Dental Management of Patients with Bleeding Disorders

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Continuing Education Units: 3 hours


Disclaimer: Participants must always be aware of the hazards of using limited knowledge in integrating new techniques or procedures into their practice. Only sound evidence-based dentistry should be used in patient therapy.

This continuing education course will provide dental professionals with general information for managing patients with bleeding disorders. Specifics of this course include: basic physiology of the hemostatic system; common bleeding disorders and their etiologies; requisite laboratory testing; and current evidence-based guidelines for the purpose of developing individualized treatment plans for such patients. Having a greater appreciation of these essentials will enable the dental practitioner to successfully treat patients with bleeding disorders.

Conflict of Interest Disclosure Statement
• The author reports no conflicts of interest associated with this work.

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Overview

Within the body’s vascular system, blood flows in its liquid state while clotting components of the hemostatic system circulate in their inactive forms. Once activated, the hemostatic components undergo a series of reactions to produce a clot at the site of an injured blood vessel, resulting in repair of the injury. If this healthy hemostatic system becomes defective, by means of a hypercoaguable condition or a bleeding disorder, abnormal clotting or blood loss is predictable, respectively. Consequently, hemostasis can be considered an unstable system. Having a working knowledge of the hemostatic system is vital for understanding pathophysiology while managing patients with bleeding or clotting problems.

Physiologically, hemostasis is the body’s mechanism designed to prevent blood loss by forming a clot within injured blood vessels. When activated, the hemostatic system involves a number of intricate and biochemical events, including three main phases: the vascular phase, the platelet phase and the coagulation phase.\(^2,3\) The vascular phase involves vasoconstriction of arteries and veins, exposure of collagen, and release of specialized tissue factors that activate platelets to the injured area. The platelet phase involves platelet adhesion and aggregation of platelets (thrombocytes) to form a fragile, jelly-like temporary clot, termed a hemostatic platelet plug. This platelet plug strives to seal the injured area(s) or gap(s) in the vessels to temporarily prevent blood loss. The coagulation phase involves activation of a “cascade” of twelve clotting factors (or plasma coagulation factors) that ultimately produce strands of fibrin. Fibrin binds the platelet plug to form the permanent, tight clot, termed the hemostatic clot. To maintain equilibrium, the body’s fibrinolytic system is activated: anticlotting mechanisms in the fibrinolytic system prevent the expansion of the final clot; cause dissolution of the existing clot; and complete the repair of the injured vessel.\(^2,4,5\)

The microscopic illustration of the hemostatic clot (thrombus) displays a matrix of platelets, red blood cells, white blood cells, and fibrin (Figure 1).

Alterations in the hemostatic system result in a myriad of bleeding disorders. Disorders of the body’s hemostatic system can lead to serious clinical clotting or bleeding consequences. Regarding bleeding disorders, they can be acquired, inherited or drug-induced. Characterized by a group of distinct conditions, bleeding disorders can affect the “ability of blood vessels, platelets, and coagulation factors to maintain hemostasis.”\(^2\) Major causes of bleeding result in the body’s inability to form a hemostatic plug or a clot, affecting the platelet phase and/or the coagulation phase, correspondingly.

For the platelet phase, common causes of bleeding include decreased platelet count and/or abnormal platelet function. For the coagulation phase, common causes of bleeding can include deficiencies in the
clotting factors. When treating dental patients with bleeding disorders, dentists and dental hygienists should possess an awareness of common bleeding disorders as well as an awareness of a patient’s predisposition to bleeding during restorative, periodontal or surgical procedures.

Affecting up to 150 patients in a dental practice of 2000 adults, potential bleeding disorders will be encountered. Common drug-induced causes of bleeding disorders seen in dental practices include patients on anticoagulation or antiplatelet therapy. Patients on “low-intensity” anticoagulation therapy are at a 1% risk for a major bleed and an 8% risk for a minor bleed during multiple invasive dental procedures. When a “high-intensity” anti-coagulation therapy is warranted, patients have a “five-fold” risk for bleeding. Anti-coagulation therapy is widely prescribed for individuals with a history of mechanical heart valves, secondary myocardial infarction, cerebral vascular accidents, or thrombophlebitis. Additionally, millions of patients who are on anti-platelet therapy to prevent cardiovascular disorders or inflammatory joint disorders will likely cause bleeding problems during invasive dental procedures.

The most common inherited bleeding disorder is von Willebrand’s disease, which affects platelet function and, in some cases, causes a clotting factor deficiency (Factor VIII). Of the common genetic disorders Hemophilia A (a factor VIII deficiency) occurs in about 80% of all inherited coagulation disorders, and Hemophilia B (a factor IX deficiency) occurs in about 13%. Affecting a smaller percentage of the population in the United States, these inherited conditions require extreme care and possibly specialized treatment planning to prevent a clinical bleed during invasive dental procedures.

Depending on the cause, medical and dental management may differ for any one of the bleeding disorders. Therefore, it is imperative dental professionals conduct comprehensive clinical assessments and communicate with the patient’s supervising physician to develop appropriate treatment planning strategies to treat such patients.

Inevitably, dentists and dental hygienists will treat a considerable number of patients with bleeding problems in the dental environment; although, many clinicians may perceive these patients’ bleeding complications as a significant challenge. Hence, this continuing education course plans to address such challenges, including: knowledge about the hemostatic system; interpretation of laboratory testing; an overview of underlying causes of common bleeding disorders; clinical management options to address the risk of bleeding during and after invasive dental procedures; and the presentation of current recommendations regarding managing patients on anti-coagulation and anti-platelet therapy. Acquiring knowledge of these essentials will greatly enhance the management of patients with bleeding disorders in the dental office.

**Learning Objectives**

Upon completion of this course, the dental professional should be able to:

- List the primary hemostatic components of blood.
- List and briefly describe the three phases of hemostasis.
- Describe the basic physiology of hemostasis.
- List and briefly describe common bleeding disorders (genetic, acquired and/or medication-induced).
- Discuss the pathophysiology of common bleeding disorders.
- List and describe the associated etiologies of common bleeding disorders.
- List the frequently prescribed and OTC drugs that cause anticoagulation effects (antiplatelet and anti-thrombotic effects) on the hemostatic system.
- List the common blood laboratory tests to diagnose and evaluate common bleeding disorders.
- Become familiar with interpretation of common blood laboratory tests (normal and abnormal values) used in the dental office.
- Discuss the medical/dental management strategies for patients with bleeding disorders.
- Discuss treatment plans (assessment, diagnosis, plan, implementation and evaluation) that provide safety and comfort for managing patients with bleeding disorders in the dental environment.
• List and describe hemostatic agents (local and systemic) to prevent and/or reduce the clinical bleed in patients with bleeding disorders during and after invasive dental procedures.
• Gain knowledge about the current evidence-based recommendations for the purpose of managing patients with disorders of coagulation while providing invasive dental procedures.

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Introduction
When a patient presents with a bleeding disorder, how should dental providers proceed to manage the complexity of the case? Management of such medically-complex patients involves “an understanding of basic physiology of hemostasis,” which can greatly enhance one’s comprehension of most bleeding and clotting disorders.1 In addition to this composite of knowledge, clinical application of recent evidence-based recommendations can contribute to the management of these patients who may potentially require specialized medical and/or dental care.

This continuing education course will provide dental professionals with general information for managing patients with bleeding disorders. Specifics of this course include: basic physiology of the hemostatic system; common bleeding disorders and their etiologies; requisite laboratory testing; and current evidence-based guidelines for the purpose of developing individualized treatment plans for such patients. Having a greater appreciation of these essentials will enable the dental practitioner to successfully treat patients with bleeding disorders.

Normal Hemostasis: The Making of a Blood Clot
Hemostasis is defined as “the termination of a bleed by mechanical or chemical means or by the complex coagulation [clotting] process of the body...”6 Composing of a coordinated sequence of events, hemostasis consists of vasoconstriction of the blood vessel, platelet adhesion and aggregation, and thrombin and fibrin synthesis (Diagram 1). The general sequence of events in hemostasis is briefly presented by describing the three main phases: vascular, platelet and coagulation phases.

Vascular phase: Immediately, when blood vessels are injured, vasoconstriction of the arteries and veins begins. Within the injured vessel wall, exposure of subendothelial tissues, collagen, and basement membrane contribute to prothrombotic activities. Clotting activities include platelet aggregation and adhesion via release of adenosine diphosphate (ADP) and von Willebrand factor (vWF).

Additionally, the release of a tissue factor (formerly known as tissue thromboplastin) during this phase initiates coagulation via the extrinsic pathway.1,3,5 At this point, the initial layer of the platelet plug is established at the site of the injury.

Platelet phase: “Platelets are cellular fragments from the cytoplasm of megakaryocytes” that survive in the vascular system for 8–12 days. They are essential for the clotting process in the blood. Primary hemostatic functions of platelets include: maintaining the health of the inner lining of the vascular wall; formation of a platelet plug during vessel wall injury; and initiation of the coagulation phase, which leads to the stabilization of the platelet plug.5

During the platelet phase, platelets become sticky and adhere to one another and to the site of injury after contact with exposed collagen and subendothelial tissue component vWF glycoprotein...
Ib. Additionally, Adenosine Di-phosphate (ADP) is released by exposed subendothelial tissues that cause platelets to aggregate, change shape, release dense and a-granule contents and synthesize thromboxane A2 that can further act as a feedback activator potentiating platelet responses by binding to thromboxane receptor (TP). A product of platelets, thromboxane, causes another surge of platelet aggregation.

In summary, platelets adhere to the damaged subepithelial surface, change shape, become sticky, and aggregate to form a hemostatic platelet plug at the injured blood vessel site. Under these normal conditions, adequate numbers and function of platelets are required, resulting in the primary cessation of the bleed by the hemostatic platelet plug formation.

Coagulation phase: Virtually simultaneously with the vascular and platelet phases, the extrinsic, intrinsic and common pathways, containing 12 circulating plasma proteins, (also termed plasma coagulation factors) are initiated (Table 1). These plasma proteins are produced in the liver. More specifically, of the 12 plasma proteins, factors II, VII, IX and X are Vitamin-K dependent for synthesis. The coagulation factors (F) are activated in a cascade-like manner within their respective pathways. The “faster” extrinsic pathway is initiated by F-VII when exposed to a tissue factor (or a membrane protein) within the injured vessel; and the intrinsic pathway is initiated when F-XII contacts with injury-exposed subendothelial tissues. Subsequently, coagulation factors in the intrinsic pathway activate one another; F-XII activates F-XI; F-XI activates IX; and F-IX activates F-VIII. Both pathways merge and F-X is activated, yielding the activation of the common pathway. Subsequently, prothrombin is converted to thrombin; thrombin acts as a catalyst for the conversion of fibrinogen; fibrinogen is the precursor to fibrin.

Fibrin is thus converted to a stringy, insoluble protein that forms an intricate network of minute delicate structures called fibrils. At this point, blood cells and plasma are enmeshed in the network of fibrils to form the clot. Therefore, fibrils are responsible for tightly binding the platelet plug, stabilizing the plug, and affixing it to the site of injury. Resulting in a semi-solid, gelatinous mass, it is termed the hemostatic clot or thrombus. This definitive clot prevents blood from leaking out of blood vessels after injury. Within approximately 9 to 18 minutes, the fibrin clot is produced (Diagram 2). Under these physiological conditions, it is important to note that too few
Table 1. Coagulation Phase.\textsuperscript{7}

<table>
<thead>
<tr>
<th>List of 12 Circulating Coagulation Factors</th>
<th>Intrinsic Pathway</th>
<th>Extrinsic Pathway</th>
<th>Common Pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor I Fibrinogen</td>
<td></td>
<td></td>
<td>P</td>
</tr>
<tr>
<td>Factor II Prothrombin</td>
<td>P</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor III Tissue Factor</td>
<td>P</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor IV Calcium</td>
<td></td>
<td></td>
<td>P</td>
</tr>
<tr>
<td>Factor V Proaccelerin</td>
<td>P</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor VII Proconvertin</td>
<td></td>
<td></td>
<td>P</td>
</tr>
<tr>
<td>Factor VIII Antihemophilic factor</td>
<td>P</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor IX Plasma thromboplastin</td>
<td>P</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor X Stuart-Power factor</td>
<td></td>
<td></td>
<td>P</td>
</tr>
<tr>
<td>Factor XI Plasma thromboplastin antecedent</td>
<td></td>
<td></td>
<td>P</td>
</tr>
<tr>
<td>Factor XII Hageman factor</td>
<td>P</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor XIII Fibrin-stabilizer factor</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Diagram 2. Coagulation Cascade
platelets, abnormal platelets, platelets that do not function normally, or deficiencies of clotting factors may not form normal clots; thus, disorders of the hemostatic system can result.\textsuperscript{1,2,5}

Finally, anticlotting mechanisms (broadly termed fibrin degradation products) in the fibrinolytic pathway are activated to prevent the formation of more clots and to allow for the dissolution of the definitive clot.\textsuperscript{1,5} The expected outcome is accomplished: repair of the injured blood vessel wall results and bleeding ceases.

**Laboratory Assessment of Hemostasis**

Many of the bleeding disorders can be diagnosed and monitored by way of laboratory testing. When a significant coagulation disorder occurs in the vascular or platelet phase a clinical bleeding problem is observed immediately after injury, or during invasive medical or dental procedures. Conversely, when a significant disorder affects the coagulation phase (clotting factors), the clinical bleed will most likely not be observed until several hours or longer after the injury or invasive procedure.

Various laboratory screening tests can be ordered by the dentist when the patient reports a bleeding disorder, when the patient responds positively to a family history of a bleeding disorder; or when the clinician observes a sign/symptom of a bleeding problem during the clinical exam. Patients with unknown bleeding problems should be referred to their physician or to a hematologist for further evaluation. Laboratory tests provide an assessment of adequate numbers of platelets, proper functioning of platelets, sufficient levels of plasma coagulation factors, and proper functioning of the fibrinolytic pathway. When evaluating defects in the hemostatic system prior to invasive dental treatment, dental professionals should become familiar with the following common blood laboratory tests.\textsuperscript{1}

**Common Blood Laboratory Tests**

**Platelet Count** is a routine blood laboratory test that provides a quantitative assessment of circulating platelets in the vascular system. A normal platelet count should be within the range of 150,000 to 450,000 cells/mm\textsuperscript{3} of blood.\textsuperscript{8} When the platelet count is less than 100,000 cells/mm\textsuperscript{3}, *thrombocytopenia* is diagnosed. Patients presenting with a platelet count between 50,000 and 100,000 cells/mm\textsuperscript{3} will predictably bleed mildly with severe trauma or with dental surgical procedures. When the platelet count is less than 20,000 cells/mm\textsuperscript{3} an excessive and prolonged bleed is predictable; thus, this high-risk condition will require medical attention prior to dental invasive procedures.\textsuperscript{2} Ultimately, thrombocytopenia can prevent the formation of a hemostatic plug, resulting in hemorrhage.

**The Ivy Bleeding Time** laboratory test has been routinely used as a screening test for assessing adequacy of platelet function. Abnormal platelet function is termed *thrombocytopathy*. When performed, the bleeding time test calculates the time required for a standard skin incision to stop bleeding by the formation of a hemostatic plug.\textsuperscript{3} The normal range of the Ivy Bleeding Time test is usually between 2 and 10 minutes.\textsuperscript{8}

Over the years, this test was presumed to provide a measurement of bleeding risk in patients by way of a prolonged bleeding time result. Consequently, its current use and application have been deemed very limited because of its recognized unreliability to predict bleeding risk based on an abnormal test result.\textsuperscript{10,11} This test fails to produce quantifiable and useful information for several reasons. According to an original article by authors Peterson et al., the following major conclusions were drawn regarding this test:\textsuperscript{10}

1. Given the normal results of a standard bleeding time test one cannot exclude the possibility of a significant clinical bleed with invasive dental procedures.

2. Without a positive medical history finding related to a bleeding disorder/platelet disorder, the bleeding time test is not a “useful predictor” of an excessive bleed when performing invasive dental procedures; and

3. The results of a prolonged bleeding time cannot reliably identify patients who are taking anti-platelet therapy; thus, a prolonged bleeding time cannot be linked to the ingestion of aspirin or NSAIDs.\textsuperscript{10,11} Therefore, the bleeding time test is merely a tool to screen for platelet disorders; it is not an effective clinical testing method for predicting the quantity of a bleed associated with an increased bleeding time in such patients.\textsuperscript{10}
Platelet Function Analyzer (PFA-100) is a sophisticated laboratory screening testing devise that is currently being used in place of the Ivy Bleeding Time test. Platelet function tests or platelet function assay (PFA) evaluate the qualitative function of platelets.

These tests provide an assessment of platelet adhesion, platelet activation and platelet aggregation during the development of a platelet plug, or primary hemostasis. Generally, these tests measure the time it takes for a clot to form (platelets to clump together) to prevent blood loss as the closure time. The PFA test (and other platelet function tests) has not been shown to predict the likelihood that a patient will bleed excessively during invasive procedures; although, it’s full clinical utility has yet to be established.

Prothrombin Time (PT), measures the patient’s ability to form a definitive clot by monitoring the proper functioning of the extrinsic coagulation pathway (Factor VII) and the common pathway (Factors V, X, prothrombin and fibrinogen). Factors VII, X and prothrombin are Vitamin K-dependent for their synthesis and become unstable when coumarin-like drugs are prescribed. A normal coagulation profile indicates adequate levels or percentages of clotting factors in the extrinsic and common pathways. Generally, the laboratory testing range is between 11–15 seconds. Testing results beyond 15 seconds indicate an abnormal or prolonged PT. This outcome is indicative of deficient coagulation factors needed to form a fibrin clot, resulting in a prolonged bleed in the body. An active bleed caused by anticoagulation therapy, coumarin-like drugs, is most commonly monitored by the international normalized ratio (INR) laboratory test.

International Normalized Ratio (INR) In 1983, the World Health Organization Committee on Biological Standards established a more precise laboratory testing method, the INR, to monitor patients taking anticoagulation drugs (warfarin therapy). Consequently, laboratory materials (thromboplastin reagents) and laboratory techniques were internationally instituted for the purpose of standardizing the assigned values. Patients with a normal coagulation profile result in an INR value of 1.0. The “low intensity” INR range is between 2.0 and 3.0; and the “high-intensity” INR range is between 2.5 and 3.5. What governs the intensity of anticoagulation therapy? The intensity is determined by the patient’s predisposition to abnormal clotting. Patients diagnosed at high risk clot formation, will require higher intensity of anticoagulation. From a pharmacological standpoint, anticoagulant drugs inactivate Factor VII within the extrinsic pathway by inhibiting Vitamin K action; Vitamin K is required by the liver to synthesize Factor VII.

Activated Partial Thromboplastin Time (aPTT) also measures the patient’s ability to effectively form a definitive clot by evaluating the effectiveness of the intrinsic and common pathways of the coagulation cascade. It tests for deficiencies in the intrinsic pathway, specifically factors VIII, IX, XI, XIII; and deficiencies in the common pathway, specifically factors V and X, prothrombin and fibrinogen. A normal aPTT is usually 25 to 40 seconds. The aPTT is the laboratory test most often used by physicians to monitor heparin therapy and to diagnose the hemophilias, which result in a prolonged or increased aPTT time.

Thrombin Time laboratory test assesses the conversion of fibrinogen to insoluble fibrin by adding thrombin to the patient’s blood sample. Specifically, this test bypasses the extrinsic, intrinsic and common pathways to determine the stability of the clot. Normally, the range of this test is between 9 and 13 seconds. A prolonged time, in excess of 16 to 18 seconds, is considered abnormal.

Common Bleeding Disorders Excessive or prolonged bleeding may result from:
1. extremely fragile blood vessels;
2. decreased number of platelets or impaired platelet function;
3. abnormalities in the blood clotting coagulation factors;
4. defects in the fibrinolytic pathway; or
5. a combination of these.

The following information provides an overview of the various abnormalities in the hemostatic system.

Blood Vessel Wall Abnormalities Blood vessel wall abnormalities, or increased fragility of the blood vessels, are relatively common but do not usually cause a serious bleed. When
### Table 2. Blood Laboratory Tests that Evaluate Hemostasis and Bleeding Disorders

<table>
<thead>
<tr>
<th>Laboratory Tests</th>
<th>Measures Normal Function</th>
<th>*Normal Values/Ranges</th>
<th>Importance in Diagnosing Bleeding Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet Count</td>
<td>Adequate platelet numbers</td>
<td>150,000 to 450,000/mm³</td>
<td>Assess thrombocytopenia or inadequate numbers of platelets</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>100,000 cells/mm³</td>
</tr>
<tr>
<td>Ivy Bleeding Time</td>
<td>Adequate platelet function</td>
<td>2-10 minutes</td>
<td>Screening test for thrombocytopeny; von Willebrand’s disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Prolonged time: &gt;9-10 minutes</td>
</tr>
<tr>
<td>Platelet Function Tests</td>
<td>Assess function of platelets: attachment, activation, and aggregation</td>
<td></td>
<td>Discriminates between normal and abnormal function of platelets</td>
</tr>
<tr>
<td>Prothrombin Time (PT)</td>
<td>Assess the time it takes to form a fibrin clot when calcium and tissue factor are added to the plasma (extrinsic pathway: coagulation function of factor VII; common pathway: factors V, X, prothrombin and fibrinogen)</td>
<td>11 to 15 seconds</td>
<td>Assess defects in the extrinsic pathway of the coagulation system: anticoagulant therapy (warfarin); Prothrombin deficiency; vitamin K deficiency; liver disease; antiplatelet drugs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Prolonged time: &gt;30 seconds</td>
</tr>
<tr>
<td>International Normalized Ratio (INR)</td>
<td>Coagulation function of the extrinsic pathway: Factors V, VII, X, prothrombin and fibrinogen</td>
<td>1.0</td>
<td>Monitors oral anticoagulation therapy: warfarin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>INR greater than 1.2 in patients not on anticoagulation therapy. In patients on anticoagulants, therapeutic range is between 2.0 and 3.5</td>
</tr>
<tr>
<td>Partial Thromboplastin Time (activated aPTT)</td>
<td>Assess the time it takes to form a fibrin clot when calcium and partial thromboplastin containing phospholipids are added to the plasma (intrinsic pathway: coagulation function of factors VIII, IX, XI and XII)</td>
<td>25 to 40 seconds</td>
<td>Assess defects in the intrinsic pathway of the coagulation system: anticoagulant therapy (heparin); von Willebrand’s disease; hemophilia A and B</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Prolonged time: 45 to 50 seconds</td>
</tr>
<tr>
<td>Thrombin Time</td>
<td>Thrombin is added to blood to convert fibrinogen to fibrin</td>
<td>24 to 35 seconds</td>
<td>Assess defects in the conversion of fibrinogen to fibrin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Prolonged or beyond normal</td>
</tr>
</tbody>
</table>

*Normal values or ranges may vary among different laboratories.
evaluating the laboratory tests for this condition, one can expect a normal platelet count, bleeding time and coagulation times (PT and aPTT). Pathophysiologically, this condition manifests itself by observable extraoral and intraoral signs of hemorrhage: petechiae and ecchymosis are found in the skin or on the mucous membranes, particularly on the gingiva. Very rarely, significant hemorrhage may occur, particularly in the joints, muscles, and subperiosteal locations. Excessive bleeding may also take the form of menorrhagia (abnormal long and heavy menstrual periods), nosebleeds, gastrointestinal bleeding, or hematuria (abnormal presence of blood in the urine). 

Causes of Blood Vessel Wall Abnormalities

- Infections (i.e., septicemia, infective endocarditis, several forms of rickettsioses)
- Drug reactions (i.e., hypersensitivity vasculitis)
- Scurvy, Henoch-Schönlein purpura
- Hereditary hemorrhagic conditions.

Platelet Related Bleeding Disorders

Thrombocytopenia
The important role of platelets in hemostasis is to form the temporary hemostatic plug, primarily requiring a sufficient number of platelets. When a quantitative reduction of platelets exists, it can result in a significant cause of generalized bleeding. Patients presenting with a platelet count of less than 100,000 cells/mm$^3$ are diagnosed with thrombocytopenia. When the platelet count is under 50,000 cells/mm$^3$, bleeding will be excessive postoperatively; thus, a platelet transfusion may be necessary prior to invasive treatment. Moderate to severe thrombocytopenia (less than 50,000 cells/mm$^3$) is usually manifested by petechiae in the skin or on the mucous membranes; purpura or ecchymoses on the skin; spontaneous mucosal bleeding; or intracranial hemorrhage. In the oral cavity, bleeding gingiva is a common sign, spontaneous bleeding associated with brushing or flossing may be observable, and bleeding from teeth extractions is possible. This condition is diagnosed by a platelet count laboratory test, or by a complete blood count (CBC). Depending on the cause, thrombocytopenia can be a consequence of increased platelet destruction, decreased platelet production, decreased platelet survival, or increased splenic sequestration. 

Thrombocytopenia is the leading cause of bleeding disorders, as presented in the following major categories.

Causes of Decreased Production of Platelets

- Generalized diseases of the bone marrow
  - Aplastic anemia
- Drug-induced thrombocytopenia
- Cytotoxic drugs
- Alcohol
- Thiazide diuretics
- Infections: measles, HIV
- Ineffective megakaryopoiesis

Causes of Platelet Destruction or Decreased Platelet Survival

- Immunologic destruction
  - Immune thrombocytopenic purpura (ITP)
  - Infections
    - HIV, infectious mononucleosis, cytomegalovirus (CMV)
  - Drug-associated
    - Quinine or quinidine
    - Methylldopa
    - Sulfonamides
    - Heparin
    - Gold
    - D-penicillamine
    - P-aminosalicylic acid
- Nonimmunologic destruction
  - Thrombotic thrombocytopenic purpura
  - Giant hemangiomas
  - Hemolytic anemias

Thrombocytopathy
Caused by a platelet disorder, thrombocytopathy is characterized by impairment in platelet function, but adequate numbers of platelets are normally present. Thrombocytopathy may be congenital or acquired. The PFA-100 test (or other platelet function tests) provides an assessment of the adequacy of platelet function, and contributes to the diagnosis of the following disorders:

Causes of Platelet Destruction or Decreased Platelet Survival

- Inherited disorders
  - von Willebrand’s disease: consists of a platelet dysfunction and a Factor VIII deficiency (Refer to inherited coagulation disorders)
• Acquired disorders
  ◦ Drug-induced defects
    ◦ *Aspirin (antiplatelet)
    ◦ **Nonsteroidal anti-inflammatory drugs (NSAIDS)
    ◦ ***Other antiplatelet drugs
  ◦ Alcohol in combination with aspirin or NSAIDS
  ◦ Uremia
  ◦ Myeloproliferative disorders

*Aspirin and aspirin-containing drugs are by far the most common reason for platelet dysfunction, frequently resulting in a prolonged bleeding time. Aspirin, a nonsteroidal salicylate, acts as an inhibitor of cyclooxygenase; thus, inhibits the synthesis of prostaglandins and interferes with the production of thromboxane $A_2$. The net result of aspirin therapy is to inhibit platelet aggregation, hence, the formation of a platelet plug (Diagram 3).

Aspirin therapy, prescribed or self-administered, is a leading drug widely used by millions of people in the U.S. for its cardioprotective properties (Chart 1). Its anti-platelet action prevents thrombus formation by impairing platelet function and by interfering with their ability to form an intact platelet plug. As a result, aspirin causes irreversibility of platelet function for the duration of their lifetime, approximately 7–10 days. Use of aspirin therapy is indicated for primary and secondary prevention of thromboembolism, myocardial infarction and cerebrovascular accident.

Although the blood thinning properties of aspirin cause an increased risk of a clinical bleed, proper management usually includes maintaining patients on “low-dose” aspirin therapy (75 to 100 mg) to prevent the risk of a clot-threatening event. The following evidence-based outcome supports this practice management. Authors Ardekian et al. presented the results of a clinical study which quantified the “intraoperative” and “postoperative” bleeding in dental patients taking 100 mg of aspirin daily and those who discontinued their aspirin regimen for seven days. Conclusions established was that no statistical difference was found regarding “excessive” bleeding between the experimental group (patients who continued aspirin therapy) and the control group (patients who discontinued aspirin therapy) who underwent various, complex surgical procedures. Although the findings in this study concluded the more complex the surgical dental procedure the more significant the bleed, it is recommended that suturing and local hemostatic agents can be used to control the clinical bleed (Table 3).

Moreover, Brennan et al. recently presented a “new recommendation” in their medical

![Diagram 3. The effect of aspirin on platelets.](image-url)
<table>
<thead>
<tr>
<th>Medication</th>
<th>Indication for Use</th>
<th>Effects on Dental Treatment</th>
<th>Strategies to Address Perioperative and Postoperative Bleed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Treatment of mild-to-moderate pain, inflammation, and fever; prevention and treatment of acute coronary syndromes, acute ischemic stroke, and transient ischemic episodes; management of rheumatoid arthritis, rheumatic fever, osteoarthritis; adjunctive therapy in revascularization procedures (coronary artery bypass graft, percutaneous transluminal coronary angioplasty, carotid endarterectomy), stent implantation.</td>
<td>Key adverse event(s) related to dental treatment: As with all drugs which may affect hemostasis, bleeding is associated with aspirin. Hemorrhage may occur at virtually any site; risk is dependent on multiple variables including dosage, concurrent use of multiple agents which alter hemostasis, and patient susceptibility. Many adverse effects of aspirin are dose related, and are rare at low dosages. Other serious reactions are idiosyncratic, related to allergy or individual sensitivity. See clopidogrel.</td>
<td>• No specific remedy&lt;br&gt;• Consider platelet transfusion ± DDAVP&lt;br&gt;• Normal platelet function returns within 7 to 10 days after discontinuation</td>
</tr>
<tr>
<td>Cilostazol (Pletal)</td>
<td>Used for symptomatic management of peripheral vascular disease, primarily intermittent claudication.</td>
<td>No significant effects or complications reported.</td>
<td>• No specific remedy&lt;br&gt;• Normal platelet function returns within 4 days after discontinuation</td>
</tr>
<tr>
<td>Clopidogrel (Plavix)</td>
<td>To decrease the rate of a combined end point of cardiovascular death, MI, or stroke.</td>
<td>Aspirin in combination with clopidogrel (Plavix), prasugrel (Effient), or ticagrelor (Brilinta) is the primary prevention strategy against stent thrombosis after placement of drug-eluting metal stents in coronary patients. Any elective surgery should be postponed for 1 year after stent implantation, and if surgery must be performed, consideration should be given to continuing the antiplatelet therapy during the perioperative period in high-risk patients with drug-eluting stents.</td>
<td>• No specific remedy&lt;br&gt;• Consider platelet transfusion ± DDAVP&lt;br&gt;• Normal platelet function returns within 7 to 10 days after discontinuation</td>
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**Chart 1. Oral Antiplatelet Comparison Chart.**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Description</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prasugrel</td>
<td>To reduce the rate of thrombotic cardiovascular events (including stent thrombosis) in patients who are to be managed with percutaneous coronary intervention for unstable angina, non-ST-segment elevation MI, or ST-elevation MI.</td>
<td>See clopidogrel. • No specific remedy • Consider platelet transfusion ± DDAVP • Normal platelet function returns within 5 to 9 days after discontinuation</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>Used in conjunction with aspirin for secondary prevention of thrombotic events in patients with unstable angina, non-ST-elevation myocardial infarction, or ST-elevation myocardial infarction managed medically or with percutaneous coronary intervention and/or coronary artery bypass graft.</td>
<td>See clopidogrel. • No specific remedy • Consider aminocaproic acid, tranexamic acid, recombinant factor VIIa • Normal platelet function returns within 3 to 5 days after discontinuation</td>
</tr>
<tr>
<td>Ticlopidine</td>
<td>Use platelet aggregation inhibitor that reduces the risk of thrombotic stroke in patients who have had a stroke or stroke precursors (Note: Due to its association with life-threatening hematologic disorders, ticlopidine should be reserved for patients who are intolerant to aspirin, or who have failed aspirin therapy); adjunctive therapy (with aspirin) following successful coronary stent implantation to reduce the incidence of subacute stent thrombosis.</td>
<td>No significant effects or complications reported; if a patient is to undergo elective surgery and an antiplatelet effect is not desired, ticlopidine should be discontinued at least 7 days prior to surgery. • No specific remedy • Consider platelet transfusion ± DDAVP • Normal platelet function returns within 5 to 10 days after discontinuation</td>
</tr>
<tr>
<td>Brand Name</td>
<td>Chemical Name</td>
<td>Mechanism of Action</td>
</tr>
<tr>
<td>------------</td>
<td>---------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Gauze</td>
<td>2&quot; x 2&quot; sterile gauze pads; place pressure on wound to close or apply finger pressure</td>
<td></td>
</tr>
<tr>
<td>Gelfoam</td>
<td>Absorbable gelatin sponge material; provides stable 'scaffold' for clot formation</td>
<td>Should not be used under epithelial incisions or flaps, inhibits healing</td>
</tr>
<tr>
<td>Surgical</td>
<td>Oxidized regenerated cellulose; exerts physical effect rather than physiological</td>
<td></td>
</tr>
<tr>
<td>Bleed X</td>
<td>Hemostatic product containing microporous poly-saccharide hemispheres (potato starch); dehydrates blood and accelerates clotting</td>
<td>No known contraindications</td>
</tr>
<tr>
<td>Tisseel</td>
<td>Fibrin sealant; adhesive action that binds fibrin to the clot</td>
<td></td>
</tr>
<tr>
<td>Cykloapron</td>
<td>Tranexamic acid</td>
<td>Used in the form of a mouthwash after surgical procedures to inhibit postoperative bleeding; can be administered parenterally or as an 4.8% aqueous solution (4 times daily for 1 week)</td>
</tr>
<tr>
<td>Suturing</td>
<td>Apposition of soft tissue</td>
<td></td>
</tr>
<tr>
<td>Amicar</td>
<td>Aminocaproic acid</td>
<td>Antifibrinolytic agent</td>
</tr>
<tr>
<td>Electrocautery</td>
<td>Tool to slow intraoperative bleeding and interfere with postoperative episodes</td>
<td>Use cautiously to avoid excessive tissue necrosis</td>
</tr>
</tbody>
</table>

Every drug or dental product is not without side effects/adverse events or drug interactions; dental provider must use dental drug reference prior to their use and/or consult with the patient's supervising physician.
management update review article based on similar studies which demonstrated aspirin’s limited effects on bleeding during routine dental extractions. When taking low–dose aspirin (up to 320 mg), it is recommended patients “not discontinue the use of daily aspirin before routine dental extractions (to include multiple routine extractions).”

More interesting, and supported by recent evidence, the chemical properties of low dose aspirin exert its antithrombotic and cardioprotective properties up to 320 mg taken on a daily basis. (Beyond this dosage, aspirin “may be less effective as an antithrombotic” drug.)

In conclusion, it is recommended that a clinical bleed caused by routine dental extractions, can be managed by standard local hemostatic measures (with direct packing of gauge, from suturing to hemostatic agents). Additionally, it is recommended dental professionals adhere to the expert opinion that the benefits of continuing antiplatelet therapy deceases the risk of a cardiovascular episode. This strategy, therefore, outweighs the benefits of a decreased risk of bleeding complications with surgery following cessation of aspirin.

Outside of this standard practice, when complex surgical procedures are planned, Brennan et al. indicated that more research is warranted in this area to predict the amount of the bleed. When indicated, the “discontinuation of aspirin therapy should be limited to 3 or fewer days” to reduce the risk of a thromboembolic event. Other medical and dental providers may suggest a 7–10 day aspirin cessation protocol; for this reason, the risk benefit ratio must be considered during the consultation with the patient’s physician.

**Non steroidal anti–inflammatory drugs (NSAIDs) cause abnormal platelet function; thus, bleeding tendencies can be expected. Once the drug is discontinued thrombocytopenia is reversed within 1–5 half–life’s of the drug. And, when considering aspirin and NSAIDs as pain relievers after dental procedures, dental professionals should not prescribe these analgesics when optimum blood clotting/hemostasis is desired.

***Other antiplatelet drugs irreversibly inhibit platelet aggregation, causing platelet dysfunction (Chart 1). Normal platelet aggregation/function returns when the antiplatelet drug is discontinued and only when new platelets are produced, usually within a range of 3 to 10 days. It is recommended that prescription antiplatelet drugs, when prescribed with or without aspirin, not be discontinued for minor dental surgical procedures. However, more studies are needed to examine the quantity of the bleed during major or complicated surgical dental procedures. Thus, prudent treatment planning takes into account the use of hemostatic agents and dental procedures used as local measures to control bleeding during and/or after the invasive dental procedure (Table 3).

In the event these antiplatelet drugs are to be discontinued, it is prudent to consult with the patient’s supervising physician or cardiologist, especially when patients present with coronary artery stents: the American Heart Association strongly advises against the discontinuation of dual antiplatelet therapy in patients with coronary artery stents within 12 months after placement. If antiplatelet therapy (i.e., aspirin and clopidogrel) is suddenly discontinued it may increase the risk of a fatal event in these patients.

Coagulation Factor Disorders

**Anticoagulation Therapy**

Warfarin Sodium is a coumadin derivative listed in the drug class as an oral anticoagulant. It interferes with the liver’s synthesis of Vitamin K-dependent clotting factors; resulting in depletion of blood clotting factors II, VII, IX, and X. Its therapeutic effect is to prevent further development of the hemostatic plug; and it prevents new thromboembolic clot formation. Thrombosis is the formation of abnormal blood clots (termed thrombi) that develop within the vascular system. Thrombi are carried through the bloodstream (termed emboli) which can potentially occlude the lumen of an artery or a vein and shut down a vital organ. The following conditions increase the risk of a thromboembolic event: deep venous thrombophlebitis (inflammation of a vein); atrial fibrillation (rapid, random contractions of the atria); myocardial infarction (heart attack); mechanical heart valves (artificial heart valves); carotid artery disease; or peripheral vascular disease. Additionally, clots form because there is an existing hypercoaguable condition where by the blood
levels, and possibly, placed patients at risk for a thromboembolic event.

The current literature cautions dental practitioners not to discontinue warfarin therapy due to the risk of producing a thromboembolic event, increasing the morbidity and mortality risks for the patient. After a 2007 comprehensive and critical review of English-language, randomized clinical trials, by Aframanian et al., as part of the World Workshop of Oral Medicine IV, the authors produced a “Class I” recommendation which was supported by scientific evidence and expert opinion: It is recommended that for patients who fall “within the therapeutic range of an INR of 3.5 or below, warfarin therapy need not be modified or altered for simple single dental extractions.” Aframanian et al. also concluded that the “more complicated and invasive oral surgical procedures”, coupled with a higher range of the INR (3.5 and greater), one should consult with the prescribing physician to consider bleeding management options. Hence, patients with an INR above the therapeutic range of 3.5 are at an “increased risk of prolonged bleeding.”

More specifically, the following clinical guidelines summarize dental management strategies

<table>
<thead>
<tr>
<th>“Low Intensity” Warfarin Therapy INR of 2.0 to 3.0, with a target of 2.5 (5-7mg/day for 3-6 months)</th>
<th>“High Intensity” Warfarin Therapy INR of 2.5 to 3.5, with a target of 3.0 (7-10mg/day, long term)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Prophylaxis of venous thrombosis (high risk surgery)</td>
<td></td>
</tr>
<tr>
<td>• Treatment of pulmonary embolism</td>
<td></td>
</tr>
<tr>
<td>• Prevention of systemic embolism</td>
<td></td>
</tr>
<tr>
<td>• Tissue heart valves in aortic or mitral position for the first 3 months</td>
<td></td>
</tr>
<tr>
<td>• Tissue valves with history of pulmonary embolism</td>
<td></td>
</tr>
<tr>
<td>• Tissue heart valves with atrial fibrillation</td>
<td></td>
</tr>
<tr>
<td>• Acute MI</td>
<td></td>
</tr>
<tr>
<td>• Atrial fibrillation</td>
<td></td>
</tr>
<tr>
<td>• Valvular heart disease</td>
<td></td>
</tr>
<tr>
<td>• Mitral valve prolapse with history of atrial fibrillation or embolism</td>
<td></td>
</tr>
<tr>
<td>• Mechanical prosthetic heart valves</td>
<td></td>
</tr>
<tr>
<td>• Prevention of recurrent MI</td>
<td></td>
</tr>
<tr>
<td>• Treatment of thrombosis associated with antiphospholipid antibodies</td>
<td></td>
</tr>
</tbody>
</table>

Table 4. Recommended Therapeutic Range for Warfarin Therapy.²
for patients on Coumadin therapy who are anticoagulated in the “low intensity” and “high intensity” therapeutic ranges, and who are scheduled for various simple and complex surgical and non-surgical procedures:

**Low intensity INR 2.0-3.0**
- Consult with the patient’s physician and obtain recent INR laboratory results prior to the invasive dental procedure. It is important to obtain an INR lab result within 24 hours of highly invasive procedures.
- If the INR is between the range of 2.0-3.0:
  - When performing highly invasive non-surgical or simple surgical procedures, one can proceed if the INR is within therapeutic range 2.0-3.0. (Non-surgical invasive procedures can include subgingival debridement with slight to moderate inflammation.) Proceed with attention to control bleeding with standard local hemostatic measures.
- If the INR is greater than 2.5:
  - When performing complex surgical procedures or subgingival debridement with severe inflammation, consult with the patient’s physician to allow the INR to drift down to a safe INR range between 2-2.5. Proceed with attention to control bleeding with standard local hemostatic measures.
- Considerations for transiently interrupting the anticoagulation therapy must be discussed with the patient’s physician.

**High intensity INR 2.5-3.5**
- Consult with the patient’s physician and obtain recent INR laboratory results prior to the invasive dental procedure.
- When performing non-surgical (subgingival debridement with slight to moderate inflammation) and simple surgical procedures maintain INR in the 2.5-3.5 range; proceed with attention to standard local hemostatic measures to limit and control bleeding.
- When performing complex surgical procedures or subgingival debridement with severe inflammation consult with the patient’s physician; it may be safe to proceed in the lower ranges of INR 2.5-3.0 with attention to local hemostatic measures. Considerations for transiently interrupting the anticoagulation therapy must be discussed with the patient’s physician.
- Consider use of low molecular weight heparin preparations to bridge the patient through the invasive procedure as a substitute anticoagulant.

It can be concluded that most simple and routine invasive dental procedures can be safely performed when the INR is ≤ 3.0/3.5; and it is advised not to proceed when the INR value is out of range or when complex, surgical and non-surgical procedures are planned.\(^4,15,20\) When allowing for higher normal therapeutic ranges of INR during invasive dental procedures, consider operator experience. Under these conditions, it is prudent to consult with the patient’s supervising physician; obtain results of an INR laboratory test within 24 hours of the invasive dental procedure; and be prepared to use hemostatic measures to manage the expected clinical bleed for all planned dental procedures. Equally compelling and widely accepted, presented by authors Jeske and Suchko, is the fact that “the risk of experiencing a thromboembolism outweighs the risk of experiencing excessive perioperative and/or postoperative bleeding.”\(^20\)

While the current recommendations should be tailored towards the patients’ individual needs, dental professionals must consider the following dental implications when treating anticoagulated patients:
- Identify the fundamental cause of the bleeding disorder for which anticoagulation therapy is indicated.
- Consider operator experience with complex invasive dental procedures.
- Consider preexisting infection and/or the degree of inflammation of the soft tissues.
- Consider the extensiveness of the invasive procedure, especially significant soft tissue and bone trauma.
- Consider bleeding management strategies and the availability of local hemostatic measures when the risk of a bleed is expected.
- Consider the probable risk of inducing a thromboembolic event when discontinuing or altering the anticoagulant drug; thus, resulting in coagulation profiles that are in the suboptimal therapeutic range.
- Implement a heightened awareness when treatment planning: consider the complexity of the invasive dental procedure; seek medical
Heparin: Managing dental patients on standard heparin and low molecular weight heparin (LMWH) is important when providers need to control bleeding during and following invasive dental procedures. Standard heparin itself is not considered an anticoagulant but serves as the catalyst that inhibits plasma thrombin as well as coagulation factors IX, X, XI, XII and plasmin; thus, preventing the conversion of fibrinogen to fibrin. LMWHs exert their potentiating anticoagulant effects more so on factor Xa.

These drugs are used as a prophylaxis antithrombic agent and in the treatment of thromboembolic disorders. Treatment with standard heparin usually consists of IV infusions in a hospital setting which requires monitoring with the aPTT laboratory test. LMWH preparations are administered subcutaneously on an out-patient basis. Their dosage is calculated based on the patient’s body weight and is given on every 12-hour basis.

When considering substituting LMWH preparations, dalteparin (Fragmin), for Coumadin when a dental surgical or nonsurgical procedure is planned, one must consult with the patient’s physician to strictly and safely manage the medication schedules. The following short-term heparinization schedule is recommended: Coumadin is discontinued 4 days prior to the invasive dental procedure and Fragmin is started. During this 4-day period Fragmin is administered every 12 hours. An evening dose of Fragmin is administered on day 4; the invasive dental procedure is scheduled 12 hours after the evening dose of Fragmin. On the morning of the dental procedure Fragmin is held back. During the evening of the surgical procedure both Fragmin and Coumadin are resumed and continued until the INR is within the therapeutic range of 2.0-3.5. At this point, Coumadin is continued and Fragmin is discontinued.

Inherited Coagulation Disorders
A number of congenital blood clotting factor deficiencies exist; but three diseases account for more than 90% of all inherited coagulant deficiencies. Deficiencies for discussion include: Hemophilia A, Hemophilia B, and von Willebrand’s disease. These diseases can present with mild to severe forms, which parallels the degree of deficiency of the blood coagulation factor.

Hemophilia A, also known as classic hemophilia, is caused by a defect or a deficiency in the activity or the amount of factor VIII, respectively. This hemophilia is a hereditary blood disorder that is transmitted as an X-linked recessive trait, thus, predominately affecting males over females. Its incidence rate is about 1 in 5,000 male births.

The severity of this condition is related to the degree of the deficiency of factor VIII; therefore, the greater the deficiency of the blood level factor the greater the bleed. Regarding hemostasis, minimally 30% of factor VIII is required for normal activity. Approximately 60% of individuals with hemophilia A possess a severe degree of deficiency, which is less than 1% of factor VIII (Table 5).

Table 5. Classifications of Hemophilia A and B.

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advice from the patient’s physician; and retrieve the results of the most recent INR test.

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Clinical characteristics of Hemophilia A include: bleeding into joints (hemarthrosis), commonly affecting knees, elbows and ankles; bleeding into soft tissues exhibiting extensive ecchymoses; bleeding into a closed space such as muscle can lead to life-threatening blood loss; intracranial bleeding; and bleeding into other sites such as gastrointestinal and urinary tracts.\textsuperscript{1,2,22}

**Hemophilia B**, also known as Christmas disease or plasma thromboplastin component deficiency, is transmitted in a sex-linked recessive fashion similar to Hemophilia A. It is a bleeding disorder caused by a deficiency or defective factor IX within the intrinsic pathway of the coagulation system (Table 5).\textsuperscript{1,2,5} Not as prevalent as Hemophilia A, Hemophilia B accounts for 10–15% of all hemophiliacs. It is diagnosed by a positive family history, a history of bleeding episodes and a prolonged aPTT test with a normal PT test, along with inadequate levels of factor IX. Replacement therapy for factor IX is more variable because factor IX is distributed within and outside of the blood system, intravascular and extravascular respectively. Although, both purified and recombinant factor IX products (or high-purity FIX [factor IX] products) are recommended for the prevention or treatment of bleeding in patients with hemophilia B. Clinical features of hemophilia B are similar to hemophilia A: they include: deep tissue hemorrhage in joints, brain, and muscles.\textsuperscript{1,5,22,23}

**von Willebrand’s Disease (vWD)** is a disease that includes a composite of two disorders:
1. An inherited disorder of platelet adhesion, which involves a deficiency and/or a qualitative defect in von Willebrand’s tissue factor (vWF); and, in some cases,
2. Deficient or low levels of Factor VIII. Hence, this bleeding disorder leads to “a combined defect in platelet plug formation and fibrin formation.”\textsuperscript{22}

vWD is one of the most common inherited bleeding disorders; it presents itself clinically by spontaneous bleeding from “mucous membranes, excessive bleeding from wounds, menorrhagia, and a prolonged bleeding time in the presence of a normal platelet count.”\textsuperscript{22} In most cases it is transmitted as an autosomal dominant disorder, grouped into 3 major variants: Type I (deficiency in vWF), Type II (qualitative defect in vWF), and Type III (both Type I and II defects), from a mild form to a severe form.\textsuperscript{24} vWD is diagnosed by a positive family history; history of a serious bleed from trauma or surgical procedures; spontaneous bleeding from mucous membranes, and laboratory tests showing prolonged aPTT, abnormal assay results (a decrease in factor VIII level); prolonged bleeding time and/or abnormal platelet function.\textsuperscript{1,2,5,24}

Bleeding management options depend on the clinical condition of the patient and the type of vWD that is diagnosed (Type I, II or III). Such options include: Desmopressin, adequate plasma levels of von Willebrand’s factor, and factor VIII concentrates (FVIII).\textsuperscript{2,23}

Management and treatment of dental patients with inherited bleeding disorders present unique challenges to the dental practitioner. Firstly, knowledge about the bleeding disorder and its coagulation defect are necessary. Secondly, consultation with the patient’s hematologist should direct the dental professional to perform the invasive dental procedure in the dental office or in the hospital setting. This decision should be based upon the severity of the patient’s condition as well as the possible need for infusion of factor replacement therapy.\textsuperscript{25} Lastly and extremely critical, treatment planning must focus on individualized bleeding management strategies (Tables 6 and 7). Hence, comprehensive patient assessment, analysis of laboratory tests, collaboration with the supervising physician, and careful treatment planning to include hemostatic approaches are important elements in minimizing the bleed during and after invasive dental procedures.

**Patient and Clinical Assessment**
Assessment should include a systematic approach of collecting, organizing, and evaluating all patient data. Data must be retrieved from the personal, medical and dental histories, the pharmacological history, laboratory testing, and inspection of the extra and intraoral structures. This subjective and objective evidence is vital to the development of a proper treatment plan and dental management of patients with bleeding disorders when performing invasive dental procedures. All of these required pieces of information are essential when considering the legal and ethical responsibilities...
health care providers must exercise when caring for their patients.

Examining the medical history questionnaire is the first step in identifying whether or not it includes questions regarding the suspect or history of bleeding disorders. Questions should include the following: the determination of a known history or a family history of a bleeding disorder, history of bleeding episodes related to a dental procedure, areas of petechiae, purpura and ecchymosis, easy brusing, frequent nose bleeds (epitaxis), blood in the urine (hematuria), clotting problems, bleeding in the joints (hemarthrosis), deep muscle hematomas, excessive menstrual bleeding, alcohol abuse problems, cirrhosis of the liver, and unusual bleeding following an injury or a surgical procedure. A verbal inquiry or follow-up approach can include who, what, where, when, why, or how questions. Such questions that pertain to bleeding disorders can include:

- What is the bleeding disorder?
- What is the etiology of the bleeding disorder?
- What are the hemorrhagic signs and symptoms? Location of the hemorrhagic signs and symptoms?

- What prescription medications, OTC drugs and/or supplements are being taken?
- What are the results of the blood laboratory tests?
- Who is the supervising physician, cardiologist or hematologist?
- When was the bleeding disorder diagnosed? (bleeding history and/or family history)
- What bleeding complications have been encountered? (specifically, spontaneous bleeding with injury or a prolonged bleed related to dental or medical surgeries)
- How is the bleed medically or dentally managed?

Included in the pharmacological history the dental provider should query the patient about prescription medications that cause bleeding tendencies, specifically anticoagulation therapy, antiplatelet or nonsteroidal anti-inflammatory drugs, or heparin therapy. Just as important, patients should be asked about taking over-the-counter drugs containing aspirin; and they should be questioned about supplements and herbs that may exacerbate the bleed when patients are taking anticoagulants. There are more than 200 over-the-counter aspirin-containing drugs available to individuals as well as multiple combinations of herbal therapies that can affect the hemostatic pathways.

<table>
<thead>
<tr>
<th>Table 6. Dental Management of Patients with Hemophilia.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-treatment of invasive procedure:</strong></td>
</tr>
<tr>
<td>Consult with hematologist</td>
</tr>
<tr>
<td>Confirm diagnosis and severity of hemophilia</td>
</tr>
<tr>
<td>Patients with mild to moderate hemophilia are usually treated in the dental office</td>
</tr>
<tr>
<td>Patients with severe hemophilia are usually treated in a dental-based hospital setting</td>
</tr>
<tr>
<td><strong>Management recommendations:</strong></td>
</tr>
<tr>
<td>Hemophilia A: Factor VIII replacement, desmopressin (increases factor level)</td>
</tr>
<tr>
<td>e-aminocaproic acid (stabilizes the clot)</td>
</tr>
<tr>
<td>Hemophilia B: Purified Factor IX products</td>
</tr>
<tr>
<td>von Willebrand’s: Factor VIII replacement; vWF in some cases; and Hemophilia A management recommendation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 7. Dental Management of Patients with Hemophilia.</th>
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<tbody>
<tr>
<td><strong>Management during invasive procedure:</strong></td>
</tr>
<tr>
<td>Use good surgical technique</td>
</tr>
<tr>
<td>Use hemostatic agents</td>
</tr>
<tr>
<td>Hematologist will monitor hospitalized patient</td>
</tr>
<tr>
<td><strong>Management after the procedure:</strong></td>
</tr>
<tr>
<td>Monitor bleeding:</td>
</tr>
<tr>
<td>Hospitalize the pt if bleeding is not controlled</td>
</tr>
<tr>
<td>Examine pt 24-48 hrs post procedure: treat infection and/or bleeding issues</td>
</tr>
<tr>
<td>Avoid aspirin, use acetaminophen with or without codeine</td>
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</tbody>
</table>
Following the patient and clinical assessments, dental professionals should perform a thorough extraoral and intraoral examination to identify deviations from normal that are indicative of bleeding disorders. Long-standing history of clinical findings in patients with mild to severe bleeding disorders often result in petechiae, ecchymoses, spontaneous gingival bleeding, and hemorrhages into the soft tissues. The most common oral finding associated with bleeding disorders is petechiae, which present as purple or red, 1 to 2 mm spots that appear as a result of minute hemorrhages within the dermal layers. Their locations are most often on the mucosal surfaces.27 Ecchymoses, larger than petechiae, are flat, reddish blue or purplish discolorations of the skin or mucosa.27 These hemorrhagic lesions result from spontaneous leakage of blood into the surrounding tissues (extravasation). This severe bleeding results from trauma, including surgery, by underlying blood vessels or by fragility of the vessel walls.1 In severe disorders, gingival bleeding may spontaneously occur.

Based on the outcome of the patient’s histories and head and neck (extra- and intraoral) examination, positive findings relative to the suspicion of a bleeding disorder should warrant a physician consultation and a laboratory screening evaluation. Hence, a proper diagnosis can be made and optimal dental care can be provided.

Treatment Planning Considerations
Appropriate management for patients with bleeding disorders who require routine invasive dental procedures, including subgingival debridement (scaling and root planing), restorative procedures or simple surgical procedures, consists of the following:

**Step 1:** Take accurate, comprehensive histories: personal, medical, dental and pharmacological. Perform a thorough extra and intraoral examination to identify lesions indicative of a bleeding disorder. When a known bleeding disorder is evident, understand the pathophysiology and its related impact on dental treatment. When an unknown bleeding disorder is suspected, refer the patient to his physician or a hematologist to establish a diagnosis. Definitive diagnosis of the bleeding/clotting disorder can be established by the physician or hematologist by ordering the “Prolonged Clotting Time Profile” laboratory tests.

**Step 2:** Consult with the supervising physician to obtain additional information about the patient’s disorder or bleeding history. Continue to investigate and/or to obtain medical clearance to treat. Secondly, retrieve and evaluate the blood laboratory test results while scheduling the appointment within 24 hours of the results.

**Step 3:** Develop an appropriate treatment plan: establish whether or not the invasive dental procedure will be carried out in the dental office or in a hospital-based dental facility. Possibly, prior to invasive treatment, consider blood and/or clotting factor replacement therapy for patients with hemophilia; and, patients with platelet disorders may require platelet transfusion therapy. In addition, other medical interventions may be required beyond infusion therapies for the respective disorders; for example, fibrinolytic defects, vascular defects or modification of anticoagulant therapy may require specialized medical care. When performing the invasive dental procedure recommendations include: minimize tissue trauma; consider hemostatic systems for predictable extensive bleeding during and after complex surgical procedures; consider alternative pain control techniques other than nerve-block anesthesia, especially for patients with coagulopathies; emphasize periodontal health to minimize gingival inflammation which can result in increased bleeding; and/or consider using a combination of local hemostatic systems to manage bleeding episodes. Specialty dental procedures (restorative, endodontic or surgical) can adhere to these fundamental guidelines in their approach to manage bleeding episodes, but most importantly, various invasive oral procedures carry a range of bleeding risk.2,17,24,26

When considering the management of a clinical bleed during various invasive dental procedures, hemostatic measures can include the following systemic or local applications: hemostatic irrigant; absorbable gelatin sponge containing a thrombin solution; gauze-soaked squares and/or mouthrinses with fibrin or tranexamic acid (TXA);
Table 3. Drug Products and Dental Procedures Used as Local Measures to Limit and Control Bleeding During Invasive Dental Procedures

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Chemical Name</th>
<th>Mechanism of Action</th>
<th>Contradictions</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gauze</td>
<td></td>
<td>2&quot; x 2&quot; sterile gauze pads; place pressure on wound to close or apply finger pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gelfoam</td>
<td></td>
<td>Absorbable gelatin sponge material; provides stable 'scaffold' for clot formation</td>
<td>Should not be used under epithelial incisions or flaps, inhibits healing</td>
<td></td>
</tr>
<tr>
<td>Surgical</td>
<td></td>
<td>Oxidized regenerated cellulose; exerts physical effect rather than physiological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleed X</td>
<td>Hemostatic product containing microporous poly-saccharide hemispheres (potato starch); dehydrates blood and accelerates clotting</td>
<td>No known contraindications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tisseel</td>
<td>Fibrin sealant; adhesive action that binds fibrin to the clot</td>
<td></td>
<td>Technique sensitive: requires special attention to preparation; reserved for complex procedures</td>
<td></td>
</tr>
<tr>
<td>Cykloapron</td>
<td>Tranexamic acid</td>
<td>Used in the form of a mouthwash after surgical procedures to inhibit postoperative bleeding; can be administered parenterally or as an 4.8% aqueous solution (4 times daily for 1 week)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suturing</td>
<td></td>
<td>Apposition of soft tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amicar</td>
<td>Aminocaproic acid</td>
<td>Antifibrinolytic agent</td>
<td>No longer available for topical use</td>
<td></td>
</tr>
<tr>
<td>Electrocautery</td>
<td>Tool to slow intraoperative bleeding and interfere with postoperative episodes</td>
<td>Use cautiously to avoid excessive tissue necrosis</td>
<td></td>
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</tr>
</tbody>
</table>

Every drug or dental product is not without side effects/adverse events or drug interactions; dental provider must use dental drug reference prior to their use and/or consult with the patient's supervising physician.
aminocaproic acid (EACA); vasoconstrictors in local anesthetics; surgical techniques and sutures; ice packs; and/or a combination of these measures (Table 3).

Regarding patients on warfarin therapy, pharmacological evidence driven by a current, comprehensive literature review by investigators Patatanian and Fugate concluded the following outcomes regarding the use of hemostatic mouthwashes on patients with various INR target ranges: based on several small clinical studies, tranexamic acid and epsilon aminocaproic acid hemostatic mouthwashes are shown to be effective and safe in this selective population; although, TXA is “6–10 times more potent than EACA.” Neither hemostatic agent is prepared as a solution for local delivery; however, the pharmacist can prepare this hemostatic prescription as an aqueous preparation as indicated by the dental provider. Supporting this literature review is a Class I recommendation by Aframanian et al., based on a Level of Evidence A, by multiple randomized controlled trials. The use of a 2-day regimen of a 4.8% tranexamic acid mouthwash is helpful in achieving adequate clotting in patients on oral anticoagulation therapy after the simple oral surgical procedures.

More importantly, when selecting a hemostatic therapy that achieves adequate hemostasis when performing invasive dental procedures on patients with bleeding disorders one must consider the following elements:

• The specific bleeding disorder.
• The need for a hemostatic agent and/or intervention.
• The type of local and/or systemic hemostatic agent.
• The need for a consultation with the patient’s supervising physician to determine the need for coagulation factor replacement as indicated.
• The severity of the bleeding disorder.
• The specific invasive dental procedure that will induce a bleed intraoperatively and postoperatively.

Conclusion
As health care providers we are ethically and legally obligated to provide the highest standards of care for our dental patients, while actively maintaining appraisal of the literature. Most importantly, it is our responsibility to continue our professional journey as lifelong learners, especially for the treatment of medically-compromised patients.

In this continuing education course, learning encompassed both the basic physiological events of hemostasis and the pathophysiological events associated with thrombohemorrhagic disorders. Knowledge of these essentials is important for proper treatment planning and dental management of such patients. Additionally, complex cases of clotting and bleeding disorders most likely require physician consultation, interpretation of laboratory testing, and prudent decision making when selecting a dental or hospital treatment site. Generally, comprehensive assessment of data, including laboratory tests; diagnosis of the condition; individualized treatment planning with regards to controlling the bleed; and careful manipulation of tissues during implementation is tantamount to successful management of dental patients with bleeding disorders.
Course Test Preview
To receive Continuing Education credit for this course, you must complete the online test. Please go to:

1. Based on the three phases of hemostasis, the development of a hemostatic plug is the result of which phase in the hemostatic system:
   a. The vascular phase
   b. The platelet phase
   c. The coagulation phase
   d. The fibrinolytic phase

2. Common causes of a bleed during the platelet phase include:
   a. Thrombocytopeny
   b. Thrombocytopenia
   c. Deficiencies in the plasma coagulation factors
   d. Both (a) and (b) only

3. Twelve circulating plasma proteins, (also termed plasma coagulation factors) are found in which pathways:
   a. Intrinsic and extrinsic pathways
   b. Platelet and coagulation pathways
   c. Common pathway
   d. Both (a) and (c) only

4. Which plasma coagulation factor is non-existent in the coagulation phase?
   a. Factor III
   b. Factor IV
   c. Factor V
   d. Factor VI

5. Which plasma coagulation factors are Vitamin K-dependent and pharmacologically (anti-coagulants) depressed by indirect means?
   a. Factors II, III, IV, and V
   b. Factors II, VII, IX and X
   c. Factors VII, VIII, IX and X
   d. Factors X, XI, XII, and XIII

6. Factor VII is located in which of the following pathways?
   a. Common pathway
   b. Fibrinolytic pathway
   c. Extrinsic pathway
   d. Intrinsic pathway

7. Which blood laboratory test monitors patients on warfarin therapy?
   a. Ivy Bleeding Time
   b. PFA 100
   c. INR
   d. aPTT
8. Which blood laboratory test monitors patients on heparin therapy and assess defects in the intrinsic pathway of the coagulation system?
   a. Thrombin time
   b. PT
   c. INR
   d. aPTT

9. Patients with a platelet count of less than ____________ manifest thrombocytopenia.
   a. 150,000/mm³
   b. 100,000/mm³
   c. 50,000/mm³
   d. 20,000/mm³

10. Which of the following ranges is recommended for “low intensity” Warfarin therapy?
    a. 1.0 to 2.0
    b. 2.0 to 3.0
    c. 3.0 to 3.5
    d. 3.5 and greater

11. “High intensity” Warfarin therapy (2.5-3.5) is indicated for which of the following conditions?
    a. Mechanical prosthetic heart valves
    b. Prevention of recurrent MI
    c. Prophylaxis of venous thrombosis
    d. Both (a) and (b) only

12. Aspirin and aspirin-containing drugs exert their anti-thrombotic action by irreversibly inhibiting which of the following hemostatic components?
    a. Adequate amounts of plasma coagulation factors
    b. Adequate function of platelets (aggregation and stickiness)
    c. Adequate numbers of platelets
    d. Adequate amounts of fibrin

13. Based on a literature review by Armenian et al., it is recommended that patients who fall “within the therapeutic range of an INR of _________ or below, warfarin therapy need not be modified or altered for simple single dental extractions.”
    a. 2.0
    b. 2.5
    c. 3.0
    d. 3.5

14. Inherited blood coagulation disorders include all of the following, EXCEPT:
    a. Hemophilia A
    b. Hemophilia B
    c. Immune Thrombocytopenic Purpura (ITP)
    d. von Willebrand’s disease

15. Patients with hemophilia B have varying degrees of which of the following plasma coagulation factor deficiencies?
    a. Factor VII
    b. Factor VIII
    c. Factor IX
    d. Factor X
16. **Two defects exist in patients with von Willebrand’s disease, affecting normal hemostasis and resulting in a potential clinical bleed. Which of the following components comprise of this hemorrhagic condition?**
   a. Factor VII and platelets
   b. Factor VIII and platelets
   c. Factor IX and platelets
   d. Factor VIII and factor I5

17. **Which stringy, insoluble protein is responsible for tightly binding the platelet plug to form the hemostatic clot?**
   a. Prothrombin
   b. Thrombin
   c. Fibrinogen
   d. Fibrin

18. **Which common oral manifestation is present as tiny purple or red, 1 to 2 mm spots that appear as a result of minute hemorrhages?**
   a. Petechiae
   b. Hematuria
   c. Ecchymosis
   d. Epitaxis

19. **When taking low-dose aspirin (40 to 320 mg) during invasive dental procedures, it is recommended patients _____________ before routine dental extractions or its equivalent procedure.**
   a. Do not continue use of daily aspirin
   b. Alter anti-platelet drug therapy
   c. Continue use of daily aspirin
   d. Consult with the patient’s supervising physician

20. **When considering a local hemostatic agent to control a clinical bleed during invasive procedures, which of the following is NOT an appropriate choice for patients with a bleeding disorder?**
   a. tranexamic acid mouthrinse
   b. absorbable gelatin sponge containing a thrombin solution
   c. oral administration of epsilon aminocaproic acid
   d. nerve-block anesthesia
References

About the Author

Sandra D’Amato-Palumbo, RDH, MPS

Sandra is a tenured Associate Professor and Program Director in the Dental Hygiene Program, Division of Health Professions at the University of New Haven in Connecticut. She has been a full-time faculty member in the program since 1996, spanning the freshman, junior and senior-level curriculum, including the clinical, community-based and academic areas. Her areas of expertise reflect the following courses taught in the Program: Introduction to Dental Hygiene I and II, Dental Hygiene Clinical Concepts III-V, Dental Hygiene Research, Oral Medicine, Senior Internships, Senior Projects, Oral Pathology and the Community-Based Program. In addition to her academic teaching schedule, Sandra continues to serve on various state and local advisory committees; continues to lecture at state-wide and national conferences; and maintains consultant positions in the state of Connecticut. Sandra has been an active member of the New Haven Dental Hygienists’ Association and the Delta Lambda Chapter of Sigma Phi Alpha Dental Hygiene Honor Society.

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