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Hemophilia: diagnostics and treatment

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What is hemophilia?

- Hemophilia A: deficiency of factor VIII (85%)
- Hemophilia B: deficiency of factor IX (15%)

Hemophilia: Defect of secondary hemostasis due to impaired clot formation: primary hemostasis is normal

- Defect primary hemostasis : immediate increased bleeding tendency

- Defect secondary hemostasis: delay in bleeding

Hemophilia genetics

- X-recessive
- Men are affected
- Prevalence: 8,5 per 10.000
- 1600 patients in the Netherlands
- Taiwan ca 2400 patients; 1000 diagnosed
- 50% sporadic - 50% familiar

How to recognise increased bleeding tendency i.e. hemophilia?

- Bruises on exceptional places and with nots
- Mucosa bleeds
- Joint and muscle bleeds: spontaneous or after a trauma
- Prolonged or re-bleeding after (minor) medical intervention

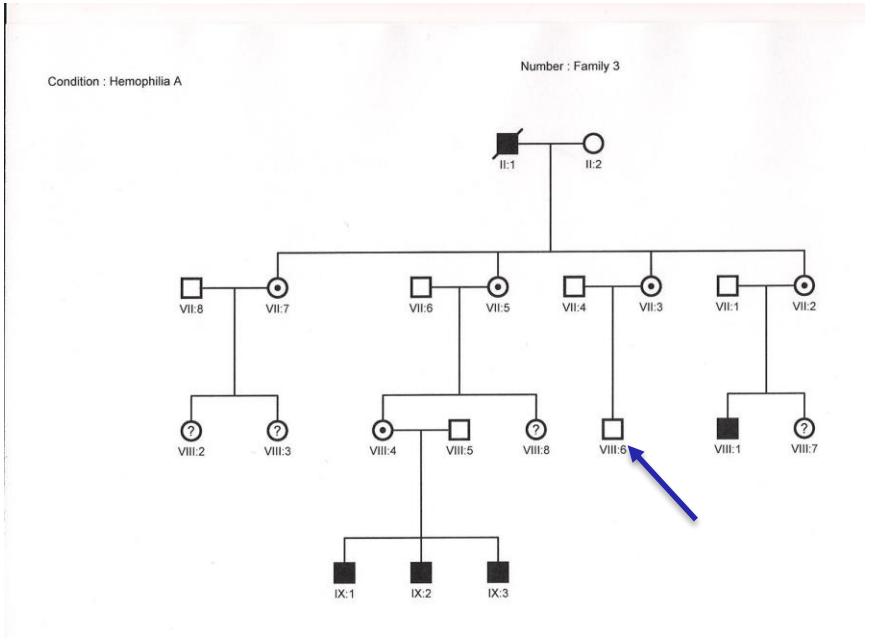
How to recognise hemophilia?

- Less common: postpartum bleeding
  - Cephal hematoma
  - Sub-Galeal hematoma
  - Intracerebral hematoma

Screening increased bleeding tendency

Screening

- Bleeding history (ISTH bleeding score or Tosseto bleeding score)
- Family history
- Family tree
- Medication
- Medical examination
- Lab assays



Screening test bleeding tendency

- In case of positive family history: FVIII or IX assay
  - When not possible APTT (or mixing test)

- In case of negative family history: general screening
  - Bleeding time
  - Platelet counts
  - Activated prothrombin time: APTT
  - Prothrombin time: PT
  - Thrombin time: TT

Screening test bleeding tendency

	Deficiency
• PT ↑, APTT=N	FVII
• APTT ↑, PT=N	FVIII, IX, XI, (XII)
• PT↑ APPT ↑	Prothrombin, V, X
• PT↑, APPT ↑,TT ↑	Fibrinogen
• Bleeding time ↑	thrombocytopenia, thrombopathia, VW disease

NB heparin

NB APTT↑ infection, antiphospholipid syndrom

NB FXII deficiency has no clinical effect

Severity of hemophilia

- Severe: FVIII/IX < 1 % 40%
- Moderate : FVIII/IX 1-5 % 20%
- Mild: FVIII/IX > 5-40 % 40%

- Normal: 100 %(range 60-150%)

Clinical signs hemophilia

Hemophilia A and B are clinically identical

Clinical signs depend on the remaining clotting factor level

- Severe hemophilia: frequent bleeding, mostly joints
- Moderate hemophilia: infrequent bleeding, mostly joints
- Mild hemophilia: bleed occasionally, there is always a clear cause
- All types: bleeding after medical intervention and trauma

Clinical signs (severe) hemophilia

- Joint bleeds 70-80%
- Muscle bleeds 10-20%
- Other major bleeds 5-10%
- CNS < 5%
- Mucosa bleeds
- Subcutaneous bleeds

Joint bleeds most frequent symptom in severe hemophilia

1st joint bleed:1,4 yrs

- Knee 45%
- Elbow 30%
- Ankle 15%
- Shoulder 3%
- Wrist 3%
- Hip 2%
- Other 2%

Repeated bleeds into joints

- Development of Target joints
  - Muscle atrophy
  - Functional limitation
  - Iron deposits
- Later: Synovitis
- Finally: Arthropathy
  - Pain
  - Deformation
  - Crippling disability

Principals of treatment

- Bleeds must be treated as soon as possible
- Do not wait for (more) clinical signs
- Bleeds should be treated with clotting factor concentrates (If available)
- Veins must be treated with care
- After a bleed has stopped: rehabilitation! → comprehensive care

Principals of treatment regimens

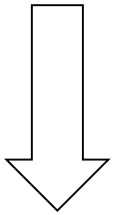
- according to WFH guidelines *(wfh.org)*
- Clotting factor level required for the treatment of bleeds are mostly the same for hemophilia A and B
- Dosage is dependent of severity and location of the bleeding
- Dosage is dependent of the availability of clotting factor

Principals of treatment

- Sufficient stock of clotting factor concentrate (or cryo)!!
- Joint bleeds and arthropathy can be prevented with prophylaxis and good motor development

Why prophylaxis?

severe hemophilia → ‘moderate hemophilia’



prevention of bleeds

Objectives of Regular Prophylaxis

Prevention of bleeds → prevention of:

- target joints
- loss of function & pain
- synovitis
- joint damage and functional loss

Preservation of HR QoL and participation in society

Prophylaxis should be given near by home, or at home

Regular prophylaxis

- Low dose: 3 x week 10-15 U/kg *FVIII* or 2 x week 20-30 U/kg *FIX*
- Intermediate dose: 25 U/kg 3-3.5 x week *FVIII* or 2 x week 30-50 U/kg F*IX*
- High dose: 50 U/kg *FVIII* 3 x week or 2 x week 50 U/kg *FIX*

Regular prophylaxis outcome

- Short term outcome: joint bleeds / year ↓
- Less severe bleedings
- Long term outcome: arthropathy and pain ↓
  functionality and participation↑
- Treatment costs: annual clotting factor use (IU/kg/yr) ↑
- Effect on bone mineral density

Regular longterm prophylaxis outcome

Health Related Quality of Life ↑

- ↓ days loss of work
- ↓ pain
- ↓ depression
- ↑ ADL
- ↑ Social activities
- ↑ sport participation

Outcome of longterm prophylaxis 10-25 U/kg FVIII 3 x week (Fischer Haemophilia 2011, 17:433)

	1-6 years (n=46)	10-17 years (n=47)	18-65 years (n=52)
Bleeds/ year	3.1	3.3	2.1
Joint bleeds/year	0	1.4	1.1
% joint bleeds of total	21%	50%	60%
% traumatic bleeds	29%	51%	42%

experiences with long-term low-dose prophylaxis

Bangkok 1995: 2x / week prophylaxis 8-10 IU/kg

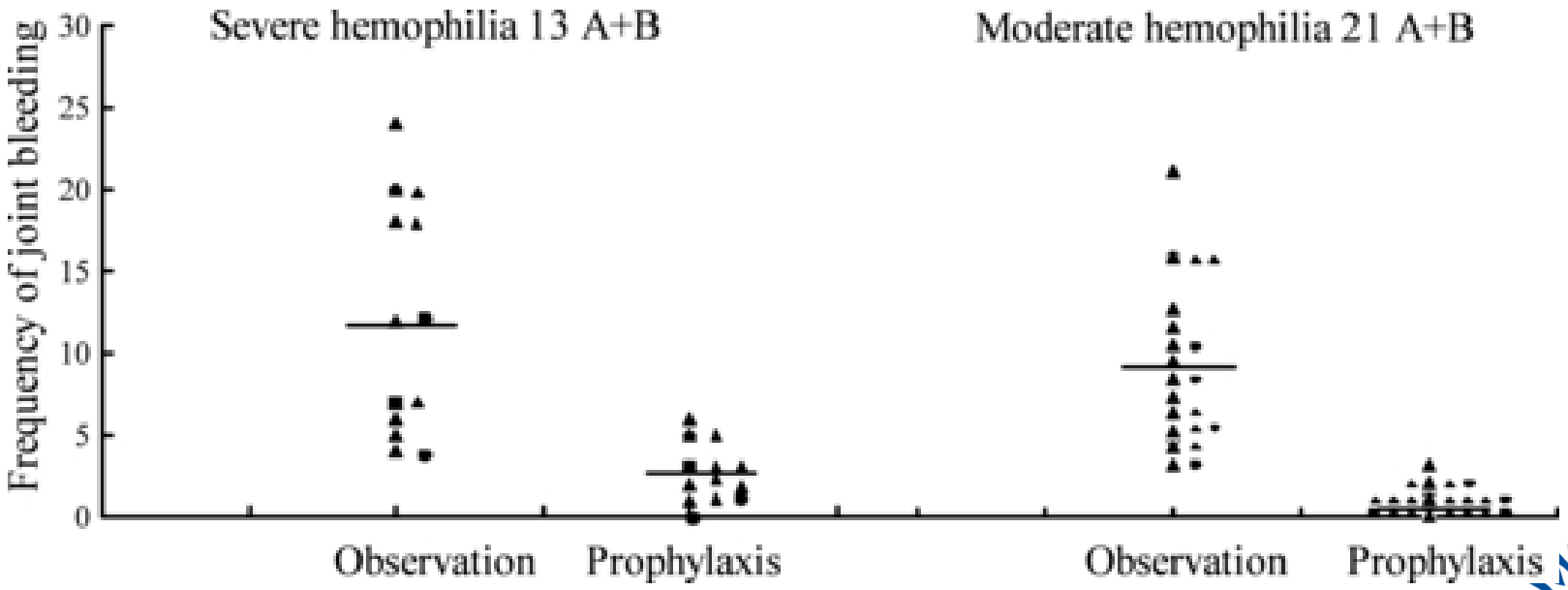
No.	Age	FVIII:C (%)	Venipuncture	FVIII concentrate (unit/kg)
1	12	2.6	patient	8
2	13	3.5	father	10
3	11	< 1	father	10
4	16	< 1	patient	9.6
5	11	1.6	nurse	8
6	13	2.2	nurse	10

No.	Body weight (kg)		Bleeding (episodes/yr)		Hospitalization (d/yr)	
	Before	After	Before	After	Before	After
1	62	59	24	3	7	-
2	25	29.5	18	3	35	-
3	24	26.5	7	2	20	-
4	40.5	43	17	6	23	-
5	31	34	2	-	7	-
6	38	44	1	-	3	-

Chuansumrit et al. Southeast Asian J Trop Med Pub Health 1995; 26: 243-6

low-dose prophylaxis in China: 2 x wk 10 U/kg FVIII (Wu et al Haemophilia 2011 70-74)

- 34 patients median age 7.8 years
- 12 weeks before start prophylaxis mean 9.9 bleeds (range 3-24)
- During 12 weeks prophylaxis mean 1.7 bleeds (range 0-6)
- Joint function improved 67%



Temporaly prophylaxis 4-12 weeks

- Temporarily:
  - after severe bleed
  - target joint
  - synovitis
  - after surgery
  - for rehabilitation

Principals of treatment: products

When there is no inhibitor:

- Hemophilia A is treated with factor VIII containing products
- Hemophilia B with factor IX containing products

Principals of modern treatment: it all started with plasma

Hemophilia A:

- Whole blood (1840)
- Plasma (1923)
- Cryoprecipitate (1964)
- Factor VIII concentrate (1979)
- Monoclonal Factor VIII (1988)
- Recombinant factor VIII (1994)
- Long acting factor VIII (2015)

Hemophilia B:

- Whole blood
- Plasma
- Fresh Froozen Plasma
- PCC (1964)
- FIX concentrate (1992)
- Recombinant FIX (1998)
- Long acting FIX (2016?)
- Gen therapy?

Principals of treatment

- Pk studies are the same for all products except for long-acting FVIII
- Children < 6 years
  - Recovery ↓
  - Clearance ↑
  - FVIII half life ↓

Long acting products

- rFVIIIFc: Half life ↑ with 2-6 hrs
- rFIXFc: Half life ↑ = >90 hrs

- Clinical results are good
- No side effects
- So far no increased inhibitors against FVIII/IX

Side effects of treatment

- Viral transmission (HCV, HIV, HBV) (plasma derived factor)
- Allergic reactions (low purified products)
- Inhibitor development in hemophilia A (all products)

Inhibitor development in hemophilia A: risk factors

- Patient related
  - Severity of hemophilia
  - Family history
  - Gen defect (nonsense mutation, inversion intron-22)
  - Polymorphism
  - Ethnicity (Afro-American)

- Treatment related
  - 1st treatment period > 3-5 consecutive days especially with dose 35 U/kg (40-50%)↑
  - Product?
  - Young age 1st treatment ↑
  - Start of low dose prophylaxis between 20-75 exposures ↓
    (Gouw Blood 2013)

Inhibitor detection might be affected by:

- Method, sensitivity and specificity of the assay
- Definition of
  - high and low responder, and
  - transient inhibitor
- Frequency of inhibitor testing
- Patient population: gen defect, severity of hemophilia
- Length of follow-up
- Cumulative incidence versus prevalence

Inhibitor development in hemophilia A: risk factors in relation to product

- No relation with vW containing product
- No relation with switching product
- No difference between plasma derived and recombinant product? →→ conflicting data

- No evidence that intermediate purity FVIII is safer than ultra pure (monoclonal) plasma product

Studies on inhibitor development in hemophilia A in relation to product

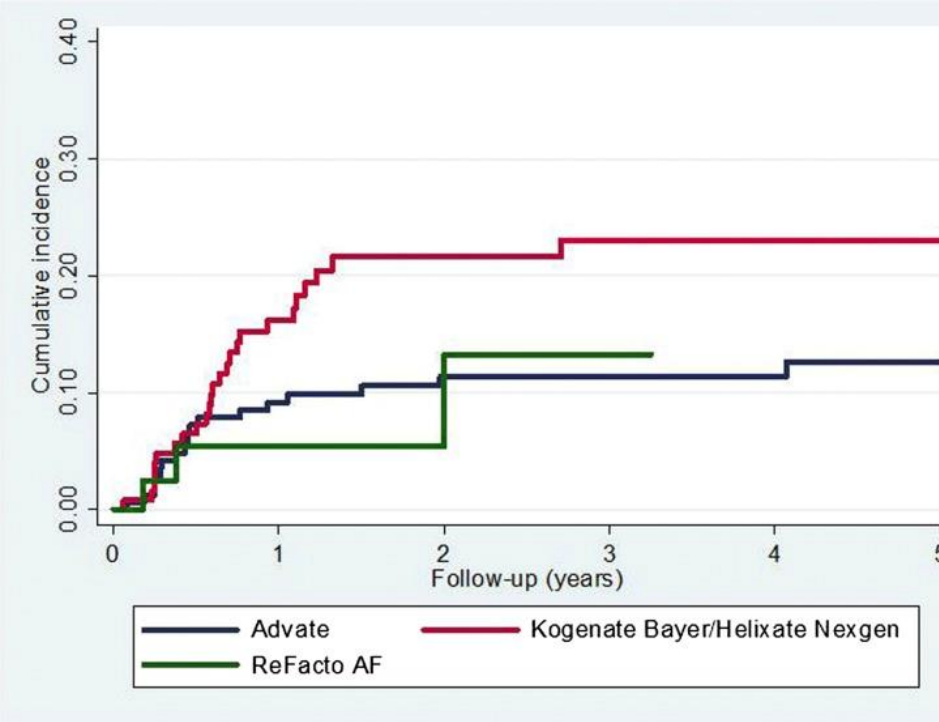
- Intermediate purified : 89 PUPs born 1975-1985 : 25 inhibitors (28%); 21 > 5 BU/ml (24%) (Addiego et al Lancet 1993: 462)

- Monoclonal purified: severe HA 38 patients: 6 inhibitors 16% (Lusher sem hematol 1994)

- Rodin study (Gouw et al NEJM 2013; 368:231): severe HA 574 patients: 177 inhibitors 32,4%
  - No difference between pFVIII and rFVIII
  - No difference with vW containing product
  - No effect switching product
  - 2nd generation product 1,6 increased risk

Factor VIII brand and inhibitor incidence 2000-2011 (Collins Blood 2014: 3389)

- 407 PUPs severe HA
- 118 (29%) inhibitors
  - 60 high titer
  - 58 low titer



- 45/128 (35,2%) inhibitors on Kogenate Bayer/Helixate NexGen
- 42/172 (24.4%) inhibitors on Advate (p=0.04) RR 1.75 all/ 2.1 high titer
- Refacto 15/44 (34%) however no more high titers than Advate

Inhibitor development in Hemophilia A

- FranceCoag Network Study (Calvez Blood 2014:3398):
  - 492 PUPs included
  - rFVIII (Kogenate 2nd generation, and Advate 3e generation), pdFVIII (Factane)

Results:

- inhibitor risk 30% lower after pdFVIII compared to rFVIII

FranceCoag Network Study (Calvez Blood 2014:3398)

-sub analysis patients on rFVIII

- 114/303 (37%) inhibitors
- significant increased inhibitor risk with 2nd generation product compared to 3rd generation recombinant product (60%)

Difference? Production using: baby hamster kidney (BHK) cells and versus Chinese hamster ovary (CHO) cells??

Inhibitor development in hemophilia A

- Meta analysis Marcucci et all (Thromb Haemost 2015: 958)
  - 761 PUPs moderate-severe HA
  - 27% inhibitors
    - 40 % rFVIII
    - 22% pFVIII
  - High intensity treatment 51%
  - Low intensity treatment 24%

Adjusted analysis showed: only intensity of treatment increased risk on inhibitor

Inhibitor development in Hemophilia A

- Sippet study (Peyvandi abstract ASH 2015):
  - 251 patients(PUPs) 0-81 months old
    - 125 pFVIII
    - 126 rFVIII
  - 1-50 exposure days (ED) (median 22)

- 76 inhibitors :50 > 5 BU/ml: 90% within 20 ED
  - 26,7% pFVIII : 18,5% > 5 BU/ml
  - 44,6% rFVIII : 28,4% > 5 BU/ml (RR 1,7)

Inhibitor development in Hemophilia A Sippet study

- Explication of difference between pFVIII and rFVIII
  - type rec product (more 2nd generation??): inhibitor devlopment with Advate is comparable with pFVIII
  - Intensity of treatment
  - Ethnicity
  - Gen defect

conclusions

- Hemophilia is a hematological disorder: increased bleeding
- It causes orthopedic problems
- Adequate treatment (prophylaxis) prevents arthropathy
- If there is no sufficient supply, lower doses can be given
- Most severe side effect: inhibitor development, probably increased risk for PUPs on 2nd generation rFVIII

Conclusion: Treatment with AHF makes a difference: It improves quality of life