Haemostasis & Bleeding disorders

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Normal Haemostasis

Is a protective mechanism that has evolved to maintain physiological Haemostasis.
Blood coagulation is complex and finely balanced system of activating & inhibitory feed-back 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)

Blood Vessels

It is the first line of defense in haemostasis. Vascular endothelium synthesizes & releases a variety of factors and also has receptors for large no. of molecules.
Endothelium is usually activated by trauma, or stimulated by thrombin, cytokines or shear stress

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

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, TXA2, adrenaline, 5HT,
vasopressin and platelet activating factor.
This helps in the forming of a platelet plug
at the site of injury & stops bleeding.

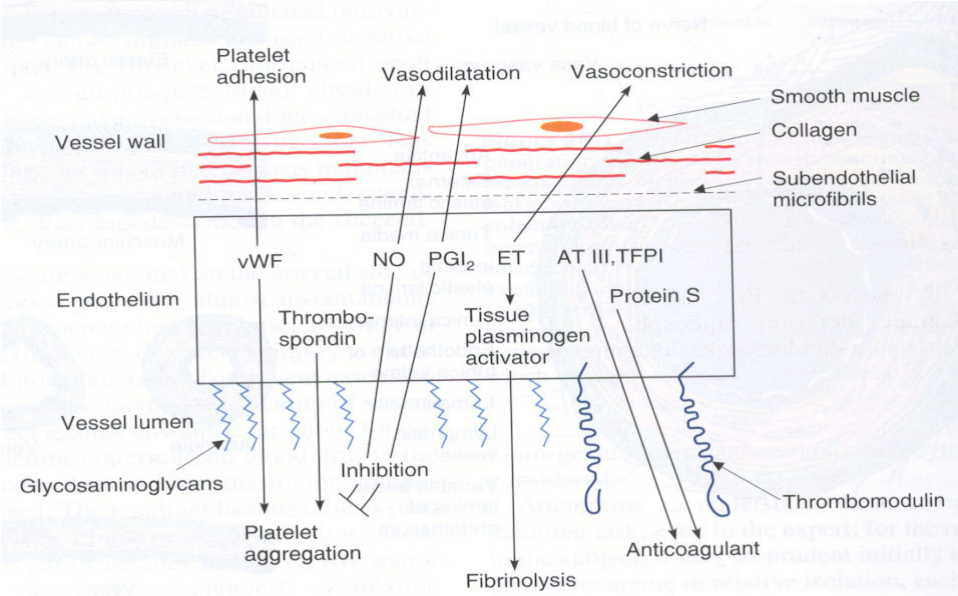


Figure 26.3 Haemostatic and vasculoregulatory factors expressed by endothelial cells. NO = nitrous oxide; ET = endothelin; vWF = von Willebrand factor; PG = prostaglandin; AT III = antithrombin III; TFPI = tissue factor pathway inhibitor.

Some important platelet dense body and α granule content	
Dense bodies	
ADP	Aggregation, vasoconstriction
ATP	Degrades to ADP
5-HT	Vasoconstriction, aggregation
Calcium	?
Pyrophosphate	?
Alpha-bodies	
PF 4	Heparinoid neutrolization
Beta thromboglobulin	? chemotaxis
Thrombospondin	? Aggregation
PDGF	Mitogenesis, vessel repair
vWF	Adhesion, aggregation
Fibrinogen	Aggregation, coagulation
Factor V	? prothrombinase activity
Fibronectin	Fibroblast & platelet adhesion
PAI-1	Inhibition of fibrinolysis
α2 Antiplasmin	Inhibition of fibrinolysis

Coagulation Factors (IMP.) :

Table 26.4 Some characteristics of clotting factors in man

Traditional name	*Preferred nomenclature*	*Mol. Wt*	*plasma conc. (µg/ml)*	*Half-life (h)*	*Gene size; location**	*Product†*
Fibrinogen	Factor I	340 000	2-4 x 10^3	90	50kb; C4q26-q28	3026
Aα-chain		56 000				
Bβ-chain		52 000				
	gama-chain	46 000				
Prothrombin	Factor II	72 000	120	65	24 kb; 11p11	579
Tissue factor	Factor III	45 000	0	-	12.6 kb; 1p21	263
Calcium	Factor IV	40	100	-	-	-
Proaccelerin	Factor V	330 000	10	15	6.8 kb; 1q21-25	2224
Proconvertin	Factor VII	48 000	1	5	12.8 kb; 13q34	406
Antihaemophilic factor	Factor VIII	360 000	0.05	10	190 kb; Xq28	2332
Christmas factor	Factor IX	57 500	4	25	35 kb; Xq26	415
Stuart-Prower factor	Factor X	55 000	12	40	25 kb; 13q34	445
Plasma thromboplastin antecedent	Factor XI	160 000	6	45	25 kb; 4q35	1214
Hageman factor	Factor XII	85 000	40	50	13.5 kb; 5q33	536
Fibrin stabilizing factor	Factor XIII	320 000	20	200	a 160 kb; 6 p ter; b 28 kb; 1q31	a = 731 b = 641
Fletcher factor	Prekallikrein	90 000	40	35	?	619
Fitzgerald factor‡	High mol. Wt Kininogen	120 000	70	150	27 kb; C3q26	626

* Chromosome number and band location.
† Number of amino acids.
‡ Also known as Williams, Flaujeac or Reid factors.

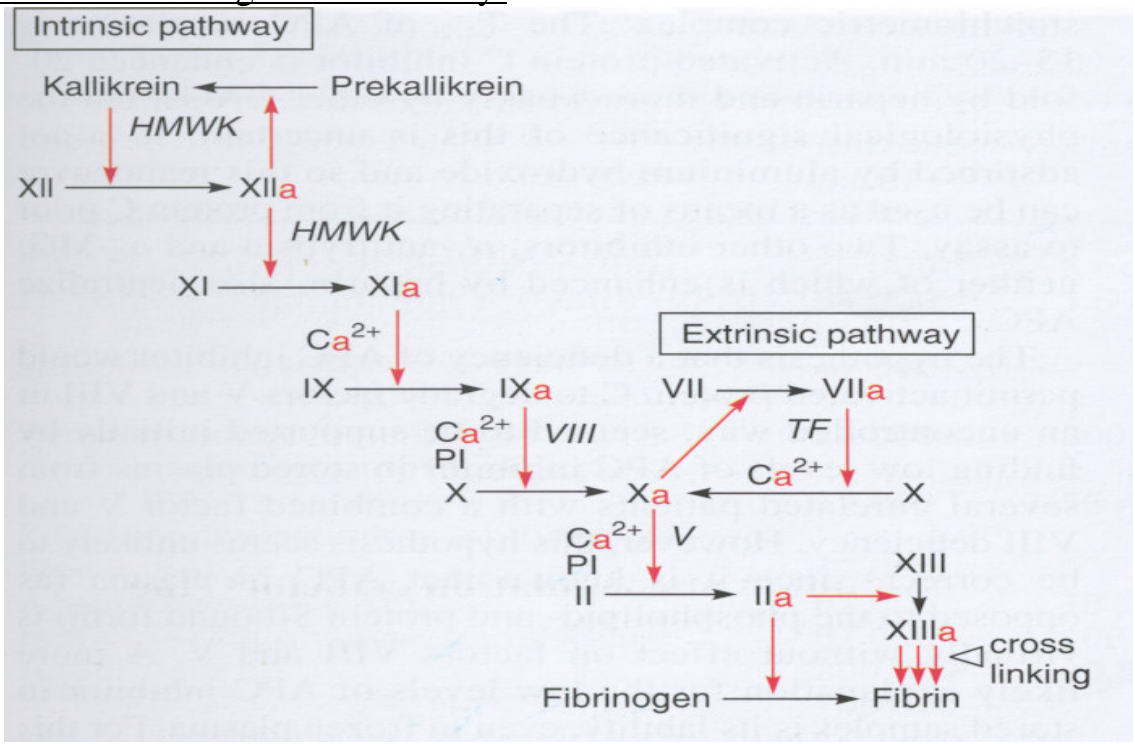
Naturally Occurring Anticoagulants in Blood:

Table 26.5 Some characteristics of inhibitors of procoagulant serine proteases

Inhibitor	*Mol. wt (kDa)*	*Plasma conc.*		*T1/2 (h)*	*Chromosomal position*	*Major substrate*	*Other substrates*
		μg/ml	*μmol/l*				
Antithrombin	58	125	2.5	60	1q23–q25	IIa, Xa	IXa, XIa, XIIa
Heparin cofactor II	66	80	1.2	?	22q11	IIa	–
α_1-antitrypsin	55	1500	20–30	96	14q31–q32	XIa, Xa	Plasmin
C_1 esterase inhibitor	105	180	2.8	40	11p11–q13	KK, XIa	XIa
α_2-antiplasmin	70	70	1.0	60	18p11–q11	Plasmin	KK, XIIa, XIa
α_2-macroglobulin	725	2500	3.0	240	?	KK	IIa
Tissue factor pathway inhibitor	32	0.1	0.003	?	2q31–q32	TF–VIIa	Xa

KK = kallikrein

Traditional Coagulation Pathway:



Problems with traditional coagulation pathway

- No explanation why FVIII or FIX deficiency causes clinically severe bleeding, since the extrinsic pathway ought to bypass the need for FVIII and 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 observed experimentally

New Concept of Blood Coagulation

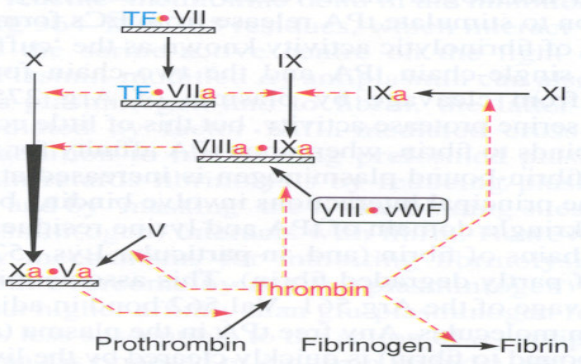


Figure 26.12 Thrombin generation network initiated by TF–VIIa. Symbols as in Figure 26–1. The activator complexes Xa–Va and IXa–VIII, assemble on the surface of an activated platelet. Factor VIII bound to vWF is inactive. Direct activation of X by TF–VIIa allows a small amount of thrombin to be generated,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

Type of Bleeding
Mucosal & Skin OR Joint & Muscles
Past Surgical History
Family history (-ve in 30%)
If +ve family history, we check pattern of inheritance
Drugs

Examination

Skin & oral mucosa
Joints
Associated abnormalities

Investigations

Prothrombin time
Partial thomboplastin time
Platelet count
Bleeding time
Thrombin time

First-line tests in a case of bleeding tendency: (very important !)

First-line tests used in investigation acute haemostatic failure				
Test			Platelet count	Condition
PT	APTT	TT		
N	N	N	N	Disorder of platelet function Factor XIII deficiency Disorder of vascular haemostasis Normal haemostasis
long	N	N	N	Factor VII deficiency Early oral anticoagulation
N	long	N	N	Factor VIII:C, IX, XI, XII, Prekallikrein, HMWK deficiency. vWD. Circulating anticoagulants
long	long	N	N	Vitamin K deficiency Oral anticoagulant Factors: V, VII, X & II deficiency
long	long	long	N	Heparin Liver disease Fibrinogen deficiency Hyperfibrinolysis
N	N	N	low	Thrombocytopenai
long	long	N	low	Massive transfusion Liver disease
long	long	long	low	DIC Acute liver disease

VERY IMP!

Thrombocytopathy	*Molecular abnormality*	*Functional abnormality*
Defect of adhesion		
Bernard-Soulier syndrome	GPIb,GPV,GPIX ↓	**F V:VWF binding to platelets ↓ Platelet adhesion to microfibrils ↓**
von Willebrand platelet syndrome	GPIb ↑	**V:VWF binding to platelets ↑ Plasmatic FV:VWF level ↓ Platelets adhesion to sub endothelium ↓**
Defect of reactivity to collagen	GPIa ↓	**Platelet adhesion to collagen ↓**
Defect of activation		
Abnormality in intracellular ca++ fluxes	?	**Defect in enzymatic reactions and metabolic events responsible for activation Platelet release and aggregation ↓**
Abnormality in prostaglandin pathway	Cyclooxygenase or thromboxane synthetase deficiency	**Platelet release and aggregation ↓**
Defect of reactivity to ADP	Receptors number ↓	**Defect in activation and aggregation to ADP**
Defective response to epinephrine	Decrease in platelet α2 adrenergic receptors	**Defect activation induced by epinephrine**
Montreal platelet syndrome	Decrease Calpine	**Spontaneous aggregation by increased exposure of binding sites for adhesive proteins?**
Defect of adhesive proteins		
Grey platelet syndrome	a-granule content and typical a-granules number ↓	**Release of adhesive proteins ↓ Adhesion and aggregation ↓**
Defect of secretion of dense granules		
Δ-storage pool disease	Dense bodies number ↓ and function ↓	**Release of ADP ↓ Aggregation ↓**
Defect of aggregation		
Glanzmann disease	GPIIb and GPIIIa ↓	**Fibrinogen binding ↓ Aggregation ↓**
Variant thrombasthenia	Abnormal GPIIb-GPIIIa complex	**Idem**
Defect of procoagulant activity		
Platelet factor 3 deficiency	Abnormality in phospholipids involved in binding of factors Va and Xa	**Defect of activation in situ of plasmatic factors**

Inherited Platelet disorders

Inherited Thrombocytopenias:

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

Treatment of Platelet disorders:

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

Inherited Bleeding disorders (IMP.)

Disorder	Screening tests				Specific assays* (u/dl)
	PT	*PTTK*	*TCT*	*BT*	
Haemophilia A	N	↑	N	N	Factor VIII <50 vWF:Ag N Ricof N
von Willebrand's disease	N	↑ or N	N	↑ or N	Factor VIII <50 vWF:Ag <50 or N Ricof <50 or N
Haemophilia B	N	↑	N	N	Factor IX <50
Factor XI deficiency	N	↑	N	N	Factor XI <35
Factor X deficiency	↑	↑	N	N	Factor X <50
Factor V deficiency	↑	↑	N	N or ↑	Factor V <50
Factor VII	↑	N	N	N	Factor VII <50
Factor II	↑	↑	N	N	Factor II <50
Afibrinogenaemia	↑	↑	↑	↑	Fibrinogen undetectable
Dysifibrinogenaemia	↑	↑	↑	↑	Fibrinogen N or ↓
Factor XIII deficiency	N	N	N	N	Fibrin solubility ↑ Factor XIII <5%
Factor V plus VIII deficiency	↑	↑	N	N	Factor V <50 Factor VIII <50
Hyperplasminaemia	N	N	N	N	Euglobulin clot lysis time short (α2-antiplsmin absent)

PT = prothrombin Time; PTTK = activated partial thromboplastin time; TCT = thrombin clotting time; BT = bleeding time; ↑ = increased, ↓ = decreased; N = normal.

* Factor VIII (formerly VIII:c); vWF:Ag, von Willbrand factor antigen (formerly VIIIR: Ag); Ricof, ristocetin cofactor.

Hemophilia – A

X-Linked recessive disorder
Males are affected and females are carriers.
Deficiency of FactorVIII 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 of Hemophilia:

	Factor VIII or IX level	Clinical Presentation
Severe	<2%	Spontaneous haemarthrosis & muscle haematomas
Moderate	2 – 10 %	Mild trauma or surgery cause haematomas
Mild	10 - 50 %	Major injury or surgery result in excess bleeding

Findings on investigation

Hematology:

- CBC ◊ normal
-Clotting studies:-
  PT normal

  Bleeding time N
  APTT
  VIII: C
  vWF: Ag *normal*
-Gene analysis and family studies

Diagnostic imaging:

Joint X-ray 2nry osteoarthritic changes
U/S , CT in loin pain (psoas bleeds, renal capsule bleeds,retroperitonial bleeds

Hemophilia – A Complications:

-Complications of disease:
  Joint damage
  Muscle damage (fibrosis)
-Complications of therapy:
  Inhibitors
  Blood transmitted infections:
    Hepatitis A, B & C
    HIV
    Parvovirus B 19

Hemophilia – A, Management:

1) Factor VIII replacement:

- Treatment of bleeding
  DDAVP in mild cases
  Hemarthrosis/minor trauma (50-70%)
  Surgery/major trauma (80-120%)
- Prophylactic treatment
  All children with hemophilia
  Start at the age of 6-12 months
  Raise level to 20% (3/week)

2) Supportive treatment:

-Treatment of complications
Joint & muscle damage (repeated bleeds)
Physiotherapy
Surgery
- Therapy related complications
Inhibitors
FEIBA, Recombinant Factor VIIa
Immunosuppression
Blood transmitted infections
Hepatitis B & C, HIV

von-Willibrand disease(vWD)

Autosomal dominant disorder (but some forms are autosomal recessive)
Affects 1% of the population
Big variation in severity
Family history
Reduced or abnormal vW Factor
Patients with von Willebrand Disease are unable to make platelet plug
vWF acts as a carrier for FVIII

**Von-Willedrand's factor has two functions: helps in the adhesion of the platelets & stabilizes (carries) factor 8:C to form the whole factor 8 complex*
Therefore, sometimes Von-Willdrand's disease is misdiagnosed as Haemophilia A

(vWD) Classification:

Type 1 (partial deficiency of vW factor)
Type 2 (qualitative def. of vWF)
2a (↓ plt dependent function with absent HMW multimers of vWF)
2b (variants with ↑ affinity for plt gp 1b)
2m (as 2A but HMW multimers present)
2n (variants with ↓ affinity for FVIII)
Type 3 (complete def. of vWF)

(vWD)Clinical features:

>>>>There is huge variation in its level in the same individual so the manifestation can vary as well as the outcome of investigations, so normal level in the blood doesn't exclude the disease in one check-----} repeat the test

>>>>VWD manifest itself as platelet deficiencies in that it involve the skin and mucous membrane more than the muscle and joint bleeding

Skin & mucosal bleeding

- Easy bruising
- Recurrent gum & nose bleeds
- Increased menstrual bleeding
- Bleeding after dental extraction or other surgical procedures

(vWD) Diagnosis

Diagnosis can be difficult

Blood tests performed to determine the amount, structure and function of von Willebrand Factor

Since levels can vary, sometimes tests may need to be repeated.

Bleeding time usually prolonged

Multimer analysis

(vWD) Management:

Local measures

DDAVP (1-deamino-8-arginine vasopressin) In type 1 and type 2-A

vWFactor concentrate (highly purified)

Intermediate purity vWF (8Y, Hemate P)

Cryoprecipitate

Factor VIII may be needed

Cryoprecipitate (Cryo)

-Cryoprecipitate is prepared by thawing fresh frozen plasma. After centrifugation, the supernatant plasma is removed and the insoluble cryoprecipitate is refrozen.

-Cryoprecipitate provides a source of coagulation factors. Factor VIII, Factor XIII and von Willebrand Factor.

-Fibrinogen and fibronectin are also present

Acquired Thrombocytopenias

Immune Thrombocytopenias:

*Allo-immune
- Neonatal allo-immun thrombocytopenia
- Post-transfusion purpura
- Refractions to platelet transfusion

*Auto-immune
- Idiopathic thrombocytopenic Purpura (ITP)
-Secondary auto-immune Purpura
-Acute (post viral) Thrombocytopenia

*Drug induced immune
- Drug-dependent
- Drug-independent (auto- immune)

Idiopathic Thrombocytopenic Purpura (ITP):

	Acute	Chronic
Peak age	8-2	40-20
incidence Sex	F=M	F=3M
Ouset	Sudden	insidious
Duration	<6 months	>6 months
Disorder Associated	preceding viral infection	1-Idiopathic 2-Secondary

Clinical Features:

Main feature is bleeding (mucosal & skin) and severity depends on the degree of thrombocytopenia.
Risk of serious bleeding when Plt < 10x109/L
Splenomegaly is not a feature.
Features of secondary disease……

Lab Diagnosis:

-Isolated thrombocytopenia
- Normal or increased number of megakaryocytes
-↑ Mean Platelet volume
-Other causes should be ruled out
-Demonstration of auto-antibodies
-Peseudothrombocytopeneia
-SLE tests

Pathogenesis:

1-Production of antibodies
2-Coating of Platelets
3- Removal by RE system (Spleen & Liver)
4-AB may be directed against megakaryocytes.

Drug Induced Thrombocytopenia

- Drug history
- Quinine, Quinidine, Sulphonamides, trimethroprim, Gold, Heparin

Management:

-Steroids
- Splenectomy
-IVIG
-Refectory patients (20%)
Immunosuperssion : (Azathioprine, Cyclophosphamide & Cyclosporine)
Danazol
Rituximab
-Platelet transfusion should be avoided unless bleeding occure.

Acquired defects of Clotting

1-Massive transfusion

Dilution of coagulation factors
Crystalloids
Packed red cells
Activation of clotting factor
Breakdown of Plt, 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 Plt count ≤ 50, transfuse platelet 6-10 unit
- If PT & APTT significantly prolonged, we give plasma (FFP)
- If ↓ fibrinogen < 1g/DL, consider giving cryoprecipitate.

2-Liver Diseas

-All the coagulation factors except VWF, are synthesized by the liver.
- Liver also synthesizes AT III, Protein C & S, α2 antiplasmin & Plasmonigen
-Liver is responsible to clear activated components of coagulation & fibrinolysis.
- Hepatocellular damage is accompanied by complex disturbances of haemostasis
-Low Plt count (Splenic or liver sequestration, Plt dysfunction)
-DIC may occur
-Fibrinogen well preserved till late but may be abnormal.

Management

Try vitamin K (because deficiency is common)
PT & APTT should be corrected within 5 seconds of normal by giving FFP, for liver biopsy & other procedures.
Platelet transfusion if it is in a low count
DDAVP may help

3-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 & Plt aggregation is impaired.

-Peritoneal or haemodialysis partially corrects the defect.
-Anemia should be corrected
-DDAVP reduces BT & minor surgery can be performed.
-Conjugate oestrogens.

Coagulopathy in Cancer:

Thrombocytopenia
Decreased production
Chemo/radiotherapy
Marrow infiltration
Accelerated destruction
Hypersplenism
DIC
Immune thrombocytopenia

Functional Plt abnormalities
Myeloproliferative disorders
Myeloma (Paraprotein)
Coagulation changes
DIC
Circulating anticoagulants

Disseminated intravascular coagulation (DIC)

Definition:
No consensus.
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 (Muller-Bergaus et al 1995).

CLINICAL CONDITIONS ASSOCIATED WITH DIC

INFECTIONS **(Severe sepsis)**
- Bacterial (30-50 %)
- Viral
- Parasitic

SEVERE TRAUMA (50-70 %)
- General
- Head trauma

CANCER
- Solid tumours
- Haem. Malignancies (15-20 %)
- APML

OBSTETRIC CONDITIONS
- Placental abruption
- Amniotic fluid embolism
- Retained dead foetus

VASCULAR DISORDERS
- Giant haemangiomas (Kasabach-Merrit syndrome)
- Large aortic aneurysm (1 %)

SEVERE ALLERGIC/TOXIC REACTIONS

ABO mismatched transfusion

Snake bite

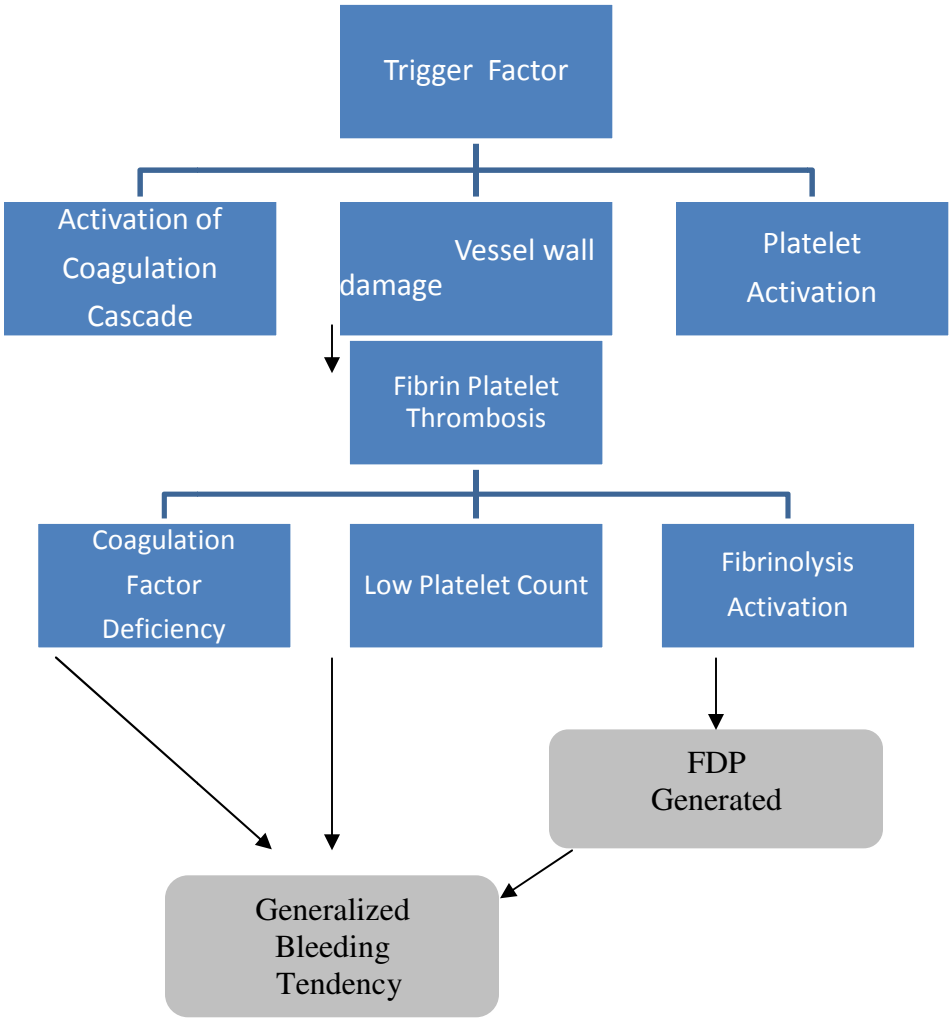
PATHOGENESIS OF DIC

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 ischaemia 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,indothelial damage & following thromdin generation

Pathogenesis of DIC



Lab Diagnosis of Acute DIC

↑ PT
↑ APTT
↑ Thrombin time
↓ Platelets
↓ Fibrinogen < 1.0 g/L Normal 1.5-4.0 g/L)
↑ FDP & D-Dimer

Management of DIC

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 concentrates in refractory cases.

Remember :

Platelet dysfunction>>>bleeding through the skin & mucosal membranes

coagulation factors dysfunction>>>bleeding through muscles & joints

long life bleeding suggests inherited diseases
new bleeding must be acquired

! *DDAVP is helpful in the treatment of mild haemophilia A,and in type 1 & type 2 A vWD, it's not effective in haemophilia B*

The most common acquired cause of platelet dysfunction is the intake of aspirin
The most common acquired disease of platelet is thrombocytopenia

The most inherited type in KSA is Glanzmann's Thrombosthenia
where platelet aggregation is inhibited

COMMON Q

Haemophilia:

1)X-linked recessive disorder
2) can be associated with bleeding in joint
3) in haemophilia A, 10% of patient have VIII antibodies
4)there is bleeding in muscle
5) if 50% of factor VIII in plasma, the patient should be asymptomatic

Regarding immuno-thrombocytopenia purpura, most true:

1)if it was 2ry to drug, it appears within 2months of using that drug
2)Prednisolone may be used
3)splenectomy is the only treatment
4) splenectomy is the last treatment of choice

The most specific diagnostic test for DIC:

1)fibrinogen degenerative products
2)fibrin
3)PT
4)PTT
5)bleeding time

Which of the following statement regarding immune thrombocytopenia is the most correct:

1)palpable spleenomegaly is frequently present
2)spleenectomy is the treatment of choice
3)platelet transfusion should be used only for life threatening bleeding
4)medication that will cause thrombocytopenia will do so withen two months of their use
5)spherocytes are usually present on the peripheral blood smear

Vitamin K related coagulation factor all Except:

1)VII
2)X
3)IX
4)V
5)prothrompin

You cannot always
HAVE HAPPINESS,
but you can always
GIVE HAPPINESS !