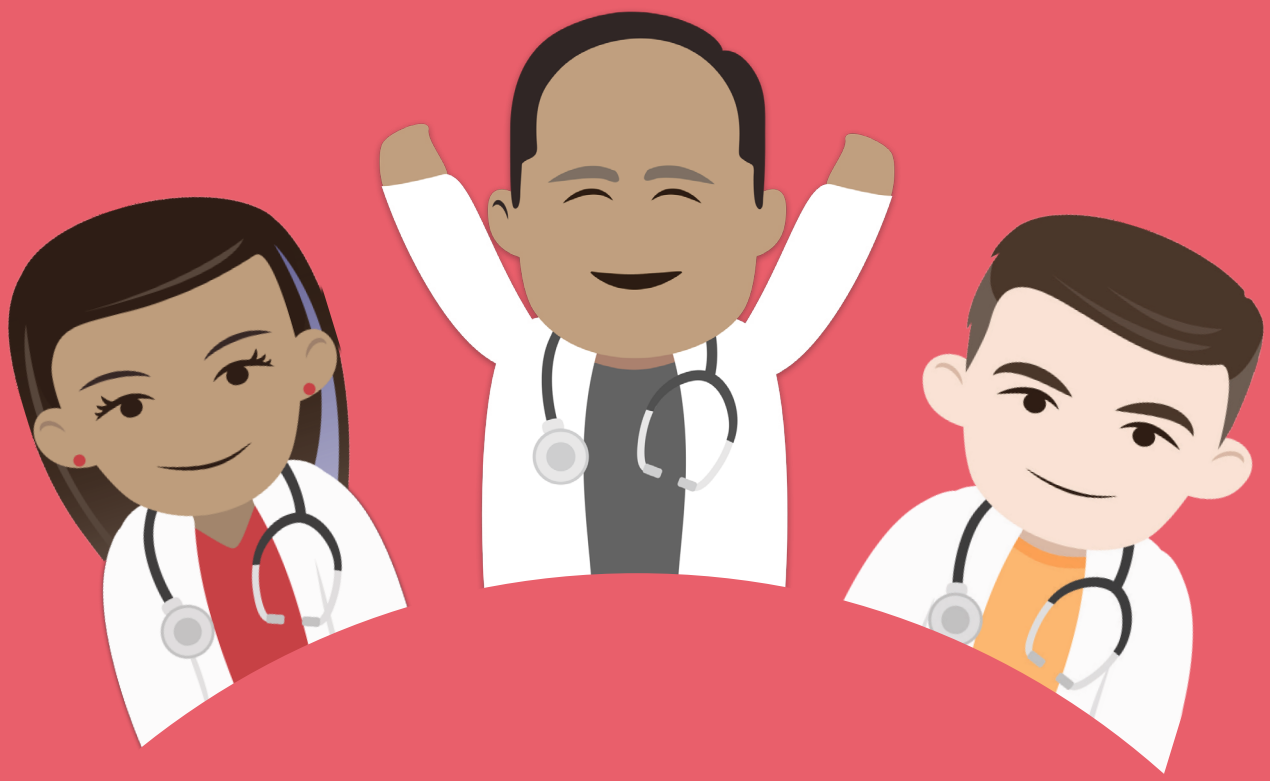
Hematology and Coagulation Essentials
Chapter 8

MANAGING COAGULATION DISORDERS



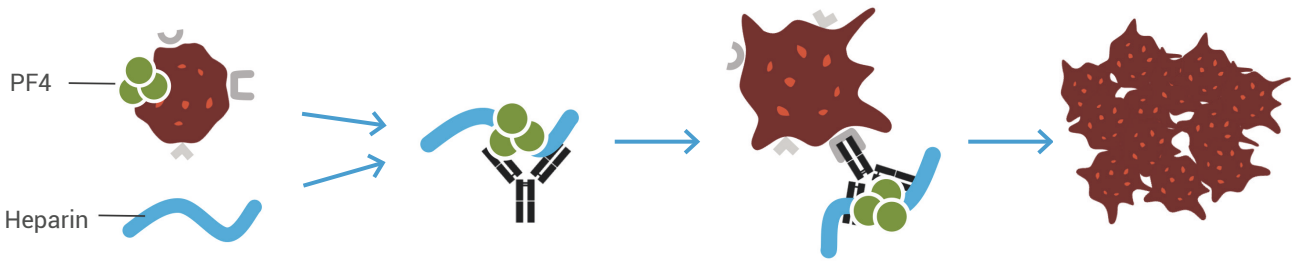
Amer Wahed

Managing coagulation disorders

ASSESSING FOR HEPARIN INDUCED THROMBOCYTOPENIA (HIT)

Heparin induced thrombocytopenia (HIT)

HIT results from an autoantibody directed against endogenous platelet factor 4 (PF4) in complex with heparin. The antibody activates platelets and results in both arterial and venous thrombosis. Its presence is associated with a mortality rate as high as 20%.



PF4 platelet complex

PF4 heparin autoantibody complex

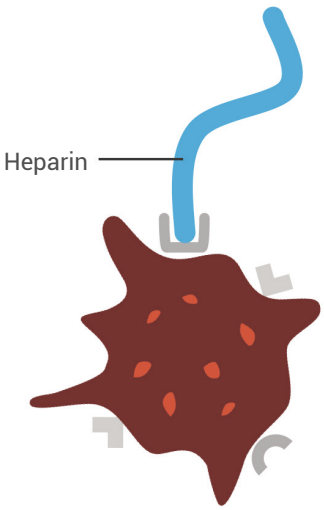
Activated platelet

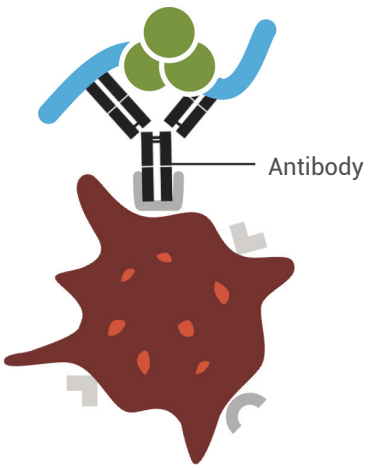
Thrombus

Types of HIT

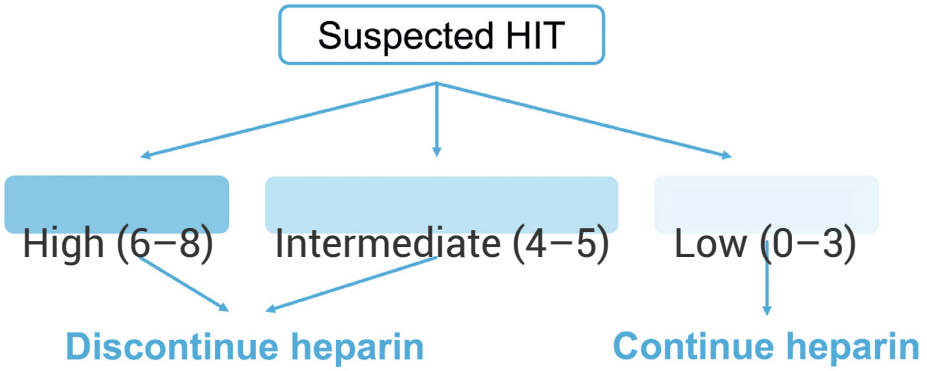
Type I HIT results in a mild drop in platelet count within the first two days and appears to be due to the direct effect of heparin on platelets. Platelet counts typically do not drop below 100,000. Type I HIT is clinically insignificant.

Type II HIT results when the platelet count drops after four days of heparin administration.
The drop in platelet count is typically 50% or more from the baseline platelet count.
This is clinically significant.





If using the 4Ts score the probability of HIT is high or intermediate. All forms of heparin should be stopped, testing for HIT should be initiated and a non-heparin anticoagulant should be administered.



4Ts score: **t**hrombocytopenia, **t**iming of platelet count fall, **t**hrombosis, and other causes for **t**hrombocytopenia

Testing for HIT

HIT ELISA

This is an immunoassay that detects the presence of antiplatelet factor 4 antibody in the patient's serum. It is important to note, however, that the presence of antiplatelet antibodies does not necessarily mean that the antibodies are functionally active and able to activate platelets and result in thrombosis.

The results of a HIT ELISA are published as optical density (OD) values.

OD values < 1 means that HIT, and the associated chance of thrombosis, are unlikely.

OD values > 1.4 means HIT, and the associated chance of thrombosis, are likely.

OD values > 2 mean the probability of HIT is 90% or greater, and the risk of thrombosis is high.

Heparin-induced platelet aggregation (HIPA)

This is a functional assay, which means the assay detects antiplatelet antibodies capable of causing HIT. This assay is not sensitive, but has a specificity > 90%. A positive result is indicated when platelet aggregation occurs at low heparin concentrations, but not at high concentrations.

Serotonin release assay

This is another functional assay. This test is considered to be the gold standard for HIT. However, it is most often performed in a reference lab, and the results can take longer to obtain than other tests.

A positive assay is indicated when there is release of 14C-serotonin from platelets at low concentrations of heparin but not at high concentrations.

Managing coagulation disorders

DIAGNOSING HEMOPHILIA

History

Patients with hemophilia will have a significant history of bleeding. In infants, there may be bleeding in the central nervous system (CNS). Excessive bleeding from circumcision, heelpricks, and venipuncture sites may be evident. Older children often have a positive history of bruising and bleeding into muscles and joints. Bleeding from oral sites, GI bleeding, and hematuria are also commonly observed.

Laboratory tests

Initial laboratory tests typically ordered for a patient with bleeding include complete blood count (CBC), prothrombin time (PT), and partial thromboplastin time (PTT).

Hemophiliacs will have prolonged PTT. A mixing study should demonstrate correction of prolonged PTT.

These are the three most important differential diagnoses for an individual with bleeding and prolonged PTT, which corrects with mixing study.

- Hemophilia A
- Hemophilia B
- von Willebrand disease (VWD)

Factor VII and IX assays, as well as a VWD panel, should be ordered next.

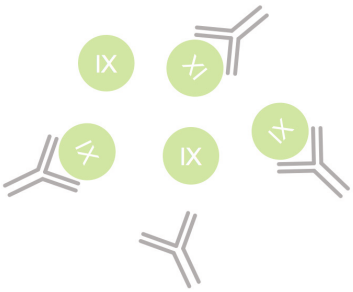
If the factor VIII assay reveals low levels of factor VIII, this suggests a diagnosis of hemophilia A.

If the factor IX assay reveals low levels of factor IX, this suggests a diagnosis of hemophilia B.

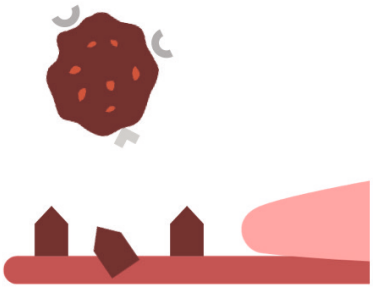
In both hemophilia A and B, VWF antigen, and VWF functional activity are normal.

Next, genetic testing is appropriate for most patients. Genetic testing is also appropriate for carrier detection.

Hemophilia A



Hemophilia B



von Willebrand disease

The diagnostic criteria for hemophilia A are
factor VIII activity below 40%
OR
factor VIII activity > 40% with a positive factor VIII gene mutation.

The diagnostic criteria for hemophilia B are
factor IX activity below 40%
OR
factor IX activity > 40% with a positive factor IX gene mutation.

Hemophilia is divided into mild, moderate, and severe types

- Mild hemophiliacs are those with > 5% of factor activity.
- Moderate hemophiliacs are those with factor activity of 1–5%.
- Severe hemophiliacs are those with < 1% factor activity.

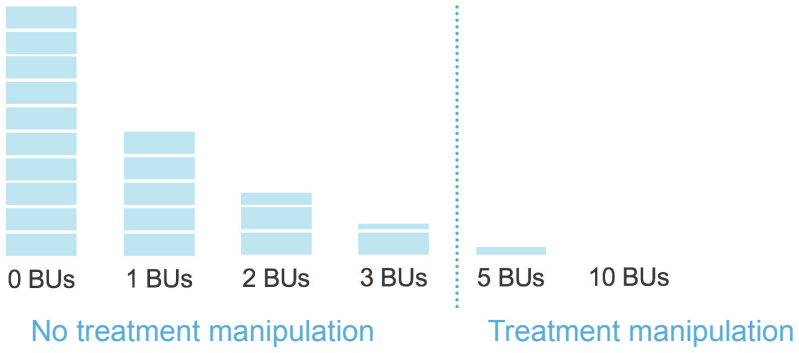
Inhibitors

In patients with hemophilia A and B, inhibitors to factor VIII or IX, respectively, may develop with treatment. Inhibitors are more likely to develop in hemophiliacs with severe disease. Inhibitors may also be formed transiently.

Factor VIII or IX inhibitors can also develop spontaneously in certain individuals. This is referred to as acquired hemophilia.

Factor VIII or IX inhibitor screens
The amount of inhibitor present in the circulation may be quantified by the Bethesda assay. Individuals with inhibitor levels quantified at greater than five Bethesda units will require treatment manipulation.

Individuals who have inhibitor levels less than five Bethesda units typically do not require treatment manipulation.



Bethesda assay

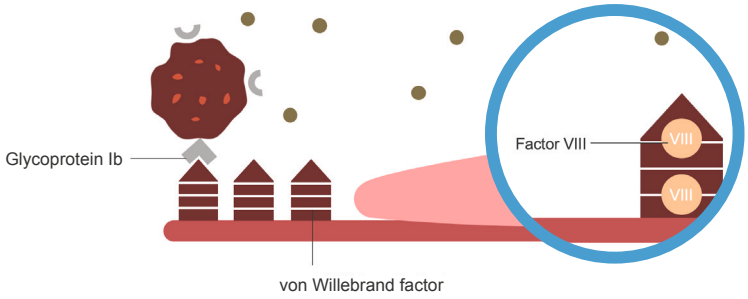
Managing coagulation disorders

UNDERSTANDING VON WILLEBRAND DISEASE (VWD)

This is the most common inherited bleeding disorder, described by Erik von Willebrand in 1926. It is 150 times more prevalent than hemophilia, with 1–2% of the world's population affected by this disease.

Function of von Willebrand factor (VWF)

- Produced by the endothelium and megakaryocytes and released as a series of multimers.
- Helps in platelet adhesion by binding with platelet glycoprotein Ib.
- Binds with factor VIII and prevents degradation of factor VIII.
- Larger multimers work better than the smaller ones.



Types of VWD

Generally speaking there are three types of VWD: I, II, and III.

Type I and III deal with quantitative defects of VWF.

In **type I** there is a mild deficiency of VWF. This condition is transmitted as autosomal dominant and accounts for about 75% of all cases of VWD. Patients may be asymptomatic or have mild features of bleeding.

In **type III,** there is a severe deficiency of VWF, resulting in severe bleeding. This condition is transmitted as autosomal recessive.

Type II deals with qualitative defects of VWF. There are four subtypes of type II VWD.

In **type IIA**, the large and intermediate size multimers are missing. Since larger multimers of VWF work best, the reduction in multimer size results in clinical features of bleeding.

In **type IIB**, VWF has an abnormally increased affinity for platelet glycoprotein Ib. This results in increased binding of VWF and glycoprotein Ib. There is also loss of large multimers of VWF.

In **type IIM** (M for multimer), the VWF is present, but functionally defective.

In **type IIN** (N for Normandy), the VWF cannot bind with factor VIII. Thus, factor VIII is easily degraded. All other aspects of VWF function is normal; however, the patient bleeds due to low levels of factor VIII. This condition thus mimics hemophilia.

Type IIN is transmitted as autosomal recessive. All other subtypes of type II are transmitted as autosomal dominant.

Pseudo, or platelet type, VWD

In this condition, the problem is not with VWF but rather the pathology lies with the platelets themselves. The glycoprotein Ib of platelets have an increased affinity for VWF. The condition thus mimics VWD type IIB.

Acquired VWD

Sometimes VWD disease may be acquired. Examples of such conditions are aortic stenosis, cardiopulmonary bypass (CPB), tumors, and autoimmune states.

Acquired VWD may result from different mechanisms. Certain tumors adsorb VWF, resulting in low levels. In autoimmune states, antibodies may bind with VWF and either have it cleared or rendered dysfunctional.

Managing coagulation disorders

INTERPRETING TESTS FOR VON WILLEBRAND DISEASE (VWD)

The following diagnostic tests are indicated for VWD

- Complete blood count (CBC)
- Bleeding time
- Partial thromboplastin time (PTT)
- VWD panel
- Ristocetin-induced platelet aggregation
- Multimer analysis
- VWF-factor VIII binding assay

CBC
Patients with type IIB or pseudo VWD, may demonstrate thrombocytopenia. In both cases, VWF binds to platelets in the blood stream and bundles of platelets are removed from the circulation, resulting in thrombocytopenia.

Bleeding time
Although this test is not ordered often, bleeding time in patients with VWD will be prolonged as a result of defective platelet adhesion.

PTT
Factor VIII levels are reduced in patients with VWD, which results in prolonged PTT. A mixing study should show correction of PTT.

VWD panel
A VWD panel consists of three tests:
- Factor VIII levels
- VWF antigen levels
- VWF functional activity (ristocetin factor activity or VWF:RCoF)

In type I VWF, mild deficiencies will be detected on all three tests.

In type III VWF, significant deficiencies will be detected on all three tests.

In type II VWF, the results will vary depending on the subtype.

In type IIN, factor VIII levels will be low; all others will be normal.

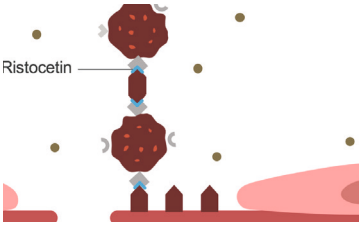
In type IIM, VWF antigen levels will be normal; functional activity and factor VIII levels will be low.

In type IIA and B, results may vary.

Ristocetin-induced platelet aggregation

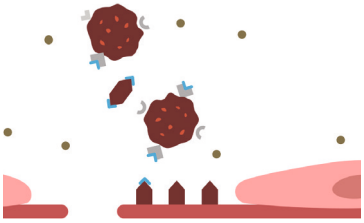
Ristocetin is an antibiotic that induces VWF and platelet glycoprotein Ib interaction and results in platelet clumping. In healthy people, platelet aggregation is observed with high doses of ristocetin and not with low doses.

In VWD there is reduced platelet aggregation at high doses of ristocetin, but low doses are not affected.



However, in type IIB there is increased aggregation with low doses of ristocetin. This is because, in type IIB, the VWF already has increased affinity for platelet glycoprotein Ib and even a small dose of ristocetin is enough to cause aggregation.

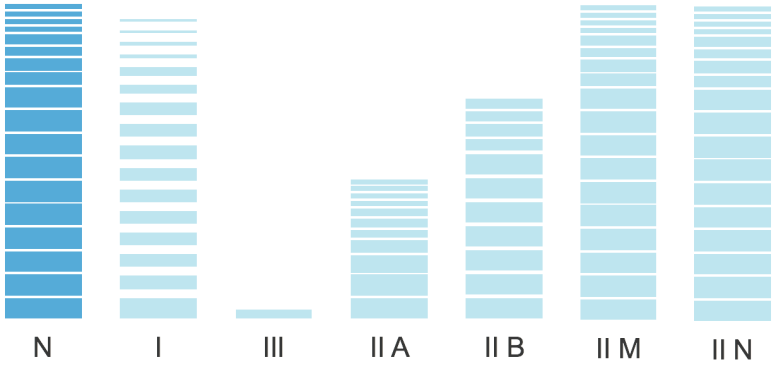
In type IIN, ristocetin induced platelet aggregation is normal.



Multimer analysis

Multimer analysis is performed using electrophoresis to lineup the various VWF multimers according to size. This allows us to determine whether there is a global deficiency of multimers or a deficiency in multimers of a particular size (large, intermediate, or small).

- In type I VWD, there is a mild deficiency of all types of multimers.
- In type III VWD, there is a severe deficiency of all types of multimers.
- In type IIA VWD, there is loss of large and intermediate-sized multimers.
- In type IIB VWD, there is loss of large multimers.
- In type IIM and type IIN VWD, the multimer size distribution will be normal. This is because, in type IIM VWD, VWF is produced but does not function and in type IIN, the structure of VWF is not altered, but it is defective because it cannot bind to factor VIII. So in both these cases multimer analysis is unremarkable.



Multimer analysis

Factor VIII—VWF binding assay

This is an ELISA-based test that measures the binding of VWF and factor VIII. Type IIN VWD can be diagnosed using this assay.