

Bleeding Disorders of Importance in Dental Care and Related Patient Management

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ABSTRACT

Oral care providers must be aware of the impact of bleeding disorders on the management of dental patients. Initial recognition of a bleeding disorder, which may indicate the presence of a systemic pathologic process, may occur in dental practice. Furthermore, prophylactic, restorative and surgical dental care of patients with bleeding disorders is best accomplished by practitioners who are knowledgeable about the pathology, complications and treatment options associated with these conditions. The purpose of this paper is to review common bleeding disorders and their effects on the delivery of oral health care.

MeSH Key Words: blood coagulation/physiology; blood coagulation disorders/complications; dental care

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Dentists must be aware of the impact of bleeding disorders on the management of their patients. Proper dental and medical evaluation of patients is therefore necessary before treatment, especially if an invasive dental procedure is planned. Patient evaluation and history should begin with standard medical questionnaires. Patients should be queried about any previous unusual bleeding episode after surgery or injury, spontaneous bleeding and easy or frequent bruising. For the purpose of history-taking, a clinically significant bleeding episode¹ is one that:

- continues beyond 12 hours
- causes the patient to call or return to the dental practitioner or to seek medical treatment or emergency care
- results in the development of hematoma or ecchymosis within the soft tissues or
- requires blood product support.

Most reported bleeding episodes are minor and do not require a visit to the dentist or the emergency department and do not affect dental treatment significantly.

The patient should be asked for any history of significant and prolonged bleeding after dental extraction or bleeding from gingivae. A history of nasal or oral bleeding should be noted. Many bleeding disorders, such as hemophilia and von Willebrand's disease, run in families; therefore, a family history of bleeding disorders should be carefully elicited.

A complete drug history is important. If a patient is taking anticoagulant drugs, it will be important to consult his or her physician before any major surgical procedure. In addition, a number of medications may interfere with hemostasis and prolong bleeding. Drugs of abuse, such as alcohol or heroin, may also cause excess bleeding² by causing liver damage resulting in altered production of coagulation factors. Illicit injection drug use carries an increased risk of transmission of viral pathogens that may lead to viral hepatitis and altered liver function.

A general examination of the patient might indicate a tendency to bleed. Multiple purpurae of the skin, bleeding wounds, evident

Table 1 Common bleeding disorders

Coagulation factor deficiencies	<p>Congenital Hemophilia A and B von Willebrand's disease Other factor deficiencies (rare)</p> <p>Acquired Liver disease Vitamin K deficiency, warfarin use Disseminated intravascular coagulation</p>
Platelet disorders	<p>Quantitative disorder (thrombocytopenia) Immune-mediated Idiopathic Drug-induced Collagen vascular disease Sarcoidosis Non-immune-mediated Disseminated intravascular coagulation Microangiopathic hemolytic anemia Leukemia Myelofibrosis</p> <p>Qualitative disorder Congenital Glanzmann thrombasthenia von Willebrand's disease Acquired Drug-induced Liver disease Alcoholism</p>
Vascular disorders	<p>Scurvy Purpura Hereditary hemorrhagic telangiectasia Cushing syndrome Ehlers-Danlos syndrome</p>
Fibrinolytic defects	<p>Streptokinase therapy Disseminated intravascular coagulation</p>

hematomas or swollen joints may be evident in patients with severe bleeding defects. In addition, patients may show signs of underlying systemic disease. Patients with liver disease may have jaundice, spider nevi, ascites and other signs of impaired hepatic function. A cardiac patient can show tachycardia or hypertension, which may make hemostasis more difficult to achieve. Evidence of petechiae, ecchymoses, hematomas or excessive gingival bleeding should direct the practitioner's attention toward a possible underlying bleeding disorder. When a bleeding disorder is suspected, laboratory investigations, including blood counts and clotting studies, should be carried out. Preoperative laboratory tests of the hemostatic system^{1,2} are:

- bleeding time to determine platelet function (normal range: 2–7 minutes)

- activated partial thromboplastin time to evaluate the intrinsic coagulation pathway (normal range: 25 ± 10 seconds)
- international normalized ratio to measure the extrinsic pathway (normal range: 1.0)
- platelet count to quantify platelet function (normal range: 150,000–450,000/ μ L).

Types of Bleeding Disorders

Bleeding disorders can be classified as coagulation factor deficiencies, platelet disorders, vascular disorders or fibrinolytic defects (**Table 1**).^{3,4}

Among the congenital coagulation defects, hemophilia A, hemophilia B (Christmas disease) and von Willebrand's disease are the most common. Hemophilia A is due to a deficiency of clotting factor VIII or antihemophilic factor. It is an inherited X-linked recessive trait found in males. Symptoms may include delayed bleeding, ecchymosis, deep hematomas, epistaxis, spontaneous gingival bleeding and hemarthrosis. A factor VIII level of 6% to 50% of normal factor activity (mild hemophilia) is associated with bleeding during surgery or trauma; 1% to 5% with bleeding after mild injury; and < 1% (severe hemophilia) with spontaneous bleeding.³

Management of hemophilia A among patients undergoing dental surgery consists of² increasing factor VIII levels, replacing factor VIII and inhibiting fibrinolysis (**Table 2**). Desmopressin (DDAVP) is used to achieve a transient increase in factor VIII level through the release of en-

dogenous factor VIII in patients with hemophilia A and von Willebrand's disease. It may be sufficient to achieve hemostasis in mild forms of these diseases. DDAVP may be combined with antifibrinolytic agents to increase its effectiveness.²

Options for factor VIII replacement are factor VIII concentrates, fresh frozen plasma and cryoprecipitate. Highly purified forms of factor VIII concentrates, manufactured using recombinant or monoclonal antibody purification techniques, are preferred because of their greater viral safety.^{5,6} New generations of recombinant factor VIII are being developed that are free from human and animal proteins, in an attempt to further improve their safety.⁷ In patients who produce antibodies to factor VIII, a higher dose of concentrated factors can be considered, but a focus on local measures is critical.

Antifibrinolytic therapy can be used postoperatively to protect the formed blood clot. Epsilon-aminocaproic

Table 2 Presurgery treatment for hemophilia A⁴

Condition	Treatment and dose	Potential complications
Mild bleeding	Dose: 15 U/kg factor VIII every 8–12 hours for 1–2 days Target: 30% of normal level	Hemarthrosis, oropharyngeal or dental bleeding, epistaxis, hematuria
Major bleeding	Dose: 50 U/kg factor VIII every 8–12 hours for 7–14 days Target: 80% to 100% of normal level	Same potential complications as for mild bleeding, as well as central nervous system hemorrhage, retroperitoneal hemorrhage, gastrointestinal bleeding
Adjunctive therapy	Desmopressin, tranexamic acid or epsilon-aminocaproic acid (for mild disease)	

Table 3 Systemic diseases causing coagulopathies¹

Disease	Common causes	Resulting coagulation defect
Renal failure and uremia	Diabetes mellitus Glomerulonephritis Pyelonephritis Hypertension	Inhibition of adhesion and primary aggregation of platelets from glycoprotein IIb–IIIa deficit
Hepatic failure	Alcohol abuse Hepatitis B and C Cancer (e.g., hepatocellular carcinoma)	Obstructive jaundice: deficiency of vitamin K-dependent factors II, VII, IX and X Loss of liver tissue and all clotting factors except VIII and von Willebrand's factor
Bone marrow failure	Alcohol abuse Cancer (e.g., leukemia) Myelosuppressive medications (e.g., chemotherapy for cancer) Uremia from renal failure	Reduced number of functioning platelets Anemia from bone marrow suppression

acid and tranexamic acid are the common agents used. Tranexamic acid in an oral rinse helps prevent postoperative bleeding from surgical wounds. Postoperative use of epsilon-aminocaproic acid can considerably reduce the level of factor required to control bleeding when used in conjunction with presurgical infusion of factor VIII concentrate.^{8–10}

Hemophilia B is the result of factor IX deficiency. It is managed by replacement therapy with highly purified, virally inactivated factor IX concentrates. Prothrombin complex concentrates can also be used for factor IX replacement.

von Willebrand's disease is the most common hereditary coagulation disorder with an incidence of 1 in 10,000. It is not sex linked. It is classified as Type I to Type IV and may vary in severity. For mild conditions, use of DDAVP may be sufficient, but severe disease warrants factor VIII replacement.

Other than congenital diseases, coagulation defects may be acquired and from a variety of sources (**Table 3**). In liver diseases, the synthesis of clotting factors may be reduced due to parenchymal damage or obstruction.¹¹ These patients may have a variety of bleeding disorders depending on the extent of their liver disease. Management options for hemostatic defects in liver disease⁵ include vitamin K and fresh frozen plasma infusion (immediate but temporary effect) for prolonged prothrombin time and partial thromboplastin time; cryoprecipitate for replacement of factor VIII deficiency; and replacement therapy for disseminated intravascular coagulation. Patients suffering from viral hepatitis are a potential source of cross infection, and necessary precautions should be taken during procedures. Drug doses frequently need to be modified in these patients due to impaired liver function. The patient's physician should be consulted before making any changes in the drug regimen.

Table 4 Principal agents for systemic management of patients with bleeding disorders³

Agent	Description	Common indications
Platelets	1 unit = 50 mL; may raise count by 6,000	Platelet count < 10,000 in nonbleeding individuals < 50,000 presurgical level < 50,000 in actively bleeding individuals Nondestructive thrombocytopenia
Fresh frozen plasma	1 unit = 150–250 mL 1 hour to thaw Contains factors II, VII, IX, X, XI, XII, XIII and heat-labile V and VII	Undiagnosed bleeding disorder with active bleeding Severe liver disease When transfusing > 10 units of blood Immune globulin deficiency
Cryoprecipitate	1 unit = 10–15 mL	Hemophilia A, von Willebrand's disease, when factor concentrates and DDAVP are unavailable Fibrinogen deficiency
Factor VIII concentrate	1 unit raises factor VIII level 2% Heat-treated contains von Willebrand's factor Recombinant and monoclonal technologies are pure factor VIII	Hemophilia A with active bleeding or presurgery; some cases of von Willebrand's disease
Factor IX concentrate	1 unit raises factor IX level 1–1.5% Contains factors II, VII, IX and X Monoclonal formulation contains only factor IX	Hemophilia B, with active bleeding or presurgery Prothrombin complex concentrates used for hemophilia A with inhibitor
Desmopressin	Synthetic analogue of antidiuretic hormone 0.3µg/kg IV or SC Intranasal application	Active bleeding or presurgery for some patients with von Willebrand's disease, uremic bleeding of liver disease, bleeding esophageal varices
Epsilon-aminocaproic acid	Antifibrinolytic: 25% oral solution (250 mg/mL) Systemic: 75 mg/kg every 6 hours	Adjunct to support clot formation for any bleeding disorder
Tranexamic acid	Antifibrinolytic: 4.8% mouth rinse (not available in the United States) Systemic: 25mg/kg every 8 hours	Adjunct to support clot formation for any bleeding disorder

Note: IV = intravenous; SC = subcutaneous.

Coagulopathies can be drug induced. Warfarin, low-molecular-weight heparin and dicumarol (coumadin) are the most commonly used anticoagulant drugs. Treatment must be modified in accordance with the medications that the patient is taking and their impact on coagulation.

Platelet disorders can be hereditary or acquired and may be due to decreased platelet production, excess consumption or altered function. The most common clinical features are bleeding from superficial lesions and cuts, spontaneous gingival bleeding, petechiae, ecchymosis and epistaxis.

The minimum blood platelet level before dental surgical procedures is approximately 50,000/µL; extensive

surgery may require > 100,000/µL. Replacement therapy may be required if the count is below this level. Usually, platelet transfusion is carried out 30 minutes before surgery. In patients with platelet levels below 100,000/µL prolonged oozing may occur, but local measures are usually sufficient to control the bleeding. In cases of idiopathic thrombocytopenic purpura, an acquired platelet disorder, oral systemic steroids may be prescribed 7–10 days before surgery to increase the platelet count to safe levels.¹² Patients with Glanzmann thrombasthenia, an autosomal recessive disorder causing a defect in platelet aggregation, are given platelet infusion before surgery.

Table 5 Local hemostatic agents

Brand name	Generic name or description
Gelfoam (Pfizer, Markham, Ont.)	Absorbant gelatin sponge material
Bleed-X (QAS, Orlando, Fla.)	Microporous polysaccharide hemispheres
Surgicel (Ethicon, Markham, Ont.)	Oxidized cellulose
Tisseel (Baxter, Mississauga, Ont.)	Fibrin sealant
Thrombostat (Pfizer)	Topical thrombin
Cyklokapron (Pfizer)	Tranexamic acid
Amicar (Wyeth, Markham, Ont.)	Epsilon-aminocaproic acid

A number of drugs interfere with platelet function (**Appendix A**). Acetylsalicylic acid (ASA) and dipyridamole are used therapeutically for platelet function inhibition. Discontinuation of these drugs is not required for routine procedures.

Vascular defects are rare and usually associated with mild bleeding confined to skin or mucosa.¹³ Scurvy, hereditary hemorrhagic telangiectasia and other vascular defects are usually treated with laser ablation, embolization or coagulation. Recognizing vascular lesions during examination, aspiration or advanced imaging may lead to modification of treatment planning.

Fibrinolytic defects may occur in patients on medical therapy and those with coagulation syndromes where fibrin is consumed (disseminated intravascular coagulation). Recognition is important and oral care must be managed in consultation with a hematologist.

Oral Findings

Platelet deficiencies can cause petechiae or ecchymosis in oral mucosa and promote spontaneous gingival bleeding. These disorders may be present alone or in conjunction with gingival hyperplasia in cases of leukemia. Hemosiderin and other blood degradation products can cause brown deposits on the surface of teeth due to chronic bleeding.

People with hemophilia may have multiple bleeding events over their lifetime. The frequency of bleeding depends on the severity of hemophilia. Hemarthrosis of the temporomandibular joint is uncommon.³

The incidence of dental caries and periodontal diseases is higher in patients with bleeding disorders, which may be because of lack of effective oral hygiene and professional dental care due to fear of oral bleeding.

Dental Management

The management of patients with bleeding disorders depends on the severity of the condition and the invasiveness of the planned dental procedure. If the procedure has limited invasiveness and the patient has a mild bleeding disorder, only slight or no modification will be required. In patients with severe bleeding disorders, the goal is to minimize the challenge to the patient by restoring the hemostatic system to acceptable levels and maintaining hemostasis by local and adjunctive methods. The patient's physician should be consulted before invasive treatment is undertaken. In patients with drug-induced coagulopathies, drugs may be stopped or the doses modified. For irreversible coagulopathies, replacement of missing factors may be necessary (**Table 4**).

Pain Control

In patients with coagulopathies, nerve-block anesthetic injections are contraindicated unless there is no better alternative and prophylaxis is provided, as the anesthetic solution is deposited in a highly vascularized area, which carries a risk of hematoma formation.^{14,15} The commonly used blocks require minimum clotting factor levels of 20% to 30%. Extravasation of blood in the oropharyngeal area by an inferior alveolar block or in the pterygoid plexus can produce gross swelling, pain, dysphasia, respiratory obstruction and risk of death from asphyxia.¹⁶⁻¹⁸ Anesthetic infiltration and intraligamentary anesthesia are potential alternatives to nerve block in many cases. An anesthetic with a vasoconstrictor should be used when possible. Alternative techniques, including sedation with diazepam or nitrous oxide-oxygen analgesia, can be employed to reduce or eliminate the need for anesthesia. Patients undergoing extensive treatment requiring factor replacement may be treated under general anesthesia in a hospital operating room.

Oral Surgery

Surgical procedures carry the highest risk of bleeding, and safety precautions are needed. For coagulopathies, transfusion of appropriate factors to 50% to 100% of normal levels is recommended when a single bolus infusion is used in an outpatient setting. In patients with hemophilia, additional postoperative factor maintenance may be required after extensive surgeries. This can be done with factor infusion, DDAVP, cryoprecipitate or fresh frozen plasma depending on the patient's condition. The patient's hematologist should be consulted before planning, and patients with severe disease should be treated in specialty centres.

Local hemostatic agents (**Table 5**) and techniques such as pressure, surgical packs, sutures and surgical stents may be used individually or in combination and may assist in the local delivery of hemostatic agents, such as topical thrombin and vasoconstrictors. However,

caution is needed with the use of vasoconstrictors because of the risk of rebound vasodilatation, which may increase late bleeding risk. The use of absorbable hemostatic materials may favour clot formation and stability. However, these materials also carry a risk of infection and may delay healing; they should therefore be avoided in immunosuppressed patients. Topical thrombin is an effective agent when applied directly on the bleeding wound as it converts fibrinogen to fibrin and allows rapid hemostasis in a wound. Topical fibrin glue can reduce the amount of factor replacement needed when used along with antifibrinolytic agents.¹⁹⁻²² Fibrin glue has also been effectively used in conjunction with other hemostatic measures.

The use of drugs affecting bleeding mechanisms does not usually pose a significant problem in dental treatment. If ASA has to be withdrawn, this should be done at least 10 days before surgery. In most cases, ASA therapy does not need to be stopped, and local hemostatic measures are sufficient to control bleeding. Similarly, other antiplatelet drugs, such as clopidogrel and dipyridamole, usually do not need to be stopped. The patient's physician should be consulted before any decision is made to modify the patient's drug regimen, and the potential risk-benefit ratio should be determined. For patients taking warfarin, their international normalized ratio (INR) should be measured before a surgical procedure. The normal therapeutic range is 2.0-3.0. According to current recommendations, most oral surgical procedures can be performed without altering the warfarin dose if the INR is less than 3.0.²³ If INR values are greater than 3.0, physician referral is suggested. It is important to consider the risk of reducing the level of anticoagulation in patients on warfarin due to the risk of a thromboembolic event.²⁴ Patients taking heparin are often those who are on hemodialysis due to end-stage renal disease. Heparin has a short half-life (about 5 hours) and patients can often be treated safely on the days between dialysis.

Periodontal Procedures

Periodontal health is of critical importance in patients with bleeding disorders³ as inflamed and hyperemic gingival tissues are at increased risk of bleeding. Periodontitis may cause tooth mobility and warrant extraction, which may be a complicated procedure in these patients. Patients with coagulopathies may neglect their oral health due to fear of bleeding during tooth brushing and flossing, which leads to increased gingivitis, periodontitis and caries.

Periodontal probing, supragingival scaling and polishing can be done normally without the risk of significant bleeding. Factor replacement is seldom needed for subgingival scaling and root planing if these procedures are done carefully. Ultrasonic instrumentation may result in less tissue trauma. For severely inflamed tissues, initial

treatment with chlorhexidine mouthwashes and gross debridement is recommended to reduce tissue inflammation before deep scaling.²⁵ Factor replacement may be required before extensive periodontal surgery and use of nerve blocks. Periodontal packing materials and custom vinyl mouthguards (stents) are used to aid in hemostasis and protect the surgical site, but these can be dislodged by severe hemorrhage or subperiosteal hematoma formation.³ Antifibrinolytic agents may be incorporated into periodontal dressings for enhanced effect. Post-treatment antifibrinolytic mouthwashes are usually effective in controlling protracted bleeding.

Restorative and Endodontic Procedures

General restorative procedures do not pose a significant risk of bleeding. Care should be taken to avoid injuring the gingiva while placing rubber dam clamps, matrices and wedges. A rubber dam should be used to prevent laceration of soft tissues by the cutting instruments. Saliva ejectors and high-speed suction can injure the mucosa in the floor of the mouth and cause hematoma or ecchymosis; thus, they should be used carefully.

Endodontic therapy is preferred over extraction whenever possible in these patients. Endodontic therapy does not usually pose any significant risk of bleeding and can be performed routinely. Endodontic surgical procedures may require factor replacement therapy.

Prosthodontic Procedures

These procedures do not usually involve a considerable risk of bleeding. Trauma should be minimized by careful post-insertion adjustments. Oral tissue should be handled delicately during the various clinical stages of prosthesis fabrication to reduce the risk of ecchymosis. Careful adjustment of prostheses is needed to reduce trauma to soft tissue.

Orthodontic Procedures

Orthodontic therapy can be carried out without bleeding complications, although care should be taken that appliances do not impinge on soft tissues and emphasis should be put on excellent, atraumatic oral hygiene.

Choice of Medications

Many medications prescribed in dental practice, especially ASA, may interfere with hemostasis. In addition, many drugs interact with anticoagulants, increasing their potency and the risk of bleeding. When used for prolonged periods, ASA and nonsteroidal anti-inflammatory drugs (NSAIDs) can increase the effect of warfarin. Penicillins, erythromycin, metronidazole, tetracyclines and miconazole also have potentiating effects on warfarin. Care should be taken when prescribing these drugs to patients with bleeding tendencies or those receiving anticoagulant therapy, and it may be

desirable to consult the patient's physician before planning the dose regimen. ❖

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Appendix A Drugs that may interfere with hemostasis¹²

<p>ASA and ASA-containing compounds</p> <p>Alka-Seltzer (ASA)</p> <p>Alka-Seltzer XS (ASA, caffeine, acetaminophen)</p> <p>Anadin, Anadin Maximum Strength (ASA, caffeine)</p> <p>Anadin Extra, Anadin Extra Soluble (ASA, caffeine, acetaminophen)</p> <p>Asasantin Retard (ASA, dipyridamole)</p> <p>Askit (ASA, aloxiprin, caffeine)</p> <p>Aspav (ASA, papaveretum)</p> <p>Aspro Clear, Maximum Strength Aspro Clear (ASA)</p> <p>Carpin (ASA)</p> <p>Co-codaprin (ASA, codeine phosphate)</p> <p>Codis 500 (ASA, codeine)</p> <p>Disprin, Disprin CV, Disprin Direct (ASA)</p> <p>Disprin Extra (ASA, acetaminophen)</p> <p>Disprin tablets (ASA, caffeine, chlorphenarmine, phenylephrine)</p> <p>Imazin XL (ASA, isosorbide mononitrate)</p> <p>Migramax (ASA, metoclopramide hydrochloride)</p> <p>Nurse Sayles' Powders (ASA, caffeine, acetaminophen)</p> <p>Phensic (ASA, caffeine)</p> <p>Veganin (ASA, acetaminophen, codeine)</p> <p>Other nonsteroidal anti-inflammatory drugs</p> <p>Acelofenac</p> <p>Azapropazone</p> <p>Celecoxib</p> <p>Diclofenac</p>	<p>Diflunisal</p> <p>Etodolac</p> <p>Fenbufen</p> <p>Fenoprofen</p> <p>Flubriprofen</p> <p>Ibuprofen</p> <p>Indomethacin</p> <p>Ketoprofen</p> <p>Ketorolac</p> <p>Mefenamic acid</p> <p>Meloxicam</p> <p>Nabumetone</p> <p>Naproxen</p> <p>Phenylbutazone</p> <p>Piroxicam</p> <p>Rofecoxib</p> <p>Sulindac</p> <p>Tenoxicam</p> <p>Tiaprofenic acid</p> <p>Tolfenamic acid</p> <p>Antibiotics/antifungals</p> <p>Aztreonam</p> <p>Cephalosporins (2nd and 3rd generation)</p> <p>Erythromycin</p> <p>Fluconazole</p> <p>Imipenem</p> <p>Isoniazid</p> <p>Ketoconazole</p> <p>Meropenem</p>	<p>Metronidazole</p> <p>Miconazole</p> <p>Penicillins</p> <p>Piperacillin</p> <p>Rifampicin</p> <p>Sulfonamides</p> <p>Tetracyclines</p> <p>Ticarcillin</p> <p>Trimethoprim</p> <p>Other medications</p> <p>Ateplase</p> <p>Amiodarone</p> <p>Anabolic steroids</p> <p>Barbiturates</p> <p>Carbamazepine</p> <p>Chloral hydrate</p> <p>Cholestyramine</p> <p>Chronic alcohol use</p> <p>Cimetidine</p> <p>Corticosteroids</p> <p>Dipyridamole</p> <p>Disulfiram</p> <p>Heparin</p> <p>Omeprazole</p> <p>Acetaminophen</p> <p>Phenytoin</p> <p>Quidine</p> <p>Sucalfate</p> <p>Tamoxifen</p> <p>Vitamin E (megadose)</p> <p>Warfarin</p>
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