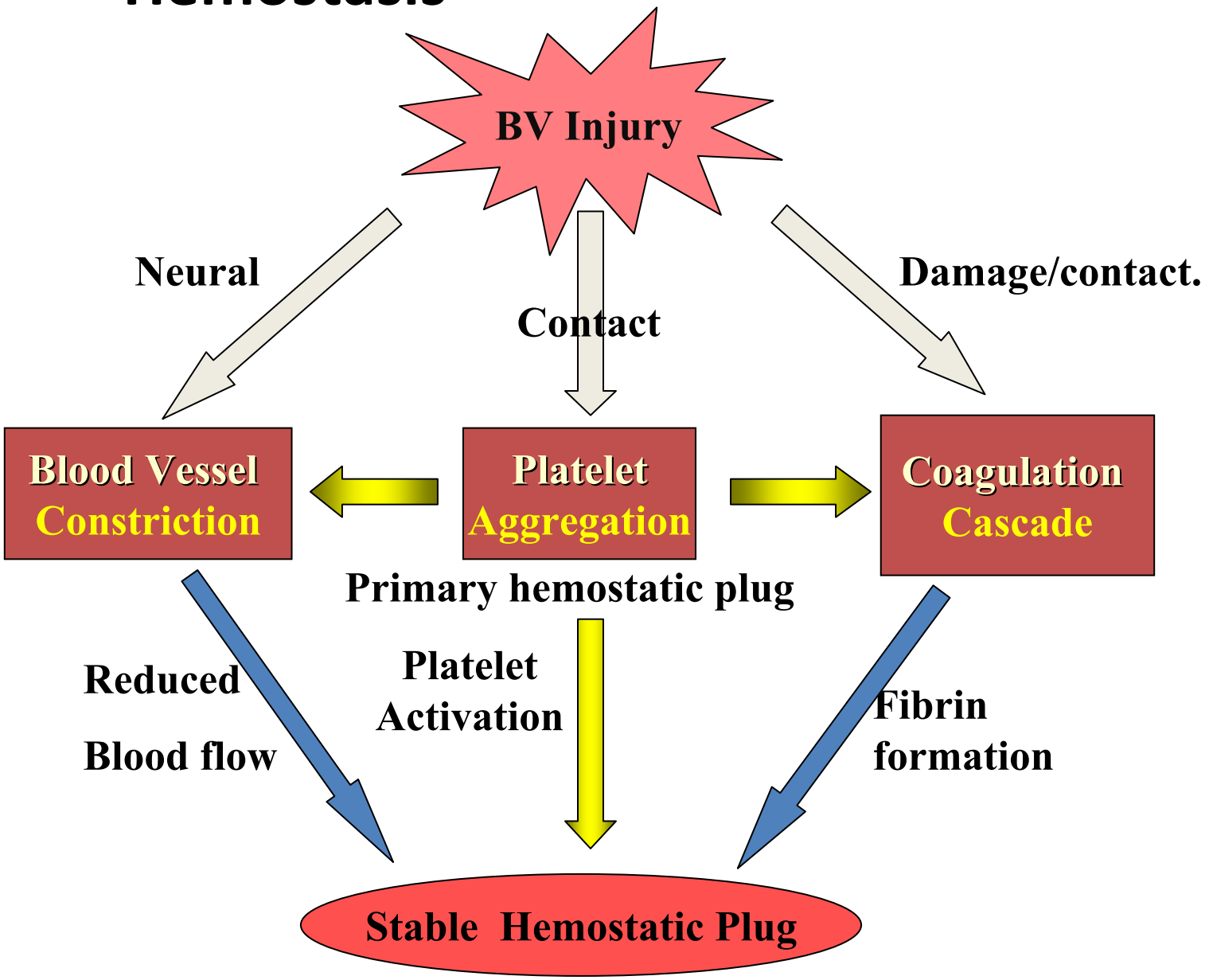
Bleeding Disorders 1

Feras M Farajeh, MD

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

“Coagulation Screen”

A- **common screening tests:**

1- Platelet count and morphology

2- Bleeding time (plt count must be normal)

3- Partial Thromboplastin Time (aPTT, PTT)

4- Prothrombin Time (PT)

5- Thrombin time (TT)

Coagulation screen 2

B- **Specialized tests**:

1- FXIIIA quantitative test

2- Clot retraction

3- Mixing studies

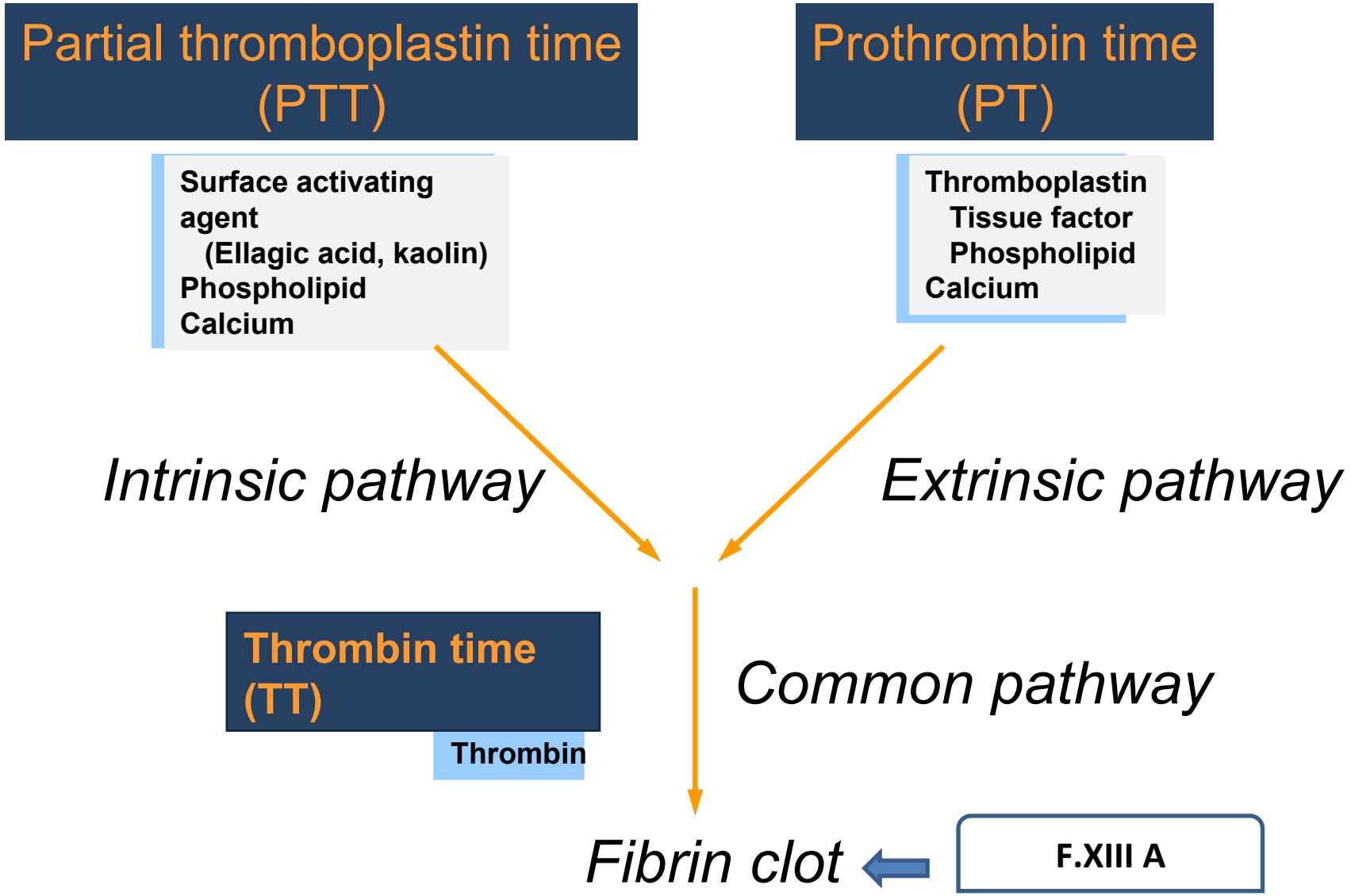
4-Factors assay

5-VW Factor quantitative assay

6- Platelet aggregation

C- **Other rare tests**

Laboratory Evaluation of the Coagulation Pathways



Clinical Features of Bleeding Disorders

	Platelet	**Coag 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

Table 1. Bleeding score

SYMPTOMS (up to the time of diagnosis)	SCORE				
	0[$]	1[$]	2	3	4
Epistaxis	No/trivial	- > 5/year or - more than 10 minutes	Consultation only*	Packing or cauterization or antifibrinolytic	Blood transfusion or replacement therapy (use of hemostatic blood components and rFVIIa) or desmopressin
Cutaneous	No/trivial	For bruises 5 or more (> 1cm) in exposed areas	Consultation only*	Extensive	Spontaneous hematoma requiring blood transfusion
Bleeding from minor wounds	No/trivial	- > 5/year or - more than 10 minutes	Consultation only*	Surgical hemostasis	Blood transfusion, replacement therapy, or desmopressin
Oral cavity	No/trivial	Present	Consultation only*	Surgical hemostasis or antifibrinolytic	Blood transfusion, replacement therapy or desmopressin
GI bleeding	No/trivial	Present (not associated with ulcer, portal hypertension, hemorrhoids, angiodysplasia)	Consultation only*	Surgical hemostasis, antifibrinolytic	Blood transfusion, replacement therapy or desmopressin

Hematuria	No/trivial	Present (macroscopic)	Consultation only*	Surgical hemostasis, iron therapy	Blood transfusion, replacement therapy or desmopressin
Tooth extraction	No/trivial or none done	Reported in ≤25% of all procedures, no intervention**	Reported in >25% of all procedures, no intervention**	Resuturing or packing	Blood transfusion, replacement therapy or desmopressin
Surgery	No/trivial or none done	Reported in ≤25% of all procedures, no intervention**	Reported in >25% of all procedures, no intervention**	Surgical hemostasis or antifibrinolytic	Blood transfusion, replacement therapy or desmopressin
Menorrhagia	No/trivial	Consultation only* or - Changing pads more frequently than every 2 hours or - Clot and flooding or - PBAC score>100#	- Time off work/school > 2/year or - Requiring antifibrinolytics or hormonal or iron therapy	- Requiring combined treatment with antifibrinolytics and hormonal therapy or - Present since menarche and > 12 months	- Acute menorrhagia requiring hospital admission and emergency treatment or - Requiring blood transfusion, Replacement therapy, Desmopressin, or - Requiring dilatation & curretage or endometrial ablation or hysterectomy)
Post-partum hemorrhage	No/trivial or no deliveries	Consultation only* or - Use of syntocin or - Lochia > 6 weeks	- Iron therapy or - Antifibrinolytics	- Requiring blood transfusion, replacement therapy, desmopressin or - Requiring examination under anaesthesia and/or the use of uterin balloon/package to tamponade the uterus	- Any procedure requiring critical care or surgical intervention (e.g. hysterectomy, internal iliac artery legation, uterine artery embolization, uterine brace sutures)
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

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

Hemophilia A and B

	Hemophilia A	Hemophilia B
Coagulation factor deficiency	Factor VIII	Factor IX
Inheritance	X- linked	X-linked
Incidence	1/10,000 males	1/50,000 males
Complications/clinical	Soft tissue bleeding	

Severity of bleeding is related to factor level

<1% - Severe - spontaneous bleeding

1-5% - Moderate - bleeding with mild injury

5-25% - Mild - bleeding with surgery or trauma

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.

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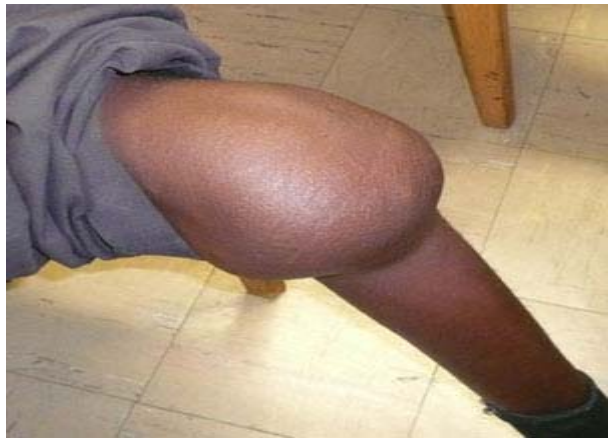
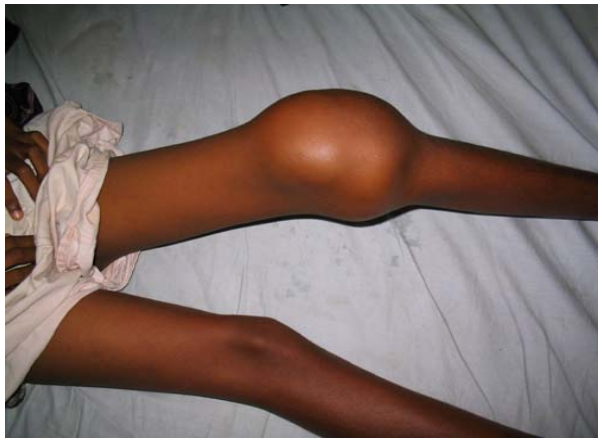
△ HA





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**

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.

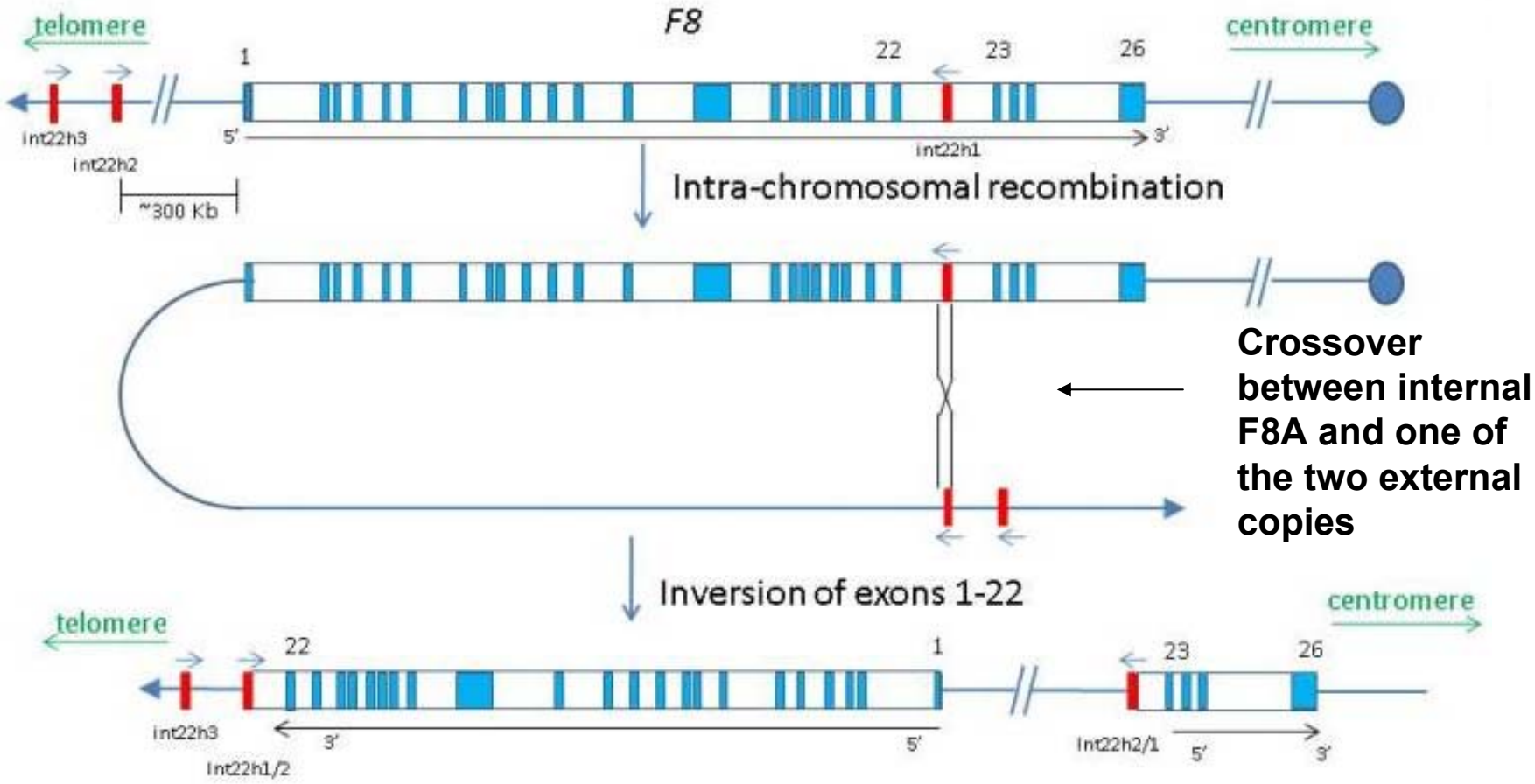
other reported mutation include deletion, insertion and point mutations causing nonsense, missense or splice site mutation.

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.

The “flip tip” inversion in the factor VIII gene



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

Hemophilia A and B registry. End of March.2017

	Hemophilia	Total	M	SEVERE <1	MOD 1-5	MILD >5
1	Haemophilia-A	279	279	162	37	80
2	Haemophilia-B	68	68	57	5	6

Common Bleeding Disorders End of March. 2017

Serial NO.	Disorder	Total NO.	M	F	$\bar{x}$ Age/Yr of diagnosis at THL M	$\bar{x}$ Age/Yr of diagnosis at THL F	$\bar{x}$ Age/Yr of diagnosis at THL M+F	Severity % SEVERE <1	Severity % MODERATE 1-5	Severity % MILD >5
1	Haemophilia-A	279	279	0	8.3	0	—	162	37	80
2	Haemophilia-B	68	68	0	7.1	0	—	57	5	6
3	VWD	157	64	93	14.3	22	18.15	—	—	—
4	Glanzmann	114	47	67	12	8.5	10.25	—	—	—
5	TOTAL NO. OF COMMON-BLEEDING DISORDER	618	458	160	—	—	—	219	42	86

Patelets and Bleeding Disorders ((uncommon+rare)) End of March.2017

				MEAN-AGE/YEAR			SEVERITY %		
Disorder	Total NO.	MALE	FEMALE	MALE	FEMALE	MALE+FEMALE	SEVERE <1	MODERATE 1-5	MILD >5
F.II def	5	3	2	—	—	—	0	0	5
V	11	6	5	12	27.5	19.75	3	2	6
VII	50	25	25	18	25	21.5	0	5	45
X	23	13	10	3.65	5.7	4.7	6	6	11
XI	37	19	18	19.4	17.43	18.45	13	2	22
XII	3	2	1	—	20	20	0	0	3
XIII A	20	17	3	20	15.5	17.75	9	1	10
Hypo-fib	13	9	4	23	16	19.5	—	—	—
A-fib	11	3	8	4.5	5.3	4.9	—	—	—
dys-fib	6	1	5	—	16.5	16.5	—	—	—
Vit K-like def	29	18	11	12	28	20	—	—	—
SPD	1	1	0	18	—	18	—	—	—
BSS	1	0	1	—	28	28	—	—	—
GT	114	47	67	12	8.5	10.25	—	—	—
Total NO of bleeders)	324	164	160						

Uncommon Bleeding Disorders End of March. 2017

				Mean- Age/Year			Severity %		
Disorder	Total NO.	M	F	M	F	M+F	SEVERE <1	MOD 1-5	MILD >5
FV Def	11	6	5	12	27.5	19.75	3	2	6
FVII Def	50	25	25	18	25	21.5	0	5	45
FX Def	23	13	10	3.65	5.7	4.7	6	6	11
FXI Def	37	19	18	19.4	17.43	18.45	13	2	22
FXIII A Def	20	17	3	20	15.5	17.75	9	1	10
Hypo-fib	13	9	4	23	16	19.5	___	___	___
Vit K-Like def	29	18	11	12	28	20	___	___	___
TOTAL UNCOMMON BLEEDING DISORDER	183	107	76						

Very Rare Bleeding Disorders End of March.2017

Disorder	Total NO.	M	F	M	F	M+F	SEVERE <1	MOD 1-5	MILD >5
FII Def *	5	3	2	___	___	___	0	0	5
FXII Def	3	2	1	__	20	20	0	0	3
A-fib	11	3	8	4.5	5.3	4.9	__	__	__
dys-fib	6	1	5	___	16.5	16.5	__	__	__
TOTAL-NO RARE BLEEDING DISORDER	25	9	16				0	0	8

* A case of combined mild factor II and moderate factor X deficiency was detected

Treatment of Severe/ Moderate hemophilia

A-Factor Replacement

1- On demand/hospital based

2- On demand/home based

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

B-Treatment of target joint

C- Physiotherapy/rehabilitation

D-Genetic counseling

E- Education

Dosing guidelines for hemophilia A

- **Mild / Moderate bleeding**
  - Target level: 30% dosing q8-12h; 1-2 days (25-40U/kg)
  - Hemarthrosis, oropharyngeal or dental, epistaxis, hematuria
- **Major bleeding**
  - Target level: 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)

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

Complications of therapy

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

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

Novel therapies

- Emicizumab: Bispecific factor IXa and Factor X-directed antibody that bridges activated factor IX and factor X in order to restore the function of missing activated factor VIII necessary for effective hemostasis.

Adjunctive Therapy

- DDAVP (Stimate) can be used to increase Factor VIII levels or to aid in hemostasis in mild disease.
- Acts by releasing VWF from storage. Factor VIII is trafficked with VWF.
  - tranexamic acid (Lysteda) can stabilize the fibrin clot.

Other issues in hemophilia

- Hepatitis B
- Hepatitis C
- HIV

Treatment of Inhibitors

1-Recombinant factor VIIa

2-By- Passing Agents (Mixture of partially activated vitamin K-dependent clotting proteases including VIIa

3-Porcine factor VIII (if available)

4-High dose factor VIII (if low titre inhibitor)

5-ITT (Induction of tolerance with daily/ twice weekly factor VIII infusions

Optimal dose not established)

Hemophilia: genetic testing for carriers and patients

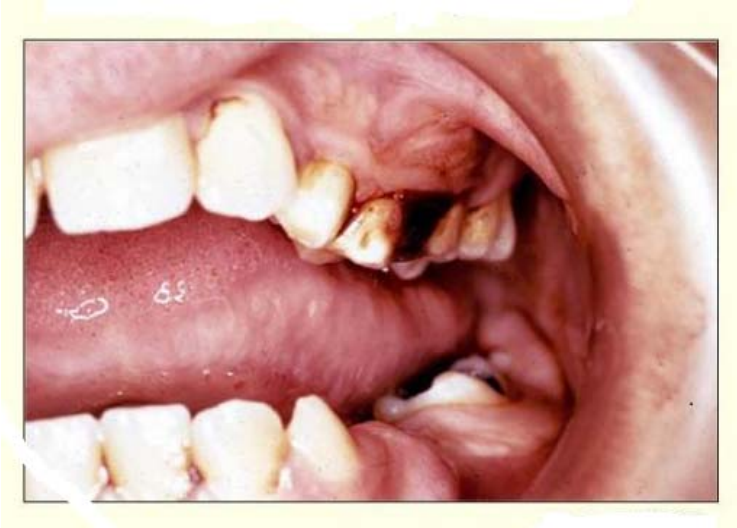
- **DNA testing should be done** if possible
  - Identification of causative mutation in an affected relative helpful, since mutations run in families particularly for families with missense mutations
  - Can be applied for females carriers, pre-implantation(PGD), CVS in utero testing

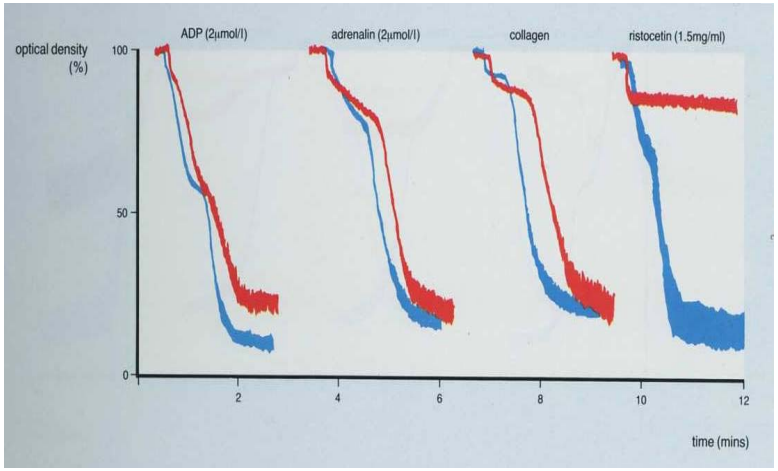
Case 5 B

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

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.

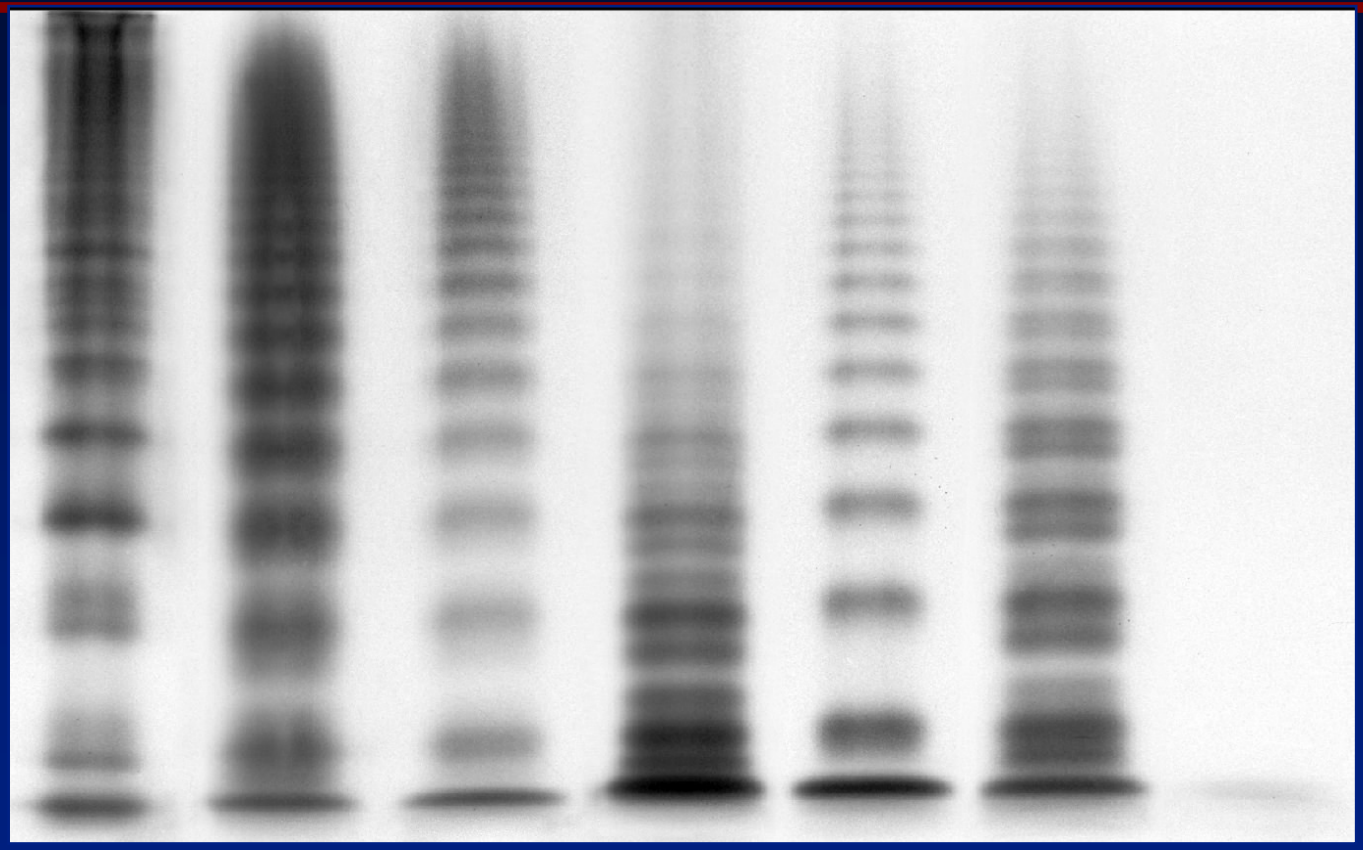
2- Dental consultation/ mouth hygiene & care.

3-Education and counseling.

4- Screening of family.

5- ?? DDAVP for therapy of mild bleeding

Case 5 B VWF Multimers

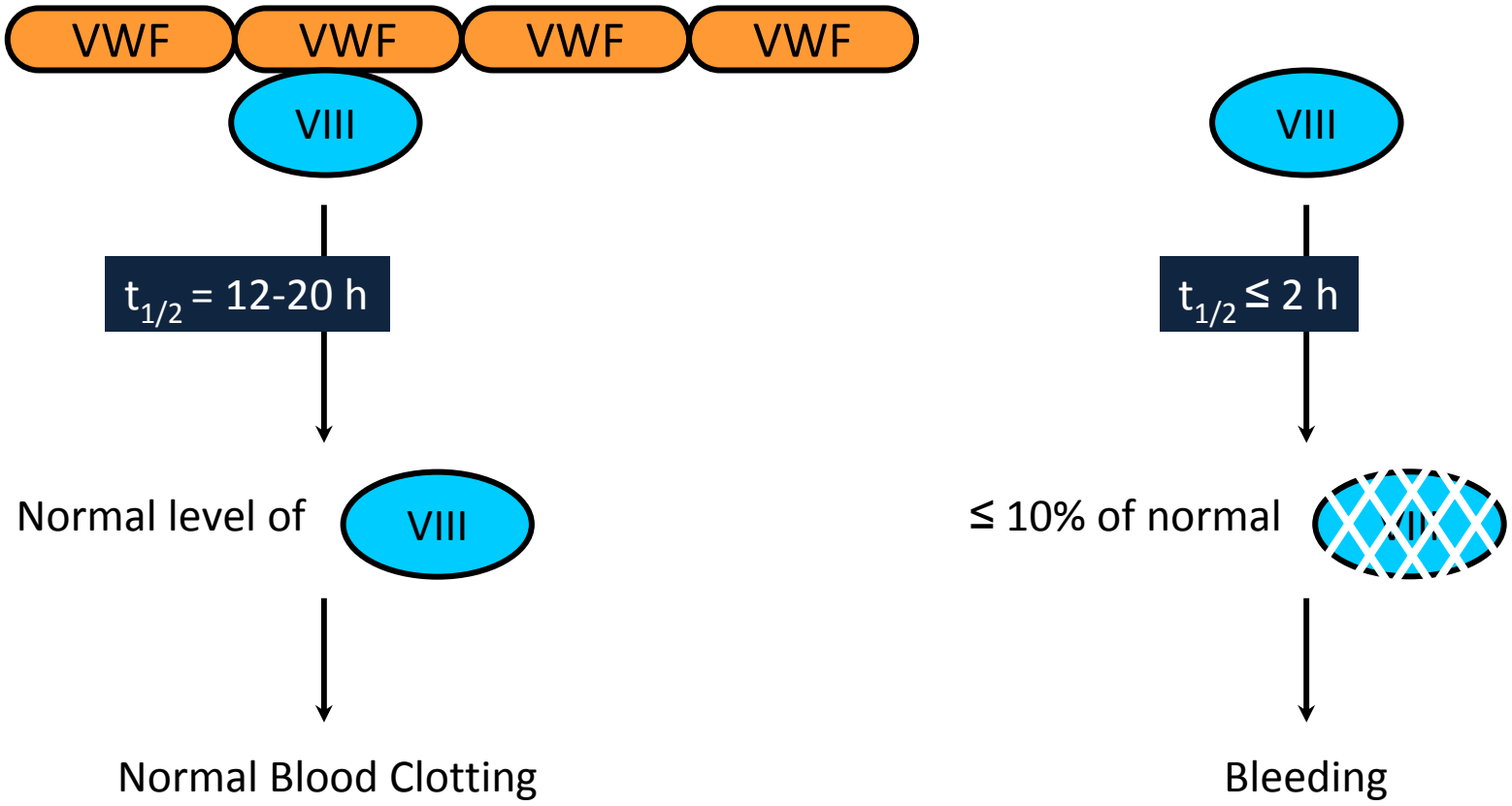


von Willebrand Disease: Clinical Features

- von Willebrand factor
  - Synthesis in endothelium and megakaryocytes
  - Forms large multimer
  - Carrier of factor VIII
  - Anchors platelets to subendothelium
  - Bridge between platelets

  Von Willebrand Disease
- Inheritance - autosomal dominant
- Incidence - 1/10,000
- Clinical features - mucocutaneous bleeding, prolonged bleeding from wounds/cuts

VWF and Factor VIII Survival



Laboratory evaluation of von Willebrand disease

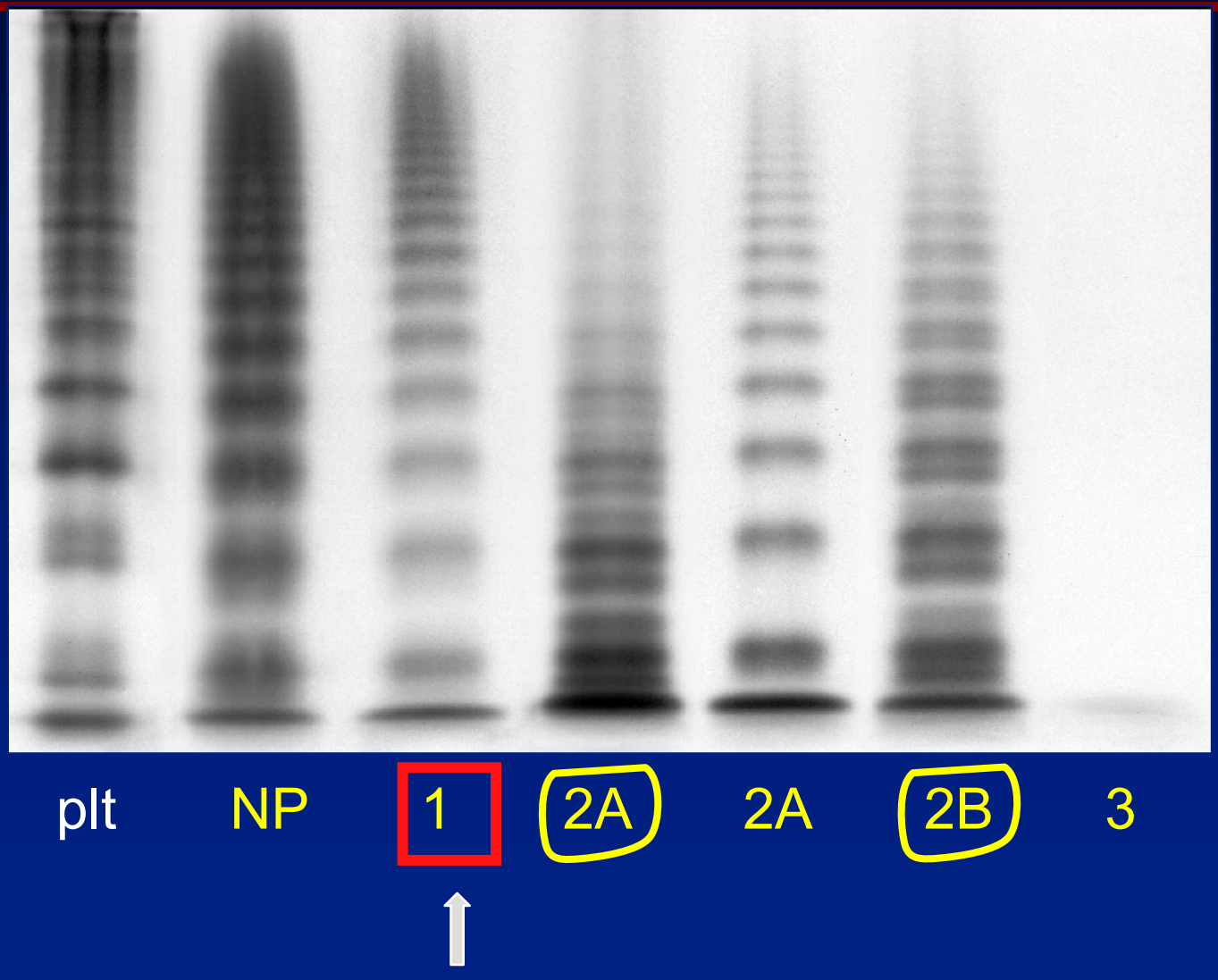
Classification

- 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

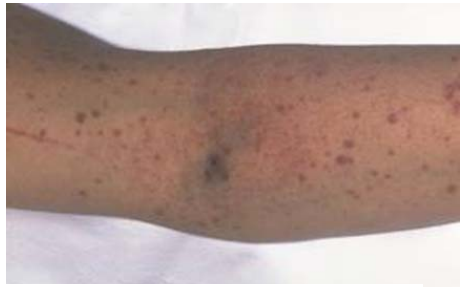


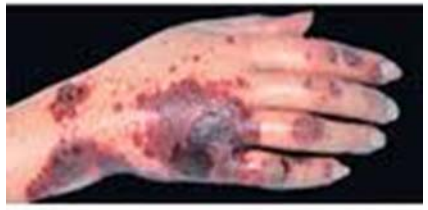
Treatment of von Willebrand disease Varies by Classification

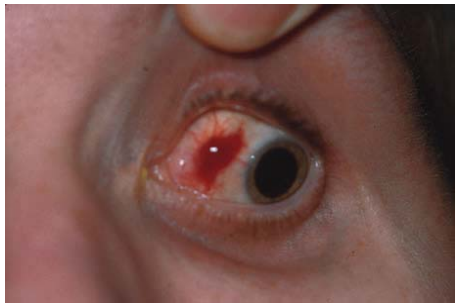
- Cryoprecipitate
  - Source of fibrinogen, factor VIII and VWF
  - Only plasma fraction that consistently contains VWF multimers
  - Correction of bleeding time is variable
- DDAVP (Deamino-8-arginine vasopressin)
  - Increases plasma VWF levels by stimulating secretion from endothelium
  - Duration 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

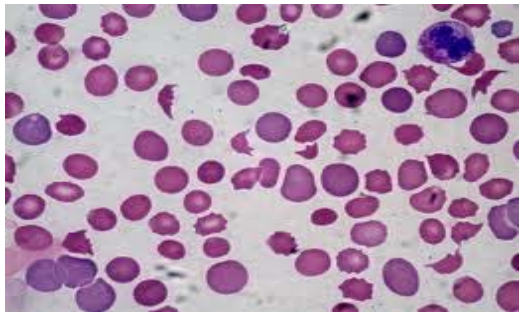
Case 5 C

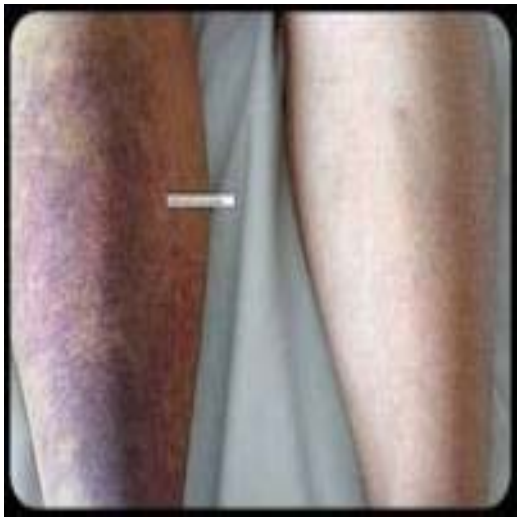
37 yr old lady was admitted with high fever, chills, rigors and severe dysuria.P/E shown. Temp 40.5,BP 80/50, P122 regular, low volume. Bleeding from needle puncture sites and bruising. Hb 9g/dl, retcs 6%, bilirubin 5 (d1), WBC 19k, Plt 25k, PT >50s, PTT > 100s, TT >30s, D-Dimer +++, Creatinine 2.3.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









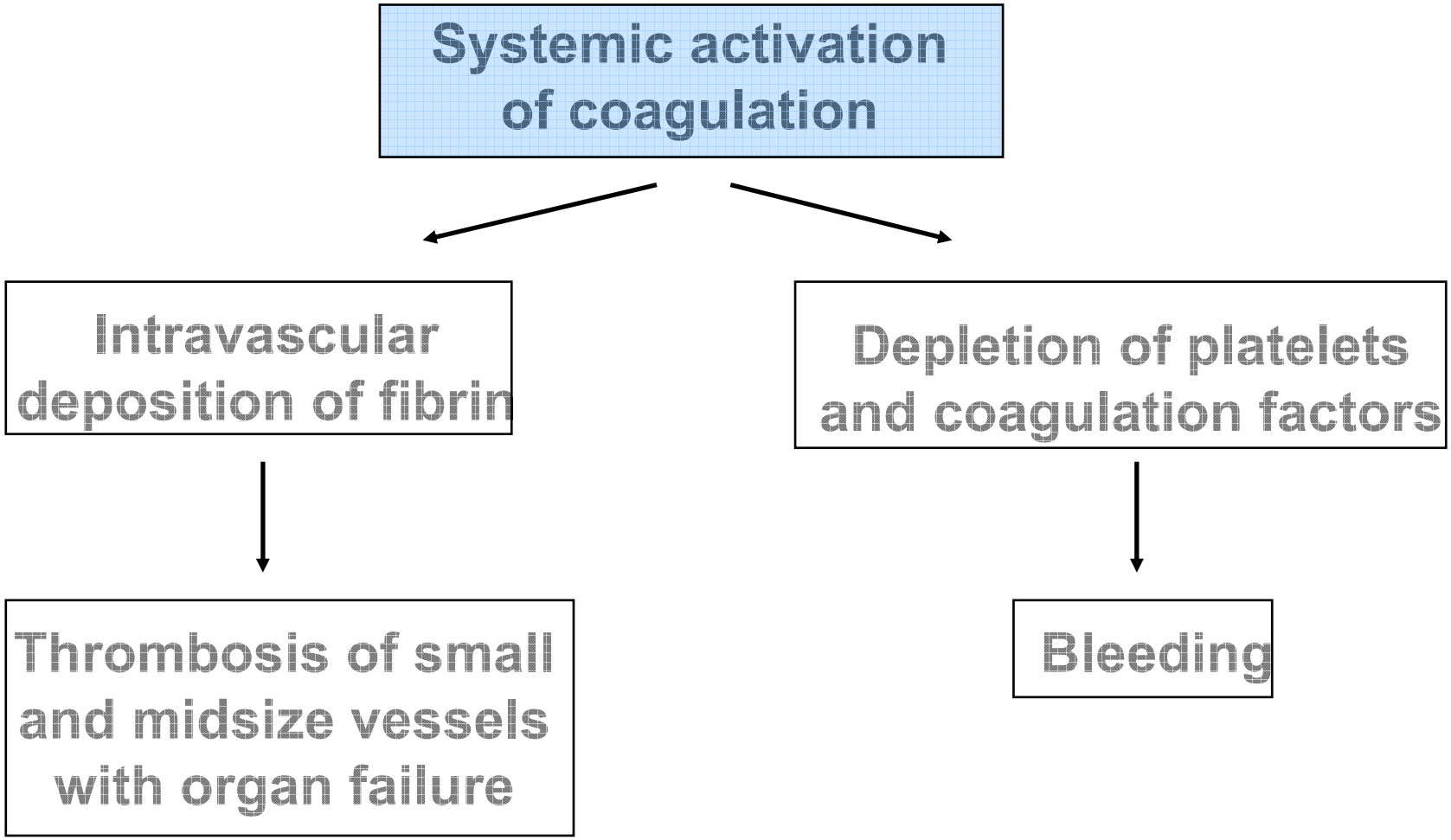


Common clinical conditions associated with Disseminated Intravascular Coagulation

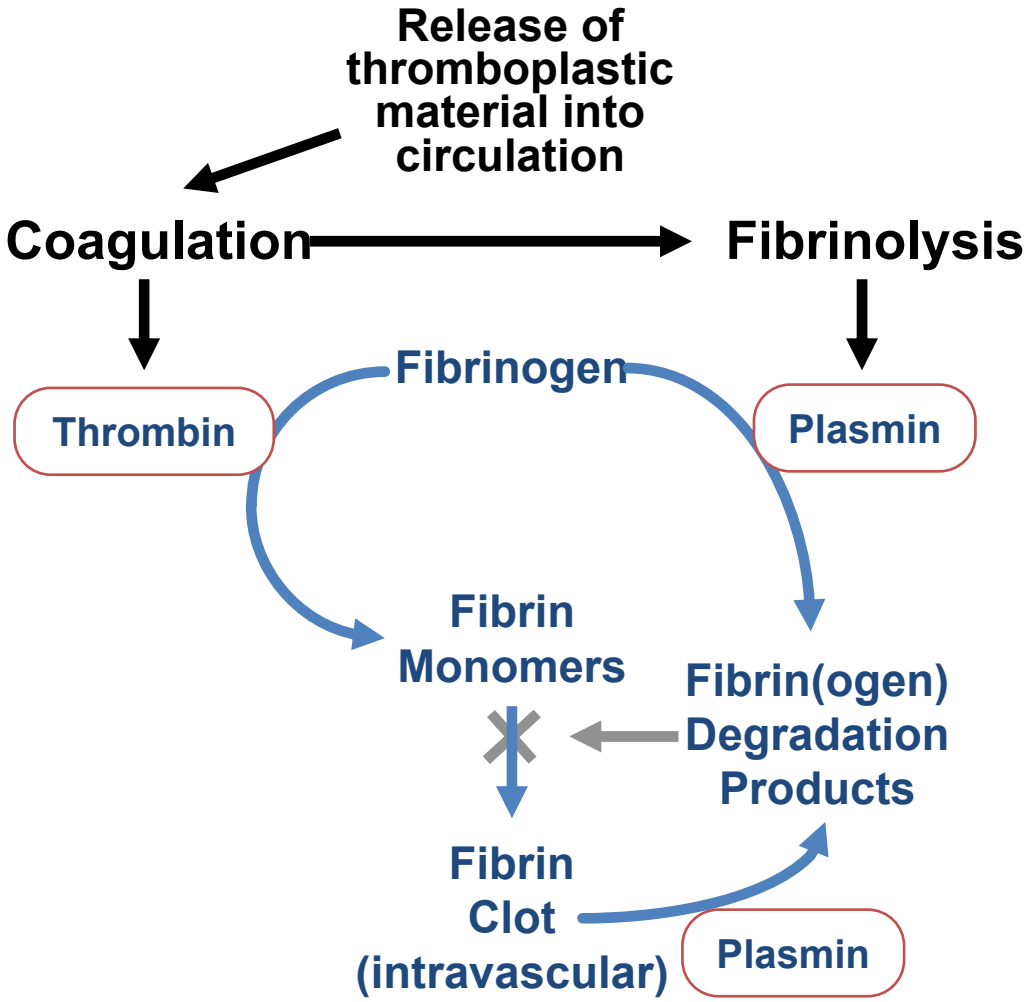
Activation of both coagulation and fibrinolysis tiggered by

- Sepsis
- Trauma
  - Head injury
  - Fat embolism
- Malignancy
- Obstetrical complications
  - Amniotic fluid embolism, Abruptio placentae
- Vasculitis
- 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)