CONGENITAL COAGULATION DISORDERS IN CHILDREN
CASE 1: GIRL 7-YR-OLD

- APTT: 42 (22-36 sec)
- TP: 13.8 (8.6-13.8 sec)
- INR: 1.24 (0.8-1.3)
- Fibrinogen: 310 (150-450 mg/dl)

ENT surgery - deafness

FXI: 48 (70-150 %)

Exacyl: 500 mg, tds

Day -1 to Day+5
CASE 2: BOY 13-YR-OLD

Inguinal hernia repair

- APTT: 29 (22-36 sec)
- TP: 16,4 (8,6-13,8 sec)
- INR: 1,51 (0,8-1,3)
- Fibrinogen: 203 (150-450 mg/dL)

FVII: 20% (70-150%)
Exacyl, rFVIIa, PCC
**CASE 3 : BOY 14-YR-OLD**

**Cardiac surgery**

- APTT : **142** (22-36 sec)
- TP : 11 (8,6-13,8 sec)
- INR : 0,99 (0,8-1,3)
- TT : 15 (15-24 sec)
- Fibrinogen : 291 (150-450 mg/dl)

- FVIII : **89** (50-150 %)
- FIX : **74** (50-150 %)
- FXI : **73** (70-150 %)
- FXII : **2** (70-150 %)

**Isolated FXII deficiency**
CASE 4: GIRL 3-YR-OLD

Bleeding tendency

• APTT: >180 (22-36 sec)
• TP: > 100 (8,6-13,8 sec)
• INR: > 7 (0,8-1,3)
• TT: 120 (15-24 sec)
• Fibrinogen: < 50 (150-450 mg/dl)

Congenital afibrinogenemia

Genetic analysis

Del1 FGA C.431_432 del AA (exon4)
Del2 FGA C.1055 del C (exon5)

Fg concentrate - Haemocomplettan (1 x / 15 days)
CASE 5: GIRL 16-YR-OLD

Wisdom teeth extraction tendency

- PFA-ADP: 226 (65-111 sec)
- FVIII: 66 (50-150 %) → 200 %
- vWF ag: 25 (50-150 %) → 113 %
- vWF ac: 20 (50-150 %) → 143 %

Blood group: A+

vWD: type I

DDAVP
CASE 6: GIRL 16-YR-OLD

Tonsillectomy

- APTT: 51 (22-36 sec)
- INR: 1.1 (0.8-1.3)
- TT: 18 (15-24 sec)
- Fibrinogène: 446 (150-450 mg/dl)

Haemophilia A carrier – No response to DDAVP

- FVIII: 9% (50-150%)
- FvW ag: 58% (50-150%)
- FvW ac: 52% (50-150%)
**CASE 7 : GIRL 12-YR-OLD**

- APTT : **47** (22-36 sec)
- TP : 11.1 (8.6-13.8 sec)
- INR : 1.05 (0.8-1.3)
- TT : 19 (15-24 sec)

**Wisdom teeth extractions**

- FVIIIc : 7%
- vWF: Ag : 7%
- vWF : Ac : 4%

Haemate-P 1000 units + Tranexamic acid
**Bleeding Disorders**

- **Acquired (frequent)**
  - Overanticoagulation
  - Liver failure
  - Disseminated intravascular coagulation (DIC)

- **Inherited (rare)**
  - Haemophilia A and B
  - Von Willebrand disease
  - FVII, FXI, FII, … deficiency (rare)
PREVALENCE OF BLEEDING DISORDERS IN BELGIUM

- Patients on oral anticoagulant: 150,000
- Severe von Willebrand Disease (VWD): 10,000
- Haemophilia A (FVIII) and B (FIX): 1,000
- FXI deficiency (estimate): 500
- FVII deficiency (estimate): 300
- FXIII deficiency: 10
# HAEMOSTATIC THERAPY

## Primary Haemostasis
- Platelet concentrates
- DDAVP (Minirin)
- FVIII-vWF concentrates
- Antifibrinolytics (EXACYL)

## Secondary Haemostasis
- Fresh frozen plasma (FFP)
- Clotting factors concentrates
  - Fibrinogen
  - rFVIIa (Novo Seven)
  - PCC (II, VII, IX and X)
  - FVIII, FIX, FXI,…

## Fibrinolysis
- Tranexamic acid (Exacyl)

---

**Vascular injury**
THROMBUS FORMATION

Platelets

Fibrin
**THE COAGULATION “TRIPTYCH”**

1. **Platelets plug**
   - Primary Haemostasis
   - Platelets
   - Von Willebrand F

2. **Fibrin Formation**
   - Coagulation cascade
   - Coagulation factors

3. **Clot destruction**
   - Fibrinolysis
Blood coagulation: A three step process

- Primary haemostasis
- Coagulation
- Fibrinolysis

Vascular injury

Clot destruction
Vessel wound repair and remodelling
Angiogenesis
COAGULATION

Fibrinogen $\xrightarrow{\text{Thrombin}}$ Fibrin
aPTT

TCA

APTT = activated partial thromboplastin time

COAGULATION CASCADE

Intrinsic

Extrinsic

Tissue Factor

PTT / INR

Fibrin Clot

Cedric Hermans – UCL.
BLOOD TESTS OF HAEMOSTASIS

Primary Haemostasis
- Platelet count
- Platelet function
- Bleeding time
- PFA-100
- Platelet aggregation tests

Coagulation Cascade
- Prothrombin Time (INR)
- APTT
- Thrombin Time
- Fibrinogen
- Point of care
  - INR (point-of care)
  - ACT (activated clotting time)
  - RoTEM

Fibrinolysis
- Euglobulin lysis time
- D-dimers
- RoTEM
BLEEDING SYMPTOMS

• Severe bleeding symptoms
  - Infancy
    • Haemophilia
    • Platelet disorders
    • Rare factor deficiencies
  - Adulthood
    • Associated with another disease (liver)
    • Associated with antithrombotic therapy

• Mild bleeding symptoms
  - Increased bleeding tendency (surgery-trauma)
  - Tendency to skin bleeding, epistaxis, menorrhagia
  - Spontaneous life-threatening bleeds = rare
HAEMOSTATIC “CHALLENGES” THAT CAN REVEAL A BLEEDING TENDENCY

- Delivery
- Circumcision
- Tonsillectomy
- Wisdom teeth Extraction
- Appendicectomy does not always result in bleeding complications
### Bleeding Symptoms Are Frequently Reported

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Profuse menstruation</td>
<td>44%</td>
</tr>
<tr>
<td>Nosebleeds</td>
<td>5% - 36%</td>
</tr>
<tr>
<td>Bleeding at delivery</td>
<td>19.5% - 23%</td>
</tr>
<tr>
<td>Bleeding after tonsillectomy</td>
<td>2% - 11%</td>
</tr>
<tr>
<td>Bleeding after surgery</td>
<td>6%</td>
</tr>
<tr>
<td>Bleeding from small wounds</td>
<td>2%</td>
</tr>
<tr>
<td>Various symptoms (1 or more)</td>
<td>40 - 50% in men</td>
</tr>
<tr>
<td></td>
<td>50 - 60% in women</td>
</tr>
</tbody>
</table>

# Bleeding Severity

<table>
<thead>
<tr>
<th>Bleeding severity</th>
<th>Clinical Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trivial, non relevant</td>
<td>Does never interfere with daily activities or require medical attention</td>
</tr>
<tr>
<td>Minor (or Clinically relevant non Major)</td>
<td>Severe enough to interfere with the patients’ everyday life, or to seek medical attention; may be treated at home</td>
</tr>
<tr>
<td>Major</td>
<td>May cause permanent damage to the patient or threaten his/her life</td>
</tr>
</tbody>
</table>
BLEEDING AND BLEEDING DISORDERS

• Bleeding symptoms are reported by up to 40% of otherwise normal people (low specificity)

• The prevalence of inherited bleeding disorders ranges from 1 : 1.000 to 1 : 10.000

• The likelihood of having a bleeding disorder in a subject with a bleeding symptom is at best

\[ LR = \frac{1}{1000} = 0,0025 = 1 : 400 \]

\[ 40\% \]
Bleeding Assessment Tools

- Designed to standardize data collection and interpretation
- The most severe presentation of each bleeding symptom is scored from 0 (if absent) up to 3 or 4 (major bleeding, requiring transfusion or surgery)
- The sum of symptom scores is known as the patient bleeding score (BS)

Tosetto et al, *JTH* 2006
Rydz et al, *JTH* 2012
# BLEEDING SCORE

<table>
<thead>
<tr>
<th>Symptômes</th>
<th>Points</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epistaxis</strong></td>
<td></td>
<td>No or not significant</td>
<td>Yes</td>
<td>Packing/ cauterisation</td>
<td>Transfusion</td>
</tr>
<tr>
<td><strong>Cutaneous</strong></td>
<td></td>
<td>No or not significant</td>
<td>Petechiae</td>
<td>Hematomas</td>
<td>Consultation</td>
</tr>
<tr>
<td><strong>Bleeding from minor wounds</strong></td>
<td></td>
<td>No or not significant</td>
<td>Yes (1–5 episodes / year)</td>
<td>Consultation</td>
<td>Surgical haemostasis</td>
</tr>
<tr>
<td><strong>Oral cavity</strong></td>
<td></td>
<td>No or not significant</td>
<td>Yes</td>
<td>Consultation</td>
<td>Surgery / transfusion</td>
</tr>
<tr>
<td><strong>GI bleeding</strong></td>
<td></td>
<td>No or not significant</td>
<td>Yes</td>
<td>Consultation</td>
<td>Surgery / transfusion</td>
</tr>
<tr>
<td><strong>Tooth extraction</strong></td>
<td></td>
<td>No or not significant</td>
<td>Yes</td>
<td>Suturing / Local suturing</td>
<td>Transfusion</td>
</tr>
<tr>
<td><strong>Surgery</strong></td>
<td></td>
<td>No or not significant</td>
<td>Yes</td>
<td>New surgery-intervention</td>
<td>Transfusion</td>
</tr>
<tr>
<td><strong>Menorrhagia</strong></td>
<td></td>
<td>No or not significant</td>
<td>Yes</td>
<td>Consultation, OC, iron</td>
<td>Surgery / transfusion</td>
</tr>
<tr>
<td><strong>Post-partum haemorrhage</strong></td>
<td></td>
<td>No or not significant</td>
<td>Yes (iron supplement)</td>
<td>Transfusion, curetage</td>
<td>Hysterectomy</td>
</tr>
<tr>
<td><strong>Muscle haematomas</strong></td>
<td></td>
<td>No or not significant</td>
<td>Yes</td>
<td>Consultation</td>
<td>Surgery / transfusion</td>
</tr>
<tr>
<td><strong>Haemarthrosis</strong></td>
<td></td>
<td>No or not significant</td>
<td>Yes</td>
<td>Consultation</td>
<td>Surgery / transfusion</td>
</tr>
</tbody>
</table>

Adapted from Rodeghiero et al. JTH, 2006: 925
LIMITATIONS OF BLEEDING SCORES (BS)

• The most validated BS has been used specifically for VWD (BS could be used for other bleeding disorders, particularly to decide the necessity and/or the extent of lab investigations)

• No validation for platelet dysfunction disorders

• BS have been designed for adults and no data are available for children

• BS are less reliable in patients with few haemostatic challenges

• Family history is not considered

• Predictive value of future bleeding not established?
INVESTIGATION OF A BLEEDING DISORDER BEGINS IN THE CLINIC?

- Clinical history
  - Personal
  - Family
  - ?Bleeding Score
  - Pattern/type of history
  - Drug history

All may direct laboratory investigations

- Strong history?
  - Familial? Gender?
  - Joints? Mucosal?
  - Acquired?
EVALUATION OF THE BLEEDING TENDENCY BEFORE INVASIVE PROCEDURES

History (including family) / physical examination

SCREENING TESTS (APTT, PT, TT, Fg)

Positive
- Confirmation tests
  - Assays of clotting factor (FXI, FVIII, IX)

Negative
- (Complementary tests if high clinical suspicion)
  - Primary haemostasis (VWF – Platelet function)
  - Fibrinolysis
  - Factor XIII (very rare)
# Bleeding History and Normal Screening Tests (APTT, PT, TT)

<table>
<thead>
<tr>
<th>Rule out</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Von willebrand disease (if no associated FVIII deficiency)</td>
</tr>
<tr>
<td>• Platelet disorders</td>
</tr>
<tr>
<td>• Mild haemophilia (mild F8 or F9 deficiency not impacting on APTT)</td>
</tr>
<tr>
<td>• FXI deficiency (APTT not always prolonged in case of FXI deficiency)</td>
</tr>
<tr>
<td>• Other diseases (rare or exceptional)</td>
</tr>
<tr>
<td>– Hyperfibrinolysis</td>
</tr>
<tr>
<td>• Alpha-2 antiplasmin deficiency</td>
</tr>
<tr>
<td>• PAI-1 deficiency</td>
</tr>
<tr>
<td>– Facteur XIII (cross-linking) deficiency</td>
</tr>
</tbody>
</table>
IMPORTANT MESSAGES REGARDING BLOOD CLOTTING TESTS

1. A normal clotting screen does not always exclude a factor deficiency *(see above)*

2. An abnormal clotting screen does not always indicate a factor deficiency *(anti-phospholipid antibodies)*

3. A low FVIII does not always indicate haemophilia *(VWD)*

4. A normal FVIII level does not always exclude (mild) haemophilia *(chromogenic versus one-stage assay)*
# Coagulation Factors Deficiencies

<table>
<thead>
<tr>
<th>Clotting factor</th>
<th>Disease(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVIII</td>
<td>Haemophilia A</td>
</tr>
<tr>
<td></td>
<td>Von Willebrand Disease (type 1 – type 2 N)</td>
</tr>
<tr>
<td></td>
<td>Combined FV-FVIII deficiency</td>
</tr>
<tr>
<td>FIX</td>
<td>Haemophilia B</td>
</tr>
<tr>
<td>FXI</td>
<td>Haemophilia C</td>
</tr>
<tr>
<td>FVII</td>
<td>No so rare</td>
</tr>
<tr>
<td>FXII</td>
<td>No bleeding tendency</td>
</tr>
<tr>
<td>FI (Fibrinogen)</td>
<td>Rare</td>
</tr>
<tr>
<td>FV</td>
<td>Rare</td>
</tr>
</tbody>
</table>
von Willebrand disease (VWD)

- Prof. Erik von Willebrand (Helsinki) 1926
  - Family from Föglö, Åland islands

- Mucosal bleeding, prolonged bleeding time, autosomal inheritance

- Commonest inherited bleeding disorder
  - Prevalence studies:
    - Referral based: 23 - 113 per million
    - Population based: 8.2 - 16 per 1000
    - Severe cases: 1 per 10,000
Dr Erik A. von Willebrand
1870-1949
(Finland)
FUNCTIONS OF VWF

1. Factor VIII binding
2. Platelet adhesion
3. Platelets aggregation
VON WILLEBRAND FACTOR

FVIII – Von Willebrand factor complex

FVIII ≠ VWF

Von Willebrand factor

Endothelium
VON WILLEBRAND DISEASE

Pathophysiology of VWD

Secondary deficiency of FVIIIc not efficiently protected

Primary quantitative or qualitative defect of VWF
MEAN FEATURES OF VWD

• Pathophysiology
  – Deficiency (quantitative or qualitative) of VWF
  – Secondary deficiency of F8 in some patients

• Laboratory diagnosis
  – Prolongation of the PFA-100
  – vWF assays: Antigen and Activity
  – FVIIIc level
  – Consider influence of blood group O, stress, pregnancy, oestrogens

• Management
  – DDAVP and EXACYL in most patients
  – vWF (+FVIII) concentrates in a small subset of patients
**Von Willebrand Disease**

VWD: the most frequent inherited hemorrhagic disorder

- Prevalence: 0.82 – 1.6 /100

<table>
<thead>
<tr>
<th>Type</th>
<th>Defect</th>
<th>Desmopressin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Partial quantitative defect</td>
<td>Usually efficient</td>
</tr>
<tr>
<td>Type 2A</td>
<td>Qualitative defect</td>
<td>Possibly efficient</td>
</tr>
<tr>
<td>Type 2B</td>
<td>Qualitative defect</td>
<td>Contra-indicated</td>
</tr>
<tr>
<td>Type 2M</td>
<td>Qualitative defect</td>
<td>Usually not efficient</td>
</tr>
<tr>
<td>Type 2N</td>
<td>Qualitative defect</td>
<td>Usually not efficient</td>
</tr>
<tr>
<td>Type 3</td>
<td>Total quantitative defect</td>
<td>Not efficient</td>
</tr>
</tbody>
</table>

Most of patients with type 2 and type 3 VWD need replacement therapy
TREATMENT OPTIONS OF VWD

• On Demand
  – At the time of bleeding

• Prophylactic
  – Peri-operative
  – Long term prophylaxis
    • GI bleeds
    • Joint bleeds

• Specific treatment
  – Endogenous VWF/FVIII
    • DDAVP
  – Exogenous VWF/FVIII
    • Concentrates

• General measures
  – Anti-fibrinolytics
  – Oral contraceptive pill
Desmopressin (DDAVP) (Minirin® Ferring)

- Synthetic analogue of vasopressin
- Induces a release of endothelial FVIII
- Dosage: 0.2 - 0.3 µg/kg iv (subcutaneous)
- Intra-nasal spray (Octostim®)
- Response and tolerance should be evaluated!
- For mild (sometimes moderate) haemophilia A
- Not effective in haemophilia B
- Side-effects: flush, fluid retention
- Contra-indicated in elderly patients or with hypertension
- Cheap: 10 vials = €35
- Spray Octostim 150 µg/dose = €333
**Desmopressin (DDAVP) – Minirin**

DDAVP: 1-deamino-8-arginin vasopressin,

- **Release of von Willebrand factor / FVIII**
  - $x$ 2 to 4 circulating levels of vWF and FVIII

**Intravenous**
- 0.3µg/kg

**Nasal Spray Octostim**

Response to DDAVP should be tested in every VWD patient.
Other Hemostatic Treatment: Tranexamic Acid (EXACYL)

- Antifibrinolytic, stabilises the clot
- Indicated for ENT surgery, dental treatment
- Appropriate for local and systemic uses
- Oral or intravenous administration
- Contra-indicated for urinary tract bleedings (obstruction with clots)
- Dosage: 1 g 3–4x/day (adults) and 20 mg/kg 3x/day (children)
TRANEXAMIC ACID: HOW DOES IT WORK?

- Plasminogen
  - Exacyl (Tranexamic acid)
  - Plasmin
  - Fibrinogen → Fibrin → PDFs

**Dosages:**
- Exacyl: 1 g / 8 hours (adults)
- Pills: 250 - 500 mg / Vials: 1 g
Replacement Therapy of vWD

- Indicated for patients unresponsive to DDAVP
- Plasma-derived concentrates (FVIII-vWF) only available
- Pure plasma-derived nanofiltrated VWF available (WILFACTIN)
TREATMENT OF VWD

Monotherapy (Pure VWF)

- Exogenous VWF
- Protection
- Endogenous FVIII

Dual therapy (FVIII-VWF)

- Exogenous VWF
- Exogenous FVIII
FVIII and VWF Concentrates

- **FVIII**
  - (Haemophilia)
    - Kogenate
    - Helixate
    - Refacto
    - Advate

- **FVIII + FvW**
  - (Haemophilie and VWD)
    - Haemate-P
    - Wilate

- **FvW**
  - (vWD)
    - Wilfactin
HAEMOPHILIA

Blood Coagulation Defect

Debilitating Arthropathy
Bleeding complications in patients with haemophilia

Intra-Cranial

Ilio-psoas Muscle

Hip
FVIII and FIX Concentrations

Normal Range

- >150%
- 50–150%
- 25–49%
- 6–24%
- 1–5%
- <1%

Haemophilia

Pregnancy, Inflammation,…

Mild

Moderate

Severe
Factor Level
(\%)  

Moderate  

Severe  

Phenotype  
Bleeding Episodes/Year without Replacement  

Mild  

Moderate  

Severe  

<1%  

1–5%  

6–24%  

25–49%  

50–150%  

>150%  

<1%  

1–5  

0–1  

0  

0  

0  

0  

0  

52
Regular self-administration of F8 or F9 concentrate in order to prevent bleeding episodes (20-40 units/kg – 3x/week or 1x/2days)
**Mean Features of Haemophilia**

- Deficiency of F8 (HA) or F9 (HB)

- Isolated prolongation of the APTT (in most cases)

- Factor assays needed to determine severity (severe, moderate, mild)

- Development of antibodies neutralising F8 (rarely F9) in some patients (mainly patients with severe HA)
# Treatment of Haemophilia According to Severity

<table>
<thead>
<tr>
<th>Type of haemophilia</th>
<th>Therapy</th>
<th>Frequency of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>FVIII - FIX concentrates</td>
<td>Frequent</td>
</tr>
<tr>
<td>Moderate</td>
<td>FVIII or DDAVP</td>
<td>Occasional</td>
</tr>
<tr>
<td>Mild</td>
<td>DDAVP or FVIII concentrate</td>
<td>Rare</td>
</tr>
</tbody>
</table>
TREATMENT MODALITIES OF HAEMOPHILIA

On-demand (Therapeutic, Preventive)

Prophylaxis (Prevention)

Continuous Infusion (Surgery)
Frequently Performed Invasive Procedures in Patients with Haemophilia

- Major orthopaedic surgery (knee replacement)
- Liver biopsy (performed by the trans-jugular route)
- Circumcision
- Central venous access device (Port-A-Cath) insertion
- Tonsillectomy
- Dental extraction
- Prostate surgery
CORRECTION OF F8 OR F9 DEFICIENCY

Fresh Frozen Plasma
Cryoprecipitate

1 FFP (200 ml) = 200 units of F8
1 ml FFP = 1 unit of F8

Concentrates of F8 or F9
Plasma-derived
Biotechnology

Vials of 250 to 3000 units

F8 or F9 dosing: between 10 and 100 units/kg
**CHOICE OF FVIII CONCENTRATES**

**Plasma-derived**
- Plasma-derived FVIII (National blood services)
  (International companies)

**Biotechnology**
- ReFacto AF® / XYNTHA®
- Kogenate FS®
- Advate®
<table>
<thead>
<tr>
<th>Concentrate</th>
<th>Name</th>
<th>Dosing</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVIII</td>
<td>Advate (Baxter)</td>
<td>250-500-1000-1500 units</td>
<td>253 - 1481 euros</td>
</tr>
<tr>
<td></td>
<td>Kogenate (Bayer)</td>
<td>250-500-1000 units</td>
<td>258 - 987 euros</td>
</tr>
<tr>
<td></td>
<td>Refacto (Pfizer)</td>
<td>250-500-1000-2000 units</td>
<td>212 - 1631 euros</td>
</tr>
<tr>
<td></td>
<td>Factane (CAF-DCF)</td>
<td>1000 units</td>
<td>894 euros</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FIX</td>
<td>Benefix (Pfizer)</td>
<td>500-1000-2000 units</td>
<td>387-1521 euros</td>
</tr>
<tr>
<td></td>
<td>Nonafact (CAF-DCF)</td>
<td>500-1000 units</td>
<td>273-537 euros</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVIII-VWF</td>
<td>Wilate (octapharma)</td>
<td>450-900 units (FVIII)</td>
<td>420-832 euros</td>
</tr>
<tr>
<td></td>
<td>Haemate-P (ZLB)</td>
<td>500-1000 units (FVIII)</td>
<td>273-537 euros</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VWF</td>
<td>Wilfactin (LFB)</td>
<td>1000 units (VWF)</td>
<td></td>
</tr>
<tr>
<td>FVIIa</td>
<td>NovoSeven</td>
<td>50-100-250 x 103</td>
<td></td>
</tr>
<tr>
<td>FII, VII, IX, Xa</td>
<td>FEIBA (Baxter)</td>
<td>250-500-1000 units</td>
<td></td>
</tr>
<tr>
<td>FII, VII, IX, X</td>
<td>PPSB (CAF-DCF)</td>
<td>250-1000 units</td>
<td></td>
</tr>
</tbody>
</table>
AMOUNT OF CONCENTRATE

- 1 unit of FVIII/kg increases plasmatic level of FVIII of 2% (0.02 U/ml)
- 1 unit of FIX/kg increases plasmatic level of FIX of 1% (0.01 U/ml)

Units to Infuse = \((\text{Target Level} - \text{Basal Level}) \times \text{Weight (Kg)}\) / Recovery Factor
Recovery in a Patient of 50kg Treated with 2,000 Units of FVIII (40 U/kg)

Estimated Recovery: 2
Target Level FVIII: 80%
Basal FVIII Level: 5%
Post-infusion FVIII Level: 75%

Calculated Recovery (K): 1.75

K = Δ x Weight
    Units of Factor

Hermans C: Hospital patient case.
HALF-LIFE OF FVIII / FIX

Factor VIII: 8–12 hr

Factor IX: 16–18 hr
**Replacement Modalities During Surgery**

<table>
<thead>
<tr>
<th>Repeated Bolus</th>
<th>Continuous Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVIII</td>
<td>FVIII</td>
</tr>
<tr>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Time</td>
<td>Time</td>
</tr>
</tbody>
</table>

Hermans C: Hospital patient case.
CHECK-LIST BEFORE INVASIVE PROCEDURE

- Type of clotting factor deficiency (FVIII, FIX?) and severity
- Type of treatment (DDAVP, clotting factor [avoid switching])
- Recovery? DDAVP response?
- Inhibitor status?
- Viral serology (hepatitis C, HIV,…)
- Venous access?
- Amount of concentrate required to cover procedure?
- Coordination with the ward, pharmacy, other specialists
- Appropriate schedule (beginning of the week)
- Traceability of concentrates
Communication is Mandatory

- Information should be obtained from all involved before surgery:
  - Nurses
  - Surgeon
  - Anaesthesist
  - Physiotherapist
  - Pharmacist
  - Intensive care unit
Challenges of Replacement Therapy

- Replacement therapy should be supervised by experts in haemophilia care and other inherited bleeding disorders.
- Treatment has to be individualised.
- Haemostatic levels of FVIII and FIX dependent on surgery:
  - Dental care: 30-40%
  - Appendicectomy: 50%
  - Cardiac / CNS surgery: 80 – 100%
**Frequency of Rare Coagulation Factor Deficiencies**

*UK, Iran & Italy (Peyvandi 1999)*

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>4,637 (UK)</th>
<th>4,595 (Iran)</th>
<th>4,286 (Italy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemophilia A</td>
<td>77%</td>
<td>65%</td>
<td>80%</td>
</tr>
<tr>
<td>FV deficiency</td>
<td>0.6%</td>
<td>1.5%</td>
<td>0.5%</td>
</tr>
<tr>
<td>FVII deficiency</td>
<td>1.3%</td>
<td>6.6%</td>
<td>1.3%</td>
</tr>
<tr>
<td>FX deficiency</td>
<td>0.5%</td>
<td>1.3%</td>
<td>0.2%</td>
</tr>
<tr>
<td>FXIII deficiency</td>
<td>0.5%</td>
<td>1.7%</td>
<td>0.4%</td>
</tr>
</tbody>
</table>
# Replacement Therapy of Rare Clotting Factor Deficiencies

<table>
<thead>
<tr>
<th>Deficiency</th>
<th>Half-life</th>
<th>Normal level</th>
<th>Haemostatic level</th>
<th>Substitution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen</td>
<td>3–5 days</td>
<td>&gt; 150 mg/dl</td>
<td>100 mg/dl</td>
<td>Fibrinogen or PFC</td>
</tr>
<tr>
<td>Prothrombin</td>
<td>2.5 days</td>
<td>&gt; 70 %</td>
<td>&gt;30%</td>
<td>PFC – PCC</td>
</tr>
<tr>
<td>Factor V</td>
<td>12 hours</td>
<td>&gt; 70 %</td>
<td>&gt;25%</td>
<td>PFC – platelets</td>
</tr>
<tr>
<td>Factor VII</td>
<td>6 hours</td>
<td>&gt; 70 %</td>
<td>&gt;20%</td>
<td>PFC, PCC, pFVII, rFVIIa</td>
</tr>
<tr>
<td>Factor X</td>
<td>30 hours</td>
<td>&gt; 70 %</td>
<td>10–40%</td>
<td>PFC, PCC</td>
</tr>
<tr>
<td>Factor XIII</td>
<td>9–10 days</td>
<td>100 %</td>
<td>&gt;1%</td>
<td>FXIII, PCC</td>
</tr>
</tbody>
</table>
For clotting factors:
Haemostatic levels < Normal range

In most cases, haemostatic treatment should not aim to correct levels into the normal range.
For every clotting factor deficiency, please...

- Assess clotting factor level and degree of deficiency (severe ?)
- Repeat bleeding history (personal and family)
- Detect co-morbidities or treatments that could increase risk of bleeding
- Exclude presence of inhibitor (neutralizing antibodies)
- With respect to treatment:
  - Use tranexamic acid in most cases
  - Concentrates only if indicated
  - Prefer concentrates to FFP
  - Recombinant treatment if available: first choice in children
THANK YOU FOR YOUR ATTENTION

Visit our Website: http://www.hemophilie-ucl.be and discover our computer-generated movie on blood coagulation and haemophilia

Also on youtube.com: Haemophilia + Movie