The State of
Acquired Hemophilia
By Jennifer Kester

Treatment for this difficult-to-diagnose form of hemophilia has to be individualized for each patient, but the prognosis is often good.

Hemophilia is a blood disorder affecting approximately 20,000 males in the United States, with positive tests for approximately one in every 5,000 births, according to the National Hemophilia Foundation. Hemophilia A, typified by a drop in clotting factor VIII, and its rarer cousin, hemophilia B, marked by a deficiency of clotting factor IX, are relatively straightforward to diagnose. These forms of hemophilia are passed down genetically and often are discovered in the first weeks after birth.
What Is AH?

AH is a rare blood disorder marked by sudden bleeding in patients without a previous personal or family history of hemophilia. Incidences of acquired hemophilia are believed to occur in up to one case per million persons per year. However, it’s likely that available statistics underestimate the true figure, given that AH can be difficult to diagnose and many cases of AH remain uncounted unless discovered during surgery or testing for other disorders.

Almost all known cases of AH are characterized by autoantibodies that either disrupt the functioning of coagulation factor VIII or that clear this clotting factor from the plasma, which results in unpreventable bleeding in AH patients. Approximately half of AH incidences have been linked to a wide variety of underlying medical conditions, such as collagen, vascular and other autoimmune diseases (different studies put the percentage of cases between 16.7 percent and 18 percent); lymphoproliferative malignancies or solid tumors (between 6.7 percent and 14.7 percent of cases); skin diseases (between 3.3 percent and 4.5 percent of cases); possible drug reactions (between 2.0 percent and 4.5 percent of cases); and pregnancy (between 2.0 percent and 11 percent of cases). Other reported factors for AH include diabetes, respiratory diseases such as asthma, acute hepatitis B infection and acute hepatitis C infection. A 2007 study cited by Medscape suggests that in up to 63.3 percent of cases reported, the occurrence of AH remains without an identifiable source. However, because the occurrence may be a result of adverse drug reactions in patients taking several such medications, the figure for this reported factor might be artificially low. According to the World Federation of Hemophilia, pharmaceuticals implicated in the acquisition of AH include antibiotics such as a penicillin, sulphonamides and ciprofloxacin; immunological drugs such as interferon and fludarabine; psychotropics such as phenytoin, flupentixol and zuclopenthixol; as well as the antiplatelet agent clopidogrel. And, since this list is not exhaustive, clinicians should look to other recently used medications as the source for AH in patients.

Diagnosing AH

Despite the common threat to the functioning of coagulation factor VIII, there are very different symptoms between AH and the hereditary form of hemophilia A. Typical symptoms for hemophilia A include blood in the urine or stool, hemorrhaging in the gastrointestinal or urinary tracts, and swelling in the joints. For reasons still not clear, patients with AH display a different set of symptoms, including bleeding into the skin and musculature, haematemesis, haematuria, as well as longer-than-usual postpartum or postoperative bleeding. Often, the condition is misdiagnosed as other types of acquired bleeding disorders, including disseminated intravascular coagulation.

Commonly, AH patients exhibit an unexplainable and prolonged activated partial thromboplastin time (aPTT), which is an indicator for determining the efficiency of both

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the contact activation pathway and common coagulation pathways. For patients with any of the above symptoms, as well as a prolonged aPTT at less than 45 percent mean normal level, clinicians measure the levels of clotting factors VIII, IX, XI and XII, and a low level of clotting factor VIII alone is highly suggestive of the appearance in the blood of an inhibitor related to AH. Other indications of AH are normal prothrombin time assays, template bleeding times, and platelet and leukocyte levels. Tests for the presence of lupus anticoagulant or heparin are often conducted to rule out these factors in a patient’s symptoms. The antibodies in acquired hemophilia directed toward clotting factor VIII are typically polyclonal IgG4 antibodies, although more rarely, they are of the IgM or IgA varieties.

The World Federation of Hemophilia suggests repeating tests after a few days if an inhibitor is not at first revealed. The Bethesda assay, used to measure residual clotting factor VIII after incubating the patient plasma with normal plasma for two hours at 37 degrees Celsius, may be used to determine the quantity of the inhibitor in the patient’s plasma. Making diagnoses more difficult, clotting factor VIII may form a complex with other antibodies, which may create some residual clotting factor VIII activity and, thus, interfere with ascertaining AH’s signature drop in factor VIII. The upshot for clinicians is that AH patients may still exhibit factor VIII baseline levels even as they have high-titer inhibitory antibodies.

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**Treatment Options**

The first objective for the treatment of AH is to control the affected areas of bleeding, while the long-term objective is to remove the inhibitor causing the disorder in the first place. Due to bleeding complications, the World Federation of Hemophilia recommends patients receive care in specialist hemostasis units that have experience in treating the disorder and the requisite blood products for treatment, which must be specific to the needs of each patient. In the U.S., the federal government supports a network of hemophilia care centers. Experts on staff provide not just direct treatment, but also education and support for specialists and AH patients. The Centers for Disease Control and Prevention provides a list of more than 100 centers on its website.

For many patients, especially those cases appearing postpartum or due to drug-induced inhibitors, the AH inhibitors may disappear on their own, and these patients, therefore, require only initial care with follow-up for maintaining their blood supply after the original hemorrhaging. However, older patients with underlying malignancies and other autoimmune disorders experience cases of AH that do not resolve on their own. For these patients, practitioners need to weigh the use of steroids against a range of health factors. Historically, because human factor VIII is likely to face the same assaults as the patients’ own factor VIII, clinicians had widely prescribed the use of porcine factor VIII. It was believed that the similarity to human factor VIII would provide some hemostatic effects, while being different enough to avoid inactivation by the bodies’ production of antibodies. However, results proved inconclusive on its uses.

For the last 30 years, according to the National Hemophilia Foundation, the typical treatment for AH bleeding episodes included the use of activated prothrombin complex concentrates, such as Factor VIII Inhibitor Bypassing Activity (FEIBA), which contains activated factors VII, IX and X. According to the World Federation of Hemophilia, doses of 50 to 100 units are to be provided intravenously in the treatment of AH, although doses exceeding 200 units per kilogram within any 24-hour period carry the risk of venous thromboembolism. FEIBA is no longer approved by the FDA to treat AH.

In 2006, the U.S. Food and Drug Administration (FDA) approved another bypassing agent for the treatment of AH, Novo Nordisk’s NovoSeven, which also is FDA approved for the treatment of bleeding episodes in patients with congenital