# New Zealand National Guidelines for the Management of Haemophilia 2022

## National Treatment protocols Version 2

Compiled by the National Haemophilia Treaters Group (NZ)

Te Whatu Ora
Health New Zealand

# DISCLAIMER

The information in this document is a treatment guideline only. It is aimed at offering guidance to local medical and paediatric teams who may deal with issues for people with haemophilia and is not intended as a substitute for consultation with a haematologist, or paediatrician experienced in the management of haemophilia. All patients with haemophilia admitted to hospital, MUST be discussed with the Regional Haematologist at the time of admission and the patients haemophilia treatment centre at the first possible opportunity.

A list of appropriate specialists is included in these guidelines.

Revised: January 2022

Scheduled update: January 2024

# CONTENTS PAGE

# GENERAL PRINCIPLES OF MANAGMENT

## Specialist management

All patients with haemophilia, other significant congenital bleeding problems or acquired factor deficiencies, should be registered with a Regional Haemophilia Centre and reviewed if required by a specialist haematologist. The frequency of review will depend on the severity of the haemophilia.

## Terminology

| Severity | Factor FVIII or IX activity |
|---|---|
| Severe | <1% |
| Moderate | 1–5% |
| Mild | >5–40% |

**Note –** The plasma concentration of factor VIII or IX does not always correlate with the clinical severity of the disease. Some patients with factor concentrations between 1% and 5% have clinically severe disease.

**FVIII –** refers to all types of factor VIII products used to treat patients with factor VIII deficiency. This may be of recombinant or plasma derived origin.

**FIX –** refers to all types of the Factor IX product used to treat patients with factor IX deficiency. It may be of recombinant or plasma derived origin.

## Pain Relief

Pain relief must be adequate **especially for large joint and muscle bleeds.**

Nonsteroidal anti-inflammatories should not be used. Cox2 inhibitor use should be discussed with the regional treatment centre.

## Acute Joint Bleeding

Minor joint bleeds should be treated with ice application, analgesics and rested in a functional position. All joint bleeds should be assessed by, or discussed with, the haemophilia centre physiotherapist.

**Ice application –** the icepack is covered with a cloth and placed on the skin for 20 minutes each hour.

**Rest in a functional position –** this involves immobilising upper limb joint bleeds in a sling. Bed rest for severe lower limb bleeds or crutches to prevent weight bearing. A back slab may be useful in certain instances for joint immobilisation and protection against further injury.

**Exercises** (initially static) must be started as soon as the pain has subsided and should be overseen by a physiotherapist.

## Dosing

**Factor VIII dosing approximation:** 1 unit/kg b.w. = 2% rise in factor VIII activity.

**Factor IX dosing approximation:** 1 unit/kg b.w. = 1% rise in factor IX activity.

## Recording Treatment

Patients should be encouraged to keep a record of all bleeding episodes and details of their product usage.

Records of product issue are kept on a centralised database currently managed in Dunedin and accessible to the treatment centre staff.

# VACCINATIONS

Routine vaccinations are recommended for all patients. Patients who are receiving factor prophylaxis should receive these intramuscularly (IM) on the day of factor administration. Moderate and severe patients who are not yet receiving factor prophylaxis should receive these subcutaneously (SC). For mild patients the balance between the risk of bleeding and potential decrease in vaccine efficacy needs to be considered[1]. Many children will manage with an experienced IM administrator, an icepack applied 5 minutes prior to the injection and application of firm pressure for 5–10 minutes after the vaccination[2].

Children should be routinely vaccinated by their general practitioner for standard public health vaccinations. Prolonged local pressure for 5-10 minutes is recommended at the injection site.

Immunsations may be less effective in patients with HIV.  Live vaccinations are also contraindicated in patients with HIV.  Pneumococcal vaccination and yearly influenza vaccination is recommended for patients with HIV.

## Hepatitis B Vaccination

This is part of the routine NZ immunisation schedule. Patients who require human derived products or components should have regular follow-up of their hepatitis B immune status and re-vaccination when appropriate.

## Hepatitis A Vaccination

Vaccination should be considered in patients who are Hep A IgG negative and receiving plasma products. Patients who are hepatitis C positive, but Hepatitis A IgG negative, should be given the Hepatitis A vaccine.

**References**
[1]Cook IF.  Subcutaneous vaccine administration – an outmoded practice. Hum Vac & Immunoth. 2021; 17(5):1329-1341.
[2]World Federation of Hemophilia. Guidelines for the Management of Hemophilia 2nd Edition

# PROPHYLAXIS

This refers to the infusion factor products (usually recombinant) in anticipation of bleeding or in order to prevent bleeding. This contrasts with on-demand therapy given at the first sign of a bleed.

Prophylaxis may be:

## Primary Prophylaxis (long term)

This is given to infants identified as being at high risk of recurrent bleeding placing them at risk of arthropathy. Primary prophylaxis is usually reserved for people with severe haemophilia (i.e. with factor VIII or factor IX activity of <1%), but people with factor concentrations 1–5% can develop disabling arthropathy. Regular prophylaxis is often introduced after one or two severe bleeding episodes within the first 12-18 months of life and is considered standard of care for children with severe haemophilia A or B. The aim is to minimise acute bleeding episodes. There are now a variety of products with regular and extended half lives.

## Single Dose Prophylaxis

An injection of product may be given prior to an event (e.g. sporting) to prevent bleeding occurring in relation to that activity.

## Secondary Prophylaxis

Refers to limited term prophylaxis where there is a high requirement for on demand therapy. Regular injections over a limited time period may reduce the frequency of bleeding or re-bleeding from a target joint. Often used in the treatment of a chronic synovitis.

## Prophylaxis in Haemophilia A

**Aim: to prevent spontaneous bleeding.**

This is generally achieved by preventing a trough of <1%. Many international guidelines in first world countries are now recommending higher troughs where this can be achieved. Recovery and half-life of FVIII can vary with age and between different individuals and therefore pharmacokinetic assessment is recommended in order to optimise prophylaxis (dose and frequency).

This is done at the treatment centre using web-based PK assessment tools such as WAPPS-Hemo (www.wapps-hemo.org) or myPKFiT (www.mypkfit.com)

## Prophylaxis in Haemophilia B

**Aim: to prevent spontaneous bleeding.**

This is generally achieved by preventing a trough of <1%. Recovery and half-life of FIX can vary with age and between different individuals and therefore pharmacokinetic assessment is recommended in order to optimise prophylaxis (dose and frequency).

This is done at the treatment centre using web-based PK assessment tools such as WAPPS-Hemo (www.wapps-hemo.org).

# MANAGEMENT OF MAJOR AND MINOR BLEEDING EPISODES IN HAEMOPHILIA PATIENTS

The management of bleeding episodes within haemophilia patients varies depending on the haemophilia severity, the site of the bleed and the cause of the bleeding episode. People with haemophilia do not necessarily bleed more markedly than non-affected individuals, but without management they are likely to bleed for longer increasing the amount of blood lost.

As a general rule 1IU/kg of factor VIII will increase the persons levels by 2% while for factor IX 1IU/kg will increase the level by 1% but will last longer.

## Major head injury or intra cerebral bleed

**Immediately treat suspected intracranial bleed or significant head injury. It must not be delayed until radiological investigations confirm bleeding.**

1. Admit to hospital and give immediate therapy.
2. Administer first dose of treatment at 50-70IU/kg rFVIII or 80-100IU/kg rFIX prior to any investigations.
3. Seek urgent haematologist consultation – in hours from the local haemophilia treatment centre and out of hours from the regional haematology service.
4. If there is likelihood of ongoing need for factor product in a smaller centre consider ordering further doses of factor at this point or transfer of the patient as appropriate. Transfer of the patient should be seriously considered if ongoing factor levels cannot be done in a timely fashion to inform management.

**Aim: to increase factor level to 80-100% with trough levels of 50%, for 72 hours then dose reduction over 14 days or longer under supervision. Monitor factor levels before and after treatment.**

| Type of bleed | Haemophilia A | | Haemophilia B | |
|---|---|---|---|---|
| Haemar-throsis | 20–50U/kg depending on severity | Contact haematology service re ongoing treatment – may be needed in 12 hours | 30–60U/kg depending on severity | Contact haematology service re ongoing treatmen – may be needed in 24 hours |
| Muscle bleed | 40U/kg | Contact haematology service re ongoing treatment within 12 hours | 50–60U/kg | Contact haematology service re ongoing treatment within 24 hours |
| Dental | 20U/kg +tranexamic acid 25mg/kg | | 30U/kg +tranexamic acid 25mg/kg | |
| Epistaxis | Local measures, tranexamic acid 25mg/kg , rFVIII 20U/kg if needed | | Local measures, tranexamic acid 25mg/kg, rFIX 30U/kg if needed | |
| Major surgery or life threatening bleed | 50–75U/kg then a continuous IVI | 4-5U/kg/hr to maintain lab FVIII level >80U/dL with trough levels >50IU/dL | 80U/kg | 20-40U/kg 12-24hrly to maintain test FIX level >40U/dL |
| Ileopsoas haemor-rhage | 50U/kg | Contact haematology service re ongoing treatment within 12 hours | 80U/kg | Contact haematology service re ongoing treatment within 12 hours |
| Haematuria | NOT for tranexamic acid. Bed rest and IVF at 150% maintenance. rFVIII 20U/kg can be used if bleeding significant or prolonged >1–2/7. Also d/w urology. | | NOT for tranexamic acid. Bed rest and IVF at 150% maintenance. rFIX 30U/kg can be used if bleeding significant or prolonged >1–2/7. Also d/w urology. | |

# CONTINUOUS INFUSION REGIMEN

## To be used in consultation with the haematology service

This protocol is using Standard half life FVIII Products. These timings may vary if using EHL FVIII.

1. Give a bolus dose sufficient to achieve a plasma FVIII activity of 80%.

**The infusion rate is calculated from the formula:**

**Infusion rate (IU/kg/hr) = clearance (mls/kg/hr)* x steady state concentration (IU/ml)**

**Estimated clearance rates are:*
*- 4 mls/kg/hr (adult);*
*- 5 mls/kg/hr for children less than 12 years of age*

These clearance rates fall during the course of the infusion.

**Example:**
Infusion rate to achieve a steady state concentration of 80% (0.8 IU/ml) on the first day is:

**Adult Infusion rate = 4ml/kg/hr x 0.8IU/ml = 3.2IU/kg/hr**

OR the following approximations on initial infusion rate can usually be made:

- **For adults** assume an initial infusion rate 3 IU/kg/hr.
- **For children** assume an initial infusion rate 4–5 IU/kg/hr.

It is important to regularly monitor patients levels to ensure you are achieving the aimed for FVIII activity level. E.g. Twice daily FVIII levels on first 2 days and then daily going forward if achieving a steady state saturation.

Due to the small volume most recombinant products mix up in to it is often necessary to increase the volume of water for injections in the infusion to achieve a flow rate that keeps the IVC from occluding.

Due to the longer half-life of FIX it is rare to use within a Continuous infusion regime.

# MILD HAEMOPHILIA

People with mild haemophilia can often be managed conservatively with RICE for mild injuries. For minor bleeds and minor surgical procedures in mild haemophilia A, non-blood product treatment with DDAVP and Tranexamic acid is used. DDAVP is not effective in haemophilia B.

## DDAVP

DDAVP is a synthetic analogue of the antidiuretic hormone Vasopressin, can release factor VIII:C and von Willebrand factor from endothelial storage sites. VWF levels increase 3–4 fold and FVIII:C increases 3–5 times. It comes as Minirin (4mcg/ml) or Octostim (15mcg/ml), Octostim is usually preferred due to the dose required.

The DDAVP effect on factor VIII parameters lasts for 6–8 hours. Patients may become progressively unresponsive to DDAVP with repeated doses as stores are used. Responsiveness to DDAVP will return when the drug has been discontinued for two days.

It is recommended that a DDAVP trial is carried out prior to surgery to assess the response as some individuals respond poorly to treatment. Do not do a DDAVP trial within four days of planned surgery.

Rapid infusion may lead to flushing, headache and tacycardia. Repeated administration may lead to water overload due to its antidiuretic effect and electrolyte monitoring is recommended.

It is contraindicated in patients <2 years, with hyponatraemia and in closed head injuries. Relative contraindication is recent MI or stroke or known severe vascular disease.

All patients should go home with information on fluid restriction for 24 hours (see Appendix 1).

**Treatment regimen:**
0.3 µg/kg I.V. 30 minutes prior or subcutaneously 60 minutes prior to procedures. Used with Tranexamic Acid 20mg/kg/dose (max 1g) PO tds to qid (IV dose is 10mg/kg).

The SC route is generally preferred due to lower risk of side effects. Intravenous DDAVP (0.3 µg/kg) is diluted in 30 - 50 ml of isotonic saline and administered no more than one hour before surgery. The first 5 ml is given over five minutes - provided the patient does not show marked tachycardia or other adverse reactions the remainder of the dose may be given over the next 15 minutes.

## Tranexamic acid

Tranexamic Acid is a fibrinolytic inhibitor, should be administered concurrently unless there is renal bleeding, liver disease with the threat of DIC, or an increase of thrombotic events.

## Factor viii concentrate in mild haemophilia

Some people with mild or moderate haemophilia can develop inhibitors so recombinant product use should be discussed with a haemophilia centre unless the situation is an emergency. For more major bleeding episodes or surgery in patients with mild haemophilia, target factor levels should be similar to those recommended for severe or moderate deficiency patients.

# MANAGEMENT OF PREGNANCY AND DELIVERY IN HAEMOPHILIA

Successful management of mother and baby demands a team approach. Collaboration and good communication between the obstetrician, midwife, haematologist, neonatologist and genetic counsellor is essential. **See the VWD chapter for information on obstetric management in VWD.**

## Management of mother

**Pre-pregnancy:**

- pre-pregnancy counselling should be offered to all potential carriers.
- some families may wish to consider assisted pregnancy options such as pre-implantation genetic diagnosis
- establish carrier status.
- determine factor VIII/IX gene abnormality.
- assay clotting factor (VIII/IX) level
- some females have factor levels that can put them at risk of bleeding

**Please refer any pre-pregancy counselling discussion to the regional haemophilia treatment centre in the first instance.**

## On diagnosis of pregnancy

- plan management with obstetrician and haematologist.
- testing such and chorionic villus sampling (CVS) or amniocentesis may require haemostatic cover.

## For females affected by haemophilia

Management is complex and should be discussed with a trained haemophilia treater or genetic counsellor regarding options.

**Parents who wish to consider termination of pregnancy:**

- CVS and gene testing on male fetuses
- Determination of sex of fetus at 14 - 16 weeks can be performed and if male, proceed to amniocentesis and gene testing – however this may lead to less time for consideration of options.
- In some cases a blood test non-invasive prenatal testing (NIPT) testing for fetal DNA in the maternal blood may be available but it is not currently publicly funded.

Parents not wishing to terminate but would like to know whether fetus is affected can be managed as above.

**Parents who do not want termination and are not insistent about prior knowledge of haemophilia status of fetus or mother not informative on DNA testing:**

- Determine sex of infant by conventional ultrasound during second trimester.
- If female fetus, manage mother as detailed below but no additional intervention needed for newborn.
- If male fetus, 50% risk of haemophilia, so proceed as if fetus affected until proven otherwise.

## During pregnancy

- Assay maternal factor VIII/IX level at booking. If reduced, repeat in the third trimester or before any invasive procedures.
- If factor VIII/IX level <50%, increase level to >50% for procedures such as CVS, amniocentesis, or termination.
- For females in the third trimester, with a level < 80% rFVIII is required for most surgical procedures[1]
- Factor IX deficiency rFIX is required for most surgical procedures
- Discuss delivery plan – a written management plan from the haemophilia treatment centre may be required for more complex deliveries. Have appropriate treatment available at the time of delivery in line with the proposed treatment plan.

## At onset of labour:

- Plan for a vaginal delivery unless contraindicated for obstetric reasons. The aim is for the least traumatic delivery for the infant.
- Avoid scalp monitoring.
- Avoid vacuum delivery.
- Avoid vaginal delivery of breech.
- Usually avoid forceps delivery. However, forceps delivery may be less traumatic than Caesarean section if the head is deeply engaged in pelvis, and rotation not required, and expectation of easy procedure, and performed by experienced staff.
- Prolonged labour, especially second stage, should be avoided with early recourse to Caesarean section.

## Postpartum

**For females with a factor level of if <50% before pregnancy:**

- Monitor factor VIII level daily after birth (acute phase protein and level falls post delivery).
- Give rFVIII or consider DDAVP (note significant hyponatraemia can occur particularly if oxytocin was administered during delivery) if levels <80% for:
- => 3 days if normal vaginal delivery
- => 5 days if caesarean section
- Tranexamic acid 1g tds can be used for 5-7 days post delivery

**For haemophilia B carrier with a factor level of if <50% before pregnancy:**

- Give replacement with one dose for normal delivery and a second dose at D3 for caesarean section no need to monitor daily.
- Tranexamic acid 1g tds can be used for 5–7 days post delivery

**References**
Leebeek FWG, Duvekot J, Kruip MJHA. How I manage pregnancy in carriers ofhemophilia and patients with von Willebrand disease. Blood 2020;136(19):2143-2150.

# POTENTIAL NEW CASES OF HAEMOPHILIA

## Newborn males

- Take blood from umbilical cord (or peripheral vein if cord blood specimen unobtainable or unsatisfactory) for **urgent** (result <3 hours) factor VIII/IX level.
- If urgent factor VIII/IX assay unavailable, do coagulation screen (upper limit normal APTT in newborn approximately 40 seconds).
- Avoid heel pricks for coagulation studies or factor assays.
- Oral Vitamin K prophylaxis is effective in preventing classical haemorrhagic disease of the newborn, but ineffective in preventing late HDN. Increasing the dose or giving it weekly for a longer period increases the efficacy of the oral prophylaxis. Alternatively, IM Vitamin K can be given providing pressure is maintained for a minimum of 5-10 minutes.
- Factor IX concentration may be unreliable in the newborn (until approximately 6 months of age). A low level does not confirm haemophilia and a repeat may be necessary.

**If factor assay indicates severe (<1%) or moderate (1 - 4%) factor VIII/IX the staff at the haemophilia treatment centre should be contacted and a plan for communicating the results made.**

- Confirm diagnosis with a further factor VIII/IX level.
- A cranial USS at about D3-4 post delivery should be considered after a normal delivery and is required after an assisted/traumatic delivery or for premature infants.
- A CT scan (in preference to ultrasound) of head should be performed if clinical suspicion of ICH. If there is a clinical suspicion of ICH the factor replacement should be given prior to imaging.

**In newborns without a family history of haemophilia,** factor levels should be considered if coagulation screen shows prolonged APTT, particularly if significant or unusual haemorrhage occurs 'spontaneously' e.g. subgaleal haemorrhage, large cephalhaematoma, or if excessive bleeding occurs with procedures even if:

- coagulation screen suggests DIC
- thrombocytopenia coexists with prolonged APTT

## Newborn females

In females born to families with severe haemophilia cord blood factor VIII/IX level should be measured detect the occasional carrier female with low levels at risk of symptomatic bleeding.

# VON WILLEBRAND DISEASE

## Background

Von Willebrand disease (VWD) is a common bleeding disorder, due to a defect of platelet adhesion, secondary to an abnormality of the von Willebrand factor. The presentation is usually with mucosal bleeding and bleeding with surgery.  A history of menorrhagia is not uncommon in women with this disorder and other symptoms include easy bruising, epistaxis and abnormal bleeding with lacerations. There may be a family history.

While it is the larger VWF molecule that is deficient this molecule acts to hold FVIII in the circulation and so with VWF deficiency there is often also low FVIII levels.

## Minor bleeds

Most patients with type I VWD can be managed with Tranexamic acid and/or DDAVP (see below). DDAVP increases VWF and FVIII levels. Some, but not all, type IIA VWD patients respond to DDAVP. In type IIB disease DDAVP fails to shorten the bleeding time and may produce a severe transient thrombocytopenia. DDAVP is contraindicated in type IIB VWD and pseudo-von Willebrand disease. It is predictably useless in type III VWD.

## Surgery and major bleeds

For patients with mild Type I von Willebrand disease, DDAVP with or without Tranexamic Acid is usually satisfactory for many surgical procedures.

Patients with more severe Type I or Type II disease and in particular Type III disease usually require the infusion of normal von Willebrand factor.

Currently this is available in concentrates of plasma-derived factor VIII (the CSL Biostate vial contains 2 units of von Willebrand cofactor activity for every 1 unit of factor VIII).

Each biostate vial is labels with FVIII IU and VWF IU.

**The Biostate should be prescribed as factor VIII units and rounded to the nearest vial size.**

- Recombinant factor VIII products are not suitable as they contain no vWF.
- Von Willebrand factor concentrates without factor VIII are not currently available in N.Z.

The actual dose recommendations in the literature are quite varied. Because the factor VIII level is a major determinant of operative bleeding and because of the ease of assay of factor VIII, the factor VIII activity level (not von Willebrand factor level) is used in dosage schedules and to monitor treatment. In major surgery it may be necessary to monitor vWF levels but this will need discussion with the specialised coagulation laboratory pre-operatively.

**A recommended dosage schedule is on the following page.**

## Doses of FVIII-VWF concentrates for vwf patients unresponsive to DDAVP:

| Type of bleeding | Dose (IU/KG) of FVII | Number of infusions | Objective |
|---|---|---|---|
| Major surgery | 40<br>then<br>30 | once a day<br><br>once a day | maintain FVIII >50% until healing is complete |
| Minor surgery | 30 | once a day or every other day | FVIII >30% until healing is complete |
| Dental Extractions | 15 | single | FVIII >30% for up to 6 hrs |
| Spontaneous or post-traumatic bleeding | 15 | single | single FVIII >30% for up to 6 hrs |

Bleeding is usually controlled provided adequate (>50%) FVIII levels are maintained irrespective of the bleeding time. Attention to local haemostasis (sutures, cautery, wound packing) is essential perioperatively.

Concurrent tranexamic acid is recommended in most settings.

## Pregnancy

Von Willebrand factor and factor VIII rise during pregnancy. In many cases of von Willebrand disease type 1, factor VIII, vWF antigen and vWF activity will reach normal concentrations.

Because of this initial testing for VWD is unreliable during pregnancy. Note that in patients with VWD type 2 and 3 this rise will not necessarily lead to improvement in VWF activity and bleeding may still persist.

In most patients, if the factor VIII levels are going to normalise, this will occur before 34 weeks gestation.

After delivery the factor VIII levels fall rapidly. Delayed post-partum haemorrhage at 10-14 days is a significant risk.

The risk of peri-delivery haemorrhage is approximately 40%. Primary postpartum haemorrhage is approximately 15–20%. Secondary postpartum haemorrhage is 20–28%. It is not clear if bleeding is confined to only those women who fail to normalise factor levels in pregnancy. Although levels may normalise, unaffected women will have supra-normal vWF levels at this stage of pregnancy.

## Management in Pregnancy

- A careful personal and family bleeding history is important.
- In patients with suspected vWD test at 30-34 weeks (or earlier if preterm delivery is likely).
- Request von Willebrand screen (record blood group).
- Avoid epidural anaesthesia (see below).

**Remember: normal levels in pregnancy do not exclude a diagnosis of vWD.**

## Management at delivery

**Treatment options:**

Many patients will not need treatment at the time of delivery or post partum. If the Factor VIIIc parameters are normal at 30-34 weeks manage expectantly but with a high index of suspicion for postpartum haemorrhage.

In women with type 1 whose factor levels fail to normalize (>50%) or in those with types 2 or 3, consider prophylaxis as below:

- DDAVP (0.3 µg/kg) given following clamping of umbilical cord
- Plasma derived factor VIII (CSL Biostate 500 units/reconstituted bottle). This should be used if there is a history of significant bleeding with a previous delivery. 20–30 FVIII units/kg (40–60 VWF units/kg). This may need to be continued 12 hourly for 3–5 days

**Note: with DDAVP significant hyponatraemia can occur particularly if oxytocin was administered during delivery**

## Post partum haemorrhage

In the event of postpartum bleeding, where prophylaxis has not been given, treatment will be:

- DDAVP (0.3 µg/kg) given following clamping of umbilical cord (note this is not appropriate for repeated use as stores become used and it becomes ineffective.
- Plasma derived factor VIII (CSL Biostate 500 units/reconstituted bottle). 20–30 FVIII units/kg (40–60 VWF units/kg). This may need to be continued 12 hourly for 3-5 days

**Note: with DDAVP significant hyponatraemia can occur particularly if oxytocin was administered during delivery**

## Spinal – epidural anaesthesia for labour and delivery

The majority of patients with type I von Willebrand disease normalise factor VIII parameters in pregnancy. If factor VIII and von Willebrand factor levels are normal at 36 weeks there is no reason to manage the delivery in any special way but rather to follow normal routine practice, including use of episiotomy.

**Note: recent guidelines recommend avoiding neuroaxial anaesthesia in types 2 and 3 VWD.**

The issue of whether or not spinal or epidural anaesthesia is used depends on the willingness of the anaesthetist. It should be acknowledged that if coagulation parameters have normalised with a normal platelet count, there is minimal, if any, bleeding risk associated with an atraumatic lumbar puncture. The risk is lower with a spinal than an epidural.

If the anaesthetist is conversant with the risks, and following full discussion with the patient, it may be acceptable to proceed with spinal anaesthesia if required (particularly for lower segment Caesarean section) if:

- A coagulation screen (including an assessment of platelet function (PFA)) and platelets are normal at the time that procedure is planned.
- That the lumbar puncture is performed by an experienced anaesthetist with an atraumatic technique.
- Consider the use of Tranexamic acid and /or DDAVP at the time of the needle ( if a traumatic tap occurs), best discussed with a haematologist.
- Strict neurological evaluation following the procedure with early intervention if
- there are any signs of a haematoma.

## The infant

Von Willebrand disease is an autosomal dominant inherited condition with variable penetrance (approximately one third of at risk infants will inherit the condition).

- Avoid invasive fetal monitoring (e.g. scalp vein sampling) when possible. Care with instrumental deliveries.
- Give vitamin K at birth.

**Infants are not routinely tested unless they have unexplained bleeding problems.**

## Miscarriage

Bleeding during pregnancy requires urgent obstetric consultation.

Patient with an early miscarriage may require no additional treatment. If there is a need for intervention to remove retained products or prolonged bleeding, treatment with Tranexamic acid and /or DDAVP should be considered.

Patients with a personal history of miscarriage or bleeding during pregnancy may require more frequent monitoring of von Willebrand factor parameters during pregnancy.

**References**
Leebeek FWG, Duvekot J, Kruip MJHA. How I manage pregnancy in carriers of hemophilia and patients with von Willebrand disease. Blood 2020;136(19):2143-2150
Pavord S et al. on behalf onf the Royal College of Obstetrics and Gynaecologists Management of inherited bleeding disorders in Pregnancy. Green top guideline no 71. BJOG 2017;124e193-e263

# PLATELET DISORDERS

## Congenital platelet function defects

Platelet disorders can be treated with DDAVP, platelet transfusion or recombinant factor VIIa. In all cases antiplatelet drugs such as aspirin and anti-inflammatories should be avoided.

**Management:**

- Tranexamic acid and compression for minor bleeding
- Platelet transfusions for more major bleeding
- DDAVP and/or rFVIIa may be useful in some disorders

DDAVP shortens the bleeding time, at least partially, in the majority of patients with minimal bleeding disorders secondary to platelet function abnormalities. The mechanism for this effect is unknown and may be due to vessel wall constriction.

In cases of more severe bleeding a platelet transfusion may be required. However in some inherited conditions platelet transfusion has a risk of development of anti platelet antibodies to platelet glycoproteins that the individual is missing e.g. in Glannzmann. HLA typing should be performed when the patient is well and HLA matched platelets used where possible. Platelet transfusion should not be withheld for severe bleeding because of the risk of isoimmunization.

There is some evidence that patients with congenital bleeding disorders respond to recombinant factor VIIa, however this should not be used without consultation with a haematologist or if it is in the patients treatment plan.

## Specific conditions

**Bernard Soulier syndrome:**

- Tranexamic acid
- Treat with platelets

**Glanzmanns thrombasthenia:**

- Tranexamic acid
- DDAVP anecdotally beneficial (0.3mcg/kg)
- Recombinant Factor VIIa 80-140mcg/kg. (may require NPPA)
- Platelets for bleeding

**Platelet storage pool disorders:**

- Tranexamic acid
- Platelets for bleeding
- DDAVP can be trialed

## Acquired platelet function defects

### Uraemia

DDAVP normalises the uraemic bleeding time prolongation in approximately 75% of patients at one hour after beginning the infusion. The effect lasts four/six hours.

There are no controlled trials that show that DDAVP stops spontaneous bleeding or prevents excessive blood loss after surgery.  Further management such as dialysis or cryoprecipitate should be discussed with a specialist haematologist.

### Hepatic Cirrhosis

The use of thromboelastography in monitoring cirrhotic patients undergoing surgery is recommended as both pro and anticoagulation factors are affected.  DDAVP may shorten a prolonged bleeding time in patients with cirrhosis.

Consider using in those patients undergoing invasive procedures. Cases in which plasma infusions fail to normalise coagulation may respond to DDAVP.

There are no controlled trials to establish the efficacy of DDAVP in arresting blood loss in cirrhotic patients.

### Myeloproliferative Disorders

The platelet defect in patients with myeloproliferative disorders is variably responsive to DDAVP infusion.

# GENETIC TESTING

The use of genotypic diagnosis, in conjunction with conventional assays, is now a routine part of the modern management of many bleeding disorders. Accurate carrier detection and prenatal diagnosis are essential elements in any genetic diagnostic service. All individuals with bleeding disorders and their families should have access to genetic services via their treatment centre. Genetic counselling should be available before, during, and after genetic analysis for all potentially affected individuals and those at risk of being carriers.

People who request genetic information about their bleeding disorder should be referred to the regional haemophilia treatment centre.

# PRODUCT INFORMATION

With the ongoing development of new products and changes in product availability due to tender processes, the list below covers the generic types of products available.

## Factor VIII deficiency

### Recombinant FVIIIa

This can be a regular or an extended half life product (EHL). These have a variety of methods of half life extension including PEGylation, protein fusion etc. Regular products are given 3–4 times weekly while EHLs are generally given twice a week for rutine prophylaxis.

### Human derived FVIIIa

This is rarely used in haemophilia currently – the product is more commonly used in von Willebrand disease and is currently the CSL product BiostateTM.

### Emicizumab

This is a bispecific monoclonal antibody that draws factors IX and X together replacing the action of FVIII.

### DDAVP (Desmopressin)

Synthetic ADH that acts by releasing addition stored FVIII in patients who have low levels but is not effective in severe disease where no stores are present.

### Tranexamic acid

Anti-fibrinolytic treatment. This agent is effective even when bleeding is not associated with laboratory evidence of accelerated fibrinolysis. Mechanism of action thought to be inhibition of tissue fibrinolysis and consequent stabilisation of clots.

Dose is 20mg/kg (max 1g) PO 6–8 hourly.

### Recombinant FVIIa (Novoseven)

Used for patients with inhibitors to factor VIII.

### FEIBA NF

Factor VIII Inhibitor Bypassing Activity (activated PCC). A human derived product used as an alternative to recombinant FVIIa.

## Factor IX deficiency

### Recombinant FIXa

This can be a regular or an extended half life product (EHL). These have a variety of methods of half life extension including PEGylation, protein fusion etc. Regular products are usually given 2 times weekly while EHLs are generally given once a week.

### Tranexamic acid

Anti-fibrinolytic treatment. This agent is effective even when bleeding is not associated with laboratory evidence of accelerated fibrinolysis. Mechanism of action thought to be inhibition of tissue fibrinolysis and consequent stabilisation of clots.

Dose is 20mg/kg (max 1g) PO 6–8 hourly.

### Recombinant FVIIa (Novoseven)

Used for patients with inhibitors to factor IX.

## Von willebrand disease

### DDAVP (Desmopressin)

Synthetic ADH that acts by releasing addition stored FVIII in patients who have low levels but is not effective in severe disease where no stores are present.

### Tranexamic acid

Anti-fibrinolytic treatment. This agent is effective even when bleeding is not associated with laboratory evidence of accelerated fibrinolysis. Mechanism of action thought to be inhibition of tissue fibrinolysis and consequent stabilisation of clots.

Dose is 20mg/kg (max 1g) PO 6–8 hourly.

### Human derived FVIIIa

The CSL product BiostateTM contains both FVIII and von Willebrand factor – a 500IU vial will have 500IU of FVIII and 1000IU of VWF. By convention doses are charted in FVIII units and will only be accepted by blood bank as such.

# APPENDIX 1

## DDAVP – Estimated Fluid Guidelines for Children to age 18

**Please limit your fluid intake for 24 hours following the administration of DDAVP.**

DDAVP can decrease your child's urine output for 12-24 hours after it is given. This can lead to too much water being stored in the body which can be a problem especially for young children. The guidelines below are to make sure your child doesn't have too much fluid during the 24 hours after DDAVP when they may be less able to get rid of it.

| Weight in kilograms | Maximum 24 hour fluid intake |
|---|---|
| 11–15 | 700mls |
| 16–20 | 900mls |
| 21–30 | 1 Litre |
| 31–40 | 1.4 Litres |
| 41–50 | 1.4 Litres |
| 51–73 | 1.6 Litres |
| 74–91 | 1.8 Litres |
| 92–114 | 2 Litres |

1. Adjust slightly for exercise, heat, and thirst.
2. Utilize 3/4 maintenance fluid orders for children receiving DDAVP pre-operatively and post-operatively.
3. Do not try to drink more if you are not feeling thirsty. It is okay to drink less than the above allowance.
4. Fluid intake includes such things as milk on cereal, jelly, ice blocks, soup or broth.