bloody easy

Coagulation Simplified…

Third Edition

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We hope you enjoy the third edition of Bloody Easy: *Coagulation Simplified*. Like previous editions we hope to provide basic foundational learning in coagulation and the assessment of bleeding disorders and coagulopathies. Major updates include an overview of mixing studies in Chapter 2, the ISTH-BAT in Chapter 5, and new sections on Bleeding Disorder of Unknown Cause and Acquired hemophilia A in Chapter 6.

First Edition, March 2013
Second Edition, February 2019
Third Edition, May 2026

General Disclaimer:

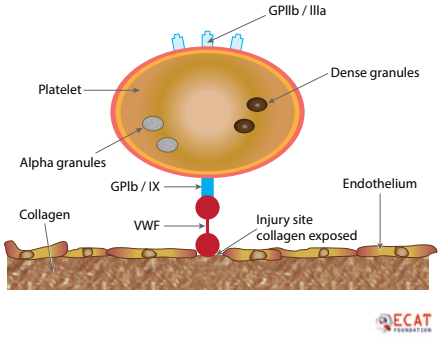
Hemostasis is a complex process in which multiple components of the blood clotting system are activated in response to vessel injury to control bleeding.

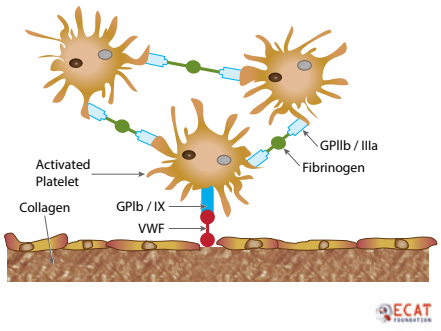
Hemostasis is composed of four major events:

1. Primary hemostasis
2. Secondary hemostasis
3. Fibrin clot formation and stabilization
4. Inhibition of coagulation

1. Primary hemostasis = vasoconstriction and platelet plug formation:

- The key component of primary hemostasis is the platelet.
- Primary hemostasis is triggered by injury to the vessel wall, exposing subendothelial collagen.
- **Vasoconstriction** occurs at the site of injury to reduce blood flow.
- **Adhesion:** von Willebrand factor adheres platelets to exposed subendothelial collagen via the platelet receptor glycoprotein Ib / IX (GPIb / IX). Platelets also adhere directly to collagen via other receptors.
- **Aggregation:** Platelets aggregate with each other with the help of fibrinogen that binds to activated glycoprotein IIb / IIIa (GPIIb / IIIa), forming a platelet plug. Platelet aggregates also provide the phospholipid surface necessary for coagulation factor activation.





2. Secondary hemostasis = activation of coagulation factors and generation of thrombin:

Initiation of coagulation

- Tissue factor (TF) is released from injured tissue cells, endothelial cells and monocytes.
- TF and Factor VIIa form the TF / Factor VIIa complex also known as the extrinsic tenase complex.
- The extrinsic tenase complex activates a small amount of Factor IX and X to generate a small amount of thrombin.
- Factor XII (and other "contact" factors) play a minor role in the activation of Factor XI.

Amplification phase

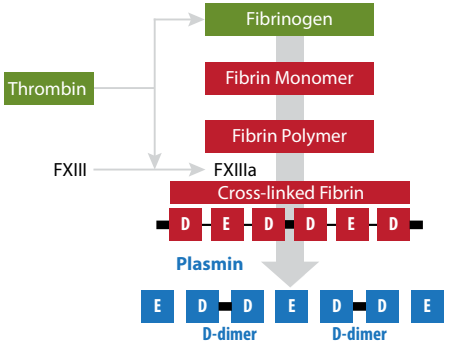
- Thrombin activates Factor V to Va, Factor VIII to VIIIa and activates more platelets.
- Thrombin also activates FXI to FXIa.

Propagation phase

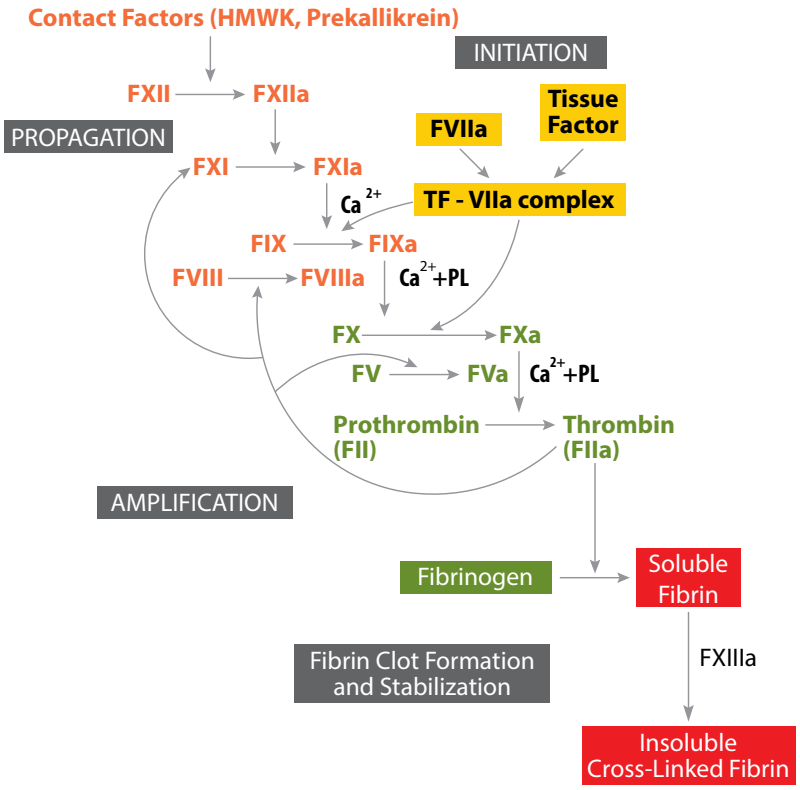
- Additional Factor Xa is produced when TF / Factor VIIa complex activates Factor IX. The resultant Factor IXa along with Factor VIIIa forms the intrinsic tenase complex which then converts more Factor X to Xa.
- Factor Xa and Va along with calcium and a phospholipid (PL) surface (activated platelets) form the prothrombinase complex which converts prothrombin (Factor II) to large amounts of thrombin (Factor IIa). This is also known as the "thrombin burst", which is essential to convert enough fibrinogen to fibrin to form the fibrin clot.

3. Fibrin clot formation and stabilization:

- Thrombin converts fibrinogen to fibrin monomers which polymerize to form a soluble clot.
- Thrombin also activates Factor XIII which cross-links the fibrin monomers and stabilizes the clot.



Secondary hemostasis, fibrin clot formation and stabilization:



*PL = phospholipid (activated platelet surface)

*Ca^{2+} = ionized calcium

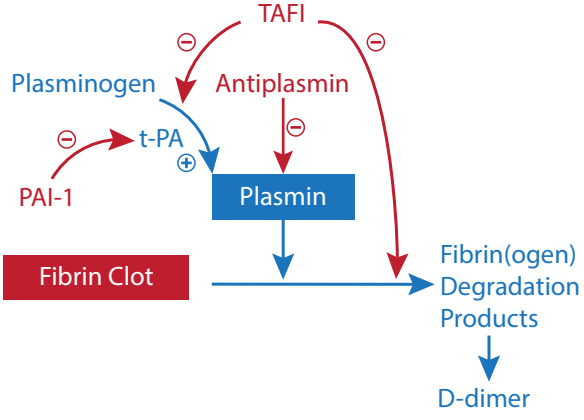
4. Inhibition of coagulation = inhibition of thrombin generation and fibrin clot breakdown (fibrinolysis):

Inhibition of thrombin generation

- At the same time that a clot is being formed, the clotting process also starts to shut itself off to limit the extent of the thrombus formed.
- Thrombin binds to the membrane receptor thrombomodulin and activates Protein C to Activated Protein C (APC).
- APC combines with its cofactor Protein S which then inhibits Factors Va and VIIIa, slowing down the coagulation process.
- Thrombin bound to thrombomodulin becomes inactive and can no longer activate procoagulant factors or platelets.
- The endogenous anticoagulant, antithrombin inhibits the activity of thrombin as well as several of the other activated factors, primarily Factor Xa.

Fibrinolysis

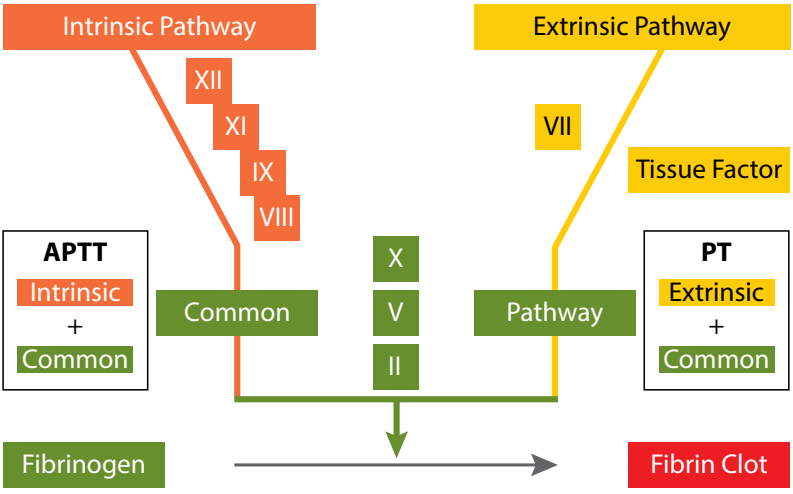
- Tissue plasminogen activator (t-PA) converts plasminogen to plasmin which breaks down cross-linked fibrin to several fibrin degradation products, the smallest of which is D-dimer.
- Thrombin activatable fibrinolysis inhibitor (TAFI) inhibits the formation of plasmin and suppresses fibrinolysis.
- Anti-plasmin and plasminogen activator inhibitor-1 (PAI-1) inhibit plasmin and t-PA respectively.



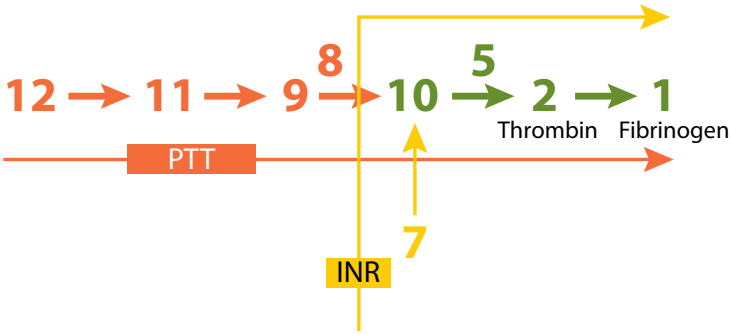
Evaluating coagulation in the laboratory

- In the coagulation laboratory, the coagulation factors are divided into:
  - Extrinsic pathway factors (Factor VII)
  - Intrinsic pathway factors (Factors XII, XI, IX, VIII)
  - Common Pathway factors (Factors X, V, II, Fibrinogen)

- Memorizing which factors belong to the extrinsic, intrinsic and common pathways respectively will make evaluating the causes of abnormal coagulation tests easier.



▲ Here is another picture to help with memorizing the coagulation cascade without the Roman numerals:



- The common pathway factors can be memorized by thinking of the denominations of dollars in Canada: factors 10, 5, 2 and 1
- The PT / INR pathway starts with factor 7 and includes the common pathway factors
- The APTT pathway starts from the left at factor 12, counts backwards to factor 8 (skipping factor 10) and includes the common pathway factors

Sample collection for coagulation testing

- To assess coagulation "in vitro," the laboratory measures the time taken to form a clot.
- Blood is collected into a blue top tube containing sodium citrate anticoagulant (which chelates calcium) to prevent blood clotting in the tube during transport.

ATTENTION

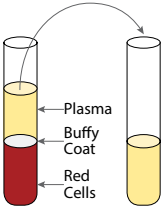
Sodium Citrate Tube (Blue Top)

Coagulation testing MUST only be sent in a sodium citrate (blue top) tube.

- Plasma (the liquid component of blood that contains the clotting factors) is then separated from the platelets (phospholipid source) by centrifugation.
- Later we will see how adding back phospholipids and calcium is important in standardizing routine coagulation tests.
- Some common problems that may result in spurious coagulation test results are:
  - Blood collected into incorrect type of tube (not a sodium citrate tube)
  - Incorrect plasma to citrate ratio (e.g., underfilling of tube or patient's hematocrit > 0.55 L / L)
  - Heparin contamination of sample (e.g., incorrect order of sample collection or sample collected from central lines)
  - Clotting in tube from traumatic venipuncture or inadequate mixing

Sodium Citrate Tube (Blue Top)

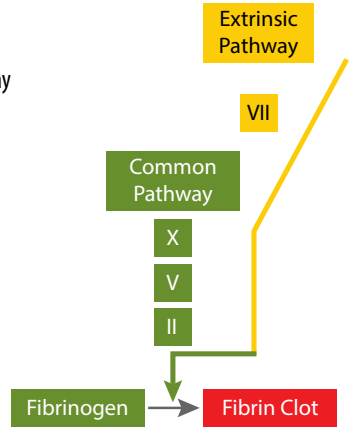
Centrifugation



ECAT FOUNDATION

Prothrombin Time (PT)

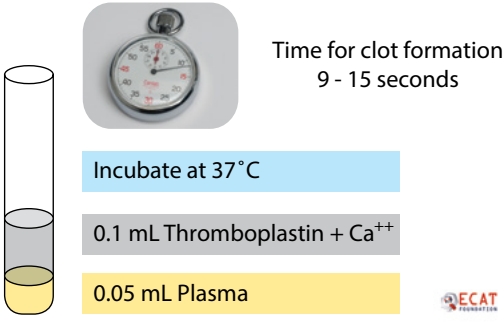
- The PT is used to assess deficiencies or inhibitors of the extrinsic pathway factors (Factor VII) and common pathway factors (Factors X, V, II, Fibrinogen).



- **Measurement of PT:**

  PT reagent contains a source of tissue factor (also known as thromboplastin), phospholipids and calcium chloride. Plasma is warmed to 37 ° C. Pre-warmed PT reagent is added and the time in seconds for clot formation is measured.

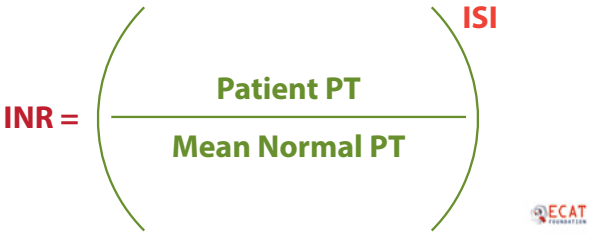
- The PT is dependent on the reagent and instrument used and will vary between laboratories. A normal PT is approximately 9-15 seconds.



International Normalized Ratio (INR)

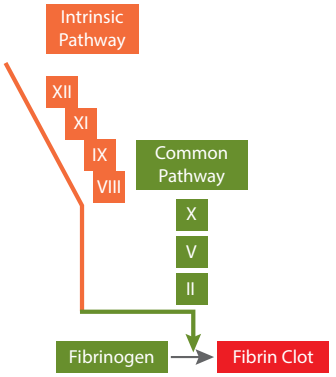
- The International Normalized Ratio (INR) was developed to standardize the PT to allow for monitoring of oral vitamin K antagonist therapy (e.g., warfarin) across different labs.
- The PT in seconds is used to calculate the INR.
- Each lot of PT reagent needs to have an International Sensitivity Index (ISI) determined / assigned, which indicates how sensitive the reagent is to deficiencies in the Vitamin K dependent factors compared to the World Health Organization reference standard.
- The INR is the ratio of the patient's PT value over the geometric mean of the PT (generated from a minimum of 20 normal volunteers) and raised to the power of the ISI of the reagent used to obtain the PT:

  $INR = (PT \text{ of patient} / \text{geometric mean normal } PT)^{ISI}$

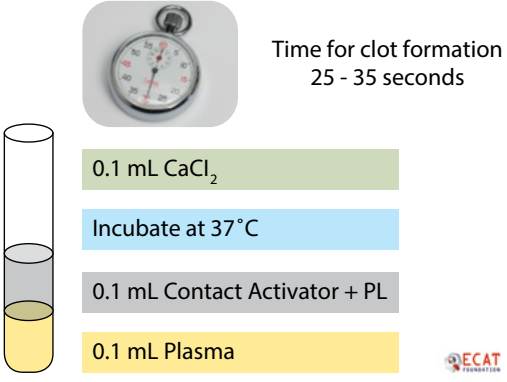


Activated Partial Thromboplastin Time (APTT)

- The APTT is used to assess deficiencies or inhibitors of the intrinsic pathway factors (Factors XII, XI, IX, VIII) and common pathway factors (Factors X, V, II, Fibrinogen).



- **Measurement of APTT:**
  The APTT reagent contains a contact activator (e.g., silica, ellagic acid or kaolin) and phospholipids but does not contain tissue factor or calcium chloride. The intrinsic factors are "activated" when patient plasma is mixed with APTT reagent and incubated at 37 ° C. Calcium chloride is added and the time in seconds for the plasma to clot is measured.
- Since the APTT reagent lacks tissue factor it is a "partial thromboplastin" and the test is called an activated partial thromboplastin time.
- The APTT is dependent on the reagent and instrument used and will vary between laboratories. A normal APTT is approximately 25-35 seconds.



Mixing Study

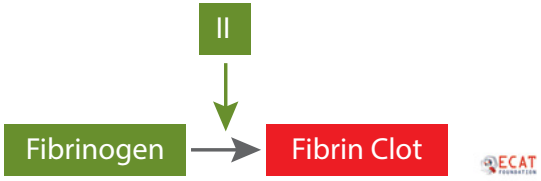
- A 50:50 mixing study can be used as a quick next step in the setting of a prolonged PT or APTT to help distinguish between a factor deficiency vs an inhibitor. An inhibitor can be specific (e.g. acquired factor inhibitor) or non-specific (e.g. inhibitory anticoagulant drug or lupus anticoagulant).

- Steps of a 50:50 Mixing Study:
  1. Mix equal parts patient plasma and normal pooled plasma in a 1:1 ratio.
  2. Run the PT (or APTT) assay on the mixed plasma
  3. If the PT (or APTT) fully corrects, this suggests that the PT (or APTT) prolongation was due a factor deficiency. If the PT (or APTT) does not fully correct, this is suggestive of an inhibitor.

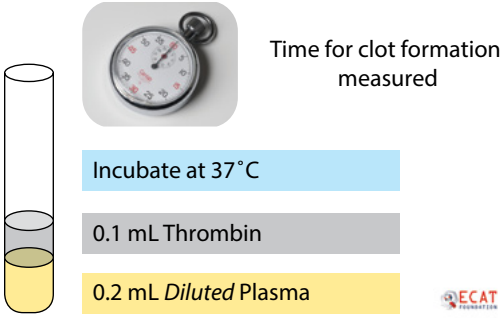
- Mixing studies have limitations:
  - A weak inhibitor may still cause the mixing study to correct. Conversely, multiple or severe factor deficiencies (such as in the case of supra-therapeutic warfarin) can lead to incomplete correction on mixing.
  - Some inhibitors (notably Factor VIII inhibitors) are time- and temperature- dependent, and as a result, the immediate (non-incubated) 50:50 mix may still correct.
  - Due to the limitations above, further testing (e.g. lupus anticoagulant testing, individual factor assays, or testing for anticoagulants) may be indicated depending on the clinical scenario.

Thrombin Time (TT)

- The TT is used to assess deficiencies or dysfunction of fibrinogen or the presence of an inhibitor of thrombin (Factor IIa). The most common cause for TT prolongation is anticoagulant drug therapy (e.g., heparin or direct thrombin inhibitor). Other causes include quantitative or qualitative fibrinogen abnormalities and increased products of clot breakdown (e.g., fibrin degradation products in disseminated intravascular coagulation).



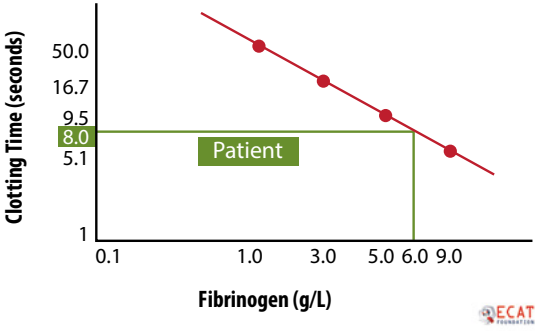
- **Measurement of TT:**
  The patient's plasma is warmed at 37 ° C and thrombin reagent is added. The time in seconds that it takes for the plasma to clot is measured.
- The TT is dependent on the reagent and instrument used and will vary between laboratories.



Fibrinogen

- The fibrinogen assay assesses fibrinogen activity.
- Hypofibrinogenemia is usually acquired due to loss of fibrinogen (e.g., bleeding), consumption (e.g., hyperfibrinolysis after traumatic injury, disseminated intravascular coagulation) or decreased production (e.g., severe liver disease). Other rare causes include congenital hypofibrinogenemia and dysfibrinogenemia (an abnormal fibrinogen).
- Fibrinogen is an acute phase reactant and may be non-specifically elevated with acute or chronic inflammation.
- **Measurement of fibrinogen based on the Clauss method:**

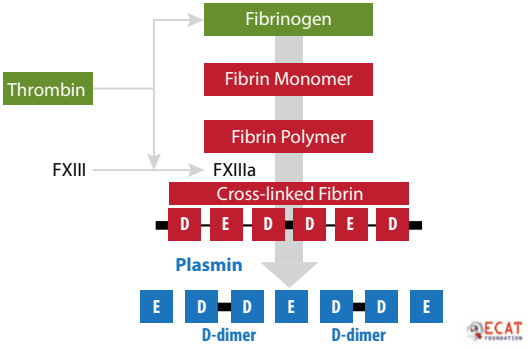
  The plasma is diluted with a physiological buffer, warmed to 37 ° C and a high concentration of thrombin is added. The thrombin cleaves fibrinogen to fibrin monomers which polymerize. The time in seconds for the plasma to clot is measured. The time in seconds is inversely proportional to fibrinogen activity which is obtained from a standard calibration curve. The longer the clotting time, the lower the concentration of fibrinogen in the sample.



- The Clauss fibrinogen activity is a standardized test as laboratories use a WHO calibrated plasma for the calibration curve. While there may be small differences in the reference ranges between laboratories, the reference range will be approximately 1.5-4 g / L.

D-Dimer

- D-dimers are breakdown products generated by the action of plasmin on cross-linked fibrin. A D-dimer contains two cross-linked D fragments.



- A negative D-dimer can be used to rule out venous thromboembolism (VTE) in selected outpatients (those with low to moderate clinical probability of VTE). Ideally, D-dimer should only be used as part of a validated VTE diagnostic algorithm.
- An elevated D-dimer is not specific to thrombosis and may be associated with a host of other non-specific diseases or inflammatory states (e.g., recent surgery or trauma, cancer, acute or chronic infectious or inflammatory diseases, disseminated intravascular coagulation, healthy elderly, normal pregnancy, etc.).
- **Measurement of D-dimer:**

  There are several different assays available to measure D-dimer. These include qualitative (positive or negative), semi-quantitative or quantitative methods, such as ELISA (Enzyme Linked Immunosorbent Assay) or LIA (Latex Immunoassay) which use a monoclonal antibody to various epitopes of D-dimer. Quantitative D-dimer measurements obtained by the various assays are not standardized due to the variability in the monoclonal antibody used. D-dimer results must be interpreted based on the assay used.
- Reporting units vary between assays, e.g., DDU (D-dimer units) or FEU (Fibrinogen equivalent units).

Anti-Xa assay

- An Anti-Xa assay can be used to measure the anticoagulant activity of an anticoagulant that inhibits clotting Factor Xa such as heparin, low molecular weight heparin (LMWH), fondaparinux or direct Xa inhibitors (rivaroxaban, apixaban and edoxaban).

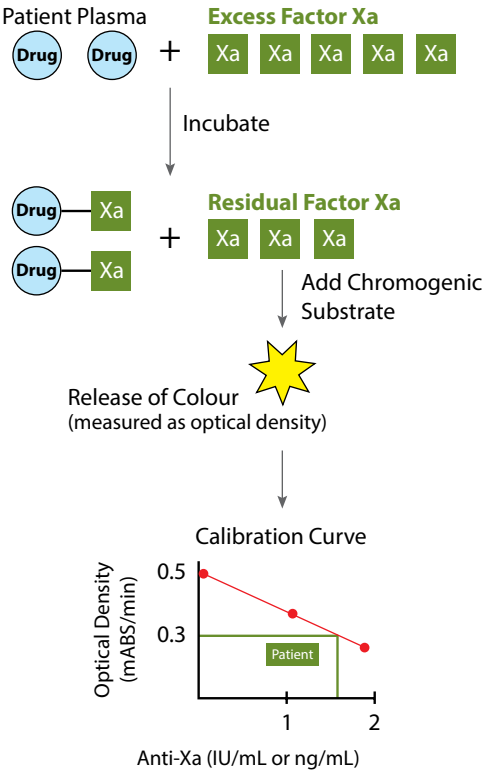
ATTENTION

Check that your coagulation laboratory has validated the Anti-Xa assay for the anticoagulant that you wish to monitor.

- **Measurement of Anti-Xa activity:**

  A known amount of Factor Xa is added in excess to the plasma sample containing the drug. A complex forms between the drug and factor Xa. A chromogenic substrate is added which hydrolyses the unbound or "residual" factor Xa and the release of colour is measured at a specific wavelength as an optical density (OD). The OD is converted to a drug concentration reported in international units (IU) or ng/mL using a drug-specific calibration curve.

- The therapeutic level of the Anti-Xa assay is specific for the drug being assessed.

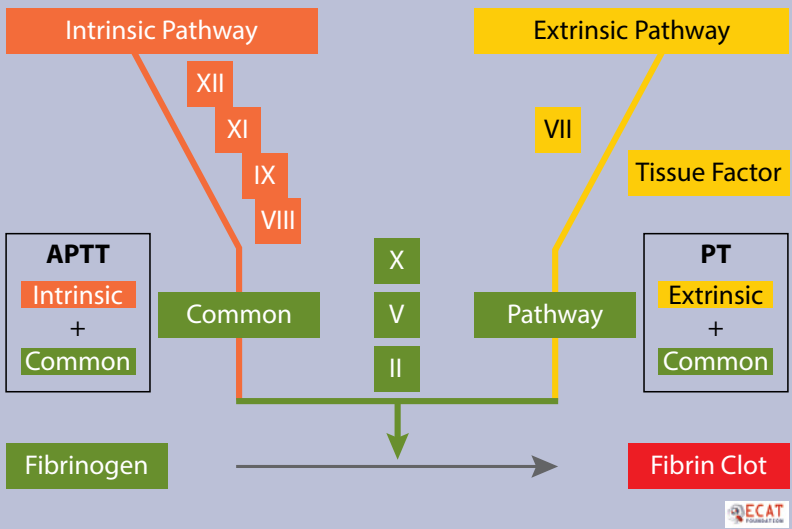


Summary

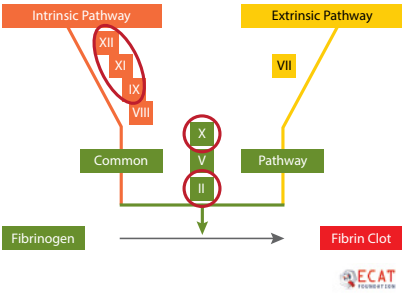
- In the coagulation laboratory, the coagulation factors are divided into:
  - Extrinsic pathway factors (Factor VII)
  - Intrinsic pathway factors (Factors XII, XI, IX, VIII)
  - Common pathway factors (Factors X, V, II, fibrinogen)
- The PT is most sensitive to the extrinsic and common pathway factors and the APTT is most sensitive to the intrinsic and common pathway factors.
- The PT and PTT can be normal in mild factor deficiencies.
- The thrombin time is most sensitive to fibrinogen and presence of inhibitors of thrombin (Factor IIa).
- The Anti-Xa assay only assesses the inhibition of factor Xa.

ATTENTION

Reference ranges for common coagulation tests vary between laboratories due to instrument / reagent differences.



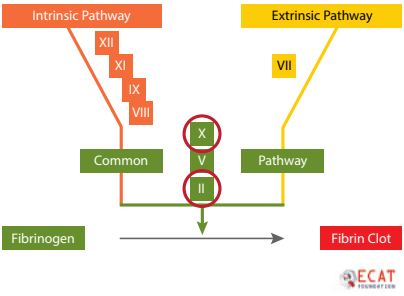
Unfractionated Heparin (UFH)



- Unfractionated heparin is a mixture of varying chain lengths of glycosaminoglycans derived from pig intestine.
- It is an "indirect" anticoagulant. It exerts its anticoagulant effect by combining with antithrombin (via 5 saccharide units – pentasaccharide) and inhibiting the coagulation factors IIa, Xa, IXa, XIa and XIIa.
- It can be administered either intravenously (IV) or subcutaneously (SC).
- UFH can be monitored using the APTT or the anti-Xa assay.
- Half-life is 60-90 minutes; half-life for SC heparin is longer.
- Elective reversal.
  - Discontinue IV unfractionated heparin 4 hours prior to the planned procedure
- Urgent reversal in the setting of significant bleeding.
  - Antidote: Protamine
  - Administer 1 mg of protamine per 100 units of unfractionated heparin given in the last 2-2.5 hours
  - Maximum rate protamine 5 mg/min. Dose not to exceed 50 mg in any 10 minute period.
  - Adverse effects of protamine: hypotension, hypersensitivity

Low Molecular Weight Heparins (LMWHs)

- LMWHs are produced by "fractionating" heparin molecules into smaller chain lengths.
- LMWHs are "indirect" anticoagulants. They exert their anticoagulant effect by combining with antithrombin (via 5 saccharide units – pentasaccharide) and inhibiting only the coagulation factors Xa and IIa.



- LMWHs are administered subcutaneously (SC).
- Several preparations are commercially available – dalteparin, enoxaparin, nadroparin, tinzaparin, etc. They vary in their relative inhibition of factors Xa and IIa also known as the Xa:IIa ratio.
- LMWHs generally do not require lab monitoring but if they are monitored, then the anti-Xa assay is used (NOT the APTT).
- Half-life is 3-6 hours. LMWHs are renally cleared therefore the half-life will be prolonged in patients with renal failure.

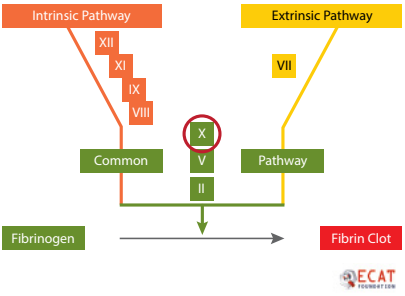
ATTENTION

Consider measuring anti-Xa levels in the following populations:

- CrCl < 30 mL / minute
- Weight < 40kg
- Weight > 100kg
- Pregnancy

- Elective reversal.
  - Discontinue LMWH 12-24 hours prior to planned procedure depending on the dose of the LMWH, the specific procedure and renal function
- Urgent reversal.
  - Protamine may reverse the antithrombin (IIa) activity of LMWH but will not reverse the anti-Xa activity. Furthermore, protamine would only affect the intravascular LMWH, not the subcutaneous depot

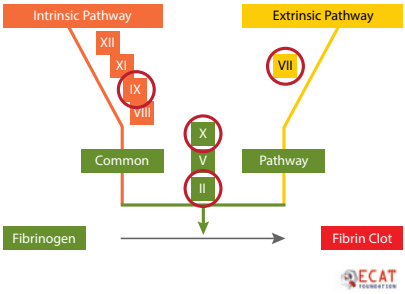
Fondaparinux



- Fondaparinux is a synthetic pentasaccharide.
- Fondaparinux is an "indirect" anticoagulant. It exerts its anticoagulant effect by combining with antithrombin. The fondaparinux-antithrombin complex inhibits only coagulation factor Xa.
- It is administered subcutaneously (SC).
- Fondaparinux generally does not require lab monitoring, but if it is monitored, the anti-Xa assay is used (NOT the APTT).
- Half-life is 17-21 hours. It is renally cleared so the half-life will be prolonged in patients with renal failure.
- Elective reversal.
  - For most procedures, stop prophylactic fondaparinux 24 hours before and therapeutic fondaparinux 1-2 days before if renal function is normal
- Urgent reversal.
  - Protamine has no effect
  - There is no evidence to support the use of tranexamic acid, PCCs, FEIBA or recombinant activated VIIa

Warfarin

- Warfarin is an oral Vitamin K antagonist.
- Clotting factors II, VII, IX and X as well as natural anticoagulant proteins, Protein C and Protein S, require the action of Vitamin K to become activated so that they may participate in coagulation. By inhibiting Vitamin K, warfarin prevents the activation of these factors.



- It is monitored using the PT which is converted to an INR.
- Individual doses vary and the dose is adjusted to prolong the INR into a therapeutic range.
  - Target INR = 2.5 (range = 2.0-3.0) for most indications requiring therapeutic anticoagulation
  - Target INR = 3.0 (range = 2.5-3.5) for therapeutic anticoagulation for mechanical mitral valves
- The INR can be measured by sending a citrated plasma sample to the lab (blue top tube) or using a drop of whole blood from a finger-prick using point-of-care devices.
- Half-life is 36-42 hours.

Warfarin (continued)

- Elective reversal.
  - Stop warfarin 5 days before major invasive procedure
  - Note: bridging therapy may be considered for selected patients at high risk for thrombosis
- Urgent reversal.
  - Antidotes:
    - Vitamin K
      - IV vitamin K acts more quickly than the oral route (6-12 hours vs. 18-24 hours)
      - Vitamin K works quickly because it activates factors and does not require synthesis of new factors

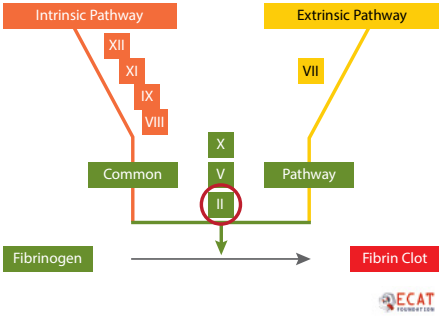
ATTENTION

Vitamin K should not be administered subcutaneously.

    - Prothrombin complex concentrates (PCCs) (Octaplex, Beriplex)
      - PCCs contain vitamin K dependent clotting factors (II, VII, IX, X, Protein C and S) and a small amount of heparin
      - Contraindicated in patients with heparin-induced thrombocytopenia
  - For emergent reversal of warfarin (reversal within 6 hours), give vitamin K 5-10mg IV and PCCs. At present, a PCC dose of 1000 IU is recommended for INR 1.5-3.0
  - If urgent reversal is not required, vitamin K alone may be administered

Direct Thrombin Inhibitors (DTIs)

- DTIs are synthetically derived and directly inhibit thrombin (Factor IIa). They are called "direct" because unlike heparin, LMWH and fondaparinux, they do not require antithrombin to inhibit their target.



- DTIs include intravenously administered drugs like argatroban and bivalirudin which are used primarily in the treatment of Heparin-Induced Thrombocytopenia (HIT).
- DTIs also include the oral drug dabigatran which is used for the prevention of stroke related to non-valvular atrial fibrillation and in the prophylaxis and treatment of venous thromboembolism.
- Dabigatran does not require routine monitoring. Since the drug inhibits thrombin, APTT, TT and PT may be variably affected.
- Half-life of dabigatran is 15 hours (12-18 hours).
  - Renally cleared so half-life will be prolonged in patients with renal failure
- Elective reversal of direct thrombin inhbitors

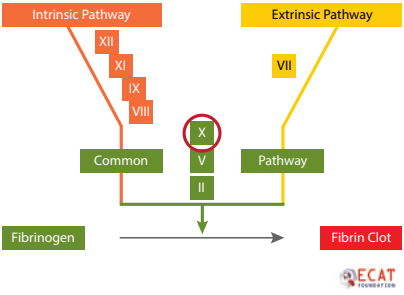
Drug (dose regimen)	Renal Function	Moderate Bleed Risk Surgery (< 12-25% residual drug effect)	Major Surgery Including Neuraxial Procedures (High Bleed Risk) (<10% residual drug effect)
Dabigatran BID	CrCl ≥50 mL / min	Last dose 2 days before surgery/procedure (i.e. skip 2 doses)	Last dose 3 days before surgery/procedure (i.e. skip 4 doses)
Dabigatran BID	CrCl 30-49 mL / min	Last dose 3 days before surgery/procedure (i.e. skip 4 doses)	Last dose 5 days before procedure (i.e. skip 8 doses)

Direct Thrombin Inhibitors (continued)

- Urgent reversal of dabigatran.
  - Antidote: Idarucizumab 5g IV administered in two boluses of 2.5g no more than 15 minutes apart
  - Activated charcoal if ingested within 2 hours
  - Hydration to correct pre-renal dysfunction
  - There is no definitive evidence to support the use of tranexamic acid, PCCs, FEIBA or recombinant factor VIIa
  - Consult an expert in hematology or transfusion medicine

Direct Factor Xa inhibitors

- Direct factor Xa inhibitors are synthetically derived and directly inhibit Factor Xa. They are called "direct" because unlike heparin, LMWH and fondaparinux, they do not require antithrombin to inhibit their target.



- Direct Xa inhibitors include rivaroxaban, apixaban and edoxaban, which are used for the prevention of stroke related to non-valvular atrial fibrillation and in the prophylaxis and / or treatment of venous thromboembolism. Other factor Xa inhibitors are under development.
- Rivaroxaban, apixaban and edoxaban do not require routine monitoring. Since the drug inhibits factor Xa, PT and APTT may be variably affected. The effect of these drugs can be measured using the anti-Xa assay.

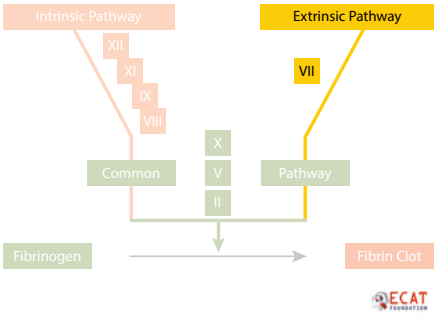
- Half-life: Rivaroxaban 7-8 hours; apixaban 8-12 hours; edoxaban 10-14 hours.
  - Partially renally cleared so half-life will be prolonged in patients with renal failure
- Elective reversal.

Drug (dose regimen)	Renal Function	Moderate Bleed Risk Surgery (< 12-25% residual drug effect)	Major Surgery Including Neuraxial Procedures (High Bleed Risk) (<10% residual drug effect)
Rivaroxaban OD	CrCl ≥30 mL / min	Last dose 2 days before surgery/procedure (i.e. skip 1 dose)	Last dose 3 days before surgery/procedure (i.e. skip 2 doses)
Apixaban BID	CrCl ≥30 mL / min	Last dose 2 days before surgery/procedure (i.e. skip 2 doses)	Last dose 3 days before surgery/procedure (i.e. skip 4 doses)
Edoxaban OD	CrCl ≥30 mL / min	Last dose 2 days before surgery/procedure (i.e. skip 1 dose)	Last dose 3 days before surgery/procedure (i.e. skip 2 doses)

- Urgent reversal.
  - For life threatening bleed, consider PCC (Octaplex or Beriplex) 1500-2000 units IV STAT
  - There is no definitive evidence to support the use of tranexamic acid, PCCs, FEIBA or recombinant factor VIIa
  - Consult an expert in hematology or transfusion medicine

Prolonged PT / INR with normal APTT

If the PT / INR is prolonged but the APTT is not, the probable cause is related to Factor VII (FVII).



What is the differential diagnosis?

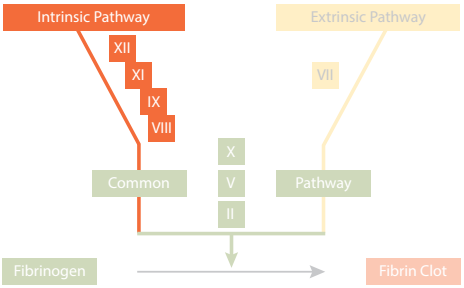
- Congenital deficiency of FVII.
- Acquired deficiency of FVII.
  - Early warfarin therapy or early vitamin K deficiency (FVII has the shortest half-life of the vitamin K dependent factors so FVII levels will be lower than the other Vitamin K dependent factors (IX, X and II) early on in the course of warfarin therapy or Vitamin K deficiency)
  - Early liver disease
- PT may be elevated in the presence of a DTI (e.g., dabigatran) or anti-Xa (e.g., rivaroxaban, apixaban, edoxban).
- Specific inhibitors to FVII can occur but are exceptionally rare.

To distinguish between factor deficiency and inhibitor

- Perform an immediate 50:50 mixing study (See Chapter 2)
- If the PT prolongation corrects on mixing the prolongation is likely due to a factor deficiency (due to replacement of factor(s) from the normal plasma).
- If it does not correct the prolongation it is likely due to an inhibitor.
- A partial correction may represent multiple factor deficiencies or an inhibitor.

Prolonged APTT with normal PT / INR

If the APTT is prolonged but the PT / INR is not, the probable cause is related to the intrinsic pathway – either Factors VIII, IX, XI or the contact factors (Factor XII, Prekallikrein or High Molecular Weight Kininogen).



What is the differential diagnosis?

- Congenital deficiency of Factors VIII, IX, XI or contact factors – usually a single factor deficiency.
  - Deficiencies of Factors VIII and IX are generally associated with bleeding
  - von Willebrand's disease can have low factor VIII and be variably associated with bleeding
  - Factor XI deficiency is variably associated with bleeding
  - Contact factor deficiencies (e.g. Factor XII deficiency) can profoundly elevate the APTT but do not result in a bleeding tendency

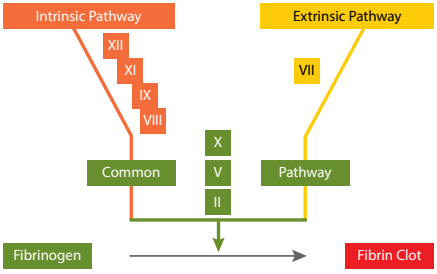
- Acquired causes of prolonged APTT may be due to inhibitors – either specific or non-specific.
  - Specific inhibitors are directed against specific factors (commonly against Factor VIII)
  - Non-specific inhibitors may be drugs (e.g., heparin, rivaroxaban, apixaban, edoxaban) or antiphospholipid antibodies that target coagulation proteins bound to phospholipids (also known as lupus anticoagulants)
  - The APTT may also be elevated in patients on direct thrombin inhibitors (DTI) (e.g., dabigatran, argatroban, bivalirudin)

To distinguish between factor deficiency and inhibitor

- Perform an immediate 50:50 mixing study (see Chapter 2).
- If the APTT prolongation corrects on mixing the prolongation is likely due to a factor deficiency (due to replacement of factor(s) from the normal plasma).
- If it does not correct the prolongation it is likely due to an inhibitor.
- A partial correction may represent multiple factor deficiencies or an inhibitor.

Prolonged APTT and PT / INR

If the PT / INR and the APTT are both prolonged, there could be multiple factors affected in the intrinsic and extrinsic pathways or a single factor deficiency in the common pathway – Factors X, V, II (prothrombin) or a severe deficiency of fibrinogen.



What is the differential diagnosis?

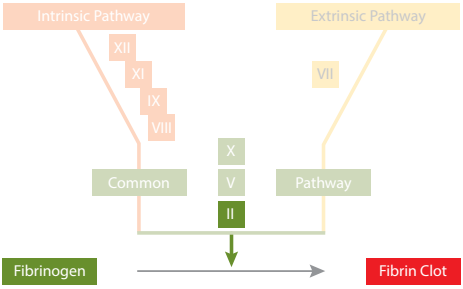
- Acquired causes.
  - Non-specific inhibitors - drugs (e.g., excessive doses of heparin, direct thrombin inhibitors or direct Xa inhibitors) or antiphospholipid antibodies that target coagulation proteins bound to phospholipid (also known as lupus anticoagulants)
  - Specific inhibitors directed to a factor within the common pathway
  - Severe vitamin K deficiency (low vitamin K dependent factors II, VII, IX and X)
  - Supratherapeutic warfarin therapy (low vitamin K dependent factors II, VII, IX and X)
  - Severe liver disease (due to impaired production of multiple coagulation factors)
  - Consumptive coagulopathy (e.g., disseminated intravascular coagulation) due to increased consumption of multiple coagulation factors
  - Isolated Factor X deficiency (e.g., associated with systemic amyloidosis)
  - Severe depletion of fibrinogen due to massive hemorrhage or fibrinolysis
  - Hemodilution (post operative sample, massive transfusion, pre-analytical causes)
- Congenital deficiency of Factors X, V, II or fibrinogen – usually a single factor deficiency.
  - Deficiencies of Factors X, V, II or fibrinogen may be associated with bleeding depending on the severity of the phenotype

As previously discussed, an immediate 50:50 mixing study may help in providing clues as to whether the cause of the prolongation is due to a factor deficiency or an inhibitor. However, specific factor levels and inhibitor studies will be more informative.

Prolonged Thrombin time (TT) with normal or prolonged APTT and PT / INR

If the thrombin time is prolonged, the probable cause is related to either thrombin (Factor IIa) or fibrinogen.

The PT / INR and APTT are not sensitive to mild to moderate deficiencies of fibrinogen; the TT may be the only prolonged screening test in those instances.



What is the differential diagnosis?

- Acquired causes.
  - Drugs (e.g., heparin, direct thrombin inhibitors)
  - Specific inhibitors directed to either factor II or fibrinogen (extremely rare)
  - Consumptive coagulopathy (e.g. disseminated intravascular coagulation) due to increased fibrin degradation products in the circulation that interfere with fibrin polymerization
  - Acquired hypofibrinogenemia
    - Severe liver disease
    - Massive hemorrhage
    - May occur with systemic t-PA treatment
- Congenital deficiency of fibrinogen (hypofibrinogenemia or afibrinogenemia) or a qualitative abnormality (dysfibrinogenemia).

History

- The history is the most important tool in determining the pre-test probability of the existence of a bleeding disorder and helping to distinguish congenital from acquired causes.

ATTENTION

The bleeding history is the most important predictor of a bleeding disorder.

- Details to inquire about on history.
  - Onset of bleeding – spontaneous or with hemostatic challenges (dental extractions, surgery, postpartum)
  - Location of bleeding – skin, mucous membranes, muscles, joints
  - Pattern of bleeding – bruises, petechiae, hematomas
  - Duration and severity of bleeding episode
  - Menstrual history – ask about duration, the size/type of menstrual products, and frequency of changing
  - Treatments / interventions required to stop bleeding – local pressure, cautery / packing for nosebleeds, other interventions
  - History or symptoms of anemia / iron deficiency – fatigue, prior iron supplementation
  - Previous blood transfusions
  - Medication history
  - Family history of bleeding problems

- A congenital bleeding disorder would more often be associated with a lifelong history of excessive bleeding or bruising and a positive family history for bleeding; however, the lack of family history does not rule out a congenital bleeding disorder.
- Standardized bleeding assessment tools (BATs) should be used to assess bleeding risk. An example is the International Society on Thrombosis and Haemostasis Bleeding Assessment Tool (ISTH-BAT) for von Willebrand disease and platelet function disorders.

ATTENTION

Standardized bleeding assessment tools (BATs) should be used to assess bleeding risk.

Physical Examination

- Should include examination of:
  - Skin – pallor, jaundice, size and location of bruises, petechiae, hematomas, telangiectasia
  - Hepatosplenomegaly and lymphadenopathy
  - Joints – range of motion, evidence of hypermobility

Diagnostic Approach

- Congenital causes of bleeding include:
  - von Willebrand disease (VWD)
  - Platelet function disorders (PFD)
  - Hemophilia A and B
  - Factor XI deficiency
  - Other coagulation factor deficiencies
  - Collagen vascular disorders (Ehlers Danlos Syndrome)
  - Hypo / dysfibrinogenemia

  VWD is the most common congenital cause of bleeding.

- Acquired causes of bleeding include:
  - Medications (e.g., antiplatelet agents, anticoagulants, antidepressants, anticonvulsants)
  - Hepatic or renal disease
  - ITP (immune thrombocytopenia)
  - Bone marrow disorders
  - Acquired coagulation factor deficiencies (Factor VIII, von Willebrand Factor)
  - Cushing's syndrome

  Medications are the most common acquired cause of bleeding.

ATTENTION

VWD is the most common congenital cause of bleeding. Medications are the most common acquired cause of bleeding.

Investigations

- Initial investigations should be directed by the history and include:
  - CBC and peripheral blood film
  - PT / INR and APTT
  - + / - Thrombin time
  - + / - Fibrinogen
  - + / - Hepatic, renal function
  - + / - Ferritin
- The initial investigations may be normal in both VWD and PFD.
- Subsequent investigations will depend on the clinical history and initial test results and may include:
  - von Willebrand screen
  - Testing of specific coagulation factors
  - Platelet function testing
- Ideally, specialized investigations should be done under the supervision of a hematologist.

ATTENTION

A bleeding time is no longer recommended for the investigation of bleeding disorders.

Here is an example of a bleeding assessment tool validated for the assessment of VWD and platelet function disorders:

The ISTH Bleeding Assessment Tool has been validated for VWD and PFD

- The bleeding score is determined by scoring the worst episode for each symptom (each row) and then summing all of the rows together.
- "Consultation only" refers to a patient consulting a medical professional (doctor, nurse, dentist) because of a bleeding symptom where no treatment was given.

SYMPTOMS (up to time of diagnosis)	0	1	2	
Epistaxis	No/trivial	> 5/year or More than 10 minutes	Consultation only	
Cutaneous	No/trivial	5 or more bruises >1cm in exposed areas	Consultation only	
Bleeding from minor wounds	No/trivial	> 5/year or More than 10 minutes	Consultation only	
Oral cavity	No/trivial	Present	Consultation only	
GI bleeding	No/trivial	Present (not associated with ulcer, portal hypertension, hemorrhoids, angiodysplasia)	Consultation only	
Hematuria	No/trivial	Present (macroscopic)	Consultation only	
Tooth extraction	No/trivial or none done	Reported in </= 25% of all procedures, no intervention	Reported in > 25% of all procedures, no intervention	
Surgery	No/trivial or none done	Reported in </= 25% of all procedures, no intervention	Reported in > 25% of all procedures, no intervention	
Menorrhagia	No/trivial	Consultation only or Changing pads more frequently than every 2 hours or Clot and flooding or PBAC score >100	Time off work/school > 2/year or Requiring antifibrinolytics or hormonal or iron therapy	
Post-partum hemorrhage	No/trivial or no deliveries	Consultation only or Use of syntocin or Lochia > 6 weeks	Iron therapy or antifibrinolytics	
Muscle hematomas	Never	Post trauma, no therapy	Spontaneous, no therapy	
Hemarthrosis	Never	Post trauma, no therapy	Spontaneous, no therapy	
CNS bleeding	Never	-	-	
Other bleeding	No/trivial	Present	Consultation only	

Interpretation:

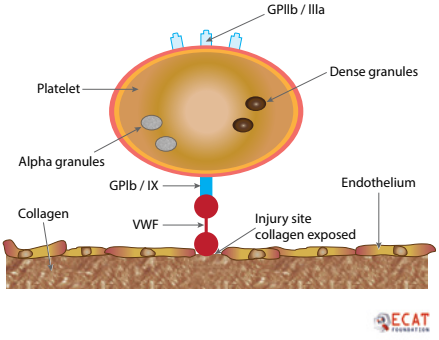
- Adult males: A score of 4 or more is considered "abnormal"
- Adult females have age specific cut-offs:
  - Adult females age 18-30: A score of 5 or more is considered "abnormal"
  - Adult females age 31-51: A score of 6 or more is considered "abnormal
  - Adult females age 52-88: A score of 7 or more is considered "abnormal
- Child (age < 18 years): A score of 3 or more is considered "abnormal"
- A bleeding score < 2 makes a bleeding disorder unlikely

SCORE		
	3	4
	Packing or cauterization or antifibrinolytic	Blood transfusion or replacement therapy (hemostatic blood components and rFVIIa) or desmopressin
	Extensive	Spontaneous hematoma requiring blood transfusion
	Surgical hemostasis	Blood transfusion, replacement therapy, or desmopressin
	Surgical hemostasis or antifibrinolytic	Blood transfusion, replacement therapy, or desmopressin
	Surgical hemostasis or antifibrinolytic	Blood transfusion, replacement therapy, or desmopressin
	Surgical hemostasis or iron therapy	Blood transfusion, replacement therapy, or desmopressin
	Resuturing or packing	Blood transfusion, replacement therapy, or desmopressin
	Surgical hemostasis or antifibrinolytic	Blood transfusion, replacement therapy, or desmopressin
	Requiring combined treatment with antifibrinolytics and hormonal therapy or Present since menarche and >12 months	Acute menorrhagia requiring hospital admission and emergency treatment or Requiring blood transfusion, replacement therapy, desmopressin or Requiring dilatation & curettage or endometrial ablation or hysterectomy
	Requiring blood transfusion, replacement therapy, desmopressin or Requiring exam under anaesthesia and/or use of uterine balloon/package to tamponade the uterus	Any procedure requiring critical care or surgical intervention (e.g. hysterectomy, internal iliac artery ligation, uterine artery embolization, uterine brace sutures)
	Spontaneous or traumatic, requiring desmopressin or replacement therapy	Spontaneous or traumatic, requiring surgical intervention or blood transfusion
	Spontaneous or traumatic, requiring desmopressin or replacement therapy	Spontaneous or traumatic, requiring surgical intervention or blood transfusion
	Subdural, any intervention	Intracerebral, any intervention
	Surgical hemostasis, antifibrinolytics	Blood transfusion or replacement therapy or desmopressin

von Willebrand Disease (VWD)

Definition

- von Willebrand factor (VWF) adheres platelets to exposed subendothelial collagen and also acts as a protective carrier of Factor VIII.
- von Willebrand's disease = Inherited quantitative deficiency OR qualitative dysfunction of VWF.
- Autosomal inheritance.
  - Men and women are both affected
- Three types:
  - Type 1: partial quantitative deficiency of VWF
    - Most common form
  - Type 2: qualitative defect of VWF
    - 4 subtypes: 2A, 2B, 2M, 2N
  - Type 3: quantitative absence of VWF
    - Rare severe form



Clinical Presentation

- Mucosal bleeding (e.g., heavy menstrual bleeding, post-partum hemorrhage, GI hemorrhage), easy bruising are most common symptoms.
- Excessive and prolonged post-operative bleeding.
- Bleeding into muscles, joints, CNS – rare, mainly in Type 3 VWD.

Diagnosis:

- Bleeding history with a bleeding assessment tool (BAT).
- Investigations:
  - CBC – subtype 2B can also have a low platelet count.
  - APTT may be prolonged (but not always).
  - PT / INR is normal.
  - VWD Screen:
    - VWF antigen = VWF quantity assessment
    - VWF activity = VWF quality assessment
    - Factor VIII activity = VWF protective carrier assessment
- If BAT and VWD screen are positive – refer to hematologist for additional testing to determine subtype.

Management

- Prevent bleeding.
  - Avoid trauma – e.g. arterial punctures, surgery/procedures without prophylactic therapy
  - Caution with antiplatelet agents (e.g., aspirin, clopidogrel) and regular NSAIDs
  - Increase VWF / FVIII activity prior to invasive procedures (e.g., dental work)
  - Most patients do not require prophylactic therapy on a regular basis
- If suspect serious bleeding or trauma – treat first, investigate later.
  - Ask patient if they have a wallet card with diagnosis or therapy recommendations
  - Consult Hematology or Hemophilia centre for advice (www.ahcdc.ca, www.hemophilia.ca)
  - Type 1: DDAVP 0.3 mcg / kg IV or SC (dose cap 20 mcg / dose in Canada; no dose cap in other countries) for patients with a proven previous response
    - If DDAVP non-responder or response unknown, then consider plasma-derived purified VWF / Factor VIII concentrate IV
  - Type 2: usually plasma-derived purified VWF / FVIII concentrate IV
  - Type 3: plasma-derived purified VWF / FVIII concentrate IV
  - Tranexamic acid (Cyclokapron) 25 mg / kg po q8h or 10mg / kg IV q8h for mucosal bleeding
  - If VWF / Factor VIII concentrate indicated, consult product monograph for dosing

Disorders of Platelet Function

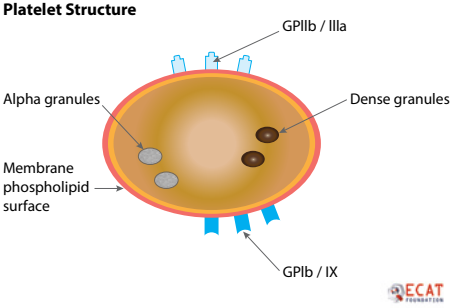
Definition

- Platelet disorders can occur on the basis of defects in the platelet membrane, receptors or granules.
  - Membrane surface promotes activation of blood clotting
  - Receptors allow the platelet to interact with the blood vessel wall, other blood cells and coagulation factors (thrombin, VWF and fibrinogen)
  - Granule contents are released when platelets are activated
- Can be inherited or acquired.
- Autosomal inheritance.
  - Men and women are both affected

Clinical Presentation

- Mucosal bleeding (e.g., heavy menstrual bleeding, post-partum hemorrhage), easy bruising are most common symptoms.
- Excessive and prolonged post-operative bleeding.

Platelet Structure



Inherited platelet disorders can be divided into several groups:

1. Disorders of platelet adhesion (e.g., Bernard Soulier syndrome)
2. Disorders of platelet aggregation (e.g., Glanzmann thrombasthenia)
3. Disorders of platelet granules (e.g., gray platelet syndrome)
4. Disorders of platelet pro-coagulant activity (e.g., Scott syndrome)
5. Combined abnormalities of number and function (e.g., MYH9-related disease)
6. Non-specific abnormalities (most common)

Diagnosis:

- Bleeding history with bleeding assessment tool (BAT).
- Important to exclude anti-platelet medication (e.g., aspirin, clopidogrel, NSAIDs) or concurrent disease (e.g., chronic kidney disease).
- CBC and blood film: some disorders are also associated with a low platelet count or abnormal platelet morphology.
- If BAT screen is positive – refer to hematologist for platelet function testing.

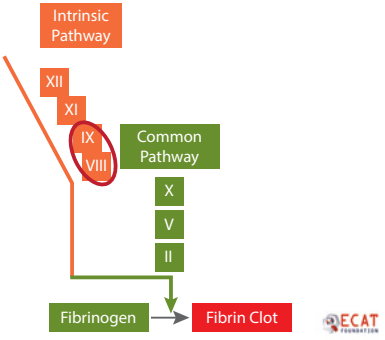
Management

- Depends on the particular disorder and on the severity of bleeding.
- Prevent bleeding.
  - Avoid trauma – e.g. arterial punctures, surgery/procedures without prophylactic therapy
  - Caution with antiplatelet agents (e.g., aspirin, clopidogrel) and regular NSAIDs
  - Most patients do not require prophylactic therapy on a regular basis
- If suspect serious bleeding or trauma – treat first, investigate later.
  - Ask patient if they have a wallet card with diagnosis or therapy recommendations
  - Consult Hematology or Hemophilia centre for advice (www.ahcdc.ca, www.hemophilia.ca)
  - Options may include:
    - DDAVP 0.3 mcg / kg IV or SC (dose cap 20 mcg / dose in Canada; no dose cap in other countries)
    - Tranexamic acid (Cyclokapron) 25 mg / kg po q8h or 10 mg / kg IV q8h for mucosal bleeding
    - Platelet transfusion
    - In cases of life-threatening bleeding, recombinant factor VIIa (Niastase) may be considered

Hemophilia A and B (Factor VIII and IX deficiency)

Definition

- Hemophilia A = Inherited Factor VIII deficiency.
- Hemophilia B = Inherited Factor IX deficiency
- X-linked inheritance.
  - Males predominantly affected; almost always presents in childhood for severely affected males
  - Female carriers can be symptomatic
- 30% have de novo mutation (i.e., negative family history).

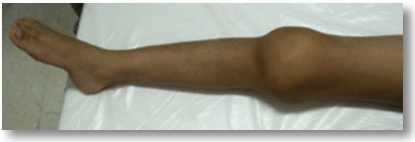


Grades of Severity:

Severity Grade	Clotting Factor Activity	Bleeding Symptoms
Severe	<0.01 IU / mL (<1%)	Spontaneous bleeding into joints / muscles Severe bleeding with minimal trauma/surgery
Moderate	0.01-0.04 IU / mL (1-4%)	Occasional spontaneous bleeding Severe bleeding with trauma / surgery
Mild	0.05-0.40 IU / mL (5-40%)	Severe bleeding with major trauma / surgery

Clinical Presentation

- Classically bleed into joints, muscles, soft tissue.
  - May also have mucosal and CNS bleeds
- Excessive and prolonged post-operative bleeding.



Diagnosis

- Detailed bleeding and family history.
- APTT usually prolonged.
- PT / INR is normal.
- Low Factor VIII activity in Hemophilia A.
- Low Factor IX activity in Hemophilia B.

Management

- Prevent bleeding.
  - Avoid trauma – e.g. arterial punctures, surgery/procedures without prophylactic therapy
  - Caution with antiplatelet agents (e.g., aspirin, clopidogrel) and regular NSAIDS
  - Replace missing factor prior to invasive procedures
  - Some patients, especially those with severe hemophilia require prophylactic factor replacement therapy on a regular basis
  - Emicizumab (Hemlibra), a bispecific monoclonal antibody that mimics the function of factor VIII, may be used as an alternative to prophylactic factor replacement therapy. It is not a treatment for bleeding; only to be used to prevent bleeding.
    - Note that emicizumab will affect clotting-based laboratory tests, including the APTT and APTT based factor VIII activity, leading to potentially misleading or falsely normal or high values
    - To circumvent this issue, chromogenic FVIII assays using bovine components can be used instead
- Coordinate patient care with Hemophilia centre (www.ahcdc.ca, www.hemophilia.ca).
- If suspect serious bleeding or trauma – treat first, investigate later.
  - Ask patient if they have a wallet card with diagnosis or therapy recommendations
  - Consult Hematology or Hemophilia centre for advice
  - Rest, compression, elevation for affected muscles and joints
  - Factor replacement therapy if indicated
  - DDAVP 0.3 mcg / kg IV or SC (dose cap 20 mcg / dose in Canada; no dose cap in other countries) for patients with mild Hemophilia A (not B) and a proven previous response
  - Tranexamic acid (Cyclokapron) 25 mg / kg po q8h or 10 mg/ kg IV q8h for mucosal bleeding

Hemophilia A and B (continued)

Factor Replacement Therapy

- Calculation of factor replacement therapy is based on the baseline level, the desired level for the clinical bleeding situation and the rise in factor expected with replacement.
- Factor VIII replacement: each IU / kg results in 2% rise in Factor VIII activity and has a half-life of 8-12 hours for standard product (half-life is longer for extended half-life products).
- Factor IX replacement: each IU / kg results in 0.5 - 1% rise in Factor IX activity and has a half-life of 18-24 hours for standard product (half-life is longer for extended half-life products).
- Provide the initial dose as below and consult a hematologist (ideally affiliated with a hemophilia treatment center for advice on further dosing).

Situation	Desired Factor Level (IU / mL)	Dose of Recombinant Factor VIII (IU / kg)	Dose of Recombinant Factor IX (IU / kg)
Minor bleed	0.25-0.35	15-20	25-40
Moderate bleed / minor surgery	0.35-0.6	20-30	35-70
Severe bleed / major surgery	0.8-1.0	40-50	80-120

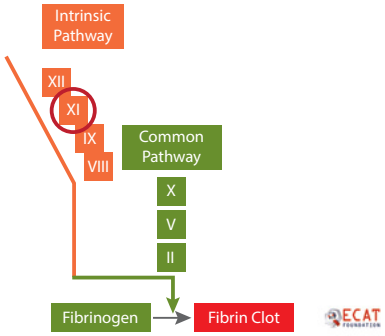
Example

- A patient with severe Hemophilia A and a baseline factor of < 0.01 U / mL who weighs 70 kg presents with a major joint hemorrhage.
- The desired factor level is 0.8 - 1.0 IU / mL.
- The dose of recombinant factor VIII would be 50 IU x 70 kg = 3500 IU.

Factor XI Deficiency

Definition

- Inherited deficiency of Factor XI.
- Autosomal recessive inheritance.
  - Prevalent in Ashkenazi Jewish population



Clinical Presentation

- Poor correlation between Factor XI levels and bleeding tendency.
- Personal bleeding history is more predictive of future bleeding risk.
- Mucosal bleeding (e.g., heavy menstrual bleeding, GI hemorrhage), easy bruising.
- Excessive and prolonged post-operative bleeding.
- Spontaneous bleeding is rare.

Diagnosis

- Detailed bleeding and family history.
- APTT may be prolonged.
- PT / INR is normal.
- Low factor XI activity.

Management

- Prevent bleeding.
  - Avoid trauma – e.g. arterial punctures, surgery/procedures without prophylactic therapy
  - Caution with antiplatelet agents (e.g., aspirin, clopidogrel) and regular NSAIDs
  - Increase FXI activity prior to invasive procedures (e.g., dental work)
  - Most patients do not require prophylactic therapy on a regular basis
- Coordinate patient care with Hemophilia centre (www.ahcdc.ca, www.hemophilia.ca).
- If suspect serious bleeding or trauma – treat first, investigate later.
  - Ask patient if they have a wallet card with diagnosis or therapy recommendations
  - Treatment options:
    - Plasma derived Factor XI concentrate
    - If Factor XI concentrate not available, frozen plasma (FP) can be used instead
    - Tranexamic acid (Cyclokapron) 25 mg / kg po q8h or 10 mg / kg IV q8h for mucosal bleeding
    - DDAVP 0.3 mcg / kg IV or SC (dose cap 20 mcg / dose in Canada, no dose cap in other countries)

Bleeding Disorder of Unknown Cause (BDUC)

Definition

- A diagnosis of exclusion characterized by normal hemostatic investigations despite a clinically significant bleeding tendency
- Previously also known as "Bleeding of Unknown Cause", "Unclassified Bleeding Disorder", or "Bleeder NYD"

Clinical Presentation

- BDUC patients have a similar bleeding history as other mild-to-moderate bleeding disorders.
- Mucosal bleeding (e.g., heavy menstrual bleeding, GI hemorrhage) or easy bruising are common
- Excessive and prolonged post-operative bleeding.
- Spontaneous bleeding is rare.

Diagnosis

- A detailed bleeding and family history
- Careful past medical and medication history to exclude other causes of bleeding
- At minimum, the recommended investigations to establish the diagnosis includes PT, APTT, fibrinogen, VWF screen, factor VIII, factor IX, factor XI, and platelet function testing.

Management

- Prevent bleeding.
  - Avoid trauma – e.g. arterial punctures, surgery/procedures without prophylactic therapy
  - Caution with antiplatelet agents (e.g., aspirin, clopidogrel) and regular NSAIDs
- Coordinate patient care with Hemophilia centre (www.ahcdc.ca, www.hemophilia.ca).
- If suspect serious bleeding or trauma – treat first, investigate later.
- Ask patient if they have a wallet card that dictates therapy
- Treatment is a staged approach, depending on severity or risk of bleeding:
  - Tranexamic acid 25 mg / kg po q8h or 10 mg / kg IV q8h
  - DDAVP 0.3 mcg / kg IV or SC (dose cap 20 mcg / dose in Canada, no dose cap in other countries)
  - Platelet transfusion
  - Consider rFVIIa in the event of excessive bleeding despite above measures

Acquired hemophilia A

Definition

- An acquired autoimmune bleeding disorder caused by the development of autoantibodies (inhibitors) against coagulation factors, most commonly Factor VIII (acquired hemophilia A).
- Occurs most commonly in:
  - Older adults
  - Pregnant or postpartum women
  - Patients with an underlying autoimmune disease, malignancy, or following certain medications (e.g. antibiotics)
  - Up to 50% are idiopathic

Clinical Presentation

- Sudden onset of severe or spontaneous bruising/bleeding in a patient with no prior personal or family history of bleeding
- Extensive subcutaneous ecchymoses (large bruises) and soft tissue hematomas are the common symptoms
- Mucosal bleeding (epistaxis, GI, or hematuria)
- Excessive and prolonged post procedural or post-partum bleeding
- High risk of death driven by lack of recognition
- Early recognition of bleeding and treatment is critical!

Diagnosis of Acquired Hemophilia A

- Isolated prolonged APTT
- Normal PT / INR and normal fibrinogen
- Low factor VIII activity level with a detectable Factor VIII inhibitor
- Screen for underlying causes (autoimmune disease, malignancy, pregnancy, medications)

Management of Acquired Hemophilia A

- Medical emergency – early Hematology involvement is essential. Coordinate care urgently with Hemophilia Treatment Centre (www.ahcdc.ca, www.hemophilia.ca)
- Control of bleeding
  - Bypassing agents:
    - Recombinant activated factor VIIa (rFVIIa, Niastase)
    - Activated prothrombin complex concentrate (aPCC, FEIBA)
    - Recombinant porcine factor VIII (Obizur)
      - Restricted to Hemophilia Treatment Centres
  - Human Factor VIII concentrates are generally ineffective unless inhibitor titer is very low
  - Tranexamic acid may be used for mucosal bleeding. Avoid combination with aPCC (FEIBA) given risk of consumptive coagulopathy and thrombosis.
  - Avoid invasive procedures (e.g. arterial punctures) or surgery if at all possible as they may cause uncontrollable bleeding and precipitate massive hemorrhage and hemorrhagic death
- Inhibitor eradication
  - Immunosuppressive therapy often initiated promptly to stop the production of the autoantibody (typically steroids, cyclophosphamide, or rituximab)
  - Emicizumab (Hemlibra) can be used in acquired hemophilia A to reduce bleeding risk during the period of inhibitor eradication.
  - Note that emicizumab will cause a falsely normal or high APTT and APTT-based Factor VIII activity level.

Key References

Chapter 1: The Basics of Coagulation and Clot Breakdown

Hoffman M. A cell-based model of coagulation and the role of factor VIIa. Blood Rev 2003 Sep;17 Suppl 1:S1-5.

O'Donnell JS, O'Sullivan JM, Preston RJS. Advances in understanding the molecular mechanisms that maintain normal haemostasis. British journal of haematology. 2019;186(1):24–36.

Palma-Barqueros V, Revilla N, Sánchez A, Zamora Cánovas A, Rodriguez-Alén A, Marín-Quílez A, et al. Inherited Platelet Disorders: An Updated Overview. International journal of molecular sciences. 2021;22(9).

Chapter 2: Routine Coagulation Tests

CLSI. One-Stage Prothrombin Time (PT) Test and Activated Partial Thromboplastin Time (APTT) Test. 3rd Edition. CLSI guideline H47. Clinical and Laboratory Standards Institute; 2023.

Hughes PR, Lewis MN, Adams SS. Bleeding and Bruising: Primary Care Evaluation. Am Fam Physician. 2024;110(5):504-514.

William E Winter, Sherri D Flax, Neil S Harris, Coagulation Testing in the Core Laboratory, Laboratory Medicine, Volume 48, Issue 4, November 2017, Pages 295–313,

Johnston M. Monitoring heparin therapy. In Quality in Laboratory Hemostasis and Thrombosis. Ed Kitchen S, Olson JD, Preston FE. 2009. West Sussex: Blackwell Publishing Ltd. Pg 170-78.

Tripodi A. Monitoring oral anticoagulant therapy. In Quality in Laboratory Hemostasis and Thrombosis. Ed Kitchen S,

Olson JD, Preston FE. 2009. West Sussex: Blackwell Publishing Ltd. Pg 179-89.

Selby R, Meijer P, Favaloro E. D-dimer Diagnostics: Can I use any D-dimer assay? Bridging the Knowledge-to-Action gap. Res Pract Thromb Haemost. 2024 Jan. 8(1): 1023-35. Published online 2024 Feb 1. doi: 10.1016/j.rpth.2024.102335.

Chapter 3: Anticoagulant Drugs

Creager MA, Barnes GD, et al. 2026 AHA/ACC/ACCP/ACEP/CHEST/SCAI/SHM/SIR/SVM/SVN Guideline for the Evaluation and Management of Acute Pulmonary Embolism in Adults: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. Published online February 19, 2026.

Kearon C, et al. Comparison of fixed-dose weight-adjusted unfractionated heparin and low-molecular-weight heparin for acute treatment of venous thromboembolism. Jama. 2006;296(8):935-42.

Douketis JD, et al. Perioperative Management of Antithrombotic Therapy: An American College of Chest Physicians Clinical Practice Guideline. Chest 2022;162(5):E207-E243.

Shaw JR, et al. Periprocedural Management of Oral Anticoagulation. Med Clin North Am 2020;104(4): 709-726.

Siegal DM. What Have We Learned About DOAC Reversal? Hematology Am Soc Hematol Educ Program. 2019;2019(1):198-203.

National Advisory Committee on Blood and Blood Products. Recommendations for the use of prothrombin complex concentrates in Canada. 2022. Available at https://nacblood.ca/en/resource/recommendations-use-prothrombin-complex-concentrates-canada

Useful Website: Thrombosis Canada. Available from: https://thrombosiscanada.ca/

Chapter 4: Evaluating Abnormal Coagulation Tests

Lippi G, Pasalic L, Favaloro EJ. Detection of mild inherited disorders of blood coagulation: current options and personal recommendations. Expert Rev Hematol. 2015 8(4):527-542.

Rydz N, James PD. Approach to the diagnosis and management of common bleeding disorders. Semin Thromb Hemost 2012 Oct;38(7):711-19.

Samuelson B, Cuker A, Siegal DM, Crowther M, Garcia DA. Laboratory assessment of the anticoagulant activity of direct oral anticoagulants: A systematic review. Chest. 2017 151(1):127-138.

Gosselin R, et al. An update on laboratory assessment for direct oral anticoagulants (DOACs). Int J Lab Hematol. 2019;41(Suppl. 1):33–39.

Verhovesk M, Moffat KA, Hayward CPM. Laboratory testing for fibrinogen abnormalities. Am J Hematol. 2008 83(12): 928-31.

Douxfils J, et al. Laboratory testing in patients treated with direct oral anticoagulants: a practical guide for clinicians. J Thromb Haemost 2018;16:209-19.

Chapter 5: Approach to the Evaluation of the Bleeding Patient

Elbaz C, Sholzberg M. An illustrated review of bleeding assessment tools and common coagulation tests. Res Pract Thromb Haemost. 2020;4(5):761-773.

Rodeghiero F, Tosetto A, Abshire T, Arnold DM, Coller B, James P, Neunert C, Lillicrap D; ISTH/SSC joint VWF and Perinatal/Pediatric Hemostasis Subcommittees Working Group. ISTH/SSC bleeding assessment tool: a standardized questionnaire and a proposal for a new bleeding score for inherited bleeding disorders. J Thromb Haemost. 2010 Sep;8(9):2063-5.

Bowman M, Mundell G, Grabell J, Hopman WM, Rapson D, Lillicrap D, James P. Generation and Validation of the Condensed MCMDM1-VWD Bleeding Questionnaire. J Thromb Haemost 2008 Dec;6(12):2062-66.

James P, Bowman M, Grabell J, Dwyre L, Rapson D. Prospective Validation of the Condensed MCMDM1-VWD Bleeding Questionnaire for Platelet Function Disorders. J Thromb Haemost 2011; 9 (Suppl 2), p 549, P-WE-092.

Doherty D, Grabell J, Christopherson PA, Montgomery RR, Coller BS, Lavin M, O'Donnell JS, James PD; Zimmerman Program Investigators. Variability in International Society on Thrombosis and Haemostasis-Scientific and Standardization Committee endorsed Bleeding Assessment Tool (ISTH-BAT) score with normal aging in healthy females: contributory factors and clinical significance. J Thromb Haemost. 2023 Apr;21(4):880-886.

Useful Website: Clinical and Molecular Hemostasis Research Group: Available at http://www.path.queensu.ca/labs/james/bq.htm

Chapter 6: Diagnosis and Management of Common Bleeding Disorders

James PD, Connell NT, Ameer B, et al. ASH ISTH NHF WFH 2021 guidelines on the diagnosis of von Willebrand disease. Blood Adv. 2021;5(1):280-300.

Connell NT, Flood VH, Brignardello-Petersen R, et al. ASH ISTH NHF WFH 2021 guidelines on the management of von Willebrand disease. Blood Adv. 2021;5(1):301-325.

Bolton-Maggs PHB. Factor XI deficiency. 3rd ed. Treatment of Hemophilia No. 16. Montreal: World Federation of Hemophilia; 2008. Available at http://www1.wfh.org/publication/files/pdf-1141.pdf. Accessed 25 Feb 2013.

Cox K, Price V, Kahr WH. Inherited platelet disorders: a clinical approach to diagnosis and management. Expert Rev Hematol 2011;4:455-72.

Hayward CP, Moffat KA, Raby A, Israels S, Plumhoff E, Flynn G, Zehnder JL. Development of North American consensus guidelines for medical laboratories that perform and interpret platelet function testing using light transmission aggregometry. Am J Clin Pathol 2010 Dec;134(6):955-63.

Lillicrap, D. The basic science, diagnosis, and clinical management of von Willebrand disease. Treatment of Hemophilia No. 35. Montreal: World Federation of Hemophilia, 2008. Available at http://www1.wfh.org/publication/files/pdf-1180.pdf. Accessed 25 Feb 2013.

Srivastava A, Santagostino E, Dougall A, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. Haemophilia. 2020;26 Suppl 6:1-158.

Baker RI, Choi P, Curry N, et al. Standardization of definition and management for bleeding disorder of unknown cause: communication from the SSC of the ISTH. J Thromb Haemost. 2024;22(7):2059-2070.

Tiede A, Collins P, Knoebl P, Teitel J, Kessler C, Shima M, Di Minno G, d'Oiron R, Salaj P, Jiménez-Yuste V, Huth-Kühne A, Giangrande P. International recommendations on the diagnosis and treatment of acquired hemophilia A. Haematologica. 2020 Jul;105(7):1791-1801.

Useful Websites:

Association of Hemophilia Clinic Directors of Canada. Available from: http://www.ahcdc.ca/

Canadian Hemophilia Society. Available from: http://www.hemophilia.ca/

World Federation of Hemophilia. Available from: www.wfh.org