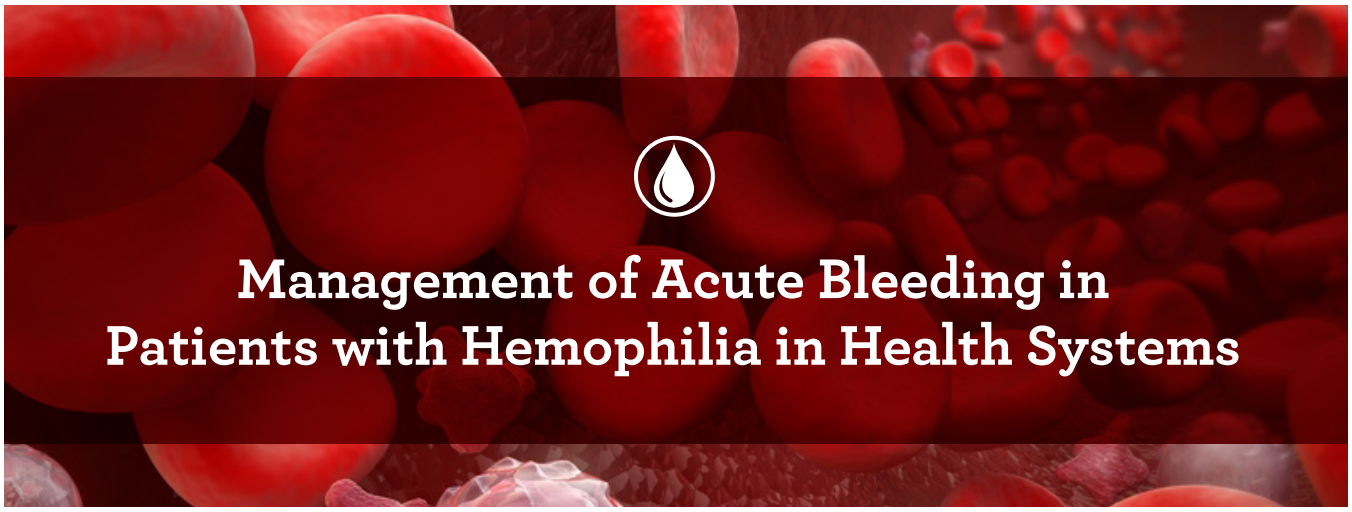
e-Newsletter **ASHP ADVANTAGE** MARCH 2013



Management of Acute Bleeding in Patients with Hemophilia in Health Systems

ASHP Advantage is coordinating a series of learning opportunities related to managing acute bleeding in patients with hemophilia.

These opportunities are designed to build on each other to provide an overview of hemophilia and treatment options, especially in patients with acute bleeding or planning surgery with a high risk for bleeding. The educational activities provide live and on-demand formats, and faculty members are experts in hematology. The series is supported by an educational grant from Novo Nordisk Inc.

A Midday Symposium, *Challenges in Managing Acute Bleeding in Patients with Hemophilia,* was conducted and simultaneously webcast on December 4, 2012, at the 47th ASHP Midyear Clinical Meeting and Exhibition in Las Vegas, Nevada. Attendees submitted questions about unresolved issues related to the management of acute bleeding in patients with hemophilia by health-system pharmacists, and these questions served as the guide for Initiative Chair William E. Dager, Pharm.D., BCPS (AQ-Cardiology), and faculty member Mark T. Reding, M.D., when they developed content for a live webinar held on February 27, 2013. This webinar was the primary source of content explored in the two e-newsletters that are part of the educational initiative.

If you missed the Midyear symposium, it is now available as a web-based activity and is approved for two hours of continuing pharmacy education credit. Its on-demand format is convenient since it may be completed at any time. For more information and to access the web-based activity, go to the web portal at www.ashpadvantage.com/stopbleeding.

FACULTY ROUNDTABLE

Visit the Stop Bleeding web portal or click here to listen to Dr. William E. Dager and fellow faculty Drs. Surabhi Palkimas and Mark T. Reding discuss important issues related to managing acute bleeding in patients with hemophilia. The discussion is available in three parts, each lasting 13 to 19 minutes:

- Monitoring and dosing considerations
- Considerations in controlling bleeding and preventing thrombosis
- Pharmacist's role

Sign up to be notified of updates related to this educational initiative. The second e-newsletter in this series will focus on system issues related to managing bleeding in patients with hemophilia.

www.ashpadvantage.com/stopbleeding

ACUTE BLEEDING IN HEMOPHILIA

WHY FOCUS ON HEMOPHILIA?

Hemophilia is a common congenital bleeding disorder that affects 20,000 Americans.[1]

The disorder is the result of a deficiency or absence of clotting factor VIII (hemophilia A) or clotting factor IX (hemophilia B). Hemophilia A is most common, accounting for 80% of all cases. Hemophilia is caused by a genetic abnormality on the X chromosome and primarily affects males (roughly 1 of every 5000 male births).[2] Females rarely are affected, although they may be carriers of the genetic abnormality. Although most patients with hemophilia have a family history of the disorder, about one in three cases are acquired through spontaneous genetic mutation.

Hemophilia typically manifests as unusually heavy or prolonged bleeding or unexplained bruising or bleeding.[1] Hemarthrosis (i.e., bleeding into the joints, usually of the ankles, knees, and elbows) is the most common complication of hemophilia. Repeated hemarthrosis can lead to hemophilic arthropathy characterized by cartilage and bone destruction, bone remodeling, and progressive loss of function. Bleeding in soft tissues, deep muscles, and organs can cause pain and damage. Intracranial hemorrhage can lead to brain damage and death.

Clotting factor deficiencies and bleeding associated with hemophilia often are treated by infusing clotting factor concentrates derived from donated plasma or recombinant DNA technology.[3] Administration of clotting factors prevents and controls bleeding episodes and plays a vital role in preventing hemophilic arthropathy. However, these products are costly, so it is important that they are used judiciously and waste is minimized.

Patients with hemophilia usually are managed in specialized treatment centers, so health-system pharmacists may be unfamiliar with treatment of the disorder. However, patients with hemophilia and traumatic bleeding or who are planning surgeries with a high risk for bleeding may be admitted to hospitals or other health systems. Therefore, health-system pharmacists should be aware of the approaches used in managing acute bleeding in these patients.

BLEEDING MANAGEMENT

In recent years, great advances have been made in transfusion therapy for the management of acute bleeding in patients with hemophilia, especially the introduction of recombinant factor VIII and recombinant factor IX for clotting factor replacement therapy in 1992 and 1998, respectively.

Guidelines for dosing and use of these products are largely empiric because few studies designed to define optimal dosing have been conducted. There is considerable variability in current factor replacement therapy practices based on provider and institutional preferences and differences in access to resources, even among developed countries. Nevertheless, the general approach to using these products is similar. The goal is to provide sufficient but not excessive amounts of the clotting factor to promote hemostasis. Compared with clinicians in developing countries, clinicians in the United States tend to use clotting factor concentrates more liberally to treat hemophilia, which increases costs.

The small patient population and high cost of treatment have made it difficult to perform clinical studies comparing treatment approaches for the management of acute bleeding in patients with hemophilia. An extensive literature review and survey of practices at 26 European hemophilia treatment centers was conducted to provide insight into the optimal factor replacement therapy during invasive procedures in patients with hemophilia.[4] The literature review identified 110 original papers published between 1965 and 2007, only two of which were randomized controlled trials. These two trials involved patients undergoing dental surgery (i.e., procedures with a relatively low risk for serious bleeding). Thirty-five clinical studies of patients undergoing major surgery were identified, including

eight high-quality case-control or cohort studies and 27 case reports or case series. Analysis of this literature was hindered by a lack of details regarding clotting factor levels, the duration of factor replacement therapy, and bleeding complications. Thus, current practices in the use of factor replacement therapy to manage acute bleeding in patients with hemophilia undergoing surgery are not considered evidence-based medicine. Clinical studies are needed to identify the optimal treatment approach.

Considerations in providing clotting factor replacement therapy for the management of acute bleeding in patients with hemophilia include the target clotting factor level, duration of therapy, dosing, mode of administration, and patient monitoring. The normal clotting factor range in patients with hemophilia is 60% to 140%. However, the level required for adequate hemostasis in a patient with acute bleeding or undergoing surgery depends on several variables, including the type of bleeding event or surgery, degree of postoperative immobility, and amount of tension on the surgical incision. Clotting factor consumption during active bleeding or surgery also should be taken into consideration in setting a target factor level.

The target factor level can change over time in a patient (e.g., during the postoperative recovery period). For example, an initial target level of 80% to 100% often is used for major bleeding or surgery, with a higher target if substantial clotting factor consumption is anticipated during surgery. A lower target level of 60% to 80% often is used once the patient is stable and for minor bleeding or surgery.

The duration of factor replacement therapy varies among institutions and is largely empiric based on local opinion and experience. Most surgical wounds are well healed from a hemostatic point of view by the fourth or fifth postoperative day, so factor replacement therapy usually is provided for 7 to 14 days after major surgery. More prolonged therapy often is used during rehabilitation with aggressive physical therapy after orthopedic surgery because of bleeding concerns even after hemostasis is achieved postoperatively. Factor replacement therapy typically is continued for 3 to 5 days following minor surgical procedures. A similar approach is used in determining the duration of factor replacement therapy to manage nonsurgical bleeding (i.e., a longer duration of therapy for severe nonsurgical bleeding, and a shorter duration of therapy for minor nonsurgical bleeding).

A recent trend to use ideal body weight instead of actual body weight for dosing of factor replacement therapy in obese patients has been observed because ideal body weight correlates more closely with the blood volume than does actual body weight in these patients. This approach reduces dosing requirements and costs.

Limited published data are available to support the use of the ideal body weight or demonstrate whether morphometric variables (e.g., fat mass index, body mass index) should be taken into consideration when determining the optimal dosing of factor replacement therapy for overweight and underweight patients with hemophilia.[5] Body mass index (BMI) reflects body weight relative to height, but it does not differentiate between lean and fat body mass. Fat mass index (FMI) is analogous to BMI, but it reflects body fat mass (measured using bioelectric impedance analysis) relative to height. FMI may more accurately reflect obesity than BMI.[6] In an observational study of replacement factor VIII therapy in 46 patients with hemophilia A approximately half of whom were overweight or obese based on both BMI and FMI, patients with a high FMI were over treated and those with a low FMI were under treated. Factor replacement therapy should be individualized based on clinical response (especially bleeding and factor levels in patients with dosing based on ideal body weight) until additional data become available to clarify the influence of morphometric variables on dosing requirements.

Dose rounding for clotting factor concentrates (i.e., rounding off the calculated dose based

on available container sizes) can minimize waste, resulting in substantial cost savings. In the past, doses were rounded to within 10% more or less than the calculated dose, but a more conservative practice to use doses rounded to within 4% more or less than the calculated dose is becoming more common.

Factor replacement therapy usually is given by bolus infusion. Peak clotting factor levels typically are measured 15 minutes after completion of the infusion, but there is interpatient variability in clotting factor recovery and half-life. Continuous infusion (after an initial bolus dose) is an alternative mode of administration for clotting factor concentrates that is often used for patients with severe bleeding or undergoing major surgery. Use of this mode of administration avoids peaks and troughs in factor levels (i.e., it provides consistent levels), which allows blood to be drawn for factor level measurement at any time once steady state has been achieved. Continuous infusion also may reduce the likelihood of delayed or missed doses and allow the use of a lower target factor level to reduce dosing requirements and costs, without increasing the risk of inhibitor (i.e., antibody) formation.[7,8] Studies comparing bolus and continuous infusion have not been performed. The choice of mode of administration often is based on provider and institutional preference.

PATIENT ASSESSMENT

Assessment of patients with hemophilia who plan to undergo surgery with a high risk for bleeding should include risk factors for complications, including advanced age, frail physical condition, and the presence of scar tissue from multiple prior procedures, which prolongs the surgical procedure.

Conservative, minimally-invasive procedures should be considered for older, frail patients to minimize the risk for complications. Preoperative erythropoiesis-stimulating drug therapy and iron supplementation might be used to correct anemia.

Assessment of patients with hemophilia and suspected or overt bleeding involves the measurement of blood pressure, heart rate, hemoglobin, and clotting factor levels and takes into consideration the presence of swelling and bruising. Hypotension and tachycardia often reflect volume depletion due to bleeding. A low hemoglobin concentration may be particularly useful for detecting internal bleeding. Clinicians may need to differentiate bleeding related to hemophilia (i.e., coagulopathic bleeding) from local or anatomic bleeding. The presence of bruising in multiple locations and certain clinical features (e.g., low factor levels, elevated International Normalized Ratio or activated partial thromboplastin time, falling fibrinogen levels or platelet counts) suggest a coagulopathic etiology to bleeding. The presence of petechiae reflects a severely low platelet count or platelet dysfunction and is not caused by hemophilia itself. In postoperative patients, the surgical site (i.e., dressings, wound packing) and drains should be inspected to determine whether the volume of blood loss is appropriate for the type of procedure. Local or anatomic bleeding should be suspected if the factor level is at the target in a patient with hemophilia. Contrary to what is typically assumed, postoperative bleeding in a patient with hemophilia often is not due to inadequate factor replacement therapy.

Frequent reassessment is warranted for patients with hemophilia and acute bleeding because of the dynamic nature of bleeding in this patient population. Clinicians should look beyond laboratory test results to consider the patient's overall clinical status to accurately determine the cause of bleeding in postoperative patients.

Lack of hemostatic efficacy of factor replacement therapy may be attributed to inadequate factor levels, other coagulation defects (e.g., thrombocytopenia, acidosis, citrate toxicity), anatomic bleeding, or development of inhibitors (i.e., antibodies to clotting factors). Approximately 30% of patients with severe hemophilia A and up to 5% of patients with severe hemophilia B develop inhibitors as a result of an immune response to exogenously administered clotting factors, which are recognized as foreign substances.[2,9] These inhibitors usually develop at a

young age in patients with hemophilia (i.e., the inhibitors usually are present when adults with hemophilia are admitted to the hospital for active bleeding or plans for surgery). Inhibitors neutralize the procoagulant effects of clotting factor concentrates, make bleeding more difficult to control, and increase the likelihood of hospitalization for bleeding.

Standard clotting factor VIII or IX concentrates may be used to manage bleeding episodes in patients with a low inhibitor titer (<5 BU/mL), but dosing requirements and costs often are substantially higher than for patients without inhibitors.[10] Clotting factor VIII and IX concentrates may not be effective for managing bleeding episodes in patients with a high inhibitor titer (5 BU/mL or higher). A bypassing agent may be used to circumvent the need for clotting factor VIII or IX (i.e., bypass these clotting factors in the coagulation cascade) in these patients. Two bypassing agents currently are available in the United States: (1) activated prothrombin complex concentrate (aPCC), which contains clotting factor VII in an activated form and clotting factors II, IX, and X mainly in a non-activated form, and (2) recombinant factor VIIa (rFVIIa). These two products are comparable in their efficacy for controlling bleeding, but this efficacy is unpredictable.[11] The efficacy of bypassing agents depends on the type of bleeding, timing of treatment initiation, and patient characteristics. If one of the two agents is ineffective, the other should be tried. Sequential therapy (i.e., alternating aPCC and rFVIIa) may be helpful in patients with life-threatening bleeding and inhibitors. A laboratory method for monitoring of therapy with bypassing agents beyond general measures (i.e., hemoglobin concentration or hematocrit) has not been established.

Various adjunctive agents, including antifibrinolytic agents, desmopressin, steroids, rituximab, immune globulin IV, and cytotoxic immunosuppressant agents, such as cyclophosphamide, are also available to promote hemostasis in patients with inhibitors.[12] However, some of these agents (e.g., rituximab) have a high cost and slow onset of action, limiting their usefulness for patients with acute bleeding. Decisions about the use of such agents should be delayed until a need for them is confirmed.

Hemophilic patients receiving clotting factors and undergoing major surgery (e.g., major orthopedic surgery for advanced joint disease) may be at risk for venous thromboembolism (VTE) once bleeding is controlled. Prophylaxis against VTE may be warranted for high-risk patients, although limited data are available to support this practice. Mechanical prophylaxis usually is appropriate. Pharmacologic prophylaxis should be considered for high-risk patients without inhibitors. The prophylactic therapy used for patients without hemophilia usually is used with factor VIII or IX replacement therapy for patients with hemophilia. However, pharmacologic prophylaxis should not be used for patients with inhibitors because these patients require bypassing agents, which tend to be less consistently effective than clotting factor VIII or IX replacement therapy in patients without inhibitors. The risk of bleeding generally is a greater concern than the risk for VTE in patients with inhibitors. Daily reassessment of the risk for bleeding and the risk for thrombosis is needed in patients with hemophilia undergoing major surgery. The rationale for clinical decisions about VTE prophylaxis should be documented in the patient medical record, especially if it is not consistent with the institution's VTE prophylaxis guidelines.

Managing acute bleeding in patients with hemophilia can pose a challenge to health-system pharmacists who are unfamiliar with treatment of the disorder. An understanding of the issues involved can help position pharmacists to optimize the use of costly clotting factor concentrates and bypassing agents and enhance patient outcomes.

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For complete information about educational activities that are part of this initiative, visit www.ashpadvantage.com/stopbleeding. There is no charge for the activities, and ASHP membership is not required.

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