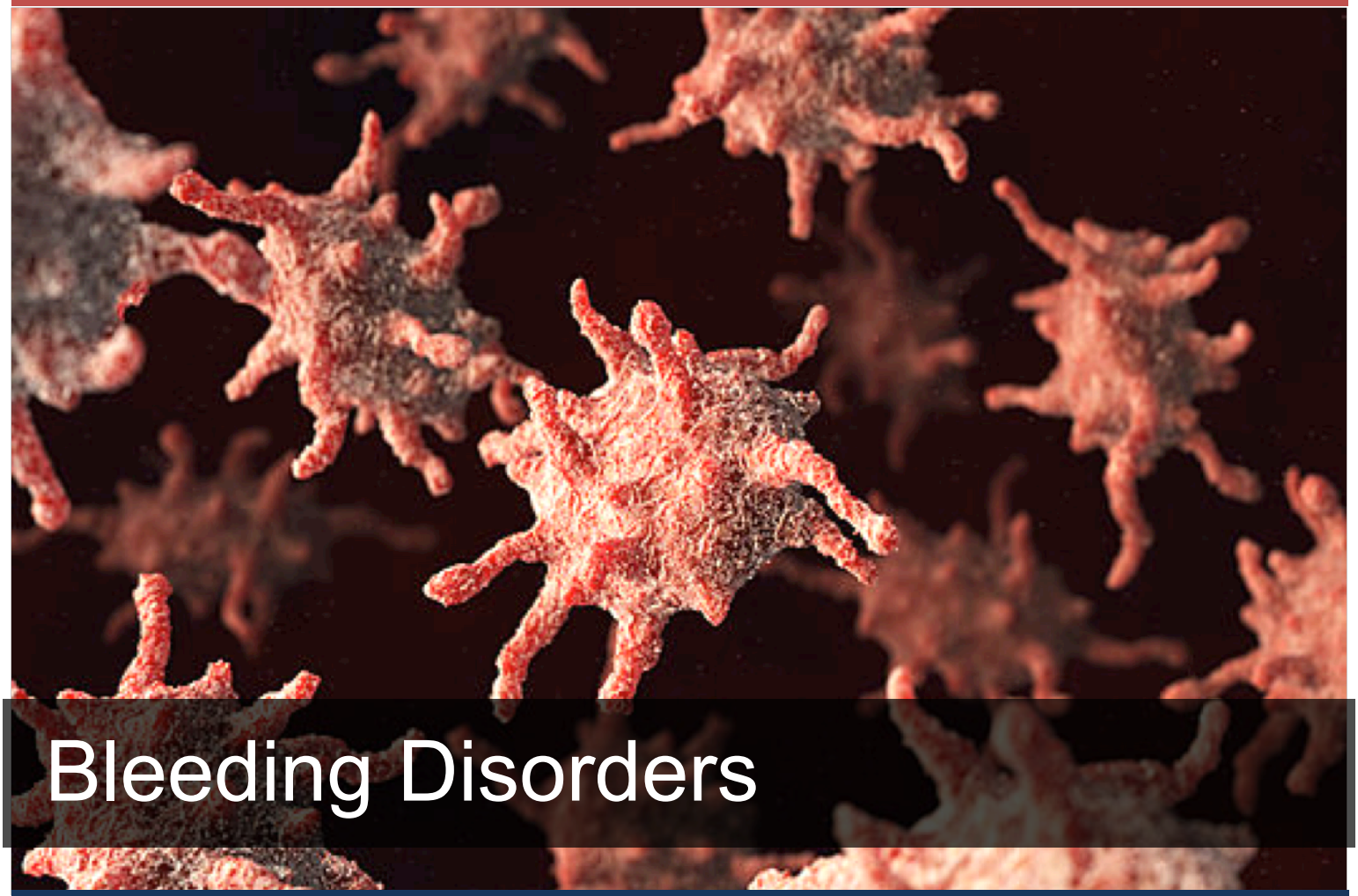


Bleeding Disorders

429 Medicine Team

Dr. Aamer Aleem's lecture, 427 Team Medicine Notes, Kumar & Clark's Clinical Medicine 7E, Toronto Notes 2011, Step-Up to Medicine 7E

Note: The last two pages contain extra notes from Step Up

Questions: http://ask.fm/TeamNotes429

BLEEDING DISORDERS

NORMAL HEMOSTASIS

A protective mechanism that has evolved to maintain physiological: Hemostasis.

Blood coagulation is complex and finely balanced system of activating & inhibitory feedback or feed-forward pathways with integration & coordination of its five major components i.e., blood vessels, blood platelets, coagulation factors, coagulation inhibitors, fibrinolytic system (links with immune system)

Three Phases of Hemostasis

1. Primary Hemostasis
- goal is rapid cesstion of bleeding
- vessel injury results in collagen/subendothelial matrix exposure and release of vasoconstrictors
- blood flow is impeded and platelets come into contact with damaged vessel wall (Figure 12a)
  - adhesion: platelets adhere to subendothelium via vWF
  - activation: platelets are activated resulting in change of shape and release of ADP and thromboxane A_2
  - aggregation: these factors further recruit and aggregate more platelets resulting in formation of localized hemostatic plug

2. Secondary Hemostasis
- platelet plug is reinforced by production of fibrin clot in secondary hemostasis (Figure 12b)
- extrinsic pathway
  - initiation of coagulation in vivo
- intrinsic pathway
  - amplification once coagulation has started

3. Fibrin Stabilization and Fibrinolysis (resolution)
- conversion from soluble to insoluble clot
- once healing initiated, clot dissolution (anticoagulant pathway)

BLOOD VESSELS

Blood vessels are the 1st line of defense in hemostasis. Vascular endothelium synthesizes & releases a variety of factors and also has receptors for large # of molecules. Endothelium is usually activated by trauma, or stimulated by thrombin, cytokines or shear stress

- Leukocyte & Platelet adhesion
- Inflammation
- Phagocytosis
- Vascular Permeability

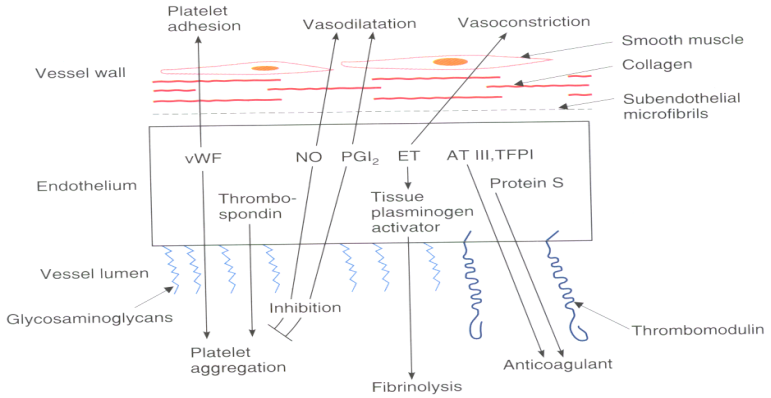


Figure 26.3 Haemostatic and vasculoregulatory factors expressed by endothelial cells. NO = nitrous oxide; ET = endothelin; vWF = von Willebrand factor; PG = prostaglandin; AT III = antithrombin III; TFPI = tissue factor pathway inhibitor.

PLATELETS

Platelets are fragments of the cytoplasm of megakaryocytes formed in the bone marrow and are non-nucleated.

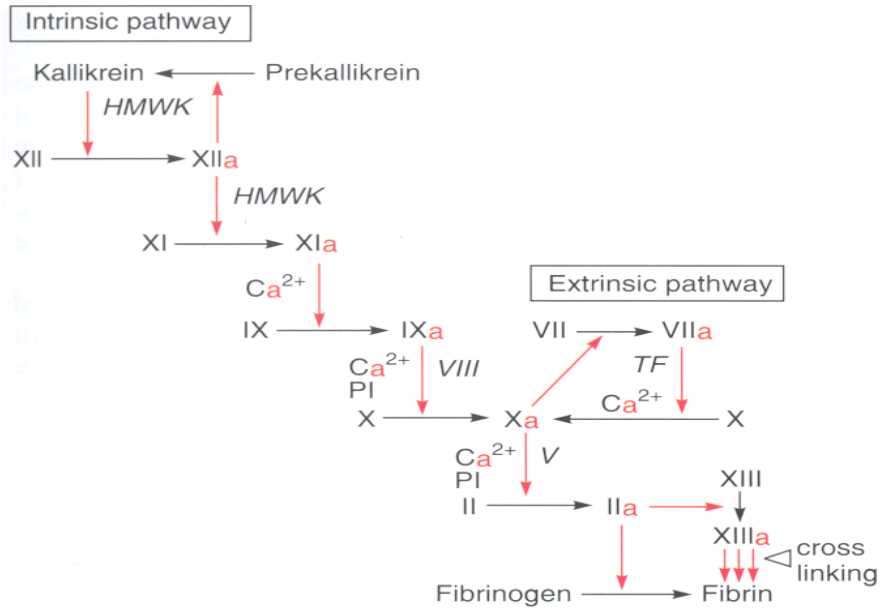
Many substances can induce platelet aggregation e.g., ADP, TXA_2, adrenaline, 5HT, vasopressin and platelet activating factor. This helps in forming a platelet plug at the site of injury & stop bleeding.

Table 26.3 Some important platelet dense body and α-granule contents

Dense bodies	
ADP	Aggregation, vasoconstriction
ATP	Degrades to ADP
5-HT	Vasoconstriction, aggregation
Calcium	?
Pyrophosphate	?
Alpha-granules	
PF4	Heparinoid neutralization
Beta-thromboglobulin	? Chemotaxis
Thrombospondin	? Aggregation
PDGF	Mitogenesis, vessel repair
vWF	Adhesion, aggregation
Fibrinogen	Aggregation, coagulation
Factor V	? Prothrombinase activity
Fibronectin	Fibroblast and platelet adhesion
PAI-1	Inhibition of fibrinolysis
α_2-antiplasmin	Inhibition of fibrinolysis

COAGULATION PATHWAY

TRADITIONAL COAGULATION PATHWAY



PROBLEMS WITH TRADIONAL COAGULATION PATHWAY

- No explanation why FVIII or FIX deficiency causes severe bleeding, since the extrinsic pathway out to bypass the need for FVIII & FIX
- No explanation for less severe bleeding in FXI deficiency
- No explanation for absent bleeding in FXII deficiency
- No explanation for the lag phase followed by explosively rapid thrombin generation

NEW APPROACH TO COAGULATION

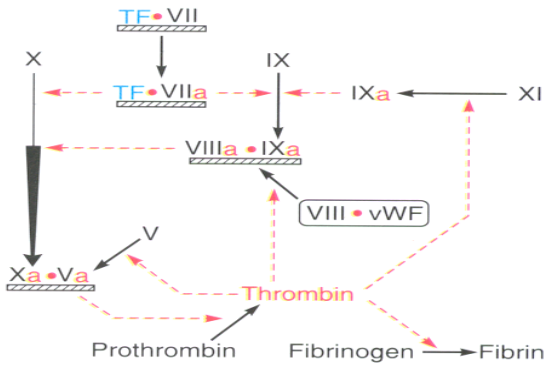


Figure 26.12 Thrombin generation network initiated by TF–VIIa. Symbols as in Figure 26–1. The activator complexes Xa–Va and IXa–VIII, assemble on the surface of an activated platelet. Factor VIII bound to vWF is inactive. Direct activation of X by TF–VIIa allows a small amount of thrombin to be generated, which feeds back to activate the cofactors V and VIII, leading to an explosive burst of further thrombin generation.

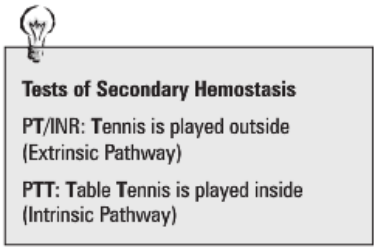
APPROACH TO A PATIENT WITH BLEEDING TENDENCY

HISTORY & EXAMINATION

- Vascular/platelet **or** coagulation defect?
  - **Vascular/platelet bleeding** → characterized by:
    - Easy bruising & spontaneous bleeding from small vessels.
    - Bleeding into the skin (purpura).
      - **Petechiae:** small skin hemorrhages varying from pinpoint size to a few millimeters in diameter & which do not blanch on pressure.
      - **Ecchymoses:** larger areas of bleeding into the skin.
    - Bleeding also from mucous membranes (especially the nose & mouth).
  - **Coagulation disorders** → are typically associated with:
    - Bleeding after injury or surgery.
    - More severe forms: Haemarthroses (bleeding into joints) & muscle hematomas.
- Family history (if +ve, what is the pattern of inheritance?)
- Past Hx: Intercurrent diseases, **surgical history**
- Alcohol & drugs

INVESTIGATIONS

- CBC & blood film: platelet count (normal 150-400 × 10^9/L) & morphology and any other blood diseases e.g. lymphoma, leukemia
- Bleeding time (BT): measures platelet plug formation in vivo (normal 3-10 minutes), if prolonged → platelet function defects



- **Coagulation tests:**
    - Prothrombin time (PT) → measures FVII, FX, FV, prothrombin & fibrinogen (classic 'extrinsic' pathway). Normal = 12 – 16 sec
    - Activated partial thromboplastin time (APTT) or PTT with kaolin (PTTK) → measures XII, XI, IX, VIII, X, V, prothrombin & fibrinogen (classic 'intrinsic' pathway). Normal = 30-50 sec
    - Thrombin time (TT) → measures common pathway. Prolonged with fibrinogen deficiency, dysfibrinogenaemia or inhibitors. Normal = 12-14 sec
- **Specific test:**
    - Factor assays (esp. suspected hereditary disorders-hemophilia): confirm coagulation defects, especially where a single inherited disorder is suspected
    - Platelet function tests (as platelet aggregation & platelet granule contents)
    - Special tests of coagulation (FDP – TT) include estimation of fibrinogen and FDP (Fibrin/Fibrinogen Degradation Product), platelet function tests e.g. platelet aggregation and platelet granule contents
    - Bone marrow study

Test				Condition
PT	**APTT**	**TT**	**Platelet count**	
↑	N	N	N	Factor VII deficiency Anticoagulant therapy
N	↑	N	N	Factor deficiency vWD Inhibitors e.g. Heparin therapy, FDP
↑	↑	N	N	Common Pathway Factor deficiency Vitamin K deficiency Oral anticoagulant therapy Liver disease
↑	↑	↑	N	Hypo/dysfibrinogenaemia Heparin Liver disease Systemic hyperfibrinolysis
↑	↑	↑	↓	**DIC** (FDP, D-dimer, Fibrinogen) Liver disease
N	N	N	N	**Factor XIII deficiency:** *Clot solubility* **Thrombasthenia (congenital drug induced):** *Platelet function (BT, clot retraction, platelet aggregation, platelet glycoprotein analysis)* **Disorders of vascular hemostasis:** *Tourniquet test* **Scurvy:** *Serum ascorbate level*

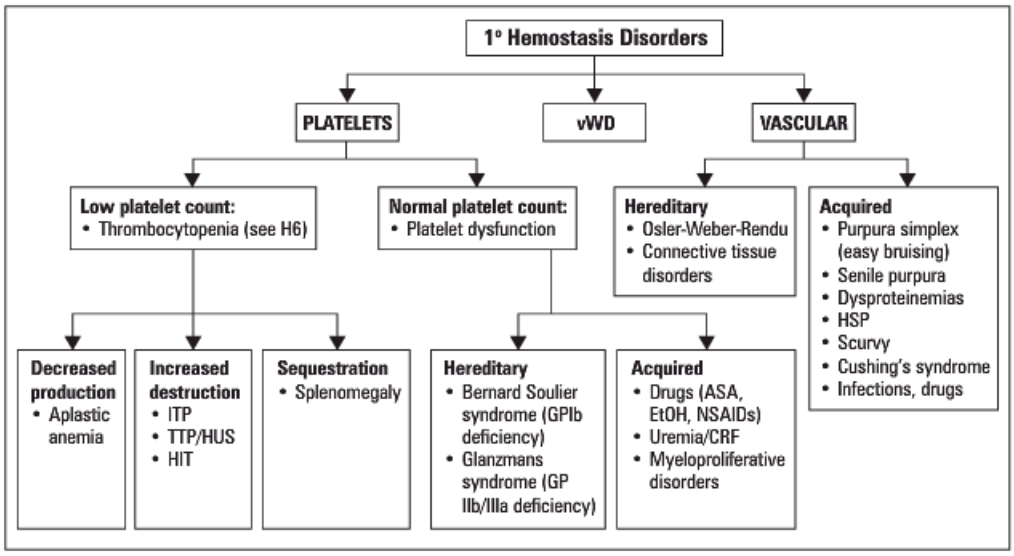


Figure 13. Approach to Disorders of Primary Hemostasis CRF = Chronic Renal Failure

Disorders of Primary Hemostasis:

VASCULAR DISORDERS

CHARACTERISTICS:

- Easy bruising & bleeding into skin (purpura: petechiae & ecchymoses)
- Sometimes bleeding from mucus membranes
- RARELY severe bleeding
- Lab investigations → BT is normal or increased

TYPES:

SENILE PURPURA

- Ecchymoses
- Results from increased vessel fragility due to connective tissue damage to the dermis caused by chronic sun exposure

PURPURA DUE TO INFECTIONS

Mainly caused by damage to the vascular endothelium (esp. rash in meningococcal septicemia)

HENOCH-SCHÖNLEIN PURPURA

- Immune disorder (type III – immune complex hypersensitivity reaction) often proceeded by an acute upper respiratory tract infection
- Symptoms include:
  - Purpura (mainly on the legs & buttocks)
  - Abdominal pain
  - Arthritis
  - Hematuria & glomerulonephritis
- Recovery is usually spontaneous, but some patients develop renal failure

CONNECTIVE TISSUE DISORDERS

Ehlers-Danlos, osteogenesis imperfecta, pseudoxanthoma elasticum, Marfan's syndrome

SCURVY (VITAMIN C DEFICIENCY)

PLATELET DISORDERS

INHERITED PLATELET DISORDERS

PLATELET DYSFUNCTION (NORMAL COUNT)

Thrombocytopathy	Molecular Abnormality	Functional Abnormality
Bernard-Soulier syndrome	GPIb, GPV, GPIX↓	Failure of platelet adhesion and moderate thrombocytopenia (GPIb: binding site for VWF)
Von Willebrand syndrome	↑GPIb	↑vWF binding to platelets, ↓platelet adhesion to subendothelium
Glanzmann's thrombasthenia	↓GPIa	Defective fibrinogen binding and failure of platelet aggregation

THROMBOCYTOPENIAS

- May-Hegglin thrombocytopenia
- Thrombocytopenia with absent radii (TAR)
- Wiskott-Aldrich syndrome
- Epstein's Syndrome

ACQUIRED THROMBOCYTOPENIAS

Allo-Immune	**Autoimmune**	**Drug-Induced**
Neonatal	Idiopathic thrombocytopenic purpura	Drug dependent
Post-transfusion purpura	Secondary autoimmune purpura	Drug-independent (autoimmune)
Refractions to platelet transfusion	Acute (post-viral) thrombocytopenia	

IDIOPATHIC THROMBOCYTOPENIC PURPURA

- Main feature is bleeding (muco-cutaneous) and severity depends on the degree of thrombocytopenia
- Risk of serious bleeding when platelet count < $10x10^9$/L
- Splenomegaly is **NOT** a feature
- Features of secondary disease

Features	Acute ITP
Peak Age	2-6 years
Sex Predilection	None
History of Recent Infection	Common
Onset of Bleed	Abrupt
Duration	Usually weeks
Spontaneous Remissions	80% or more

LAB INVESTIGATIONS

- Isolated thrombocytopenia
- Normal or increased number of megakaryocytes in the bone marrow
- ↑ Mean Platelet volume
- Other causes of thrombocytopenia should be ruled out
- Pseudo-thrombocytopenia
- SLE tests

PATHOGENESIS

- Production of antibodies
- Coating of Platelets
- Removal by RE system (Spleen & Liver)
- Antibodies may be directed against megakaryocytes
- Drug Induced Thrombocytopenia
    - Drug history e.g. Quinine, Quinidine, Sulphonamides, trimethroprim, Gold, Heparin

MANAGEMENT

- Steroids
- Splenectomy
- IVIG
- Refectory patients (20%)
    - Immunosuppression: Azathioprine, Cyclophosphamide & Cyclosporine
    - Danazol
    - Rituximab
    - Thrombopoietic stimulating agents
- Platelet transfusion should be avoided unless bleeding

TREATMENT OF PLATELET DISORDERS

- Avoid antiplatelet drugs & trauma
    - Local measures
    - DDAVP infusion
    - Platelet transfusion (HLA compatible)
    - Bone marrow transplantation

VON WILLEBRAND DISEASE

INVESTIGATIONS

1. Ristocetin induced platelet agglutination (the antibiotic ristocetin causes von Willebrand factor to bind the platelet receptor glycoprotein Ib (GpIb), so when ristocetin is added to normal blood, it causes agglutination. In von Willebrand disease, where von Willebrand factor is absent or defective, abnormal agglutination occurs)

2. VIII:C (The LMW component of factor VIII, which has coagulant activity)
3. vWF:Ag (assay for the quantitative determination of von Willebrand factor)
4. vWF multimeric analysis (analysing the concentration and distribution of VWF multimers present in plasma)

VWD Type	Multimer Analysis
1	Partial deficiency of vWF (present but in low concentrations)
2A	Absence of large & intermediate multimers
2B	Absence of large multimers
2M	Multimers normal (all present), platelet function ↓
2N	↓ Affinity for FVIII
3	Severe vWF deficiency; multimers absent

TREATMENT OF BLEEDING AND SURGERY IN VWD

1. DDAVP (Desmopressin acetate) for minor bleeding and surgery in type 1 & 2A
2. Intermediate purity FVIII (8Y, Hemate P)
3. If above measures fail
    a. Cryoprecipitate
    b. Platelet transfusion
4. Purified vWF factor is available

BLOOD COMPONENTS

1. Red blood cells: leukocyte reduced by filtration (LRF)
2. Autologous blood
3. Platelets: (LRF)
4. Platelets, apheresis (LRF)
5. Fresh frozen plasma (FFP)
6. Plasma, apheresis
7. Cryosupernatant plasma (CSP)
8. Cryoprecipitate (Cryo)
9. Serum albumin
10. IV immune globulin (IVIG)
11. Rh immune globulin (Anti-D)
12. Other immune globulins
13. Factor VIII, Factor VII, Factor IX
14. Factor XIII
15. Fibrinogen
16. Zoster immune globulin

Fresh Frozen Plasma

- Single donor, infection risks
- ABO typing recommended
- Should be used within 2 hours of thawing

Unit contains all factors and activity of a similar volume of plasma (250 ml) ~ 8% plasma volume

Cryoprecipitate

- Pooled
- Factors VIII, I, XIII, vWF, Fibrinogen
- Each unit provides 80 - 100 units of factor VIII

Prothrombin Complex (FEIBA, Autoplex)

- Pooled plasma preparation
- Treated to inactivate hepatitis viruses +HIV
- Reconstituted vial 30 ml = 500 FFP
- Substantial quantities of II, VII, IX, X
- Tx of Hemophilia A & B with inhibitors, warfarin overdose, severe liver disease

Disorders of Secondary Hemostasis:

COAGULATION DISORDERS

INHERITED

HEMOPHILIA A

- X-Linked recessive disorder
- Males are affected and females are carriers
- Deficiency of FVIII due to gene mutations or deletions
  - Severe (< 1%)
  - Moderate (1-5%)
  - Mild (5-40%)
- Clinical Features
  - Severe spontaneous recurrent bleeding
  - Usually muscle & joints, internal organ bleeds also occur
- Recurrent bleeds lead to joint & muscle damage
- Family history or new mutation
- Severity (see table)

Severity	Factor VIII or IX level	Clinical Presentation
Severe	<1%	Spontaneous hemarthrosis & muscle hematomas
Moderate	2 – 5 %	Mild trauma or surgery cause hematomas
Mild	5 - 50 %	Major injury or surgery result in excess bleeding

INVESTIGATIONS

- CBC: normal
- Coagulation tests
  - PT: normal
  - BT: normal
  - APTT: ↑
  - FVIII:C ↓
  - vWF:Ag normal
- Imaging:
  - Joint radiographs: secondary osteoarthritic changes
  - U/S, CT in loin pain (psoas bleeds, renal capsule bleeds, retroperitonial bleeds)

TREATMENT

1. Factor VIII concentrates for acute bleed. Sources:
    a. Donated human blood (plasma)
    b. Recombinant DNA technology (transforming non-human, mammalian cell lines to express human FVIII)
    c. Cloning of the normal FVIII gene and production of synthetic FVIII

DOSAGE

Based on the patient's body weight

Rule of thumb:

- FVIII levels will be increased 2% for every 1 unit/kg infused, thus 50 units/kg IV bolus will rise FVIII to 100%
- FIX levels will be increased 1% for every 1 unit/kg infused, thus 50 units/kg IV bolus will rise FIX to 50%

Example: 14 y/o boy with a bleed. Weight = 55 kg

- Goal: raise factor VIII level to 30% of normal
- Calculate:
    - 15 units x 55kg = 825 units **Or**
    - 30 x 55/2 = 825 units

2. DDAVP (synthetic vasopressin)
    a. Used either IV or intra-nasaly to Rx pt with mild hemophilia A with the FVIII levels>10%
    b. The drug releases FVIII stored in the endothelial cells, it can double or triple the body's plasma level of FVIII.
    c. Not all pts respond to DDAVP
    d. Dose (0.3 microgram/kg) it can be repeated 6-8 hourly
    e. Response to the second dose is less due to tachyphylaxis
3. Gene therapy:
   It involves taking normal clotting factor genes and placing them into the body of a person with hemophilia, with the hope that patients' body will begin to make clotting factors on its own. However this approach is still investigational and not yet applicable clinically.

COMPLICATIONS

- **Contamination with viruses**
  Factor concentrates, like many blood products, are made from pooled plasma. It can take up to 30,000 donations of blood to make one batch of factor concentrate and blood products have always been susceptible to contamination by viruses. (Hep A, B, C, HIV and others)

- **Development of inhibitors**
    - 10-20% have IgG antibodies to FVIII (mostly in severe cases) in pt Rx w/F concentrate
    - High doses of FVIII may **not** produce a rise in the plasma level of FVIII

    How do we deal with pts who develop inhibitors?

    - Purified porcine FVIII may not cross-react with pts antibodies.
    - Prothrombin complex (Feiba, autoplex)
    - Recombinant FVIIa also "bypass" FVIII
    - Immunosuppression/immunoabsorption

MANAGEMENT OF BLEEDING

As soon as bleeding is suspected treatment should be given according to its severity.

- Minor bleeding: (e.g. laceration, dental extraction, early joint or muscle bleeding) → FVIII level should be raised to 30-50%
- Moderate bleeding: (e.g. major joint or muscle bleeds) → FVIII raised to at least 50-70%
- Severe bleeding: (e.g. CNS, GI bleed, postoperative, major trauma) → FVIII raised to 80- 120% for 7-10 days and 100% preoperatively and maintained above 50% until healing

SURGERY IN HEMOPHILICS

- Minor surgery
    - DDAVP with Tranexamic acid may suffice (mild haemophilia). Need to check response before hand
    - Raise FVIII level 50-70%
- Intermediate & major surgery
    - FVIII raised to 80- 120% for 7-10 days and 100% preoperatively and maintained above 50% until healing
    - Twelve hourly boluses or continuous infusion

HEMOPHILIA B: CHRISTMAS DISEASE

- Deficiency of factor IX
- Inheritance and clinical features are identical to hemophilia A (but lower incidence)

TREATMENT:

- Factor IX concentrates
- Recombinant factor IX
- Desmopressin is ineffective

ACQUIRED

ACQUIRED HEMOPHILIA

- Due to the development of an inhibitor (antibody) against factor VIII in a previously normal individual
- It is rare, and affects both males and females
- It is sometimes associated with cancer, auto immune conditions and pregnancy, but most cases arise spontaneously
- Severe and often life threatening
- Treatment includes factor raVIIa, prothrombin complex, immunosuppression and rituximab (anti CD20 antibody)

MASSIVE TRANSFUSION

- Dilution of coagulation factors: Crystalloids, packed red cells
- Activation of clotting factors
- Breakdown of platelet, WBC & RBC in stored blood releasing thromboplastins (DIC)
- Risk maximum with one blood volume equivalent (8-10 units) transfusion

MANAGEMENT

- Do not use blood components indiscriminately
- Look for signs of bleeding (mucosal, wounds, puncture sites)
- If platelet count ≤ 50 transfuse platelet 6-10 units
- If PT & APTT are significantly prolonged give plasma (FFP)
- If ↓ fibrinogen < 1g/dL, consider giving cryoprecipitate

VITAMIN K DEFICIENCY

- Vit. K is needed for formation of active factors II, VII, IX & X.
- Deficiency may be due to: malabsorption, malnutrition, oral anticoagulant drugs
- Occurs in neonates with ↓ intestinal flora & ↓ dietary intake
- Lab investigations:
  - Prolonged PT & APTT
  - Normal → BT, VIII, VWF
- Clinical features: bruising, hematuria and gastrointestinal or cerebral bleeding
- Treatment (if required): phytomenadione (vitamin K1) IV

LIVER DISEASE

- All the coagulation factors except vWF, are synthesized by the liver
- Liver also synthesizes AT III, Protein C & S, α2 antiplasmin & Plasminogen
- Hepatocellular damage is accompanied by complex disturbances of hemostasis
- Low platelet count (Splenic or liver sequestration, platelet dysfunction)
- DIC may occur
- Fibrinogen well preserved till late but may be abnormal

MANAGEMENT

- Try vitamin K (as deficiency is common)
- PT & APTT should be corrected to within 5 seconds of normal by giving FFP for liver biopsy & other procedures
- Platelet transfusion if low count

RENAL FAILURE

- Significant bleeding may occur
- Defect in platelet function & platelet vessel wall interaction
- Uremic toxins seem to impair platelet function
- Bleeding time is prolonged & platelet aggregation impaired
- Peritoneal or hemodialysis partially corrects the defect
- Anemia should be corrected
- DDAVP reduces BT & minor surgery can be performed
- Conjugate estrogens

DISSEMINATED INTRAVASCULAR COAGULATION (DIC)

No consensus on definition.

DIC is an acquired syndrome characterized by activation of intravascular coagulation up to intravascular fibrin formation. The process may be accompanied by secondary fibrinolysis or inhibited fibrinolysis.

Widespread generation of fibrin within blood vessels → consumption of platelets & coagulation factors and secondary activation of fibrinolysis leading to production of fibrin degradation products (FDPs) → mixture of initial thrombosis followed by a bleeding tendency

CLINICAL FEATURES

- Patient is often acutely ill and shocked.
- Clinical presentation varies from no bleeding at all to profound haemostatic failure with widespread hemorrhage.
- Bleeding may occur from the mouth, nose and venipuncture sites
- May be widespread ecchymoses.
- Thrombotic events that may cause ischemia & multiple organ failure (esp. brain – kidney – skin)

CLINICAL CONDITIONS ASSOCIATED WITH DIC

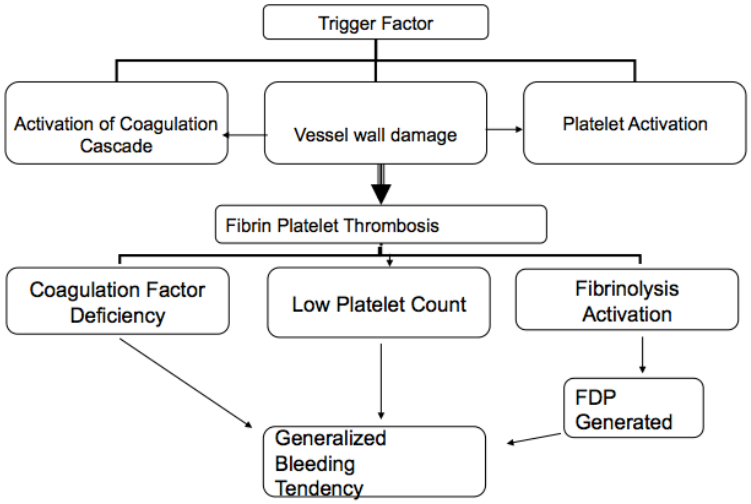
- Infections
    - Bacterial e.g. meningococcal (30-50%)
    - Viral
    - Parasitic e.g. malaria
- Severe trauma (50-70%) e.g. burns
    - General
    - Head

- Cancer
    - Solid tumors
    - Hematological malignancies (15-20%)
    - APML
- Obstetric conditions
    - Placental abruption
    - Amniotic fluid embolism
    - Retained dead fetus
- Vascular disorders
    - Giant hemangiomas (Kasabach-Merrit syndrome)
    - Large aortic aneurysm (1%)
- Severe allergic/toxic reactions
    - ABO mismatched transfusion
    - Snake bite

PATHOGENESIS

Several lines of evidence suggest that DIC contributes to **multiple organ failure** due to fibrin deposition in the small and medium- sized vessels of various organs leading to ischemia and necrosis

- Entry of tissue thromboplastin into blood stream
    - Extensive tissue trauma/surgery
    - Disseminated Cancer
    - Following incompatible blood transfusion reaction
- Direct activation of factor X or factor II (snake venom)
- Severe vascular endothelial injury in gram-negative sepsis
- Direct platelet activation in infections, endothelial damage & following thrombin generation



LAB DIAGNOSIS

- ↑ PT
- ↑ APTT
- ↑ Thrombin time
- ↓ Platelets
- ↓ Fibrinogen < 1.0 g/L Normal 1.5-4.0 g/L)
- ↑ FDP & D-Dimer
- Blood film may show fragmented RBCs

MANAGEMENT

- Patient resuscitation
- Fluids for shock
- Antibiotics
- Blood transfusion if low Hb
- Inotropic support

Treat the Cause

- In obstetric situations rapid complete evacuation of uterus may be life saving
- Specific antibiotics for sepsis
- Anti snake venom

Blood Product Replacement

- FFP in case of bleeding
- Platelet transfusion
- Cryoprecipitate if Fibrinogen < 1.0
- Heparin
- Protein C concentrate in refractory cases

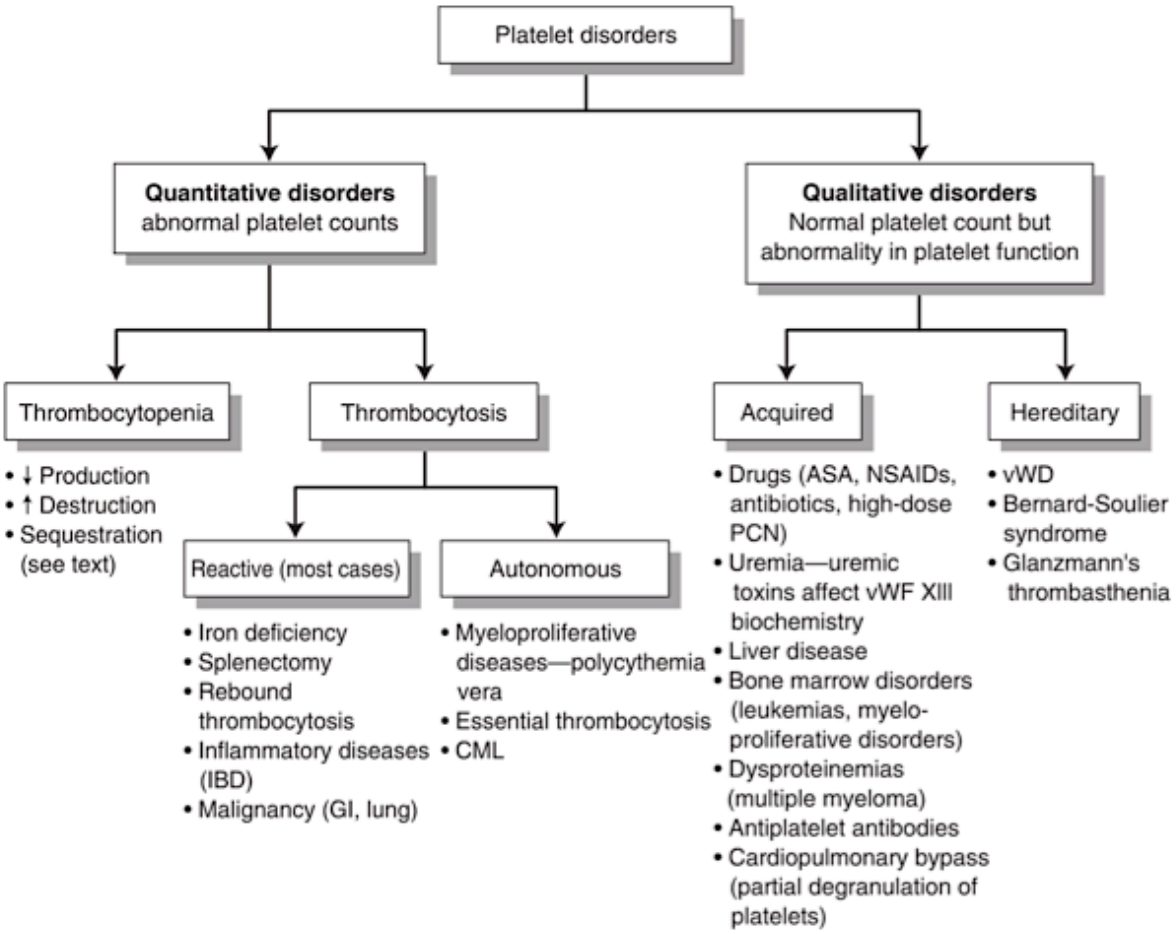
COAGULOPATHY IN CANCER

1. Thrombocytopenia
    a. Decreased production
        i. Chemo/radiotherapy
        ii. Marrow infiltration
    b. Accelerated destruction
        i. Hypersplenism
        ii. DIC
        iii. Immune thrombocytopenia
2. Functional Platelet abnormalities
    a. Myeloproliferative disorders
    b. Myeloma (Paraprotein)
3. Coagulation changes
    a. DIC
    b. Circulating anticoagulants

SUMMARY AND NOTES

(From Step-Up to Medicine)

PLATELET DISORDERS



BERNARD·SOULIER SYNDROME

- Autosomal recessive disease
- Disorder of platelet adhesion (to subendothelium) due to deficiency of platelet glycoprotein GPib-IX
- On peripheral blood smear, platelets are abnormally large. • Platelet count is mildly low.

GLANZMANN'S THROMBASTHENIA

- Autosomal recessive disease
- Disorder of platelet aggregation due to deficiency in platelet glycoprotein GPIIb-IIIa
- Bleeding time is prolonged.
- Platelet count is normal.

VON WILLEBRAND DISEASE

A. General Characteristics

1. Autosomal dominant disorder characterized by deficiency or defect of factor VIII-related-antigen (von Willebrand's factor [vWF])
2. vWF enhances platelet aggregation and adhesion (the first steps in clot formation). It also acts as a carrier of factor VIII in blood.
3. The most common inherited bleeding disorder (affects 1% to 3% of population)
4. There are three major subtypes with varying severity.
    a. Type I (most common form)-decreased levels of vWF
    b. Type 2 (less common)-exhibits qualitative abnormalities of vWF
    c. Type 3 (least common form)-absent vWF (very severe disease)

B. Clinical features

1. Cutaneous and mucosal bleeding-epistaxis, easy bruising, excessive bleeding from scratches and cuts, gingival bleeding
2. Menorrhagia (affects more than 50% of women with vWD)
3. GI bleeding is possible.

C. Diagnosis

1. Diagnosis is derived from clinical findings and laboratory information, which can be variable.
2. Prolonged bleeding time (but normal platelet count)-PTT may be prolonged (a normal PTT does not exclude this diagnosis).
3. Decreased plasma vWF, decreased factor VIII activity
4. Reduced ristocetin-induced platelet aggregation

D. Treatment

1. DDAVP (desmopressin)-induces endothelial cells to secrete vWF
2. Treatment of choice for type I vWD (the most common type)
3. Some patients with type 2 vWD may respond to DDAVP, but it is not effective in type 3 vWD.
4. Factor VIII concentrates (containing high-molecular-weight vWF)
    a. Give to all patients with vWD (any type) after major trauma or during surgery
    b. Recommended for type 3 vWD (and type 2 patients not responsive to DDAVP)
    c. Cryoprecipitate is not recommended as treatment for vWD because it carries the risk of viral transmission.
    d. Avoid aspirin/NSAIDs (exacerbate bleeding tendency)

- In many patients, vWD is mild, and is not diagnosed until surgery or trauma.
- In general, bleeding in vWD is much milder than in hemophilia. Spontaneous hemarthroses do not occur.

Factor VIII has two portions: the coagulant portion (factor VIII coagulant protein) and an antigenic portion (factor VIII antigenic protein). The antigenic protein is equivalent to vWF.

Thank You