
A CASE OF ECCHYMOSIS IN AN ELDERLY LADY

**Inter-hospital Geriatrics Meeting
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Chairperson: Dr. CS Leung**

Caritas Medical Centre

Background Information

- F/ 85 years old, widow, the closest relative is her niece
- Old age home resident
- Bedbound
- ADLD
- non-communicable
- Oral feeding

Past Medical History

1. Atrial fibrillation
2. Hypertension
3. Old cerebrovascular accident in 2004
4. Thyrotoxicosis in remission
5. Depression
6. Ezcema

FU at CMC CGAS and KCH PSY

Drug History

- Aspirin 80mg daily
- Digoxin 125 microgram daily
- Slow K 600mg BD
- Quetiapine 25mg BD (from KCH PSY)
- Zoloft 75mg daily (from KCH PSY)
- Imovane 3.75mg at bedtime PRN (from KCH PSY)
- Eurax LA BD PRN

History of Present Illness

- Found by OAH staff to have increased right chest wall and right upper limb bruises for 1 week
- Admitted to the medical ward for further management

History of Present Illness

- No other bleeding sites noticed
- No tarry stool or haematuria
- No pain symptoms noticed
- No fever
- OAH staff denied any fall, trauma or injury of patient
- No previous reported bruises over the body

Physical Examination

- Afebrile, temp:35'c
- BP:135/51, P:70
- Eyes opened, but non-communicable
- Right arm and forearm showed swelling and bruises
- Right chest wall and the right back also showed large area of ecchymosis (18cm x 12cm), with ?underlying haematoma
- No tenderness of the chest wall
- No other bleeding sites observed
- No external wound seen
- No joint swelling

Physical Examination



Physical Examination

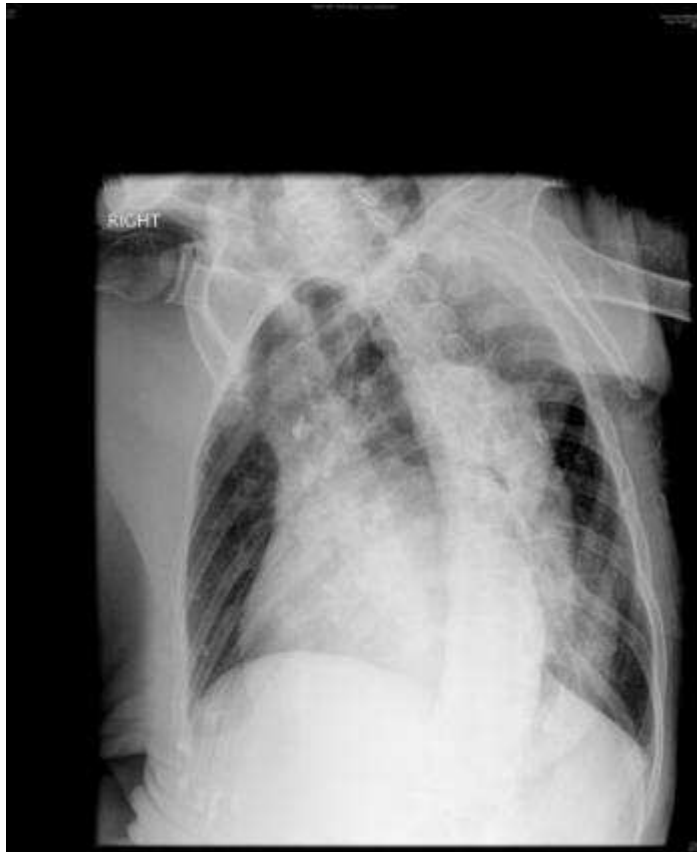
- Abdomen soft, non-tender, no mass felt
- PR: brownish
- Chest clear
- Heart sound dual, with no murmur

Investigations: CXR



No pneumothorax seen

Investigations: Rib Xray



Fracture right 4th rib, right 9th rib and left 10th rib with callus formation are present

No lung consolidation seen.

Investigations: Forearm Xray



No fracture or dislocation

Investigations

		Reference Range
Haemoglobin	4.7 L	12-15 g/dL
MCV	91.3	81-98 fL
MCH	31.9	27-34 fL
WBC	16 H	4-10x10 ⁹ /L
Platelet	219	150-400x10 ⁹
INR	1.07	
Creatinine	88	53-97 umol/L
Total bilirubin	12	3-21 umol/L
Alk. Phosphatase	80	30-120 IU/L
ALT (SGPT)	18	<40 IU/L

Further Investigations: CT Thorax (plain)



Further Investigations: CT Thorax (plain)

- 7.5 X 6.2 cm mass found in the right lateral chest wall / axillary region, most likely due to large hematoma.
- Another smaller hematoma (2 cm) noted posteriorly
- Two small hematoma (1.5 cm) noted anteriorly and inferiorly
- Atelectatic changes noted in the dependent areas of the lungs. The major airways are unremarkable. No grossly enlarged mediastinal lymph node found. Small right pleural effusion detected.
- The heart is enlarged.

Problem list

1. Chest wall haematoma, on aspirin
2. Anemia, ? Due to the blood loss in the haematoma
3. Old fracture ribs
4. Need to watch out elderly abuse

?? Elderly Abuse

- OAH staff's perspective:

Denied anything! (as expected!)

Denied any injuries, fall, trauma of the patient

- Patient's niece's perspective:

Very satisfied with the service of OAH

Didn't suspect elderly abuse

Abnormal laboratory result!

Day 1

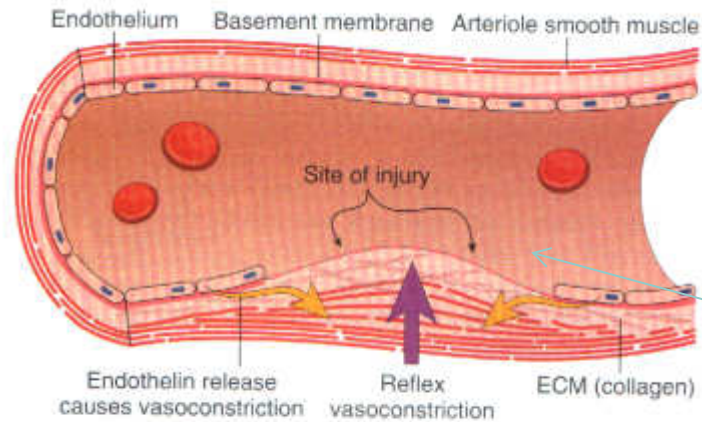
Day 2

Request No.	H0049122	H0049125	Reference Range	Units
Urgency	--	--		
PT	11.5	11.1	9 - 12	sec
INR	1.10	1.07		
APTT	52.4 H	51.9 H	26 - 39	sec

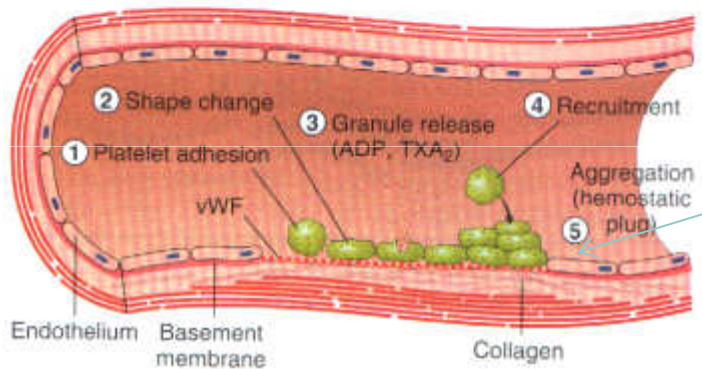
APTT increased!

Normal Haemostasis

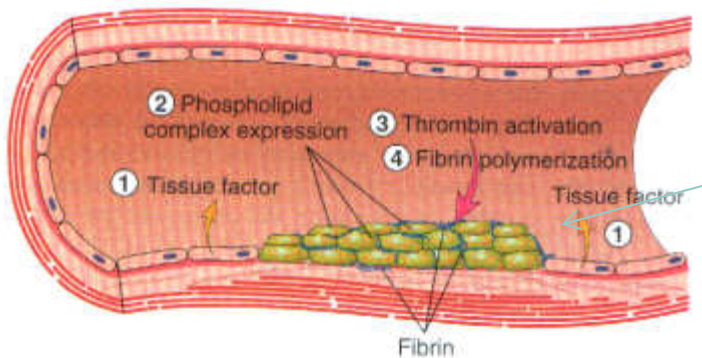
A. VASOCONSTRICTION



B. PRIMARY HEMOSTASIS



C. SECONDARY HEMOSTASIS



Tissue damage causes **vasoconstriction** and **platelet aggregation** to form the platelet plug

Endothelial damage causes release of **tissue factor** which initiates the **coagulation cascade**

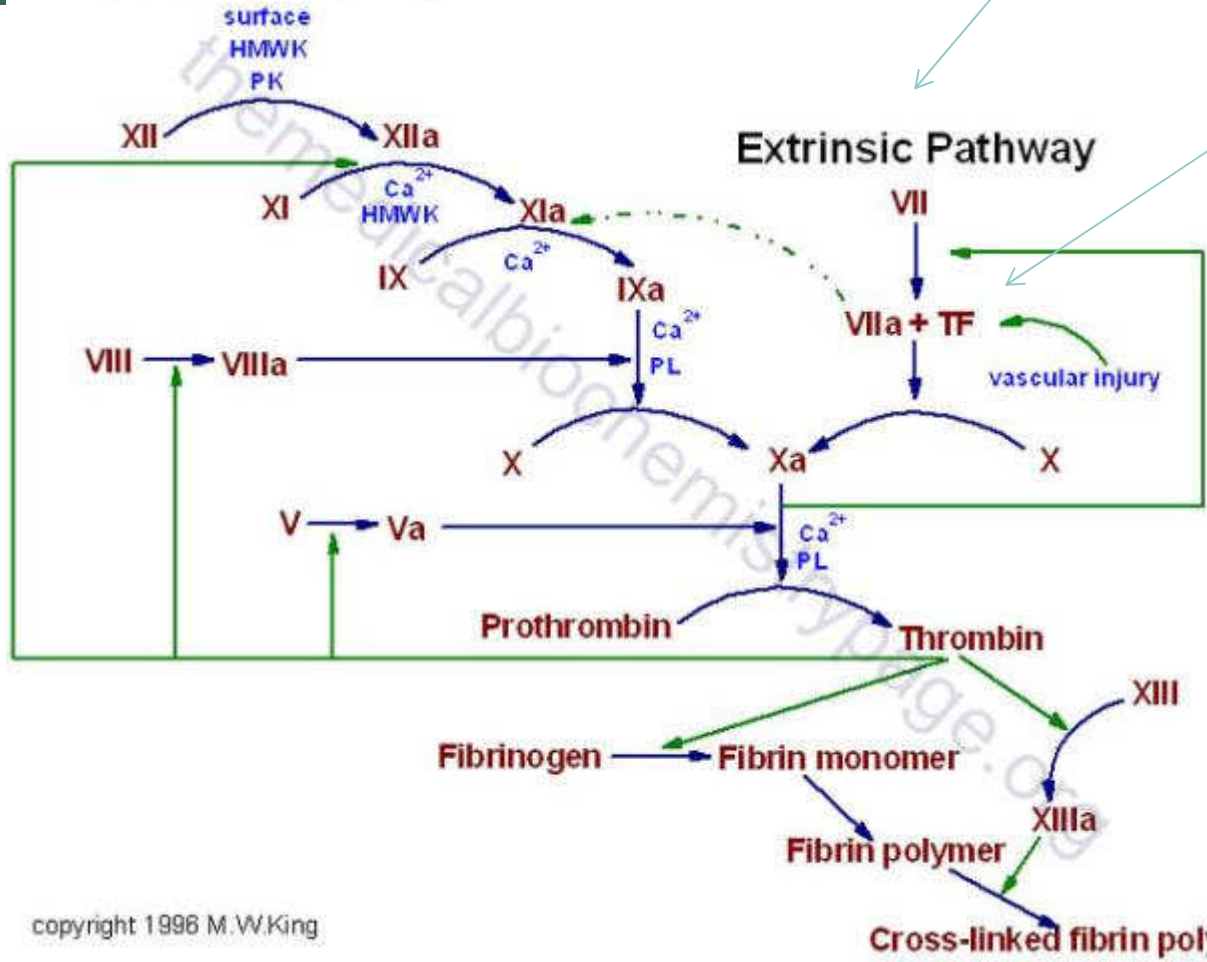
Measured by APTT

Measured by PT/INR

Tissue factor

Intrinsic Pathway

Extrinsic Pathway



Causes of isolated increased in APTT

1. Coagulation factors VIII, IX, XI and XII quantitative or qualitative deficiencies

Among them, ***factor VIII*** pathology is the commonest

2. Presence of ***lupus anticoagulant*** but it *does* not induce bleeding tendency, rather it predisposes to thrombosis

Further investigations

		Reference Range
Factor VIII: C Assay	6% L	50-200
Factor IX Assay	89%	50-200
Factor VIII Inhibitor	4.0 Bethesda unit H	0

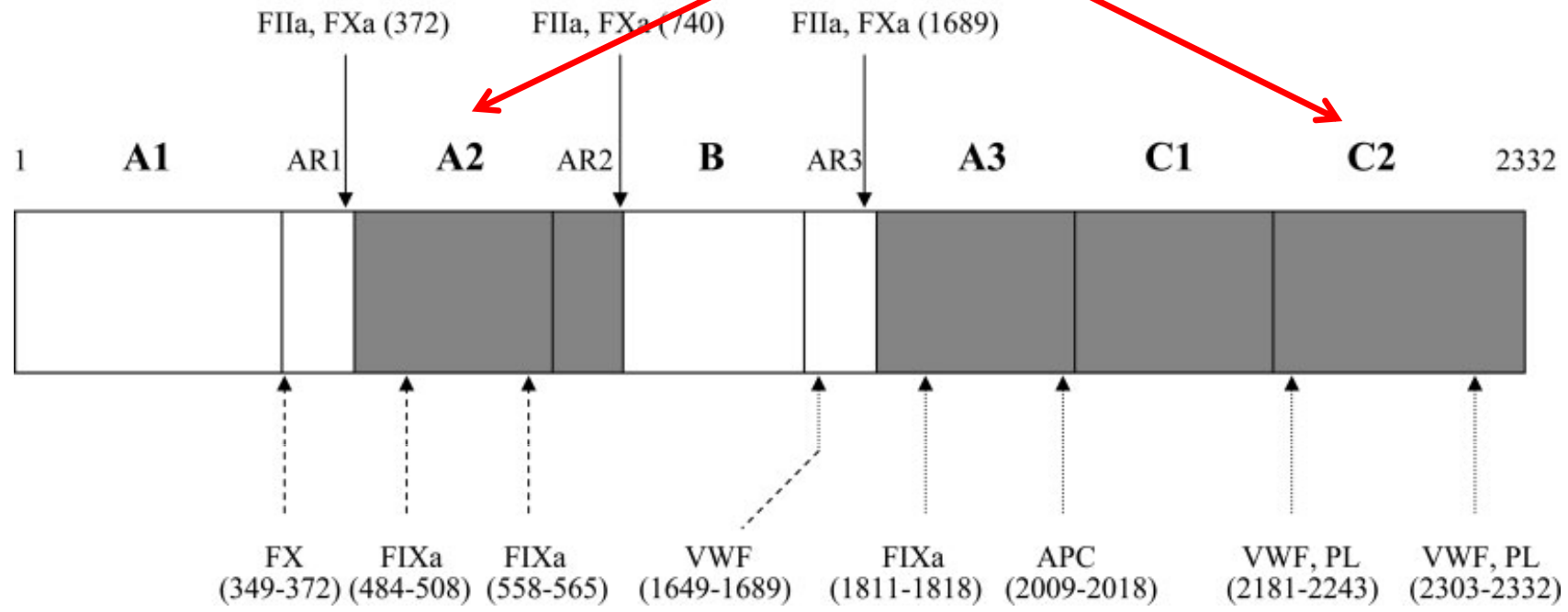
So, the diagnosis is
Acquired Haemophilia

What is Acquired Haemophilia?

- Rare but potentially life-threatening bleeding disorder
- Caused by the development of autoantibodies (mostly of IgG subclasses 1 and 4) directed against plasma coagulation factors, most frequently A2 and or C2 domains of factor VIII

HEAVY CHAIN

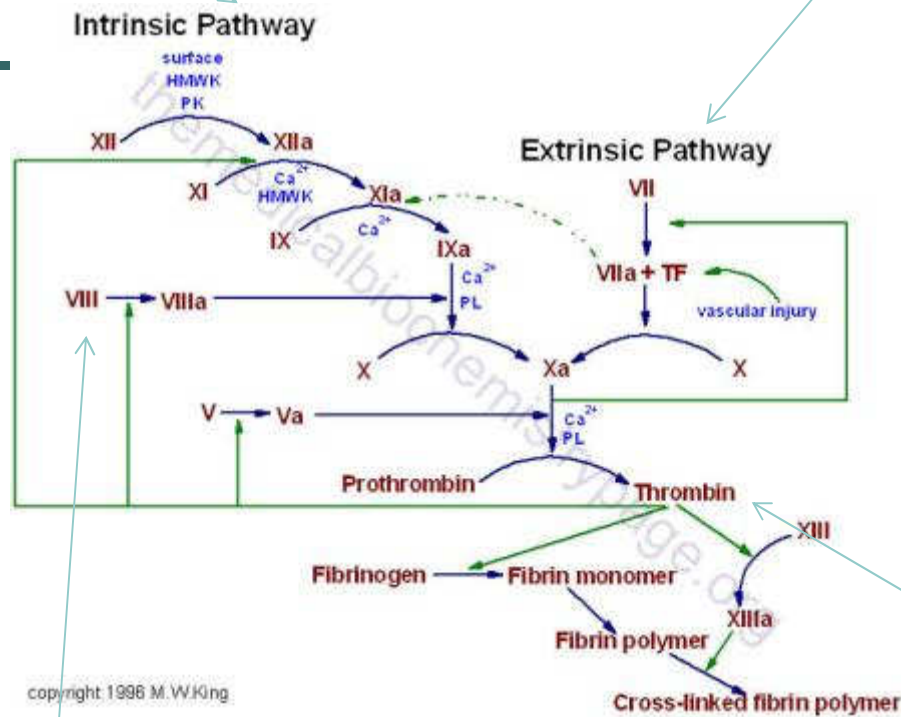
Domains that autoantibodies targeting

LIGHT CHAIN

Structure–function relationship of the circulating factor VIII molecule and main epitopes of inhibitory autoantibodies. The circulating FVIII molecule (300 kDa, 2,332 amino acid residues) is a heterodimer consisting of a heavy chain (domains A1, A2, and B) and a light chain (domains A3, C1, and C2). In plasma, FVIII is non-covalently bound to von Willebrand factor (VWF) which protects it from inactivation by activated protein C (APC). The regions involved in binding to VWF are within the light chain (residues 1649–1689 of the acidic region 3 [AR3] preceding the A3 domain, residues 2181–2243 and 2303–2332 of the C2 domain). APC interacts with the FVIII molecule at residues 2009–2018 of the A3 domain. The acidic regions 1 and 2 (AR1 and AR2) and the binding sites for the intrinsic Xase complex (FX, FIXa, phospholipid [PL] membrane) are also shown. Factor VIII is activated by thrombin and FXa, which cleave the FVIII molecule at residues 372 and 740 within the heavy chain and at residue 1689 of the light chain. Inhibitors interfere with FVIII activity by preventing the thrombin cleavage or the interaction with FIXa, FX, PL, and VWF (the ligand-binding sites that are targets for inhibitory antibodies are shown in gray).

Measured by
APTT

Measured by
PT/INR



FVIII deficiency results in insufficient generation of thrombin through the intrinsic pathway of the coagulation cascade

Acquired Vs Classical Haemophilia

- **Classical hemophilia A** is a congenital disease with FVIII gene mutation located on the sex chromosome X, resulted in FVIII deficiency
- In **classical haemophilia A**, spontaneous hemorrhages to articulations (e.g joints) are typical, while in **acquired haemophilia**, extensive blood subcutaneous extravasations and mucosal membrane bleeds are usually observed

Epidemiology

- Incidence has been reported as 1.48 and 1.34 per million/year in two UK studies
- Occurs ***equally both in women and in men, in all racial groups***, except in 20–40 year olds where the effect of pregnancy related acquired haemophilia results in a preponderance of females
- The incidence ***increases with age***, vast majority occurs in older adults. The median age at presentation is between 60 and 67 years
- The mortality rate is high, varying from 8% to 22% and severe life-threatening bleeds have been reported in more than 85% of patients

(Collins et al,2007), (Collins et al, 2004)

Age related incidence of Acquired Haemophilia

Review

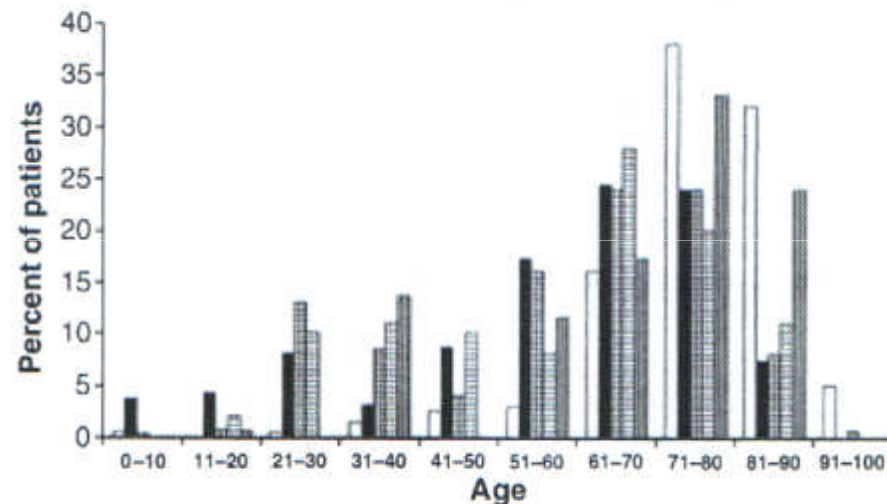


Fig 1. Age related incidence of acquired haemophilia A. Data are shown for the percentage of patients presenting with acquired haemophilia A in each decade of life in two large cohorts, a treatment study and a combined analysis of 20 cohorts. Black bars (Green & Lechner, 1981), white bars (Collins *et al*, 2007), lined bars (Morrison *et al*, 1993), hatched bars (Delgado *et al*, 2003) and grey boxes interim data from EACH2 registry (periods 0–20, 20–40 and 40–60 are combined) (Levesque *et al*, 2009).

Advances in the understanding of acquired haemophilia A: Implications for clinical practice

Peter W. Collins¹ and Charles L. Percy²

Etiologies and association of Acquired Haemophilia

1. **Idiopathic** (in ~50%)
2. Co-exist with **autoimmune disease** (in ~20%), usually systemic lupus erythematosus, rheumatoid arthritis or polymyalgia rheumatica
3. Associate with **malignant neoplasm** (in ~10%), usually lung cancer and prostate cancer, or Hematologic malignancies
4. Occur in **pregnancy** (in ~10%) or more frequently, during three months after delivery
5. Administration of **medications** (i.e. penicillin, chloramphenicol, phenytoin)

Bossi et al, 1998; Delgado et al, 2003; Green & Lechner, 1981; Hauser et al, 1995; Hay, 1998; Italian Association of Haemophilia Centres (AICE) (2006); Kessler & Asatiani, 2006; Morrison et al, 1993; Sallah & Wan, 2001; Collins et al, 2007

As in our case!



Clinical Presentations

- Can bleed after negligible or minor trauma, and may even bleed spontaneously
- Extensive ***subcutaneous*** blood extravasations
- ***Mucosal hemorrhages*** (from the gastrointestinal tract, urinary tract and female generative tract)
- Bleedings from postoperative surgical wounds and after tooth extraction procedures
- Extensive, painful intramuscular hematomas
- Retroperitoneal space hemorrhages were also described.
- Cerebral hemorrhages which usually fail to be stopped on time have the most dramatic course
- ***Spontaneous bleeds to joints are seldom observed***

Clinical Presentations

Advances in the understanding of
acquired haemophilia A:
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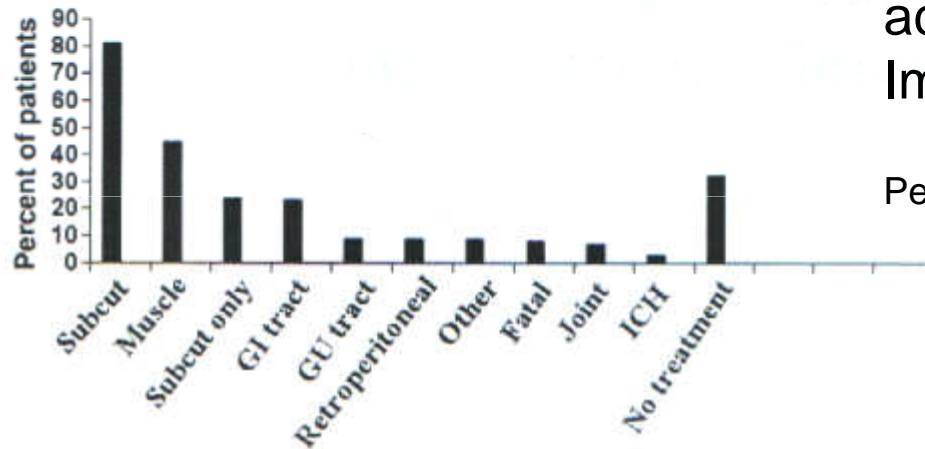


Fig 2. Bleeding symptoms at presentation in acquired haemophilia. The bleeding symptoms seen at presentation in a consecutive cohort of 172 patients with acquired haemophilia A (Collins *et al*, 2007). Subcut, subcutaneous bleed; GI tract, gastrointestinal bleeding; GU tract, genito-urinary bleeding; none, bleed did not require haemostatic therapy; fatal, bleeding that was the main cause of death; ICH, intracranial haemorrhage.

Typical Laboratory values

- 2-3 times prolongation of APTT
- Normal PT, INR, bleeding time value
- Normal platelet count and fibrinogen

Investigations of the factor VIII inhibitors – Steps 1

Mixing test

- Mixing normal and patient's plasma at 37°C, APTT measured at 0, 1, and 2 hours
- APTT prolongation not corrected when equal volumes of examined serum mix with normal serum confirms the presence of anticoagulants

Investigations of the factor VIII inhibitors – Steps 2

Determine the FVIII activity

- in healthy individuals, FVIII activity ranges between 50–150 % of normal values,
- in acquired haemophilia, FVIII activity ranges 0–15 % of normal values

Investigations of the factor VIII inhibitors – Steps 3

Measure the concentration of FVIII inhibitor

- Expressed in **Bethesda units (B.U./ml)**
- One B.U. is defined as the titer of antibodies inactivating 50 percent of the FVIII activity in the mixture of equal volumes of examined plasma and normal plasma, after a two hour incubation in a temperature of 37°C
- High titer: more than 5 BU
- low titer: less than 5 BU

Investigations of the factor VIII inhibitors

- The inhibitor titre and the factor VIII levels are not correlated with the clinical picture, thus they are not valuable in guiding therapy
- The most significant guide for therapy is clinical: ie: ***the site and the intensity of bleeding***

What we do next?

PMH Haematology team consulted:

- Suggest transfuse 4 units of ***Fresh Frozen Plasma***
- Start ***Prednisolone*** 1mg /Kg
- Check blood for autoimmune marker, *ANA, RF, Ds-DNA, Lupus anticoagulant*
- Check blood for *cancer markers*

Management

- ***Fresh Frozen Plasma*** 4 units given
- Total of 4 units of ***pack cells*** transfused to top up the Hb
- ***Prednisolone*** 40mg daily given since day 11 of admission, tail down gradually in 6 weeks

Management

- ***Autoimmune Markers:***

RF:-ve, ANA:160, antidsDNA:9

Lupus anti-coagulant: -ve

- ***Cancer markers:***

CEA:3, AFP:3, CA 125: 97 (increased)

Progress – increased CA 125

- No sign of PV bleeding
- No pelvic mass felt in physical examinations
- In view of advanced age and poor pre-morbid status, plan not for further workup

Progress

- Clinically, the chest wall ecchymosis gradually decreased in size
- Repeated CT thorax Day 30:

Right chest wall haematoma decreased in size, measured 6.0x5.0 (APxTD) cm

When *prednisolone* started



Progress

Day of admission	Day 1	Day 11	Day 15	Day 19	Day 31
<i>Hb</i>	<i>4.7</i>	<i>8.9</i>	<i>9.8</i>	<i>11.2</i>	<i>11.3</i>
Platelet	219	310	276	199	206
PT	11.5	11.8	11.0	10.7	10.6
INR	1.10	1.12	1.06	1.03	1.03
<i>APTT</i>	<i>52.4</i>	<i>61.6</i>	<i>53.4</i>	<i>49.4</i>	<i>38.8</i>

Discussion

- What is the evidence in management of the acquired haemophilia?

Treatment principles

1. Control bleeding
2. Eradicate the inhibitor by Immunosuppressants
3. Detect and treat the underlying disease
4. Protect the patient against trauma and non-essential invasive procedures

1. Treatment of the bleeding

I) Bypassing agents

1. Activated prothrombin complex concentrates (aPCC)
2. Recombinant activated factor VII (rVIIa)

II) Strategies to raise the level of circulating FVIII

1. FVIII concentrate
2. Desmopressin

?? Fresh frozen plasma

?? Is fresh frozen plasma useful?

- Fresh frozen plasma and cryoprecipitate transfusions are usually ineffective!
- The concentration of FVIII contained in them is low and quickly inactivated by antibodies
- Only in a limited number of patients with a low inhibitor titer the administration of large doses of human FVIII concentrate may prove efficient

I) Activated prothrombin complex concentrates (aPCC)

- FEIBA (Baxter-Immuno)
- Has a history of more than **30 years**, initially used in controlling bleeding in haemophilic patients who have developed inhibitory antibodies against factor VIII
- Plasma derived concentrate containing clotting factors, including **activated prothrombin complex, FVII, FIX, FX**
- Recommended dosage: 50-100 IU/kg IV bolus every 8-12 hours
- Total dose should not exceed 200 U/Kg within a 24-hour period

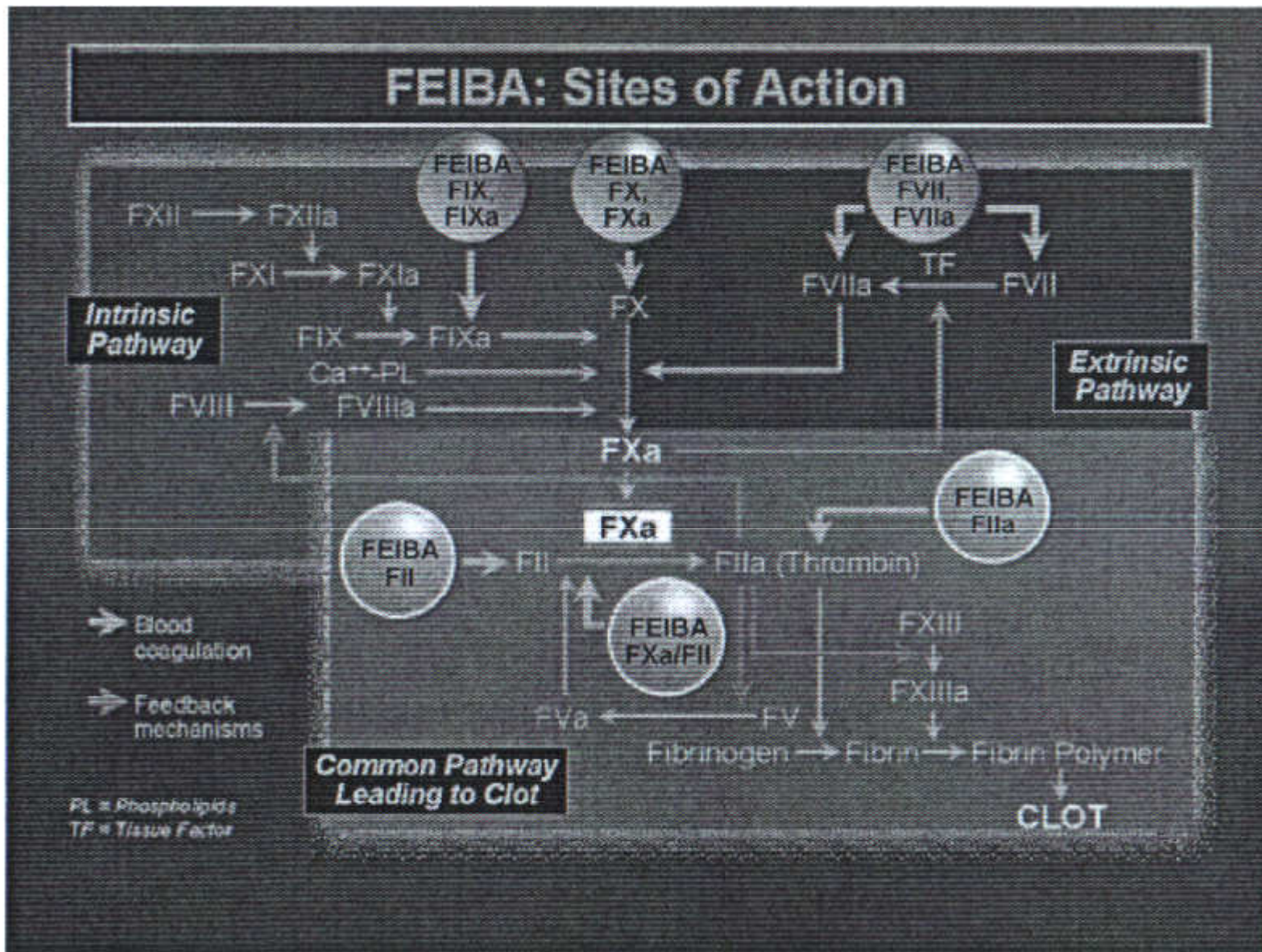


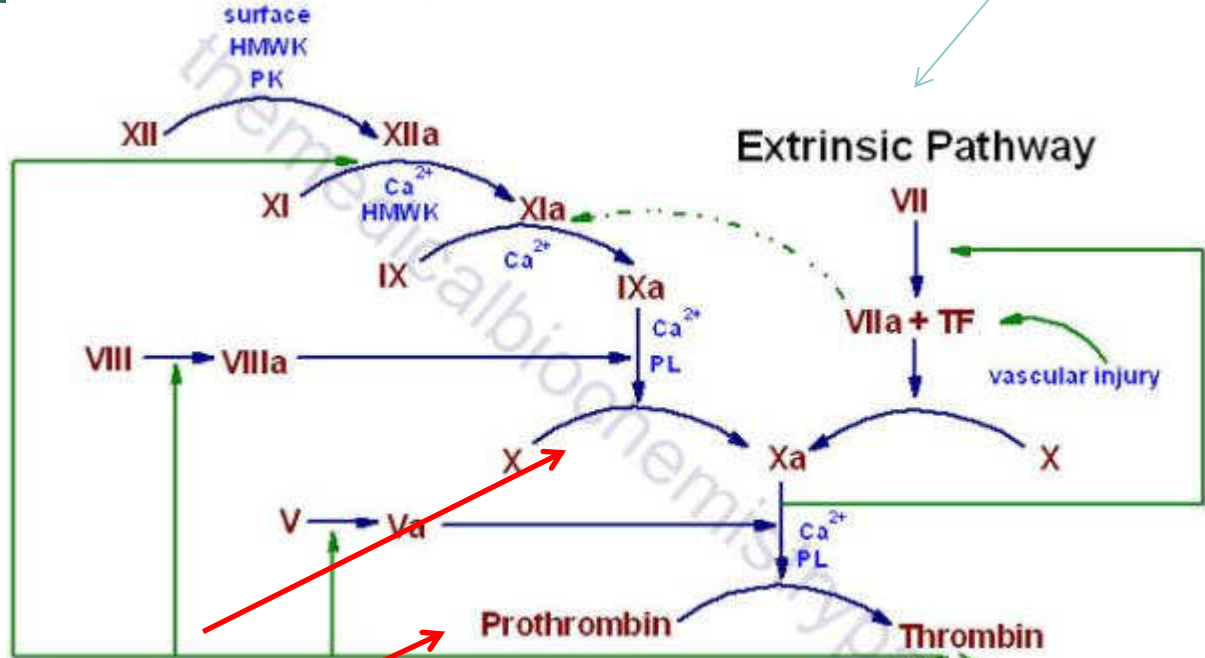
Fig. 6. Where can FEIBA[®] components enhance haemostasis? Multiple sites of action of FEIBA[®] in the coagulation process.

Measured by
APTT

Measured by
PT/INR

Intrinsic Pathway

Extrinsic Pathway

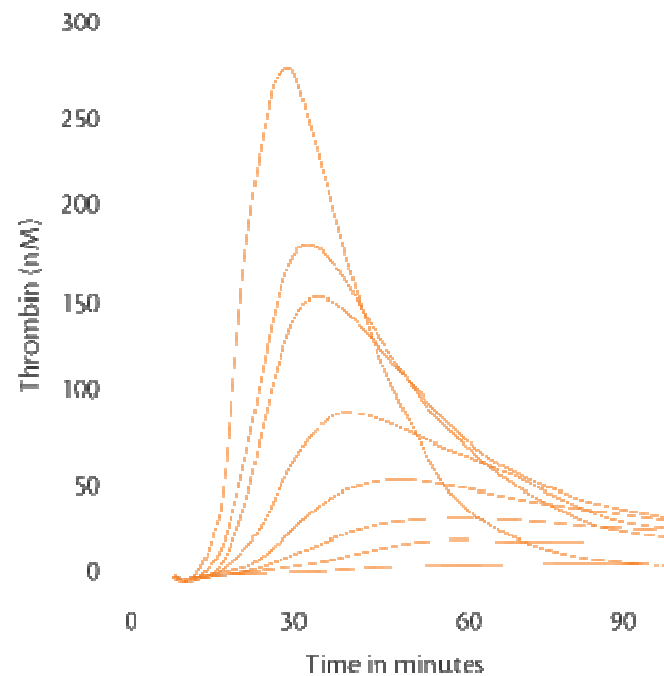


FEIBA

Fibrin monomer
Fibrin polymer
Cross-linked fibrin polymer

FEIBA

Thrombin generation after FEIBA injection
in an *in vitro* assay¹¹



- Provides rapid onset (peak at 15-30 minutes) of thrombin generation in an *in vitro* assay
- In the FENOC study, 53.2% of bleeds stopped within two hours with one FEIBA infusion and 76.1% of reported bleeds stopped within six hours with one FEIBA infusion

www.FEIBA.com

FEIBA

- Retrospective studies with FEIBA on acquired haemophilia describe 34 severe and moderate bleeds treated, in the main with 75 u/kg 8–12 hourly
- A median of 6 infusions were needed for moderate bleeds with 100% haemostatic efficacy at a median of 36 hours
- 10 infusions for severe bleeds with 76% haemostatic control at a median of 48 h

(Sallah, 2004)

I) Activated prothrombin complex concentrates (aPCC)

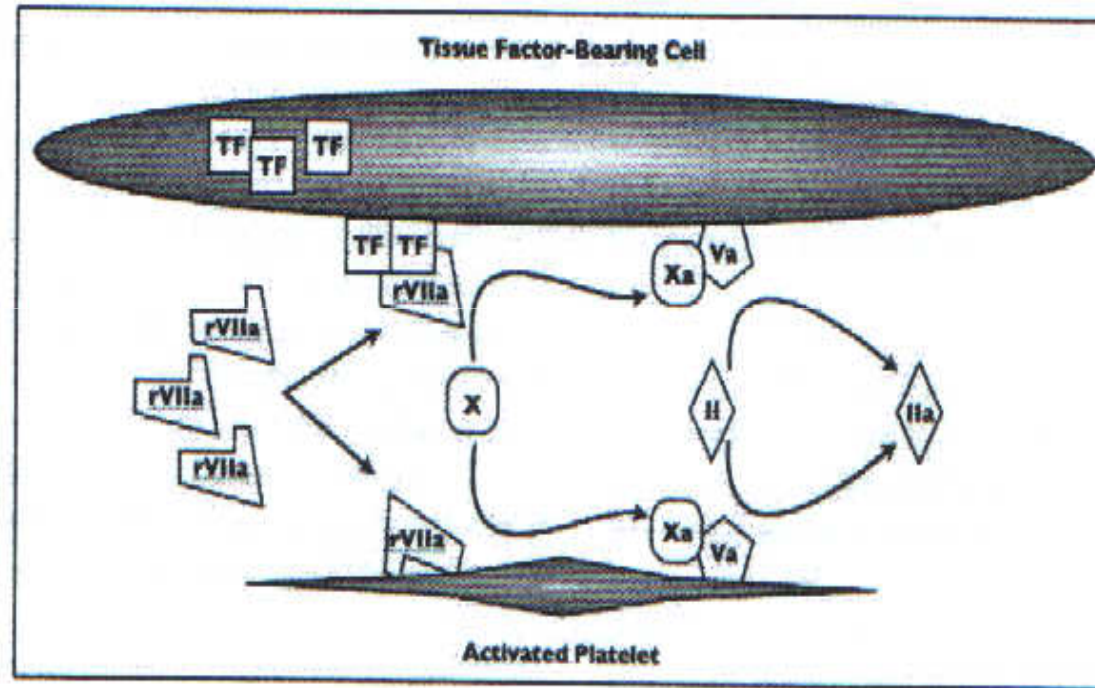
- There is ***no assay available to monitor response*** to aPCC, so clinicians should use their judgment to determine duration of treatment.
- Large doses of aPCCs may trigger an ***anamnestic rise in inhibitor titer*** because aPCC may contain some FVIII as it is derived from plasma
- aPCC has the potential to ***transmit infection*** as they are derived from plasma

II) Recombinant activated factor VII (rVIIa)

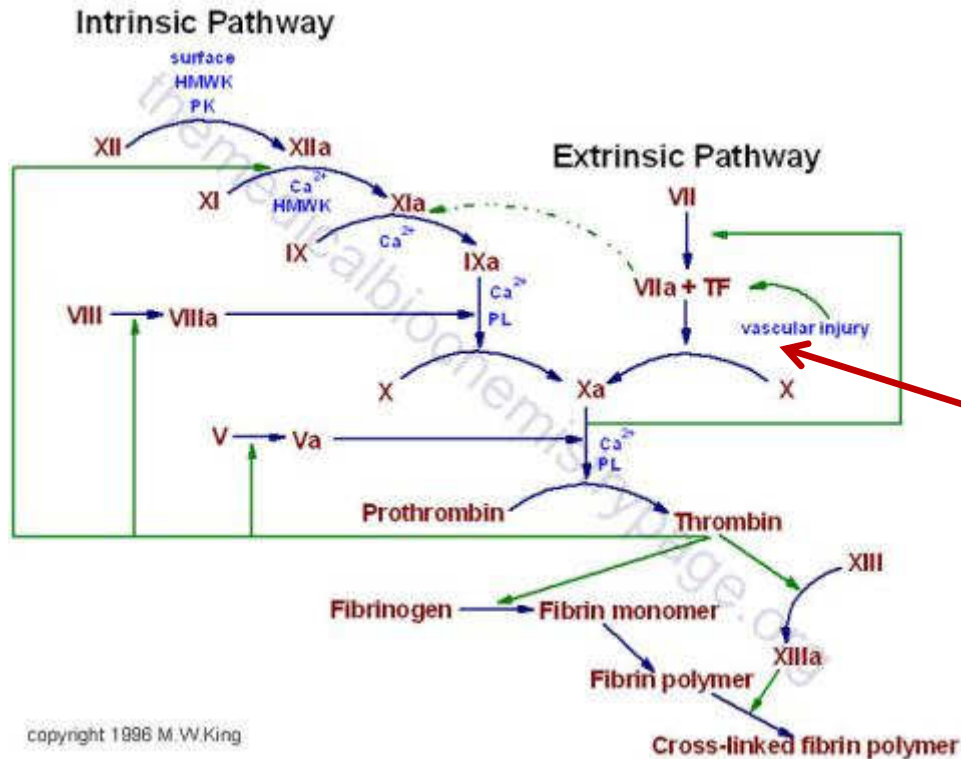
- NovoSeven
- Recombinant protein of activated factor VII
- Initially developed for use in patients with **congenital hemophilia**. USA FDA approved its use in patients with acquired haemophilia in 2006
- It is a bypassing agent which skips the need for **Factor VIII or IX** in people with inhibitors, instead activating **Factor X** directly
- The amount of factor VII required for bypassing activity is much higher than that contained in normal individuals

II) Recombinant activated factor VII (rFVIIa) : mechanism of action

1. rFVIIa complexes directly with tissue factor (TF) released from the subendothelium at sites of vascular disruption, then activates the common coagulation cascade through FX
2. rFVIIa bind to activated platelet to concentrate FX



mechanisms of action. At pharmacologic levels, rFVIIa complexes with tissue factor (TF) from the subendothelium...



- Tissue factor-factor VIIa binds to the activated platelets and can directly activate factor X to factor Xa

II) Recombinant activated factor VII (rVIIa)

- Recommended dose: 90-120 mg/kg IV bolus every 2-3 hours until bleeding is stopped
- If no response is seen after 2 doses, 120-270 mg/kg IV bolus every 2.5-3 hours should be administered
- Patients who do not respond within 24 hours are unlikely to respond if rFVIIa treatment is continued

II) Recombinant activated factor VII (rVIIa)

- A retrospective analysis of 139 patients treated with rFVIIa (Sumner et al, 2007)
- There were 182 bleeding episodes
- 103 episodes where rFVIIa was used as first-line therapy, it was effective or partially effective in 95%
- When used as second-line therapy, an effective or partially effective response was described in 80% of cases
- The mean duration of treatment was 6 days (range 1–33) Sumner et al, 2007
- well tolerated
- has few adverse effects
- does not have the potential to transmit human pathogens as it is a recombinant protein

Comparisons of rFVIIa and aPCC

- There are no comparative studies on the hemostatic efficacy and risk of adverse events using rFVIIa and aPCC in the management of bleeds in patients with acquired hemophilia
- There are no data to suggest that either agent has a superior haemostatic efficacy and ***neither*** agent has predictable efficacy in all cases
- If first-line therapy fails, the alternative bypassing agent may be successful and should be tried at a relatively early stage

Problems of the Bypass Agent

- No currently validated laboratory monitoring technique
- The administration of aPCC and rVIIa is costly
- Risk of venous thrombotic events, DIC and myocardial infarction have been reported using both aPCC and rFVIIa, although at a very low incidence rate

Problems of the Bypass Agent

- Both rFVIIa and FEIBA are associated with thrombotic events

(Aledort, 2004, 2005)

- An analysis of 139 patients treated with rFVIIa reported 12 thrombotic events, 10 are arterial thrombosis, four of whom died

(Sumner et al, 2007)

- A 10-year study of treatment by aPCC reported one episode of disseminated intravascular coagulation, one myocardial infarction and one venous thrombosis

(Ehrlich et al, 2002)

- The risk of thrombosis in patients with AHA treated with bypassing agents appears to be significantly higher than in congenital haemophilia, probably because of the additional risk factors associated with elderly patients and the complex clinical situation of many patients with AHA

III) FVIII concentrate

- Human FVIII is inadequate haemostatic therapy unless the inhibitor titre is low
- The dosing requirements are higher in these patients than in patients with congenital hemophilia. As the dose of FVIII required will need to be sufficient to overcome the inhibitor and provide an adequate haemostatic level
- The use of human FVIII in combination with immunoabsorption is more likely to result in haemostatic FVIII levels despite higher anti-FVIII inhibitor titres
- There are no published studies guide the dosing of human FVIII in acquired hemophilia

IV) Desmopressin

- Patients with very low inhibitor titers (< 3 BU) may benefit from treatment with desmopressin
- Infusion of desmopressin (0.3 µg/kg) may result in a 2- to 3-fold temporary increase in FVIII and von Willebrand factor plasma levels
- However, in most patients with acquired FVIII inhibitors, desmopressin treatment alone will not provide hemostasis

2. Immunosuppressants treatment for inhibitor elimination

- Immunosuppressive therapy should be administered **as soon as** the diagnosis is made
- The median time to remission after treatment has been reproducibly in different studies to be about 5 weeks

(Collins et al, 2007, 2009)

- 1st line: **Oral prednisone** in a daily dose of 1 mg/kg body weight for 4-6 weeks is the first line treatment
- 2nd line: **oral prednisolone** + **oral cyclophosphamide** in a daily dose of 1.5-2mg/kg body weight for 6weeks
- 3-rd line: **Rituximab** 375mg/m² each week for 4 weeks

2. Immunosuppressants treatment for inhibitor elimination

A positive response indicated by

- Inhibitor elimination
- Normalization of the FVIII plasma activity

observed in 60-70% of patients receiving
treatment

2. Immunosuppressants treatment for inhibitor elimination

- Data is controversial on the use of **steroid** alone or **steroid** combined with **cyclophosphamide**
- A review that combined data from 20 publications reported that the use of **steroids** and **cyclophosphamide** resulted in more patients achieving complete remission compared to **steroids** alone

(Delgado et al, 2003)

- However, the higher complete remission rate was not translated into a lower mortality. It may be due to the increased toxicity of **cyclophosphamide**

2. Immunosuppressants treatment for inhibitor elimination

- If the treatment is not successful after a 6-8 weeks of administration of *corticosteroids and cyclophosphamide*, the others drugs such as *rituximab*, *cyclosporine A* and other immunosuppressive and immunomodulating medications may be administered

Recurrence

- recurrence occurs in 20% of patients who have remission at a median of 7.5 months
- In such cases the second attempt to eliminate the inhibitor should be made, and the same immunosuppressive drugs which induced the first remission may be used
- Some patients even require long term immunosuppressants to prevent relapse

What we learn from this case?

- Some elderly patients could not give history and diagnosis is mainly by investigations
- Spontaneous bleeding with increased APTT in elderly should lead us to think of the diagnosis of acquired haemophilia

Summary

- Acquired haemophilia is an uncommon but potentially life threatening bleeding disorder, mostly in elderly
- Most of them are idiopathic, but can also associate with autoimmune disease or cancer
- The most common clinical presentation is subcutaneous blood extravasations or mucosal hemorrhages
- Increased APTT, decreased factor VIII activity and increased factor VIII inhibitor level are the laboratory features
- Treatment includes immunosuppressants to eradicate the inhibitors
- First line treatment to control bleeding is bypassing agents: **aPCC or rVlla**. Both agents are believed to be effective to control bleeding