Hemophilia
What the Oral and Maxillofacial Surgeon Needs to Know

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KEYWORDS

• Hemophilia • Hemophilia inhibitors • Factor VIII deficiency • Factor IX deficiency
• Bleeding disorders • Factor VIII bypass agents

KEY POINTS

- The most significant complication of hemophilia management is the development of inhibitors, which may impact surgical care.
- Acquired hemophilia A is a rare, potential cause of unexpected bleeding, and should be considered whenever a patient presents with unexpected postoperative bleeding.
- Replacement factor administered preoperatively in severe hemophiliacs should be administered within 20 minutes of the start of the procedure owing to the short half-lives of factor replacement.
- From a surgical perspective, hemophiliacs should be managed differently from the typical nonhemophiliac patient with alteration in local anesthetic technique, use of antifibrinolytic therapy, and more intensive follow-up.

INTRODUCTION

Of congenital coagulation factor deficiencies, hemophilia A and hemophilia B are among the most common, and will be encountered in the oral and maxillofacial surgery office. Both are X-linked disorders resulting in a deficiency of either factor VIII (hemophilia A) or factor IX (hemophilia B). Hemophilia A occurs in approximately 1:5000 male births and hemophilia B occurs in approximately 1:30,000 male births. There is no specific geographic or racial predilection. Classic symptoms include soft tissue bleeding and hemarthroses, which can result in debilitating arthropathy. Clinically, hemophilia A and B are indistinguishable. Certainly, any type of bleeding is possible, but 3 key areas where bleeding may be fatal are of particular concern in the hemophiliac: intracranial (leading cause of death in these patients), into the iliopsoas muscle, and in the neck and retropharyngeal space, which may impact the airway.[1] In general, the severity of clinical expression is related to level of factor activity in the plasma and is classified as mild (factor activity 5—40%), moderate (factor activity 1—5%), or severe (factor activity <1%). Normal factor level ranges from 50% to 100%.[2] Patients with mild hemophilia typically will not have spontaneous bleeding, and will only have bleeding in response to trauma, surgical procedures, or dental extractions. Those with moderate hemophilia may experience excess bleeding after trauma, surgery, or dental extractions and may also sustain joint or muscle bleeding after minor injury. Patients with severe hemophilia may experience spontaneous bleeding into joints and muscles and severe bleeding after injuries or surgery. Within the levels of severity, however, there is variable phenotypic expression. Approximately 10% to 15% of patients with hemophilia A exhibit a less severe phenotype and experience less spontaneous bleeding and consume less factor

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concentrates. This heterogeneity is the result of genetics as well as environment, and may also be related to laboratory diagnostic factors.[3]

HISTORICAL PERSPECTIVE

Historical references to hemophilia date back to the second century CE, as evidenced in the Babylonian Talmud, which indicates that if a woman has had her first 2 sons die after circumcision, she is exempt from having the third son circumcised.[4] Modern reports of an inherited bleeding disorder that was passed on from females, but only affected males, were documented in the late 1700s and early 1800s. The term *haemophilia* (literally, "affinity to blood") was first used to describe this disorder in 1828 by German physician Johann Lukas Schonlein and his student, Friedrich Hopff. Haemophilia was known as "the royal disease" because it affected various royal families in England, Germany, Spain, and Russia. The royal disease is believed to have been hemophilia B. Early treatments of hemophilia (in the 1800s) involved blood transfusions, which were often fatal, until the concept of cross-matching was introduced. In 1964, the discovery that cryoprecipitate from thawed frozen plasma contained large concentrations of factor VIII, revolutionized hemophilia management. Sadly, the 1980s brought an era during which thousands of hemophiliacs lost their lives to AIDS as plasma derived clotting factor was contaminated with human immunodeficiency virus. Pasteurization of factor concentrate was introduced in 1981 and, ultimately, all plasma-derived products were manufactured virus free by the end of the 1980s, free from human immunodeficiency virus and hepatitis B and C. Recombinant factors became available in 1992, allowing for mass production of clotting factors. Recent progress has led to the development of bypassing agents used in the management of hemophiliacs with inhibitors as well as the development of immune tolerance therapy to reduce or eliminate inhibitors (more on inhibitors elsewhere in this article).[4,5]

OVERVIEW OF COAGULATION

Upon blood vessel injury, hemostasis occurs via primary and secondary mechanisms. Primary hemostasis involves vascular contraction, platelet adhesion, and the formation of a soft platelet plug. Secondary hemostasis is initiated by the release of tissue factor (TF) and involves a complex coagulation cascade. The goal of secondary hemostasis is to stabilize the platelet plug. The traditional model of the coagulation cascade, divided into intrinsic and extrinsic pathways, is no longer considered absolute and a more cell based model has taken its place.[1,6] The initiating event is the release from injured endothelium of TF. TF combines with factor VII to form TF-factor VIIa, which activates factor X and factor IX to factor Xa and factor IXa. factor Xa combines with factor Va to form prothrombinase, and factor IXa combines with factor VIIIa to form tenase. Both prothrombinase and tenase convert factor II (prothrombin) into factor IIa (thrombin), which ultimately converts fibrinogen into fibrin. The initial amount of thrombin formed by this process is actually insufficient, so thrombin begins a feedback process, which activates previous components of the coagulation cascade, including factor V and factor VIII, ultimately propagating the coagulation cascade. Several inhibitors along the way regulate this process, including antithrombin, protein C, protein S, and TF pathway inhibitor (**Fig. 1**).[6]

CONGENITAL HEMOPHILIA

Factor VIII is made in the liver and endothelial cells and functions as a cofactor of factor IXa in the tensae complex (factor IXa–factor VIIIa), which activates factor X to factor Xa. Factor IX is made in the liver and the activated form combines with factor VIIIa forming the tensae complex (activating factor X). Lack of either factor VIII or factor IX leads to decreased thrombin formation, and an inability to form a clot. Both hemophilia A and B are X-linked recessive disorders, making hemophilia much more common in males than females. In hemophilia A, approximately 30% of mutations are de novo, and in hemophilia B, more than 33% of mutations are de novo.[6] Of the inherited clotting disorders, hemophilia A and B are the only ones that are inherited in a sex-linked recessive manner. A father with hemophilia will produce female offspring who are carriers, but no male offspring will be affected. A female carrier has a 50% chance of having a son with hemophilia and a 50% chance of having a daughter who is a carrier. It is important to recognize that up to one-third of hemophilia carriers may have reduced levels of factor VIII or factor IX and may have bleeding issues similar to that seen in mild hemophiliacs.[2,6] For this reason, it is recommended that carriers also undergo measurement of factor activity, especially before becoming a surgical patient, because they may require the same management as a mild hemophiliac.[2]

Most severe hemophiliacs will present with excessive bleeding during the first year of life.