DIAGNOSIS AND TREATMENT PROTOCOL FOR HEMOPHILIA AND VON WILLEBRAND DISEASE

References:

1. European "Guidelines for the management of hemophilia", Srivastava A et al, Haemophilia 2012
2. WFH Guidelines for the de management of hemophilia, Second print edition
3. "European Principles of haemophilia care", Colvin, Haemophilia 2008
4. "Kreuth III: European consensus proposal for treatment of haemophilia with coagulation factor concentrates" Giangrande, Haemophilia 2014

I. DISORDER DEFINITION

Hemophilia is a congenital hemorrhagic disorder transmitted hereditary X-linkat, characterized as reduced quantitative or altered qualitative synthesis of coagulation factor VIII (Hemophilia A) or of factor IX (Hemophilia B).
Hemophilia A is more frequent than hemophilia B, representing 80-85% of the total cases of hemophilia. The incidence of hemophilia A is of 1 case in 5000 – 10000 male newborns. 75% of the hemophilia cases are hereditary, and the remaining 25% (and in the opinion of certain authors even up to 50%) represent de novo hemophilia.

Taking into account the serum level of the coagulation factor, there are 3 forms of Hemophilia:
- Light form, quantity of coagulation factor >5%
- Moderate form, quantity of coagulation factor 1–5%
- Severe form, quantity of coagulation factor <1%

Hemorrhagic events

- The characteristic phenotype of hemophilia represents the tendency to bleed.
- The severity of the hemophilia hemorrhagic episodes is generally correlated to the coagulation factor (Table 1).

Hemophilia Severity	Coagulation factor level	Hemorrhagic episodes
Severe	<1 UI/dl or <1% of the normal value	Spontaneous hemorrhages at the level of the joints and muscles, in general without an identifiable cause.
Moderate	1-5 UI/dl or 1-5% of the normal value	Occasional spontaneous hemorrhages; prolonged hemorrhages following minor traumatisms or surgeries.
Light	5-40 UI/dl or 5-40% of the normal value	Severe hemorrhages following major traumatisms or surgeries; spontaneous hemorrhages are rare.

Table 1. : Correlation between the severity of the hemorrhagic episodes and the coagulation factor level

- Very often the hemorrhagic episodes are internal, at the level of the joints and muscles (Table 2).
- Some hemorrhagic events (cerebral, gastro-intestinal, neck, larynx) can endanger life and require emergency treatment

Hemorrhage location	Frequency (%)
Haemarthrosis	70-80
Muscular hemorrhages	10-20
Other major hemorrhages	5-10
SNC hemorrhages	<5

Table 2. Frequency of hemorrhagic episodes depending of their location

II. INITIAL HEMOPHILIA DIAGNOSIS PROTOCOL

II.1. Postnatal diagnosis

Diagnosis grounds
- history (characteristic hemorrhagic events, family history – family tree)
- active diagnosis for boys coming from families with hemophilia (family tree)
- approximately 50% of our newly diagnosed cases do not have family history (rare forms)

Confirming the diagnosis and determining the type of hemophilia
- activated partial time of de thromboplastin (TPTA)
- prothrombin consumption time
- global coagulation time, Howell duration have different frequently normal values in the non-severe cases and they are presented as screening tests
- correction of the assimilation duration of prothrombin or TPTA with fresh plasma, old serum and plasma absorbed on barium sulfate

Possible diagnosis	TP	TPTA	Bleeding time	No. of thrombocytes
Normal	Normal	Normal	Normal	Normal
Hemophilia A or B	Normal	*Prolonged*	Normal	Normal
Von Willebrand disease	Normal	Normal *or prolonged*	Normal *or prolonged*	Normal *or reduced*
Thrombocytes defect	Normal	Normal	Normal *or prolonged*	Normal *or reduced*

Table 3. Interpretation of the screening test

Establishing the level of severity of hemophilia
- establishing the plasma concentration of factor VIII/IX through a metric coagulation / chromogenic method (<1% severe forms; 1 - <5% moderate forms; 5-40% light forms)
- establishing the anti-FVIII or anti-FIX inhibitors, recovery test and establishing the period for administering half of the quantity of FVIII and FIX

II.2. Prenatal diagnosis
- analysis of the family tree
- diagnosis of the gender of the fetus
- bio-molecular tests in order to determine the disease's genetic substrate

• III. HEMOPHILIA TREATMENT PRINCIPLES
- The main purpose of the treatment is preventing and treating the hemorrhagic episodes.
- Prophylaxis in children suffering from severe hemophilia is recognized as standard treatment. Prophylaxis in adults can also be initiated when it is necessary, depending on the doctor's decision.
- The treatment for patients suffering from hemophilia is best managed in Comprehensive Centers for treating hemophilia.
- The acute hemorrhagic episodes must be treated as soon as possible, preferably within the 2 hours as of the moment of commencement. If there are any diagnosis doubts regarding the hemorrhagic episode, the recommendation is to administer treatment.
- The diagnosis and rapid initiation of the treatment limits the destruction of articular tissues.
- In the event of an acute hemorrhagic event, an evaluation must be performed in order to establish the stage of the hemorrhage (if it is not

obvious from the clinical perspective) and treatment with deficient coagulation factor must be initiated.

- In the event of severe, life threatening hemorrhages, especially those located at the level of the brain, neck, larynx, digestive tube, treatment with deficient coagulation factor must be initiated immediately, even before having finalized the diagnosis tests.
- In order to facilitate the correct management of emergency situations, all patients must carry with them an identification card that shall contain the following information regarding the disease: diagnosis and severity of the disease, inhibitors status, product and doses utilized for treating the disease and contact details of the attending doctor.
- If the hemorrhagic episode is not solved despite having administered the adequate dose of coagulation factor, the plasma level of the coagulation factor must be measured; if this level is significantly low, then the presence and level of the inhibitors must be measured.
- Patients with inhibitors who do not react or who are not eligible for immune tolerance induction therapy should be administered a prophylactic treatment with bypass agents.
- The decision on selecting concentrates of coagulation factors for treating patients suffering from hemophilia should not be taken only based on the cost criteria but also based on the quality criteria of the said product; the patients suffering from hemophilia must be provided with access to safe and efficient concentrates of coagulation factors in the optimum dosage; in the case of prophylaxis in children that were not previously treated (PUP), recombined concentrates of coagulation factors.
- Preserving vein access is of vital importance in patients suffering from hemophilia.
- Avoiding products that lead to platelet dysfunction, especially those that contain aspirin. The anti-inflammatory medication without steroids must be administered with caution. For example it is recommended to administer acetaminophen with or without codeine in order to control pain; when administering combined medication you must take into account the interaction between the medications.
- At home treatment administered with coagulation factor can be initiated in children of young ages with adequate vein access, after having adequately trained the family members; home treatment reduces the costs and complications associated with hemophilia and it should be a standard for patients suffering from hemophilia.

IV. HEMOPHILIA TREATMENT PROTOCOL

IV.1. Prophylaxis of hemorrhagic accidents

IV.1.1.Definitions:

Continuous primary prophylaxis: continuous and regular treatment before the articular affection documented clinically and/or by means of imagery, before the occurrence of the second haemarthrosis at the level of major joints* and before the age of 3.
Continuous secondary prophylaxis: continuous and regular treatment, initiated after the occurrence of two or several haemarthrosis at the level of major joints* and before the joints are affected and documented clinically and/or by means of imagery.
Tertiary prophylaxis: continuous and regular treatment, initiated after the joint has been affected and has been clinically documented by means of imagery.
Intermittent prophylaxis (periodical): treatment administered in order to prevent bleeding for a period of time that does not exceed 45 weeks during one year.
*Major joints: ankle, knee, hip, elbow and shoulder
Continuous treatment is defined as the treatment intent for a period of 52 weeks per year and with a minimum number of dosages defined in advance with at least 45 weeks (85%) per year.

IV.1.2.Objectives: preventing hemorrhagic accidents, relieving chronic articular disease, improving the quality of life of the patients suffering from hemophilia.

IV.1.3.Inclusion criteria (age, gender, clinical and para-clinical parameters, etc.)

1. Patients suffering from Severe congenital hemophilia (FVIII and FIX congenital deficit)

without inhibitors
2. Patients with an age between 1-18
3. Patients suffering from a severe form of the disease, regardless of the age, with a high risk of bleeding (dental therapy, invasive interventions, physical recovery)

IV.1.4.Treatment (doses, conditions for reducing the dose, treatment period)

Products:
Hemophilia A: Plasma coagulation factor VIII; Recombined coagulation factor VIII
Hemophilia B: Plasma coagulation factor IX; Recombined coagulation factor IX

Dosage:
Hemophilia A: FVIII coagulation concentrates
- 20-40 UI factor VIII/kg, every 2 - 3 days for patients over 6 years of age
- 20-50 UI factor VIII/ kg of the body, administered 3 - 4 times per week for patients with the age < 6 years.

Hemophilia B: FIX coagulation concentrate of
- 20-40 UI factor IX/kg, every 3-4 days.

Administration: intravenously, slowly. The administration interval must be established by the hematology specialist/doctor.

Administration recommendations:
- During prophylaxis in children that were not previously treated (PUPs), it is recommended to administer recombined coagulate factor VIII concentrates.
- For the long term it is generally recommended to use the same biologic product, except for the situations in which it is proven that they are not efficient or complications occur because of the said product
- A personalized, pharma-kinetic guided treatment protocol provides the possibility to establish individual doses and administration interval

IV.1.5. Treatment monitoring (clinical and para-clinical parameters, periodicity)
- Careful monitoring, through clinical examination and laboratory tests, in order to detect the development of antibodies inhibitors.
- Clinical and para-clinical monitoring of the hemorrhage events and articular status

IV.1.6. Treatment exclusion criteria

- Hypersensitivity to the active substance or to mouse or hamster excipients or proteins, with the recommendation of changing the treatment's biologic product
- Development of the anti-FVIII or anti-FIX coagulation inhibitors

IV.2. Curative treatment of hemorrhagic accidents

IV.2.1. Objective: stopping the hemorrhagic accident

IV.2.2. Inclusion criteria (age, gender, clinical and para-clinical parameters, etc.)

1. Patients with congenital hemophilia without inhibitors, with hemorrhagic episode
2. Age: any age group

IV.2.3. Treatment (dose, conditions for reducing the dose, treatment period)

Products:
Hemophilia A: Plasma coagulation factor VIII; Recombinant coagulation factor VIII
Hemophilia B: Plasma coagulation factor IX; Recombinant coagulation factor IX
The dose and duration of the substitution therapy depend on the severity of the factor VIII/ IX deficit, hemorrhage location and degree and the patient's clinical state.

Hemophilia A:

Dose:
Determining the necessary dose of factor VIII relies on the following empiric observation:
1 UI factor VIII/kg increases the plasma activity of factor VIII with 2 UI/dl.
The necessary dose is determined by utilizing the following formula:
Necessary units (UI) = body weight (kg) x desired increase of factor VIII (%) x 0.5.

Hemorrhage severity	Plasma level of the necessary FVIII (% of normal of UI/dl)	Administration frequency (hours) / treatment duration (days)
Early haemarthrosis, muscle or oral hemorrhages	20 – 40	Repeated injections are administered every 12-24 hours (from 8 to 24 hours, for patients with the age under 6), for at least one day, until the hemorrhagic episode is remitted or until the patient is healed, this being indicated by the lack of pain.
Haemarthrosis, muscle hemorrhages or enlarged hematoma	30 – 60 60 – 100	Repeated injections are administered every 12-24 hours (from 8 to 24 hours, for patients with the age under 6), for a period of 3–4 days or more, until pain or acute functional impotence are remitted.
Hemorrhages that endanger life		Repeated injections are administered every 12-24 hours (from 6 to 12 hours, for patients with the age under 6), until the danger is eliminated.

Table 4. Plasma level of the necessary FVIII, depending on the severity of the hemorrhage episode

The dose and frequency of administration must be adapted depending on the individual clinical answer. In certain circumstances (for example the presence of a low titer of anti-factor VIII anti-bodies) it might be necessary to administer higher doses than the ones calculated with the help of the formula.

Hemophilia B:

Dose:

The calculation of the necessary dose of factor IX relies on the empiric observation, in accordance to which 1 UI factor IX per kg increase the plasma activity of IX with 0.9% of the normal activity.

The necessary dose is calculated by utilizing the following formula:

Necessary units = body weight (kg) x desired increase of factor IX (%) (UI/dl) x 1.1

Hemorrhage severity	Plasma level of the necessary FVIII (% of normal of UI/dl)	Administration frequency (hours) / treatment duration (days)
Early haemarthrosis, muscle or oral hemorrhages	20 – 40	Repeated every 24 hours, for at least 1 day, until the bleeding indicated by pain is resolved or healed.
haemarthrosis, muscle hemorrhages or haemarthrosis hematoma	30 – 60 60 – 100	The perfusion is repeated at intervals of 24 hours, for 3-4 hours or more, until the pain and acute invalidity is resolved.
Hemorrhages that endanger life		The perfusion is repeated at intervals between 8-24 ore, until the vital risk is eliminated.

Table 5. Plasma level of the necessary FIX depending on the severity of the hemorrhage episode

Administration: intravenously, slowly. The administration interval must be established by the hematology specialist/doctor.

IV.2.4.Treatment monitoring (Clinical, para-clinical parameters, periodicity)

- Careful monitoring, through clinical examination and laboratory tests, in order to detect the development of antibodies inhibitors.
- Clinical and para-clinical monitoring of the hemorrhage events and articular status
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IV.2.5.Criteria for being excluded from the treatment

- Hypersensitivity to the active substance or to mouse or hamster excipients or proteins, with the recommendation of changing the treatment biologic product
- Development of the anti-FVIII/IX coagulation inhibitors

IV.3. Substitution treatment in the event of surgeries and major orthopedic surgeries

IV.3.1.Objectives: ensuring hemostasis during surgeries and major orthopedic surgeries

IV.3.2. Inclusion criteria (age, gender, clinical and para-clinical parameters, etc.)

1. Patients with congenital hemophilia without inhibitors, with require surgeries or major orthopedic surgeries
2. Age: any age group

IV.3.3. Treatment (dose, conditions for reducing the dose, treatment period)

Products:

Hemophilia A: Plasma coagulation factor VIII; Recombined coagulation factor VIII

Hemophilia B: Plasma coagulation factor IX; Recombined coagulation factor IX

Hemophilia A:

Dose:

The calculation of the necessary dose of factor VII relies on the empiric observation:

1 UI of factor VIII/kg increase the plasma activity of factor VIII with 2 UI/dl.

The necessary dose is calculated by utilizing the following formula:

Necessary units = body weight (kg) x desired increase of factor VIII (%) x 0.5.

Hemorrhage severity	Plasma level of the necessary FVIII (% of normal of UI/dl)	Administration frequency (hours) / treatment duration (days)
Minor Including dental extractions	30 – 60	Every 24 hours (from 12 to 24 hours in the case of patients with the age under 6), at least one day, until obtaining a scar.
Major	80 – 100 (pre and post operatory)	Repeated injections are administered every 8-24 hours (from 6 to 24 hours, for patients with the age under 6), until a scar is obtained, afterwards the treatment is continued for a period of at least 7 days, in order to maintain a level of the activity of Factor VIII of 30-60% (UI/dl).

Table 6 – Plasma level of necessary FVIII depending on the surgery

The dose and frequency of administration must be adapted in accordance with the individual clinical response.

In certain circumstances (for example a low titer of anti-factor VIII antibodies) it may be necessary to administer higher doses than the ones calculated with the support of the formula.

Hemophilia B:

Dose:

The calculation of the necessary dose of factor IX relies on the empiric observation, in accordance to which 1 UI factor IX per kg increases the plasma activity of factor IX cu 0.9% of the normal activity.

The necessary dose is calculated by utilizing the following formula:

Necessary unit = body weight (kg) x desired increase of factor IX (%) (UI/dl) x 1.1

Hemorrhage severity	**Plasma level of the necessary FVIII (% of normal of UI/dl)**	**Administration frequency (hours) / treatment duration (days)**
Minor Including dental extractions	30 – 60	Every 24 hours, at least one day, until healing.
Major	80 – 100 (pre and post operatory)	The perfusion is repeated every 8-24 hours, until healing, afterwards therapy shall be administered for at least 7 additional days in order to maintain the F IX activity of 30%-60%.

Table 7. Plasma level of necessary FIX depending on the hemorrhagic event's severity

Administration: intravenously, slowly. The administration interval must be established by the hematology specialist/doctor.

IV.3.4. Treatment monitoring (Clinical, paraclinical parameters, periodicity)

- In the event of major surgeries, it is mandatory to have precise monitoring of the substation therapy by analyzing the plasma activity of factor VIII/IX.
- Careful monitoring, through clinical examination and laboratory tests, in order to determine the development of inhibitor antibodies.

Response type	Response definition
Excellent	Intra and post operatory blood losses are similar (10%) to those of the patient without hemophilia • without additional doses of FVIII or FIX • the need of blood transfusions is similar to that of the patient without hemophilia
Good	Intra and post operatory blood loss is slightly elevated as compared to the patient without hemophilia (between 10-25%), yet the difference is evaluated by the surgeon/anesthetist as being clinically insignificant • without additional doses of FVIII or FIX • the need of blood transfusions is similar to that of the patient without hemophilia
Satisfactory	Intra and post operatory blood losses are slightly elevated with 25-50% as compared to the patient without hemophilia and additional treatment is needed: • additional doses of FVIII or FIX • the need of blood transfusions is two times higher than that of the patient without hemophilia
Bad/No response	Intra and post operatory blood loss is substantially elevated (>50%) as compared to the patient without hemophilia and it is not explained by the presence of a medical/surgical emergency, other than hemophilia • hypotension or unexpected transfer of ATI due to bleeding Or • substantial increase of the need of transfusions > twice as big as the expected need

Table 8. Defining efficient hemostatic efficiency of surgeries

IV.3.5. Criteria for being excluded from treatment

· Hypersensitivity to the active substance or to mouse or hamster excipients or proteins, with the recommendation of changing the treatment biologic product
· Development of anti FVIII or antiFIX inhibitors

V. PROTOCOL FOR TREATING HEMOPHILIA WITH INHIBITORS

V.1. Disorder definition

- Administering concentrates of coagulation factors can be acknowledged by the body as foreign protein stimulating the production of antibodies (immunoglobulin IgG).
- Presence of inhibitor anti-FVIII or anti-FIX antibodies is considered the most severe complication associated to hemophilia treatment
- The presence of inhibitors is suspected in every patient that does not react to the treatment with coagulation factors
- The incidence of developing inhibitors is 20-30% in patients suffering from hemophilia A severe form and 5% in patients suffering from hemophilia B
- The inhibitors are different depending on the level of answer
  – High titer (high responder) ≥5 BU; usually anamnestic response to FVIII
  – Low titer (low responder) <5 BU; rare anamnestic response to FVIII
- The transitory inhibitors are those that disappear spontaneously

- V.2. Treatment Principles

- The management of bleeding episodes in patients with inhibitors must be done in

collaboration with a center experienced in the management of inhibitors.
- Patients with low titer inhibitors can be further treated with the substitution factor in a higher dose in order to neutralize inhibitors and control the hemorrhagic event.
- It is recommended to initiate immune tolerance induction (ITI) in patients with high titer inhibitors (> 5BU).
- Patients with inhibitors who have not responded or who are not eligible for the immune tolerance induction therapy should be administered the prophylactic treatment with bypass agents.

V.3. Prophylaxis of hemorrhagic accidents

V.3.1. Objectives: preventing hemorrhagic accidents, improving the joint chronic disease, improving the quality of life for patients that suffer from hemophilia and inhibitory antibodies.

V.3.2. Inclusion Criteria (age, sex, clinical and paraclinical parameters, etc.)

1. Patients with congenital hemophilia and anti-FVIII or anti-FIX inhibitory antibodies.

V.3.3.Treatment (doses, dose reduction conditions, treatment period)

Products:
- Activated prothrombin complex concentrate (APCC) coagulation-anti-inhibitors complex

Doses:
- for patients with high antibody titer inhibitors and with frequent bleeding, and in who the ITI is low or not taken into account:

70-100 U/kg body weight, once every other day.

This dose can be increased up to 100 U/kg body weight daily, if the patient continues to bleed, and the dose can be decreased gradually.
- for patients with high inhibitor antibodies titer and ITI: concomitant administration of factor VIII concentrates.

50-100 U/kg body weight, twice a day until the titer of inhibitory antibodies of factor VIII has been reduced to <2 B.U.

Administration: intravenous slowly. This should not exceed the injection/perfusion rate of 2 U/kg body weight per minute.

V.3.4. Treatment Monitoring (clinical and para-clinical parameters, periodicity)
- Do not exceed a single dose of 100 U/kg body weight and the daily dose of 200 U/kg. Patients who receive a single dose of 100 U/kg body weight should be monitored carefully, particularly in regard to the CID risk or for symptoms of acute coronary ischemia.

V.3.5. Treatment exclusion criteria
- Hypersensitivity to the active substance or to any of the excipients
- Disseminated intravascular coagulation
- Acute coronary ischemia, acute thrombosis and/or embolism

V.4. Curative treatment of hemorrhagic accidents

V.4.1. Objectives: stop the hemorrhagic events in patients that suffer from hemophilia and anti-FVIII or anti-FIX inhibitory antibodies.

V.4.2. Inclusion criteria (age, sex, clinical and para-clinical parameters, etc.)

1. Patients with hemophilia and anti-FVIII or anti-FIX inhibitory antibodies.

V.4.3. Treatment (doses, dose reduction conditions, treatment period)

Products:
- Activated prothrombin complex concentrate (APCC) coagulation-anti-inhibitors complex
- Recombined activated coagulation factor VII (rFVIIa)

Doses:
- Activated prothrombin complex concentrate (APCC)

Bleeding in the joints, muscles or soft tissues

➢ For mild or moderate hemorrhages a dose of 50-75 U/kg body weight every 12 hours

➢ For severe hemorrhages of the muscles and soft tissues, such as retroperitoneal bleeding, the recommended doses are of 100 U/kg body weight every 12 hours.

Mucosal bleeding

➢ 50 U/kg every 6 hours, and close monitoring of the patient (the visible bleeding site, repeated measurement of the hematocrit). If hemorrhage does not stop, the dose may be increased to 100 U/kg body weight, taking care not to exceed the daily dose of 200 U/kg body weight.

Other severe hemorrhages

➢ In the case of severe hemorrhages, such as bleeding of the central nervous system, a dose of 100 U/kg body weight, every 12 hours. In individual cases, it may be administered every 6 hours, until a clear clinical improvement is obtained.

Administration: slow intravenous perfusion. This should not exceed the rate of injection/perfusion of 2U/kg body weight per minute.

• **Recombinant activated coagulation factor VII (rFVIIa)**

Mild or moderate bleeding episodes

➢ Two to three injections of 90 µg/kg administered every three hours; if further treatment is required, an additional dose of 90 µg / kg may be administered.

Or

➢ A single injection of 270 µg/kg.

Serious bleeding episodes

➢ The recommended starting dose is of 90 µg/kg, repeated every two hours until clinical improvement is observed. If continued therapy is necessary, the dose interval can be increased to 3 hours for 1-2 days. Thereafter, the dose interval can be increased successively to 4, 6, 8 or 12 hours, for as long as the treatment is deemed necessary.

Administration: intravenous bolus injection for a 2-5 minute-period.

V.4.4.Treatment monitoring (clinical and para-clinical parameters, periodicity)

• The bleeding severity and the clinical response to treatment should guide the necessary doses
• Patients should be monitored with care, especially for CID risk or thrombotic accidents

V.4.5. Treatment exclusion criteria

• Hypersensitivity to the active substance or to any of the excipients
• Disseminated intravascular coagulation
• Acute coronary ischemia, acute thrombosis and/or embolism

V.5. Substitution treatment in the case of major surgeries and orthopedic interventions

V.5.1. Objectives: to ensure homeostasis during major surgeries and orthopedic interventions

V.5.2. Inclusion criteria (age, sex, clinical and para-clinical parameters, etc.)

1. Patients with hemophilia and anti-FVIII or anti-FIX inhibitory antibodies that require major surgeries or orthopedic interventions.

V.5.3 Treatment (doses, dose reduction conditions, treatment period)

Products:

• Activated prothrombin complex concentrate (APCC) coagulation anti-inhibitors complex
• Recombinant activated coagulation factor VII (rFVIIa)

Doses:

➢ **Activated prothrombin complex concentrate (APCC)**

• - 50 to 100 U/kg body weight can be administered every 6 hours, taking care not to exceed the maximum daily dose.

Administration: slow perfusion, intravenously.

This should not exceed the rate of injection/perfusion of 2U/kg body weight per minute.

• **Recombinant activated coagulation factor VII (rFVIIa)**

- Immediately after the intervention an initial dose of 90 μg/kg should be administered. The dose must be repeated every 2 hours and afterwards every 2-3 hours in the first 24-48 hours, depending on the type of intervention and the clinical condition of the patient.
- During major surgeries, the administration should be continued every 2-4 hours for 6-7 days. Afterwards, the interval between the doses can be increased to 6-8 hours, for another 2 weeks of treatment. The patients undergoing major surgeries can be treated for 2-3 weeks until healing.

Administration: intravenous bolus injection for a 2-5 minute-period.

V.5.4.Treatment monitoring (clinical and para-clinical parameters, periodicity)

- The bleeding severity and the clinical response to treatment should guide the necessary doses
- Patients should be monitored with care, especially for the CID risk or thrombotic accidents

V.5.5. Treatment exclusion criteria

- Hypersensitivity to the active substance or to any of the excipients
- Disseminated intravascular coagulation
- Acute coronary ischemia, acute thrombosis and/or embolism

VI. PERIODIC EVALUATION PROTOCOL FOR PATIENTS SUFFERING FROM HEMOPHILIA

Joint Status

- clinical joint score
- radiological, ultrasound, MRI joint score
- orthopedic consultation

Neuro-psychic status

- neuro-psychiatric examination
- further investigations based on the patient's condition

Dental, ophthalmological, ENT status

Biological status

- coagulation, residual activity of the deficient factor
- titer inhibitors
- hepatic explorations (proteinemia, serum protein electrophoresis, transaminases, lactic dehydrogenase, alkaline phosphatase, bilirubin)
- serological exploration (HBs Ag, anti-HBs Ac, anti-HCV Ac, anti-HIV 1 and 2 Ac, anti-HTLV I and II Ac, anti-CMV IgG Ac and IgM)
- Others: blood count, urinalysis

- Other measures
- genetic advice
- psychological support and socio-professional guidance

Complications Tracking Protocol (annually)

1. Treatment Complications

1.1. Determining inhibitors (anti-factor VIII/IX antibodies infusion)

- the Bethesda metric coagulation method or the Nijmegen modified test
- in children, inhibitor dosing must be administered after the first 5 days of exposure, at 10 -15 days, after 25 days of exposure and 50 days of exposure and afterwards, twice per year; subsequently the inhibitors should be determined at least once per year, before surgery or in case of suboptimal response; inhibitors control is also required after massive substitutions (over 5 days), in those with favorable mutations for inhibitors or post-surgically.
- basal titer and anamnesis titer determination after the administration of the VIII/IX factor (<5 BU inhibitors in low titre ;> 5 BU inhibitors in high titer)

1.2. Determining infectious complications

- hepatic explorations (proteinemia, serum protein electrophoresis, transaminases, lactic dehydrogenase, alkaline phosphatase, imunocantitation)
- serological exploration (HBs Ag, anti-HBs Ac, anti-HCV Ac, anti-HIV 1 and 2 Ac, anti-HTLV I and II Ac, anti-CMV IgG Ac and IgM) twice a

year
- viral level in case of infection (HBV, HCV, HIV)

2. Disease Complications

2.1. Chronic Arthropathy
- clinical joint score - Gilbert and HJHS score (hemophilia joint health score)
- Petterson radiological joint score
- ± ultrasound score , MRI score, ± osteodensitometry score
- orthopedic consultation/physiotherapist
-

2.2. Neuro-sensorial and psychical sequelae
- neuro-psychiatric examination
- further investigations based on the patient's condition (CT, MR, EMG, nerve conduction velocity)

2.3. Dental problems
- dental examination
-

2.4. Others
- ophthalmological examination , ENT, blood count

2.5. Life quality assessment
- HaemoQoL
- Kids'Life Assessment tool
- Hemophilia activities list (HAL)
- Functional independence score in hemophilia (FISH)
- Pediatric hemophilia Activities List (Ped HAL)

VON WILLEBRAND DISEASE

I. Definition of the disease:

The von Willebrand disease is the most common congenital coagulopathy transmitted dominantly autosomally, that is affecting both sexes. The disease is characterized by qualitative or quantitative deficiency of a glycoprotein (called von Willebrand factor or FvW) in the blood, which is needed for thrombocytes adhesion to the vascular wall. Because this protein has also the role of carrier protein and the stabilizing role for the VIII coagulation factor, the VIII factor activity is sometimes decreased in proportion to the reduction

Type	Transmission	Prervalence	Bleeding phenotype
Type 1	Dominant autosomal	Up to 1%	Mild - moderate bleeding
Type 2A	Dominant (or recessive) autosomal	Not very frequent	Varied phenotype - frequent moderate bleeding
Type 2B	Dominant autosomal	Not very frequent	Varied phenotype - frequent moderate bleeding
Type 2M	Dominant (or recessive) autosomal	Not very frequent	Varied phenotype - frequent moderate bleeding
Type 2N	Recessive autosomal	Not very frequent	Varied phenotype - frequent moderate bleeding
Type 3 (severe)	Recessive autosomal	Rare (1: 250,000 to 1: 1,000,000)	Severe bleeding

Table 9. The prevalence and bleeding phenotype in patients suffering froms von Willebrand disease

Test	Type 1	Type 2				Tip 3
		A	B	M	N	
Bleeding duration	prolonged	prolonged	prolonged	prolonged	(N)	prolonged
vWF:Ag	↓	↓	(↓)	↓	↓	ND
vWF:RCoF	↓	↓	↓	↓↓	↓	ND
vWF:CBA	↓	↓↓	↓	↓↓	↓	ND
RIPA	(↓)	↓	()	↓	↓	↓↓
FVIII	(↓)	↓	(↓)	↓	↓↓	↓↓
vWF multimers	N	↓(high GM	↓(high GM) (low GM)	N	N	absent

Table 10. Specific biological features characteristic for the various subtypes of the von Willebrand disease

Legend
N-normal; ↓- reduced; ↓↓ - very reduced, (↓) - normal or reduced; ( ) - normal or increased; ND- not detectable

level of FvW.

II. Treatment Principles for the von Willebrand disease

- The disease treatment depends on the disease subtype and on the severity of the hemorrhagic manifestations.
- The long-term prophylaxis is rarely necessary, but it should be considered in cases of recurrent haem arthrosis or excessive muscle skeletal bleeding that cannot be adequately controlled with other treatments.
- The treatment of the von Willebrand disease consists in the administration of desmopressin (DDAVP) and FVIII concentrates enriched in VWF.

In deciding the therapeutic conduct for patients with von Willebrand disease the following factors should be considered:

- The type of bleeding manifestation
- The serum levels of FvW and FVIII and the von Willebrand disease subtype
- The patient's previous history of bleeding episodes and the response to treatment
- The previous response of FVIII and FVW to treatment with desmopressin (if performed)
- The presence of inhibitors
- The potential risks of treatment

Type of the von Willebrand disease	Elective treatment	Alternative or additional treatment
Type 1	Desmopressin	Antifibrinolytics Estrogen
Type: 2A 2B 2M 2N	 FVIII concentrate with vWF FVIII concentrate with vWF FVIII concentrate with vWF Desmopressin	
Type 3	FVIII concentrate with vWF	Desmopressin platelet concentrate

Table 11 - Treatment of various types and subtypes of the von Willebrand disease

Bleeding type	Dose (IU/Kg)	Number of administrations	Administration intervals	Objective/Duration of administration
Dental extraction	20	1	-	FVIII> 30 UI/dl for a period of at least 6 hours
Posttraumatic bleeding	20	1	-	
Spontaneous bleeding	45 ±12	Until bleeding resolution	24 hours	5±4 days
Major Surgical Interventions	50	1 administration/ day or 1 administration every 2 days	24-48 hours	FVIII>50 UI/dl until complete healing
Minor Surgical Interventions	30	1 administration/ day or 1 administration every 2 days	24-48 hours	FVIII> 30 UI/dl until complete healing

Table 12. dosage of FVIII concentrate enriched with vWF in patients with von Willebrand disease, unresponsive to desmopressin, depending on the type of bleeding

Recommendations regarding the minor bleeding treatment and the prophylaxis in the case of minor surgery interventions

- Minor bleeding should be treated with intravenous or nasal DDAPV
- If the response to DDAPV is inadequate, concentrated vWF should be administered with initial vWF units dosage: RCo and FVIII secondary units
- For minor surgery, prophylaxis should provide a level of vWF activity : RCo and FVIII> 30 IU/dl and preferably> 50 IU/dl for 1-5 days

Recommendations regarding the treatment of major hemorrhages and the prophylaxis in the case of major surgery

- In the case of severe hemorrhages (e.g. intracranial, retroperitoneal) or in the case of prophylaxis for major surgery interventions, the initial target of the vWF activity level: RCo and FVIII must be>100 IU/dl and the level of> 50 IU/dl should be maintained for at least 7 - 10 days
- Patients receiving concentrates with vWF

should be carefully evaluated in what concerns the thrombotic risk and measures preventing the occurrence of thrombosis should be initiated
- In order to reduce the perioperative risk of developing thrombosis, the level of vWF: RCo must not exceed 200 IU/dl and the FVIII activity must not exceed 250 IU/dl.

The therapeutic approach in the case of women with the von Willebrand disease

- For teenagers and adult women who do not want children, hormonal contraceptives are the first line of treatment for menorrhagia
- During childbirth, the serum levels of vWF: RCo and FVIII must be at least 50 IU/dl before birth giving and this level should be maintained for at least 3-5 days, with the subsequent supervision to prevent post-partum bleeding.