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1 Bleeding disorders

This guideline covers the investigation, diagnosis and treatment/management of patients with possible and known bleeding disorders.

1.1 Features of a bleeding disorder

Bleeding disorders may be either acquired or inherited. If a patient is referred for investigation of a possible bleeding disorder the following features may be present:

- Spontaneous bruising
- Excessive bruising with minor trauma
- Recurrent epistaxis
- Menorrhagia with no hormonal/local uterine cause
- Protracted bleeding after dental extractions
- Protracted bleeding after operations
- Protracted post partum bleeding
- Positive family history of a bleeding disorder especially in first degree relatives
- Spontaneous joint/muscle bleeds
- Intracranial haemorrhage

It is important to take a detailed history, including family history and medication history including NSAIDs, Aspirin, alcohol and antidepressants. A bleeding score may be completed. Examine for evidence of bruises, skin changes, signs of liver disease, hypermobile joints and skin laxity (collagen disorders). Based on the history and examination proceed to investigation (see flow charts for summary).

1.2 First line diagnostic investigations

- FBC + platelet count, baseline coagulation screen including Fibrinogen
- Factor VIII and von Willebrands factor (VWF) levels, PFA 100
- Factor XI, IX (male), XIII
- U+Es, LFTS
- Blood group

Note: patient factor assays should be performed with a minimum of 3 dilution points.

1.2.1 Clotting screens

These are used as the initial investigation in the investigation of new patients and to guide further investigations. Mild deficiencies may not prolong PT or APTT.

1.2.1.1 *Prothrombin Time (PT)*

- Assesses the extrinsic plus common pathway of the coagulation cascade
- Prolonged by deficiencies of factors VII, X, V, II, Fibrinogen
- Also prolonged in cases of Vitamin K deficiency, liver disease and Warfarin therapy

1.2.1.2 *Activated Partial Thromboplastin Time (APTT)*

- Assesses the intrinsic and common pathway of the coagulation cascade
- Prolonged by deficiencies of factors XII, XI, IX, VIII, X, V, II and Fibrinogen
- Also prolonged as a consequence of unfractionated heparin (especially given IV), occasionally therapeutic dose low molecular weight heparin and lupus inhibitors.

1.2.1.3 *Thrombin Time (TT)*

- Assesses the conversion of soluble fibrinogen to insoluble fibrin.
- Prolonged by quantitative and qualitative problems with fibrinogen, hypofibrinogenaemia and dysfibrinogenaemia respectively, liver disease and unfractionated heparin therapy.

1.2.1.4 *Fibrinogen (Clauss method)*

- Provides a quantitative assay of Fibrinogen. More sensitive to low levels of fibrinogen than above screening test, not affected by heparin.

The normal ranges given on laboratory reporting systems are for adults. For paediatric specific ranges discuss with the laboratory or haemophilia consultant. Normal ranges may vary across the network as they are reagent/analyser dependent.

1.3 Further investigations

Ideally these will be performed as part of first line investigations

1.3.1 Investigation if isolated prolonged or borderline aptt assays in order

- Factor VIII + VWF
- Factor IX / XI / XII
- Lupus inhibitor screen if factor deficiency not identified or non-parallelism (or APTT does not correct after the addition of 50% normal plasma)
- Inhibitor assay if acquired factor deficiency suspected
- Consider combined deficiency of FVIII/FV

1.3.2 Investigation if isolated prolonged pt

- Factor VII

1.3.3 Investigation if prolonged pt + aPTT but normal fibrinogen + thrombin time

- Factor II / V and X
(Some deficiencies can be more sensitive to detection with APTT)

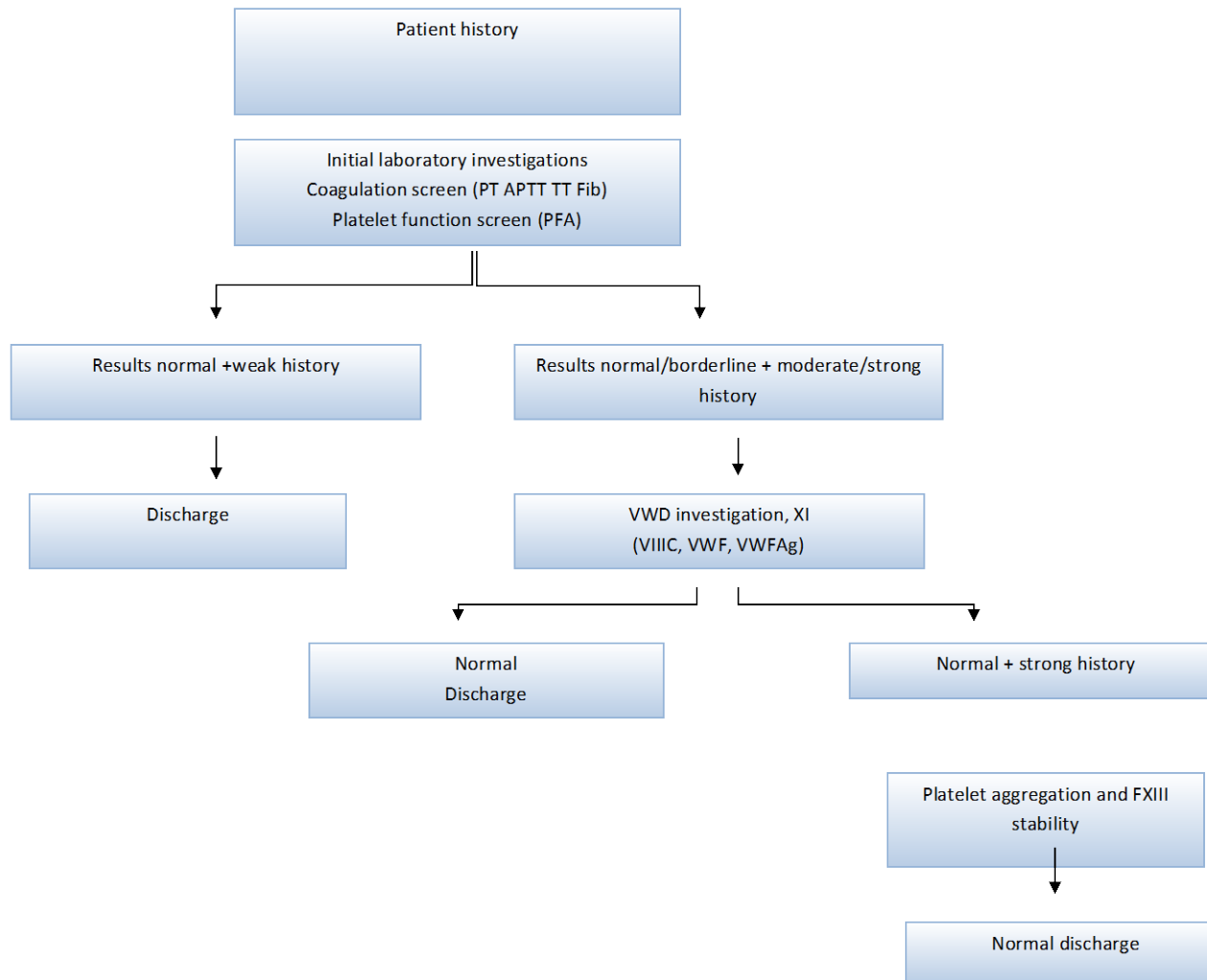
1.3.4 Investigation if normal platelet count / coagulation and von Willebrands screen +/- prolonged PFA

- Platelet aggregation
- FXIII activity +/- tests for hyperfibrinolysis

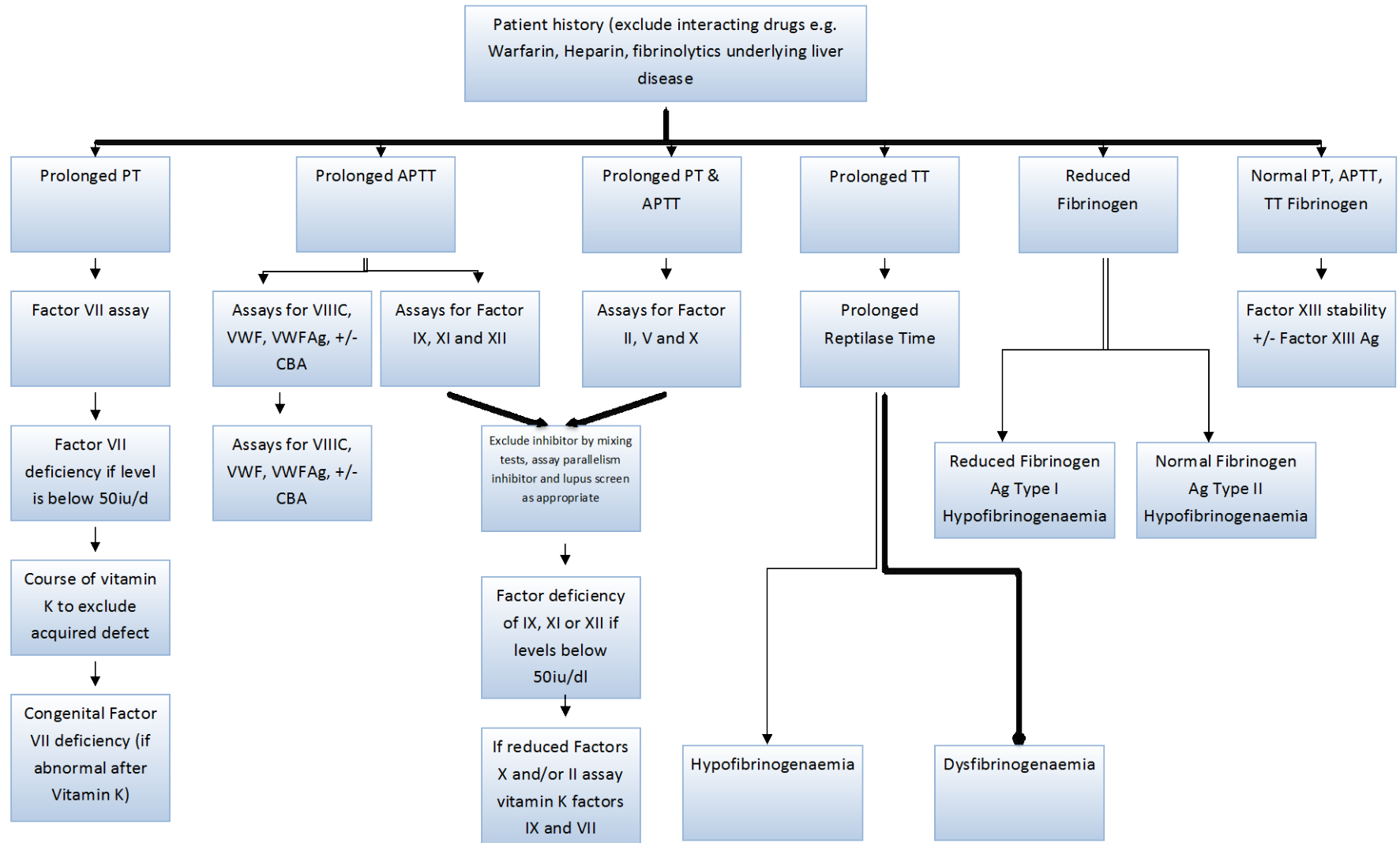
1.3.5 Additional tests as required

- FVIII:VWF binding assay to clarify between 2N VWD and mild Haemophilia A
- Collagen binding assay, low dose Ristocetin induced platelet aggregation (RIPA) and VWF multimers to classify Type 2 VWD
- Fibrinogen Antigen to clarify dysfibrinogenaemia
- Platelet nucleotides to identify platelet storage pool disorder or release/ADP receptor defect

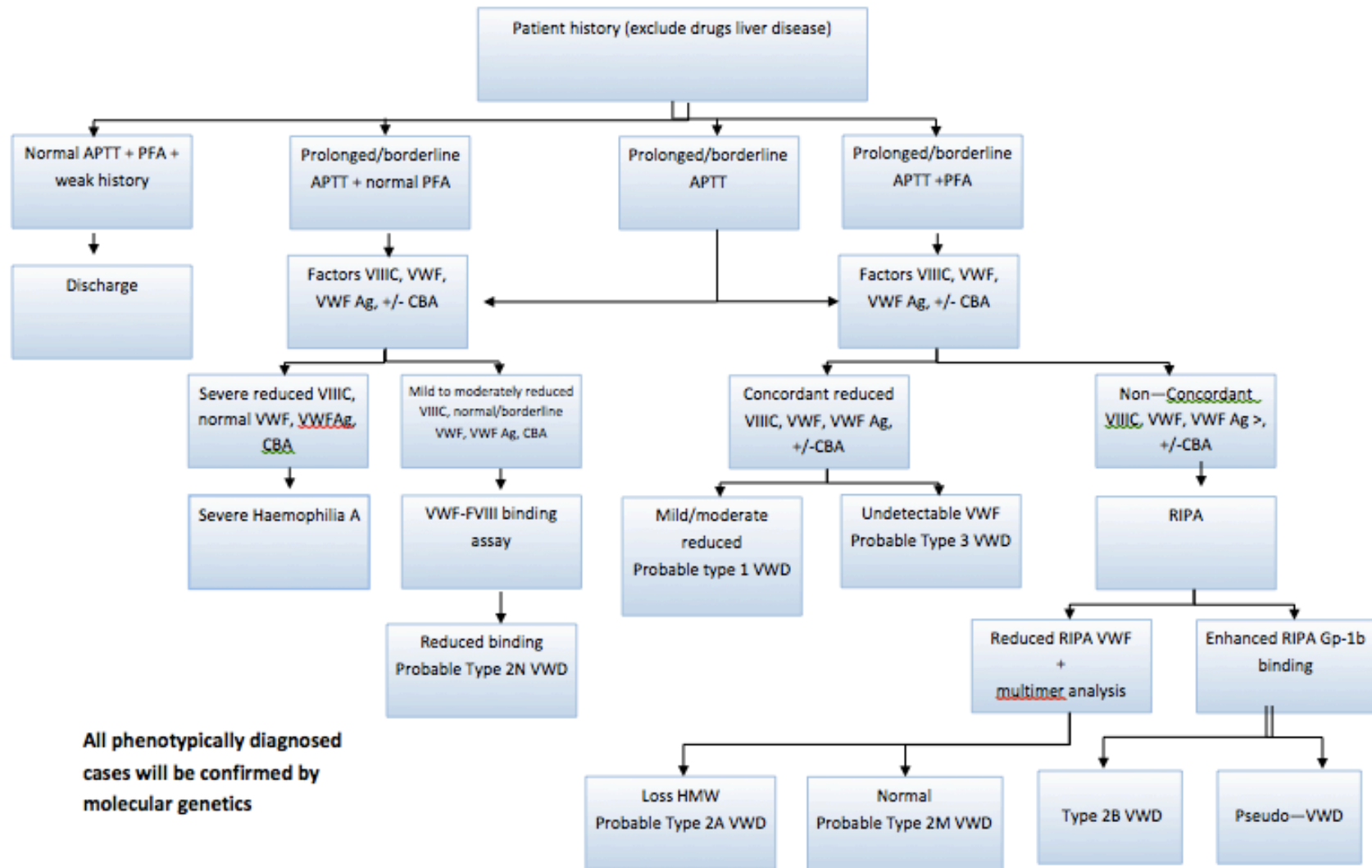
Investigation of suspected bleeding disorders (no abnormality detected)



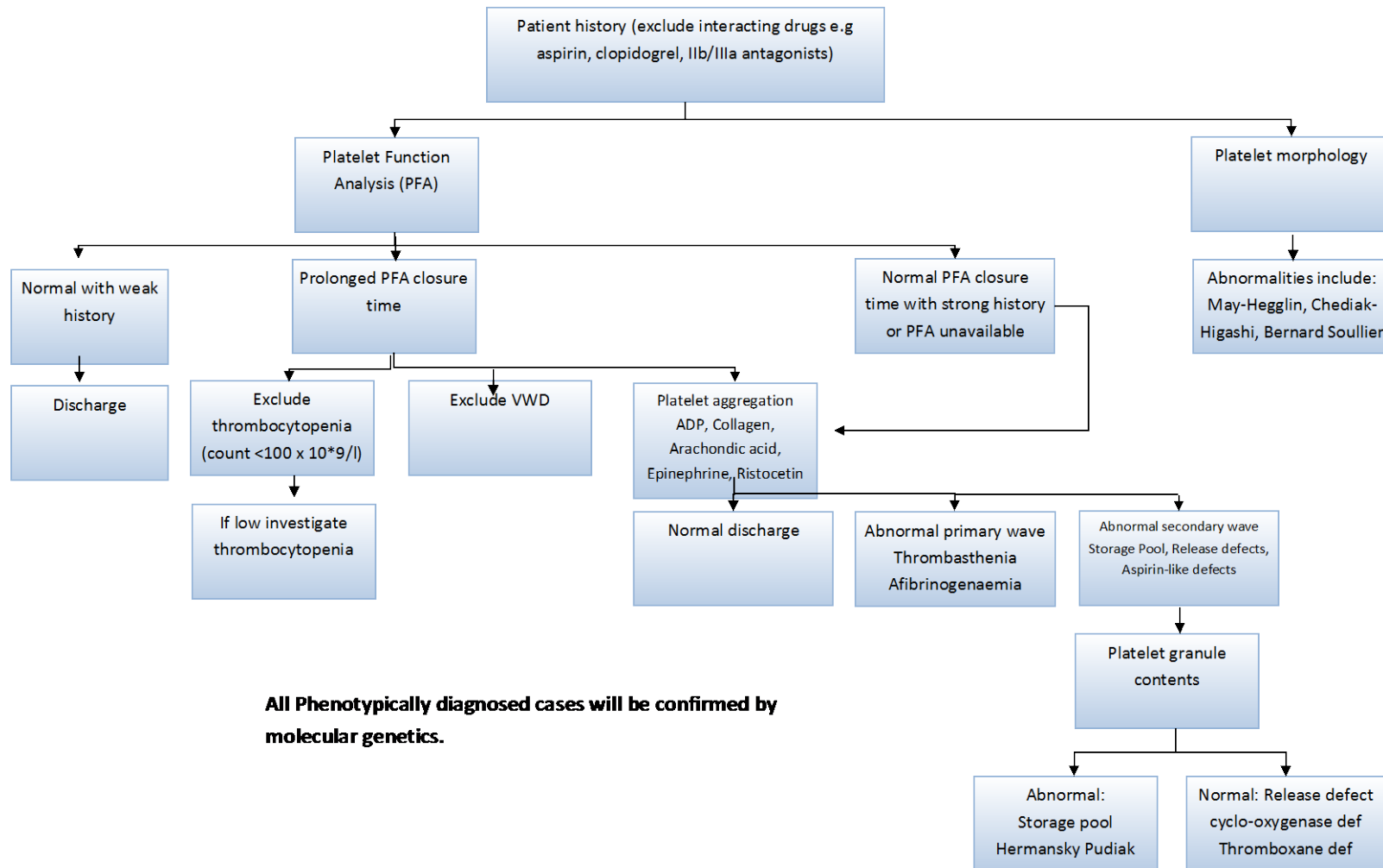
Investigation of suspected bleeding disorders (abnormality detected)



Investigation of suspected bleeding disorders (Haemophilia A and von Willebrand Disease)



Investigation of suspected bleeding disorders (potential platelet abnormality)



2 Haemophilia

2.1 Background

Haemophilia is a deficiency of either FVIII (A) or FIX (B). It is classified as severe, moderate or mild depending on factor levels. Severe haemophilia (< 1 iu/dl) is associated with spontaneous muscle and joint bleeds, moderate haemophilia (1 – 5iu/dl) is associated with muscle and joint bleeds after minor trauma and mild haemophilia (> 5 < 50 iu/dl) where musculoskeletal bleeds are very rare except after major trauma.

2.2 Haemophilia A

The Factor VIII gene is 186kD in size and found on the long arm of the X chromosome. A variety of point mutations and gene deletions can be found in people with haemophilia (PWH) but in those with the severe phenotype inversion of intron 22 occurs in 50%. 30% of cases present as spontaneous mutations, with no previous family history. The incidence of haemophilia A is 1 in 5000.

2.3 Haemophilia B

The Factor IX gene is 34kD in size and found on the long arm of the X chromosome. A variety of point mutations are commoner than gene deletions in haemophilia B. Again 30% of cases present as spontaneous mutations. The Leyden phenotype – severe haemophilia as a child then mild after puberty relates to defects in the androgen promoter region of the gene. The incidence is 1 in 30000.

2.4 Inheritance of haemophilia

It is an X-linked recessive disorder, if a couple have a child where the man has haemophilia and the woman is not a carrier then 100% of daughters will be obligate carriers and all sons will be unaffected because they inherit their X chromosome from their mother. If a carrier female has a child with an unaffected male then 50% of their daughters will be carriers and 50% of sons will have haemophilia.

Female carriers will usually have normal factor levels however some may have lower levels. It is seldom less than 0.20 IU/dl, which should suffice to protect them against significant bleeding problems in day to day life but would require treatment for invasive procedures or trauma. Therefore all carriers should have baseline line factor levels checked. Females with very low levels can occur with random inactivation of the X chromosome with normal factor gene (lyonization), Turners syndrome (XO) and partnership/union between a man with haemophilia and a carrier female.

2.5 Complications

2.5.1 Inhibitors in haemophilia

Factor VIII inhibitors occur in approximately 30% of severe haemophiliacs, usually within the first 15 to 20 exposure days to Factor VIII concentrate. Most are transient. Inhibitors can be persistent in up to 15% of patients. Factor VIII inhibitors should be considered if bleeds do not resolve after appropriate Factor VIII concentrate. They are associated with a prolonged APTT that does not correct with a 50:50 mixture with normal plasma after a 2 hour incubation (time dependant). The inhibitor can be confirmed and quantified by the Bethesda assay. If the inhibitor is < 5BU patients may respond to very high doses of Factor VIII 100 – 200iu/kg/dose but if > 5BU alternatives such as FEIBA or NovoSeven are needed. Inhibitors can be cleared in 70 – 85% by using immune tolerance therapy with Factor VIII to desensitize the immune system. Further details can be seen in section 4.

Factor IX inhibitors are uncommon occurring in approximately 1-3 % of people with severe haemophilia B. Factor IX inhibitors should be considered when bleeds do not resolve with appropriate Factor IX concentrate therapy. They may also be associated with malaise and shortness of breath after injection of FIX. They are associated with a prolonged APTT that does not correct with a 50:50 mixture with normal plasma after a 5 minute incubation i.e. not time dependant. The inhibitor can be quantified by the Bethesda assay.

Children with major factor IX deletions (or other genetic abnormalities known to be associated with a risk of inhibitor development) are at particular risk of developing an inhibitor and these can trigger severe allergic reactions. These patients should receive their first 20 - 25 exposures to factor IX in a monitored hospital setting to monitor for signs of hypersensitivity/anaphylaxis and to ensure that adrenaline and resuscitation facilities are on hand. Recombinant factor VIIa is the treatment of choice for bleeding in patients with high-responding factor IX inhibitors or reactions as FEIBA contains factor IX that could trigger further reactions.

Inhibitors in haemophilia B can sometimes be cleared by using immune tolerance therapy but the responses tend to be poor when compared to immune tolerance in haemophilia A. Anaphylactic reactions are more common in those with inhibitors. Further details in section 4.

2.5.2 Arthropathy

This is a complication as a result of repeated bleeds into joints.

2.5.3 Renal disorders

Nephrotic disorders can be seen in those with inhibitors undergoing ITT in haemophilia B and may relate to the amount of Factor IX protein that the patients are exposed to during ITT. Nephritis tends to be steroid resistant but may respond to withdrawing Factor IX treatment

2.5.4 Other complications

Other complications of haemophilia can relate to morbidity/mortality from bleeds, depending on the site and severity of the bleed. Complications of treatment include allergic reactions, anaphylaxis, Factor VIII/IX inhibitors, HBV, HCV, HIV, from contaminated blood products and possible transmission of new variant CJD.

2.6 Treatment

In haemophilia the treatment may be on demand for the treatment of acute bleeds or procedures, or for those with severe (and some moderate patients) prophylaxis. Some people affected with mild haemophilia A may respond to DDAVP with a 2 – 4 fold increase in Factor VIII levels.

Severe, moderate and mild haemophilia B patients need treatment with recombinant Factor IX concentrate or plasma derived factor in selected patients

Products used in haemophilia A:

Recombinant

Standard half life Helixate NexGen, Kogenate FS, Refacto AF, Advate, Nuwiq, NovoEight

Extended half life Elocta

Plasma derived

Optivate, Fanhdi

(The products may vary locally as they will be dependent on the national procurement of factor concentrate contract).

Products used in haemophilia B:

Recombinant

Standard half life Benefix, Rixubis

Extended half life Alprolix, Idelvion

Plasma derived

Mononine

2.6.1 Treatment of acute bleeds

2.6.1.1 *Mild haemophilia*

Minor soft tissue bleeds and nosebleeds can be managed by the use of subcutaneous DDAVP 0.3 mcg/kg (see appendix 1 DDAVP) +/- oral Tranexamic acid 15 – 25mg /kg 6 to 8 hourly.

More severe bleeds or when covering surgical/ invasive procedures may require factor concentrate – calculations as for moderate/severe.

2.6.1.2 *Moderate/severe haemophilia*

The dosage suggestion is only a guide; the management of bleeds should be discussed with the on call Haemophilia Consultant.

2.6.2 Summary of treatment in moderate/severe haemophilia without inhibitors

$$\text{Factor dose required} = \frac{(\text{Factor level required} - \text{baseline factor}) \times \text{body weight in kg}}{\text{k value}}$$

K values

FVIII k=2

FIX k= 0.8 (adults)

0.7 (children)

1.0 (plasma derived)

Bleeding site	Optimal factor Level (iu/dl)
Muscle bleed	30-50
Joint bleed	30-50
Epistaxis/mouth bleed	30-50
GI bleed	>50
Haematuria*	30-50
Retropharyngeal bleed/tongue	80-100
Intracranial	80-100
Trauma/surgery	60-100
Retroperitoneal	60-100

*Haematuria - first line management is increased oral fluid intake and conservative management. Only treat with factor concentrate if haematuria does not settle with conservative first line management. Tranexamic acid is contraindicated due to risk of clot formation within the bladder leading to acute urinary retention.

- Treatment is continued until the bleed resolves. A period of immobilization and non-weight bearing is also recommended for bleeds affecting major muscles and joints of the upper and lower limbs. In the case of iliopsoas bleeds treatment is required for a minimum of 7 days.
- Adjust ongoing dosing and frequency dependant on recovery and half-life study results.
- Standard FVIII has a half life of approximately 8-12 hours so should be given every 12 hours. Standard FIX has a half life of approximately 18 hours so often treatment can be given every 24 hours but should be guided by levels

Example 1: Male haemophilia A patient weighs 80kgs with a base-line of <1iu/dl requiring the management of a knee bleed and Factor VIII of 50 iu/dl

$$\frac{\text{Factor VIII increment (50) x Wt. in kg (80)}}{2} = 2000 \text{ units of recombinant FVIII}$$

Example 2: Male haemophilia B patient weighs 80kgs with a baseline of <1iu/dl with a knee bleed requiring a Factor IX of 50 iu/dl

$$= \frac{\text{Factor IX increment (50) x Wt. in kg (80)}}{0.8} = 5000 \text{ of recombinant FIX}$$

2.7 Recognising & treating specific bleeds

The following information is to assist staff in recognising bleeding episodes and to give advice regarding treatment. It may also be used in education of parents and carers.

Prompt treatment of joint and muscle bleeds helps to limit long-term damage and prevent joint deformities and muscle wasting.

2.7.1 Joint bleed

The signs and symptoms of a joint bleed are as follows:

- 'prickling/bubbling' sensation within the joint
- pain when using the limb
- tense, hot joint
- swelling
- diminished range of movement
- inability to weight-bear (if the bleed is in lower limb joint)
- Favouring one limb over the other
- Flexion of joint

Treatment

- Treat with adequate clotting factor replacement
- Pain relief (not NSAID)
- Follow this regime:
 - Protection
 - Rest
 - Ice - 10 mins on, minimum of 10 minutes off several times a day
 - Compression
 - Elevation

Avoid joint aspiration unless septic arthritis diagnosis likely. If aspiration is deemed essential always discuss with the haemophilia consultant and treat with Factor VIII concentrate before undertaking this, at a dose of at least 25iu/kg.

Once the bleeding has stopped the patient should gradually recommence weight bearing as instructed if the bleed was in a lower limb joint and start active exercise to improve joint range and muscle strength. Physiotherapy referral may be required to help return the joint to its pre-bleed status.

2.7.2 Muscle Bleeds

Untreated or inappropriately treated muscle bleeds can cause nerve damage, loss of function and severe muscle shortening

The signs and symptoms of a muscle bleed are as follows:

- Pain on movement progressing to pain on rest
- Tightness and swelling and sometimes bruising
- Restriction of muscle activity and immobility of associated limb
- Increased temperature of muscle(s)

Treatment

- Treat with appropriate clotting factor for 2-4 days
- Pain relief (not NSAID)
- Follow this regime:
 - Protection
 - Rest
 - Ice - 10 mins on, minimum of 10 minutes off
 - Compression
 - Elevation

Once the bleeding has stopped the patient should gradually recommence weight bearing as instructed if the bleed was in a lower limb muscle, and start active exercise to improve associated joint range, muscle strength and muscle length. Physiotherapy referral may be required to help return the muscle to its pre-bleed status.

2.7.3 Bleeds of the Mouth, Tongue and Nose

The signs and symptoms of mouth, tongue or nose bleeds:

- Prolonged bleeding from the mouth, tongue or nose
- Difficulty in breathing or swallowing
- Swallowed blood can cause nausea and vomiting
- Examine areas to identify where the bleeding is occurring

Treatment

If minor bleed apply ice to the affected area or give an ice-lolly

If bleeding persists treat with appropriate clotting factor

Note: *Bleeding from an injury to the tongue can cause swelling. Concerns relating to swallowing or breathing require immediate medical attention.*

2.7.4 Head injury in children or adults

The signs and symptoms of bleeds following head injury.

- Bruise to head
- Headache
- Irritability and dislike of bright light
- Nausea and vomiting
- Drowsiness, dizzy or confused
- Disturbance of vision or hearing
- Pupils are dilated

Treatment

- Treat with appropriate clotting factor immediately if possibility of head injury to increase FVIII/IX levels up to 100iu/dl
- Immediately contact Haemophilia on call consultant
- Urgent CT head scan (if symptoms present)
- Neurological observations for at least 24 hours

Criteria for admission

- History of significant injury e.g. fall on to hard surface
- History of severe headaches, vomiting, drowsiness after head injury
- External signs of injury – swelling / bruising of the head
- Focal neurological deficit
- Seizures
- Loss of consciousness

Note: *Symptoms of a bleed may not occur for several days after the injury*

2.7.5 Bruising

The signs and symptoms of bruising

- Discoloured area – check whether the bruise is movable (involving the sub cutaneous tissue) or fixed (involving the muscle)
- Note whether bruising is associated with pain, swelling and loss of movement
- Note whether bruise occurs around head or neck, groin or other vital organ, e.g. kidney

Treatment

- When bruise is a small area (under 2"/5cm) treatment unnecessary, observe increase in size
- Treat with ice packs to reduce swelling and discolouration

- If bruise is spreading, fixed, causing pain or limits movement of associated limb – treat with appropriate clotting factor
- When bruising of face, neck, head, throat or area of any vital organ or junction (e.g. groin, under arm, calf or forearm) treat and inform Haemophilia Centre or local hospital immediately
- Altered sensation or numbness of the affected limb requires immediate medical attention

2.8 Management of major surgery in severe haemophilia A or B

- Check baseline factor VIII/IX and inhibitor screen about 1 week pre – op. Consider bleeding history, recovery and half life studies. If no inhibitor plan for surgery.
- One hour pre – op administer bolus to increase FVIII/IX to ≥ 100 iu/dl.
- Check Factor VIII level 10 - 20 minutes post bolus.
- Go ahead with surgery.
- Continue FVIII/IX concentrate treatment 8 to 12 hourly dependent on results of Factor VIII/IX level. The intervals may vary with the extended half life products and will depend on individual PK results
- Measure FVIII/IX level the morning after surgery and aim for trough FVIII of ≥ 60 iu/dl. Aim for post-treatment FVIII/IX levels between 100 – 150 iu/dl.
- Maintenance of these levels may be needed for at least the first 5 days post-op but will be dependent on the operation itself.
- After this time the dosing, frequency and monitoring of FVIII/IX concentrate treatment depends on the operation itself. Aim to maintain trough FVIII levels ≥ 40 iu/dl until wound healing occurs and sutures are removed.
- After a knee replacement once or twice daily FVIII concentrate is likely to be needed for 10 to 14 days post-op minimum. After day 14 most severe Haemophilia A patients would restart their usual prophylactic therapy.
- Further doses of FVIII/IX are also likely to be required to cover vigorous physiotherapy.
- Continuous infusion of FVIII/FIX may be considered in certain circumstances.

2.8.1 Continuous infusion of factor VIII/IX concentrate

- Check FVIII/IX and inhibitor screen 1 week pre-op. If no inhibitor proceed with surgery
- 1 hour pre-op give bolus of FVIII/IX and aim to increase factor level to 100iu/dl
- Check factor level 10-20 minutes post bolus. Give additional factor concentrate if <100 iu/dl
- Constitute infusion – will be product dependant in 50 ml syringe

- Dose calculation
 - $(\text{iu/kg} \times \text{ml per vial}) / \text{iu/vial} = \text{ml/hour}$
 - e.g. 70 kg man, 500 iu vial 2.5ml per vial
 - $(4 \times 70) \times 2.5 / 500 = 1.4 \text{ml/hour}$

- FVIII
 - Initially infuse at 4iu/kg/hour
 - Infuse 0.9% saline via 3 way tap at 20ml/hr to reduce risk of local thrombophelbitis

- FIX
 - Initially infuse at 6 iu/kg/hour of Factor IX concentrate.
 - Infuse 0.9% saline via 3 way tap at 20mls / hour to reduce risk of local thrombophlebitis.
 - Change syringe after 12 hours (or sooner depending on patient weight and factor levels).

- Measure Factor FVIII/ IX level at end of surgery (and during if long procedure)
- Measure Factor FVIII/IX level the morning after surgery and aim for Factor FVIII/IX level of 100 iu/dl. If <100 iu/dl increase infusion rate after discussion with haemophilia centre staff and repeat further Factor FVIII/IX level after 4 - 6 hours.
- Continue Factor FVIII/IX concentrate infusion for 48 hours and maintain Factor IX level @ 100iu/dl.
- Switching to bolus will be dependent on type of surgery, any bleeding and factor levels
 - Factor FVIII twice daily
 - Factor IX once daily (half-life ~ 18 hours).
 - Aim for trough Factor FVIII/IX of $\geq 60 \text{iu/dl}$ and 20 minutes post Factor FVIII/IX level $\geq 100 \text{iu/dl}$.
- May be possible to decrease doses after day 5 and aim for trough FVIII/FIX $\geq 40 \text{iu/dl}$ until wound healing and suture removal occurs.
- If still no problems with bleeding at this stage resume normal prophylaxis.

2.9 Prophylaxis

Prophylaxis entails the administration of clotting factor concentrates at specified intervals to prevent spontaneous bleeding and bleeds secondary to trauma. Many young adults with severe haemophilia will have been on prophylaxis since childhood with the benefits of reducing joint damage and chronic arthropathy. Continuation of prophylaxis in adulthood should assist with joint preservation, improved quality of life and enable career opportunities and employment without the debilitating episodes of spontaneous bleeds.

Boys with severe haemophilia (<1 IU/dl factor VIII or IX) should be considered for prophylaxis. A decision on exactly when to start treatment will usually be taken in the paediatric clinic and discussed in the MDT, but is likely to be after the child has suffered a least one spontaneous joint bleed. If this can be delayed until the child is 18 months old or so this can usually be achieved without the use of a venous access device.

Current UKHCDO guidelines should be followed regarding prophylaxis.

Patients with moderate haemophilia A or B (i.e. Factor VIII levels 1-5 iu/dl) who have spontaneous haemarthroses, or bleeds secondary to minimal trauma should be treated prophylactically following the above protocols. Response would be measured clinically.

2.9.1 Prophylaxis dosing

Prophylaxis converts a severe haemophiliac to a moderate phenotype. This is affected by giving infusions of concentrate aiming to keep the trough Factor VIII or Factor IX level > 1iu/dl. The following are the recommended doses.

- Prophylaxis for both Haemophilia A and B is 25 - 40iu/kg/dose
- Haemophilia A:
 1. Standard Factor VIII should be administered alternate days (48 hours), unless guided by PK in which alternative intervals may be considered
 2. Extended half life FVIII should be administered as per UKHCDO guidelines on EHL products
- Haemophilia B:
 1. Standard Factor IX should be administered every 3rd day, unless guided by PK in which alternative intervals may be considered
 2. Extended half life factor IX should be administered as per UKHCDO guidelines on EHL products
- Prophylaxis should be given in the morning so that levels are lowest when one is sleeping/ waking up prior to the next dose.
- The whole vial should be given to avoid wastage.
- Inhibitor screening should be performed every 3 doses until 20 exposures days (ED's), then every 3-6 months up to 150 ED's. For Haemophilia A inhibitor testing should continue 1-2 times a year indefinitely.

- For haemophilia B, testing after 150 ED's is only required if clinically indicated.

2.9.1.1 Variations in the Standard Dose

- Children who have had successful treatment for an inhibitor and have reduced to prophylaxis every 48 hours.
- Babies and small infants often metabolise Factor VIII or Factor IX more quickly and may require a higher dose than the standard 25 - 40 iu/kg to maintain an adequate trough. Regular monitoring of the trough level, recovery and half-life will help determine the dose/frequency required.
- Older infants and small children who may have reduced Factor VIII / IX recovery studies and may have a low level inhibitor below the limit of detection by the Bethesda assay.
- If breakthrough bleeds are occurring after one particular weekly activity it may be necessary to alter the timing of prophylaxis to optimise levels at the time of that activity.
- Change from an alternate day dosing to daily dosing.
- If spontaneous bleeds continue, consider increasing the trough level by increasing the dose.

2.10 Home treatment

Prophylaxis is given by patients/carers at home and therefore adequate home treatment training is required to train the patients/carers in the safe administration of intravenous factor concentrates in the home environment. Home treatment enables the family to adapt and cope with Haemophilia and other inherited bleeding disorders with minimum disruption to their lives.

Home treatment training may be directed towards the patient themselves, or in the case of a young child, a competent adult e.g. one or both parents/carers. The duration of training is variable and depends on a variety of factors but usually competence is achieved and confidence gained after approximately three months of supportive training.

Home Treatment Training can be undertaken at the Haemophilia Centre by the Haemophilia Nurse Specialists (HNS) or the HNS will visit the patient and family at home to teach intravenous infusion techniques. The visit will coincide with when a treatment is required. The training will commence with an assessment and the training programme will be discussed.

Training will include:

- Instruction on the reconstitution (mixing) of the factor concentrates.
- Preparation and care of veins or other venous access
- Venepuncture or port access technique and the infusion of product
- Identifying and treating bleeds
- Storage and safe disposal of equipment
- Record keeping
- Care of joints and muscles
- Psychological issues related to haemophilia and the treatments
- Facing problems including reactions to treatment and finding solutions

See Appendix 5 – Home treatment proficiency checklist

2.11 Home delivery

All haemophilia patients who regularly need replacement therapy with factor concentrate are eligible for home delivery of their treatment, once the patient or carer has completed home treatment training, and has signed a partnership agreement which includes completion of home treatment records (haemtrack or paper), attending review appointments and notifying the centre of major bleeds or those not responding to therapy.

3 Clinical Management of patients with a confirmed bleeding disorder

Management is multidisciplinary with many different people involved in patient care. This includes haemophilia doctors, nurses, biomedical scientists, physiotherapists, paediatricians, play therapists, GPs, dentists, orthopaedic surgeons, rheumatologists, hepatologists, HIV specialists, psychologists.

3.1 Frequency of reviews

3.1.1 Adults

- Every 6 months for those with severe/moderate haemophilia or severe Type 2/3 VWD.
- Every 12 months for those with mild haemophilia, Type 1 VWD or other mild bleeding disorders e.g. FXI deficiency or Platelet function disorders

3.1.2 Paediatrics

- Frequency of monitoring should be 3 to 4 monthly for children/young person under the age of eighteen with severe/moderate Haemophilia A and B or severe Type 3 VWD
- Every 6-12 months for those with mild haemophilia or Type 1 VWD

3.1.3 Transition

- At a time appropriate to each child, with the aim of attending ongoing clinics where transitional issues will be discussed.
- The young person will be seen on their own and with their parent/ carer during the clinic reviews.
- Trust policy for transition care will be followed.
- Transition care should promote independent management of their condition.

3.2 Assessment

The assessment will be adapted depending on the diagnosis and severity of the bleeding disorder but may include:

- Number, severity and location of bleeds
- Joint problems e.g. pain, decreased mobility
- Dental review
- New medicines
- Prophylactic or on demand Factor concentrate treatment
- Bacterial infections for those with chronic HIV
- Any side effects of therapy including antiretroviral treatment
- Delivery of product – check if any issues

- Venous access
- Ensure understanding of inheritance and update family tree
- Psychosocial review

3.3 Examination

- Assessment of joints / muscles (see physio section)
- Signs of liver disease
- Cardiorespiratory / fundoscopy if HIV positive. Also examine for superficial lymphadenopathy / hepatosplenomegaly if HIV positive.

3.4 Investigations

- FBC
- Coagulation screen
- Factor VIII / IX activity (48, 72 or 96 hour trough)
- FVIII recovery- to be documented
 - In adults only repeat if change in product, or significant weight change
 - In children repeat as needed
- Factor VIII / IX inhibitor annually or if clinical indication e.g. poor response to treatment, 1-2 weeks pre-surgery
- U+Es, LFTS
- Vitamin D (and bone profile where indicated)
- Hepatitis A and B serology every 1 to 5 years dependant on previous antibody levels. If Hep. B titre is <100mlu/ml check at next visit, and if still low perform give a booster but if >500mlu/ml check levels after five years.

For those with co-infections

Hepatitis

- If chronic hepatitis B/C alfafoetoprotein measurements every 6 months
- If HepB sAg positive – Hep B DNA every 6 months
- Liver ultrasound scan if hepatitis B/C positive every year or every 6 months if cirrhotic

HIV

- CD4 every 6 months unless advised to be more frequent by HIV team
- HIV viral load every 6 months unless advised to be more frequent by HIV team

4 Inhibitor development in Haemophilia A and B

4.1 Background

The development of inhibitors is one of the known complications of haemophilia treatment. These are alloantibodies directed against transfused factor VIII or IX concentrate. In haemophilia A, they are mainly of the IgG subclass binding to specific epitopes within the factor VIII molecule. These epitopes appear to lie mainly within the A2 and C2 domains. The incidence of factor VIII inhibitors is reported as being as high as 30 to 50% with the majority being transient inhibitors. Factor IX inhibitors tend to be rare with an incidence of 1 – 3%.

Classically in the case of haemophilia A inhibitors tend to develop in young children between 10 to 20 (range 3 – 52) exposure days (EDs) to factor VIII concentrates. It is rare for inhibitors to develop in adults or after 150 exposures, but can occur after high usage such as covering major surgery. There appears to be no difference in the incidence of inhibitors whether the patient receives recombinant or plasma derived concentrates.

Certain defects in the factor VIII gene such as the intron 22 inversion (found in 50% of severe haemophiliacs) are associated with a higher risk of inhibitor formation. Thus apart from the greater exposure to factor VIII concentrates this probably explains why inhibitor formation is more likely to occur in those patients with the severe phenotype. A higher risk of inhibitors is seen in Afro Caribbean's, certain HLA types and those with a positive family history.

When a severe haemophiliac develops an inhibitor, the number of bleeds increases as the antibody neutralises transfused factor VIII/IX and the small amounts of factor VIII/IX produced by the patient's own hepatocytes. Bleeding episodes become refractory to transfused factor VIII/IX concentrates and need to be treated with bypassing agents and if appropriate placement on an immune tolerance therapy.

Mild or moderate Haemophilia with complex genetics mutation can also develop inhibitors; therefore this group of patients should be monitored closely when receiving high intensity Factor VIII concentrates.

4.2 Diagnosis of Factor VIII and IX inhibitors

An inhibitor is suspected if a patient has a bleed that fails to respond normally to infused factor VIII or IX concentrate. It is confirmed by a poor increase in the factor VIII or IX level despite an appropriate dose of factor VIII or IX concentrate respectively. If sufficient FVIII or IX concentrate is given to raise the FVIII or IX level to ~ 100 iu/dl a suboptimal recovery would be associated with a FVIII or IX level of < 66 iu/dl.

The presence of a factor VIII inhibitor can be confirmed by the Bethesda Assay. This quantitative test is based on the measurement of the amount of factor VIII inactivated by patient plasma in an incubation mixture over 2 hours at 37C. Factor VIII inhibitors are time

dependant hence the need for a 2-hour incubation before the Factor VIII assay is performed. Basically 1 Bethesda unit (BU) is the amount of inhibitor that would inactivate 50% factor VIII in the incubation mixture.

The Bethesda assay is also used to recognise Factor IX inhibitors but because these are immediately acting only a 5-minute incubation is needed.

Low titre inhibitors are < 5 BU and high titre ≥ 5 BU. Low titre patients may respond to high dose Factor VIII concentrate (or in the case of Haemophilia B Factor IX concentrate) but high titre inhibitors will need bypassing agents for the treatment of bleeds such as FEIBA or NovoSeven.

4.3 Management of bleeds in severe haemophiliacs with inhibitors

4.3.1 Bypassing agents

The two main agents are FEIBA (Factor VIII inhibitor bypassing activity) that contains activated Factors II, VII, IX and X and NovoSeven that is recombinant activated factor VII.

FEIBA should be given at a dose of 50 – 100iu/kg body weight 6 - 12 hourly as per SPC depending on site of haemorrhage (maximum dose 200iu/kg/day unless the severity of the bleeding warrants higher doses – must be discussed with haemophilia consultant) until bleed resolves.

NovoSeven should be given at a dose of 90 – 120mcg/kg body weight 2 - 3 hourly (half life of 2.5 hours). Most bleeds will resolve after 1 to 3 treatments. Alternatively 270mcg/kg can be given upfront, with a standard dose 6 hours later.

For bleeding episodes in patients with factor VIII / IX inhibitors of <5 BU responses may occur with very high doses of factor VIII / IX concentrates at doses of 100 – 200iu/kg.

4.3.1.1 *Prophylaxis against bleeds in inhibitor patients*

For patients who either do not have ITT or who fail ITT, there is evidence emerging that prophylactic FEIBA can significantly reduce the severity and frequency of bleeds in this group of patients. The dose is usually 50 to 100 iu/kg alternate days.

4.4 Immune tolerance therapy (ITT)

Immune tolerance induction (ITI) is recommended for patients with congenital haemophilia A or B and a confirmed factor VIII or IX inhibitor. It is recommended that prior to the initiation of ITI, bleeding should be managed on-demand using bypass therapy.

Current UKHCDO guidelines should be followed for immune tolerance. Patients should be discussed at the MDT prior to starting ITI, commissioners informed and NHD notified.

Once tolerance has been achieved it is recommended that factor VIII or IX prophylaxis start immediately.

4.4.1 Summary of dose recommendations in ITI

Historical peak	<5			5-200		>200
Starting titre	<5			<10		>10
On IT peak	<40	40-200	>200	<200	>200	
Dose (iu/kg)	50 alt d	100 /d	200 /d	100 /d	200 /d	200 /d

Whilst ITT is being used and when the factor VIII inhibitor is still present bleeding episodes will need treatment with either FEIBA or NovoSeven

5 Management of acquired haemophilia A

5.1 Background

This is a rare acquired bleeding disorder with an incidence of 1 case in 1 – 4 million. Males and females are equally affected but most patients are >60 years old. Unlike congenital haemophilia this disorder is associated with predominantly cutaneous, soft tissue, mucosal bleeding, genitourinary and gastrointestinal bleeding. Spontaneous muscle and cerebral bleeds can also occur but joint bleeds are uncommon. Bleeding after surgery, insertion of vascular lines or catheters is also common. Severe or life threatening bleeds can occur in 80% of patients with a mortality of 20 – 30%.

5.2 Disease Associations

- 60% idiopathic
- 40% associated with Autoimmune diseases – Rheumatoid etc., Malignant disease – Solid cancers, LPDs*, Drugs – Penicillin, Sulphonamides, Phenytoin, Clopidogrel, Post – partum

LPDs* = Lymphoproliferative disorders

5.3 Diagnosis

- Prolonged APTT that will not fully correct with the addition of normal plasma after a 1 to 2 hour incubation.
- Low Factor VIII
- Positive inhibitor identification via the Bethesda assay
- Lupus inhibitor excluded
- The pharmacokinetics of acquired haemophilia are complex and there tends to be a poor correlation between the factor VIII inhibitor and bleeding risk

5.4 Treatment Regimes

Treatment of acquired haemophilia has 2 arms: treatment of the bleeding and immunosuppression to remove/reduce the inhibitor.

5.4.1 Haemostatic therapy - If Factor VIII inhibitor is < 5 BU

- No need to treat if not actively bleeding
- Oral Tranexamic acid 15 – 25 mg/kg QDS for mucosal and soft tissue bleeding as long as not contraindicated (e.g. haematuria)
- DDAVP 0.3mcg/kg - can develop tachyphylaxis with decreasing responses. To be used for minor bleeds only and those patients below 65 years and without coronary heart disease.
- Recombinant factor or Plasma VIII concentrates – 100 to 200iu/kg initially.

- Aim for 15 to 30 minute post infusion Factor VIII to increase to >30 iu/dl (haemostatic level).
- Bolus treatment every 4 – 6 hours because of short half-life or
- Continuous infusion of factor VIII concentrate @ 10 – 15iu/kg/hour until bleed resolves.

5.4.2 Haemostatic therapy - If Factor VIII inhibitor is >5 BU

5.4.2.1 *FEIBA (Factor VIII inhibitor bypass agent)*

- For management of a bleed give 50 to 100iu/kg 8 to 12 hourly. Maximum 200iu/kg in 24 hours. Continue until the bleed resolves. Severe bleeds may take from 2 to 7 days to resolve.
- There is usually a > 80% response rate to FEIBA. There is no laboratory test to assess response to FEIBA so clinical judgment should be used.
- Prophylactic FEIBA should not be used in the elderly because it is prothrombotic. There have been cases of arterial thrombosis e.g. CVA and MI.
- If unresponsive to FEIBA suggest NovoSeven.

5.4.2.2 *NovoSeven (recombinant FVIIa)*

- For management of a bleed give 90mcg/kg - 2 to 3 hourly.
- Most bleeds show signs of improvement after 2 to 3 treatments.
- Major bleeds may need 2 to 3 hourly treatment for the first 24 hours and then if responding 4 to 6 hourly treatment until the bleed resolves.
- Overall response rate is >90%.
- There is no laboratory test to assess response to NovoSeven so clinical judgement should be used.
- Prophylactic NovoSeven is unlikely to be effective because the half-life is 2 to 3 hours. Probably lower risk of thrombotic events than FEIBA but still a potential complication.

5.4.3 Immunosuppressive therapy

- Prednisolone 1 mg/kg/day and assess responses after 3 weeks therapy. Complete response with inhibitor eradication is seen in ~ 30% of treated patients.
- Oral prednisone + cyclophosphamide @ 1 to 2 mg/kg/day then assess after 3 to 4 weeks. Complete response with inhibitor eradication is seen in ~ 60% of treated patients.
- If after 4 weeks no improvement in FVIII level or inhibitor quantification options include IV Rituximab @ 375 mg/m² weekly x 4 weeks or oral cyclosporine 3 to 5 mg/kg/day in divided doses and aiming for trough levels of 150 – 300.
- MMF or ciclosporin are alternative immunosuppressant that may have a role – to be discussed in MDT

6 Von Willebrand's Disease (VWD)

6.1 Background

Von Willebrand's factor (VWF) is a large plasma glycoprotein comprising a series of multimers with molecular weights varying from 800 – 20 million daltons. VWF has 2 main functions, firstly, as a carrier protein for factor VIII and secondly as an adhesive protein involved in platelet adhesion to the endothelium following vascular injury.

VWD is the commonest inherited bleeding disorder with an incidence as high as 0.1 to 1% for type 1 disease. Inheritance is autosomal dominant in the main apart from type 2N (Normandy) and type 3 VWD where inheritance is autosomal recessive. VWD is associated with mutations of the VWF gene on chromosome 12. Males and females are equally affected.

The diagnosis is made after a patient with an abnormal bleeding history is found to have a significantly reduced VWF activity (Ristocetin cofactor activity +/- collagen binding assay) and usually a reduced VWF antigen. See current UKHCDO/BCSH guidelines for further details.

6.2 Type 1 VWD

Type 1 VWD relates to a quantitative deficiency with normal or reduced Factor VIII and reduced VWF antigen plus activity. The vast majority of affected patients respond to DDAVP.

6.3 Type 2 VWD

Type 2 VWD relates to qualitative deficiency with VWF activity results being reduced to a greater extent than VWF antigen Ag (ratio < 0.6). There are different subtypes. Response to DDAVP is variable.

- Type 2A VWD relates to decreased platelet associated function and absent high molecular weight (HMW) VWF multimers.
- Type 2M VWD is associated with decreased platelet associated function but normal multimers or occasionally some ultra large forms.
- Type 2N (Normandy) VWD is associated with normal platelet associated function but defective Factor VIII binding. Inheritance is recessive hence heterozygote's tend to have normal or minimally reduced Factor VIII levels but normal VWF Ag / activity whereas homozygote's tend to have low Factor VIII levels but normal VWF Ag / VWF activity. They tend to respond to DDAVP but the half-life of the Factor VIII tends to be shorter than normal i.e. significantly < 8 hours.
- Type 2B VWD relates to increased affinity of VWF for platelet glycoprotein 1b with reduced or absent HMW VWF multimers. Low dose RIPA is enhanced. DDAVP is relatively contraindicated in type 2B VWD because it can induce greater interaction

between the defective VWF and platelets leading to thrombocytopenia. Plasma derived Factor VIII plus VWF concentrate is required for prophylaxis or bleeding episodes.

- Pseudo platelet-type VWD is a rare disorder arising from mutations in the platelet Gp1b/IX complex that causes increased binding between the abnormal platelets and VWF. Inheritance is autosomal dominant. Pseudo VWD can mimic type 2B VWD with variable degree of mild thrombocytopenia, normal Factor VIII, reduced VWF/VWF Ag ratio of < 0.6 , enhanced low dose RIPA, decreased HMW VWF multimers. Plasma/platelet mixing studies are required to distinguish Pseudo platelet-type from type 2B VWD. Addition of cryoprecipitate (containing high concentration of normal VWF) will cause platelets to aggregate in platelet rich plasma from a patient with Pseudo platelet – type VWD but not type 2B VWD.

6.4 Type 3 VWD

Type 3 VWD relates to a severe quantitative deficiency of Factor VIII / VWF antigen and VWF activity. All levels tend to be < 10 iu/dl. DDAVP is ineffective in type 3 disease. For treatment of or prophylaxis against bleeds a Factor VIII / VWF containing concentrate is required.

Summary of VWD classification

	1	3	2A	2B	2M	2N
VWF:Ag	↓	↓↓↓	↓	↓	↓	↔
VWF:RC_o	↓	↓↓↓	↓↓	↓↓	↓↓	↔
FVIII:C	↔	0.05-0.1	↔	↔	↔	0.1-0.4
VWF:RC_o/VWF:Ag ratio	>0.6	-	<0.6	<0.6	<0.6	>0.6
Multimers	N	-	Abn	Abn	N	N
RIPA	N	-	↓	↑	↓	N

6.5 Treatment

6.5.1 Summary of treatment in VWD

Type	Product
1	DDAVP or VWF containing factor concentrate in DDAVP non responders
2A/2M/2N	DDAVP 1 st line or VWF containing concentrate in DDAVP non responders
2B/3	VWF containing concentrate
Pseudo VWD	Platelet concentrates

6.5.2 DDAVP

DDAVP (1-desamino-8-D-arginine vasopressin/ desmopressin) is a synthetic analogue of anti-diuretic hormone. It was demonstrated in the late 1970's that by releasing natural stores in the body DDAVP produced a marked increase in factor VIII coagulant (FVIII:C) and von Willebrand's factor (VWF) activities. Therefore it could be effectively utilised in the treatment of mild FVIII deficiency, von Willebrand's Disease, and platelet function defects, allowing patients to undergo selective surgical procedures without the need for plasma derived products.

- In responders it can raise factor VIII/VWF levels 2 to 4 fold. A DDAVP trial is required to establish responsiveness prior to using for treatment.
- DDAVP is not recommended in children under the age of 2 because of the risk of severe hyponatraemia that may trigger seizures and coma
- It is contraindicated in patients with a history of ischaemic heart disease and therefore it is also best not to use in those over 65 years old due to the risk of ischaemic event.
- Dose is 0.3mcg/kg (to max 25 mcg total dose).

See Appendix 1 for more details on DDAVP including DDAVP trial.

6.5.3 Treatment of VWD with factor concentrate

Different VWF containing factor concentrates are available. These are plasma derived. Voncento and Wilate are the 2 main concentrates used in the centre. Levels of VWF:RCo of > 60 IU/dl and of FVIII:C of > 40 IU/dl should be achieved to achieve haemostasis.

6.5.3.1 *Voncento*

- Calculate the dose using IU of VWF:RCo
- Generally, 1 IU/kg VWF:RCo raises the circulating level of VWF:RCo by 0.02 IU/ml (2 %).
- Usually 40 - 80 IU/kg of von Willebrand factor (VWF:RCo) corresponding to 20 - 40 IU FVIII:C/kg of body weight (BW) are recommended to achieve haemostasis.
- 500IU FVIII/1200 IU VWF, 1000 FVIII, 2400 IU VWF vials available.
- Round to nearest vial size.

6.5.3.2 *Wilate*

- The ratio between VWF:RCo and FVIII:C is 1:1.
- Generally, 1 IU/kg BW VWF:RCo and FVIII:C raises the plasma level by 1.5-2% of normal activity for the respective protein.
- 20 to 50 IU Wilate/kg BW are necessary to achieve adequate haemostasis. This will raise the VWF:RCo and FVIII:C in the patients by approx. 30 to 100%.

7 Platelet function disorders

7.1 Role of platelet in normal haemostasis

Platelets are disc like structures measuring 2 to 4 μm in diameter, involved in primary haemostasis and have a life span of 7 to 10 days in the peripheral blood.

On the surface of platelets are various Glycoprotein's (GP) involved in platelet adhesion plus aggregation. Adhesion to collagen is facilitated by GP Ia. GP Ib and GP IIb / IIIa are important for binding to VWF and hence to vascular subendothelium. The binding site for GP IIb / IIIa is also the receptor for fibrinogen that is important in platelet to platelet aggregation.

The platelet plasma membrane invaginates into the platelet interior to form an open membrane system providing a large reactive surface to which selective coagulation factors can be absorbed. Platelet membrane phospholipids (Platelet Factor 3) are important in conversion of Factor X to Xa and Prothrombin (FII) to Thrombin (IIa).

Within the platelet interior there are 2 types of granules. Firstly there are dense granules containing ADP, ATP, calcium and serotonin. There are also alpha granules containing platelet derived growth factor, Beta thromboglobulin, fibrinogen, Factor V and VWF. Following platelet activation the contents of these granules are released into the open canalicular system.

Platelet adhesion

Following blood vessel wall injury platelets adhere to the exposed subendothelial connective tissues. Under shear stress platelets move along the surface of the vessel until the platelet glycoprotein Ia engages with collagen and halts further movement. Platelet Glycoprotein Ib binds to Von Willebrand's Factor that in turn binds to the subendothelial microfibrils. Following platelet adhesion the platelets become more spherical and extrude pseudopods that enhance interaction between platelets and causes platelet activation.

Platelet release reaction

Collagen and thrombin bind to their respective receptors on the surface of platelets resulting in the secretion of platelet granule contents including ADP. Collagen and thrombin also activate prostaglandin synthesis leading to generation of thromboxane A₂ (TXA₂) that further augments the release reaction and causes local vasoconstriction to slow blood flow in the area of vessel wall damage.

Platelet aggregation

Released ADP and TXA₂ from the platelets in to the surrounding plasma causes upregulation of the GP IIb / IIIa triggering platelet aggregation and fibrinogen binding. Platelet aggregation causes more ADP and TXA₂ to be released increasing platelet aggregation resulting in the formation of a primary platelet plug (primary haemostasis).

Platelet procoagulant activity

After platelet aggregation Platelet Factor 3 is exposed on the surface of platelets triggering activation of Factor X and Factor II leading to the formation of thrombin.

Irreversible platelet aggregation

High concentrates of ADP and TXA2 contribute to the irreversible fusion of platelets at the site of injury. Thrombin also encourages the fusion of platelets plus fibrin formation contributes to the stability of platelet plug.

7.2 Platelet Function Disorders

Severe platelet function disorders (PFDs) such as Glanzmann's and Bernard Soulier syndrome are rare with an incidence of ~ 1 in 1 million but the milder platelet release / secretion and storage pool disorders are likely to be commoner though the actual incidence is unknown.

The platelet function disorders often present with mucosal bleeding – bruising, epistaxes, menorrhagia and bleeds occurring immediately after trauma, dental extractions and operations.

Platelet function disorders (PFD) can be inherited in an autosomal dominant or recessive fashion.

7.2.1 Diagnostic Identification

7.2.1.1 Bernard Soulier

- Low platelet count
- Large platelets on blood film
- Abnormal aggregation with Ristocetin only
- Decreased or absent platelet Glycoprotein 1b (Gp1b) expression

7.2.1.2 Glanzmann's Thrombasthenia

- Normal platelet count
- Normal sized platelets on blood film
- Markedly abnormal if not absent aggregation with all agonists (collagen, thrombin, ADP Arachidonic acid) but normal with Ristocetin
- Decreased or absent platelet GpIIb/IIIa expression (unless type 3 functional defect)

7.2.1.3 Storage Pool Deficiency

- Normal platelet count and size
- Abnormal aggregation especially with collagen, ADP and thrombin > Arachidonic acid (AA)
- Abnormal platelet nucleotides with decreased total nucleotides, ADP concentration and raised ATP: ADP ratio (usually 2.5:1)

7.2.1.4 *Aspirin like platelet release defect*

- Normal platelet count and size
- Abnormal aggregation with AA > collagen, ADP and thrombin
- Normal platelet nucleotides

7.2.2 **Drugs and food that can affect platelet function**

The list of drugs and food that can influence platelet function is extensive. It is essential for investigation and diagnosis that interfering substances are stopped (if possible) two weeks prior to testing or identified as a potential acquired defect.

Examples of the most common:

Drugs: Aspirin, NSAIDS, Furosemide, Lidocaine, Alcohol, Beta blockers, Anaesthetics

Foods: chocolate, onions, garlic, ginger

7.2.3 **Acquired Platelet Dysfunction**

Platelet dysfunction may also be acquired. Medical conditions that have been associated with acquired platelet disorders:

- Myelodysplasia
- Myeloproliferative disorders
- Liver and kidney disease
- Monoclonal gammopathy / Myeloma

7.3 **Investigation and diagnosis**

- History
- Platelet count / size
- PFA 100 if available - assesses interaction between VWF, collagen and platelets
- Platelet Aggregation - assess responses to known platelet agonists i.e. ADP, AA, collagen, Ristocetin, adrenaline
- Platelet nucleotides (if appropriate) (see investigational flow charts section 1.4)

Stop aspirin 10 days and non-steroidal anti-inflammatory drugs 7 days pre-platelet aggregation tests.

PFA-100 and platelet aggregation can be affected by reduced platelet counts ($<80 \times 10^9/l$), low haemoglobin ($<10g/l$) and reduced fibrinogen. If these are present it may be inappropriate to perform studies or needs to be taken into account when interpreting results.

Acute bleeding

PFA-100 analysis and global assessment of haemostasis using thromboelastography may be useful in the identifying platelet function abnormalities in the acute setting following heavy blood loss e.g. surgery

7.4 Management and treatment of platelet disorders

- Avoid aspirin and NSAIDs.
- Tranexamic acid +/- DDAVP or platelet concentrates pre-dental extractions, operations and for treatment of bleeds.
- DDAVP can be useful in storage pool disorders and release defects (monitor response via improve PFA 100 closure time post infusion) but ineffective in Bernard Soulier and Glanzmann's.
- Patients with Thrombasthemia can be treated with Novo seven or platelets.
- Hepatitis A and B vaccinations (s.c. rather than I.M. injections) in case blood products

8 Presentation of patients with known bleeding disorders to emergency department

- The patient should carry at all times relevant diagnostic information supplied on the red bleeding disorder registration card.

- All patients with bleeding disorders should be discussed with the on-call Haemophilia Consultant via switchboard
- Treatment depends on the bleeding disorder and the type / site of bleed. Please see separate sections regarding the management of Haemophilia A / B, VWD and rarer bleeding disorders
- Head injury in a patient with a bleeding disorder when associated with headaches, vomiting, drowsiness is a medical emergency requiring appropriate haemostatic treatment, admission, neurological observations and a CT head scan
- Prompt treatment of the bleed is essential to allow early resolution and to minimize complications such as joint disease in patients with moderate/severe haemophilia
- Avoid aspirin / NSAIDs which will affect reduce platelet function. Avoid intramuscular injections (risk of muscle bleed) in these patients
- Universal cross-infection precautions are essential because of the risk of a transmissible infection
- Refer to SOP HH(3)/MED(SOP)/101/14 and ED pathways

9 Management of pregnancy and childbirth in women with bleeding disorders

All women with bleeding disorders should ideally be seen, reviewed and counselled pre conception. Once pregnant they should have regular reviews during the pregnancy. They should ideally be seen in the combined haematology/obstetric clinic and a detailed plan (see appendix 5) completed and discussed in the MDT by 34-36 weeks. Close liaison is required between haematologists, obstetricians, anaesthetists, paediatricians and midwives when managing these patients.

It is important to remember that Fibrinogen, Factors VII, VIII, VWF and X significantly increase throughout normal pregnancy and therefore monitoring may be required to assess the level before delivery. Other clotting Factor levels remain stable apart from Factor XI that may fall slightly.

All recommendations follow the RCOG Greentop guidelines (2017) on women with inherited bleeding disorder

9.1 Haemophilia

- For families who may wish to consider whether or not to go on with a pregnancy if affected, sex typing from maternal bloods looking at fetal DNA can be performed from 9 weeks gestation, after a confirmatory dating scan
- Pregnant carriers with a male fetus at risk of haemophilia should be offered the option of chorionic villus sampling at 11-14 weeks of gestation
- All carriers of haemophilia with male foetuses should be offered third trimester amniocentesis if no investigations previously performed to determine haemophilia status and inform options for delivery
- If no antenatal diagnosis then the fetus should be managed as if he is affected
- Maternal FVIII/FIX should be checked at booking, before any antenatal procedure and in third trimester
- Option of elective caesarean section should be discussed for delivery of affected male babies, especially those with severe haemophilia or if status unknown
- Use of ventouse and midcavity forceps should be avoided
- Fetal blood sampling (FBS) and fetal scalp electrode should be avoided in babies expected to have severe or moderate haemophilia. If mild haemophilia, judicious use with the decision made by senior obstetrician. If FBS used sustained pressure under direct vision to ensure haemostasis
- FVIII/IX >50iu/dl for epidural or spinal
- Active management of the third stage is recommended
- Levels of FVIII/IX should be maintained above 50iu/dl for at least 3 days following uncomplicated vaginal delivery or 5 days following instrumental delivery or caesarean section

- Cord blood samples and diagnostic testing is recommended for male babies, some mild cases may require retesting at 3-6 months of age
- Cranial US should be considered prior to discharge in all neonates with severe or moderate haemophilia, with cranial MRI in neonates with signs/symptoms suggestive of ICH even if normal cranial US
- Ensure appropriate and timely discussion with parents if diagnosis is made and arrangements for neonatal follow up given to parents prior to discharge
- Vitamin K should be given orally until factor levels known and if low continued orally

9.2 VWD

- All women with VWD should have FVIII, VWF Ag and activity checked at booking, in the third trimester and prior to any invasive procedures
- In type 1 VWD levels often increase into normal range, if this occurs women can be managed in standard obstetric unit
- In type 2 and 3, or severe 1 care should be multidisciplinary in a unit with specialists in high risk obstetrics as well as a haemophilia centre and ability to measure VWF and FVIII levels
- Mode of delivery guided by obstetric indications
- If fetus may have type 2 or 3 VWD, FBS, FBE, ventouse and midcavity forceps should be avoided
- If type 1 and levels normalised central neuraxial anaesthesia levels can be offered
- In Type 2B VWD the Factor VIII / VWF levels remain unchanged but thrombocytopenia can occur during pregnancy, platelet transfusion may be required as well as VWF factor replacement
- In Type 3 VWD the factor VIII / VWF levels remain very low during pregnancy and a FVIII/VWF containing factor is required for prophylaxis at the time of delivery or for the management of any bleeding. Epidural/spinal should be avoided.
- All women should be considered for tranexamic acid post partum, 1gtds for 7 -14 days
- Keep VWF/FVIII levels >50iu/dl for at least 3 days for NVD, at least 5 days following instrumental or caesarean section
- All women with VWD should be made aware of risk of delayed bleeding and be encouraged to report excessive bleeding
- Cord sample if at risk of type 2 and 3 VWD

9.3 Platelet disorders

In patients with platelet function disorders there may be some improvement in their bleeding problems during pregnancy presumably related to higher levels of VWF and better interactions between platelets and damaged blood vessel walls. For patient with more severe platelet type bleeding disorders, platelets may be required.

Individual management plans should be discussed at the MDT for those with platelet disorders.

9.4 Other bleeding disorders

For all other bleeding disorders cases should be discussed on an individual basis, a plan following RCOG green top guidelines documented and discussed in the MDT.

10 Management of dental care, treatment and extractions in patients with bleeding disorders

Dental care of patients with haemophilia and other bleeding disorders can often be complex and should be carried out in close liaison with the haemophilia centre. Good oral hygiene and preventative treatment for people with bleeding disorders is critical as bleeding into the mouth is recognised as one of the most difficult bleeds to stop.

Access to a comprehensive dental service is offered to severe haemophilia A & B and Type 3 VWD, covering routine check-ups, fillings, extractions and restorative dentistry.

For patients with mild haemophilia, VWD and other mild bleeding disorders, patients would normally be treated by their own registered dentist. They should seek advice from the Haemophilia Centre, prior to any invasive procedure to ensure appropriate medication or replacement therapy is provided.

In a complex situation if the registered dentist is unable to carry out procedure referral to the haemophilia designated dentist will be made. This service is provided by Special Care Dental Service, Solent NHS Trust. There is a single point of referral. Contact number 02380698677.

In Basingstoke the clinic is at:

Brambly's Grange Dental Clinic
Brambly's Drive
Basingstoke
RG21 8UW

Tel: 01256 462823/ 0300 1235090

The referral form can be found in reception in the haemophilia centre or on Q drive

10.1 Procedure for appointments

10.1.1 Routine

- Severe haemophiliacs and VWD's patients who are registered at the practice have routine six monthly check-ups.
- Any treatment requirements will be arranged and carried out at in consultation with the Haemophilia Centre as appropriate.

10.1.2 Emergency

Out-of-hours emergency dental care is provided through contact with the Dental Help Line 0845 0508345

10.2 Dental extractions

- Start oral Tranexamic acid 1 gram TDS the evening before, continued the day of and for 5 to 7 days thereafter. Dose in children aged < 10 years old would be 15 to 25 mg/kg 6 to 8 hourly. 5 % solution of Tranexamic acid mouthwash 10 ml 6 -8 hourly on the day of the extraction and for 5 to 7 days thereafter to be used as an adjunct.
- Aim for Factor VIII, IX or VWF activity of ≥ 50 iu/dl dependant on the underlying diagnosis. For multiple extractions aim for Factor levels of ~ 100 iu/dl.
- For those patients with mild haemophilia A and Type 1/2A VWD (if DDAVP responders) use DDAVP s/c at 0.3mcg/kg (See appendix 1).
- For moderate/severe haemophilia A treat with recombinant Factor VIII concentrate (see section 2.6. for dose calculations).
- For all subtypes of haemophilia B treat with recombinant Factor IX concentrate (see section 2.6 for dose calculations).
- Type 2B/3 VWD or those with Type 1/2A/2N who are DDAVP non-responders treat with Factor VIII/VWF containing plasma derived concentrates.
- For patients with platelet function disorders give oral Tranexamic acid and, if responsive s/c DDAVP at least pre-op. For DDAVP non-responders use platelet concentrates.
- For pain relief post-extraction use Paracetamol, codeine (over 12 years) and avoid aspirin/NSAIDs.

10.3 Dental fillings

- If a deep nerve block is not required oral tranexamic acid 1 gram tds (15 to 25mg/kg in children tds) continued for 2 to 3 days post-treatment.
- If deep nerve block is required s/c DDAVP, or factor concentrates should be given pre-treatment in conjunction with tranexamic acid

10.4 Dental scaling

- Significant bleeding may occur with dental scaling - use 5% Tranexamic acid mouthwash 10 ml 6-8 hourly on the day and for 3 to 5 to days thereafter.
- 5% Solution of Tranexamic acid mouthwash can be useful to be applied topically by the dentist during the dental procedures.

11 Hepatitis A & B vaccinations for patients with bleeding disorders

- Hepatitis A and B vaccinations are recommended for patients with bleeding disorders, using Plasma Derived Products
- The recommendation for Hepatitis A and B vaccinations is via the subcutaneous route.

Schedule

- Hepatitis A vaccinations:
 - First injection 1 ml s/c with booster 6months/1year
 - Check antibody response 6 months later.
 - For child aged ≤ 15 years old dosage of 0.5ml.
- Hepatitis B vaccinations:
 - First injection 1ml s/c
 - Second injection 4 weeks Third injection 6 months after the first.
 - For child aged ≤ 15 years old dosage of 0.5ml each time.
 - Check antibody level 3 - 6 months after third vaccination.
- Aim for detectable antibody against Hepatitis A and Hepatitis B >100 miu/ml
- If patient does not respond to first Hepatitis B vaccine (e.g. Engerix B) and antibody levels are <10 miu/ml an alternative vaccine should be used (e.g. HBvaxPRO) and repeat antibody level 3 to 6 months after third vaccination.
- If the Hepatitis B antibody remains < 10 miu/ml after using the Alternative vaccination this patient is a true non – responder.
- In responders with antibody levels of ≥ 500 miu/ml levels should be repeated after 5 years.
- If the level is between 100 – 200miu/ml repeat levels after 1 year.
- For responders who subsequently drop their levels to < 100 miu/ml a booster vaccination should be organised and recheck the level after 6 months.

12 Management of rare inherited bleeding disorders

12.1 Afibrinogenemia / Hypofibrinogenemia

Incidence

- Afibrinogenemia is 1 in 1000,000
- Autosomal Recessive inheritance
- Fibrinogen gene - chromosome 4q gene

Presentation

- Umbilical cord bleeding
- Mucosal and musculoskeletal bleeds
- CNS bleeds
- Traumatic bleeds
- Recurrent miscarriages
- Delayed wound healing – afibrinogenemia

Diagnosis

- May be prolonged PT / APTT / TT
- Very low or undetectable fibrinogen antigen / activity in cases of afibrinogenemia

Prophylaxis

- In cases of afibrinogenemia after life threatening bleed or intracranial bleed, give sufficient fibrinogen concentrate (cryoprecipitate if concentrate unavailable) to maintain fibrinogen >0.5g/l

Management of an acute bleed / surgery

- Aim for fibrinogen ≥ 1 g/l for management of an acute bleed or surgery
- Fibrinogen concentrate: Usual dose 50 to 100 mg / kg
- Half life of infused fibrinogen is 3 – 5 days and treatment may only be required every 48 hours.
- Cryoprecipitate: 2 pooled packs for adults or 15 – 20 ml / kg for children

12.2 Prothrombin deficiency

Incidence

- Severe phenotype - 1 in 2,000,000 incidence
- Autosomal Recessive inheritance
- Prothrombin gene - chromosome 11

Presentation

- Mucosal bleeds
- Musculoskeletal bleeds
- Traumatic bleeds

Half life

- 72 hours

Diagnosis

- Variably prolonged PT / APTT
- Low Prothrombin activity

Management of an acute bleed / surgery

- 1 unit of factor II containing concentrate will raise Prothrombin level by 1iu/dl.
- Aim for Prothrombin level of at least 20 iu/dl for surgery.
- Prothrombin Complex Concentrate (PCC) at a dose of 20 to 30 units per kg body weight. May only need treatment every 2 to 3 days
- If PCC unavailable use FFP 15 – 20mls per kg body weight

12.3 Factor V deficiency

Incidence

- Severe phenotype incidence - 1 in 1000,000
- Autosomal Recessive
- Factor V gene - chromosome 1q gene

Presentation

- Bruising
- Mucosal bleeds (Musculoskeletal bleeds rare)
- Post traumatic bleeds

Diagnosis

- Variably prolonged PT / APTT
- Low Factor V

Half life

- 12 to 36 hours

Management of an acute bleed / surgery

- Aim for factor V level of at > 20 iu/dl.
- There is no factor V concentrate available
- Use Octaplas 15 – 20mls per kg body weight
- If no response to FFP try platelet concentrates which are an alternative source of factor V

12.4 Combined Factor V and VIII deficiency

Incidence

- 1 in 1000,000
- Autosomal Recessive inheritance
- Chromosome 18q gene defect – LMAN1 and MCFD2
- Defective intracellular transport of Factor V and VIII

Presentation

- Variable bleeding – especially bruising and epistaxis
- Mainly traumatic

Diagnosis

- Prolonged APTT > PT
- Low Factor V and VIII activities – 5 to 20iu/dl

Management of an acute bleed / surgery

- Recombinant Factor VIII 20 – 50iu/dl 8 to 12 hourly + FFP 15 – 20mls / kg
- Aim Factor V \geq 25 iu/dl and Factor VIII \geq 50 iu/dl

12.5 Factor VII deficiency

Incidence

- 1 in 300,000 – 500,000
- Autosomal Recessive inheritance
- Factor VII gene - chromosome 13q

Presentation

- Mucosal bleeds
- Musculoskeletal bleeds
- CNS bleeds
- Variable clinical severity and poor correlation with Factor VII level

Diagnosis

- Prolonged PT only
- Low Factor VII activity

Half life

- 6 hours

Management of an acute bleed / Surgery

- NovoSeven : 15 to 30mcg / kg every 4 to 6 hours

12.6 Factor X deficiency

Incidence

- 1 in 1,000,000
- Autosomal Recessive inheritance
- Factor X gene - chromosome 13q

Presentation

- Mucosal and musculoskeletal bleeds
- Acquired deficiency associated with amyloidosis

Diagnosis

- Prolonged PT and APTT
- Low Factor X activity

Half life

- 20 - 60 hours

Management of an acute bleed / surgery

- 1 unit of Factor X containing concentrate (PCC) raises Factor X by 1.5iu/dl
- Factor X levels of ≥ 20 iu/dl should suffice
- PCC at a dose of 20 to 30 units per kg
- May only need treatment every 1 to 2 days
- If PCC unavailable use FFP 15 to 20mls per kg body weight

12.7 Combined Factors II, VII, IX and X deficiencies

Incidence

- Single case reports < 20 worldwide
- Autosomal Recessive inheritance
- chromosome 16p gene defect

Presentation

- Umbilical cord bleeds
- CNS bleeds
- Mucosal and musculoskeletal bleeds

Diagnosis

- Prolonged PT / APTT
- Low Factors II, VII, IX and X

Management of an acute bleed /Surgery

- IV vitamin K 10 mg
- PCC 20 to 30 iu per kg
- If PCC unavailable use FFP 15 – 20mls per kg

12.8 Factor XI deficiency

Incidence

- Severe phenotype the incidence is ~ 1 in 1000,000
- Autosomal recessive
- Factor XI gene - chromosome 4q gene

Presentation

- Very variable
- No correlation with FXI level
- Mucosal bleeds
- Spontaneous / musculoskeletal bleeds very rare
- Association with VWD and Platelet function defects

Diagnosis

- Prolonged APTT
- Low Factor XI activity

Half life

- 30 - 70 hours

Management of acute bleed/Surgery

- Factor XI concentrate: 10 – 15iu/ kg body weight (peak Factor XI levels should not exceed 100 u/dl)
- If no Factor XI concentrate use Octaplas/ FFP 15 to 20mls/kg
- Can also use NovoSeven 90mcg/kg every 2 to 3 hours initially

- Factor XI concentrate is not recommended in patients with cardiovascular disease because of its risk of thrombosis. Prior to surgery aim for a calculated Factor XI level of 70 iu/dl (dose should not exceed 30iu/kg body weight)
- Tranexamic Acid

12.9 Factor XII deficiency

On its own Factor XII deficiency is not associated with bleeding thus no treatment required to cover surgery. However if a patient with Factor XII deficiency has a convincing bleeding history, consider concomitant VWD, factor VIII / IX / XI deficiency or a platelet function disorder. There may also be a link between FXII deficiency and angiodysplasia.

12.10 Factor XIII deficiency

Incidence

- Severe phenotype incidence is ~ 1 in 1,000,000
- Autosomal recessive inheritance
- Factor XIII gene - chromosome 6

Presentation

- Umbilical cord bleeding occurs in 80% within few days of birth
- Life long tendency to bruising, muscle/joint bleeds, intra-cranial bleeds and bleeding after trauma
- Delayed wound healing

Diagnosis

- PT / APTT / TT / Fib all normal
- Decreased clot solubility with 5 mol/l urea
- Low Factor XIII activity

Half life

- 7 to 10 days

Prophylactic Treatment

- Fibrogammin 20-40 iu/kg every 4 weeks.
- Aim to keep the trough Factor XIII level 10-20 iu/dl

Treatment of acute bleed

- 10 – 40 iu / kg of fibrogammin (dependent on last prophylactic dose) daily until resolution of bleed
- Aim to keep peak Factor XIII levels > 50 iu/dl

Prophylaxis for surgery

- Immediately pre-op 35 iu / kg of fibrogammin, then post-op 10 to 20 iu / kg every 24 to 48 hours until wound healing

- Again aim to keep trough factor XIII > 4 iu/dl and peak levels > 50 iu/dl

13 Genetic Counselling Service

The National Service Specification for Haemophilia and Related Conditions states that all individuals with haemophilia or a related bleeding disorder and their families should have access to specialised genetic services. Genetic counselling should be available for all people potentially affected by or at risk of being a carrier of one of these conditions before and after genetic analysis.

Genetic counselling should be undertaken by health care professionals with appropriate training and expertise. The main requirements for genetic counselling will relate to the identification of potential carriers and antenatal diagnosis of potentially affected fetuses. The staff involved in counselling who may be members of the haemophilia centre team or a specialised genetics unit should provide information to patients and their families regarding the following: -

- The inheritance pattern of the condition in question
- The nature and implications of the bleeding disorder
- Treatment and complications
- Options open to family members who may wish to have genetic testing

13.1 Process

- Establish that a bleeding disorder is present in the family and establish its type plus severity
- Establish a pedigree
- Assess understanding expectations and wishes
- Address personal concerns related to testing
- Allow questions to be asked
- Ensure information and its significance is understood and accepted
- Offer a follow up appointment
- Make clear arrangements for imparting the results of testing
- For all patients and family members it is important that written information is made available and that signed informed consent is obtained before blood samples are taken for genetic analysis.

Blood samples are currently sent to the molecular haemostasis department based at ViaPath, London. They are able to screen for genetic defects associated with haemophilia A / B plus the rarer bleeding disorders. All results should be discussed with the patient / family and the implications.

13.2 Haemophilia Carriers

- Carriers of haemophilia may have low levels of Factor VIII or IX and have similar problems to patients with mild haemophilia with excessive bleeding after trauma, dental or surgical procedures. There may also be problems with menorrhagia and bleeding at childbirth.
- For these reasons haemophilia carriers with low levels of factor VIII or IX need access to appropriate obstetric and gynaecological services.
- Factor VIII or IX assays should be carried out on all carriers of haemophilia. All should be formally registered and those with low levels followed up by a local Haemophilia Centre in a similar fashion to patients with mild haemophilia.

13.3 Identification of the genetic defect responsible for haemophilia and carrier status

- Genetic counselling should be available before, during and after the process of haemophilia genetic analysis.
- A fully documented pedigree study should be carried out for each family, allowing identification of obligate carriers, possible carriers and non-carriers.
- Intragenic polymorphism and linkage analysis and/or direct gene analysis should be carried out to establish carriership for female members of the family where there is a patient with haemophilia.
- Following a diagnosis of carriership there should be specialised genetic counselling and education so that these carriers can understand the transmission of haemophilia within their own family.

14 Physiotherapy

Service provision of physiotherapy for adults and children with Haemophilia and other inherited bleeding disorders should be in line with the UK Standards of care. Adults and children should have access to a physiotherapist with specialist knowledge of haemophilia and other bleeding disorders and musculoskeletal conditions. The physiotherapist should be a member of the Haemophilia Chartered Physiotherapists Association (HCPA) and be able to attend/undertake training to ensure the continuation of best practice and provision of quality care. The specialist physiotherapist should have dedicated/protected hours and flexibility within this to manage their haemophilia caseload/service.

The physiotherapist has an important role within the medical team in the management of haemophilia

- Recognition and management of acute musculoskeletal bleeding episodes
- Long term implications of the impact of haemophilia on the musculoskeletal system
- The importance of muscle power and proprioception in providing joint protection
- Recognition of normal musculoskeletal issues related to child development and the aging process
- Promoting the positive role of physical activity, exercise and sport and offer support in choosing activities

Adults and children referred to physiotherapy should be seen within the appropriate time frame according to the clinical status and have direct access to physiotherapy, telephone triage and advice.

Acute Condition referral

A patient should be reviewed as soon as is clinically possible, normally within 24 hours. This could be a telephone triage or face to face review. It is acknowledged that when a referral occurs prior to a bank holiday/weekend, review should be the next available and clinically appropriate appointment.

Chronic Condition referral

A patient should be offered an appointment which will be within 2 weeks

Clinical review

A physiotherapist should see adult patients with a symptomatic diagnosis of haemophilia or on prophylaxis at least annually. Adults with frequent bleeding episodes, coagulation factor inhibitors, complications of bleeding episodes such as symptomatic arthropathies will require more frequent review.

A physiotherapist should see children with severe/moderate haemophilia or on prophylaxis six monthly and those with mild haemophilia annually. Children with frequent bleeding episodes, coagulation factor inhibitors, complications of bleeding episodes such as symptomatic arthropathies will require more frequent review.

For adults and children over 4 years of age the review should include

- A record of bleeding events, pain, functional difficulties and time off school / work should be noted.

- A thorough neuro-musculoskeletal assessment to monitor joint health and function
- A standardised & validated clinic examination score such as the Haemophilia Joint Health Score (HJHS), which should be incorporated into the prospective assessment of patients receiving prophylaxis.
- Validated functional and psychosocial outcome measures may also be performed for patients with haemophilia when relevant, considering the domains acknowledged in the World Health Organisation (WHO) ICF framework.

Those with a known history of intracranial haemorrhage should be monitored using appropriate assessments and if problems are identified these will be discussed within the multidisciplinary team to facilitate management or onward referral as appropriate.

15 Clinical Psychology

Patients and their families should have access to psychosocial support as part of the delivery of comprehensive care.

Clinical Psychologists have an important role within the multi-disciplinary team (MDT) in the management of haemophilia and other bleeding disorders. They help patients and families who are experiencing psychological difficulties that are contributing to, or are a consequence of, their bleeding disorder. They also work with staff within the service to support and develop psychological awareness throughout the service.

Psychological difficulties might include:

- Experiencing difficulty adjusting to their diagnosis
- Finding it difficult to manage their health condition / struggling with the burden of treatment
- Feeling depressed or anxious as a result of their health condition
- Not attending / finding it hard to attend education/work as a result of their health condition
- Not attending medical appointments or not adhering to treatment
- Difficulty managing transitions in their life / health / treatment
- Experiencing difficulty within the family – in terms of children, siblings, parents or the family as a whole
- Overall quality of life being adversely affected by their health condition.

Patients and/or their families should be offered an initial assessment appointment within 4 to 8 weeks of a referral being received by the psychology team (or more quickly if urgent). They should then be offered one-off, group or regular sessions if appropriate, be offered joint session(s) with another MDT colleague, be referred on to a more appropriate local service, or be discharged.

16 Appendix 1: DDAVP for Adults and Children over 2 years of age

Patients with mild/moderate haemophilia A, Von Willebrands Disease and platelet function defects may respond to DDAVP. It can be used for selective surgical procedures. Route of administration depends on availability of product, the individual patient and indications for use.

Subcutaneous injection (preferred route of administration)

Use Octim (15mcg/ml concentration)

In Adults and children over the age of 2 years

- 0.3mcg/kg 90 minutes prior to invasive procedure or when bleeding
- Intervals of at least 48 hours by the advise of a Haemophilia Consultant when required.
- No more than 1ml injected into one site.
- Max dose 25mcg
- Fluid restrict for 24 hours after dose
 - Adults 1.5L
 - Children- To drink what they would normally drink; if admitted and having intravenous fluids ensure to calculate age/weight specific ml/kg input for 24hr period e.g. 20/25 ml/ Kg

Intravenous Infusion (only if s/c not available)

In Adults: 0.3mcg/kg diluted in 100mls of 0.9% sodium chloride over 20 minutes 60 minutes prior to invasive procedure or when bleeding, at intervals of at least 48 hours, by advice of a Haemophilia Consultant when required.

In children over the age of 2 years: 0.3mcg/kg diluted in 50mls of 0.9% sodium chloride over 20 minutes 60 minutes prior to invasive procedure or when bleeding, at intervals of at least 48 hours, by the advice of a Haemophilia Consultant when required.

Fluid restrict as for subcutaneous

Intranasal

In Adults: 300 micrograms – one 150microgram spray into each nostril – 60 minutes prior to the invasive procedure or when bleeding, at intervals of at least 48 hours by the advise of a Haemophilia Consultant when required.

In children over the age of 2 years: 150 micrograms – one spray into one nostril - 60 minutes prior to the invasive procedure or when bleeding, at intervals of at least 48 hours by the advise of a Haemophilia Consultant when required.

Fluid restrict as per subcutaneous.

Cautions/side effects

- DDAVP is not recommended for children under the age of 2 years.
- There is a risk of severe hyponatraemia that can trigger seizures and coma which is the reason for fluid restriction
- Caution is required in pregnant women

- Contraindicated if a patient has a history of ischemic heart disease. Also best not to use in age group > 65 years because of the risk of an ischemic event
- Flushing, tachycardia, tremor, abdominal discomfort. May occasionally cause an increase or decrease in blood pressure readings.
- Headaches
- Rarely anaphylaxis
- Increased renal absorption of water via anti-diuretic effects. This can lead to hyponatraemia. Fluid restrict as above.

DDAVP trial

Patient Preparation

- Explain the whole procedure to the patient, or if a child, to the parent, explaining possible mild side effects; facial flushing is common, headache and hypertension. The patient should be advised to have something to eat before the procedure. Ensure that the patient is not pregnant or breast-feeding
- Explain that DDAVP can cause increase thirst and that fluids should be restricted to over the following 24-hour period, which will reduce the concerns associated with fluid retention.
 - Adults 1.5L
 - Children- To drink what they would normally drink; if admitted and having intravenous fluids ensure to calculate age/weight specific ml/kg input for 24hr period e.g. 20/25 ml/ Kg
- Weigh patient and record in notes
- Record all medication that the patient is currently taking, checking and discussing with a doctor if DDAVP is contraindicated
- Get DDAVP prescribed by doctor or NMP
- Advise patients that alcohol should be avoided for 24 hours because of its capacity for dehydration.
- Take patients pulse and blood pressure. Do not force or restrain a child as inaccurate readings will be presented, amuse the child and involve them in all the procedures.
- With children it may be necessary to apply Anaesthetic cream to at least two favourable sites and allow time for the local anaesthetising effect.

Pre blood tests

- For vWD patients: FVIII:C, vWF Ag, vWF activity, PFA.
- For patients with mild and moderate Haemophilia A: FVIII:C only.
- For patients with platelet function defects: Platelet Function Screen (PFA)

After DDAVP administration

- All patients should have blood pressure and pulse checked every 30 minutes for the first 90 mins.

Post DDAVP blood tests

Blood test should be taken at 90 mins (for sc), 4 - 6 hours and consider 24 hour. If IV DDAVP used first test should be at 60 mins.

- For VWD patients: FVIII:C, vWF Ag, vWF activity, PFA
- For patients with mild and moderate Haemophilia A: FVIII:C only.
- For patients with platelet function defects: Platelet Function Screen (PFA)

- The drug batch and dosage, patient's vital signs and any adverse effects should be documented in the notes and onto the electronic records system.
- Patients or carers should be informed where/how to seek help if any concerns or side effects.

The effect expected for therapeutic use is an increase in FVIII:C/vWF of three times the starting level, on average. This effect is transient. The appropriateness of DDAVP will therefore depend on the specific surgery planned and the required duration of haemostasis.

17 Appendix 2: Surgical treatment plan template

Add/ Delete sections as required.

SURGICAL treatment plan

Name:
DOB:
Hospital number:
Procedure:
Diagnosis:
Baseline:
Weight:
Product:

EVENING PRIOR TO SURGERY

1 HOUR PRIOR TO THEATRE

- Take bloods for
- Administer a bolus of
- Take 10 minutes post bolus bloods for **urgent** Factor

DO NOT WAIT FOR RESULTS AND PROCEED WITH SURGERY

POST OP CARE

- Pt will be monitored by the Haemophilia Team

AVOID IM INJECTIONS AND NSAIDS

Thromboprophylaxis: no LMWH/heparin unless discussed with team, use AV boots

No epidural/spinal unless discussed with team

Do not stop or alter this treatment protocol without instructions from the Haemophilia team.

The haemophilia team can be contacted between 9-5pm on 01256 314793. Out of hours please ring switch on 01256 473 202 and ask for the haemophilia consultant on call.

18 Appendix 3: Delivery plan template

Add/delete sections as required

Haemostasis Delivery Plan

Name:

Hospital Number:

Date of Birth:

Expected Date of Delivery:

Haemostasis Diagnosis:

Factor VIII/IX level:

On admission to labour ward:

- Take urgent Coagulation screen, Factor VIII/IX level and FBC (1 blue citrate bottles and 1 purple EDTA bottle).

Patient *can/cannot have Epidural/Spinal injection as analgesia/anaesthesia**
(*delete as applicable)

Delivery:

- Vacuum extraction (Ventouse delivery) and mid-cavity forceps should be avoided.
- Lift-out forcep by a senior obstetrician to help delivery in the late second stage could be appropriate.
- The use of scalp electrodes and fetal blood sampling should be avoided.
- A cord blood sample should be obtained for Factor VIII/IX level (1 blue citrate bottle). Send samples to the Haemostasis Laboratory, Basingstoke Hospital urgently

Immediately Post Delivery:

- Give Tranexamic acid 1g QDS orally and to continue for 7 days post partum.

Continuing Post Natal Care:

- Please contact Haemophilia Centre at Basingstoke Hospital for advice if there are any signs of post partum haemorrhage (*check below for contact details*).

24 hours post delivery:

- Mother – Take urgent FBC, Factor VIII/IX level and Coagulation Screen (1 blue citrate bottles and 1 purple EDTA bottle). Please send samples to the Haemostasis Laboratory, Basingstoke Hospital.

Neonatal Period:

- **Vitamin K should be given orally** with specific instructions for follow up doses. First dose of Vitamin K (Phytomenadione) 2mg given at birth and 2nd dose within the first week. For exclusively breast-fed babies, a third dose is given at 1 month of age.
- **Intramuscular injections and routine venepunctures should be avoided.**
- Heel pricks should be carried out carefully and pressure applied to the site for 5 minutes afterwards.

Do not stop or alter this treatment protocol without instructions from the Haemophilia team

The haemophilia team can be contacted between 9-5pm on 01256 314793
Out of hours please ring switch on 01256 473 202 and ask for the Haemophilia consultant on call.

Management plan for baby of

Date of Birth:

Hospital Number:

EDD:

Maternal diagnosis:

Fetal sex:

During labour:

- The use of scalp electrodes and fetal blood sampling should be avoided. Artificial rupture of the membranes is safe but care should be taken not to scrape the baby's head repeatedly if this is performed.

Delivery:

- Delivery should be achieved by the least traumatic method and early recourse to caesarean section should be considered especially in prolonged labour. A senior obstetrician (ST6-7 and/ or consultant) should be involved in every case. Vaginal delivery is NOT contra-indicated in the majority of cases.
- Vacuum extraction (Ventouse delivery) and mid-cavity forceps should be avoided.
- A **cord blood sample** should be obtained in a citrated tube and transported to the coagulation laboratory urgently for Factor VIII levels.

Neonatal period:

- Examine the baby for bleeding and bruising including the scalp for cephalhaematoma.
- A cranial ultrasound should be performed prior to discharge in all babies diagnosed with severe or moderate haemophilia.
- The parents should be made aware of the early signs of ICH (lethargy, vomiting, seizures and poor feeding)
- CT scan of the head is indicated if there is clinical suspicion of Intracranial Haemorrhage (ICH) and a normal ultrasound appearance.
- **Vitamin K should be given orally** with specific instructions for follow up doses. First dose of Vitamin K (Phytomenadione) 2mg given at birth and 2nd dose within the first week. For exclusively breast-fed babies, a third dose is given at 1 month of age.
- **Intramuscular injections and routine venepunctures should be avoided.**
- Heel pricks should be carried out carefully and pressure applied to the site for 5 minutes afterwards.

- Circumcision should be delayed until the coagulation status of the baby is confirmed and management plan discussed with the Haemophilia team.
- Routine immunizations should be administered intradermally or subcutaneously.
- Community midwives and health visitors should be made aware of affected babies.
- The Haemophilia Centre /on call haemophilia consultant should be informed of the birth
- **If there is any evidence of bleeding in the baby, contact the Haemophilia Centre Basingstoke Hospital urgently. The baby may need urgent FVIII/IX treatment**

19 Appendix 4: Half-Life Study charts

19.1 Factor VIII

Timing of samples to be discussed with consultant and may vary depending on the product and the individual. Ensure haemostasis laboratory aware of date and time of study.

Date			
Patient Name			
Hospital Number			
Date of Birth			
Weight			
Name of Product			
Units given			
	Time sample due	Time taken	Taken by
Pre			
Post			
20 mins			
1 hour (1-3 hours)			
4 hours (4, 5 or 6 hours)			
12 hours			
24 hours			
28 hours			
32 hours			
48 hours			
72 hours			
96 hours*			

*additional samples may be needed for EHL products

19.2 Factor IX

Timing of samples to be discussed with consultant and may vary depending on the product and individual. Ensure haemostasis laboratory aware of date and time of study.

Date			
Patient Name			
Hospital Number			
Date of Birth			
Weight			
Name of Product			
Units given			
	Time sample due	Time taken	Taken by
Pre			
Post			
20 mins			
1 hour (1-3 hours)			
4 hours (4, 5 or 6 hours)			
12 hours			
24 hours			
48 hours			
72 hours			
96 hours			
120 hours*			

* additional samples after 120 hours may be needed for EHL products

20 Appendix 5: Home treatment proficiency check list

Educational objective SKILLS – TO BE DEMONSTRATED On completion of training caregiver can demonstrate:	Skill demonstrated to caregiver/patient (Check and initial)	Caregiver/patient can demonstrate skill to nurse. (Check and initial)	Comments
1. Handwashing			
2. Preparation of equipment/supplies			
3. Aseptic technique non- touch technique			
4. Reconstitution of factor concentrate			
5. Withdrawal of factor concentrate from vial and priming of butterfly needle/gripper needle			
6. Cleaning access site			
7. Performing venepuncture/insertion of Gripper needle			
8. Administration of factor (+/- normal saline and heparin with Gripper needle)			
9. Correct withdrawal of needle			
10. Site care after access			
11. Disposal of sharps and other equipment			
12. Appropriate documentation			
13. What to do if you do not get access first time			
Additional Skills: To be determined by caregiver as specifically required.			

Comments/Recommendations:-

Contact for questions or

problems _____

21 Appendix 6: Preparation and Administration of Factor Concentrates

Various factor concentrates are available and all vary slightly in the kit provided and method of preparation. There are instructions within the concentrate boxes. This appendix is to describe the procedure for correct, safe preparation and administration of factor for all those involved in the care of haemophilia patients – Haemophilia CNS, ward nurses where applicable and medical teams.

Preparation

- Wash and dry hands
- Prepare an appropriate preparation surface, i.e. blue tray or factor mat
- Remove prescribed factor concentrate from the fridge checking expiry date, product, and dose against the prescription
- Wash and dry hands and put on gloves

- **For water syringe and factor vial based sets:**
 - Remove protective cap from vial
 - Clean stopper with alcohol swab and allow to dry
 - Peel cover off vial adapter, place over the vial and snap into place
 - Remove plastic casing, ensuring that adapter is not handled
 - Remove plunger rod from box and attach to syringe by turning clockwise into threaded stopper
 - Snap cap off syringe tip and attach syringe to vial adapter by turning clockwise
 - Slowly inject syringe contents into vial
 - Swirl **GENTLY** until factor powder completely dissolved
 - **Do NOT shake vial**
 - Turn vial upside down and draw entire contents into syringe smoothly and slowly
 - Disconnect syringe
 - Eject any air from syringe – factor is ready to administer
 - Remove gloves and re wash hands

- **For BAXJECT device, or similar:**
 - Remove caps from both vials
 - Clean stoppers with alcohol swabs and allow to dry

- Peel away paper lid of BAXJECT device – do not remove device from the package
- On a flat surface, turn the package over and press straight down to insert the CLEAR plastic spike into the stopper of the WATER vial
- Remove the plastic package, leaving BAXIJECT attached to water vial
- Turn water vial with BAXIJECT device upside down and press straight down to insert WHITE spike into factor vial
- The water will be drawn down into the factor vial
- Swirl **GENTLY** until factor powder completely dissolved
- **Do NOT shake vial**
- Remove blue cap from device and connect syringe
- Turn device over so factor vial is on top
- Withdraw factor slowly
- Disconnect syringe
- Eject any air from syringe – factor is ready to administer
- Remove gloves and re wash hands

Administration

- **If giving factor alone**, prepare tray with factor, butterfly set, alcohol swab, gauze ball, plaster and tourniquet
- Connect factor syringe to butterfly set and prime the tubing
- Take to patient, check patient ID against prescription, and obtain patient consent prior to procedure
- Involve the patient in selecting a suitable site for injection – they are often experts about their treatment and suitable venous access sites
- When treating small children, if in doubt, please seek appropriate help from experienced staff within the centre or paediatric day unit, and please ask for assistance in holding the child.
- Support patient's limb on a pillow or cushion
- Wash hands and put on gloves
- Select a suitable vein and apply tourniquet
- Cleanse skin area with alcohol swab and allow to dry. Avoid touching the skin after cleansing
- Secure vein using manual traction below proposed injection site
- Insert butterfly needle into vein and check for flashback of blood
- Once flashback obtained, remove tourniquet and infuse factor steadily
- Pause to recheck flashback if any doubt about needle placement or vein patency and infuse remaining factor
- Remove needle and apply pressure over puncture site with gauze ball for 1 – 5 minutes, until bleeding has stopped
- Apply plaster or micropore over puncture site, according to patient preference, allergies etc.

- **If blood tests required prior to factor administration** do not prime butterfly set with factor, but collect samples via butterfly set first, and then administer factor via same butterfly, as above
- Complete JAC/HCIS/Haemtrack (or hospital prescription if paper) with all appropriate treatment details

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