Haemophilia Association of Mauritius

Overview of Hemophilia in Mauritius

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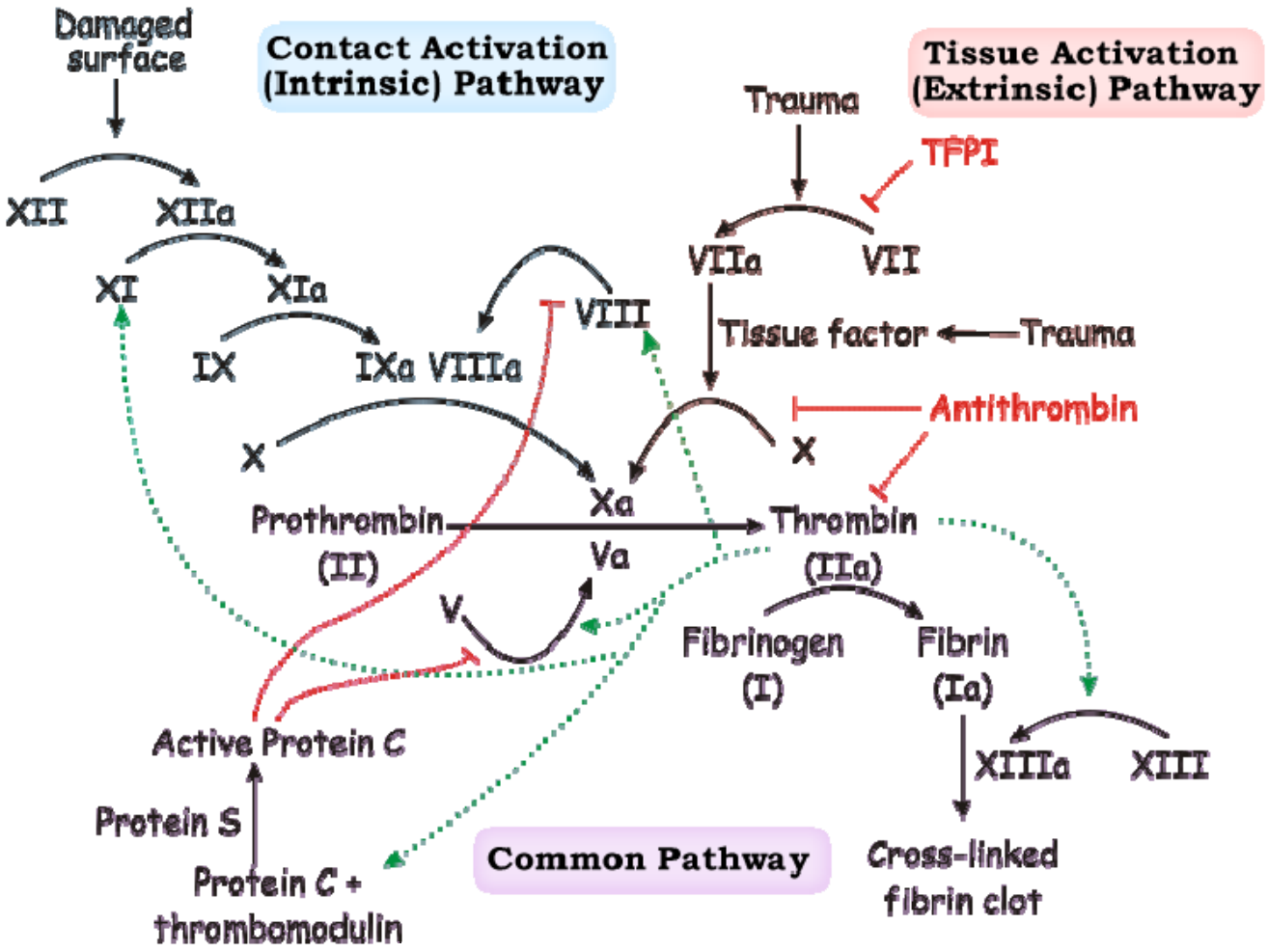
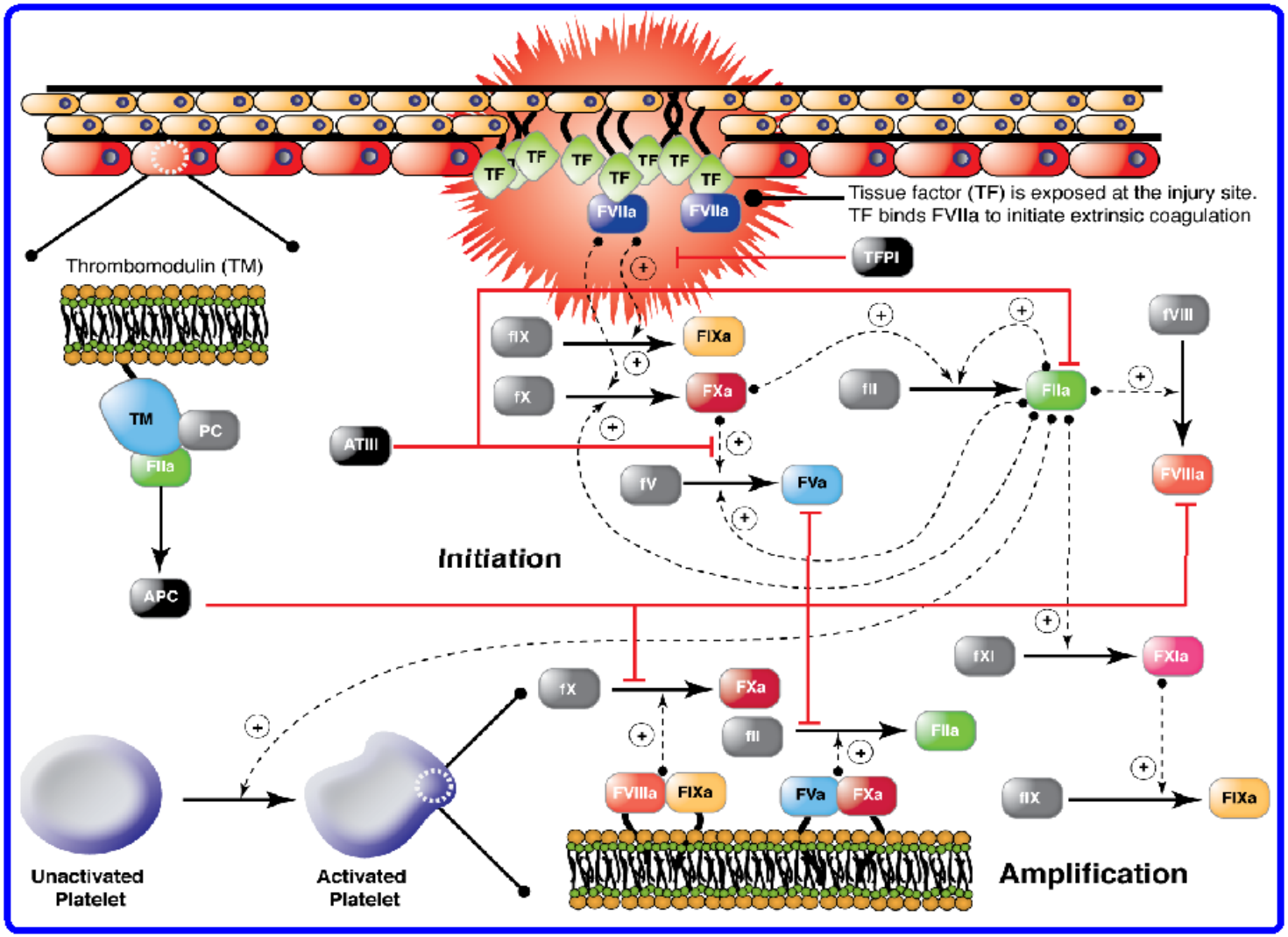
The clotting pathway



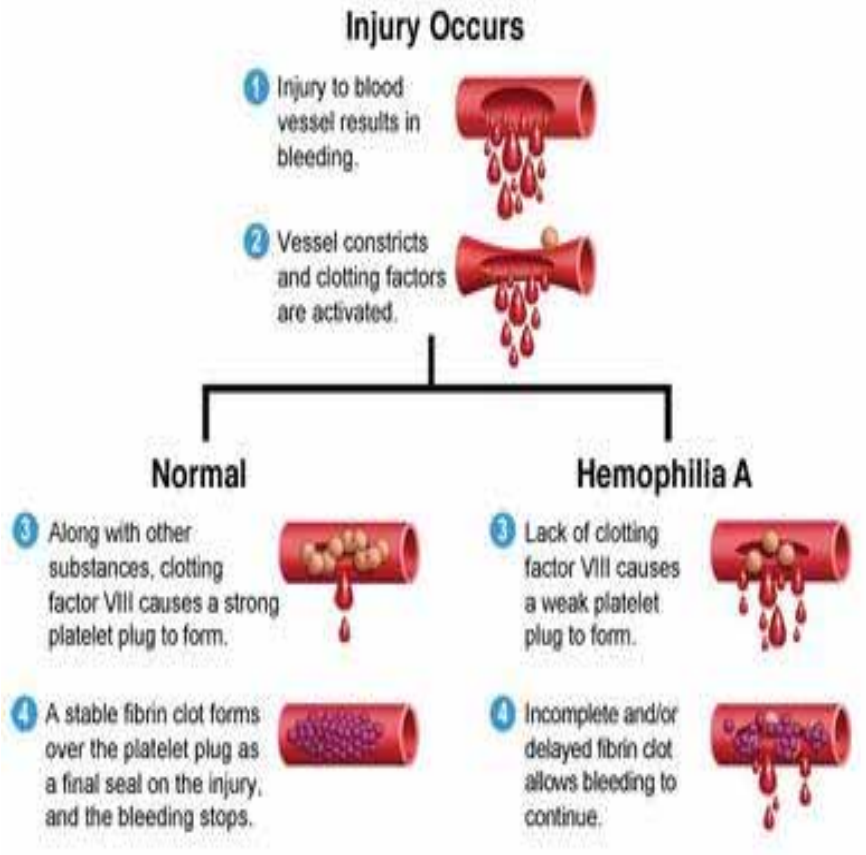
Clotting Pathway



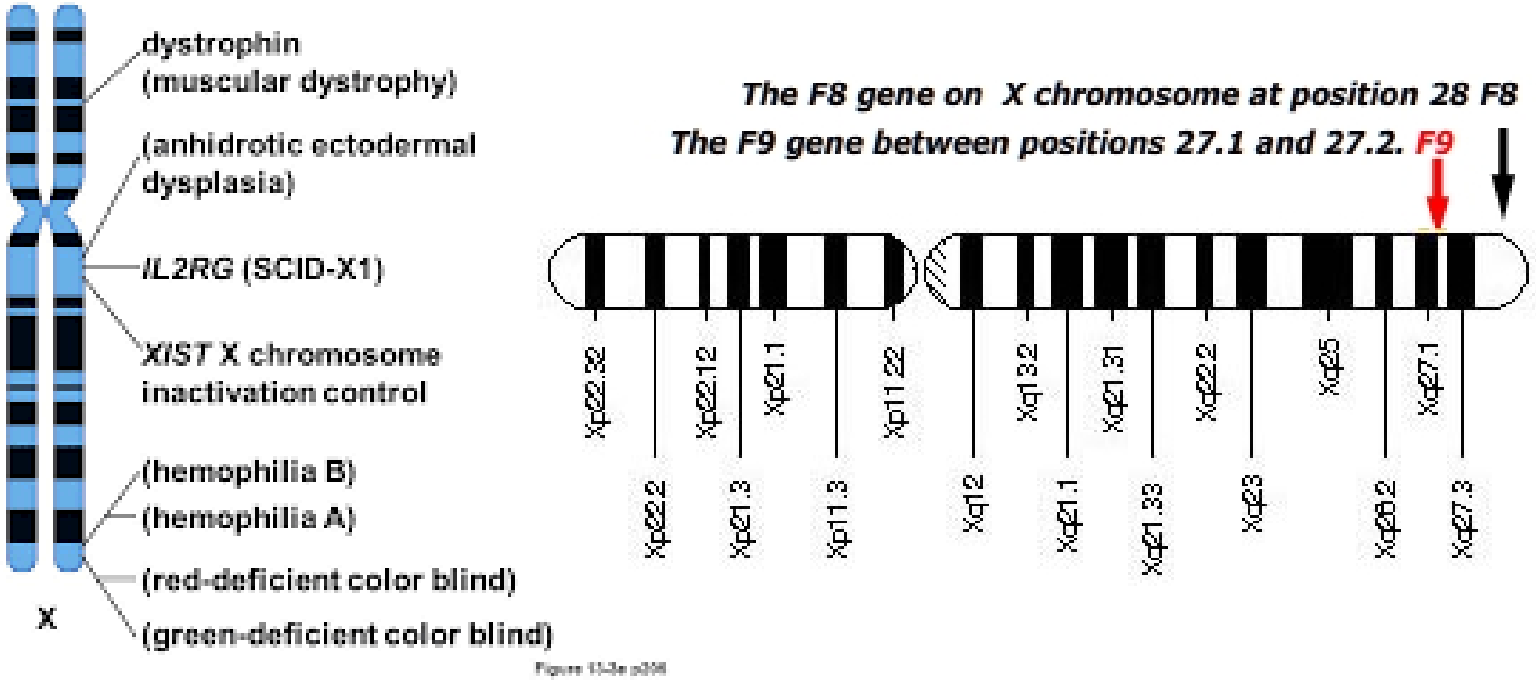
Hemophilia

Bleeding disorder:

- Deficient or inactive clotting factor (VIII or IX)=>Delayed blood coagulation=> results in prolonged bleeding, oozing, seepage into body tissue or spaces
- Affects 1 in 10 000 males worldwide
- X-linked recessive inheritance

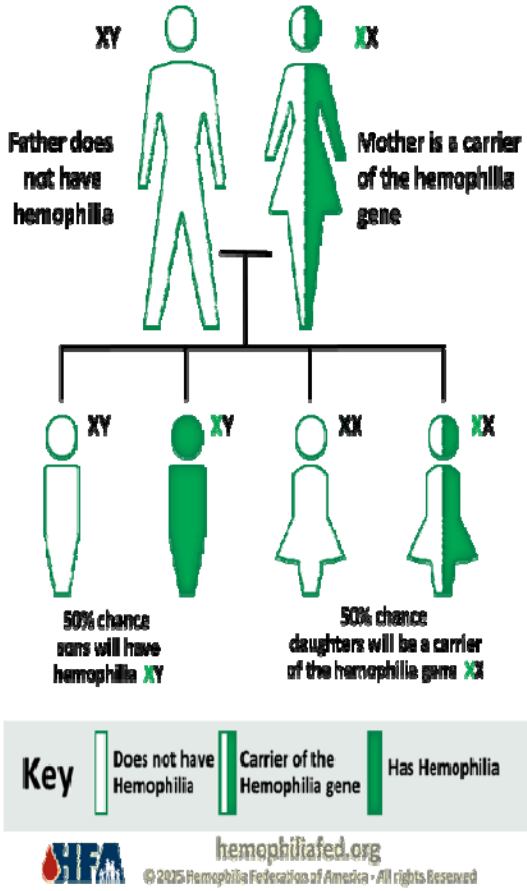


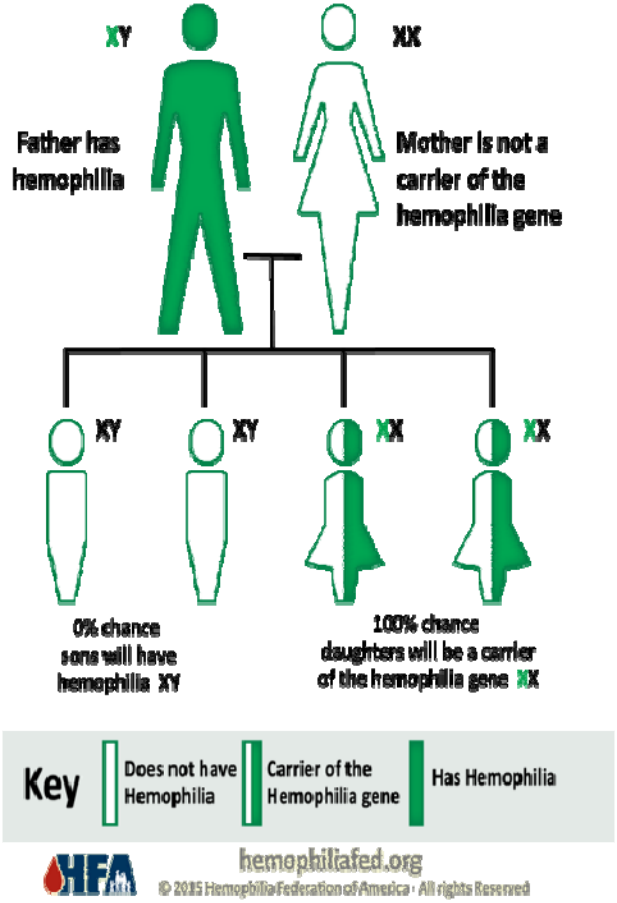
X-linked inheritance

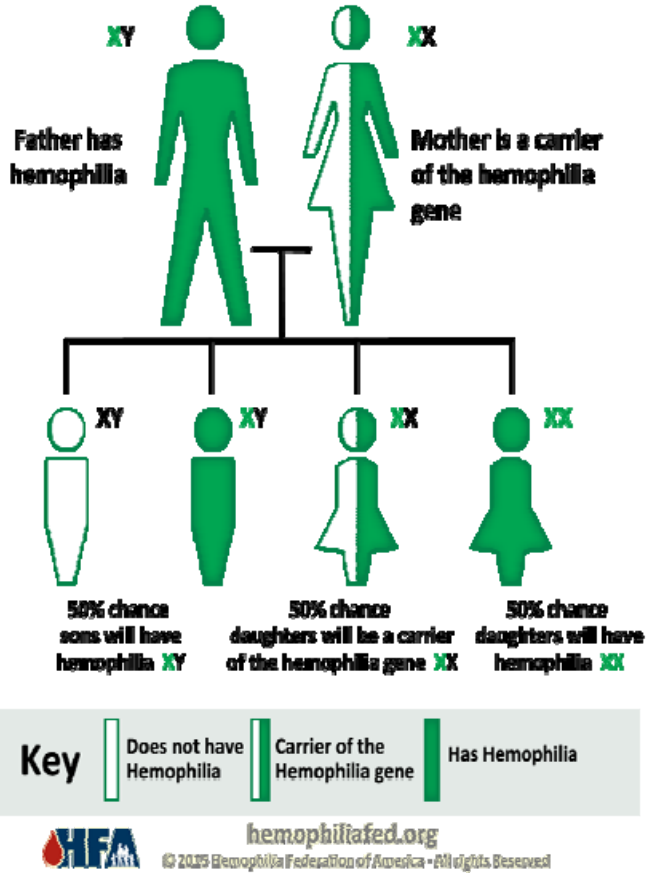


Inherited hemophilia A and B are passed in an X-linked recessive pattern
One third of patient with hemophilia, no family history of the disorder

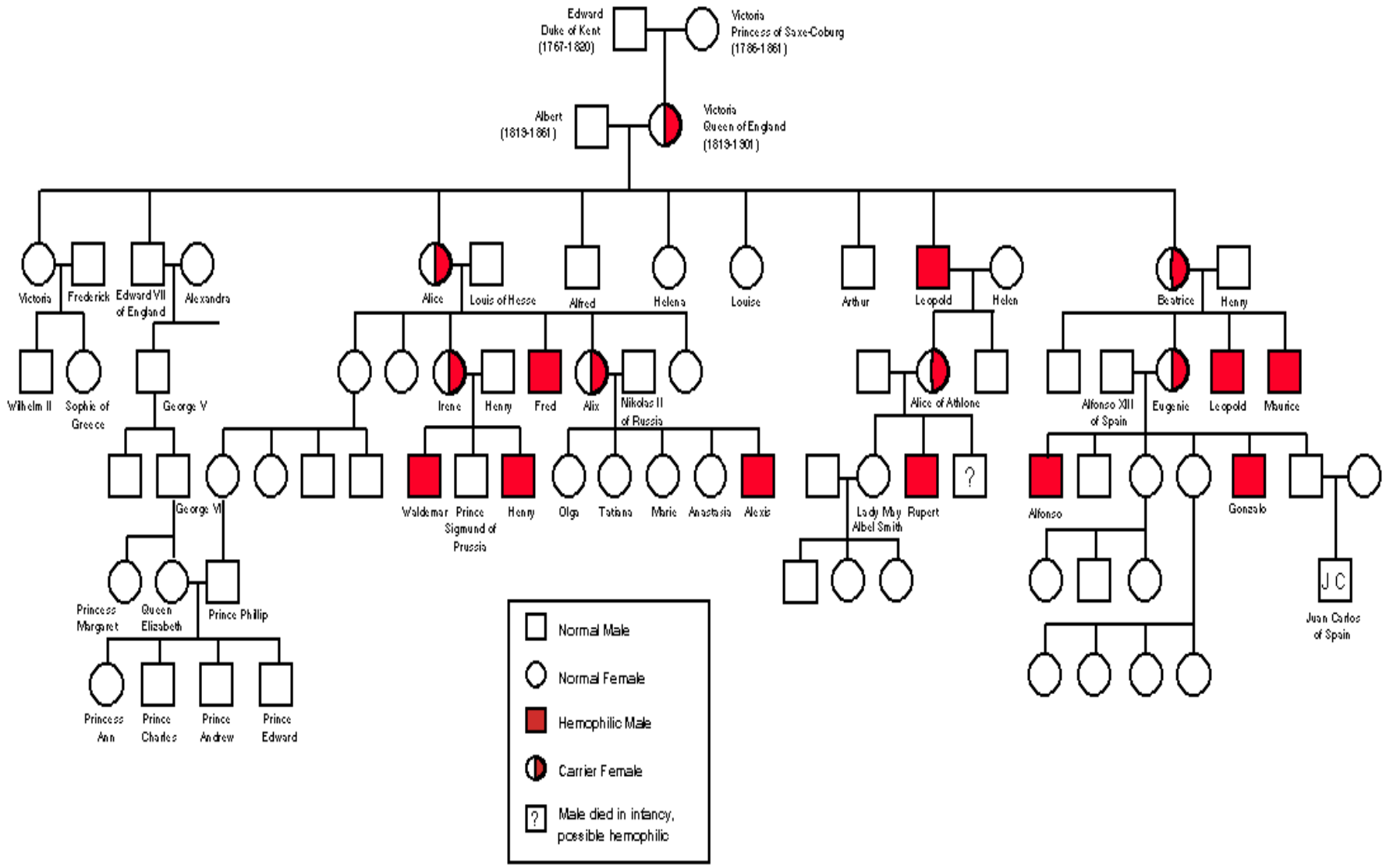
Inheritance: X-linked recessive







The Royal disease



Hemophilia

Hemophilia A

- known as classic hemophilia
  Occurs about 1/5000 males worldwide
  Results from a mutation in the Factor 8 (F8) gene on the X-chromosome.
  More than 1,300 alterations in the F8 gene have been identified

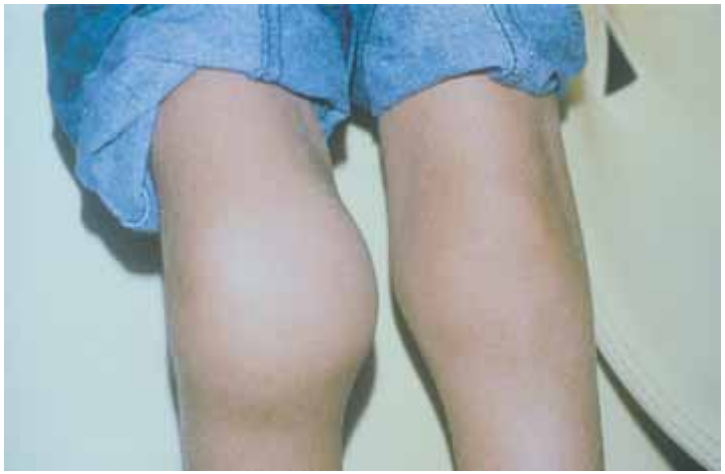
Hemophilia B
Known as Christmas disease
Occurs in about 1/20,000 males worldwide.
Results from a mutation in the Factor 9 (F9) gene on the X-chromosome.
Mutations in F9 can affect the quantity and quality of factor IX

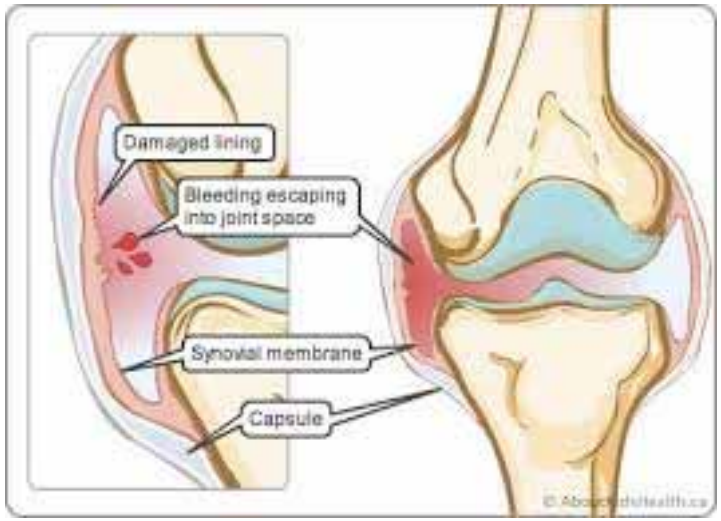
AcqIUred hemophilia :

rare and severe bleeding disorder that unexpectedly occurs in about 1 per million people per year.
Caused by antibodies which inhibit the action of clotting factors, usualy F8 or F9.
50% : cause of antibody synthesis unknown.
50% : pregnancy, autoimmune or collagen vascular disorders, malignancy, drugs, respiratory disorders and infections.

Clinical manifestations

- **Spontaneous bleeding** (epistaxis)
- Hemarthrosis(tingling and bubbly sensation, pain, swelling, reduce mobility, increase temp)
- **Deep tissue hemorrhage/hematoma**
- **Ecchymosis**(large)
- **Hematuria+, renal colic, post-circumcision bleeding**
- **Oral mucosal hemorrage, excessive bleeding with routine dental procedures**

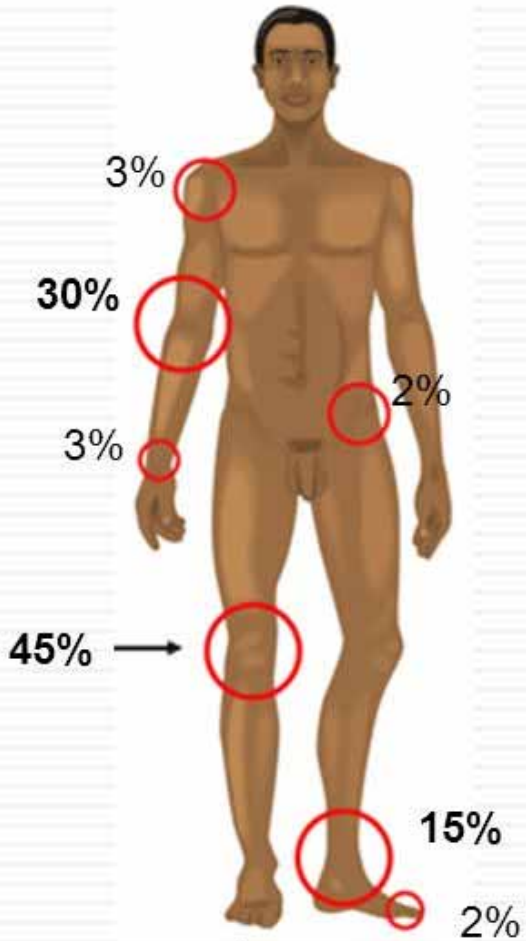




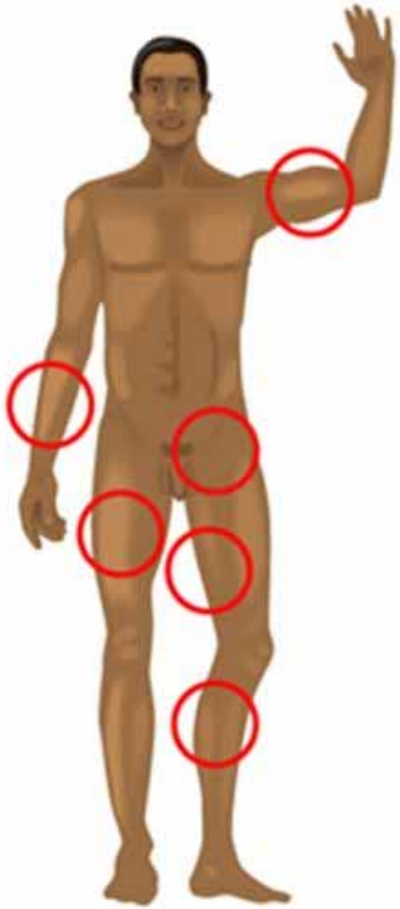
SITES OF BLEEDING IN HEMOPHILIA

Serious	Life-threatening
1-Joints (hemarthrosis)	Intracranial
2-Muscles, especially deep compartments (iliopsoas, calf, and forearm)	Neck/throat
3-Mucous membranes in the mouth, gums, nose, and genitourinary tract	Gastrointestinal

Clinical manifestation



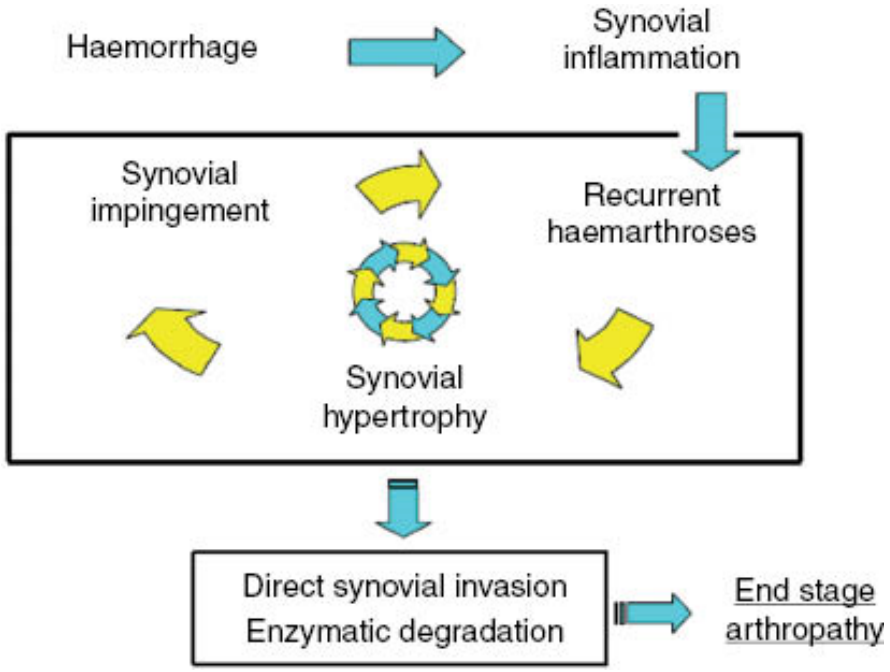
Hemarthrosis



Muscle bleed

Hemophilia in Pictures. WFH, 2005

Complications of Hemophilia



Musculoskeletal complications:

- Acute Synovitis=>chronic synovitis
- Chonic hemophilic arthropathy
- Compartment syndrome(e.g Volkmann syndrome)

Inhibitors

Transfusion related infection

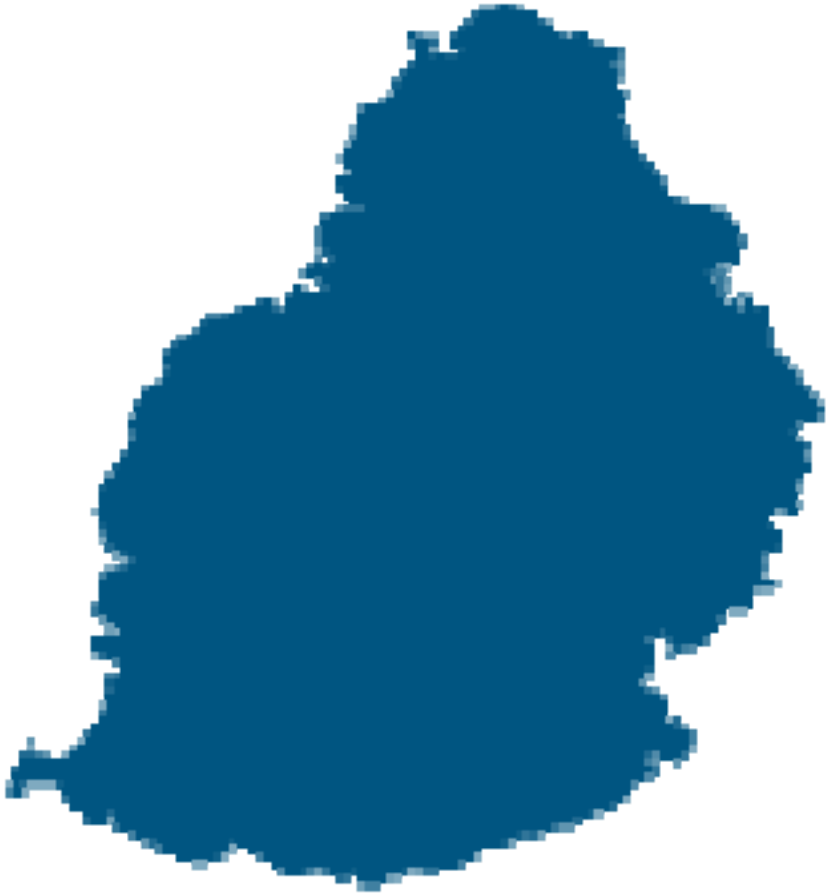
Diagnosis

- Coagulation screening tests:
  - platelet count
  - Platelet function analysis
  - Activated partial thromboplastin time(aPTT)
  - Prothrombin Time(PT)
- Factor assays

Clinical severity

Classification	Factor Activity	Clinical Presentation
Severe	<1%	Spontaneous hemorrhage from early in infancy
		Frequent hemarthrosis and muscle bleeds
		Diagnosis usually <2 years of age
Moderate	1-5%	Hemorrhage sec to trauma or surgery
		Occasional spontaneous hemarthrosis
		Diagnosis usually before age 5 to 6
Mild	>5%	Bleeding usually due to trauma or surgery
		Occasional spontaneous hemorrhage
		Diagnosis is usually later in life

Situation in



MAURITIUS

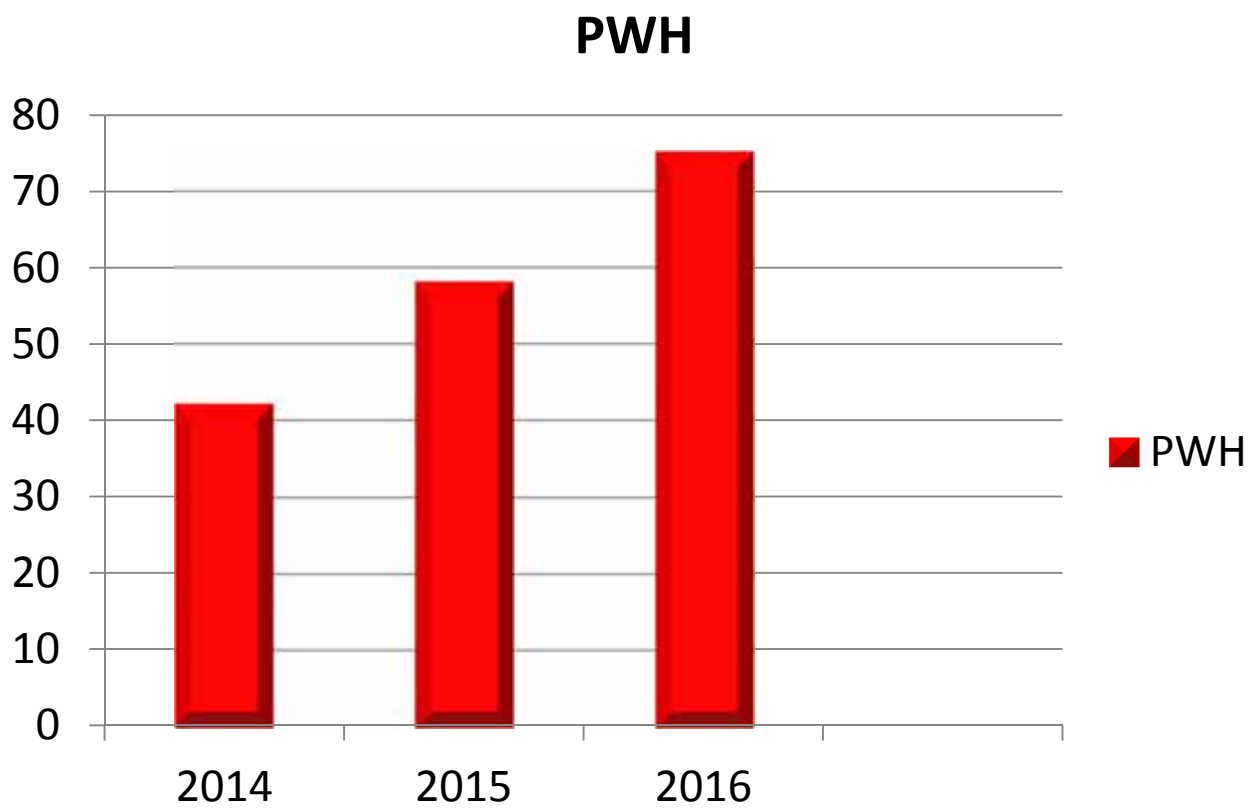
Statistics

- 2014: Most common bleeding disorder is Hemophilia A (Factor VIII Deficiency) with 25 adults and 13 children making a total of 38 cases.
- 2015: Most common bleeding disorder is Hemophilia A (Factor VIII Deficiency) with 39 adults and 6 children and 4 with age not specified making a total of 49 cases.

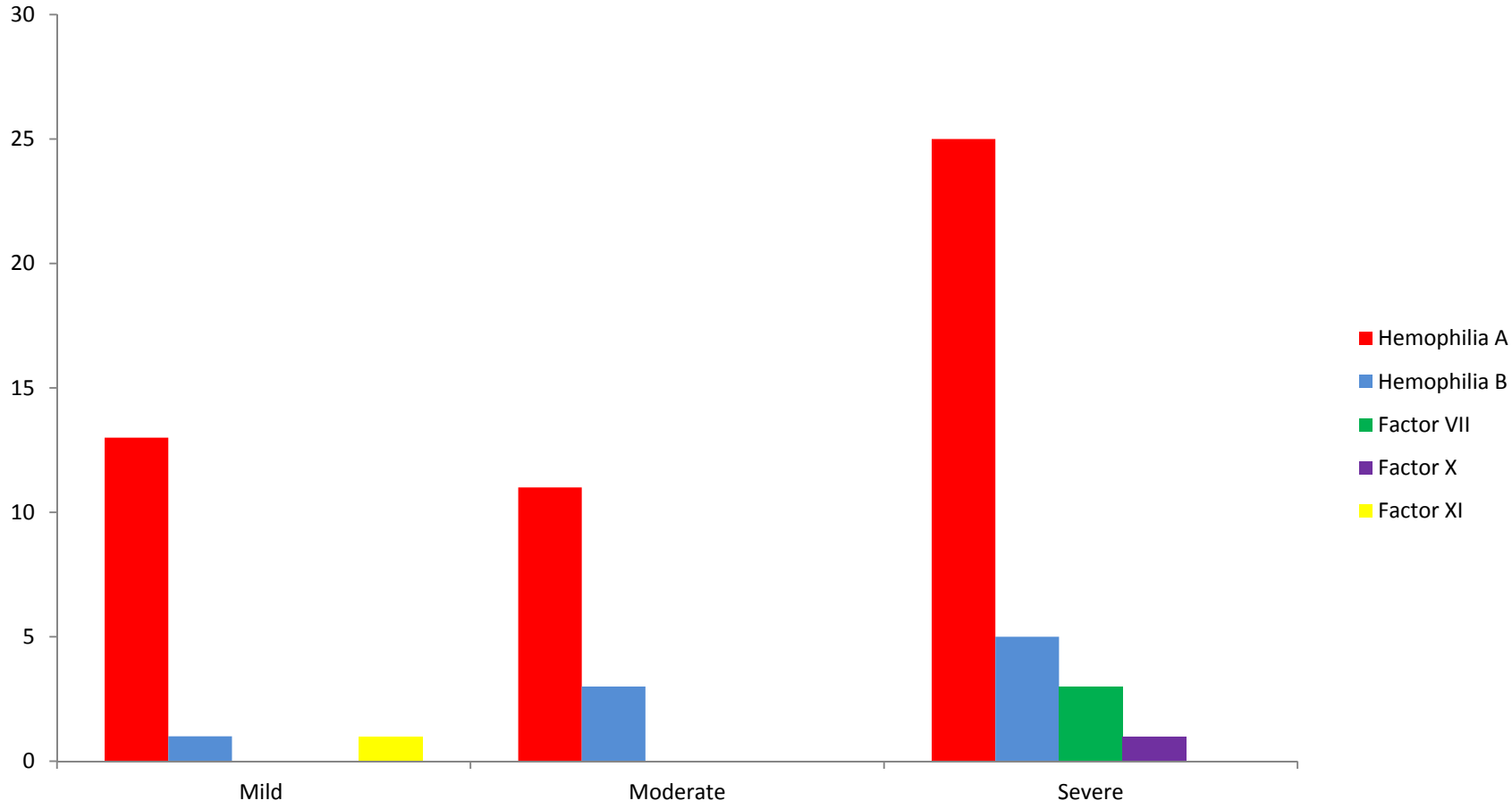
Hemophilia population

	2014		2015	
Factor deficit	No. patients	Percentage	No. Patients	Percentage
Hemophilia A	38(23, 5, 10)	82.6	49(25,11,13)	77.8
Hemophilia B	4 (all severe)	8.7	9(5,3,1)	14.3
Factor VII	3 (all severe)	6.5	3(all severe)	4.8
Factor X	1(severe)	2.2	1(severe)	1.6
Factor XI	0	0.0	1(mild)	1.6
Total	46	100	63	100

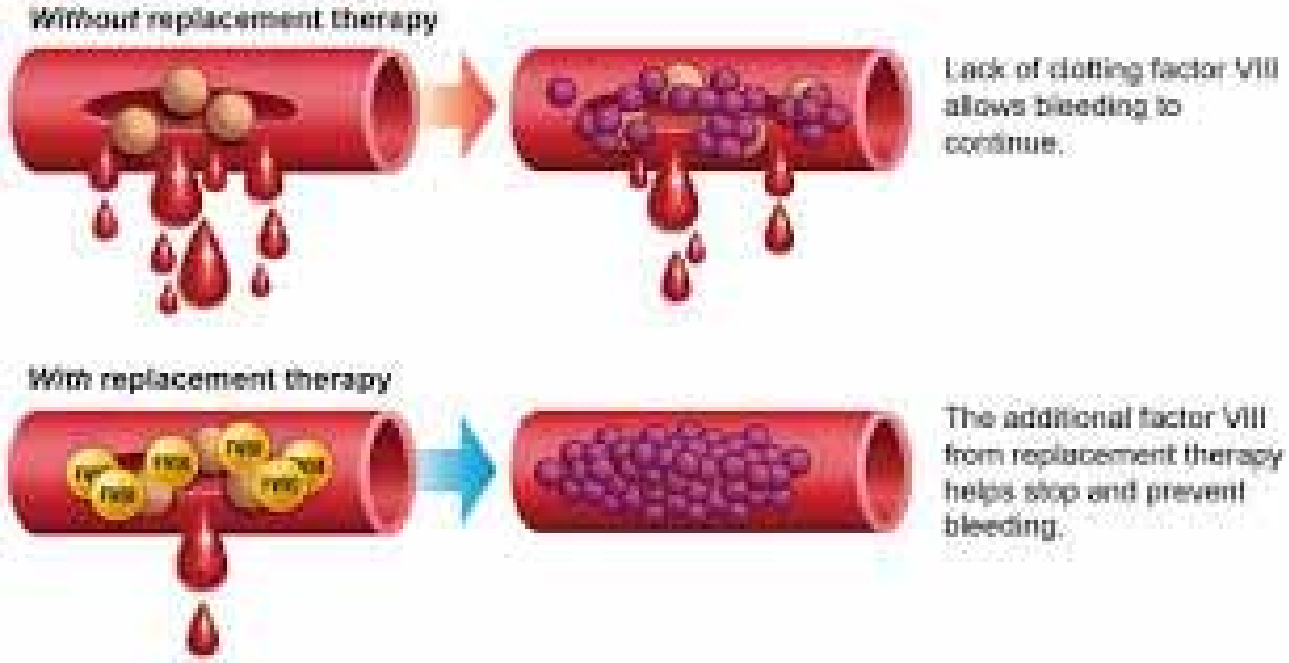
Mauritius



Type of factor deficiency and Severity



Treatment


Without replacement therapy
Lack of clotting factor VIII allows bleeding to continue.
With replacement therapy
The additional factor VIII from replacement therapy helps stop and prevent bleeding.

Hospitalisation

- Head Injury
- Trauma spine
- Trauma Abdomen
- RTA, even
- Abdominal pain
- GI bleed
- Hemarthrosis (hip, painful)
- Hematoma (psoas, at risk sites)

Treatment

- Emergency!!!
- Adjunctive treatment
- Clotting factor therapy: prophylaxis(decrease bleeding episodes and arthropathy) and on demand
- Plasma versus recombinant factor replacement

Adjunctive Treatment

- RICE
- Analgesia: OMS 1, 2, 3 (Depend on severity of pain)
- Avoid Aspirin/NSAIDS versus COX 2 inhibitors (etoricoxib)
- Avoid intramuscular injections
- Physiotherapy+++

Adjunctive Treatment

Desmopressine (DDAVP)

- Mild or Moderate

Hemophilia A

- Not before 2 yrs old
- 0.3 µg/Kg SC or IV
- FlIUd restriction
- OCTIM 1 spray<50 kg,

2>50 kg

- Beware of Tachyphylaxis

Tranexamic acid

- Antifibrinolytic agent
- Mucosal surfaces(mouth, gum, teeth, GI bleed)
- Cl in cases hematuria
- 20mg/kg children, 2-4g /day in adults in 2-3 divided doses

Advances in Treatment

Table 1
Early therapies for the treatment of haemophilia A.

Year	Therapy
1840	First successful transfusion of whole blood is performed [30]
1911	Preparation of a globulin fraction from normal plasma that shortens the coagulation time of haemophilic blood [15]
1916	Intravenous injection of fresh human serum reduces clotting time of haemophilic blood [16]
1934	Russell's viper venom ("Stypen") first used for the local treatment of bleeding in patients with haemophilia A, in those with a bleeding diathesis, and in healthy controls [31]
1935	A "coagulation-promoting" substance prepared from normal plasma was able to reduce the coagulation time of haemophilic blood to within normal values when administered intravenously or intramuscularly [20]
1936	A precipitate of whole blood plasma first shown to correct bleeding time of haemophilic blood [21]
1946	Introduction of the term "antihemophilic globulin" [22]
1953	First prothrombin complex concentrate (ACC 76®) is marketed by Behringwerke AG
1958	Prophylaxis for haemophilia A begins in Sweden [32]
1965	Cryoprecipitate revolutionizes the treatment of haemophilia [33]

Advances in Treatment

Advances in haemophilia treatment.

Year	Therapy
1968	First commercial factor VIII (FVIII) concentrates developed
1972	Medically controlled home therapy commences in Germany [63]
1977	Desmopressin is recognized to boost FVIII and VWF levels [64]
1977	Introduction of immune tolerance therapy [65]

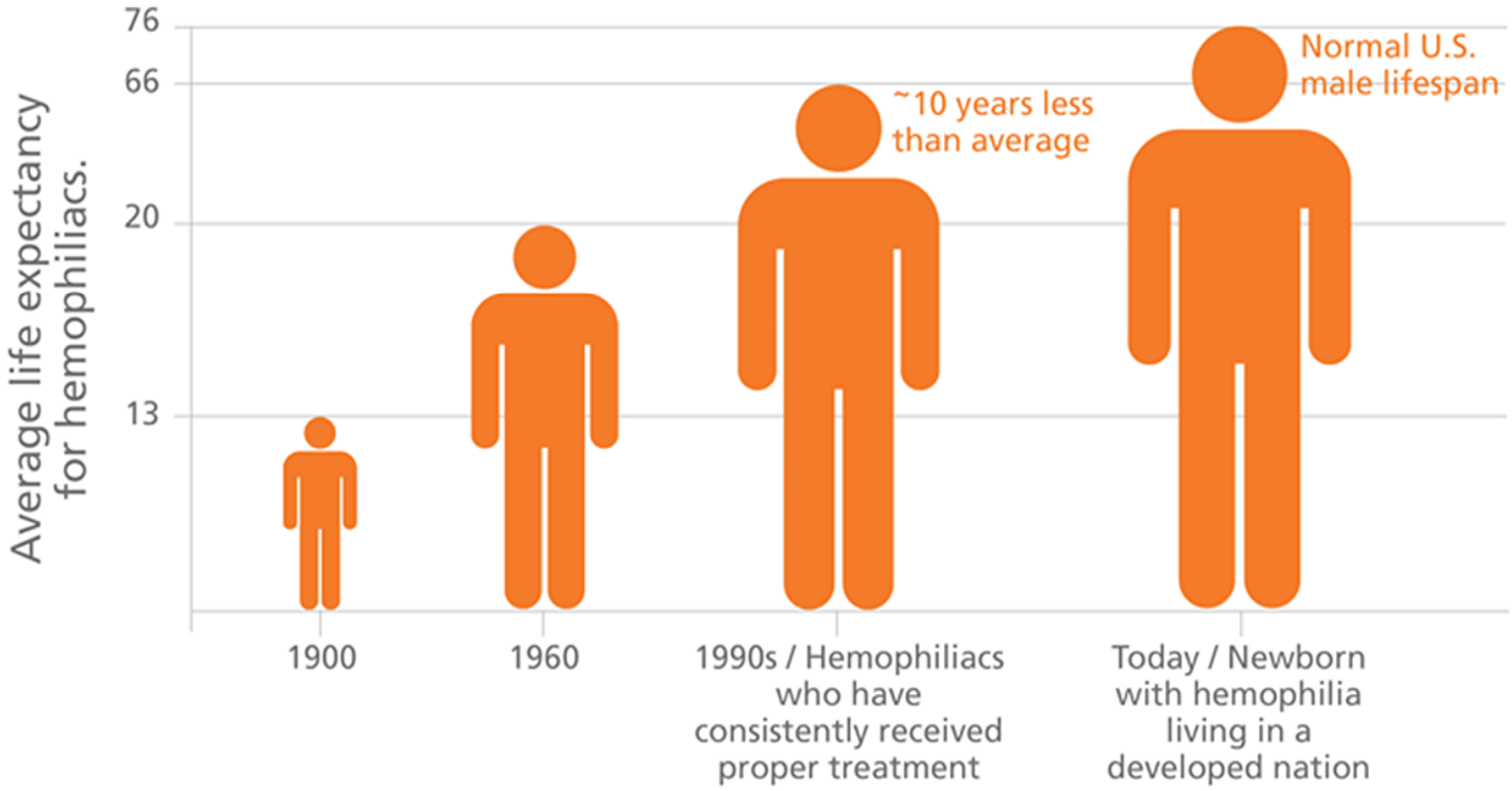
VWF, von Willebrand factor.

Availability of modern haemophilia A treatment.

Year	Therapy
1981	First pasteurized factor VIII (FVIII) concentrate (Haemate® P) available in Germany
1990	The highly purified pasteurized FVIII concentrate Beriate® P registered in Germany
1992	First recombinant FVIII product is registered
Since 2004	Further developments of recombinant FVIII products

Source: W. Schramm; Thrombosis research, 2014

Better treatments have increased Hemophiliac life expectancy



National Hemophilia Foundation. History of Bleeding Disorders.
National Haemophilia Council. What is the life expectancy of someone with haemophilia?

Prophylactic Treatment

- Factor VIII:
  - Half-life:8-10 hrs
  - 20-30IU/kg thrice weekly
  - E.g 50kg: 1000 IU-1500IU thrice weekly
- Factor IX:
  - Half-life: 18-24 hrs
  - 30-40IU/kg twice weekly
  - E.g: 1500-2000 IU twice weekly

On Demand: Clotting Factor Therapy

- Factor concentrate:
  - Factor VIII: Dose= desired level (%)* weight (kg) * 0.5
  - Factor IX: Dose= desired level (%)* weight (kg)
  - plasma concentrate or recombinant
- Activated prothrombin complexe concentrate (FEIBA)
- Activated Factor VII

Clinical situation: Hemarthrosis

- 20-30IU/kg FVIII
- 20-40IU/kg FIX
- Only one injection if treated early(home therapy)
- Re-evaluate and repeat 12 and 24 hrs later
- Recurrent episodes: consider prophylaxis

Clinical Situation: Deep Hematoma

- Volkmann, psoitis, retroperitoneal bleed..
- First day:
  - FVIII: 50IU/kg 3 x day
  - FIX: 80 IU/kg x 2 day
- Aim: keep factor assay> 50%
- REST and Immobilsation
- Physiotherapy
- DO NOT EVACUATE HEMATOMA

Clinical Situation: Head Injury

- Immediately:
  - FVIII: 50IU/kg or FIX: 80 IU/kg
  - only then CT Scan Brain
- then 2-3 injection/day
- Aim: factor assay>80 %
- Neurosurgery: Factor assay> 80% 1 week then >50% next 2 weeks

Clinical situation: Acute Abdomen

- Immediately:
  - FVIII: 50IU/kg or FIX: 80 IU/kg
  - only then USG Abdo
- In case of hematoma: 2-3 injection/day
- Aim: Factor assay> 80% 1 week then >50% next 2 weeks
- If USG Abdo normal, seek advise from surgeon

Clinical Situation: GI bleed

- Immediately
  - FVIII: 50IU/kg or FIX: 80 IU/kg
  - 2-3 injection/day
- Factor assay> 80% 1 week then >50% next 2 weeks
- Tranexamic acid 10-15 days(20mg/kg children, 2-4 g adult)
- Hb, Cause!!!

Clinical situation: Hematuria

- Bed rest
- Oral fluid++ if no pain, restriction in case of pain
- Anti spamodic drugs
- FVIII or FIX 20IU/kg if hematuria persists
- CI: antifibrinolytic agent
- Cause: MSU, Echo..

Clinical situation

- Epistaxis: Exacyl 5-8days, absorbable ribbon, 30IU/kg FVIII or 40IU/kg FIX
- Oral cavity bleed(injury or milk tooth): mouth wash, pack with gauze soaked in exacyl, cold semi-liquid food 3-4 days, Exacyl 5-10 days, >24 hrs bleed: 20-30IU FVIII or 30-40IU FIX, crust: 4-7 days

Innovative Drugs Pipeline – Hemophilia A

Company	Name	Status	Description
Biogen Idec / SOBI	rFVIIIFc (BIIB031 or Eloctate)	FDA and Health Canada approved in summer 2014	Long-acting recombinant with extended half life
Bayer	BAY81-8973 (Kovaltry in the U.S.)	FDA accepted Bayer's license application in the March 2015	Normal half life recombinant : full-length rFVIII manufactured without exposure to human and animal proteins
Novo Nordisk	Zonovate in Canada and NovoEight in the rest of the world (Turoctocog alfa)	Approved by Health Canada in January 2015. NovoEight is approved by the FDA, EMA, and regulatory authorities in Japan and Australia	Normal half life recombinant : rFVIII manufactured without exposure to human and animal proteins
Octapharma	Human-cl rhFVIII (simoctocog alfa) Nuwiq	Marketing authorization granted in Europe in August 2014 and Canada in November 2014	First rFVIII with human-like post translational modifications, which it is hoped will result in a lower rate of inhibitors
Novo Nordisk	N8-GP (turoctocog alfa pegol)	Phase III trial completed in March 2014	Recombinant with half life of 18.4 hours
Bayer	BAY94-9027	Phase III trial completed in Feb 2014	Long-acting plasma/albumin free, full length rFVIII
Baxter	Bax 855	Submitted application to the U.S. FDA in Dec 2014	Pegylated, long-acting, plasma/albumin free, full-length rFVIII
CSL Behring	rVIII-SingleChain	Results of Affinity Phase I/II study released in June 2015	Novel recombinant single-chain factor VIII designed to overcome inhibitors
Chugai Pharmaceutical Co & Roche	Anti-factor IXa/X bispecific antibody ACE910	Phase III trial by the end of 2015	Mimics coagulation factor VIII with a half-life of three weeks

Innovative Drugs Pipeline – Hemophilia B

Company	Name	Status	Description
Biogen Idec/ SOBI	rFIXFc (BIIB029 or Alprolix™)	Approved in US and Canada in 2015	Fc fusion technology to extend half-life by 2.5 times that of existing therapies
Emergent Biosolutions	Ixinity in the U.S. (previously IB1001)	FDA approved in May 2015	Normal half-life , 3rd gen rFIX manufactured in a Chinese Hamster Ovary cell line without exposure to human and animal proteins
Baxter	Rixubis(previously Bax 326)	FDA approval for pediatric treatment in October 2014. Approved for adults in US and Canada.	3rd generation rFIX
CSL Behring	rIX-FP	Applied for approval in 2015	rFIX is fused with recombinant human albumin. Phase III trials showed a longer half-life
Novo Nordisk	NN79 (N9-GP)	Marketing authorizations submitted in 2015	Long-acting with reported half life of 93 hours
OPKO Health	Factor IX-CTP	Investigational New Drug (IND) application submitted in Jan 2015	FIX fused with a carboxyl terminal peptide to extend half-life


DO'S
DON'TS

Do’s of hemophilia

- Always correct the coagulation profile(factor replacement) prior to investigations(x-ray, echo, ..)
- Always transfuse factor in RTA or severe Trauma (Brain/skull/Abdomen/Spine)
- Always transfuse factor prior to invasive procedures(suture, LP, tapping, endoscopie..)
- Always apply pressure (10 mins) at site of puncture and compression dressing (few hours)

Don’ts of Hemophilia

- Do not make patient wait
- Do not prescribe:
  - No invasive procedure apart from venepuncture prior to clotting factor therapy
  - No IM
  - Rectal temperature
  - Aspirin/ NSAIDS
  - Tight circular compression

Inhibitors

- IgG antibodies that neutralize clotting factors.
- Arise in repsonse to replacement therapy
- Incidence: 30% Hemophilia A and 5% Hemophilia B
- More frequently encountered in persons with severe hemophilia
- Often seen in conjunction with intensive FVIII exposure with surgery
- In severe hemophilia: inhibitors do not change the site, frequency, or severity of bleeding
- In moderate or mild hemophilia: neutralize endogenously synthesized FVIII=> severe
- Investigated: Inhibitor testing (periodic)
- Low responding inhibitor: < 5 BU/ml, High responding inhibitor ≥ 5 BU/ml
  - UK guidelines: every 5th exposure day, or every 3 months, until the 20th exposure then every 6-12 months thereafter.
  - before any surgical procedure (including dental work)
  - Clinical response to infused coagulation factor concentrate is unexpectedly poor.

INHIBITOR STATUS in Mauritius

- Development of inhibitors makes the management of hemophilia difficult and requires far more factor concentrates.
- One patient screened so far is found to have inhibitors to factor VIII

Bypass agents and other treatment

- Recombinant Factor VIIa (Novoseven)
  - 90µg every 2-3 hours or 270µg/injection
- Activated prothrombin complex concentrates(aPCC) (FEIBA):
  - 80IU/kg 2-3/day
  - Max: 200IU/kg
  - Perfusion rate: 2u/kg/min
- Immune Tolerance (eradicate antibody): 50-200IU/kg daily 12-24 months
- Non-Human Factors(porcin)=> no/limited cross-reactivity with anti-human antibody; no porcin factor but recombinant porcin clinical trials
- Immunosuppressants

Bypass therapy

- Safe and effective
- inferior to replacement therapy
  - thrombotic events increase
  - more costly
  - no validated and widely available methods to monitor bypass agents to guide clinicians

Transfusion–related infection

- Emergence and transmission of HIV, HBV and HCV through clotting factor products resulted in high mortality of people with hemophilia in the 1980s and early 1990s
- Many studies conducted all over the world indicate that HIV, HBV, and HCV transmission through factor concentrate has been almost completely eliminated.

Tranfusion-related infection in Mauritius

- **HIV/HCV/HBV STATUS**
- Patients in 2011 tested for HIV, Hepatitis B and Hepatitis C.
- 8 patients tested positive for hepatitis C .
- HIV and Hepatitis B screening was negative in all.

Availability of factor concentrates

- Factor VIII,FIX, FVII and FX available in hospitals
- 2014 - 1,510,000 units of VIII at unit price of Rs 9198 and 1,27,000units of IX at unit price of Rs 10956
- Treatment protocols developed and distributed


Let's
Think
About It

Issues to consider in local context

- Hemophilia Register ?? established after ethical clearance from MOH and QL in 2010
- Patient baseline profiling was done which included following information
  - Name
  - DOB/Age
  - Gender
  - Address
  - Bleeding Disorder Type
  - Baseline factor Activity
  - HIV,HBV and HCV status.
  - Inhibitor status

Patient follow up

- ?? regular follow up
- No hemophilia clinics
- No comprehensive hemophilia treatment center

- Hemophilia Register
- Capacity building
  - Laboratory diagnosis
  - Clinical management
- Management of factor procurement
- Nursing/physiotherapy/psychosocial aspects
- Diagnosing carriers and genetic counselling
- Treatment
  - Prophylaxis Vs Episodic
  - Prophylaxis : ?Who ? Dosages ?Frequency?Follow up

HOME THERAPY

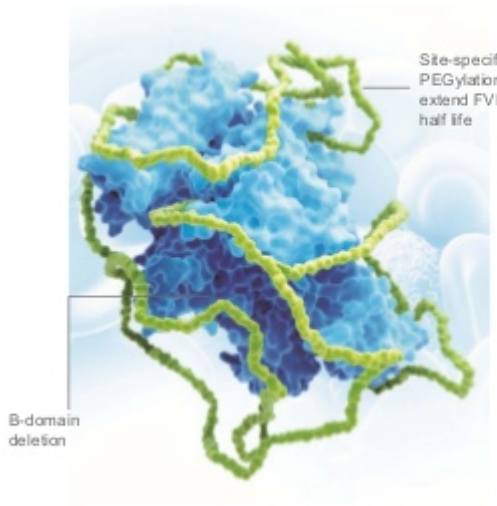
- Reduction in clinic visits by 400%, easing the burden on public health facilities.
- Increase lifespan and quality of life for people with hemophilia.
- Optimal use of expensive replacement therapy decreases the cost of treating specific bleeding episodes

The cost of NOT providing patients with home therapy:

- Increased absenteeism and reduced productivity in the workplace for patients and caregivers;
- Increased unemployment and financial burden on families if the person cannot work;
- Increased costs to employers
- Increased risk of severe complications due to delayed treatment of bleeds, which may necessitate hospitalization, surgery, and other interventions
- Decrease in school attendance and resultant educational and social gaps; possibility of not completing education leading to diminished employment options and financial impact.
- Decrease in quality of life for families: more frequent emergency hospital visits which disrupt family life, causing frictions and stresses which become additional hardships to families already burdened with medical issues

THANK YOU FOR YOUR ATTENTION

Expanding the Hemophilia Franchise – Long-Acting Site-directed PEGylated Factor VIII



- B-domain–deleted recombinant factor VIII (BDD-rFVIII) with site-specific PEGylation (BAY 94-9027)
- Attachment of PEG extends half-life without reducing FVIII activity
- Positive PROTECT VIII phase III data
- Filing US, EU and other regions planned for 2H'2015

Extended half-life factor concentrates

- Introduced in Canada in 2016
- Factor VIII
  - FVIII molecule fused with immune globulin
  - Half-life increased from 12 to 18 hours
  - # of infusions reduced from 3 to 2 per week
  - 52 fewer infusions per year
- Factor IX
  - FIX molecule fused with immune globulin or albumin
  - Half-life increased from 18 to 45 or 90 hours
  - 1 infusion per 7 or 10 days, instead of 2 per week
  - 52 to 78 fewer infusions per year
- Potential for increased protection from bleeding

(1% is not enough!)

Hemophilia Treatment

- Hemophilia A
  - Recombinant factor VIII concentrates, cryoprecipitate
  - Dose(units)= desire rise level (%) x BW (kg) x 0.5
  - Half life : 10-12 hrs
- Hemophilia B
  - Recombinant factor IX concentrates, FFP
  - Dose(units)= desire rise level (%) x BW (kg)
  - Half life : 18-24 hrs
- DDAVP
  - Increase plasma factor VIII and vWF → mild and moderate hemophilia A , type 1 vWD
  - No effect foe severe hemophilia A , severe vWD, any form of hemophilia B, life-threatening hemorrhage

Physical activities

Low risk	Swimming, snorkeling, fishing, golf, hiking, frisbee
Low to moderate risk	Bicycling, pilates, resistance training, circuit training
Moderate risk	Dance, diving, rowing, running and jogging, yoga, tennis
Moderate to dangerous	Volleyball, basketball, surfing, soccer, horse riding, karate
Dangerous*	Rugby, weight lifting, motorcycling, boxing, hockey

*These activities are not recommended for people with haemophilia.