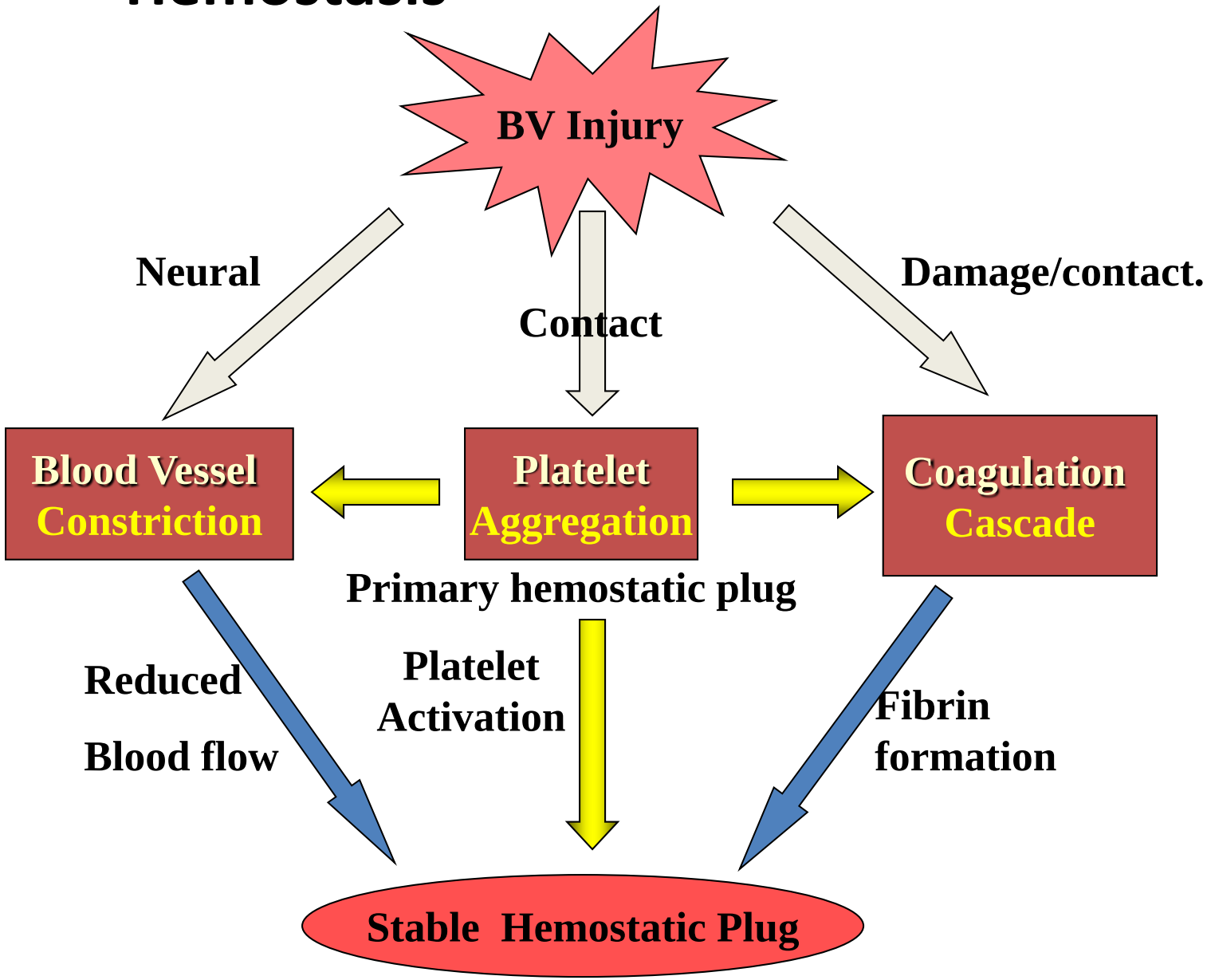
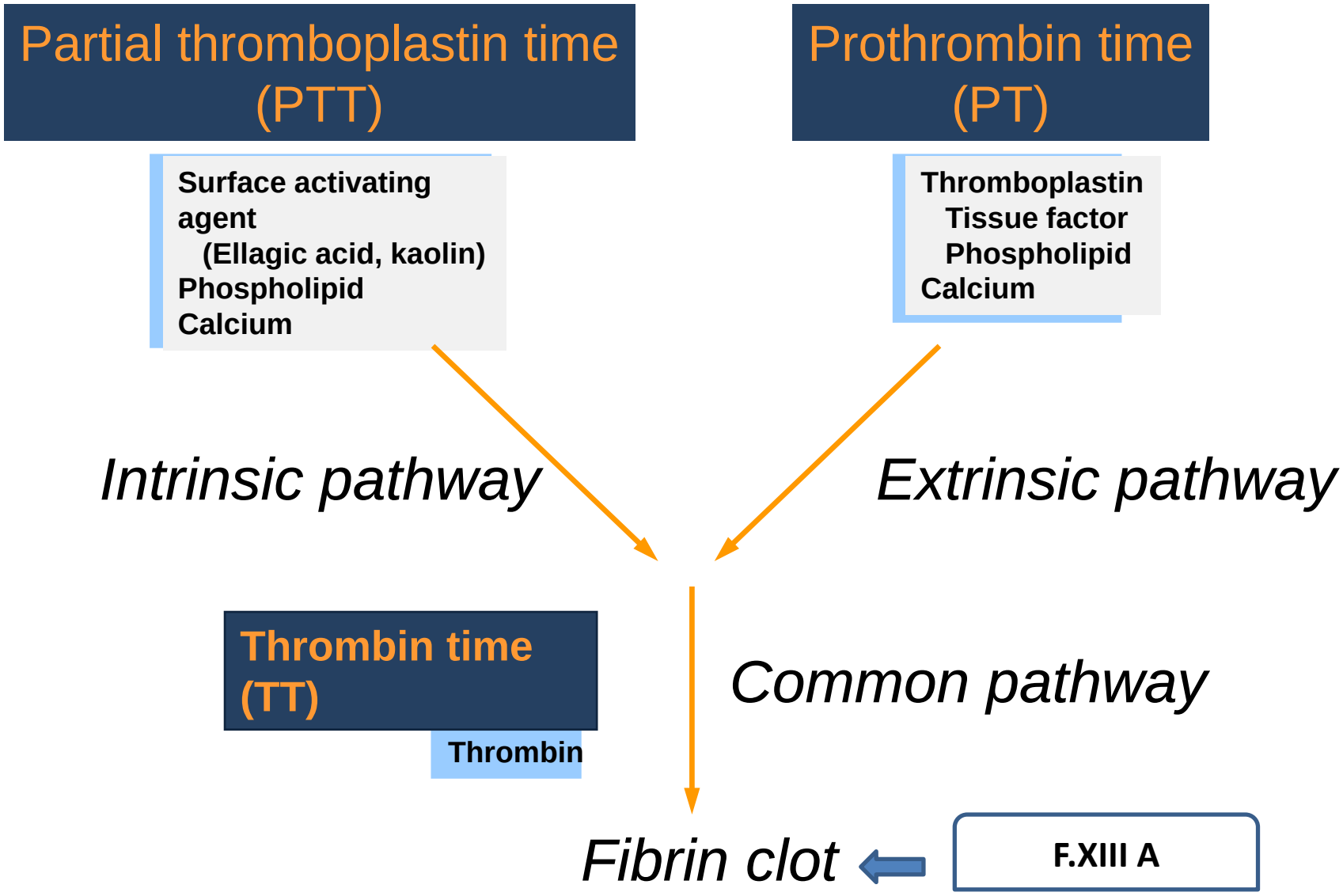
Bleeding Disorders. MS4.27.10.15

Abdallah Abbadi.MD.FRCP

Hemostasis


BV Injury
Neural
Contact
Damage/contact.
Blood Vessel Constriction
Platelet Aggregation
Coagulation Cascade
Primary hemostatic plug
Reduced Blood flow
Platelet Activation
Fibrin formation
Stable Hemostatic Plug

Laboratory Evaluation of the Coagulation Pathways



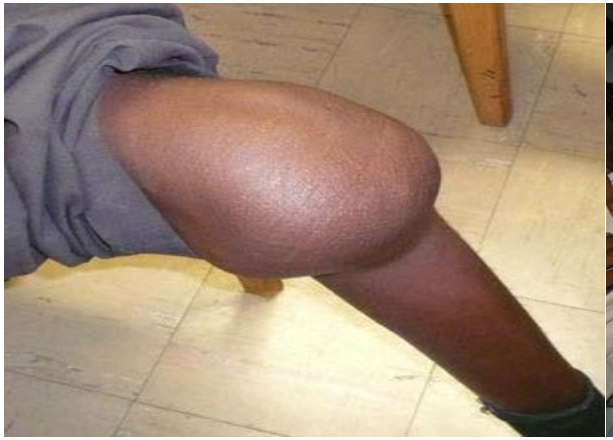
Bleeding Time(BT)

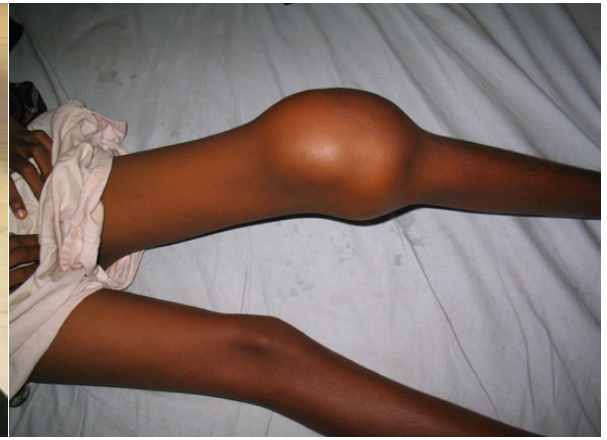
- 5-10% of patients have a prolonged bleeding time
- Most of the prolonged bleeding times are due to aspirin or drug ingestion
- Prolonged bleeding time does not predict excess surgical blood loss
- Not recommended for routine testing in preoperative patients
- Prolonged in vWD
- Prolonged in thrombocytopenia
- Prolonged in Qualitative platelet disorders

Case 5

19 yr old male complains of repeated attacks of large joint painful swelling especially in his knees for several years, with limitation of movement of the l knee joint. P/E shown. His maternal uncle has similar condition.PT 14/14 s, PTT 80/31s, with mixing 40/32s. TT 12/12s, Plt 220K, BT 5mnts. F VIII <1%. F IX 100%.No VIII inhibitors. Genetic testing INT 22 INVS.

△ HA.





Case 5: Management & Follow-up

1- Treat acute attack: FVIII* 30u/kg/ IV q 12 hrs x 2 days, then daily until it subsides. + Analgesics.

2- Evaluate for ? Synovectomy (chemical or radio-isotope or surgical).Or Joint replacement.

3- Consider for long term prophylaxis 20u/kg x 2 per week indefinitely.

4- Education/ rehabilitation

5- genetic counseling.

6- Family screening and registration

7- Screen for inhibitors x 2 per yr since therapy is different.

***FVIII: recombinant or ?plasma derived**

Hemophilia A and B

	Hemophilia A	Hemophilia B
Coagulation factor deficiency	Factor VIII	Factor IX
Inheritance	X-linked recessive	X-linked recessive
Incidence	1/10,000 males	1/50,000 males
Severity	**Related to factor level** **<1% - Severe - spontaneous bleeding** **1-5% - Moderate - bleeding with mild injury** **5-25% - Mild - bleeding with surgery or trauma**	
Complications	Soft tissue bleeding	

Clinical Features of Bleeding Disorders

	Platelet	Coagulation Factors Disorders
Site of bleeding	Skin Mucous membranes (epistaxis, gum, vaginal, GI tract)	Deep in soft tissues (joints, muscles)
Petechiae	Yes	No
Ecchymoses (“bruises”)	Small, superficial	Large, deep
Hemarthrosis / muscle bleeding	Extremely rare	Common
Bleeding after cuts & scratches	Yes	No
Bleeding after surgery or trauma	Immediate, usually mild	Delayed (1-2 days), often severe

Coagulation factor disorders

- Inherited bleeding disorders
  - Hemophilia A and B
  - vonWillebrands disease
  - Other factor deficiencies
- Acquired bleeding disorders
  - Liver disease
  - Vitamin K deficiency/warfarin overdose
  - DIC

The F8 gene

Human F8 gene maps to the most distal band (Xq28) of the long arm of the X chromosome

The gene is 186 Kb in length and comprises **26 exons.**

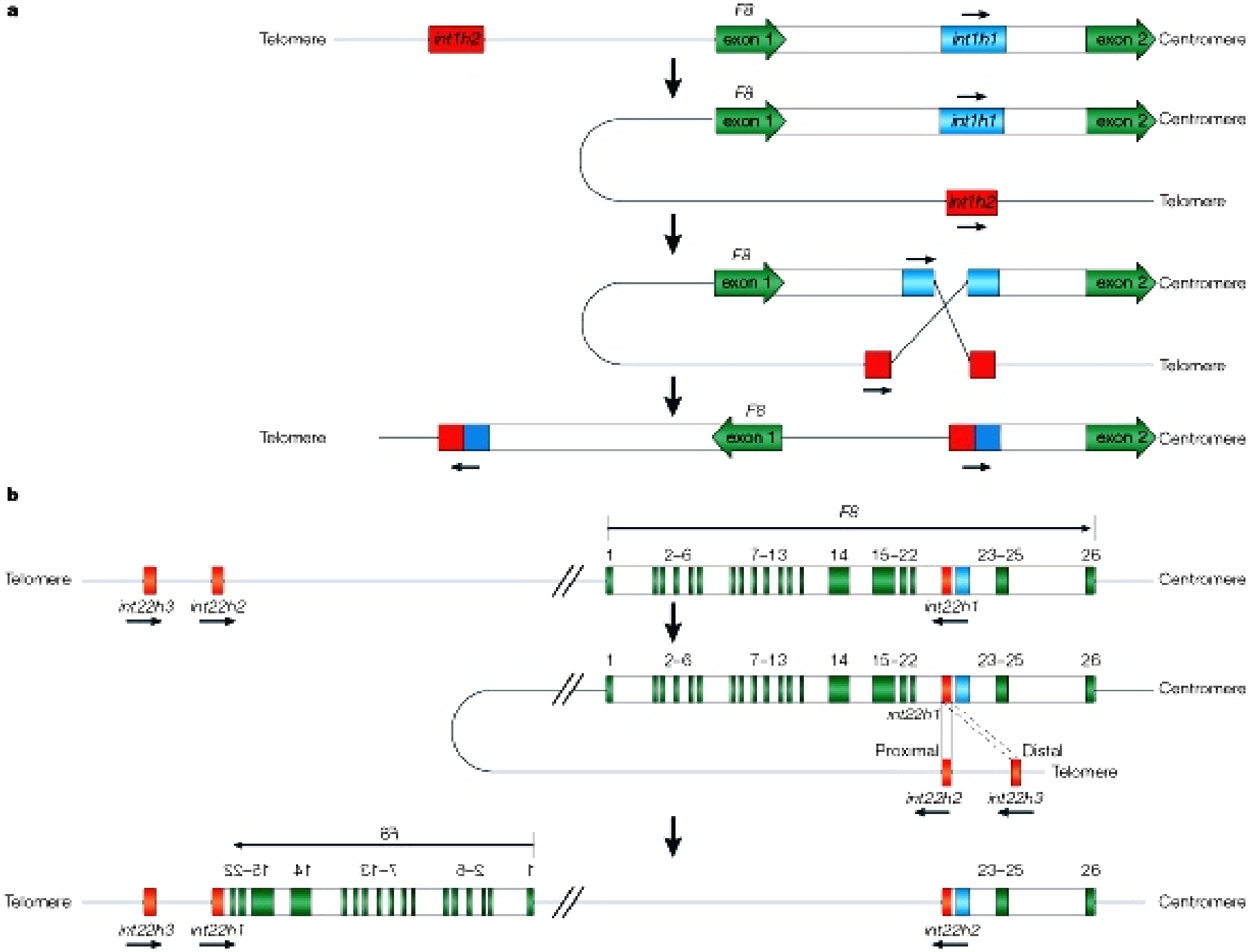
An **intron 22 inversion** is responsible for 45% of severe hemophilia A and intron 1 inversion is responsible for 3 %of severe hemophilia A.

other reported mutation include deletion, insertion and point mutations causing nonsense, missense or splice site mutation.

F8 Intron 22 Inversion

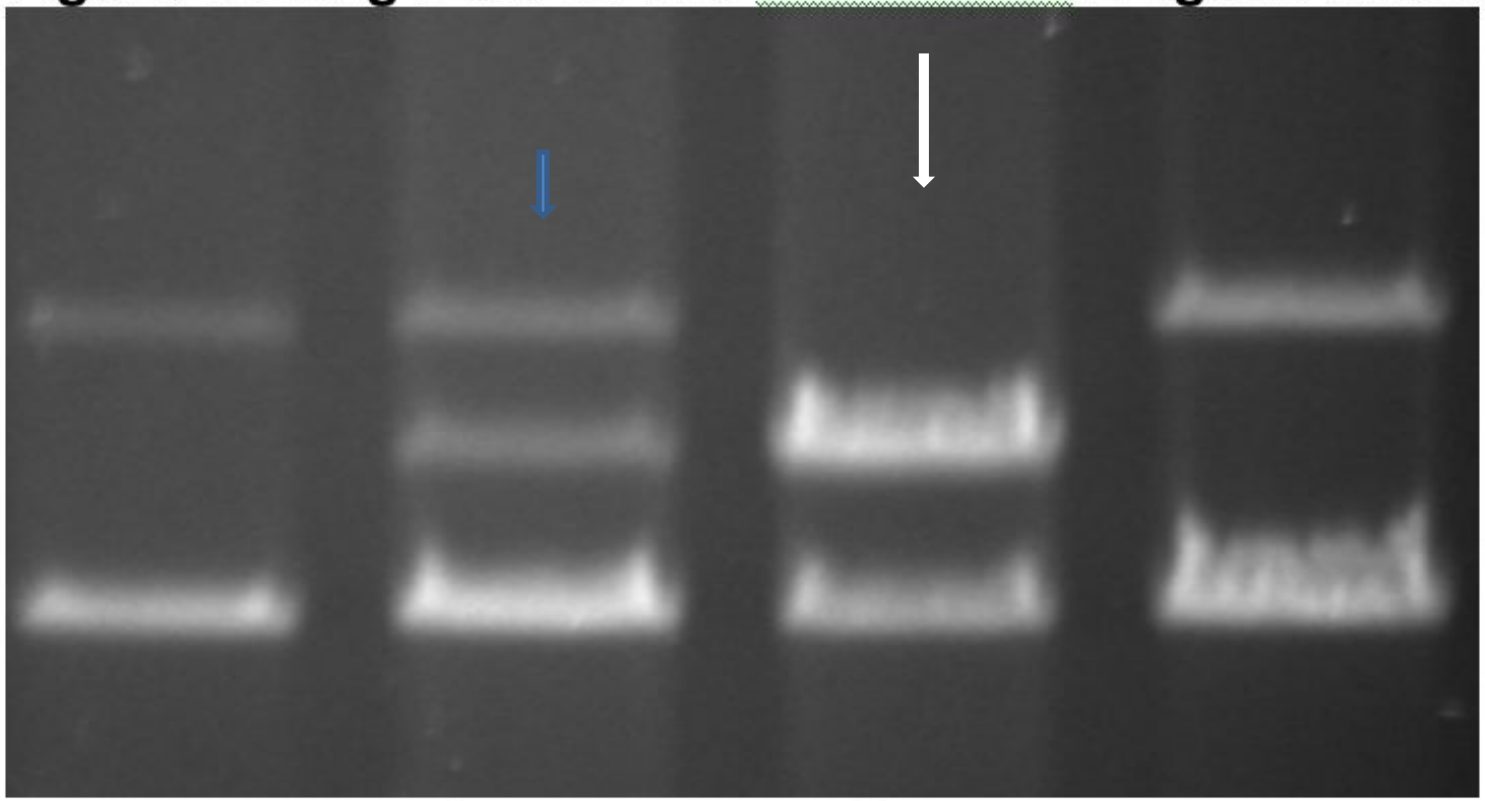
The F8 gene intron 22 inversion mutation arises from homology recombination between copies of the intron 22 homology region(int22h-1”F8A+F8B”) and repeated telomeric DNA sequences outside the F8 gene (int22h-2,int22h-3) on the long arm of chr.X

These two copies are located approximately 500Kb distal and telomeric to the F8gene.The int22h-1 and h2-, h-3 regions have 99% homology with one another.


a
Telomere
int1h2
F8
exon 1
int1h1
exon 2
Centromere
Telomere
b
F8
1
2–6
7–13
14
15–22
23–25
26
Telomere
Centromere
int22h3
int22h2
int22h1
Proximal
Distal
Telomere

Result

Figure 1. Long PCR for the FVIII intron 22 gene inversion



Genetic Screening:
Results for Hemophilia A (HA)

- **HA causative mutations identified in tested patients**

Type of Mutation	Number of Families	Number of Patients	% of families	% of patients
Itnron 22 inversion	**25**	**70**	**53%**	**38.8**
Intron 1 inversion	**1**	**1**	**2.4%**	**0.5**
Missense	**16**	**95**	**36%**	**52.7**
Frameshift (Insertion/deletion)	**4**	**14**	**9.5%**	**7**
Total	**46**	**180**		

***F8* gene mutation profile of all Jordanian hemophilia A patients examined.**

*Awidi A et al: Haemophilia. 2010 16(1):136-42

Thrombosis&Haemostas lab (THL)
Medical school / Jordan University
Common Bleeding Disorders End of July 2015

$\bar{x}$ Age/Yr of diagnosis at THL

Severity %

Serial NO.	Disorder	Total NO.	M	F	M	F	M	SEVERE <1	MODERATE 1-5	MILD >5
1	Haemophilia-A	259	259	0	8	0	2.3	150	35	74
2	Haemophilia-B	66	66	0	7.1	0	4.45	55	5	6
3	VWD	151	62	89	13	2221.5	17.25	___	___	___
4	Glanzmann	112	47	65	12	8.2	10.1	___	___	___
5	TOTAL NO. OF COMMON-BLEEDING DISORDER	588	434	145	___	___	___	205	40	80

Treatment of Severe/ Moderate hemophilia

1- On demand/hospital based

2- On demand/home based

3- **Prophylactic/ home/ intermittent X 2 per week**

4- Treatment of target joint

5- Physiotherapy

6- Genetic counseling

7- Education

Dosing guidelines for hemophilia A

- **Mild bleeding**
  - Target: 30% dosing q8-12h; 1-2 days (15U/kg)
  - Hemarthrosis, oropharyngeal or dental, epistaxis, hematuria
- **Major bleeding**
  - Target: 80-100% q8-12h; 7-14 days (50U/kg)
  - CNS trauma, hemorrhage, lumbar puncture
  - Surgery
  - Retroperitoneal hemorrhage
  - GI bleeding
- **Adjunctive therapy**
  - Tranexemic acid(Cyclokapron) or DDAVP (for mild disease only)

Complications of therapy

- **Formation of inhibitors** (antibodies)
  - 10-15% of severe hemophilia A patients
  - 1-2% of severe hemophilia B patients
- **Viral infections**

-Hepatitis B
-Hepatitis C
-HIV
-Human parvovirus
-Hepatitis A
-Others (Prion disease or BSE)

Treatment of hemophilia B

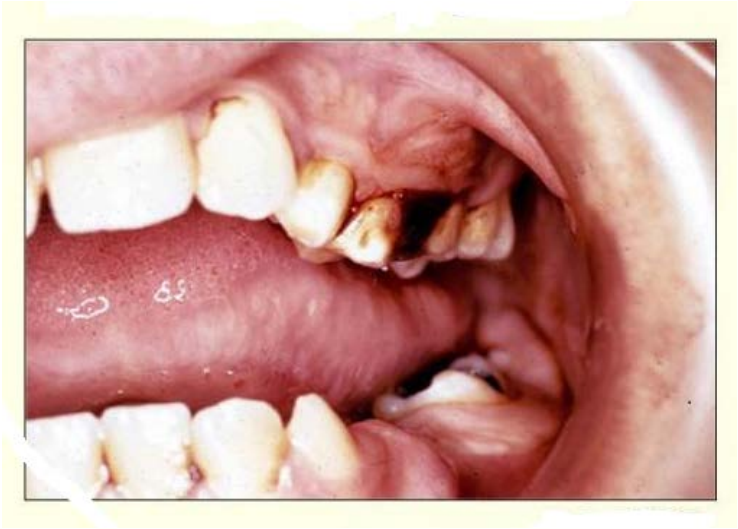
- Agent
  - High purity factor IX
  - Recombinant human factor IX
- Dose
  - Initial dose: 100U/kg
  - Subsequent: 50 U/kg every 24 hours

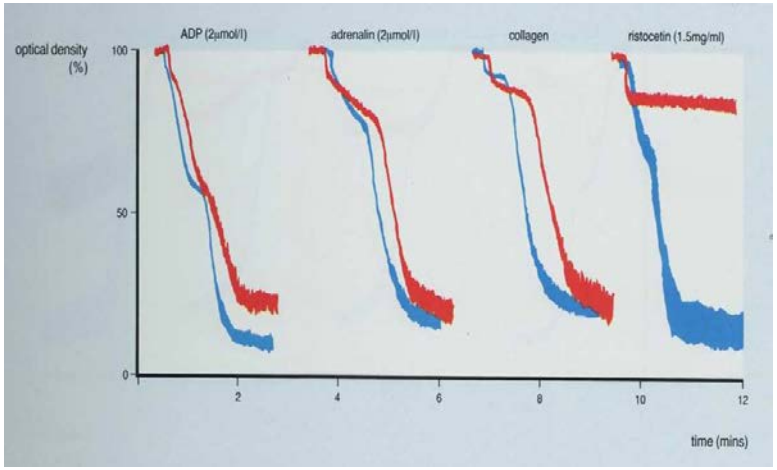
Case 5 B

27 yr old male patient was brought to E/R for prolonged bleeding after tooth extraction. He had epistaxis, gum bleeding and prolonged bleeding from wounds ever since he remembers. He was admitted several times because of bleeding. His father is reported to have epistaxis and several hospital admissions for bleeding. P/E: Pallor. P 120, BP 95/60 lying, no fever, bleeding from mouth and extraction socket.

Hb 7, WBC 13000, Plt 280k, PT 13/13, PTT 39/31, TT 12/11. BT > 15 mints. Bld group, O Pos.

Case 5 B ..continuation

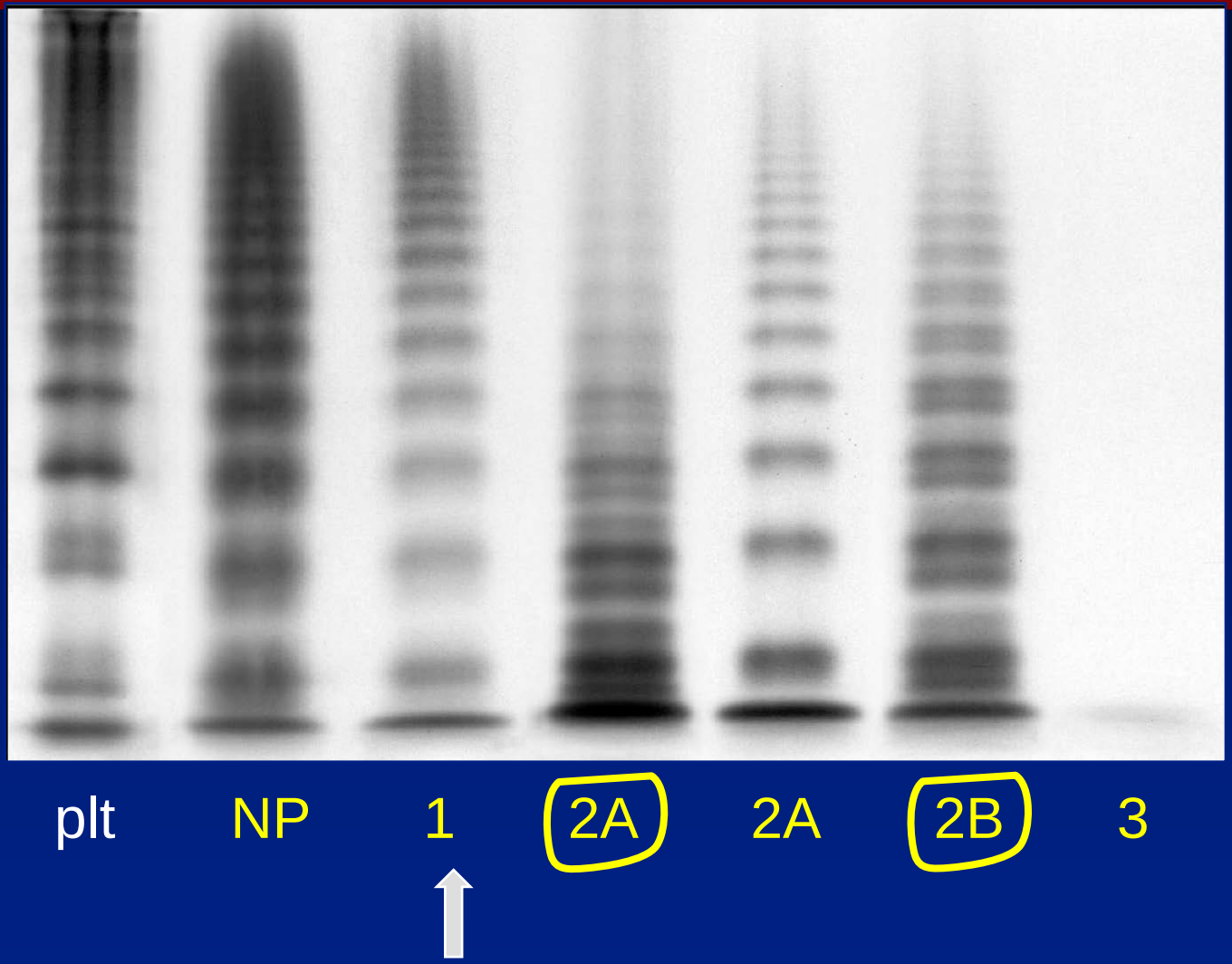




FVIII 48%, VWF 15%. Clot retraction: Normal.

Diagnosis: VWD Type I

Case 5 B VWF Multimers



Management of Case 5 B

1- Cryoprecipitate 1 bag/ per 10 kg body weight x 2 day for 3-4 days then daily for 3 more days.

2- Dental consultation/ mouth hygiene & care.

3-Education and counseling.

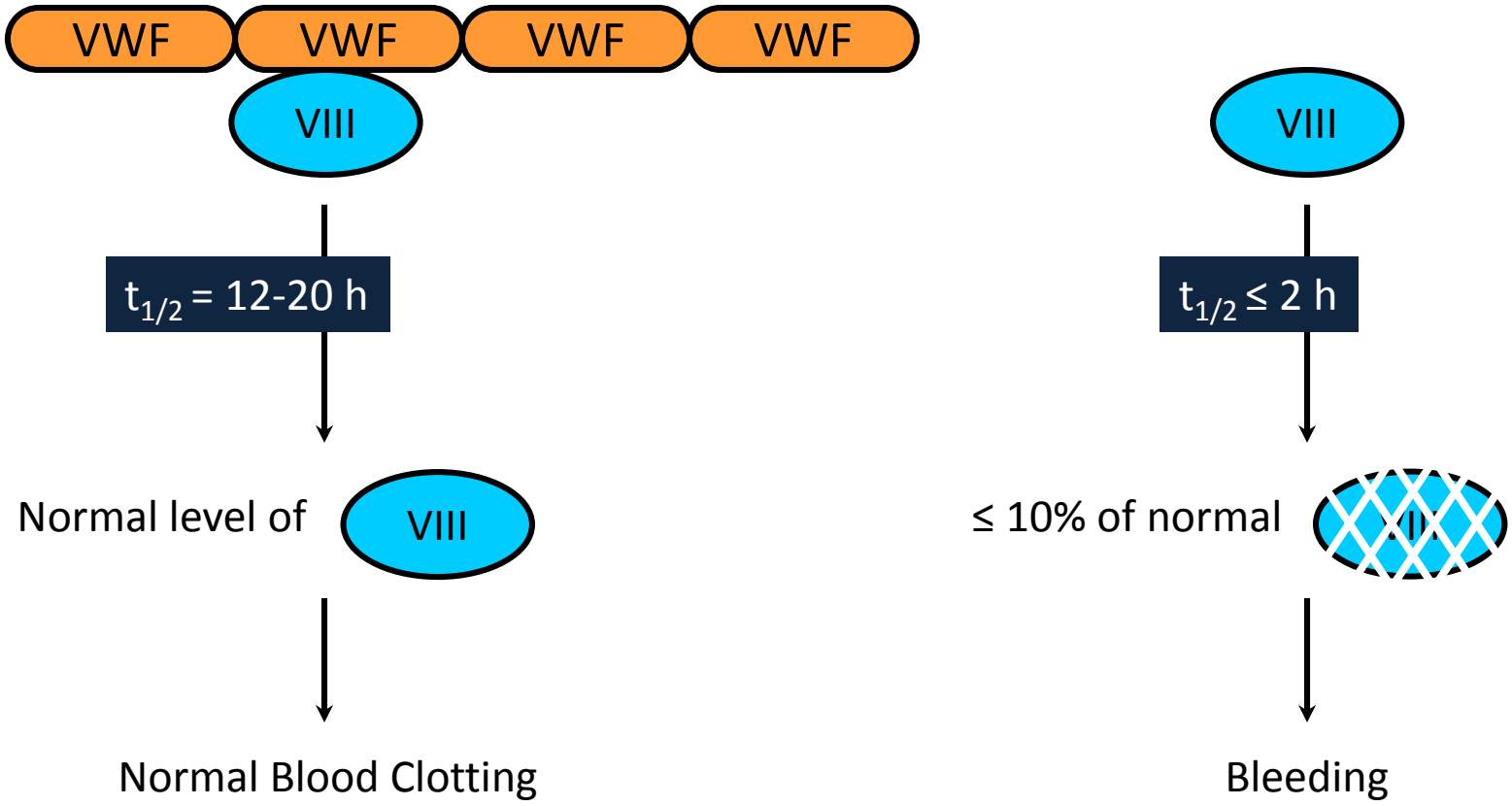
4- Screening of family.

5- ?? DDAVP for therapy of mild bleeding

von Willebrand Disease: Clinical Features

- von Willebrand factor
  - Synthesis in endothelium and megakaryocytes
  - Forms large multimer
  - Carrier of factor VIII
  - Anchors platelets to subendothelium
  - Bridge between platelets
- Inheritance - autosomal dominant
- Incidence - 1/10,000
- Clinical features - mucocutaneous bleeding

VWF and Factor VIII Survival



Laboratory evaluation of von Willebrand disease

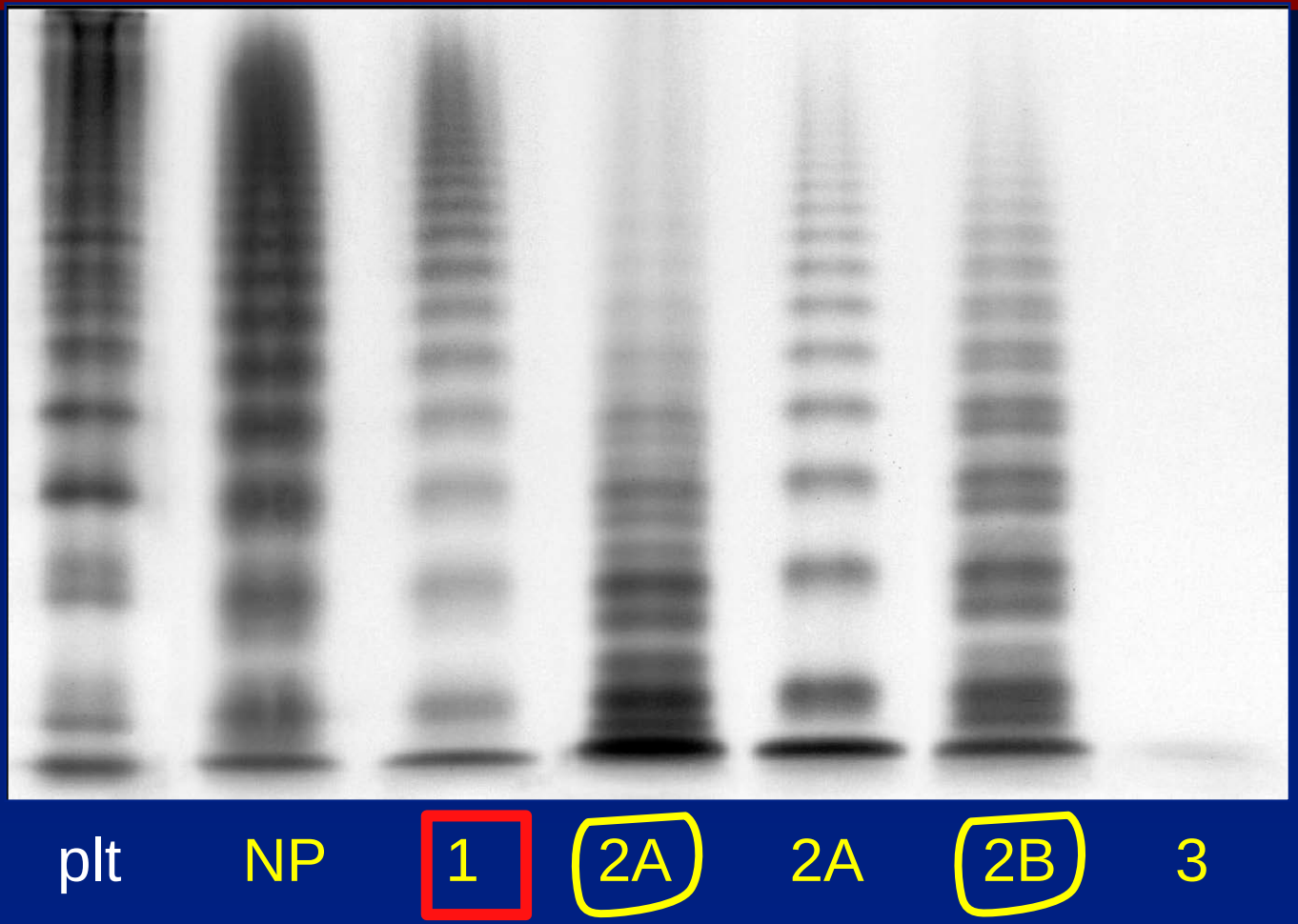
Classification

- Type 1 — Partial quantitative deficiency
- Type 2 — Qualitative deficiency
- Type 3 — Total quantitative deficiency

Diagnostic tests:

Von Willebrand type			
Assay	**1**	**2**	**3**
vWF antigen	⇓	**Normal**	⇓⇓
vWF activity	⇓	⇓	⇓⇓
Multimer analysis	**Normal**	**Normal?abnormal**	**Absent**

VWF Multimers



Treatment of von Willebrand disease Varies by Classification

- Cryoprecipitate
  - Source of fibrinogen, factor VIII and VWF
  - Only plasma fraction that consistently contains VWF multimers
  - Correction of bleeding time is variable
- DDAVP (Deamino-8-arginine vasopressin)
  - Increases plasma VWF levels by stimulating secretion from endothelium
  - Duration of response is variable
  - Used for **type 1** disease
  - Dosage 0.3 µg/kg q 12 hr IV
- Factor VIII concentrate (Humate-P)
  - Virally inactivated product
  - Used for type 2 and 3

Acquired von Willebrand Syndrome

Immune-mediated:

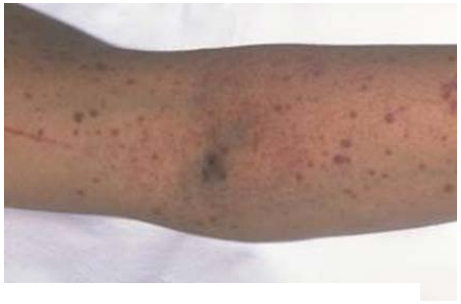
- Lymphoproliferative disease (MM, MGUS)
- Autoimmune disease (SLE)
- May respond to DDAVP, IVIG, factor concentrate

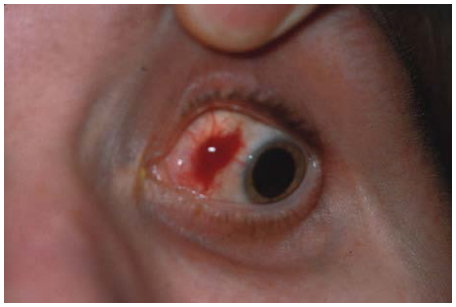
Proteolysis-mediated:

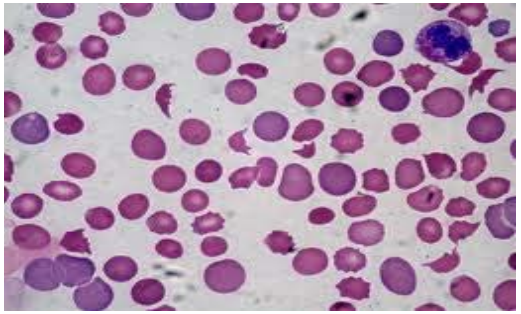
- Thrombocytosis (reactive or myeloproliferative disorders)
- Shear-induced (aortic stenosis)
- Correct the underlying disorder

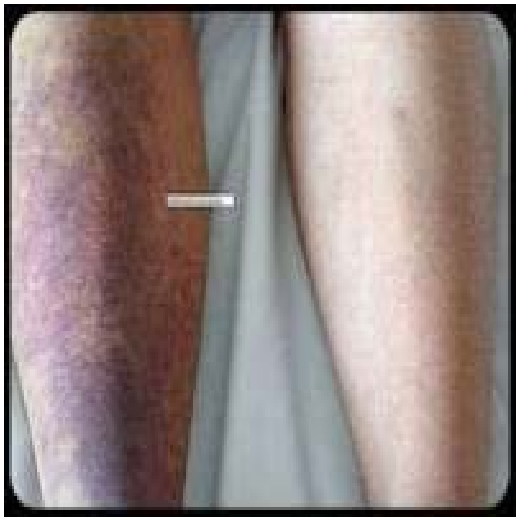
Case 5 C

37 yr old lady was admitted with high fever, chills, rigors and severe dysuria.P/E shown. Temp 40.5,BP 80/50, P122 regular, low volume. Bleeding from needle puncture sites and bruising. Hb 9g/dl, retcs 6%, bilirubin 5 (d1), WBC 19k, Plt 25k, PT >50s, PTT > 100s, TT >30s, D-Dimer +++, Creatinine 2.3. Bld film shown.Fibrinogen. 30mg/dl.



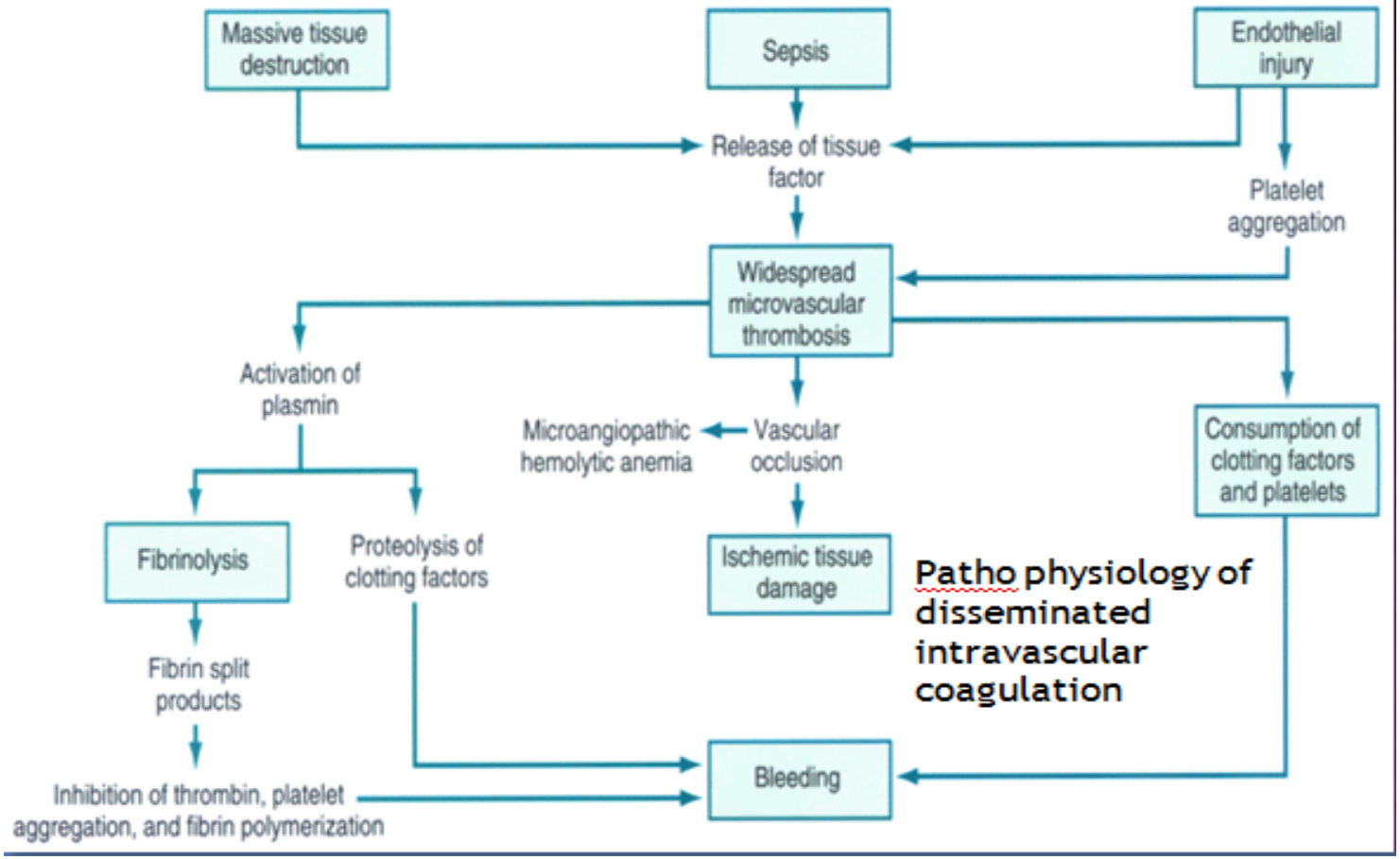






Pathogenesis of DIC

- **Two major mechanisms may trigger DIC:**
  (1) release of tissue factor or thromboplastic substances into the circulation
  (2) widespread injury to endothelial cells



Patho physiology of disseminated intravascular coagulation

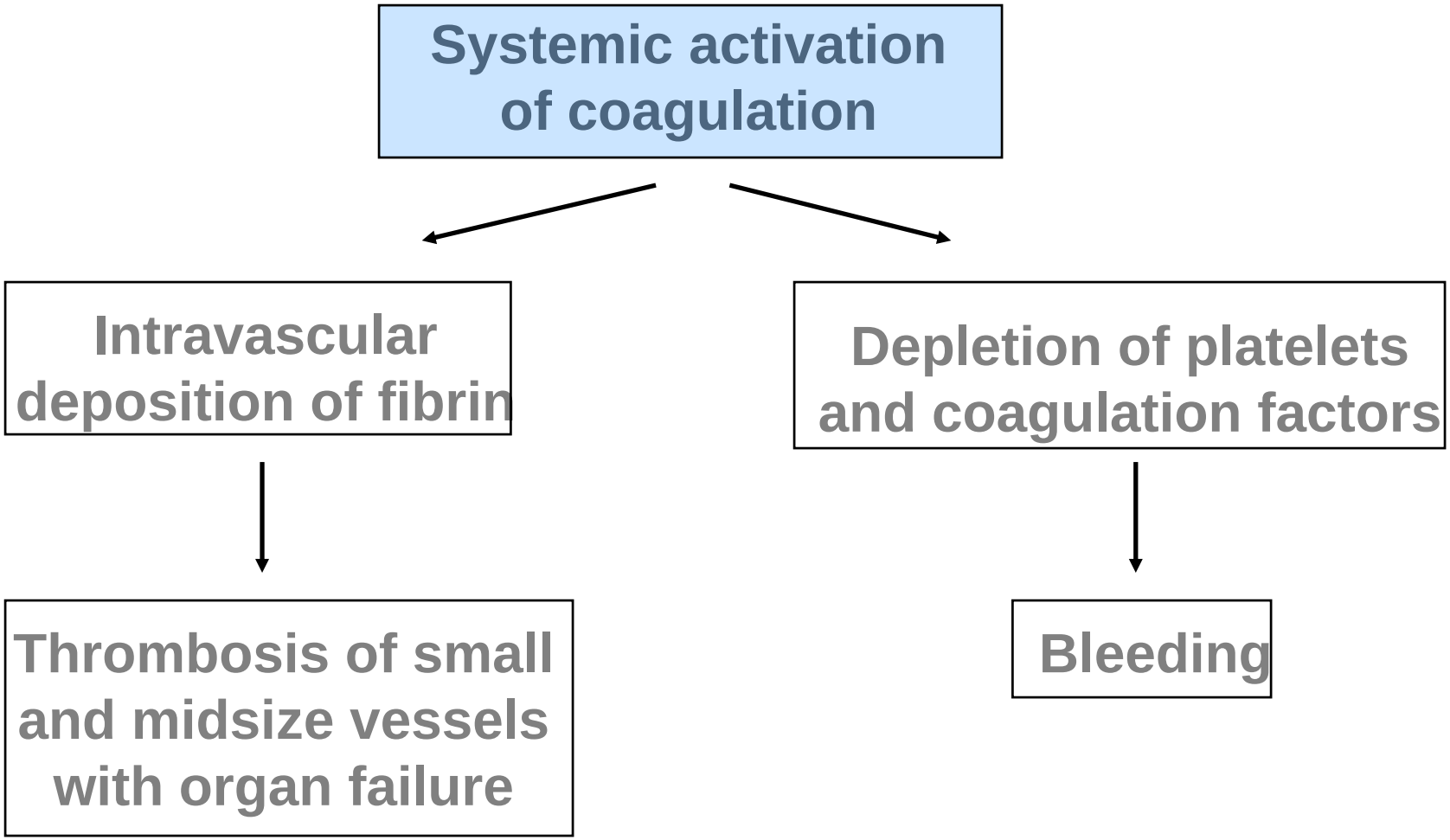
Common clinical conditions associated with Disseminated Intravascular Coagulation

Activation of both coagulation and fibrinolysis

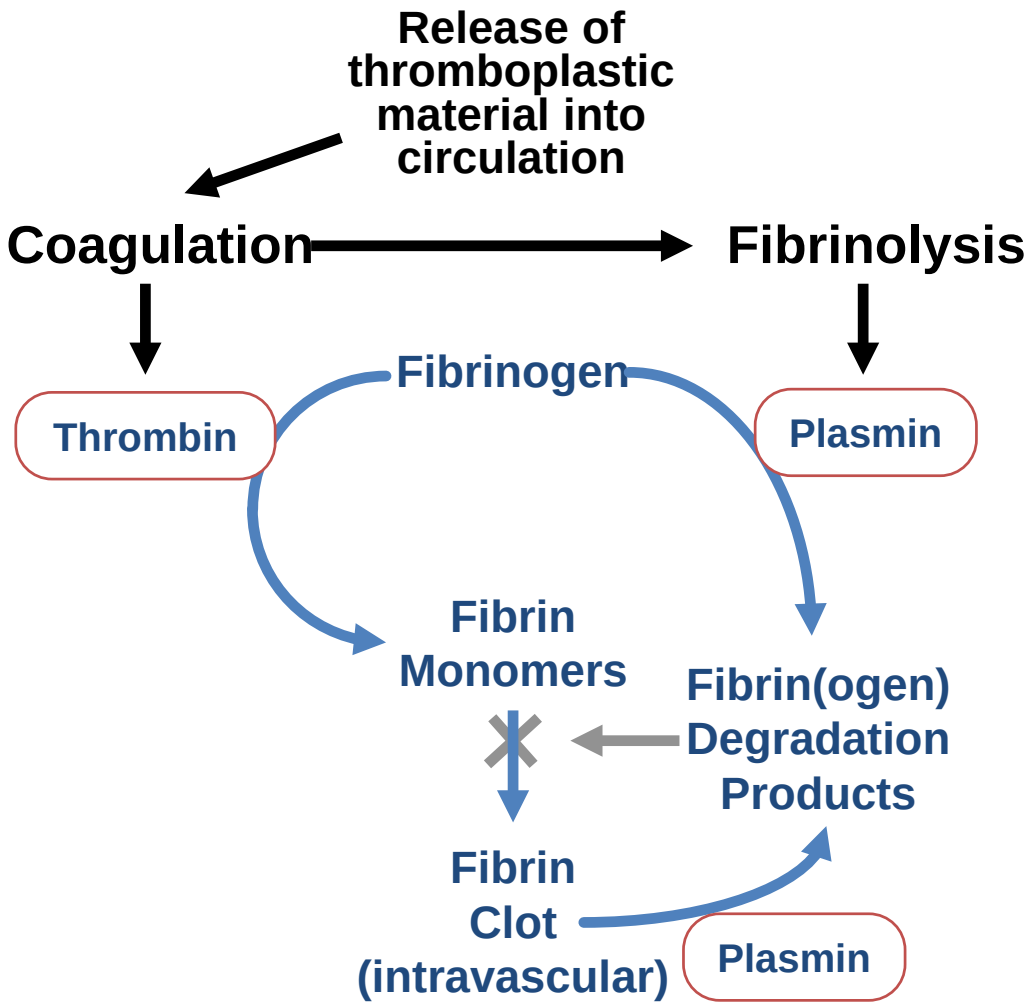
Triggered by

- Sepsis
- Trauma
  - Head injury
  - Fat embolism
- Malignancy
- Obstetrical complications
  - Amniotic fluid embolism
  - Abruptio placentae
- Vascular disorders
- Reaction to toxin (e.g. snake venom, drugs)
- Immunologic disorders
  - Severe allergic reaction
  - Transplant rejection

Disseminated Intravascular Coagulation (DIC) Mechanism



Pathogenesis of DIC



Consumption of coagulation factors; presence of FDPs
↑ aPTT
↑ PT
↑ TT
↓ Fibrinogen

Presence of plasmin
↑ FDP

Intravascular clot
↓ Platelets
Schistocytes

Case 5 C: treatment and follow-up

1- Treat vigorously with IV antibiotics after blood, urine culture and septic work-up

2- Hydrate and ensure adequate urine output

3- ? ICU care

4- Replace missing clotting factors: FFP 10 ml/kg frequency to be determined as needed

5-Plt replacement

6- Monitor PT, PTT, D-Dimer and fbgn, Plt count

7- Investigate cause of uro-sepsis.

8- TTP can easily be excluded.

Disseminated Intravascular Coagulation: Treatment approaches

- Treatment of underlying disorder
- Platelet transfusion
- Fresh frozen plasma
- Coagulation inhibitor concentrate (ATIII)
- Anticoagulation with heparin

Disseminated Intravascular Coagulation Treatment approaches

- Treatment of underlying disorder
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