients with high-responding inhibitors may be treated with large quantities of porcine F VIII; however, routine hemorrhages are often managed initially with PCCs, which provoke anamnesis in a few patients.[82] PCCs can bypass the F VIII inhibitor and are effective about 50% of the time.[86] Activated PCCs show slightly increased effectiveness (65–75%). Highly purified porcine F VIII product use can be advantageous in patients with less than 50 BU, since human F VIII inhibitors cross-react less frequently with porcine products.[82] However, because of the risk of hemostatic failure, surgery should be performed under coverage of F VIII.[87] Treatment of the patient with low-level (< 10 BU) F IX inhibitors requires higher doses of F IX complex concentrates to achieve hemostasis. Developed in the early 1990s, recombinant F VIIa is a novel product that provides an alternative treatment option for patients with hemophilia A or B with inhibitors by enhancing the extrinsic pathway.[88] It has been proven to effectively control bleeding in patients with high-titer inhibitors.[89,90]

Several methods have demonstrated temporary removal of high-titer inhibitors in both hemophilia A and B. Exchange transfusion or plasmapheresis produces a rapid transient reduction in antibody level, with a rate of 40 mL plasma per kilogram decreasing levels by half.[91] Although laborious, it may be attempted in cases of critical hemorrhage as an adjunct to high-dose F VIII concentrate therapy. Antibody removal by extracorporeal adsorption of the plasma to protein A-Sepharose or a specific F IX–Sepharose in columns has also shown promise in hemophilias A and B.[92,93]

Von Willebrand's Disease

Therapy for vWD depends on the type of vWD and the severity of bleeding. Type I is treated preferentially with DDAVP as described above. Intermediate-purity F VIII concentrates, FFP, and cryoprecipitate are held in reserve for DDAVP nonresponders.[55] Types II and III require intermediate-purity F VIII concentrates, such as Humate-P or Koate-HS, or, rarely, cryoprecipitate or FFP. Bleeding episodes in patients with platelet-type vWD are usually controlled with platelet concentrate infusions. Other therapy is used for site-specific bleeding, such as estrogens or oral contraceptive agents for menorrhagia and local hemostatic agents and antifibrinolytics for dental procedures. Occasionally, circulating plasma inhibitors of vWF are observed in multiply transfused patients with severe disease. Cryoprecipitate infusion can cause transient neutralization of this inhibitor.[94]

Disease-Related Coagulopathies

Management of disease-related coagulopathies varies with hemostatic abnormality.

LIVER DISEASE

Hepatic disease that results in bleeding from deficient vitamin K–dependent clotting factors (Fs II, VII, IX, and X) may be reversed with vitamin K injections for 3 days, either intravenously or subcutaneously. However, infusion of FFP may be employed when more immediate hemorrhage control is necessary, such as prior to dental extractions.[95] Cirrhotic patients with moderate thrombocytopenia and functional platelet defects may benefit from DDAVP therapy.[96] Antifibrinolytic drugs, if used cautiously, have markedly reduced bleeding and thus reduced need for blood and blood product substitution.[61]

RENAL DISEASE

In uremic patients, dialysis remains the primary preventive and therapeutic modality used for control of bleeding, although it is not always immediately effective.[97] Hemodialysis and peritoneal dialysis appear to be equally efficacious in

improving platelet function abnormalities and clinical bleeding in the uremic patient. The availability of cryoprecipitate[98] and DDAVP[99] offers alternative effective therapy for patients who require shortened bleeding times acutely in preparation for urgent surgery. Conjugated estrogen preparations[100] and recombinant erythropoietin[101] have also been shown to be beneficial for uremic patients with chronic abnormal bleeding.

DISSEMINATED INTRAVASCULAR COAGULATION

Although somewhat controversial, active DIC is usually treated initially with intravenous unfractionated heparin or subcutaneous low-molecular-weight heparin, to prevent thrombin from acting on fibrinogen, thereby preventing further clot formation.[102–104] It is important to expeditiously identify and institute therapy for the underlying triggering disease or condition if long-term survival is to be a possibility. The dentist may be called upon to provide a gingival or oral mucosal biopsy specimen for histopathologic examination to confirm the diagnosis of DIC by the presence of microthrombi in the vascular bed. Replacement of deficient coagulation factors with FFP and correction of the platelet deficiency with platelet transfusions may be necessary for improvement or prophylaxis of the hemorrhagic tendency of DIC prior to emergency surgical procedures. Elective surgery is deferred due to the volatility of the coagulation mechanism in these patients.

▼PROGNOSIS

Prognosis for patients with bleeding disorders depends on appropriate diagnosis and the ability to prevent and manage acute bleeding episodes. Individuals with mild or manageable disease have a normal life expectancy, with morbidity relating to bleeding episode frequency and severity. Acute DIC carries the highest risk of death by exsanguination. Individuals with severe liver disease may succumb to rupture of esophageal varices. Severe thrombocytopenia and other severe coagulopathies carry a higher risk of hemorrhagic stroke.

Advances in the treatment of hemophilia, from the use of cryoprecipitate in the 1960s to the introduction of plasma-derived factor concentrates in the 1970s, have led to dramatic improvement in quality of life and raised the lifespan for hemophiliacs from 11 years in 1921 to 60 years in 1980.[105] Viral infections, such as hepatitis B, C, and G and HIV acquired from infected blood products, have altered the prognosis for some patients.[106–110] As discussed above, before effective virucidal methods were used in the manufacture of clotting-factor concentrates in 1985, hemophiliacs were at a very high risk of contracting bloodborne viruses from factor concentrates that exposed them to the plasma of thousands of donors. HIV seroprevalence increased to 60 to 75% of patients with hemophilia (85–90% with severe hemophilia), with HIV-associated opportunistic infections and neoplasms contributing substantially to the morbidity and mortality of hemophiliacs.[106,107,109] Oral mucosal diseases are common in hemophiliacs with HIV, particularly in those with advanced immunosuppression,[110,111] and are discussed in more detail in chapter ***. HIV protease inhibitor–containing drug combinations that resulted in improved health of some HIV-infected patients in the late 1990s are showing significant clinical and laboratory benefits when used by HIV-infected hemophiliacs.[112] Co-infection with viral hepatitis remains a challenge for the next decade.

▼ORAL HEALTH CONSIDERATIONS

Oral Findings

Platelet deficiency and vascular wall disorders result in extravasation of blood into connective and epithelial tissues of the skin and mucosa, creating small pinpoint hemorrhages, called petechiae, and larger patches, called ecchymoses. Platelet or coagulation disorders with severely altered hemostasis can result in spontaneous gingival bleeding, as may be seen in conjunction with hyperplastic hyperemic gingival enlargements in leukemic patients. Continuous oral bleeding over long periods of time fosters deposits of hemosiderin and other blood degradation products on the tooth surfaces, turning them brown. A variety of oral findings are illustrated in Figures 17-4 to 17-6.

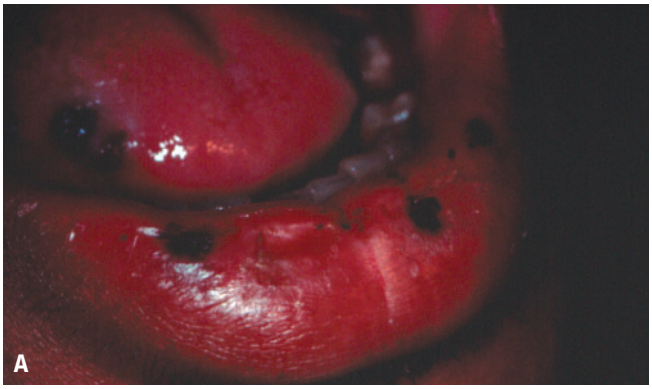
Hemophiliacs may experience many episodes of oral bleeding over their lifetime. Sonis and Musselman[113] reported an average 29.1 bleeding events per year serious enough to require factor replacement in F VIII–deficient patients, of which 9% involved oral structures. Location of oral bleeds was as follows: labial frenum, 60%; tongue, 23%; buccal mucosa, 17%; and gingiva and palate, 0.5% (Figure 17-7). Bleeding occurrences were most frequent in patients with severe hemophilia, followed by moderate, and then mild hemophilia. They most often resulted from traumatic injury. Bleeding events may also be induced by poor oral hygiene practices and iatrogenic factors. Kaneda and colleagues[114] reported frequency of oral hemorrhage by location in individuals deficient of F VIII and F IX as follows: gingiva, 64%; dental pulp, 13%; tongue, 7.5%; lip, 7%; palate, 2%; and buccal mucosa, 1%. Many minor oral bleeds, such as those from the gingiva or dental pulp, can be controlled by local measures.

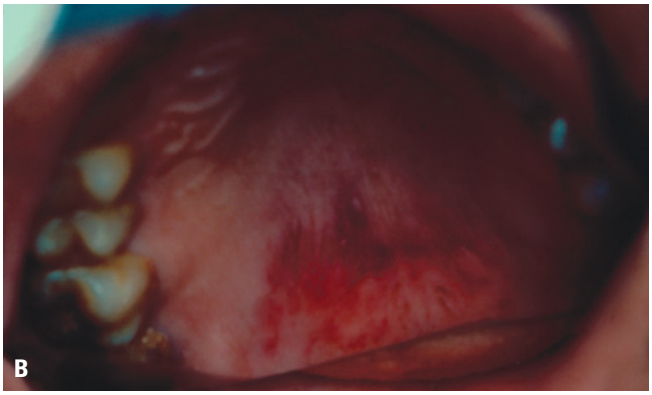
Hemarthrosis is a common complication in hemophiliacs' weight-bearing joints, yet it rarely occurs in the temporomandibular joint (TMJ). Two TMJ cases have been reported.[115,116] An acute TMJ hemarthrosis associated with F IX deficiency was resolved with factor replacement without aspiration;[115] a chronic hemophilic TMJ arthropathy required arthrotomy, arthroscopic adhesion lysis, factor replacement, splint therapy, and physical therapy in a patient with F XI deficiency.[116]

Evaluation of dental disease patterns in the patient population with bleeding disorders revealed a higher caries rate, a greater number of unrestored teeth,[117] and more severe periodontal disease[118] in individuals with severe hemophilia. The severity of dental disease in severe bleeders was attributed to a lack of proper oral hygiene and proper professional dental care.

Dental Management

Dental management required for patients with bleeding disorders depends on both the type and invasiveness of the den-





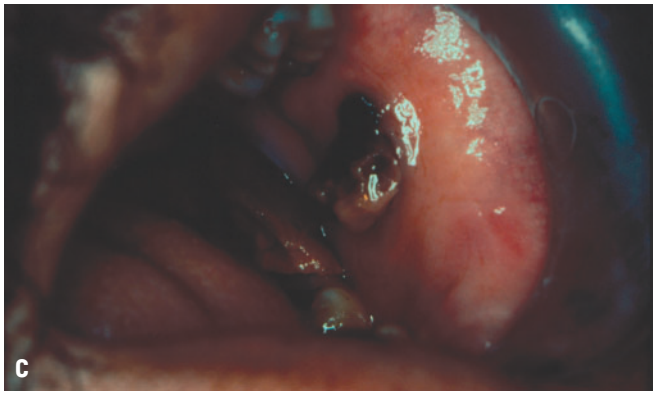
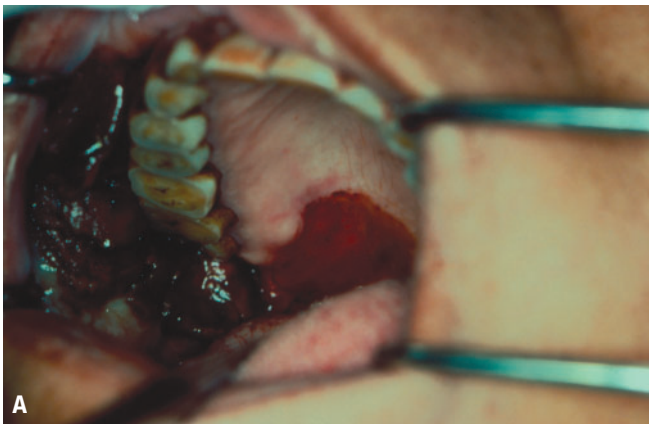


FIGURE 17-4 A 36-year-old male with idiopathic thrombocytopenia purpura and a platelet count of 5,000/mm^3. Supportive platelet transfusions and immunoglobulin therapy were used to control bleeding. **A,** Labial and tongue ecchymoses; **B,** palatal ecchymoses; **C,** buccal ecchymoses and fibrinous clot.

tal procedure and the type and severity of the bleeding disorder. Thus, less modification is needed for patients with mild coagulopathies in preparation for dental procedures anticipated to have limited bleeding consequences. When significant bleeding is expected, the goal of management is to preoperatively restore the hemostatic system to an acceptable range, while supporting coagulation with adjunctive and/or local measures. For reversible coagulopathies, (eg, coumarin anticoagulation), it may be best to remove the causative agent or treat the primary illness or defect in order to allow the patient to return to a manageable bleeding risk for the dental treatment period. For irreversible coagulopathies, the missing or defective element may need to be replaced from an exogenous source to allow control of bleeding (eg, coagulation factor concentrate therapy for hemophilia). Assessment of the coagulopathy and delivery of appropriate therapy prior to dental procedures is best accomplished in consultation with a hematologist.



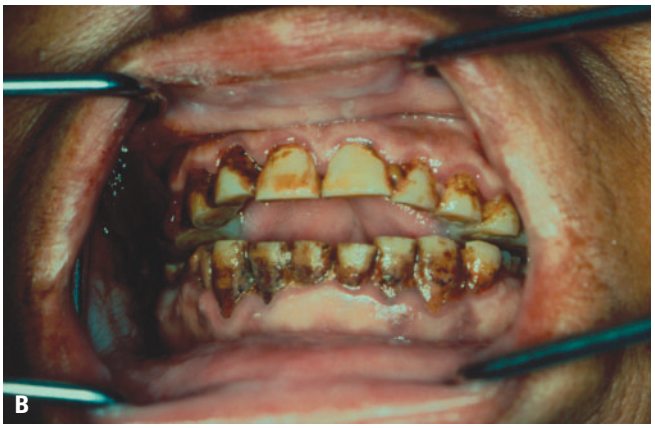


FIGURE 17-5 A 68-year-old female with acute myelogenous leukemia and a platelet count of 9,000/mm^3. Platelet transfusion and ε-aminocaproic acid oral rinses were used to control bleeding. **A,** Buccal mucosa and palatal ecchymoses. **B,** Extrinsic stains on teeth from erythrocyte degradation following continual gingival oozing.

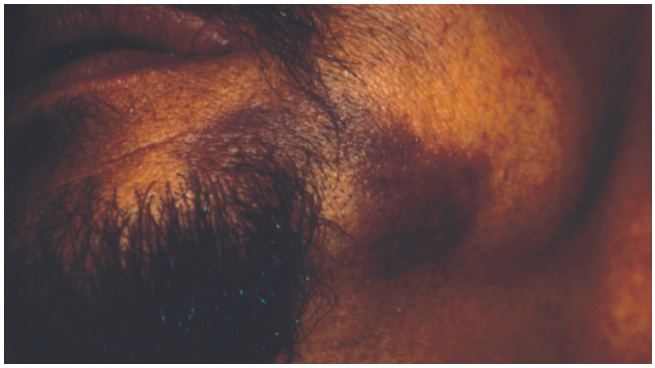


FIGURE 17-6 A 46-year-old male with severe liver cirrhosis due to hepatitis C infection. Shown is purpura of facial skin 1 week after full-mouth extractions.

Platelet Disorders

When medical management is unable to restore platelet counts to above the level of 50,000/mm^3 required for surgical hemostasis, platelet transfusions may be required prior to dental extractions or other oral surgical procedures. The therapeutically expected increment in platelet count from infusion of one unit of platelets is approximately 10,000 to 12,000/mm^3. Six units of platelets are commonly infused at a time. Patients who have received multiple transfusions may be refractory to random donor platelets as a result of alloimmunization. These individuals may require single-donor apheresis or leukocyte-reduced platelets. Local hemostatic measures are also important. The thrombasthenic patient needing dental extractions may be successfully treated with the use of hemostatic measures such as microfibrillar collagen and antifibrinolytic drugs.[32,33]

Since the antiplatelet activity of aspirin remains for the 8- to 10-day lifetime of the affected platelets, avoidance of aspirin is recommended for 1 to 2 weeks prior to extensive oral surgical procedures. Other NSAIDs have a similar but less pronounced antiplatelet effect. Adjunctive local hemostatic agents are useful in preventing postoperative oozing when aspirin therapy is in use at the time of minor oral surgery. When extensive surgery is emergently indicated, DDAVP can be used to decrease the aspirin-induced prolongation of the BT or to treat aspirin-related postoperative oozing, often eliminating the need for platelet infusion.[119]

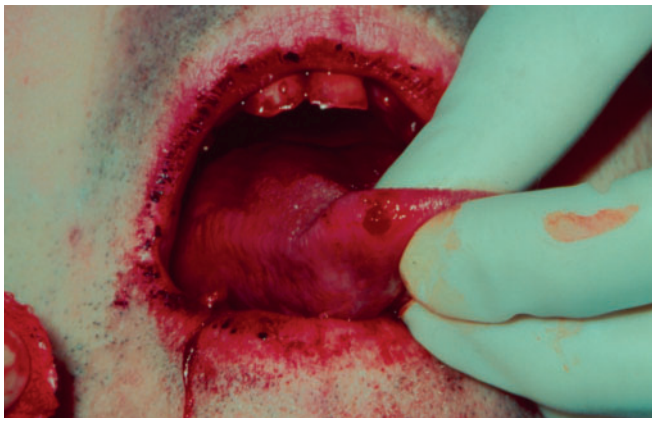


FIGURE 17-7 A 27-year-old male with type III von Willebrand's disease and a 2-week duration of bleeding from the tongue that reduced his hematocrit to 16%. Hemorrhage control was obtained with cryoprecipitate.

Chemotherapy-associated oral hemorrhages, most frequently related to thrombocytopenia, are best managed by transfusions of HLA-matched platelets and FFP, together with topically applied clot-promoting agents.[45] A pilot study suggests a possible benefit of DDAVP for the prevention or treatment of bleeding in patients with thrombocytopenia associated with hematologic malignancy.[120]

Hemophilias A and B and Von Willebrand's Disease

ORAL SURGICAL PROCEDURES

Oral surgical procedures have the greatest potential for hemorrhage of all dental procedures. Hemorrhagic problems after extractions have drastically declined over the last 20 years such that only an estimated 8% of hemophilic patients experience one or more delayed bleeding episodes.[121] Appropriate precautionary measures now allow surgery to be performed safely. To make certain that preoperative factor levels of at least 40 to 50% of normal activity have been obtained, transfusion recommendations generally aim for replacement of missing coagulation factors to levels of 50 to 100% when single-bolus infusion is used for outpatient treatment. This provides greater assurance of hemorrhage control, given the problems of possible failure of factor activity to rise as high as expected and variable plasma half-lives of 8 to 12 hours for F VIII and 18 to 24 hours for F IX. Additional postoperative factor maintenance may be indicated for extensive surgery. This can be accomplished by infusion of factor concentrates, DDAVP, cryoprecipitate, or FFP, depending on the patient's deficiency state. When postsurgical bleeding occurs due to fibrinolysis, it commonly starts 3 to 5 days after surgery and can usually be controlled by local measures and use of antifibrinolytics. Continual oozing from unstable fibrinous clots may require their removal and the repacking of the extraction socket with hemostatic agents.

Determination of factor replacement requirements for surgical hemostasis and selection of plasma product or drug therapy should be accomplished in consultation with the patient's hematologist. Canadian clinical practice guidelines[122] recommend replacement factor levels of 40 to 50% of F VIII (dose 20–25 U/kg) and F IX (dose 40–50 U/kg), used in conjunction with antifibrinolytics. Gingival or dental bleeding unresponsive to antifibrinolytics requires 20 to 30% clotting F VIII or F IX.[122] The level of factor activity required for hemostasis varies in relation to local factors. Higher hemostatic factor levels are needed for large wound cavities created by extraction of multiple or multirooted teeth, or when gingival inflammation, bleeding, tooth mobility, or apical lesions are present.[114] Kaneda and colleagues[114] report that deficient factor activity levels required for postextraction hemostasis varied from 3.5 to 25% for deciduous teeth and 5.5 to 20% for permanent teeth.[114]

Three methods of replacement therapy have been employed to maintain circulating factor levels above the 20% minimum necessary for hemostasis during surgical and healing phases. These include intermittent replacement therapy, continuous intravenous factor infusion therapy, and a single preoperative factor concentrate infusion combined with an antifibrinolytic mouthwash.[123] Factor VIII levels may be sufficiently raised by DDAVP in some patients with mild to moderate hemophilia A and vWD to allow dental extractions without transfusion.

Local hemostatic agents and techniques include pressure, surgical packs, vasoconstrictors, sutures, surgical stents, topical thrombin, and use of absorbable hemostatic materials. Although having no direct effect on hemostasis, primary wound closure aids patient comfort, decreases blood clot size, and protects clots from masticatory trauma and subsequent bleeding.[124] Sutures can also be used to stabilize and protect packing. Resorbable and nonresorbable suture materials have proven to be equally effective. Avitene (Davol Inc, Cranston, RI) or Helitene (Integra Life Sciences Plainsboro, NJ), a microfibrillar collagen fleece, aids hemostasis when placed against the bleeding bony surface of a well-cleansed extraction socket. It acts to attract platelets, causing the release phenomenon to trigger aggregation of platelets into thrombi in the interstices of the fibrous mass of the clot.[125] Topical Thrombin (Thrombogen; Johnson and Johnson,New Brunswick,NJ), which directly converts fibrinogen in the blood to fibrin, is an effective adjunct when applied directly to the wound or carried to the extraction site in a nonacidic medium on oxidized cellulose. Surgifoam (Ethicon Inc, Piscataway, NJ) is an absorbable gelatin sponge with intrinsic hemostatic properties. A collagen absorbable hemostat manufactured as a 3 × 4–inch sponge (INSTAT; Ethican Inc, Piscataway, NJ) or fabricated as a nonwoven pad is also a useful adjunct. Surgical acrylic stents may be useful if carefully fabricated to avoid traumatic irritation to the surgical site. Diet restriction to full liquids for the initial 24 to 48 hours, followed by intake of soft foods for 1 to 2 weeks, will further protect the clot by reducing the amount of chewing and resultant soft-tissue disturbances.

Antifibrinolytic drugs such as ε-aminocaproic acid[126] (EACA; Amicar; Xanodyne Pharmacal Inc, Florence, KY) and tranexamic acid (AMCA; Cyclokapron; Pharmacia Corp, Peapack, NJ) inhibit fibrinolysis by blocking the conversion of plasminogen to plasmin, resulting in clot stabilization. Postsurgical use of EACA has been shown to significantly reduce the quantity of factor required to control bleeding when used in conjunction with presurgical concentrate infusion sufficient to raise plasma F VIII and F IX levels to 50%.[123,127,128] A regimen of 50 mg/kg of body weight EACA given topically and systemically as a 25% (250 mg/mL) oral rinse every 6 hours for 7 to 10 days appears adequate as an adjunct. Tranexamic acid (4.8%) oral rinse was found to be 10 times more potent than was EACA in preventing postextraction bleeding in hemophiliacs, with fewer side effects, but it is not routinely available in the United States.[129,130] Systemic antifibrinolytic therapy can be given orally or intravenously as EACA 75 mg/kg (up to 4 g) every 6 hours or AMCA 25 mg/kg every 8 hours until bleeding stops.[122]

Fibrin sealants or fibrin glue has been used effectively in Europe since 1978 as an adjunct with adhesive and hemostatic effects to control bleeding at wound or surgical sites, but it is not available as a commercial product in the United States.[131] Its use has allowed reduction in factor concentrate replacement levels in hemophiliacs undergoing dental surgeries when used in combination with antifibrinolytics.[132–134] Use of fibrin glue does not obviate the need for factor concentration replacement in severe hemophiliacs.[133] In the United States, extemporaneous fibrin sealant can be made by combining cryoprecipitate with a combination of 10,000 units topical thrombin powder diluted in 10 mL saline and 10 mL calcium chloride. When dispensed over the wound simultaneously from separate syringes, the cryoprecipitate and calcium chloride precipitate almost instantaneously to form a clear gelatinous adhesive gel.

PAIN CONTROL

A variety of techniques are used to control pain in individuals with coagulopathies. An assessment of the patient's pain threshold and invasiveness of the dental procedure to be undertaken allows selection of an effective management approach. Some patients opt for treatment without anesthesia. Hypnosis,[135] intravenous sedation with diazepam, or nitrous oxide/oxygen analgesia, used as adjuncts to control anxiety, drastically reduce or totally eliminate the need for local anesthesia.[136] Intrapulpal anesthesia is safe and effective following access for pulp extirpation. Periodontal ligament and gingival papillary injections can be accomplished with little risk when delivered slowly with minimal volume.[137] Anesthetic solutions with vasoconstrictors such as epinephrine should be used when possible. In patients with mild disease, buccal, labial, and hard palatal infiltration can be attempted for maxillary teeth, with slow injection and local pressure to the injection site for 3 to 4 minutes.[136] If a hematoma develops, ice packs should be applied to the area to stimulate vasoconstriction, and emergency factor replacement should be administered in a hospital.

Block injections used in dentistry, including inferior alveolar, posterior superior alveolar, infraorbital, and (to a lesser extent) long buccal, require minimal coagulation factor levels of 20 to 30%. These injections place anesthetic solutions in highly vascularized loose connective tissue with no distinct boundaries, where formation of a dissecting hematoma is possible.[138] Webster and colleagues[117] reported development of hematomas in 8% of hemophilic patients not treated with prophylactic factor replacement prior to mandibular block injection.[117] Greater risk occurred with severe disease than with mild, and with hemophilia A than with B.[117] Extravasation of blood into the soft tissues of the oropharyngeal area in hemophiliacs can produce gross swelling, pain, dysphagia, respiratory obstruction, and grave risk of death from asphyxia[139–141] (Figure 17-7).

Dental treatment in the operating room under general anesthesia may be indicated when extensive procedures necessitate numerous expensive factor infusions, when patient

cooperation or anxiety prohibits outpatient clinic or office treatment, or when the patient with an inhibitor has multiple treatment needs. Although oral endotracheal intubation provides access challenges for the dental operator, it is preferred over nasal endotracheal intubation, which carries the risk of inducing a nasal bleed that can be difficult to control. The use of aspirin and other NSAIDs for pain management are contraindicated in patients with bleeding disorders due to their inhibition of platelet function and potentiation of bleeding episodes. Intramuscular injections should also be avoided due to the risk of hematoma formation.

PREVENTIVE AND PERIODONTAL THERAPIES

Periodontal health is of critical importance for the hemophiliac for two principal reasons: (1) hyperemic gingiva contributes to spontaneous and induced gingival bleeding and (2) periodontitis is a leading cause of tooth morbidity, necessitating extraction. Individuals with bleeding diatheses are unusually prone to oral hygiene neglect due to fear of toothbrush-induced bleeding. On the contrary, oral physiotherapy can be accomplished without risk of significant bleeding. Periodontal probing and supragingival scaling and polishing can be done routinely. Careful subgingival scaling with fine scalers rarely warrants replacement therapy. Severely inflamed and swollen tissues are best treated initially with chlorhexidine oral rinses or by gross débridement with a cavitron or hand instruments to allow gingival shrinkage prior to deep scaling.[118] Deep subgingival scaling and root planing should be performed by quadrant to reduce gingival area exposed to potential bleeding. Locally applied pressure and post-treatment antifibrinolytic oral rinses are usually successful in controlling any protracted oozing.[142] Local block anesthesia required for scaling may necessitate raising factor levels to a minimum of 30% of normal prior to treatment.[143] Periodontal surgical procedures warrant elevating circulating factor levels to 50% and use of post-treatment antifibrinolytics. Periodontal packing material aids hemostasis and protects the surgical site; however, it may be dislodged by severe hemorrhage or subperiosteal hematoma formation.

RESTORATIVE AND PROSTHODONTIC THERAPY

General restorative and prosthodontic procedures do not result in significant hemorrhage. Rubber dam isolation is advised to minimize the risk of lacerating soft tissue in the operative field and to avoid creating ecchymoses and hematomas with high-speed evacuators or saliva ejectors. Care is required to select a tooth clamp that does not traumatize the gingiva. Matrices, wedges, and a hemostatic gingival retraction cord may be used with caution to protect soft tissues and improve visualization when subgingival extension of cavity preparation is necessary. Removable prosthetic appliances can be fabricated without complications. Denture trauma should be minimized by prompt and careful postinsertion adjustment.

ENDODONTIC THERAPY

Endodontic therapy is often the treatment of choice for a patient with a severe bleeding disorder, especially when an inhibitor is present because extraction carries a high risk of hemorrhage, and treatment is expensive. Generally, there are no contraindications to root canal therapy, provided instrumentation does not extend beyond the apex.[144] Filling beyond the apical seal also should be avoided. Application of epinephrine intrapulpally to the apical area is usually successful in providing hemostasis. Endodontic surgical procedures require the same factor replacement therapy as do oral surgical procedures.

PEDIATRIC DENTAL THERAPY

The pediatric dental patient occasionally presents with prolonged oozing from exfoliating primary teeth. Administration of factor concentrates and extraction of the deciduous tooth with curettage may be necessary for patient comfort and hemorrhage control. Moss[29] advocates extraction of mobile primary teeth using periodontal space anesthesia without factor replacement after 2 days of vigorous oral hygiene to reduce local inflammation. Hemorrhage control is obtained with gauze pressure, and seepage generally stops in 12 hours. Pulpotomies can be performed without excessive pulpal bleeding. Stainless steel crowns should be prepared to allow minimal removal of enamel at gingival areas.[145] Topical fluoride treatment and use of pit-and-fissure sealants are important noninvasive therapies to decrease the need for extensive restorative procedures.

ORTHODONTIC THERAPY

Orthodontic treatment can be provided with little modification. Care must be observed to avoid mucosal laceration by orthodontic bands, brackets, and wires. Bleeding from minor cuts usually responds to local pressure. Properly managed fixed orthodontic appliances are preferred over removable functional appliances for the patient with a high likelihood of bleeding from chronic tissue irritation. The use of extraoral force and shorter treatment duration further decrease the potential for bleeding complications.[146]

Patients on Anticoagulants

Management of the dental patient on anticoagulant therapy involves consideration of the degree of anticoagulation achieved as gauged by the PT/INR, the dental procedure planned, and the level of thromboembolic risk for the patient.[147] In general, higher INRs result in higher bleeding risk from surgical procedures. It is generally held that nonsurgical dental treatment can be successfully accomplished without alteration of the anticoagulant regimen, provided the PT/INR is not grossly above the therapeutic range and trauma is minimized.[148,149] Greater controversy exists over the management of anticoagulated patients for oral surgical procedures.[60,150] Preparation of the anticoagulated patient for surgical procedures depends on the extent of bleeding expected. No surgical treatment is recommended for those with an INR of > 3.5 to 4.0 without coumarin dose modification.[60,150] With an INR < 3.5 to 4.0, minor surgical procedures with minimal anticipated bleeding require local

measures but no coumarin modification. At an INR of < 3.5 to 4.0, when moderate bleeding is expected (multiple extractions or removal of wisdom teeth), local measures should be used, and INR reduction should be considered. When significant bleeding is anticipated, as from full-mouth or full-arch extractions, local measures are combined with reduction of anticoagulation to an INR of < 2.0 to 3.0.[60,151] Extensive flap surgery or multiple bony extractions may require an INR of < 1.5.[60]

For surgical procedures, physician consultation is advised in order to determine the patient's most recent PT/INR level and the best treatment approach based on the patient's relative thromboembolic and hemorrhagic risks. When the likelihood of sudden thrombotic and embolic complications is small and hemorrhagic risk is high, coumarin therapy can be discontinued briefly at the time of surgery, with prompt re-institution postoperatively.[147,152,153] Coumarin's long half-life of 42 hours necessitates dose reduction or withdrawal 2 days prior to surgery in order to return the patient's PT/INR to an acceptable level for surgery.[147,154] For patients with moderate thromboembolic and hemorrhagic risks, coumarin therapy can be maintained in the therapeutic range with the use of local measures to control postsurgical oozing.[155,156]

High-risk cardiac patients undergoing high-bleeding-risk surgical procedures may be managed most safely with a combination heparin-coumarin method,[153] which allows maximal hemostasis with minimal nonanticoagulated time (14–18 hours for a 2-hour surgery, as opposed to 3–4 days with the coumarin discontinuation method). This technique, which requires hospitalization at additional cost, substitutes parenteral heparin, which has a 4-hour half-life, for coumarin. Coumarin is withheld 24 hours prior to admission. Heparin therapy, instituted on admission, is stopped 6 to 8 hours preoperatively. Surgery is accomplished when the PT/INR and aPTT are within the normal range. Coumarin is re-instituted on the night of the procedure and may require 2 to 4 days to effectively reduce the patient's procoagulant levels to a therapeutic range. Heparin is reinstituted 6 to 8 hours after surgery when an adequate clot has formed. Heparin reinstitution by bolus injection (typically a 5,000 U bolus) carries a greater risk of postoperative bleeding than does gradual reinfusion (typically 1,000 U/h).

Use of additional local hemostatic agents such as microfibrillar collagen, oxidized cellulose, or topical thrombin is recommended for anticoagulated patients. Fibrin sealant has been used successfully as an adjunct to control bleeding from oral surgical procedures in therapeutically anticoagulated patients with INRs from 1.0 to 5.0, with minimal bleeding complications.[157] In Europe, 4.8% tranexamic acid solution used as an antifibrinolytic mouthwash has proven effective in control of oral surgical bleeding in patients with INRs between 2.1 and 4.8.[158,159] Use of antifibrinolytics may have value in control of oral wound bleeding, thereby alleviating the need to reduce the oral anticoagulant dose.[160] Use of medications that interact with coumarin, altering its anticoagulant effectiveness as discussed above, is to be avoided.

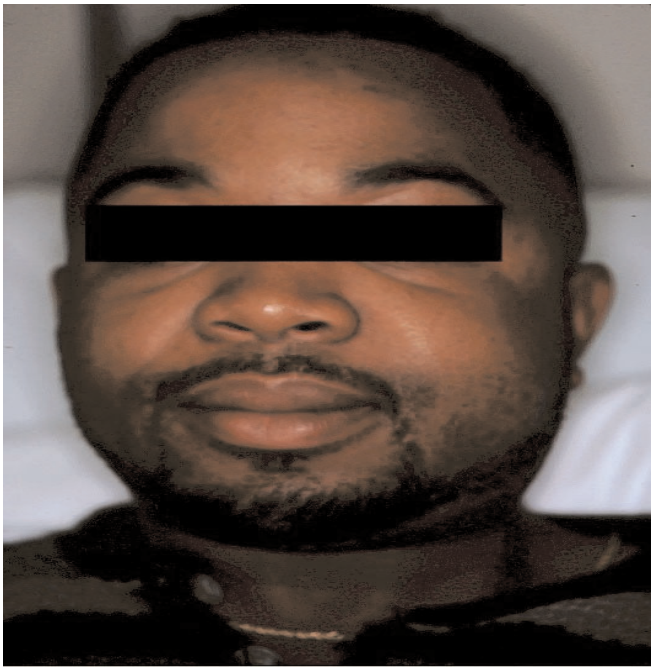


FIGURE 17-8 A 24-year-old male with severe hemophilia A and low-titer inhibitor, 3 days after inferior alveolar block–induced parapharyngeal hemorrhage. Patient presented with difficulty swallowing and pending airway compromise 8 hours after nerve block. Subsequent treatment with prothrombin complex concentrates over 3 days controlled the bleeding and began the resolution of facial swelling.

The shorter-acting anticoagulant heparin is administered by intravenous or subcutaneous route. The most common outpatient use of subcutaneous heparin is for the treatment of deep venous thrombophlebitis during pregnancy,[161] with the goal being regulation of the aPTT between 1.25 and 1.5 times control. In general, oral surgical procedures can be carried out without great risk of hemorrhage when local hemostatics are used in a patient receiving heparin subcutaneously; however, on consultation, the patient's physician may recommend withholding the scheduled injection immediately prior to the operation. Continuous intravenous heparin, with greater hemorrhagic potential than heparin delivered subcutaneously, is discontinued 6 to 8 hours prior to surgery to allow adequate surgical hemostasis. If a bleeding emergency arises, the action of heparin can be reversed by protamine sulfate.

Susceptibility to Infection

Susceptibility to infection among patients with congenital bleeding disorders is not a significant concern. Should a hematoma form as a result of an anesthetic injection or other dental trauma or spontaneously, use of a broad-spectrum antibiotic is indicated to prevent infection during resolution. If bleeding results from bone marrow suppressive systemic disease or chemotherapeutic drug use, antibiotics may be required to prevent infection from bacteremia-inducing dental procedures when production of mature functional neutrophils is substantially diminished (see "Leukemia" in Chapter 16).

Ability to Withstand Care

Patients with bleeding disorders, appropriately prepared preoperatively, are generally as able to withstand dental care as well as unaffected individuals. Consultation with the patient's physician is recommended for guidance on medical management required for higher-risk surgical dental procedures. Because of the expense of some medical management approaches to severe bleeding disorders (eg, coagulation factor replacement for severe hemophiliacs), the coumarin withdrawal–heparinization approach to extractions for patients at high risk of thrombosis, and the bleeding risk to the patient, long treatment sessions may be required to maximize treatment accomplishments while minimizing the risk and cost.

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