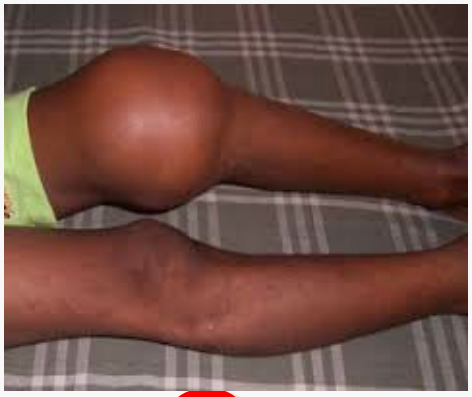
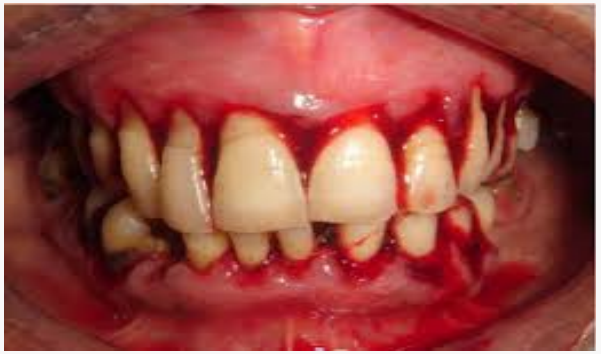
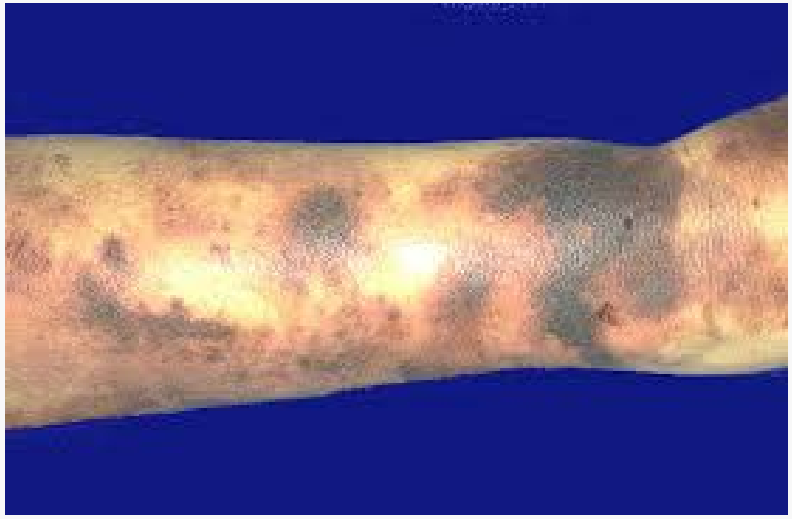




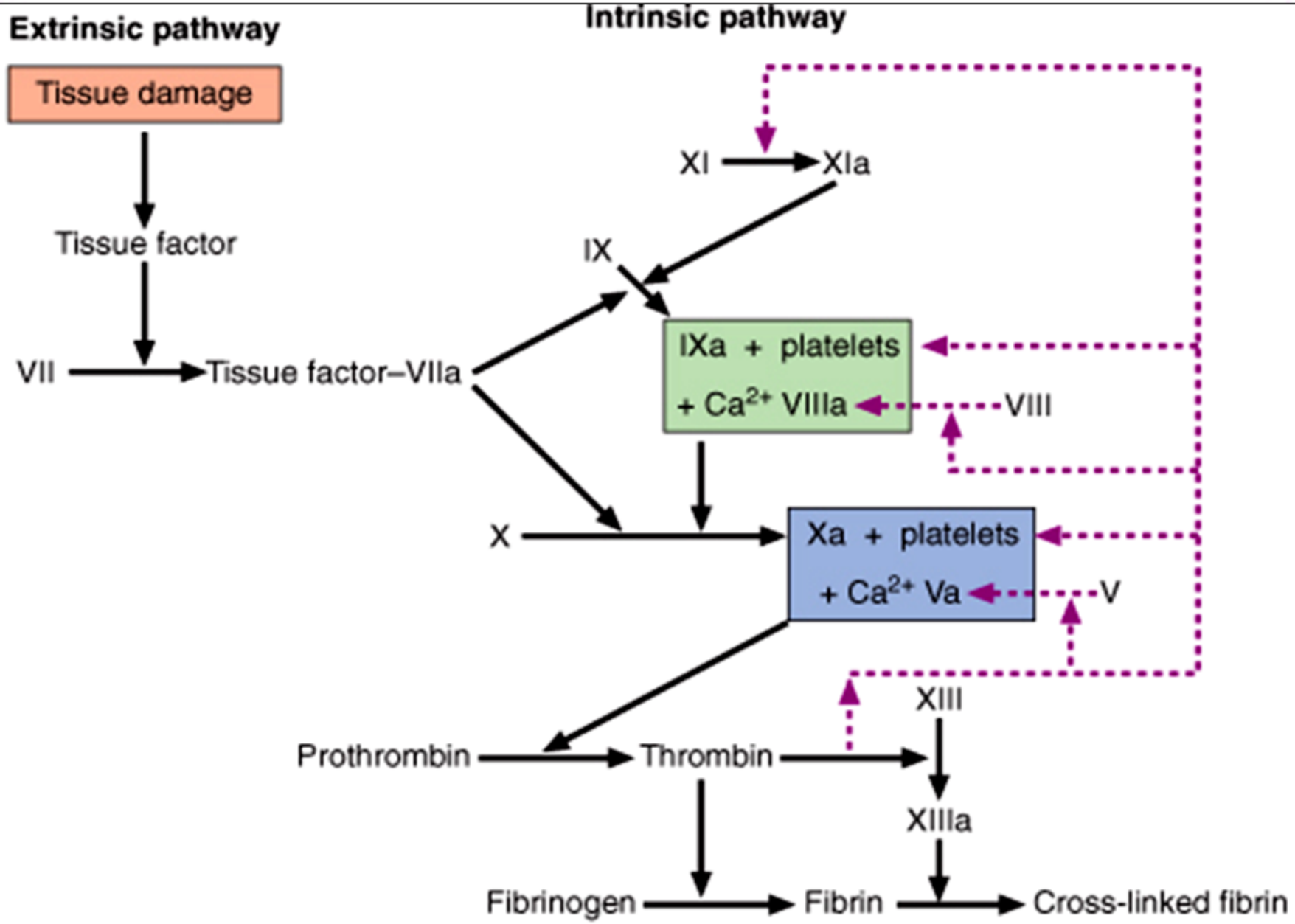
Coagulation disorders

Dr. Mousa Qasim Hussein
Professor Internal Medicine



Factor	Name	Pathway
I	Fibrinogen	Both
II	Prothrombin	Both
III	Tissue Factor	Extrinsic
IV	Calcium	Both
V	Proaccelerin	Both
VI	Accelerin	Both
VII	Proconvertin	Extrinsic
VIII	Antihemophiliac	Intrinsic
IX	Christmas Factor	Intrinsic
X	Stuart-Prower Factor	Both
XI	Plasmathromboplastin antecedent (PTA)	Intrinsic
XII	Hageman Factor	Intrinsic
XIII	Protransglutaminase	Both

Clotting factors:



Coagulation factor deficiency may be congenital or acquired and may affect one or several of the coagulation factors .

Inherited disorders are almost uniformly related to decreased synthesis, as a result of mutation in the gene encoding a key protein in coagulation.

Von Willebrand disease is the most common inherited bleeding disorder.

Hemophilia A and B are the most common single coagulation factor deficiencies, but deficiencies of all the other coagulation factors are seen

Causes of coagulopathy

1-Congenital

X-linked

- Hemophilia A and B

Autosomal

- Von Willebrand disease
- Factor II, V, VII, X, XI and XIII deficiencies
- Combined II, VII, IX and X deficiency
- Combined V and VIII deficiency
- Hypofibrinogenaemia
- Dysfibrinogenaemia

Acquired disorders may be due to:

Under-production

- Liver failure
- Vitamin K deficiency

Increased consumption

- Coagulation activation:

Disseminated intravascular coagulation (DIC)

- Immune-mediated:

Acquired Hemophilia and von Willebrand disease

- Others:

Acquired factor X deficiency (in amyloid)
Acquired von Willebrnd disease in Wilms' tumour
Acquired factor VII deficiency in sepsis

Drug-induced

- **Inhibition of function:**

Heparins
Argatroban
Bivalirudin
Fondaparinux
Rivaroxaban
Apixaban
Dabigatran
Edoxaban

- **Inhibition of post-translational modification:**

Warfarin

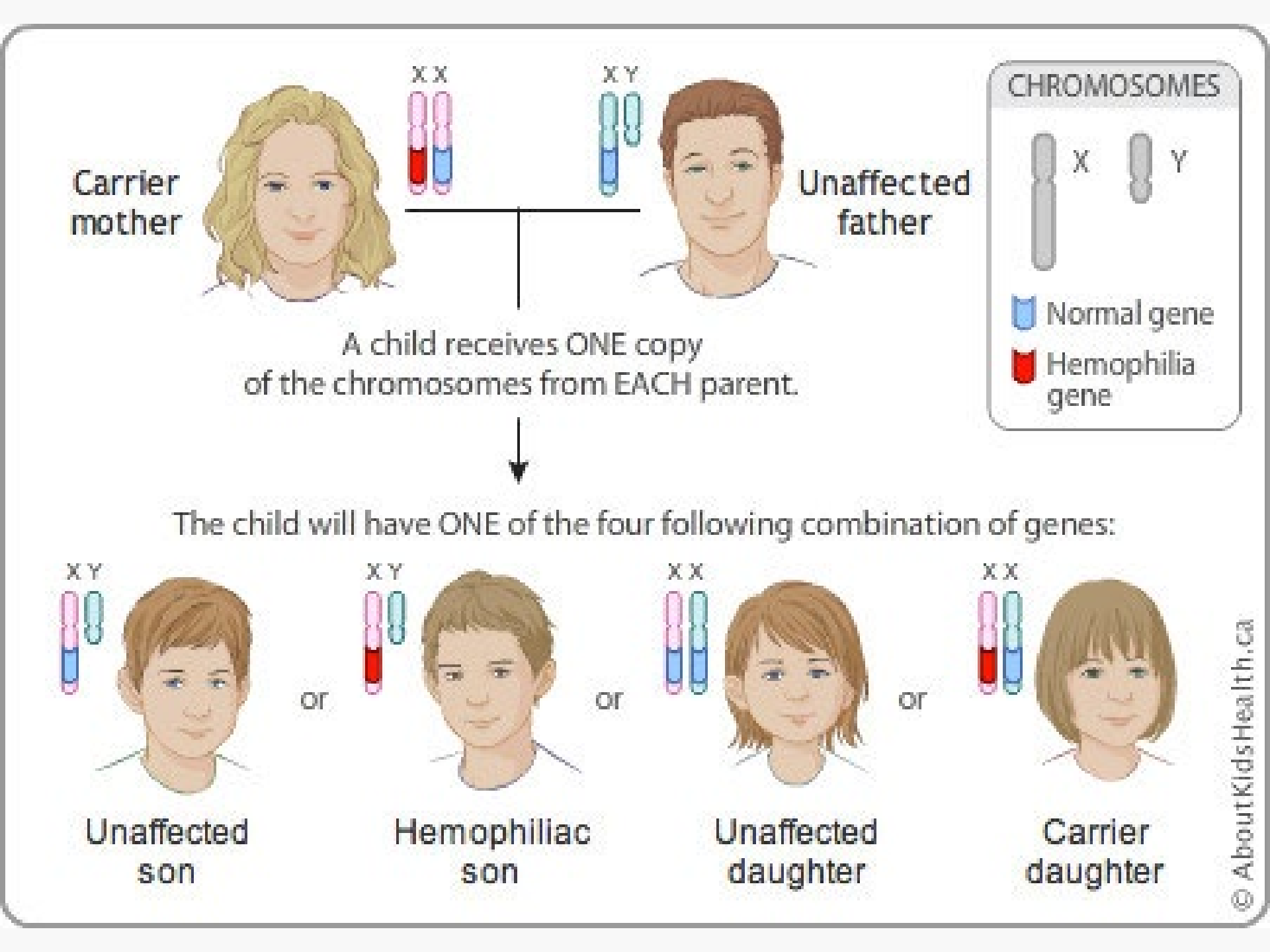
Hemophilia A

FVIII deficiency resulting in Hemophilia A affects 1/10 000 individuals.
Most common congenital coagulation factor deficiency. FVIII is primarily synthesised by the liver and endothelial cells, and has a half-life of about 12 hours.
It is protected from proteolysis in the circulation by binding to von Willebrand factor (vWF).

Genetics

hemophilia A is a sex-linked disorder, thus all daughters of hemophiliacs are obligate carriers and they, in turn, have a 1 in 4 chance of each pregnancy resulting in the birth of an affected male baby, a normal male baby, a carrier female or a normal female.

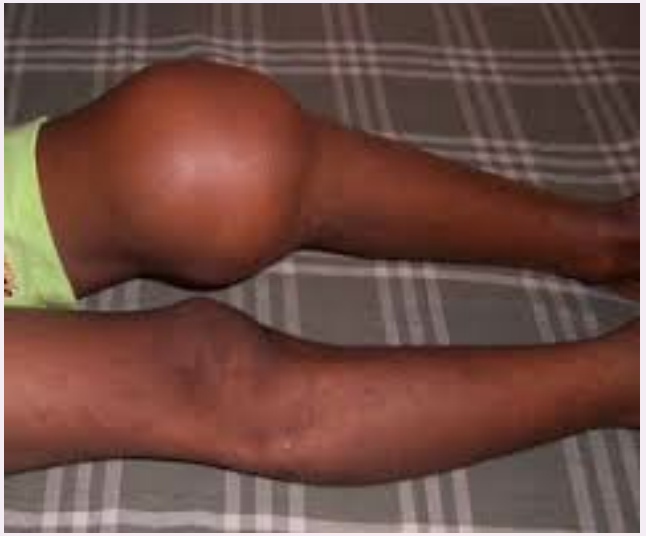
Antenatal Diagnosis by chorionic villous sampling is possible in families with a known mutation.


Carrier mother
X X
X Y
Unaffected father
CHROMOSOMES
X
Y
Normal gene
Hemophilia gene
A child receives ONE copy of the chromosomes from EACH parent.
The child will have ONE of the four following combination of genes:
X Y
or
X Y
or
X X
or
X X
Unaffected son
Hemophiliac son
Unaffected daughter
Carrier daughter
© AboutKidsHealth.ca

Clinical features:

1- Bleeding

The extent and patterns of bleeding are closely related to residual FVIII levels. Patients with severe Hemophilia (< 1% of normal FVIII levels) present with spontaneous bleeding into skin, muscle and joints. Retroperitoneal and intracranial bleeding is also a feature.



Babies with severe Hemophilia have increased risk of intracranial hemorrhage and, although there is insufficient evidence to recommend routine caesarean section for these births, it is appropriate to avoid head trauma and to perform imaging of newborn within the first 24 hours of life.

Individuals with moderate and mild Hemophilia (FVIII levels 1-40%) present with the same pattern of bleeding, but usually after trauma or surgery when bleeding is greater than would be expected from the severity of the insult.

The major morbidity of recurrent bleeding in severe Hemophilia is musculoskeletal.

Bleeding is typically into large joints, especially knees, elbows, ankles and hips.

Recurrent bleeding into joints leads to synovial hypertrophy, destruction of the cartilage and chronic haemophilic arthropathy.

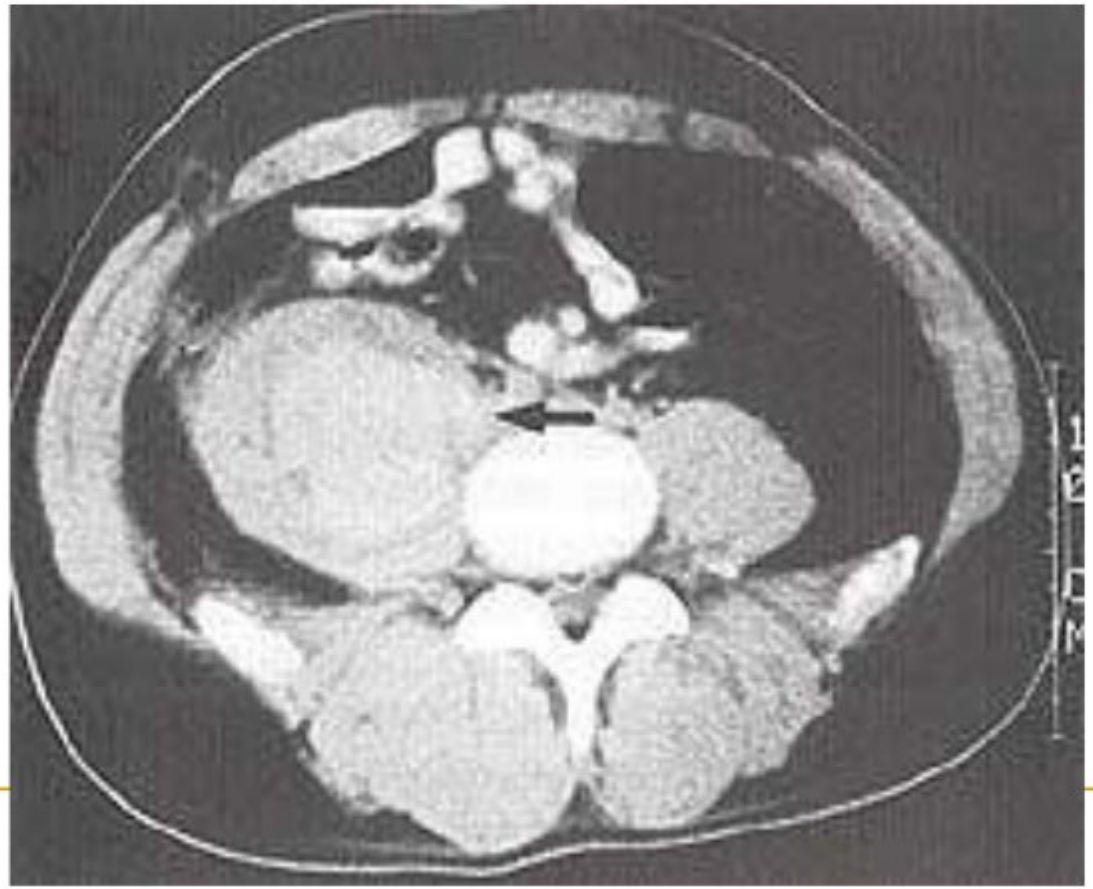
2- Muscle haematomas:

are also characteristic, most commonly in the calf and psoas muscles. If early treatment is not given to arrest bleeding, a hot, swollen and very painful joint or muscle haematoma develops.

Complications of muscle haematoma depend on their location.

1. A large psoas bleed may extend to compress the femoral nerve.
2. Calf haematomas may increase pressure within inflexible fascial sheath causing a compartment syndrome with ischaemia, necrosis, fibrosis, and subsequent contraction and shortening of Achilles tendon.

CT scan showing large hematoma of right psoas muscle



Severity of haemophilia (ISTH criteria)

Severity	Factor VIII or IX level	Clinical presentation
Severe	< 0.01 U/mL	Spontaneous haemarthroses and muscle haematomas
Moderate	0.01–0.05 U/mL	Mild trauma or surgery causes bleeding
Mild	> 0.05 to 0.4 U/mL	Major injury or surgery results in excess bleeding

(ISTH = International Society on Thrombosis and Haemostasis)

Diagnosis includes screening tests and clotting factor tests.

1-Screening tests are blood tests that show if the blood is clotting properly.

2-Clotting factor tests, also called factor assays, are required to diagnose a bleeding disorder. This blood test shows the type of hemophilia and the severity.

Screening Tests

Activated Partial Thromboplastin Time (APTT) Test

This test measures how long it takes for blood to clot. It measures the clotting ability of factors VIII (8), IX (9), XI (11), and XII (12). If any of these clotting factors are too low, it takes longer than normal for the blood to clot. The results of this test will show a longer clotting time among people with hemophilia A or B.

Prothrombin Time (PT) Test

This test also measures the time it takes for blood to clot. It measures primarily the clotting ability of factors I (1), II (2), V (5), VII (7), and X (10). If any of these factors are too low, it takes longer than normal for the blood to clot. The results of this test will be normal among most people with hemophilia A and B.

Management

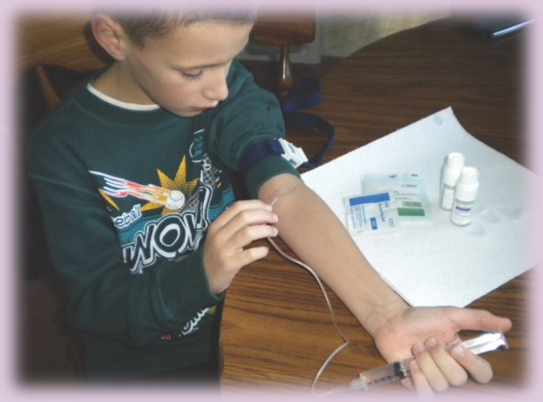
The aim of management of severe haemophilia A (and B) in high-income countries is to render patients ‘bleed free’. This can be achieved by prophylaxis using coagulation factor concentrates or, in haemophilia A, by a bispecific monoclonal antibody called emicizumab that mimics factor VIII activity.

Emicizumab binds to both activated factor IX and factor X to allow the formation of the tenase complex that results in thrombin and clot formation .

Prophylaxis using concentrates aims to achieve trough levels of factor VIII or IX that protect the patient against spontaneous bleeding. There is debate about optimal trough values needed to achieve this aim.

Prophylaxis can be provided in many different ways: daily, on alternate days, or on information from pharmacokinetic studies that inform on the best way of scheduling prophylaxis.

Practice in haemophilia A and B is also changing due to the introduction of recombinant factor concentrates that have been manipulated to alter their half-life.



In addition to standard half-life recombinant factor VIII and IX, there are new products produced by Fc fusion and pegylation/ glycopegylation that extend the half-life of the coagulation factor to the degree that it can be used to alter dosing schedules for prophylaxis.

The alternative approach, which still needs to be used in low- and middle-income countries, is to treat on demand.

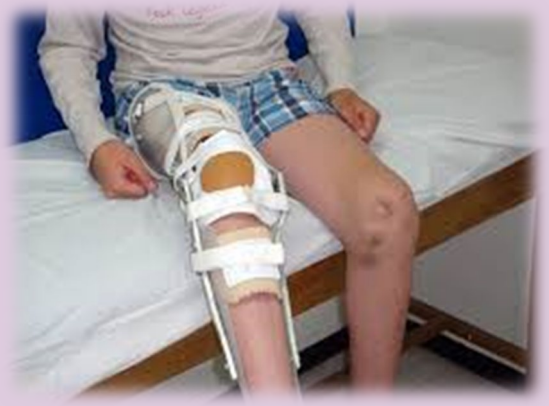
In severe haemophilia A, bleeding episodes should be treated by raising the factor VIII level, usually by intravenous infusion of factor VIII concentrate.

Factor VIII concentrates are freeze-dried and stable at 4°C and can therefore be stored in domestic refrigerators, allowing patients to treat themselves at home at the earliest indication of bleeding. Coagulation factor concentrates prepared from blood donor plasma are now screened for many blood-borne pathogens including HBV, HCV and HIV, and undergo two separate virus inactivation or removal processes during manufacture; these preparations have a good safety record.

However, factor concentrates prepared by recombinant technology are now widely available and, although more expensive, are perceived as being safer than those derived from human plasma in relation to infection risk.

In addition to raising FVIII concentrations, resting of the bleeding site with either bed rest or a splint reduces continuing haemorrhage. Once bleeding has settled, the patient should be mobilised and physiotherapy used to restore strength to the surrounding muscles.

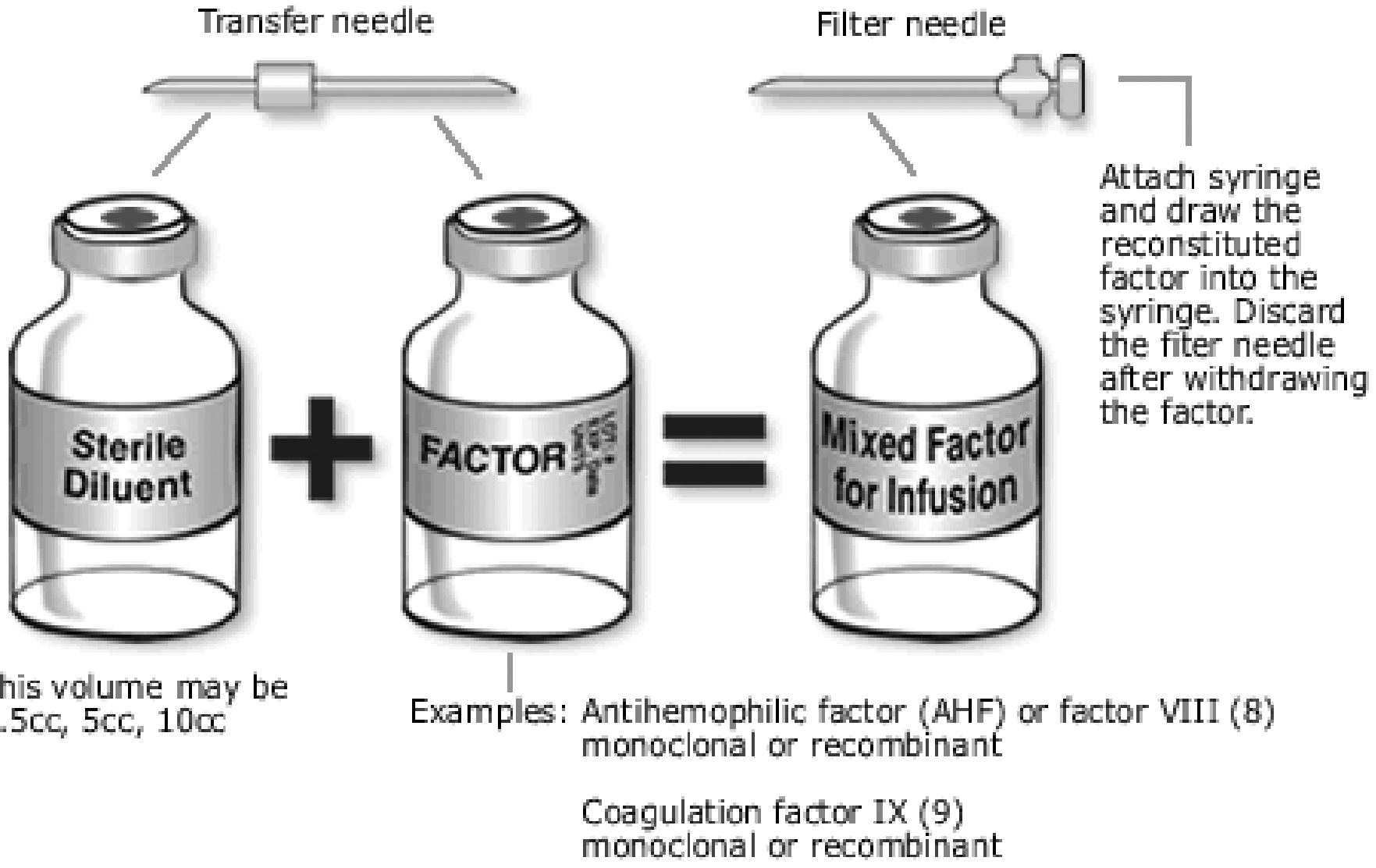
All non-immune potential recipient of pooled blood products should be offered hepatitis A and B immunization.



Vasopressin receptor agonist **desmopressin** raises the vWF and FVIII levels 3–4-fold, which is useful in arresting bleeding in mild or moderate Hemophilia A.
The dose required for this purpose is higher than that used in diabetes insipidus, usually 0.3 μg/kg, and is given IV or SC. Alternatively, the same effect can be achieved by intranasal administration of 300 μg.

Following repeated administration of desmopressin, patients need to be monitored for evidence of water retention, which can result in significant hyponatraemia. Desmopressin is contraindicated in patients with History of severe arterial disease because of a propensity to provoke a thrombotic event, and in young children where hyponatraemia can result in fits.


250 IU
Kogenate FS
octocog alfa (bhk)
(Recombinant Factor VIII)
Powder for injection
Formulated with Sucrose
with BIO-SET®
Kogenate FS vial contains 250 IU octocog alfa (bhk)
For intravenous use only
Needleless
Reconstitution
Set
Injection for the
treatment of
Haemophilia A
2.5 mL
Schering Pharma
Kogenate FS
Time
infused


Transfer needle
Filter needle
Attach syringe and draw the reconstituted factor into the syringe. Discard the fiter needle after withdrawing the factor.
Sterile Diluent
FACTOR
Mixed Factor for Infusion
This volume may be 2.5cc, 5cc, 10cc
Examples: Antihemophilic factor (AHF) or factor VIII (8) monoclonal or recombinant
Coagulation factor IX (9) monoclonal or recombinant

However, for practical purposes, the dose of FVIII is based on the knowledge that 1 U of FVIII per kilogram of body weight raises the circulating FVIII level approximately 0.02 U/mL.
Thus, to raise the FVIII level to 100 percent, that is, 1 U/mL, dose of FVIII required is approximately 50 U per kilogram of body weight, assuming the patient's baseline FVIII level is less than 1 percent of normal.
The site and severity of hemorrhage determine the frequency and dose of FVIII to be infused.

Complications of coagulation factor therapy

1-Infections

Before 1986, coagulation factor concentrates from human plasma were not fully virus-inactivated and many patients became infected with HIV and HBV/HCV. Concern that the infectious agent that causes variant Creutzfeldt–Jakob disease (vCJD) might be transmissible by blood and blood products has been confirmed in recipients of red cell transfusion , and in one recipient of factor VIII.

2- The development of anti-FVIII antibodies:

serious complication arise in about 20% of those with severe haemophilia.

Such abs rapidly neutralise therapeutic infusions, making treatment relatively ineffective.

Infusions of activated clotting factors, e.g. VIIa or FVIII inhibitor bypass activity (FEIBA), may stop bleeding.

Emicizumab has a major role in the treatment of patients with haemophilia A who have developed inhibitory antibodies.

Haemophilia B (Christmas disease)

Aberrations of the factor IX gene, which is also present on the X chromosome, result in a reduction of the plasma factor IX level, giving rise to haemophilia B. This disorder is clinically indistinguishable from haemophilia A, but is less common. The frequency of bleeding episodes is related to the severity of the deficiency of the plasma factor IX level.

Treatment is with a factor IX concentrate, used in much the same way as factor VIII for haemophilia A. The new extended half-life recombinant factor IX products made by Fc fusion, albumin fusion and pegylation offer the possibility of prophylaxis on a once-weekly or even two-weekly schedule. Although factor IX concentrates shared the problems of virus transmission seen with factor VIII, they do not commonly induce inhibitory antibodies (<1% patients); when this does occur, however, it may be heralded by the development of a severe allergic-type reaction.

Von Willebrand disease

Von Willebrand disease is a common but usually mild bleeding disorder caused by a quantitative (types 1 and 3) or qualitative (type 2) deficiency of vWF, a protein synthesised by endothelial cells and megakaryocytes, which is involved in both platelet function and coagulation.

It normally forms multimeric structure which is essential for its interaction with subendothelial collagen and platelets.
vWF acts as a carrier protein for FVIII, to which it is non-covalently bound; deficiency of vWF lowers the plasma FVIII level.

vWF also forms bridges between platelets and subendothelial components (e.g. collagen, allowing platelets to adhere to damaged vessel walls; deficiency of vWF therefore leads to impaired platelet plug formation.

Most patients with von Willebrand disease have a type 1 disorder, characterised by a quantitative decrease in a normal functional protein.

Patients with type 2 disorders inherit vWF molecules that are functionally abnormal.

Blood group antigens (A and B) are expressed on vWF, reducing its susceptibility to proteolysis; as a result, people with blood group O have lower circulating vWF levels than individuals with non-O groups.

Type of abnormality depends on site of mutation in the *vWD gene and how it* affects binding to platelets, collagen and FVIII.

1. Patients with type 2A disease have abnormalities in vWF-dependent platelet adhesion.
2. Those with mutations in the platelet glycoprotein Ib binding site, resulting in increased affinity for glycoprotein 1b, have type 2B disease.
3. Those with mutations in the FVIII binding site have type 2N disease.
4. Those with other abnormalities in platelet binding but with normal vWF multimeric structurehave type 2M disease.

Gene for vWF is located on chromosome 12 and disease is usually inherited as an autosomal dominant, except in cases of type 2N and type 3, when it is recessive.

Classification of von Willebrand disease

Type	Defect	Inheritance	Investigations
1	Partial quantitative	AD	Parallel decrease in vWF: Ag and VIII:c
2A	Qualitative	AD	Absent HWM of vWF Ratio of vWF activity to antigen < 0.7
2B	Qualitative	AD	Reduced HWM of vWF Enhanced platelet agglutination (RIPA)
2M	Qualitative	AD	Normal multimers of vWF Abnormal platelets Interactions
2N	Qualitative	AR	Defective binding of vWF to VIII Low VIII
3	Severe quantitative	AR or CH	Very low vWF activity and VIII:c Absent multimers

(AD = autosomal dominant; AR = autosomal recessive; CH = compound heterozygote; HWM = high-weight multimers of vWF; RIPA = ristocetin-induced platelet agglutination; VIII:c = coagulation factor VIII activity in functional assay; vWF = von Willebrand factor; vWF:Ag = vWF antigen measured by ELISA)

Clinical features

Patients present with haemorrhagic manifestation Similar to those in individuals with reduced Platelet function
Superficial bruising, epistaxis, menorrhagia and GI hemorrhage are common .
Bleeding episodes much less common than in sever hemophilia and excessive hemorrhage may only be observed after trauma or surgery.
Within a single family the disease can be of very variable expression so that some members may have quite sever and frequent bleeds, whereas others are relatively Asymptomatic .

Investigations

The disorder is characterised by reduced activity of vWF and FVIII.

The disease can be classified using a combination of assays which include

1. Functional and antigenic measures of vWF,
2. Multimeric analysis of the protein,
3. Specific tests of function to determine Binding to platelet glycoprotein Ib (RIPA) and FVIII.

4-Analysis for mutations in the vWF gene is informative in most cases

Management

Many episodes of mild haemorrhage can be successfully treated by local means or with desmopressin, which raises the vWF level, resulting in a secondary increase in factor VIII.

Tranexamic acid may be useful in mucosal bleeding. For more serious orpersistent bleeds, haemostasis can be achieved with selected factor VIII concentrates, which contain considerable quantities of vWF in addition to factor VIII.

Young children and patients with severe arterial disease should not receive desmopressin, and patients with type 2B disease develop thrombocytopenia that may be troublesome following desmopressin. Bleeding in type 3 patients responds only to factor VIII/vWF concentrate.

ACQUIRED BLEEDING DISORDERS

Disseminated intravascular coagulation (DIC)

DIC may complicate a range of illnesses.
Characterised by systemic activation of the pathways involved in coagulation and its regulation.
This may result in generation of intravascular fibrin clots causing organ failure, with simultaneous coagulation factor and platelet consumption causing bleeding.

Systemic coagulation activation is induced either through

1- Cytokine pathways which are activated as part of a systemic inflammatory response.

or by

2- Release of procoagulant substances such as tissue factor.

In addition

3- Suboptimal function of the natural anticoagulant pathways and dysregulated fibrinolysis contribute to DIC.

.

There is consumption of platelets, coagulation factors (notably factors V and VIII) and fibrinogen.

The lysis of fibrin clot results in production of fibrin degradation products (FDP), including D-dimers

Underlying conditions

-Infection/sepsis
-Trauma
-Obstetric, e.g. amniotic fluid embolism, placental abruption, pre-eclampsia
-Severe liver failure
-Malignancy, e.g. solid tumours and leukaemias
-Tissue destruction, e.g. pancreatitis, burns
-Vascular abnormalities, e.g. vascular aneurysms, liver haemangiomas
-Toxic/immunological, e.g. ABO incompatibility, snake bites, recreational drugs

ISTH scoring system for diagnosis of DIC	
Presence of an associated disorder	Essential
Platelets	> 100 = 0 < 100 = 1 < 50 = 2
Elevated fibrin degradation products	No increase = 0 Moderate = 2 Strong = 3
Prolonged prothrombin time	< 3 sec = 0 > 3 sec but < 6 sec = 1 > 6 sec = 2
Fibrinogen	> 1 g/L = 0 < 1 g/L = 1
Total score	
≥ 5 = Compatible with overt DIC	
< 5 = Repeat monitoring over 1–2 days	

(ISTH = International Society for Thrombosis and Haemostasis)

Clinical features

The clinical manifestations are determined by the nature, intensity and duration of the stimulus.
Low grade DIC is often asymptomatic and diagnosed by laboratory abnormalities.
Bleeding is the most common clinical finding in acute un compensated DIC, which tend to be generalized in more sever cases.
Gangrene of digits or extremities, haemorrhagic necrosis of the skin or purpura fulminans also Might be a manifestation of DIC.

Investigations

Measurement of coagulation times (APTT and PT along with fibrinogen, platelet count and FDPs, helps in the assessment of prognosis and aids clinical decision-making with regard to both bleeding and thrombotic complications.

Management

Therapy is primarily aimed at the underlying cause. These patients will often require intensive care to deal with concomitant issues, such as acidosis, dehydration, renal failure and hypoxia.

Blood component therapy, such as fresh frozen plasma, cryoprecipitate and platelets, should be given if the patient is bleeding or to cover interventions with high bleeding risk, but should not be given routinely based on coagulation tests and platelet counts alone.

- Prophylactic doses of heparin should be given, unless there is a clear contraindication.
- Established thrombosis should be treated cautiously with therapeutic doses of unfractionated heparin, unless clearly contraindicated.

Established thrombosis should be treated cautiously with therapeutic doses of unfractionated heparin, unless clearly contraindicated. Patients with DIC should not, in general, be treated with antifibrinolytic therapy, e.g. tranexamic acid.

Liver disease

Although, traditionally, severe parenchymal liver disease is associated with an excess of bleeding, it is now clear that these patients also have an increased risk of venous thrombosis.

Although there is reduced hepatic synthesis of procoagulant factors, this is balanced to a degree by the reduced production of natural anticoagulant proteins and reduced fibrinolytic activity in patients with advanced liver disease.
In severe parenchymal liver disease, bleeding may arise from many different causes.
Major bleeding, is often from structural abnormalities such as oesophageal varices or peptic ulcer, and sepsis and volume overload are common precipitants of bleeding.

-There is reduced hepatic synthesis, for example, of factors V, VII, VIII, IX, X, XI, prothrombin and fibrinogen.
-Clearance of plasminogen activator is reduced.
Thrombocytopenia may occur secondary to hypersplenism in the presence of portal hypertension and due to reduced production and activity of thrombopoietin in advanced liver disease.
In cholestatic jaundice, there is reduced vitamin K absorption, leading to deficiency of factors II, VII, IX and X, but also of proteins C and S.
Treatment with plasma products or platelet transfusion should be reserved for acute bleeds or to cover interventional procedures such as liver biopsy.
Vitamin K deficiency can be readily corrected with parenteral administration of vitamin K.

Renal faiure

The severity of the hemorrhagic state in renal failure is proportional to the plasma urea concentration. Bleeding manifestations are of platelet type with GI Bleeding, being common.

Causes:

1. Anemia and mild thrombocytopenia.
2. Accumulation of low molecular waste products, normally excreted by the kidney, that inhibit platelet function.

Treatment

-is by dialysis to reduce the urea concentration.

-Rarely, in severe or persistent bleeding, platelet concentrate infusions and red cell transfusions are indicated.

-Increasing the concentration of vWF, either by cryoprecipitate or by desmopressin, may promote haemostasis. Patients with significant renal impairment have an increased risk of anticoagulant-related bleeding, particularly with drugs that are at least partially renally excreted.

Fresh frozen plasma

FFP(150-300ml): Dose15ml/kg.

Indications: replacement of coagulation factor deficiency.

Cryoprecipitate: (10-12 ml pck):

Contain fibrinogen (150-300 mg) and coagulation factors
(80-120u FvIII and VWF)

Indications:

Hypofibrinogaemia, VW disease and haemophilia

Thank you