evropský sociální fond v ČR
EVROPSKÁ UNIE
MINISTERSTVO ŠKOLSTVÍ, MLÁDEŽE A TĚLOVÝCHOVY
OP Vzdělávání pro konkurenceschopnost
INVESTICE DO ROZVOJE VZDĚLÁVÁNÍ

Hemofílie

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Hemophilia

Incidence:

Hemopilia A (deficiency of factor VIII):
1 - 2 of 10 000 male newborns in all ethnic groups

Hemophilia B (deficiency of factor IX):
1 - 2 of 50 000 male newborns in all ethnic groups

Hereditary: X - chromosomal, recessive

Symptoms of Hemophilia

Joint bleedings (Knee 45%, Elbow 30%)	70 - 80 %
Muscle bleedings and haemorraghes of the skin	10 - 20 %
Other severe bleedings	5 - 10 %
Central nervous system (brain)	~ 5 %

Bleeding events

Figure 13. Suspected child abuse that turned out to be severe hemophilia.

Figure 14. Patient with compression of the left part of the thoracic cage due to a massive blood cyst.

Ankle bleed

Late haemarthrosis of knee

Soft tissue bleeds

- Often related to trauma
- Usually less painful than haemarthroses
- Can be very large
- Complications
  - Compartment syndrome
  - Nerve compression
  - Hypovolaemic shock

The history of blood products is >60 years long

1940	Dr. Edwin Cohn developed a plasma fractionation process by which plasma is fractionated into components by precipitation with alcohol.
1964	Cryoprecipitate by centrifugation= 6-fold concentration of FVIII
1966	First commercially available FVIII concentrate by Hyland
late 1960s	First lyophilized 400-fold concentrated (compared to plasma) FVIII concentrates
1988	First mab purified high purity FVIII concentrate (Hemofil M) with100,000 fold higher FVIII concentration
1992	First recombinant FVIII concentrate (Recombinate followed by Kogenate)
1991/92	First experiments with gene therapy in animal models using retroviral vectors
2003	First blood free rFVIII product (ADVATE)

How to calculate the right dose?

1 IU FVIII / kg b.w. raises the plasma FVIII activity by 2%

Formula:

Dose (IU/kg) = body weight (kg) x desired increase (%) x 0.5

Dosage Recommendations for FVIII Concentrates

	Type of bleed/ surgery	Required max. activity of FVIII	Frequency of infusions
Bleeds	Milder	20-40%	Every 12-24 hrs 1-3 days
	Moderate	30-60%	Every 12-24 hrs More than 3 days
	Severe or life threatening	60-100%	Every 8-24 hrs until resolved
Surgery	Minor surgery incl. dental extraction	60-80%	1 Infusion plus antifibrinolytic agent
	Major surgery	80-100%	Every 8-24 hrs

Treatment translates into Quality of life

Treatment options	Life expectation and Quality of life
No treatment or FFP only	Death under 6 years of age
FVIII concentrates 10-20 000 Units/pat./year	Become cripled, reduced actuivity; Complicationen at the age of 20
FVIII concentrates on demand) 30-50 000 Units/pat./year	Reduced actuivity; Complicationen at the age of 30
On demand, little prophylaxis; 70-80 000 Units/pat./year	Some activities possible; Complication at the age of 40
Prophylaxe from 0-15. years of age 100-120 000 Units/pat./year	Normal active life; no orthopedic damages; normal life expectation

Complications in Hemophilia

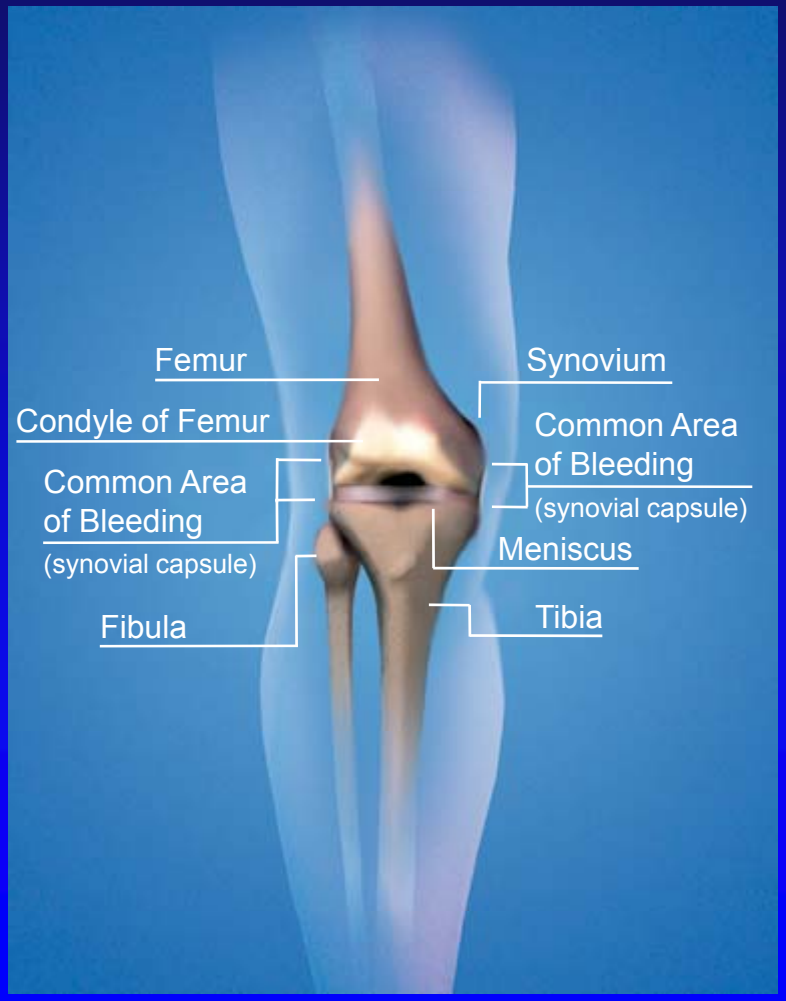
- Musculoskeletal problems
- FVIII inhibitor development
- Special issues in pediatric patients
- Management of surgery

Joint damage due to frequent bleedings into a target joint

Figure 17. Boy with severe hemophilia.

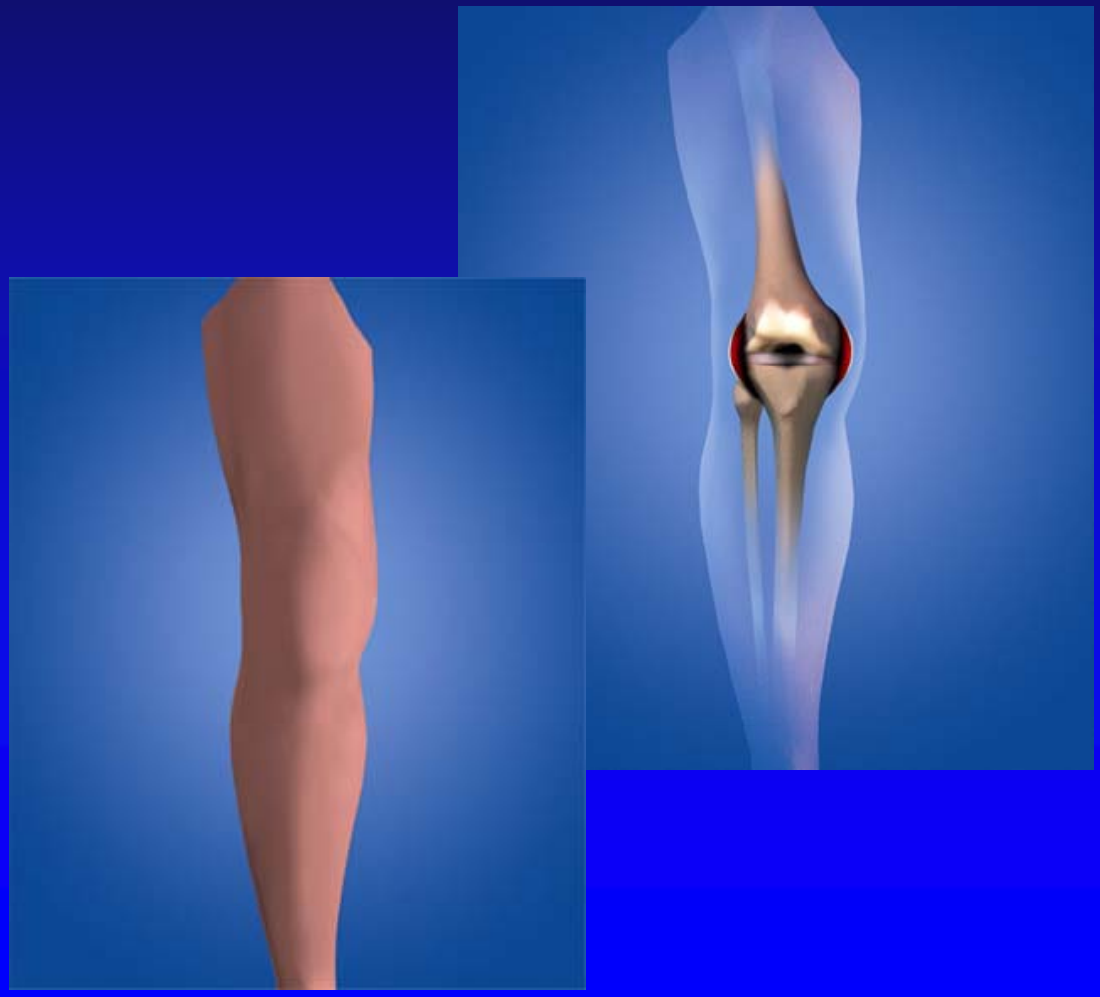
Sites of Joint Bleeding in Hemophilia: Knee

- The knee is a common target joint in hemophilia



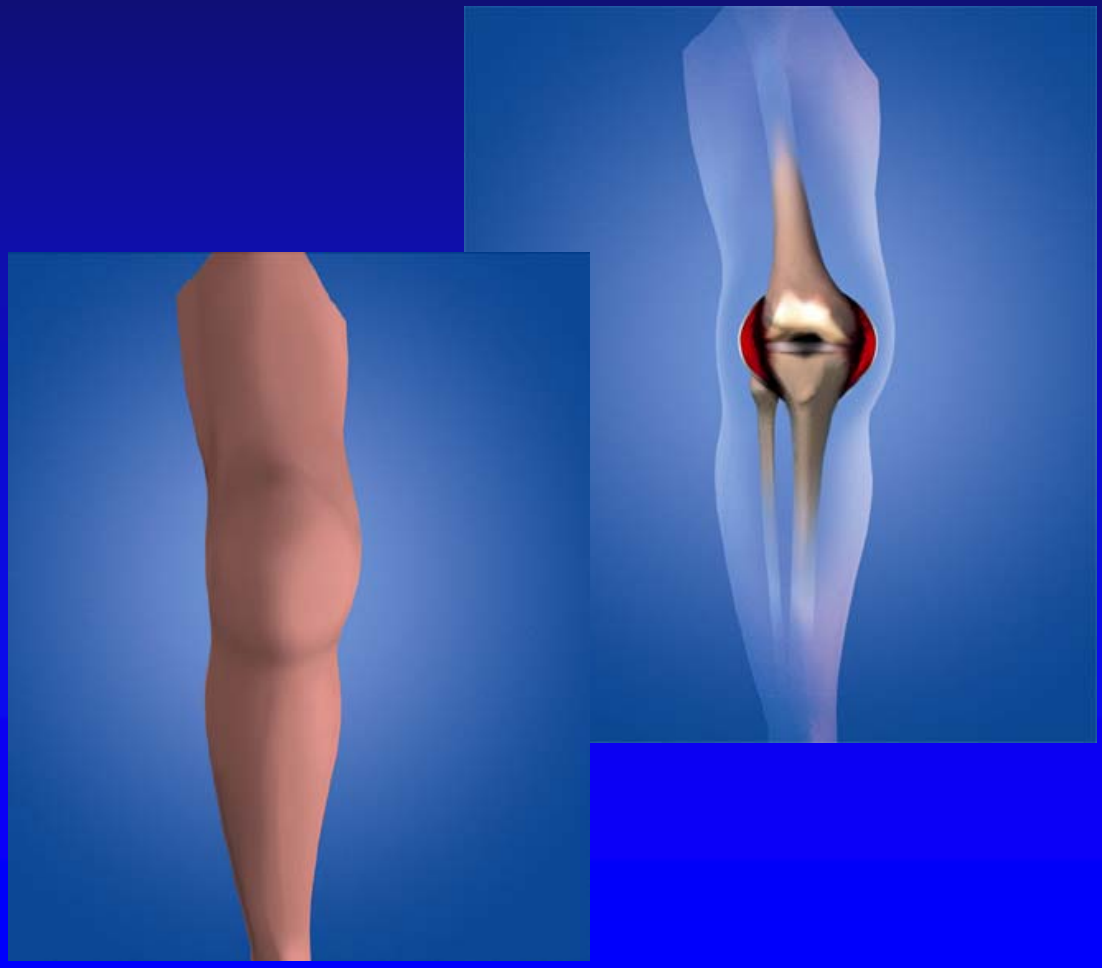
Early Joint Bleeding in Hemophilia: Knee

- Warmth, tingling
- Optimal time to initiate treatment



Late Joint Bleeding in Hemophilia: Knee

- Increased pain
- Increased swelling
- Decreased range of motion
- Therapy initiated at this time results in prolonged treatment and greater risk for joint damage

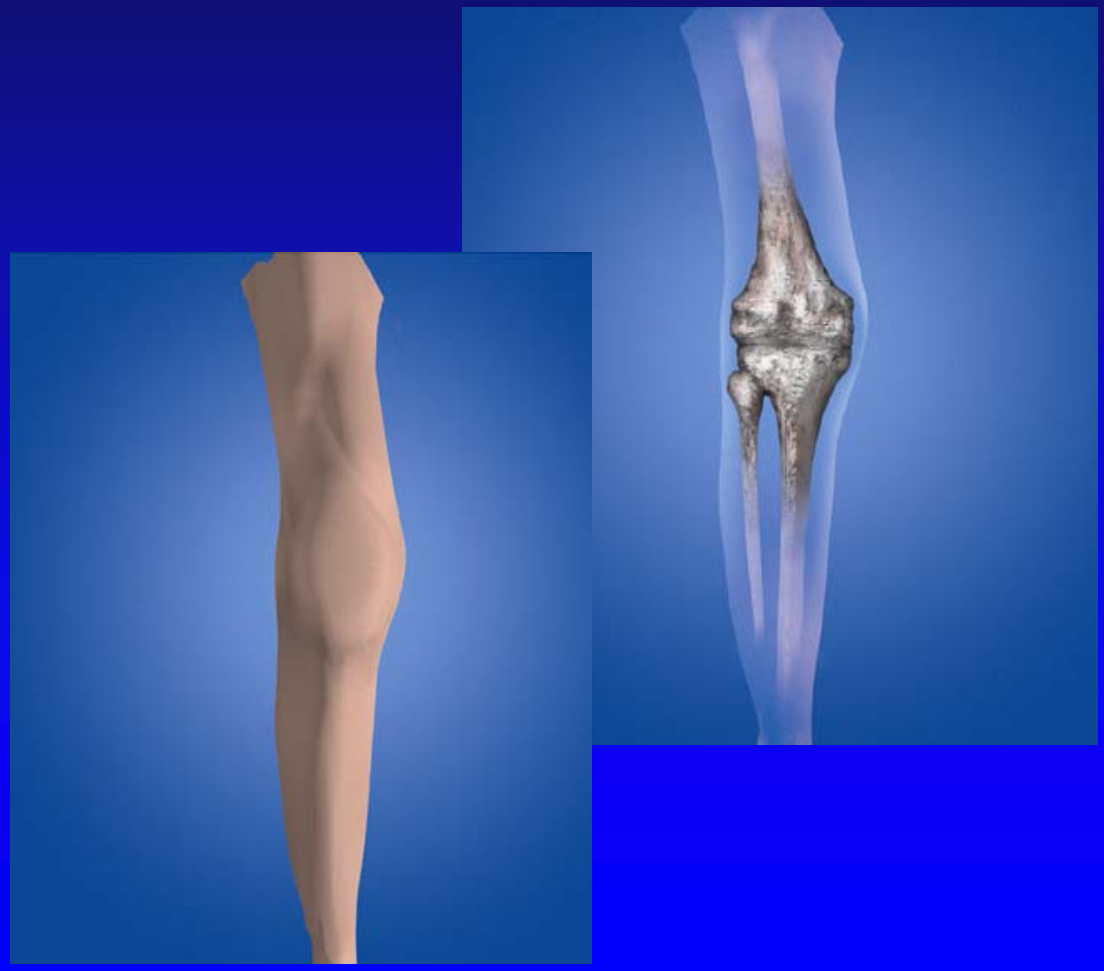


Joint Bleeding in Hemophilia: Chronic Changes

- Synovial hypertrophy and synovitis
- Swelling/effusion
- Pain
- Cartilage erosion
- Subchondral cysts
- Loss of bone density and articular surfaces
- Muscle athrophy

Late Hemophilic Arthropathy

- Chronic pain
- Poorly functioning joint
  - Advanced osteoporosis
  - Cartilage destruction
  - Joint space narrowing
- Disability
- Joint replacement or other orthopedic procedure may be required



Surgical Interventions

- Open surgical synovectomy
  - Considered for elbows
- Arthroscopic synovectomy
  - Recommended for knees and ankles
- Total joint replacement (Titanium, Steel)
  - Commonly performed for knees, hips, and shoulders
- Arthrodesis
  - Utilized for joints in which arthroplasty has failed, joint has become infected

Hilgartner MW. *Curr Opin Pediatr.* 2002;14:46-49.
Rodríguez-Merchán EC. *Semin Thromb Hemost.* 2003;29(1):87-96.

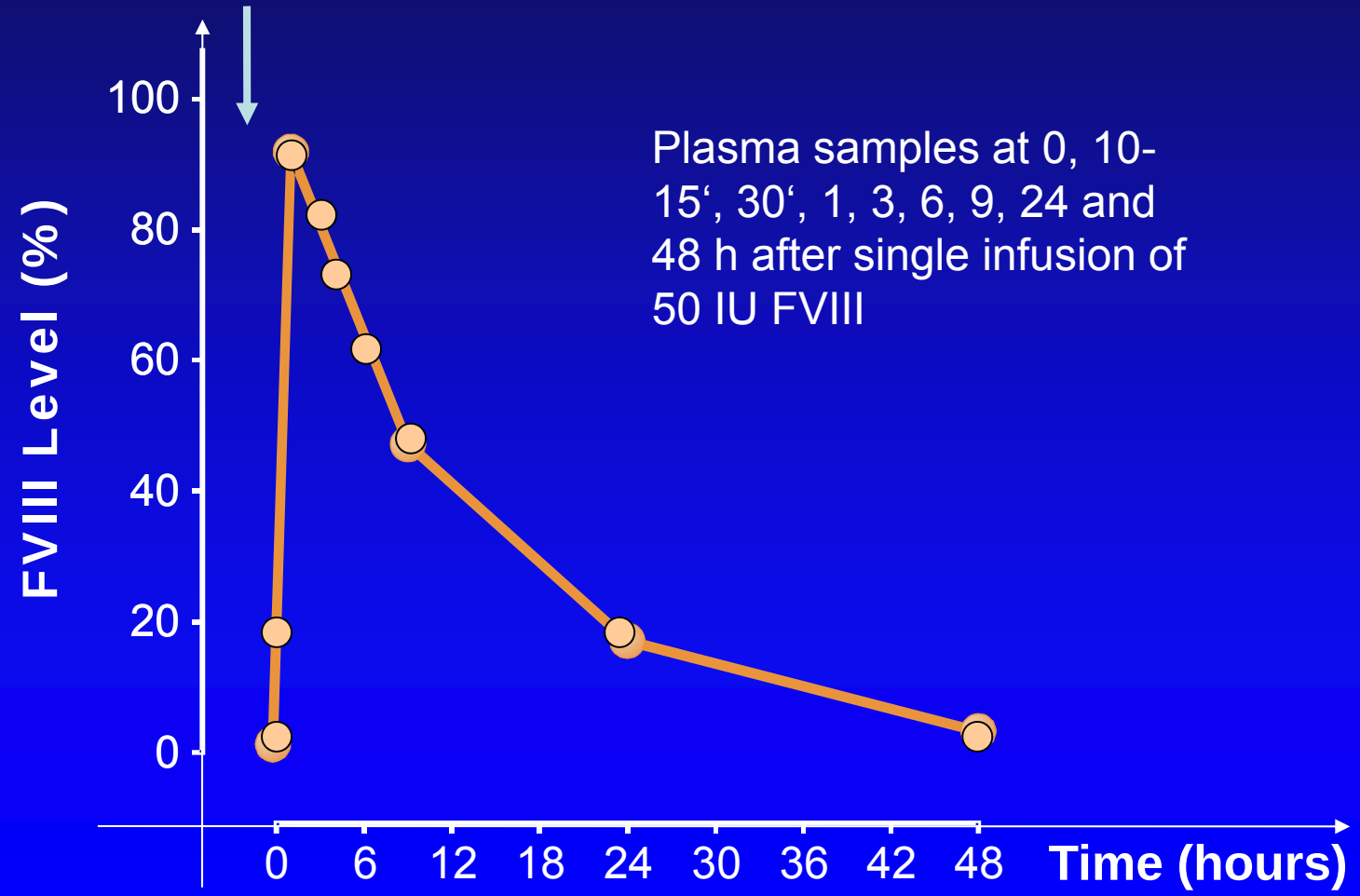
Prophylaxis: Long-Term Goals

- Prevention of chronic disease (target joint)
- Improvement in individual/family quality of life
- Reduction in long-term societal costs through prevention of disability, improved outcome, maximization of human potential

Fischer et al. *Haemophilia*. 2003;9(suppl 1):75-82.

Individual PK curve - FVIII Levels over Time

single infusion of 50 ± 5 IU/kg bodyweight FVIII at time zero



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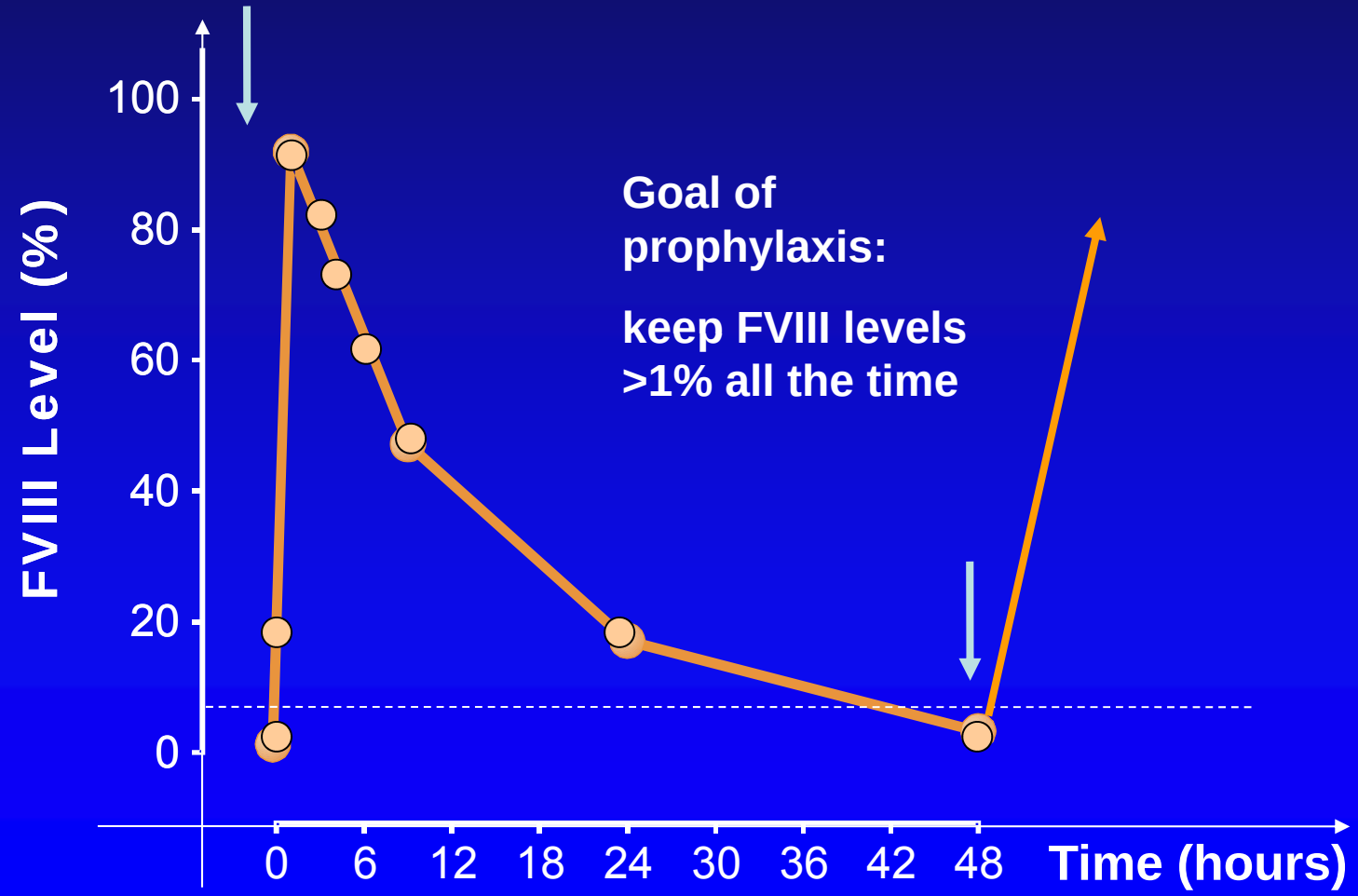

Barriers to Prophylaxis

- Cost

  Product costs only: (50kgx50IUx3x52 weeks=390,000 IU/Year x 0.83€) = **323,700 €**

  - Individual
  - Social
- Complications with venous access
- Long-term compliance
  - Individual ability
  - Caregiver commitment

Schramm W, Berger K. *Haemophilia*. 2003;9(suppl 1):111-116.
Hacker MR et al. *Haemophilia*. 2001;7:392-396.

Complications in Hemophilia

- Musculoskeletal problems
- FVIII inhibitor development
- Special issues in pediatric patients
- Management of surgery

FVIII inhibitors – incidences and general info

Incidences

Inhibitors to FVIII develop in about 30% of patients with severe hemophilia

in 1-3% in PTPs

In up to 50% in PUPs

- Inhibitors are measured in Bethesda units (BU)
- Inhibitors can be transient = disappear spontaneously; most low titer without clinical consequences
- Patients with inhibitors categorized as high or low responders
  - Low responding: ≤ 5 BU persistently despite FVIII exposure (no anamnestic response)
  - High responding: > 5 BU at any time regardless of present titer (anamnestic response)

Scandella D. Human anti-factor VIII antibodies: epitope localization and inhibitory function. *Vox Sang*. 1996;70(suppl 1):9-14.

Scandella DH. Properties of anti-factor VIII inhibitor antibodies in hemophilia A patients. *Semin Thromb Hemost*. 2000;26:137-142.

FVIII Inhibitors – Treatment options

Treatment of bleeding events in patients with inhibitors:

- Increased FVIII dose
- Bypassing agents: FEIBA or NovoSeven (rFVIIa)

ITI (immune tolerance induktion) with the goal to get rid of the inhibitor for ever

High dose und low dose FVIII protocols as well as the Malmö protocol (plasmapherese to eliminate all Ig)

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Pediatric Patients: Special Issues

- Bleed recognition
- Transitioning CVAD (Central Venous Access Device – Port-A-Cat) to peripheral venous access
- Pharmacokinetics in young children different (shorter half-life and lower in vivo recovery)
- Monitoring for FVIII inhibitors

Venous access devices

Implanted PortACath (Huber):
Injection of FVIII through a plastic membrane into a chamber that is connected to a vein

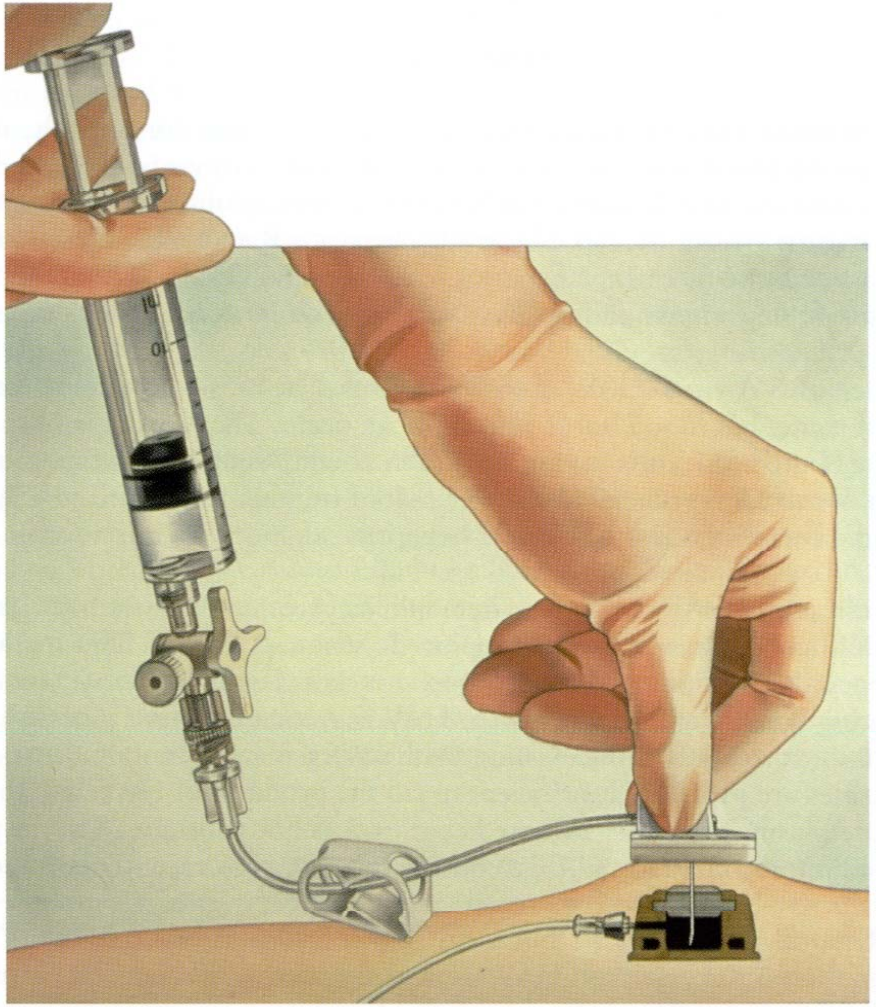

Figure 24b. Insertion of the needle through the skin.

Venous access devices

Arteriovenous fistulae
Connect a vein with an artery (end-to-side or side-to-side) in the forearm.

Goal: arterialization of the vein (stronger elastic vessel walls)

Santagostino et al (2003) B J Haematol 123:502-506

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Recommended Targets for Postoperative Plasma FVIII Levels

Procedure	Week 1 FVIII Plasma Level	Weeks 2 and 3 FVIII Plasma Level
Major surgery (joint/knee replacements, neurosurgery)	80%-110%	50%-80%
Minor surgery (arthroscopy, intra-abdominal)	50%-80%	30%-50%
Dental	As needed	As needed

CI: Dosing

- Interpatient FVIII pharmacokinetics vary considerably
- Tailor maintenance dosing to reflect individual FVIII pharmacokinetics

Rate of infusion (IU/kg/h)

=

Clearance (mL/kg/h)

×

Desired plasma level (IU/mL)

Batorova A, Martinowitz U. *Haemophilia.* 2002;8:170-177.

Děkuji za pozornost