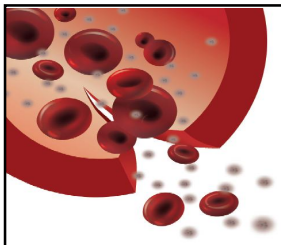
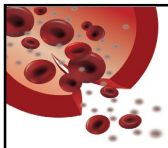


PERSONALIZED PROPHYLAXIS

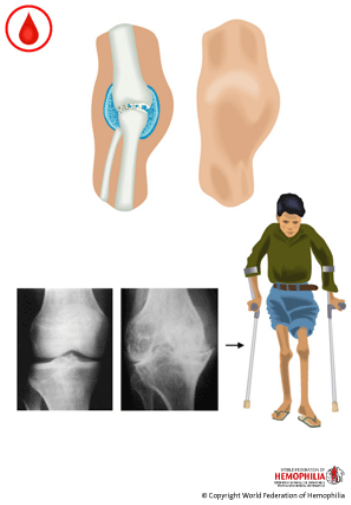
15 Sept 2018

Elina Lehtinen, Adj. Prof.
Coagulation Disorders Unit
Helsinki University Hospital
Hematology, Comprehensive Cancer Center

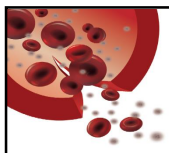


COMPLICATIONS OF BLEEDS

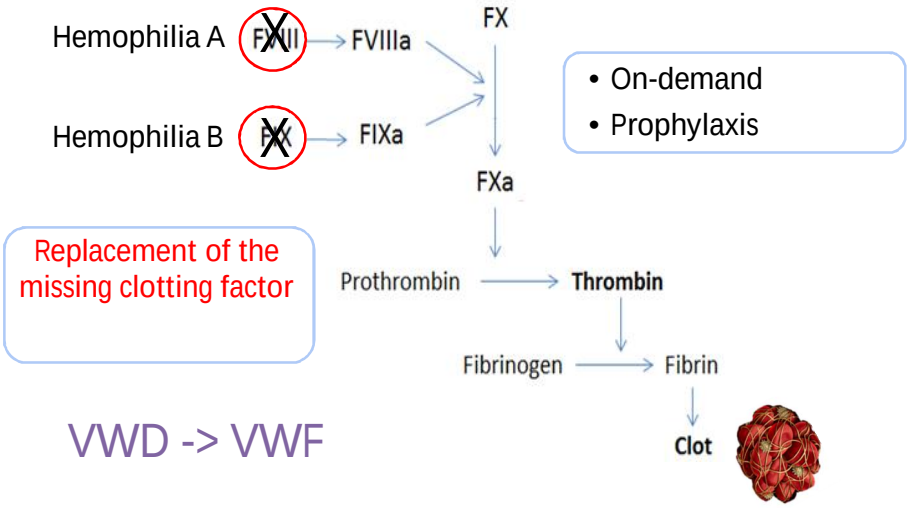
- Decreased range of motion
- Joint arthropathy
- Chronic pain
- Muscle atrophy
- Compartment syndrome
- Neurological symptoms
- Poor quality of life



Nordic Hemophilia Guideline, www.hematology.fi; Guidelines for the management of hemophilia, www.wfh.org



CURRENT TREATMENT

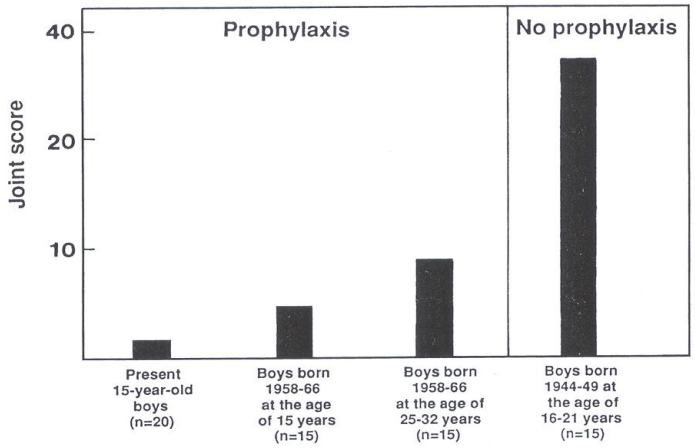


- On-demand
- Prophylaxis

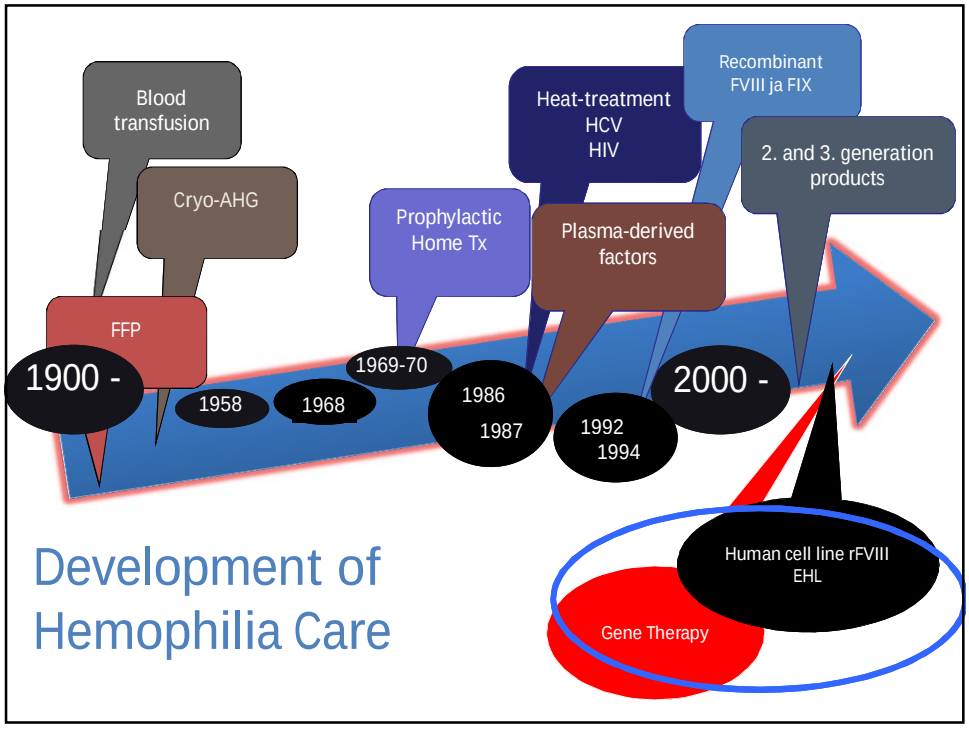
Replacement of the missing clotting factor

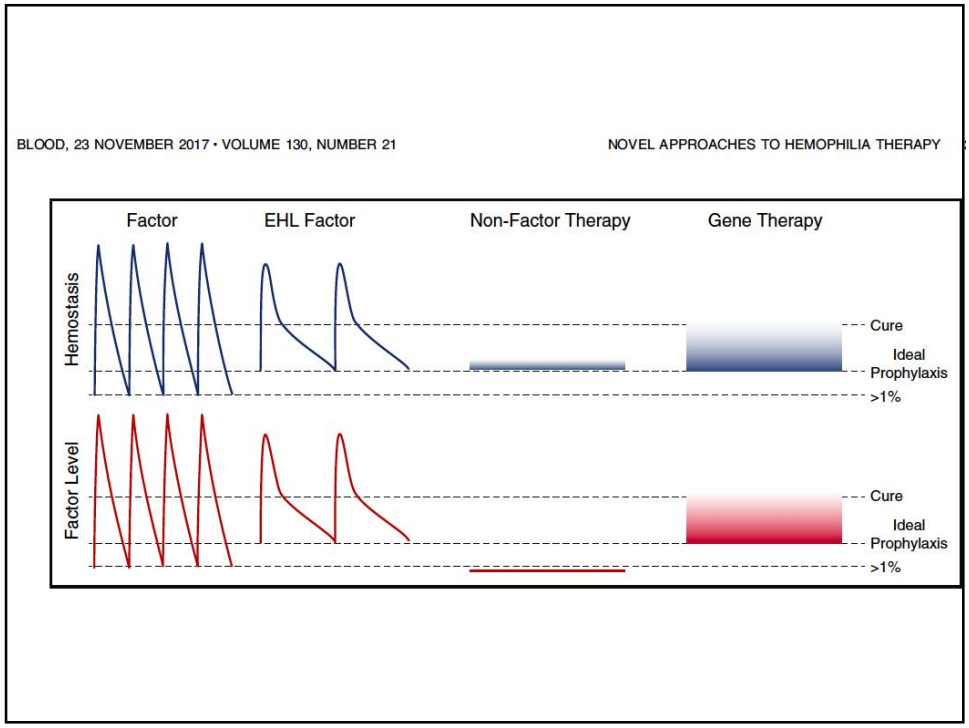
VWD -> VWF

BENEFITS OF PROPHYLAXIS



Nilsson et al J Int Med 1992; 232: 25-32


Blood transfusion
Cryo-AHG
FFP
1900 -
1958
1968
Prophylactic Home Tx
1969-70
Heat-treatment HCV HIV
1986
1987
Plasma-derived factors
1992
1994
Recombinant FVIII ja FIX
2. and 3. generation products
2000 -
Human cell line rFVIII EHL
Gene Therapy
Development of Hemophilia Care

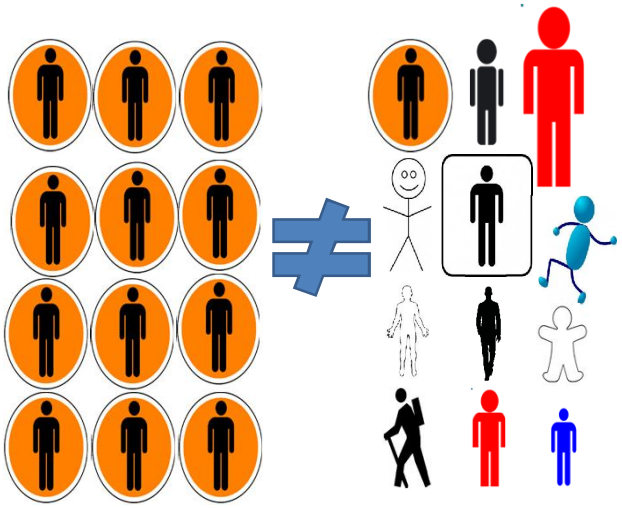

BLOOD, 23 NOVEMBER 2017 • VOLUME 130, NUMBER 21
NOVEL APPROACHES TO HEMOPHILIA THERAPY
Factor
EHL Factor
Non-Factor Therapy
Gene Therapy
Hemostasis
Factor Level
Cure
Ideal Prophylaxis
>1%
Cure
Ideal Prophylaxis
>1%

The goal of treatment is not only to stay alive and to prevent serious complications but also gain good quality of life

https://thumbs.dreamstime.com/b/young-happy-family-jumping-silhouettes-sunset-silhouette-people-group-team-time-60499935.jpg

(The Voice of the Patient. Hemophilia A, Hemophilia B, von Willebrand Disease and Other Heritable Bleeding Disorders. FDA report, 2016)

INDIVIDUALIZED TREATMENT



W are all individuals!

BLEEDING EVENTS CORRELATE TO FACTOR LEVELS

ABR

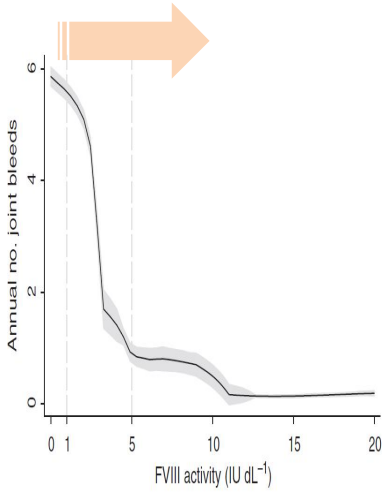
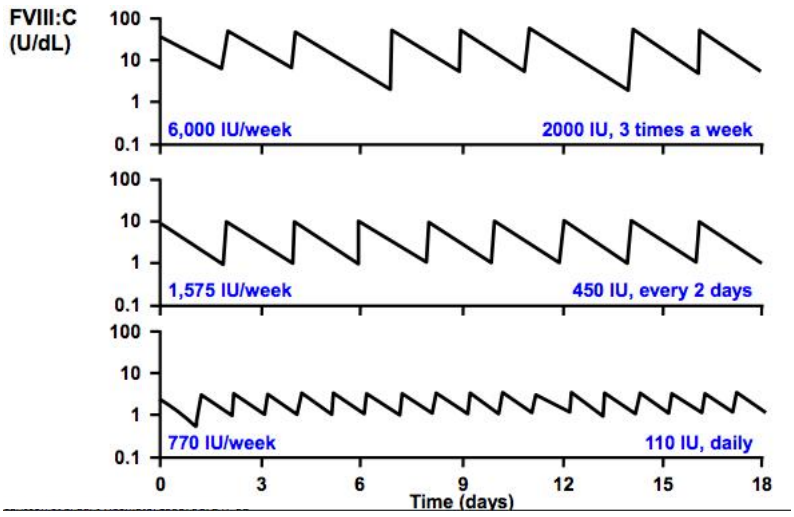


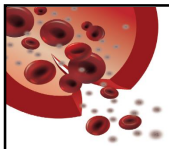
Fig. 2. Annual number of joint bleeds according to FVIII activity. Black lines are medians, shaded areas interquartile ranges.

Viite: den Uijl et al 2011 Haemophilia 17: 849-853

TAYLORED TREATMENT PLAN



Carlsson et al Eur J Haematol 1993: 51 247-52



- If factor level is <5%, risk of joint bleeds increases
- If factor level is > 15%, joint bleeds are rare

Minimum level of 10% would prevent the majority of joint bleeds and would protect from most bleeding events

- 1% minimum level not enouhg
- Ideal level = 10-15% ??

Viite: Dr. Flora Peyvandi, EHC New Technologies workshop 17.-19.11.17 Estoril

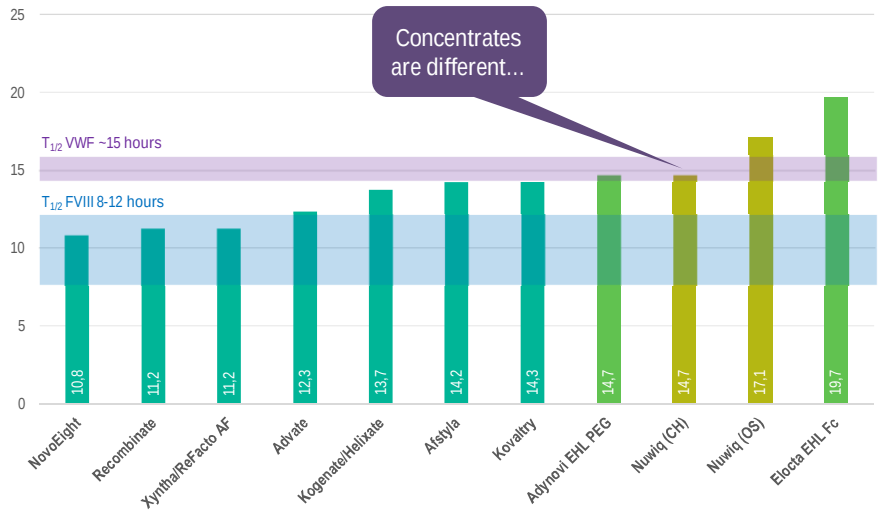
Expert consensus FVIII target levels to optimise prevention of bleeding in haemophilia

<1%	1%–3%	3%–5%	5%–15%
• Any child before the first bleed • Any patient treated on-demand • Adults on prophylaxis with a sedentary lifestyle not presenting with bleeding	• Any patients on prophylaxis not presenting with bleeding • Patients with mild bleeding phenotype • Adult and pediatric patients with a sedentary lifestyle • Any child up to 2 years or until the first bleed • Patients with moderate haemophilia	• Patients performing mild physical activity • Patients with target joints or severe progressive haemophilic arthropathy • Patients presenting with bleeding despite prophylaxis at a lower target threshold • Children on primary prophylaxis • Patients with previous life-threatening bleeding events	• Children and adults performing high-risk activity • Patients presenting with bleeding despite prophylaxis at a lower target threshold • Patients with target joints or severe arthropathy presenting with bleeding despite prophylaxis at a lower target threshold • Patients with severe comorbidities

Further target FVIII level scenarios and recommendations available in: Iorio A et al. *Haemophilia*. 2017;23(3):e170-e179

PERSONALIZED PROPHYLAXIS

Based on the patient's half-life of FVIII:C
(FDA-approved mean half-lives from US package inserts)



US package insert https://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/ucm127580.htm

STANDARD VS. EHL PRODUCTS

- STANDARD CARE

  pdFVIII/FIX
  rFVIII/FIX

T 1/2 (18-24 hours)

Dosing frequency (2-3 x /week)

- EHL

T1/2 prolongs
- rFVIII 1.4 – 1.7 x
- rFIX 3 – 5 x

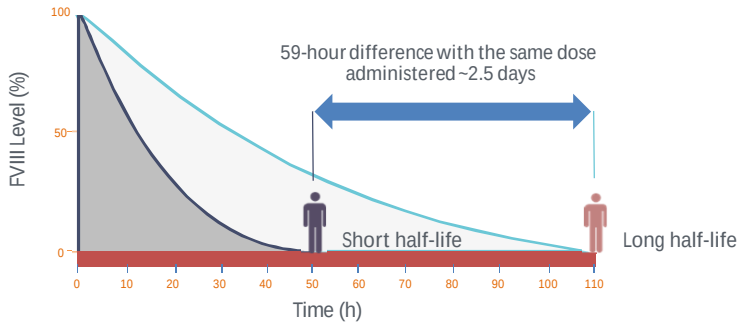
Less infusions / Higher trough

PK IN PRACTICE

- If adjusting prophylaxis to an appropriate trough level based on individual PK, in addition to monitoring bleed pattern, is useful, then the introduction of limited blood sampling for the determination of pharmacokinetics has major benefits.
- Different trough levels may be targeted
  - higher levels may be desired to manage target joints, highly active patients, or those more prone to bleeding
  - lower levels may be allowed in a patient who has not bled for a long time.
- Because pharmacokinetics changes with growth in young children and breakthrough bleeds are potentially more damaging, PK information is likely to be more useful at this age.

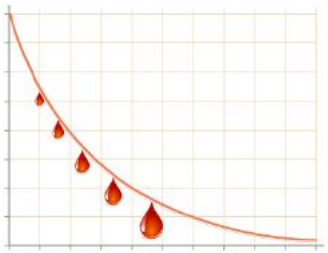
Björkman & Collins, Journal of Thrombosis and Haemostasis, 2013, 11: 180–182

ONE SIZE DOES NOT FIT ALL



(This figure is for illustrative purposes only and doesn't represent real clinical data.)

Valentino LA. *Haemophilia.* 2014 20(5):607-15. 2. Collins PW et al. *Haemophilia.* 2011;17(1):2-10, adapted



WAPPS - Hemo Service

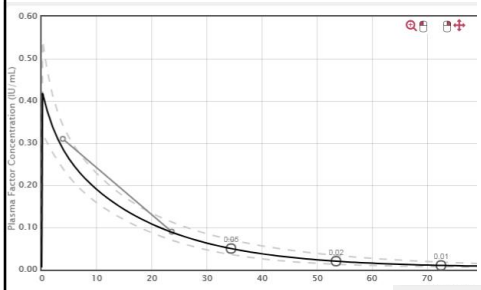
The WAPPS-Hemo service is a centralized, dedicated, actively moderated, web-accessible database that allows the input of certified hemophilia patient pharamacokinetic (PK) data.

www.wapps-hemo.org

The specific aims of the project are:

- to empower hemophilia treatment by facilitating individual PK assessment;
- to allow for the robust estimation of individual PK parameters with a reduced number of plasma samples;
- to enhance knowledge about the PK of factor VIII and IX.

Drug	Height (cm)	BW (kg)	Tot IU	IU/kg
Nuwiq	179	79	1500	19.0



	Estimate		
Parameter	Conservative	Balanced	Optimistic
Time to 0.05 IU/ml (hr)	27.75	34.25	41.00
Time to 0.02 IU/ml (hr)	42.00	53.50	64.75
Time to 0.01 IU/ml (hr)	56.25	72.50	88.75
Half-life (hr)	8.75	12.00	15.25

Convert days to hours	Plasma Factor Concentration Estimate (IU/mL)		
Time (Days)	Conservative	Balanced	Optimistic
1	0.068	0.087	0.111
2	0.017	0.026	0.041
3	0.007	0.010	0.018
4	0.005	0.006	0.010

www.wapps-hemo.org

Clinical Calculator

The clinical calculator has been available on the WAPPS-Hemo website as of June 2017. The clinical calculator recalculates the concentration-time curve time to contraction, and concentration at time x after an alternate dose is administered. The calculator also plots a regimen for a set weekly pattern. If you have any questions, or would like more information about the clinical calculator, please contact us at: wappshemo@mcmasterhkr.com

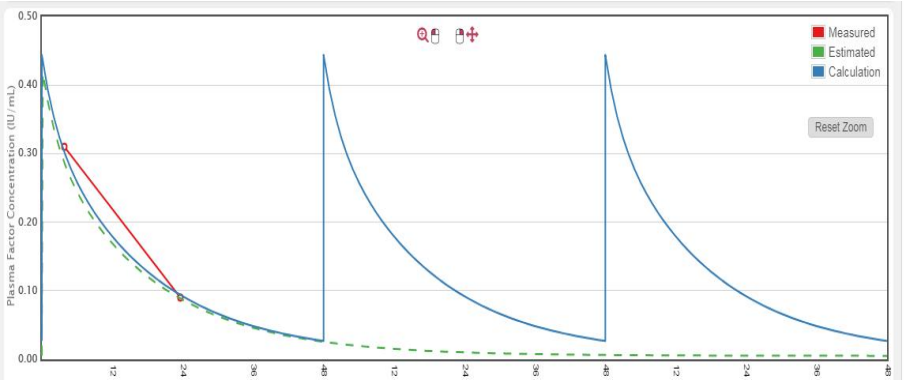
Dose: Total Units
Trough: IU/mL
Infusion Interval: TBD
Calculate

www.wapps-hemo.org

Subject 01 – Personalized prophylaxis

Regimen Estimate (Nuwiq)

Dose (IU)	Infusion Interval	Peak (IU/mL)	Trough (IU/mL)	Weekly Dosage (IU)
1500	48 hr (2 Days)	0.4439	0.0268	5250



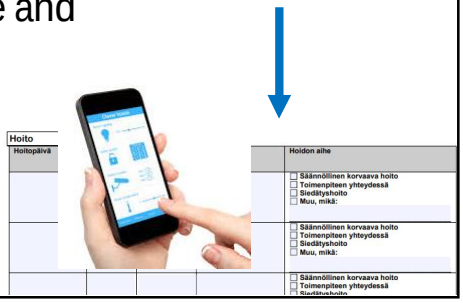
www.wapps-hemo.org

CRITERIA FOR CHOOSING TREATMENT

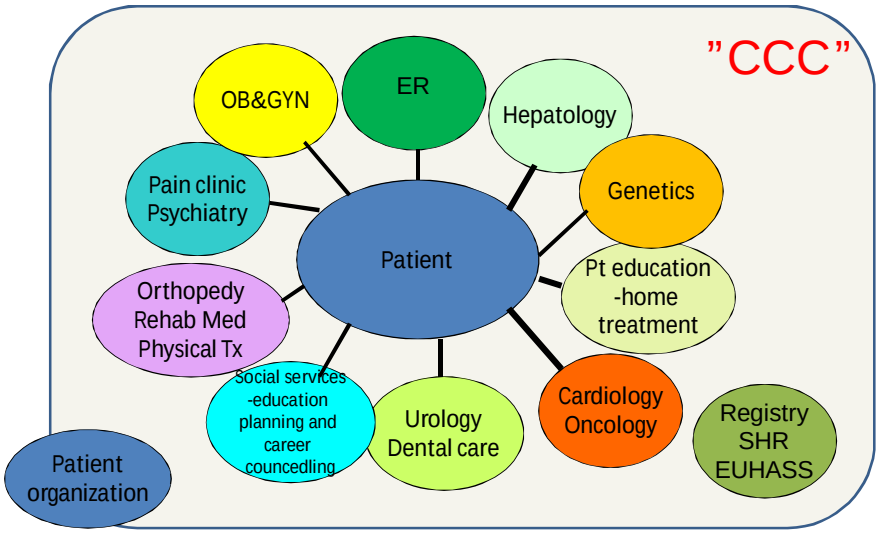
- According to natioal / international guidelines – (UKHCDO, Nordic Guideline)
- Individualized patient – doctor discussion
- Opportunities, expectations, possible side effects
- Individual response is variable - pharmakokinetics
- Is there a need?
- Goal: Higher trough or less frequent dosing?

HOW TO SWITCH?

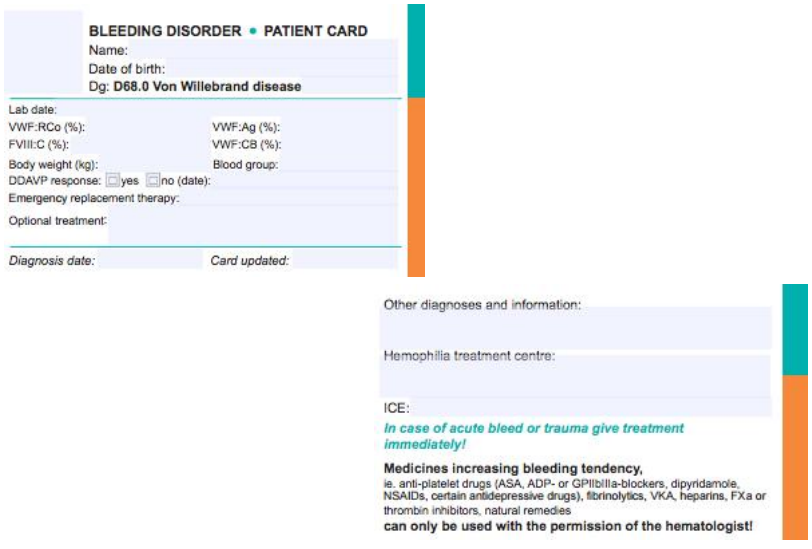
- Patient-doctor discussion regarding different options
- Benefits and possible risks
- PK, ABR, infusion management, life style
- Laboratory response before and after
- Follow-up;
  - Bleeds, Lab
  - Home treatment logs
  - Registry data



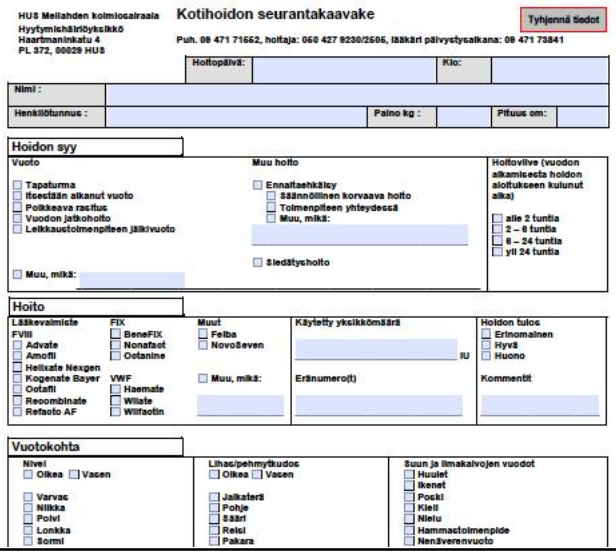
CENTRALIZED CARE
INDIVIDUALIZED CARE



Patient card



EXAMPLE OF HOME TX LOG



HUS Meilahden kolmiosairaala
Hyytymishäiriöyksikkö
Haartmaninkatu 4
PL 372, 00029 HUS

Kotihoidon seurantakaavake

Tyhjennä tiedot

Puh. 09 471 71662, hoitaja: 050 427 9230/2505, lääkäri päivystysaikana: 09 471 73841

Hoitopäivä: | Klo:

Nimi :

Henkilötunnus : | Paino kg : | Pituus cm:

Hoidon syy

Vuoto
- Tapaturma
- Itsestään alkanut vuoto
- Poikkeava raskaus
- Vuodon jatkohoito
- Leikkaustoimenpiteen jälkivuoto
- Muu, mikä:

Muu hoito
- Ennaltaehkäisy
  - Säännöllinen korvaava hoito
  - Toimenpiteen yhteydessä
  - Muu, mikä:
- Siedätyshoito

Hoitoviive (vuodon alkamisesta hoidon aloitukseen kulunut aika)
- alle 2 tuntia
- 2 – 6 tuntia
- 6 – 24 tuntia
- yli 24 tuntia

Hoito

Lääkevalmiste
FVIII
- Advate
- Amofil
- Helixate Nexgen
- Kogenate Bayer
- Octafil
- Recombinate
- Refacto AF

FIX
- BeneFIX
- Nonafact
- Octanine

VWF
- Haemate
- Wilate
- Wilfactin

Muut
- Feiba
- NovoSeven
- Muu, mikä:

Käytetty yksikkömäärä | IU

Eränumero(t)

Hoidon tulos
- Erinomainen
- Hyvä
- Huono

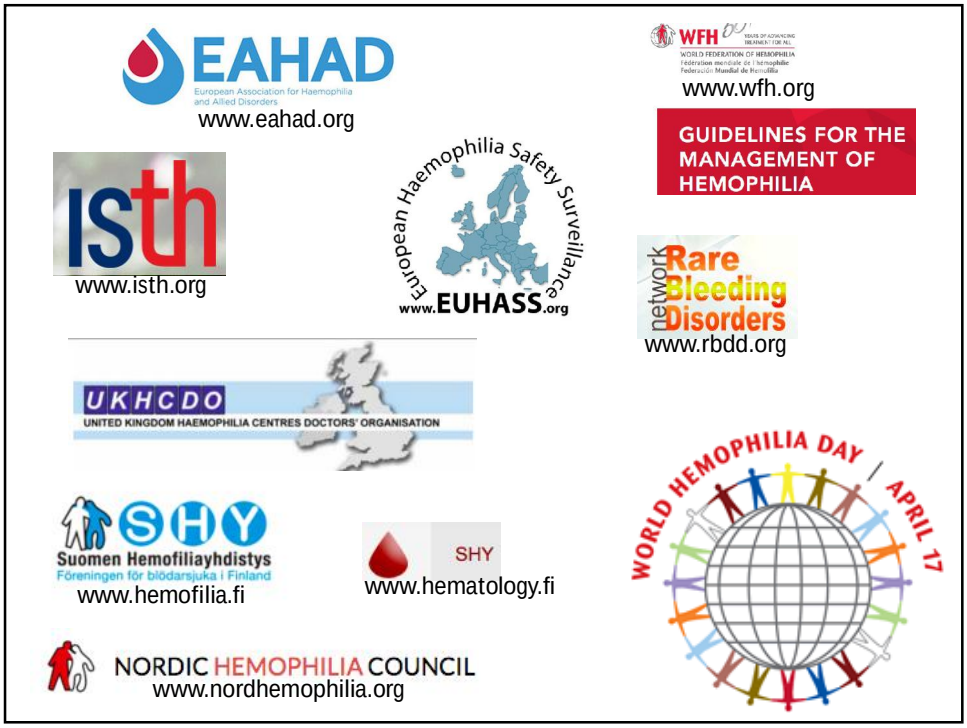
Kommentit

Vuotokohta

Nivel
- Oikea
- Vasen
- Varvas
- Nilkka
- Polvi
- Lonkka
- Sormi

Lihas/pehmytkudos
- Oikea
- Vasen
- Jalkaterä
- Pohje
- Sääri
- Reisi
- Pakara

Suun ja ilmakalvojen vuodot
- Huulet
- Ikenet
- Poski
- Kieli
- Nielu
- Hammastoimenpide
- Nenäverenvuoto



EAHAD
European Association for Haemophilia and Allied Disorders
www.eahad.org

WFH
WORLD FEDERATION OF HEMOPHILIA
www.wfh.org

GUIDELINES FOR THE MANAGEMENT OF HEMOPHILIA

isth
www.isth.org

European Haemophilia Safety Surveillance
www.EUHASS.org

network Rare Bleeding Disorders
www.rbdd.org

UKHCDO
UNITED KINGDOM HAEMOPHILIA CENTRES DOCTORS' ORGANISATION

SHY
Suomen Hemofiliayhdistys
Föreningen för blödarsjuka i Finland
www.hemofilia.fi

SHY
www.hematology.fi

WORLD HEMOPHILIA DAY / APRIL 17

NORDIC HEMOPHILIA COUNCIL
www.nordhemophilia.org