**Factor VIII Deficiency, Congenital**

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### Feature

#### Synonyms

Classic hemophilia, hemophilia A.

#### Epidemiology

1 per 5,000 male births, no racial predilection.

#### Etiology & Pathogenesis

Factor VIII (antihemophilic factor) 325,000 kDa glycoprotein largely synthesized in the liver. Factor VIII circulates in the plasma in a stable complex with von Willebrand factor (vWF), which inhibits the proteolytic degradation of Factor VIII. Factor VIII activation occurs on the platelet surface, and is initiated by thrombin or factor Xa. Activated factor VIII (factor VIIIa) is a cofactor for factor IXa activation and enhances the reaction approximately 10,000 fold.

The factor VIII gene, located on the long arm of the X chromosome at Xq28, comprises 186 kilobases, and is one of the largest human genes yet identified. Approximately 500 abnormalities of the factor VIII gene have been identified at present. Most patients with mild and moderate disease have single base-pair substitutions causing missense messages, while an intrachromosomal intron-exon recombination (intron 22 inversion) accounts for most cases of severe hemophilia A. Other common mutations are found in intron 13, intron 18 and intron 22. Due to the high rate of spontaneous mutation of the factor VIII gene, about 30% of factor VIII patients have a negative family history.

### Disease Facts

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<td>Pattern of Inheritance</td>
<td>X-linked recessive.</td>
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<td>Clinical Presentation</td>
<td>The clinical severity of bleeding in hemophilia A may be predicted from the level of factor VIII:C as following: <strong>severe</strong> (70% of patients, less than 1% FVIII:C); <strong>moderate</strong> (15% of patients, 1% - 5% FVIII:C); <strong>mild</strong> (15% of patients, 5% - 25% FVIII:C); <strong>subclinical</strong> (25% - 50% FVIII:C). A wide variety of bleeding problems may be encountered, including deep muscle and joint hemorrhage, intracranial hemorrhage, hematomas, cephalohematoma at birth, easy bruising, gastrointestinal hemorrhage, postsurgical/posttraumatic bleeding, epistaxis, intra- and retroperitoneal hemorrhage, atraumatic bleeding, etc. Factor VIII deficient patients have a particular predisposition to the development of musculoskeletal hemorrhage, which can lead to chronic scarring, pain, and loss of mobility. Severe hemophilia usually develops in infancy or early childhood, but the diagnosis may be delayed until adulthood in mild disease. Autoantibodies against factor VIII (&quot;factor VIII inhibitors&quot;) develop in 20-30% of patients with hemophilia A who receive multiple transfusions of factor VIII concentrate and occasionally in patients with other diseases. Factor VIII inhibitors can cause bleeding problems and seriously compromise the care of patients with hemophilia A. Most hemophilia patients develop “type I” factor VIII inhibitors that show high affinity, time dependent, irreversible binding to factor VIII with second-order reaction kinetics. Type I inhibitors characteristically show a rapid anamnestic response to transfused factor VIII and titers remain high for months to years. Type II factor VIII inhibitors are characterized by a rapid fall in titer following transfusion of factor VIII concentrate and a lack of a rapid anamnestic response. The presence of type II factor VIII inhibitors is often associated with underlying liver disease.</td>
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**Laboratory Features**

The aPTT is prolonged in typical hemophilia A, with correction when the patient's plasma is mixed with normal plasma in a 1:1 ratio. The PT, thrombin time, and bleeding time are normal. Diagnostic confirmation is performed by determination of functional plasma factor VIII activity (FVIII:C) using a clot detection or chromogenic assay. Immunoassays for factor VIII antigen (FVIII:Ag) can also be performed. The factor VIII:C concentration of female carriers is normally 50%, but the level can vary depending on the degree of lyonization (random inactivation) of the X chromosome.

In most patients, the presence of an inhibitor can be documented by prolongation of the aPTT with a 1:1 mix. However, a mixing study using a 4:1 mixture of patient plasma and normal plasma incubated for 2 hours at 37°C is required to document the presence of some weak inhibitors. Factor VIII inhibitors are usually quantitated by a modified aPTT using serial dilutions of patient plasma with a fixed amount of factor VIII. The relative strength (titer) of a factor VIII inhibitor is expressed in Bethesda Units (BU), the reciprocal of the dilution required to neutralize 50% of the factor VIII. Residual factor VIII activity is calculated to correct for spontaneous decay of the factor VIII:

\[
\text{Residual factor VIII activity} = \frac{\text{Factor VIII activity (Patient)}}{\text{Factor VIII activity (Control)}}
\]

The inhibitory value in BU is calculated from:

\[
\text{BU} = \log_2\left(\frac{1}{\text{Residual factor VIII}}\right) \times (\text{Dilution Ratio})
\]

The classical Bethesda assay is performed with: (1) patient plasma is mixed 1:1 with normal plasma, and (2) normal plasma mixed 1:1 with imidazole buffer (pH 7.3). Both mixtures are incubated for 2 hours at 37°C prior to the measurement of factor VIII levels. Modified Bethesda assays include the Nijmegen assay and the Oxford assay.

Chromogeneic assays are an alternative method to quantitate factor VIII inhibitors. These assays use thrombin to activate factor VIII, which serves as a cofactor for factor IXa to activate factor X. A colorless factor Xa substrate is converted to a colored product measurable with a spectrophotometer. The amount of the inhibitor is calculated as the reciprocal of the sample dilution required to achieve 50% of the optical density found in a standard factor VIII assay.

**Clinical Presentation (Cont'd)**

Inhibitors characteristically develop in patients with autoimmune diseases, malignancy, lymphoproliferative diseases, or plasma cell dyscrasias. These antibodies exhibit time-independent, reversible, low-affinity binding to factor VIII with multiphasic reaction kinetics. Type II inhibitors usually exist at low titer and show a minimal anamnestic response.

**Treatment**

Replacement therapy to raise the plasma factor VIII level to the required therapeutic range is the basis of factor VIII therapy at the present time. In the future, forms of therapy to repair the defective gene (gene therapy) may be used. Desirable factor VIII levels and other therapeutic agents are shown in the following table.
The conventional factor VIII:C assay is used for monitoring the efficacy of therapy. Generally, each unit of factor VIII concentrate will increase the level of factor VIII:C by 2%/kg of body weight. The number of units of factor VIII required to achieve the desired plasma level can be calculated from the following formula:

\[
\text{Factor VIII units} = 40 \times \text{BW} \times (\text{desired factor level} - \text{actual factor level})/100
\]

where BW is body weight in kg

Patients with factor VIII deficiency must avoid physical trauma and aspirin-containing compounds or other substances that may compromise the coagulation system.

<table>
<thead>
<tr>
<th>Disease Severity</th>
<th>Minimal Factor VIII Hemostatic Level</th>
<th>Therapeutic Agents</th>
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<tbody>
<tr>
<td>Mild bleeding</td>
<td>30%</td>
<td>DDAVP</td>
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<tr>
<td>Non-life threatening bleeding</td>
<td>50%</td>
<td>Cryoprecipitate</td>
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<tr>
<td>Preoperative</td>
<td></td>
<td></td>
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<tr>
<td>Severe bleeding CNS hemorrhage</td>
<td>80-100%</td>
<td>Factor VIII concentrates</td>
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<td></td>
<td></td>
<td>Recombinant factor VIIa</td>
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<td>Dental surgery in mild to moderate disease</td>
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<td>(\epsilon)-aminocaproic acid</td>
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**References**


Dunn AL, Abshire TC: Recent advances in the management of the child who has hemophilia. Hematol Oncol Clin North Am 18:1249-1276, viii, 2004


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References


Makris M: Systematic review of the management of patients with haemophilia A and inhibitors.


