Chromogenic Factor VIII, Activity

Chromogenic factor VIII activity is used for diagnosis of mild hemophilia A (in conjunction with one-stage clot-based factor VIII activity) and measurement of factor VIII activity in the presence of interfering drugs or lupus anticoagulants that result in underestimation by clot-based methods. It is also used for measuring factor VIII activity in patients treated with certain modified extended half-life factor VIII replacement products and emicizumab.

Disease Overview

Incidence

Hemophilia A in 1/4,000-5,000 live male births worldwide; rare in females

Inheritance

X-linked recessive, factor VIII deficiency can also be acquired due to autoantibodies

Visit the Hemophilia - Factor VIII or IX Deficiency Consult topic for additional information about factor VIII deficiency

Diagnostic Issues

Hemophilia A may be classified as mild, moderate or severe, based on factor activity.

<table>
<thead>
<tr>
<th>Disease Classification</th>
<th>Expected Factor Activity</th>
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<tbody>
<tr>
<td>Mild</td>
<td>6-35%</td>
</tr>
<tr>
<td>Moderate</td>
<td>1-5%</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt;1%</td>
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</table>
Mild hemophilia A may require both one-stage clot-based factor VIII activity and chromogenic factor VIII activity for diagnosis, due to differences in how the underlying mutations affect factor VIII activity in the tests.\(^2\)

**Monitoring Issues**

Modified extended half-life factor VIII replacement products may lead to underestimation of factor VIII activity in clot-based factor VIII assays using certain aPTT reagents.\(^3,4,5\)

<table>
<thead>
<tr>
<th>Extended Half-Life FVIII Replacement Product</th>
<th>Manufacturer</th>
<th>Modification Type</th>
<th>Effect on FVIII Activity</th>
</tr>
</thead>
</table>
| Adynovate                                   | Shire/Baxalta, Baxter | PEGylated (random) rFVIII | Acceptable recovery with chromogenic or one-stage FVIII activity for all aPTT reagents tested to date  
Relatively higher recovery with aPTT reagents with ellagic acid activators (eg, Actin FS, Actin FSL) that is not clinically significant |
| Afstyla                                     | CSL Behring  | Single chain, B-domain truncated rFVIII | Underestimated with all one-stage FVIII activity assays; package insert recommends use of correction factor which is supported by a multicenter field study\(^7\)  
Acceptable recovery with chromogenic FVIII activity assays |
| Eloctate                                    | Biogen Idec  | Fc fusion, B-domain deleted rFVIII | Acceptable recovery with chromogenic or one-stage FVIII activity for all aPTT reagents tested to date |
| Esperoct                                    | Novo Nordisk | B-domain truncated, glycoPEGylated rFVIII | Underestimated with STA-PTT A, SynthAFax, APTT Sp (chromogenic factor VIII activity recommended instead of one-stage assay using these aPTT reagents)  
Acceptable recovery with one stage FVIII activity for all other aPTT reagents tested to date |
| Jivi                                        | Bayer Healthcare  | PEGylated (site directed) B-domain deleted rFVIII | Underestimated with aPTT reagents with silica activators (eg. STA-PTT A, APTT Sp)  
Few other aPTT reagents studied to date, recovery appears acceptable with aPTT reagents with ellagic acid activators |

Factor VIII activity cannot be accurately measured using a one-stage clot-based factor VIII activity assay in the presence of emicizumab.\(^6\)

- Emicizumab is a bispecific antibody that bridges factor IX and factor X to produce activated factor X (FXa). Emicizumab effectively replaces the function of factor VIII in secondary hemostasis
Emicizumab will substitute for factor VIII function in one stage clot-based factor VIII activity assays and will result in overestimation of factor VIII activity (either native factor VIII or factor VIII concentrate administered in an acute care setting)
  
  - Interference may last for up to to 6 months following end of therapy

- In patients receiving emicizumab, patient factor VIII activity (endogenous or factor VIII concentrate) can be accurately measured using chromogenic factor VIII activity with bovine reagents
  
  - Emicizumab can bind to factor IX and X in chromogenic assays using human factor-derived reagents and will still overestimate factor VIII activity
  
  - The chromogenic factor VIII activity assay at ARUP Laboratories uses bovine reagents and is not affected by emicizumab

- Measuring factor VIII inhibitors in patients receiving emicizumab requires use of a Bethesda assay based on a chromogenic factor VIII assay (bovine reagents)

### Test Interpretation

#### Results

- Age-specific reference intervals are provided for each result on the patient chart
- Decreased factor VIII activity is expected in patients with hemophilia A (see table above for disease classification) and is associated with increased risk of bleeding

#### Limitations

- Decreased chromogenic factor VIII activity results may also be caused by:
  
  - von Willebrand disease
  
  - Specimen collection and storage issues:
    - Uncontrolled freeze-thaw cycles
    - Prolonged ambient storage
    - Activated or clotted specimens
  
  - Anticoagulant medications (assay interference)
    - Heparin (>2 U/mL)
    - Direct thrombin inhibitors
    - Direct Xa inhibitors

- Factor VIII activity may be elevated above usual baseline (normal or high result could mask underlying deficiency) in patients with acute phase responses
- Normal factor VIII activity does not exclude female hemophilia carrier status

#### References


Related Information

**Hemophilia - Factor VIII or IX Deficiency**