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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
- SA ca 5500 patients
- 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

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%

- 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

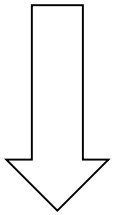
- according to WFH guidelines *(wfh.org)*
- Clotting factor level required for the treatment of bleeds are mostly the same for hemophilia A and B
- Dosage is dependent of severity and location of the bleeding
- Dosage is dependent of the availability of clotting factor

Principals of treatment

- sufficient stock of clotting factor concentrate!!
- 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 *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

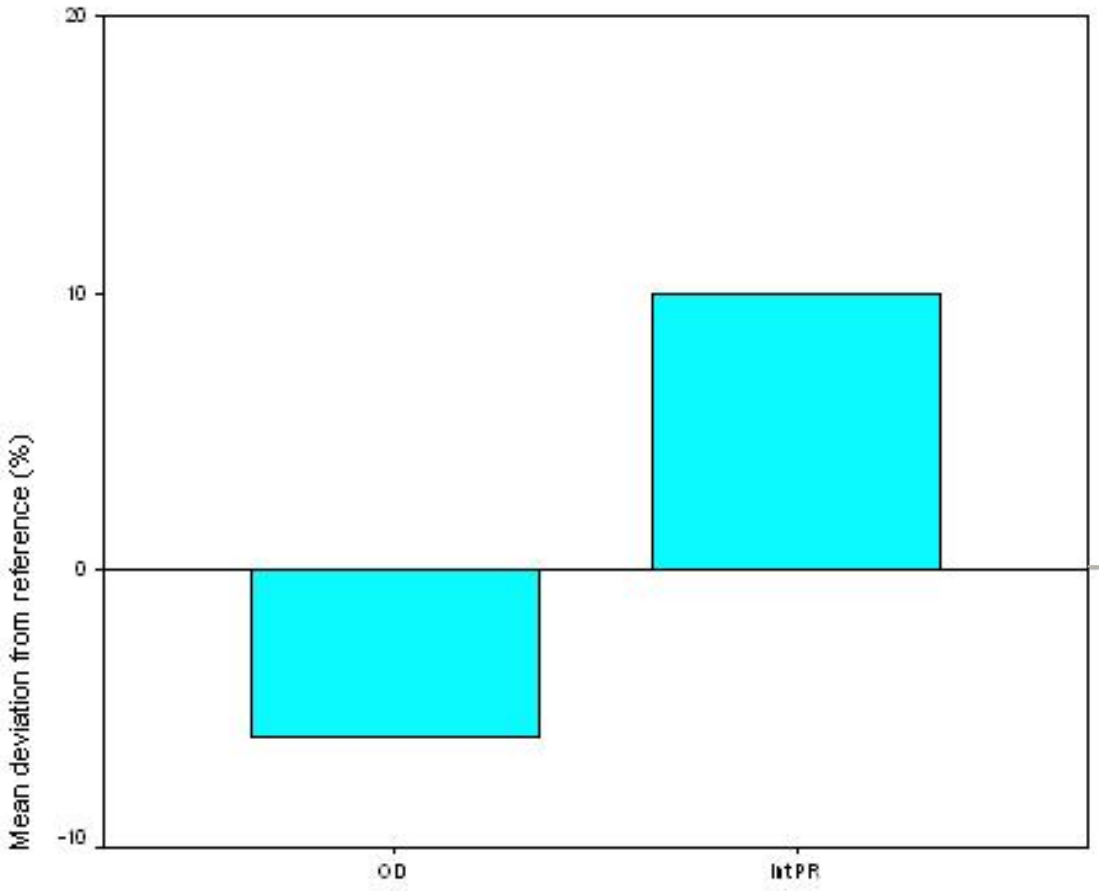
Health Related Quality of Life ↑

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

Outcome of longterm prophylaxis 10-25 U 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%

Prophylaxis vs On Demand: HRQoL (Fischer et al Haemophilia 2002; 8:745)



Mean age 21 yrs
Significant difference

→mean population value

experiences with 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

Temporaly prophylaxis 4-8 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 ↓

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 test

- Bethesda method
- Nijmegen modified inhibitor test

- APTT mixing test

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 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 or recombinant

Overall risk of inhibitor development in hemophilia A

- Intermediate purified : all 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)

- Recombinant FVIII: severe HA 407 PUPs born 2000-2011: 118 (29%), 60 > 5 BU/ml (15%) (Collins et al Blood, Oct 2014 ahead of print)

Inhibitor detection is affected by:

- Method, sensitivity and specificity of the assay
- Definition of
  - high and low responder, and
  - transient inhibitor
- Frequency of inhibitor testing
- Patient population
- Length of follow-up

- Cumulative incidence versus prevalence

conclusions

- Hemophilia is a hematological disorder: increased bleeding
- It causes orthopedic problems
- Adequate treatment prevents arthropathy
- If there is no sufficient supply, lower doses can be given
- Most severe side effect: inhibitor development

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