

bloody easy

Coagulation

Simplified...

Second Edition

Lesley Black, Rita Selby
University Health Network

Elena Brnjac, Yulia Lin, Rita Selby
Sunnybrook Health Sciences Centre

Carolyn Elbaz
University of Toronto

Paula James
Kingston General Hospital

Karen Moffat
Hamilton Regional Laboratory Medicine Program

Michelle Sholzberg
St. Michael's Hospital

Editors: Yulia Lin and Rita Selby

Published by



Ontario Regional Blood Coordinating Network



We gratefully acknowledge the support and funding provided by the Ontario Ministry of Health and Long-Term Care.

Special thanks to the past contributors and material reviewers of the first edition.

Thanks also to:

- ▲ Dale Roddick, photographer, Sunnybrook Health Sciences Centre
- ▲ Doug Nicholson, photographer, Sunnybrook Health Sciences Centre
- ▲ Reena Manohar, graphic artist, Sunnybrook Health Sciences Centre
- ▲ The ECAT Foundation



CLOT-ED Images used or modified with permission from the ECAT Foundation, The Netherlands.

We hope you enjoy the second edition of *Bloody Easy: Coagulation Simplified*. Like the first edition we hope to provide basic foundational learning in coagulation and the assessment of bleeding disorders and coagulopathies. Updates include, new direct oral anticoagulants and reversal strategies for these drugs, in elective and urgent situations, in Chapter 3. New extended half-life replacement products for hemophilia are now included in Chapter 6.

First Edition, March 2013

Second Edition, February 2019

General Disclaimer:

While the advice and information in this handbook are believed to be true and accurate at the time of publishing, neither the authors nor the publishers accept any legal responsibility or liability for any errors or omissions in the information provided, or for any of the recommendations made. Any decision involving patient care must be based on the judgement of the attending physician according to the needs and condition of each individual patient.

1. The Basics of Coagulation and Clot Breakdown	4–7
2. Routine Coagulation Tests	8–17
Evaluating coagulation in the laboratory	8
Sample collection for coagulation testing	9
Prothrombin Time (PT)	10
International Normalized Ratio (INR)	11
Activated Partial Thromboplastin Time (APTT)	12
Thrombin Time (TT)	13
Fibrinogen	14
D-dimer	15
Anti-Xa assay	16
Summary	17
3. Anticoagulant Drugs	18–25
Unfractionated Heparin (UFH)	18
Low Molecular Weight Heparins (LMWHs)	19
Fondaparinux	20
Warfarin	21
Direct Thrombin Inhibitors (DTI)	23
Direct Xa Inhibitors	25
4. Evaluating Abnormal Coagulation Tests	26–29
Prolonged PT / INR with normal APTT	26
Prolonged APTT with normal PT / INR	27
Prolonged APTT and PT / INR	28
Prolonged Thrombin Time (TT) with normal or prolonged APTT and PT / INR	29
5. Approach to the Evaluation of the Bleeding Patient	30–35
6. Diagnosis and Emergency Management of Common Bleeding Disorders	36–45
von Willebrand disease (VWD)	36
Disorders of platelet function	38
Hemophilia A and B (Factor VIII and IX deficiency)	40
Factor XI deficiency	43
Key References	45–47

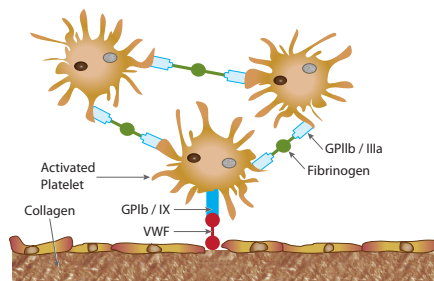
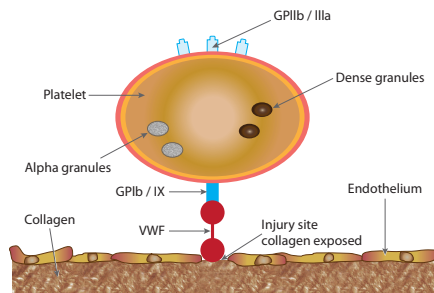
Hemostasis is a complex process in which multiple components of the blood clotting system are activated in response to vessel injury to control bleeding.

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.



ECAT PRODUCTION

ECAT PRODUCTION

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.
- ▲ TF / Factor VIIa 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.

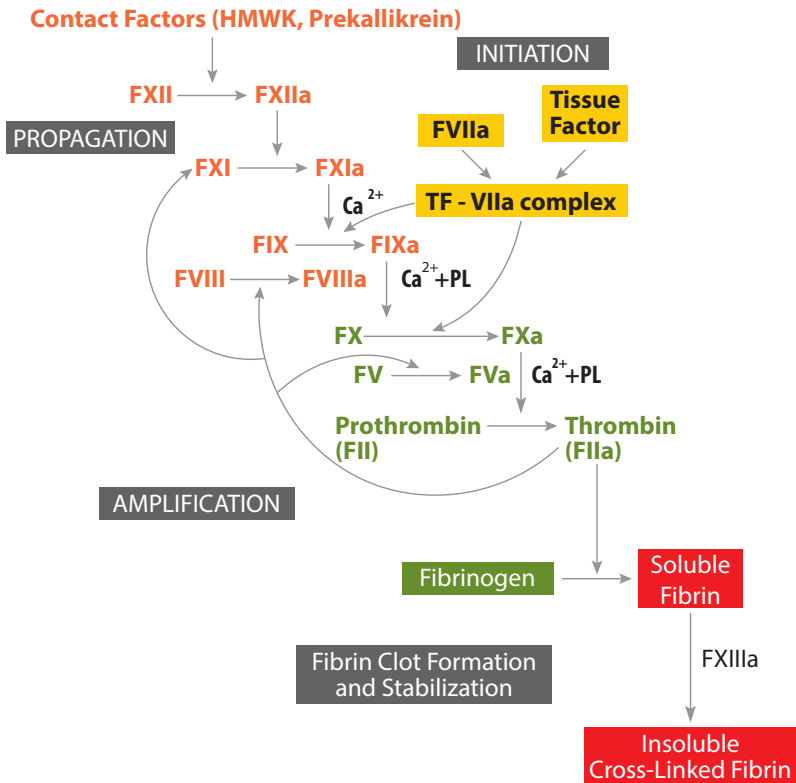
Propagation phase

- ▲ Additional Factor Xa is produced when TF / Factor VIIa complex activates Factor IX. The resultant Factor IXa along with Factor VIIIa forms the 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).

3. Fibrin clot formation and stabilization:

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

Secondary hemostasis, fibrin clot formation and stabilization:



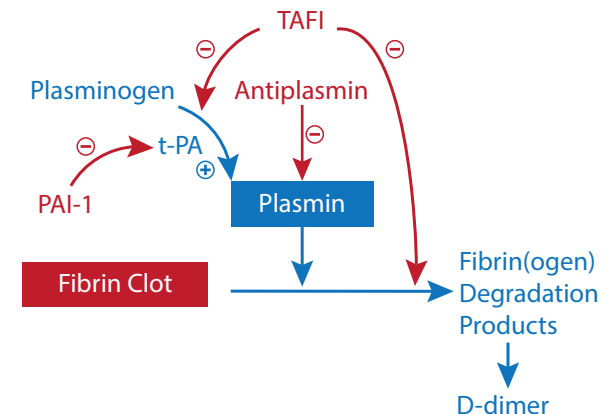
4. Inhibition of coagulation = inhibition of thrombin generation and fibrin clot breakdown (fibrinolysis):

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.

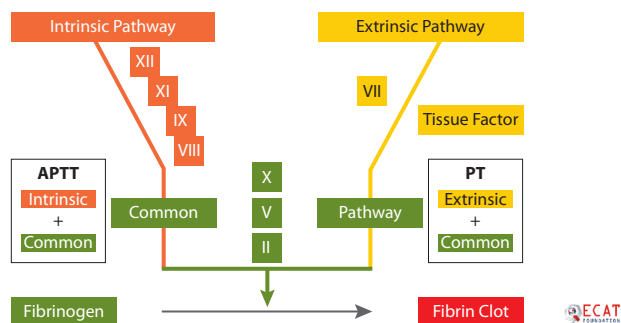
Fibrinolysis

- ▲ 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.

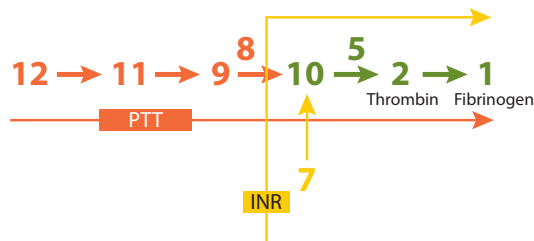


Evaluating coagulation in the laboratory

- ▲ 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

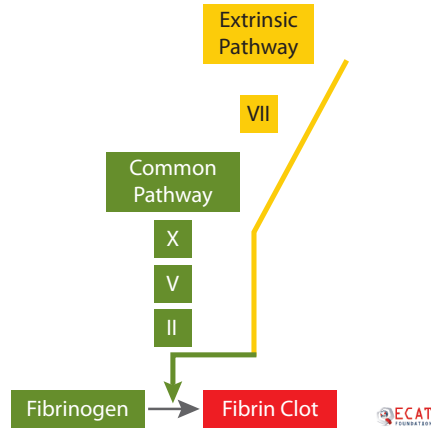
Coagulation testing MUST only be sent in a sodium citrate (blue top) tube.

- ▲ 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
 - Hemodilution of sample



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.

Time for clot formation
9 - 15 seconds

- Incubate at 37°C
- 0.1 mL Thromboplastin + Ca⁺⁺
- 0.05 mL Plasma

International Normalized Ratio (INR)

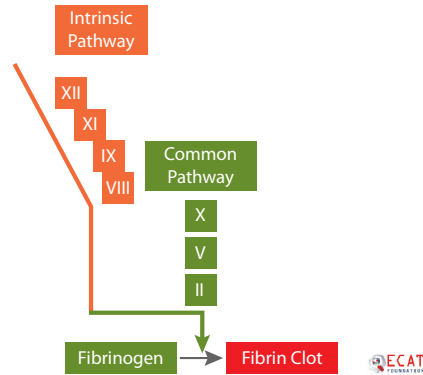
- ▲ The International Normalized Ratio (INR) was developed to standardize the PT to allow for monitoring of oral vitamin K antagonist therapy (e.g., warfarin) across different labs.
- ▲ The PT in seconds is used to calculate the INR.
- ▲ Each lot of PT reagent needs to have an International Sensitivity 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:

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

$$INR = \left(\frac{\text{Patient PT}}{\text{Mean Normal PT}} \right)^{ISI}$$

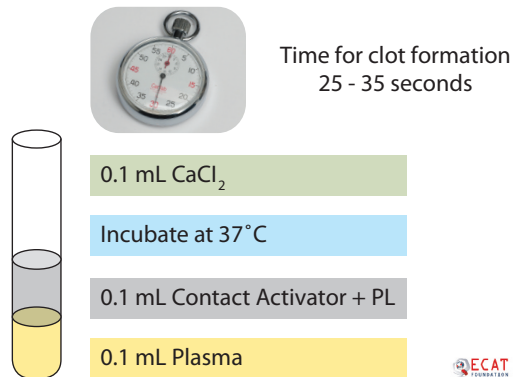
Activated Partial Thromboplastin Time (APTT)

- ▲ 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).



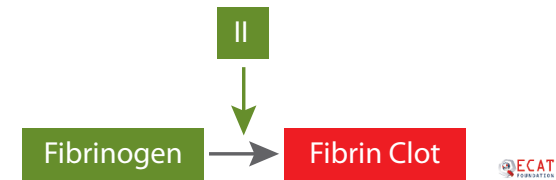
Measurement of APTT:

- 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.



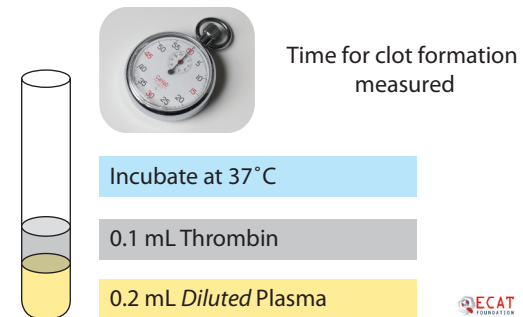
Thrombin Time (TT)

- ▲ 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).



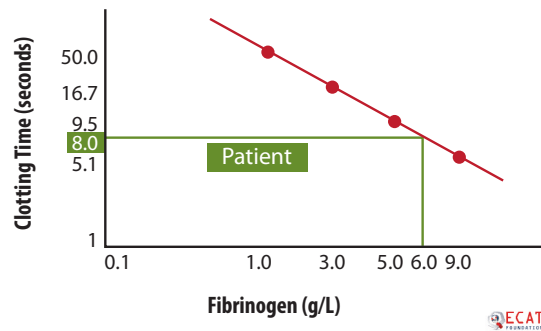
Measurement of TT:

- 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

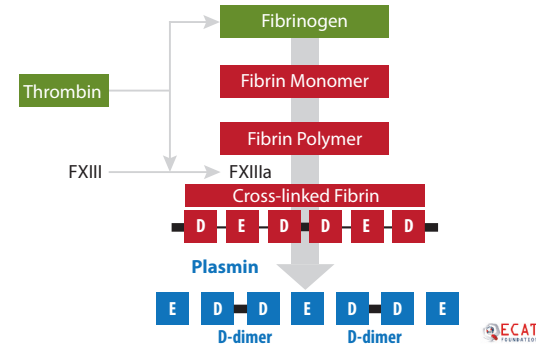
- ▲ The fibrinogen assay assesses fibrinogen activity.
- ▲ Hypofibrinogenemia is usually acquired due to loss of fibrinogen (e.g., bleeding), consumption (e.g., hyperfibrinolysis after traumatic injury, disseminated intravascular coagulation) or decreased production (e.g., severe liver disease). Other 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.



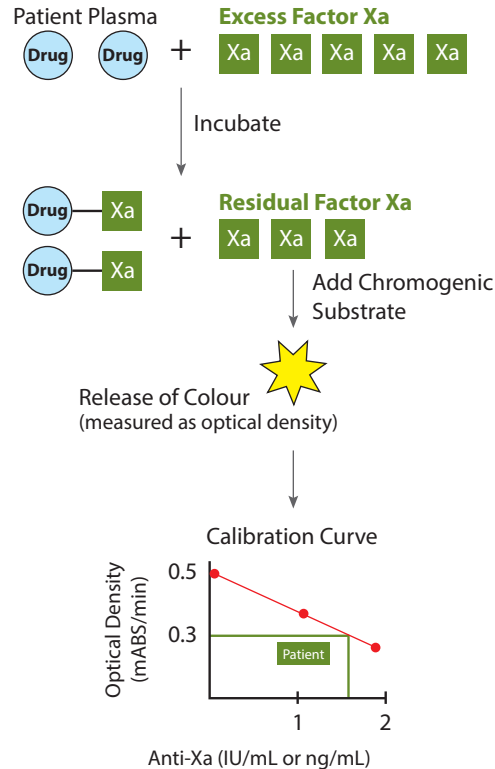
- ▲ A negative D-dimer can be used to rule out venous thromboembolism (VTE) in selected outpatients (those with low to moderate clinical probability of VTE). Ideally, D-dimer should only be used as part of a validated VTE diagnostic algorithm.
- ▲ An elevated D-dimer is not specific to thrombosis and 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).
- ▲ **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.

A T T E N T I O N

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

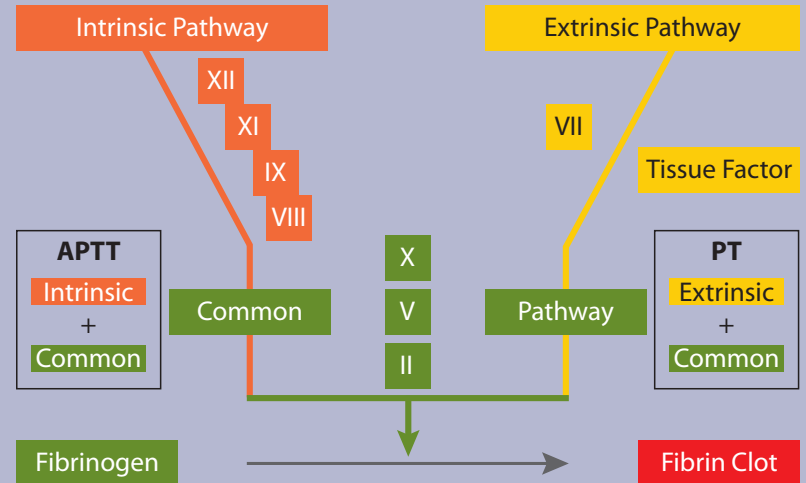


Summary

- ▲ 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 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.

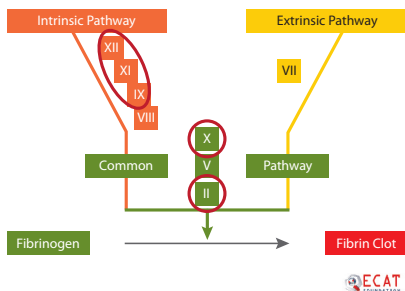
A T T E N T I O N

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



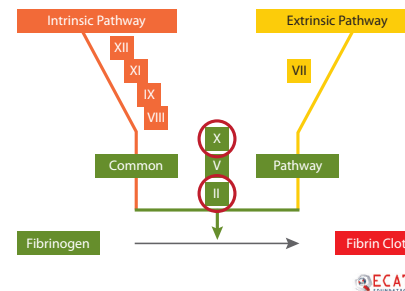
Unfractionated Heparin (UFH)

- ▲ 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
 - 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.
- ▲ 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.
 - Andexanet alpha (pending approval) may be effective for reversal of LMWH
 - 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



ATTENTION

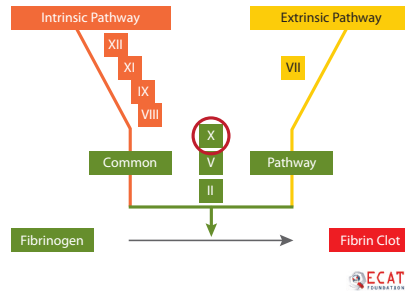
Consider measuring anti-Xa levels in the following populations:

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



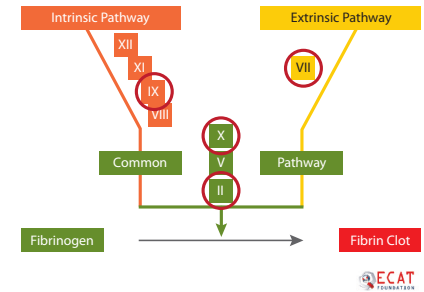
Fondaparinux

- ▲ 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.
 - Andexanet alpha (pending approval) may have a role in reversal of fondaparinux
 - 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
- ▲ Patient 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)

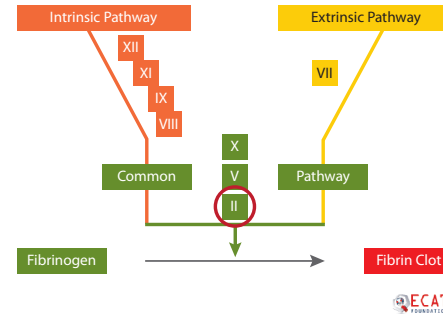
- ▲ Elective reversal.
 - Stop warfarin 5 days before major invasive procedure
 - Note: bridging therapy may be considered for selected patients at high risk for thrombosis
- ▲ Urgent reversal.
 - Antidotes:
 - Vitamin K
 - ◆ IV vitamin K acts more quickly than the oral route (6-12 hours vs. 18-24 hours)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

ATTENTION

Vitamin K should not be administered subcutaneously.

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, bivalirudin and lepirudin 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

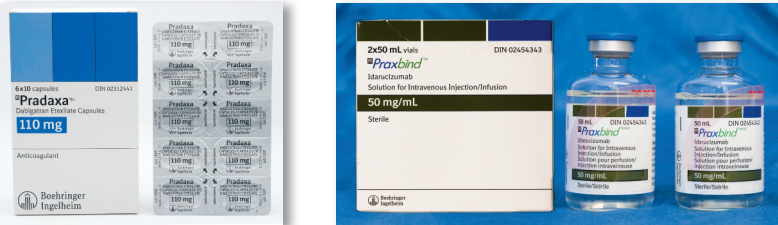
ATTENTION

Dabigatran is contraindicated in patients with CrCl < 30 mL / minute.

DRUG (dose regimen)	RENAL FUNCTION	MINOR PROCEDURES	MODERATE RISK SURGERY (12-25% residual anticoagulant effect acceptable)	MAJOR SURGERY INCLUDING NEURAXIAL PROCEDURE (<10% residual drug effect acceptable)
Dabigatran BID	CrCl ≥50 mL / min	Last dose day -1	Last dose day -2	Last dose day -3
Dabigatran BID	CrCl 30-49 mL / min	Last dose day -1	Last dose day -3	Last dose day -5

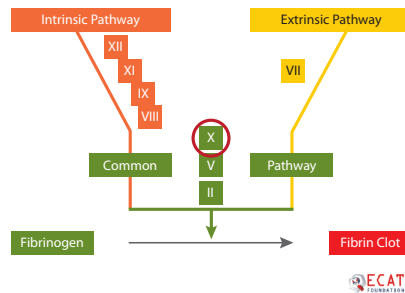
Direct Thrombin Inhibitors (continued)

- ▲ 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 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.



ATTENTION

Rivaroxaban, apixaban and edoxaban are contraindicated in patients with CrCl < 30 mL / minute.

- ▲ 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	MINOR PROCEDURES	MODERATE RISK SURGERY (12-25% residual anticoagulant effect acceptable)	MAJOR SURGERY INCLUDING NEURAXIAL PROCEDURE (<10% residual drug effect acceptable)
Rivaroxaban OD	CrCl ≥30 mL / min	Last dose day -1	Last dose day -2	Last dose day -3
Apixaban BID	CrCl ≥30 mL / min	Last dose day -1	Last dose day -2	Last dose day -3
Edoxaban OD	CrCl ≥30 mL / min	Last dose day -1	Last dose day -2	Last dose day -3

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



Prolonged PT / INR with normal APTT

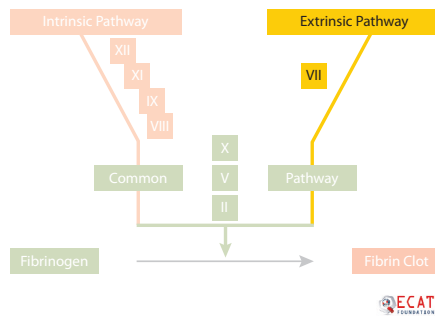
If the PT / INR is prolonged but the APTT is not, the probable cause is related to Factor VII (FVII).

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 mix. This test is performed by combining 1 part patient plasma with 1 part normal plasma. A PT is performed on the 50:50 mix.
- ▲ 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 is likely due to an inhibitor. A partial correction may represent multiple factor deficiencies or an inhibitor.

**Prolonged APTT with normal PT / INR**

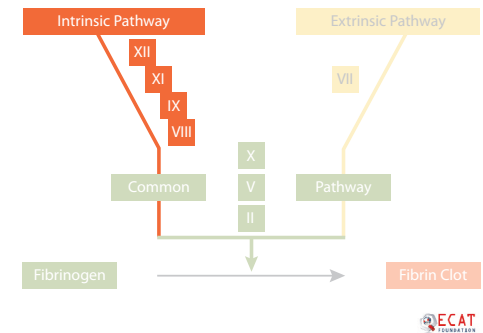
If the APTT is prolonged but the PT / INR is not, the probable cause is related to the intrinsic pathway – either Factors VIII, IX, XI or the contact factors (Factor XII, Prekallikrein or High Molecular Weight Kininogen).

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 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)

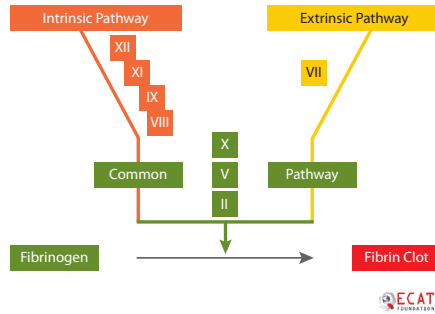
To distinguish between factor deficiency and inhibitor

- ▲ Perform an immediate 50:50 mix. This test is performed by combining 1 part patient's sample with 1 part normal plasma. Run an APTT on the 50:50 mix.
- ▲ If the APTT prolongation corrects on mixing it is likely due to a factor deficiency (due to replacement of factor(s) from the normal plasma). If it does not correct the prolongation 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?

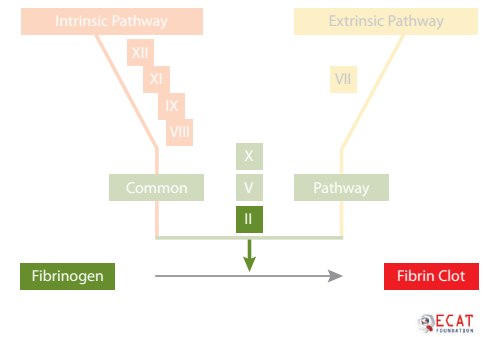
- ▲ Congenital deficiency of Factors X, V, II or fibrinogen – usually a single factor deficiency.
 - Deficiencies of Factors X, V, II or fibrinogen may be associated with bleeding depending on the severity of the phenotype
- ▲ Acquired causes.
 - Non-specific inhibitors - drugs (e.g., excessive doses 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)

As previously discussed, an immediate 50:50 mix 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?

- ▲ Congenital deficiency of fibrinogen (hypofibrinogenemia or afibrinogenemia) or a qualitative abnormality (dysfibrinogenemia).
- ▲ 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

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.
- ▲ 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
 - Treatments / interventions required to stop bleeding – local pressure, cauterization / 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

ATTENTION

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

- ▲ 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 condensed MCMDM-1 VWD bleeding questionnaire for von Willebrand disease and platelet function disorders.
- ▲ The condensed MCMDM-1 may be useful in the prediction of operative bleeding, however prospective, peri-operative validation studies have not been done.

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 purpura)
- Bone marrow disorders
- Acquired coagulation factor deficiencies (Factor VIII, von Willebrand Factor)
- Cushing’s syndrome

Medications are the most common acquired cause of bleeding.

A T T E N T I O N

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.

A T T E N T I O N

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 Condensed MCMDM-1 VWD Bleeding Questionnaire 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.

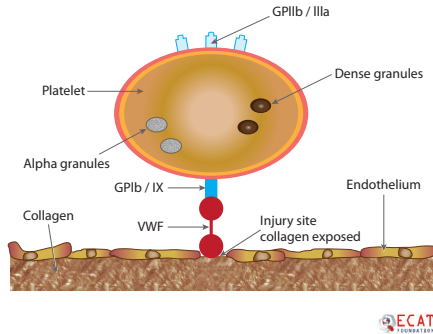
CLINICAL SITUATION	-1	0	1	2	3	4	
Epistaxis		No or trivial (≤ 5 per year)	> 5 per year or more than 10 minutes		Consultation only	Packing or cauterization or antifibrinolytic	Blood transfusion or replacement therapy or desmopressin
Cutaneous		No or trivial (≤ 1 cm)	> 1 cm and no trauma		Consultation only		
Bleeding from minor wounds		No or trivial (≤ 5 per year)	> 5 per year or more than 5 minutes		Consultation only	Surgical hemostasis	Blood transfusion or replacement therapy or desmopressin
Oral cavity		No	Reported, no consultation		Consultation only	Surgical hemostasis or antifibrinolytic	Blood transfusion or replacement therapy or desmopressin
Gastrointestinal bleeding		No	Associated with ulcer, portal hypertension, hemorrhoids, angiodysplasia		Spontaneous	Surgical hemostasis, blood transfusion, replacement therapy, desmopressin, antifibrinolytic	
Tooth extraction	No bleeding in at least 2 extractions	None done or no bleeding in 1 extraction	Reported, no consultation		Consultation only	Resuturing or packing	Blood transfusion or replacement therapy or desmopressin
Surgery	No bleeding in at least 2 surgeries	None done or no bleeding in 1 surgery	Reported, no consultation		Consultation only	Surgical hemostasis or antifibrinolytic	Blood transfusion or replacement therapy or desmopressin
Menorrhagia		No	Consultation only		Antifibrinolytics, oral contraceptive pill use	Dilation & curettage, iron therapy, ablation	Blood transfusion or replacement therapy or desmopressin
Postpartum hemorrhage	No bleeding in at least 2 deliveries	None done or no bleeding in 1 delivery	Consultation only		Dilation & curettage, iron therapy, antifibrinolytics	Blood transfusion or replacement therapy or desmopressin	Hysterectomy
Muscle hematomas		Never	Post trauma, no therapy		Spontaneous, no therapy	Spontaneous or traumatic, requiring desmopressin or replacement therapy	Spontaneous or traumatic, requiring surgical intervention or blood transfusion
Hemarthrosis		Never	Post trauma, no therapy		Spontaneous, no therapy	Spontaneous or traumatic, requiring desmopressin or replacement therapy	Spontaneous or traumatic, requiring surgical intervention or blood transfusion
Central nervous system bleeding		Never				Subdural, any intervention	Intracerebral, any intervention

Other

- ▲ For VWD, a bleeding score ≥ 4 has a sensitivity = 100%, specificity = 87%, positive predictive value (PPV) = 20%, negative predictive value (NPV) = 100%. (Bowman, 2008)
- ▲ For PFD, a bleeding score ≥ 4 has a sensitivity = 86%, specificity = 65%, PPV = 50% and NPV = 92%. (James, 2011)

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).
- ▲ 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 – including IM injections, arterial punctures, contact sports
 - Avoid 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 he / she has 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 for mucosal bleeding
 - If VWF / Factor VIII concentrate indicated, consult product monograph for dosing

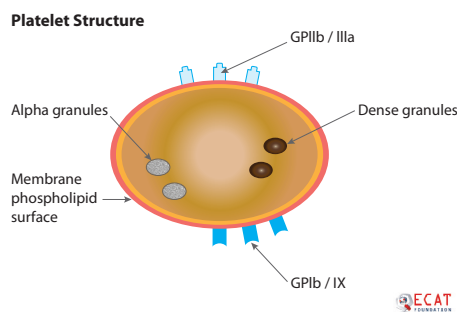
Disorders of Platelet Function

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.



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.

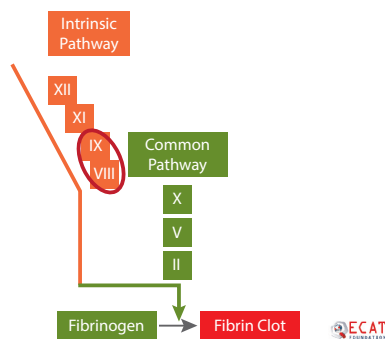
Management

- ▲ Depends on the particular disorder and on the severity of bleeding.
- ▲ Prevent bleeding.
 - Avoid trauma – including IM injections, arterial punctures, contact sports
 - Avoid 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 he / she has 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 for mucosal bleeding
 - Platelet transfusion
 - In cases of life-threatening bleeding, recombinant factor VIIa (Niasase) 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	CLOTING 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 – including IM injections, arterial punctures, contact sports
 - Avoid 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
- ▲ 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 he / she has 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 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

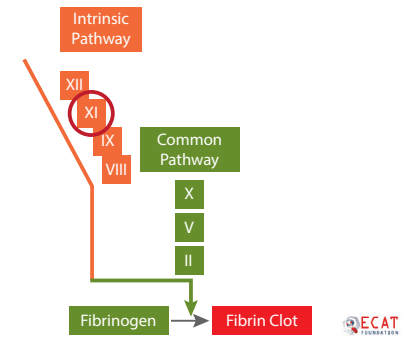
- ▲ Inherited deficiency of Factor XI.
- ▲ Autosomal recessive inheritance.
 - Prevalent in Ashkenazi Jewish population

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 – including IM injections, arterial punctures, contact sports
 - Avoid 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 he / she has a wallet card that dictates therapy
 - Treatment options:
 - Plasma derived Factor XI concentrate
 - If Factor XI concentrate not available, frozen plasma
 - Tranexamic acid (Cyclokapron) 25 mg / kg po 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)

Key References

Chapter 1: The Basics of Coagulation and Clot Breakdown

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

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

Luchtman-Jones L, Broze GJ. The Current Status of Coagulation. *Annals of Medicine* 1995;27:47-52.

Chapter 2: Routine Coagulation Tests

CLSI. One-Stage Prothrombin Time (PT) Test and Activated Partial Thromboplastin Time (APTT) Test; Approved Guideline—Second Edition. CLSI document H47-A2. Wayne, PA: Clinical and Laboratory Standards Institute; 2008.

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.

Kitchen S, McCraw A, Echenagucia M. *Diagnosis of Hemophilia and Other Bleeding Disorders. A laboratory manual*. 2nd ed.

Montreal: World Federation of Hemophilia; 2008. Available at <http://www1.wfh.org/publication/files/pdf-1283.pdf>. Accessed 25 Feb 2013.

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.

Tripodi A. D-dimer testing in laboratory practice. *Clin Chem* 2011 Sep;57 (9):1256-62.

Wells PS. The role of qualitative D-dimer assays, clinical probability, and noninvasive imaging tests for the diagnosis of deep vein thrombosis and pulmonary embolism. *Semin Vasc Med* 2005 Nov;5 (4):340-50.

Chapter 3: Anticoagulant Drugs

Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012 Feb;141(2 Suppl):e445-885

Douketis JD, Spyropoulos AC, Spencer FA, Mayr M, Jaffer AK, Eckman MH, Dunn AS, Kunz R. Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012 Feb;141(2 Suppl):e3265-505

Elmer J, Wittels KA. Emergency reversal of pentasaccharide anticoagulants: a systematic review of the literature. *Transfusion Med* 2012 Apr;22(2):108-15.

Garcia DA, Baglin TP, Weitz JJ, Samama MM; American College of Chest Physicians. Parenteral Anticoagulants. *Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines*. *Chest* 2012 Feb;141(2 Suppl):e245-435.

Majeed A, Agren A, Holmstrom M, Bruzelius M, Chairati R, Odeberg J, Hempel E, Magnusson M, Frisk T, & Schulman S. (2017). Management of rivaroxaban- or apixaban-associated major bleeding with prothrombin complex concentrates: a cohort study. *Blood*, 130(15), 1706-1712.

National Advisory Committee on Blood and Blood Products. Recommendations for the use of prothrombin complex concentrates in Canada. 2011. Available at <http://www.nacblood.ca/resources/guidelines/PCC.html>. Accessed 25 Feb 2013.

Key References (continued)

Schulman S, Crowther MA. How I treat with anticoagulants in 2012: new and old anticoagulants, and when and how to switch. *Blood* 2012 Mar 29;119(13):3016-23.

Spyropoulos AC, Douketis JD. How I treat anticoagulated patients undergoing an elective procedure or surgery. *Blood* 2012;120:2954-62.

Thrombosis Canada. (2018). Clinical Guide. NOACs/DOACs: Peri-operative management, 1–7. <http://thrombosiscanada.ca/wp-content/uploads/2018/05/NOACs-DOACs-Perioperative-Management-2018May17.pdf>

Useful Website:

Thrombosis Canada. Available from: <https://thrombosiscanada.ca/>

Chapter 4: Evaluating Abnormal Coagulation Tests

Lippi G, Pasalic L, Favalaro 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.

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

Chapter 5: Approach to the Evaluation of the Bleeding Patient

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.

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

American Society of Hematology. Clinical Practice Guideline on the Evaluation and Management of von Willebrand Disease (VWD). Quick Reference Guide, 2012. Assessed November 27, 2018.

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.

Nichols WL, Hultin MB, James AH, Manco-Johnson MJ, Montgomery RR, Ortel TL, Rick ME, Sadler JE, Weinstein M, Yawn BP. von Willebrand disease (VWD): evidence-based diagnosis and management guidelines, the National Heart, Lung and Blood Institute (NHLBI) Expert Panel report (USA). *Hemophilia* 2008 Mar;14(2):171-232

Srivastava A, Brewer AK, Mauser-Bunschoten EP, Key NS, Kitchen S, Llinas A, Ludlam CA, Mahlangu JN, Mulder K, Poon MC, Street A; Treatment Guidelines Working Group on Behalf of The World Federation of Hemophilia. Guidelines for the management of hemophilia. *Haemophilia*. 2013 Jan;19(1):e1-47.

World Federation of Hemophilia. Guidelines for the Management of Hemophilia (2nd Edition), 2012. Available at <https://www1.wfh.org/publication/files/pdf-1472.pdf>. Accessed November 27, 2018.

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

To order this resource, please visit the **Transfusion Ontario** website:
www.transfusionontario.org