

national guidelines

Management of Haemophilia

Treatment Protocols

*Compiled by the
Medical Advisory Committee of
Haemophilia Foundation of New Zealand*

2005

Disclaimer

The information in this document is a treatment guideline only 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.

A list of appropriate specialists, who are all members of the Medical Advisory Panel of The New Zealand Haemophilia Foundation, is included in these guidelines

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GENERAL PRINCIPLES OF TREATMENT

SPECIALIST MANAGEMENT

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

TERMINOLOGY

Severity	Factor VIII 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. The dosing schedules are those generally recommended for plasma derived factor IX. Higher doses may be needed for patients receiving BeneFIX because of the lower recovery.

PAIN RELIEF

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

ACUTE JOINT BLEEDING

Minor joint bleeds should be treated with ice application, analgesics and rested in a functional position.

- **Ice Application** - the icepack is covered with a cloth and placed on the skin for 20 minutes.
- **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. Maintaining muscle function and strength are crucial after a bleed.

GENERAL PRINCIPLES OF TREATMENT

RECOVERY

The factor VIII (or IX) level measured after a given dose of the specific factor can be expressed as (factor) “recovery”. This should be reviewed at least every two years but more frequently during rapid growth phases in childhood and adolescence, or where the presence of an inhibitor is suspected.

$$\text{Recovery (K)} = \frac{\text{observed increase in factor activity}}{\text{expected increase in factor activity}} \quad \text{Target K values} = 0.8 - 1.2 \text{ for factor VIII}$$

$$\text{Observed Increase} = \text{post-treatment factor level} - \text{pre-treatment factor level (units/ml)}$$

$$\text{Expected Increase (units/ml)} = \frac{\text{units administered}}{\text{plasma volume (ml)}}$$

$$\text{Plasma Volume (mls)} = \begin{array}{l} 41 \times \text{weight in kg (adults)} \\ 50 \times \text{weight in kg (children)} \end{array}$$

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 use will be kept at each treatment centre.

Vaccinations

Routine vaccinations are recommended for all patients. These must be administered **subcutaneously**.

Children should be routinely vaccinated by their general practitioner for standard public health vaccinations. No specific prophylaxis is required. Prolonged local pressure for a minimum of 10 minutes is recommended at the injection site. If tetanus vaccination is being given, prophylactic cover is preferred because of the local irritant effect associated with this vaccine. Vaccination that may be required for travel abroad can be given in the normal manner but gammaglobulin should not be given by intramuscular injection.

HEPATITIS B VACCINATION

All patients who are sero-negative for hepatitis B and who may require blood products at any stage should be vaccinated against hepatitis B. Such patients require 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.

PROPHYLAXIS

This refers to the infusion of blood or recombinant products 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)

Given to infants identified as being at high risk of recurrent bleeding into target joints and at risk of arthropathy. Primary prophylaxis is usually reserved for the very severe cases with factor VIII or factor IX of $\leq 1\%$ of normal, as people with factor concentrations above 1% rarely develop disabling arthropathy. Regular prophylaxis is introduced after one or two severe bleeding episodes within the first 1 - 2 years of life. The aim is to minimise acute bleeding episodes. This is normally achieved with treatment given twice (factor IX) or three times (factor VIII) weekly. Factor usage corresponds to 2,000 - 3,000 IU/kg/year.

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 rebleeding from a target joint. Often used in the treatment of a chronic synovitis.

Who should receive prophylaxis?

Primary prophylaxis is standard treatment for infants with severe haemophilia (<1% factor) who declare themselves as high risk for the development of haemophilic arthropathy.

When should treatment start?

In general treatment is commenced within the first 12 - 24 months of life. It is normally commenced following the first significant spontaneous bleed (joint or soft tissue). A Port-A-Cath device may be needed to facilitate vascular access.

Short-term prophylaxis may be required for a patient with recurrent bleeding into a target joint.

PROPHYLAXIS

HAEMOPHILIA A

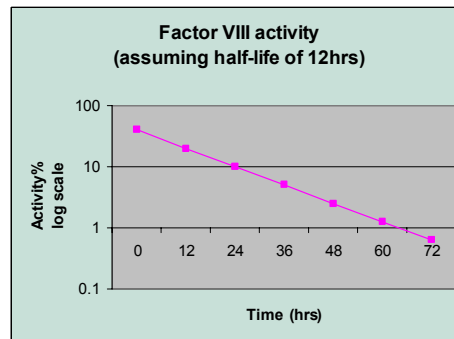
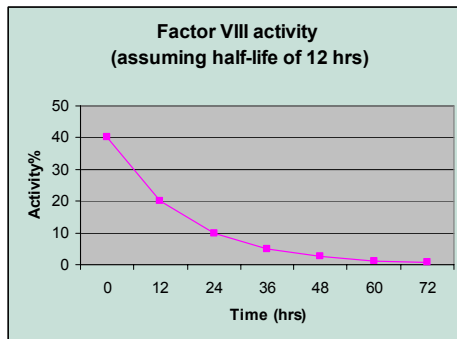
Aim to prevent spontaneous bleeding.

This is generally achieved by a peak factor VIII of 40% (assume half-life of 12hrs)

Variable schedule daily to three times weekly. (TIW)

FVIII 20u/kg/dose Three times/week (Mon, Wed, Fri)

A higher dose may be needed on Friday. 72hrs before next dose.



In patients with a shorter half-life or breakthrough bleeds the dosing should be increased. A dose between 25u and 40u/kg/dose may be required.

Dosing on alternate days should be considered if breakthrough bleeds are a problem.

It is advisable to calculate the recovery and half-life in all cases. In some patients it may be necessary to individualise the treatment protocol and recommend treatment as frequently as once daily.

HAEMOPHILIA B

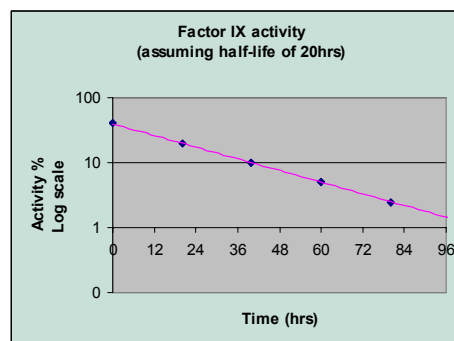
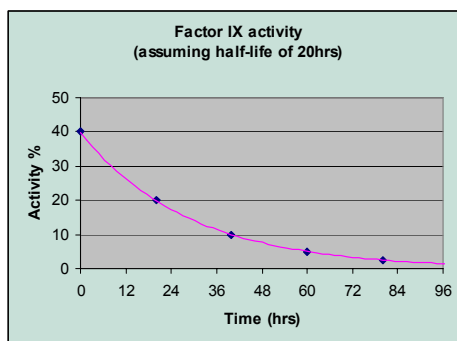
Aim to prevent spontaneous bleeding.

This is generally achieved by a peak factor IX of 40% (assume half-life of 20hrs)

Treatment is normally given twice weekly.

FIX 40u/kg/dose Twice/week

(Mon, Thurs)



In patients with a shorter half-life or breakthrough bleeds the dosing should be increased. A dose up to 60u/kg/dose may be required.

Dosing three times a week should be considered if breakthrough bleeds are a problem.

It is advisable to calculate the recovery and half-life in all cases. In some cases it may be necessary to individualise treatment and recommend more frequent administration.

MANAGEMENT OF BLEEDING

Small bleeds can be managed with one or two bolus doses.
Larger bleeds require repeated doses or treatment with a continuous infusion.
Doses for specific bleeds are detailed below.

CONTINUOUS INFUSION REGIMEN

1. Give a bolus dose sufficient to achieve a plasma FVIII activity of 80%.
2. The infusion rate is calculated from the formula:

$$\text{Infusion rate (IU/kg/hr)} = \text{clearance (mls/kg/hr)} \times \text{steady state concentration (IU/ml)}$$

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:-

$$\begin{aligned} \text{infusion rate (IU/kg/hr)} &= 4 \text{ (mls/kg/hr)} \times 0.8 \\ &= 3.2 \text{ IU/kg/hr}^* \end{aligned}$$

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.

Important Note

The volume of the sterile water ampoules differ for different products:

KogenateSF –	2.5ml.
Refacto -	4ml.
Recombinate –	10ml.
Biostate	5ml.

HAEMARTHROSES

SPONTANEOUS

If treated early a single dose of replacement product may be sufficient. If symptoms do not settle, a second dose 12 to 24 hours later should be considered.
Specialist advice should be sought if the bleed has not settled after two doses.

AIM To achieve a peak factor level of 30 to 40% activity

TREATMENT REGIMEN

FVIII 20 u/kg
FIX 30 u/kg

TRAUMATIC, LATE, OR MORE MAJOR BLEED (EXCLUDING KNEES/HIPS)

In more major bleeds a dosing schedule with repeated doses should be used.

AIM To increase factor level to 30 - 40%. Repeat dosing schedule.

TREATMENT REGIMEN

FVIII 20 u/kg → 10-15 u/kg @ 12 hrs → 10 u/kg @ 24 hours.
FIX 30 u/kg → 15-20 u/kg @ 12 hrs → 15 u/kg @ 24 hours.

If symptoms persist after 24 hours continue with the 24 hour dose regimen until symptoms settle.

Note – In children the plasma half-life of factor VIII and factor IX may be reduced. In these cases it may be necessary to give treatment every 8 hours.

MAJOR HIP, KNEE, OR SHOULDER BLEEDS AND MAJOR TRAUMATIC BLEEDS

Admit to hospital if necessary. Repeated dosing schedule.

AIM To increase factor level to 60 - 80% initially with dose reduction.

TREATMENT REGIMEN

FVIII 30 - 40 u/kg → 20 u/kg 12 hourly for 2 - 5 days according to severity.
FIX 50 - 60 u/kg → 40 u/kg daily for 2 - 5 days according to severity.

Dose reduction under consultant supervision.

Treatment with a continuous infusion should be considered (see above).

MUSCLE BLEEDS

Consider admission to hospital for major muscle bleed.
Repeated dose schedule or continuous infusion.

- AIM** To increase factor level to 80% with trough levels \geq 40% initially.
Dose reduction over 7 - 10 days under consultant supervision.

PHYSICAL MEASURES

Immobilisation is important.
Ice or a cooling pack should be used on an acute bleed.

TREATMENT REGIMEN

FVIII 40 u/kg → 20 u/kg 12 hourly up to 5 days, then reduce appropriately
FIX 50 - 60 u/kg → 40 u/kg daily up to 5 days, then reduce appropriately

Physiotherapy is important to maintain a full range of movement. Factor replacement may be necessary prior to exercise.

Follow-up - After a significant muscle bleed follow-up is recommended to ensure no evidence of compression or compartment syndrome. Pseudotumours can develop from an inadequately treated muscle bleed.

Psoas bleed

Patients with a psoas muscle bleed may require hospital admission and prolonged replacement therapy for up to 7 to 10 days. Further treatment may be required prior to mobilisation and physiotherapy.

MAJOR HEAD INJURY OR INTRA-CEREBRAL BLEED

NOTE: In a suspected intracranial bleed or significant head injury treatment must be given immediately. It must NOT be delayed until radiological investigations confirm bleeding.

Admit to hospital and give immediate therapy. Urgent Haematologist consultation must be sought. Multiple dosing schedule or continuous infusion.

- AIM** To increase factor level to 80% with a trough levels \geq 50% for 72 hours then dose reduction over 14 days or longer under supervision.
Monitor factor levels pre and post treatment

TREATMENT REGIMEN

Continuous infusion is most appropriate

Alternatively use

FVIII 40 - 50 u/kg → 25 u/kg 8 hourly for 72 hours → reducing dose.
FIX 50 - 60 u/kg → 30 u/kg 12 - 24 hourly for 72 hours → reducing dose.

SURGERY

All surgery should be discussed with a Regional Haematologist, and treatment individualised.

Liver or Renal biopsy should be referred to Regional Haemophilia Services.

MINOR PROCEDURES - ENDOSCOPY & SKIN LESIONS

- AIM** To increase factor level to 50%.
This is most easily achieved with a multiple dose schedule.
Combine with an antifibrinolytic therapy.

TREATMENT REGIMEN

FVIII 25 - 30 u/kg, repeat dose at 24 hours and as required.

FIX 50 u/kg, repeat dose at 24 hours and as required

Tranexamic acid 1 g tds, 7 - 14 days.

Topical agents as required.

MAJOR PROCEDURES - GENERAL OR ORTHOPAEDIC SURGERY.

Consultation between blood centre, surgeon, and haematologist is essential.

Prepare a written management protocol.

Ensure appropriate target levels by factor level monitoring.

- AIM** To increase factor level to a target of 80-100% with a trough level > 50%.

TREATMENT REGIMEN

Continuous infusion is most appropriate.

Alternatively use:

FVIII 40 - 50 u/kg with post dose level available before/during surgery.

FVIII 25 u/kg 8 hours after start of surgery then 8 hourly for 24 hours.

FVIII 25 u/kg 12 hourly for 48 hours; pre/post dosing levels.

FVIII 20 u/kg daily 5 days.

FVIII 10 - 15 u/kg daily 5 - 7 days.

Total therapy for 10 - 14 days.

Monocomponent factor IX (e.g. Mono FIX) for Haemophilia B (FIX deficient) patients.

DENTAL PROCEDURES

Dosage levels depend on the precise nature of the procedure. The treatment regimen should be planned in consultation with the oral surgeon.

Nerve blocks (e.g. inferior dental nerve block) are not contraindicated provided satisfactory factor levels are achieved and there is close liaison between a haematologist and dental surgeon experienced in the management of haemophilia.

Infiltration local anaesthesia has a low risk of complications and periodontal (intraligamental) local anaesthesia can be used without risk.

ROUTINE EXTRACTION WITH LOCAL ANAESTHETICS.

AIM To increase factor level to 30%, follow-up treatment according to response. Use local and/or systemic antifibrinolytic agents.

TREATMENT REGIMEN

FVIII 15 - 20 u/kg preoperatively, repeat dose next day if required.

FIX 30 u/kg preoperatively, repeat dose next day if required.

Tranexamic acid syrup (500mg/5mls) 5 - 10 mls 6 hourly, hold in mouth \geq 2 minutes before swallowing.

An alternative is to crush tranexamic acid tablets in warm water and use as a mouthwash. (This tastes more bitter than the syrup).

If not swallowed, consider giving additional systemic tranexamic acid tablets. (1g t.d.s orally.)

DENTAL EXTRACTION WITH SURGICAL FLAPS (GENERAL ANAESTHESIA)

AIM To increase factor level to 40 - 60%, with multiple dosing or continuous infusion.

TREATMENT REGIMEN

FVIII 20 - 30 u/kg preoperatively → 20 u/kg @ 12 hrs → 20 u/kg @ 24 hours.

FIX 40 u/kg preoperatively → 20 u/kg @ 12 hrs → 20 u/kg @ 24 hours.

Tranexamic acid syrup (500mg/5mls) 5 - 10 mls 6 hourly, hold in mouth \geq 2 minutes before swallowing. If not swallowed, consider giving additional systemic tranexamic acid (1g t.d.s. orally)

CHRONIC KNEE SYNOVITIS

Medical management should be used initially but if there is a failure to respond within 10 - 12 weeks arthroscopic synovectomy or radionuclide synovectomy should be considered. A treatment plan should be developed in consultation with the relevant specialists.

MEDICAL MANAGEMENT -

TREATMENT REGIMEN

FVIII 15 - 20 u/kg daily or FIX 20 - 30 u/kg daily for two weeks, then review.

Ongoing intensive treatment daily to three times weekly as required.

Prednisone 1 mg/kg for 5 days.

Night splinting to immobilise; day splints to protect joint.

Isometric exercises of adjacent muscles.

Endpoint - Continue up to three months. If no response, do not continue beyond three months and consider alternative management.

RADIONUCLIDE SYNOVECTOMY

Patients

- Usually > 10 years old.
- Mild-moderate but not advanced arthritis (cartilage should remain).
- Beta emission isotope preferred (Yttrium 90).
- Yttrium 90 is obtained as the silicate in colloidal suspension. T^{1/2} 7 days.

Pre-synovectomy

- Factor concentrate to give factor level \geq 30% for 48 hours.
- For inhibitor patients, use a single dose of FVIIa (Novo Seven) or FEIBA

TREATMENT REGIMEN

5 - 7 mCi Yttrium by intra-articular injection. Xylocaine and dexamethasone by intra-articular injection through the same intra-articular needle to add sufficient volume to distribute the isotope.

Splint the joint or place in plaster cast to immobilise for 48 - 72 hours.

Repeat injections may be necessary to maximum 14 mCi per patient.

Outcome

- Expect 80% reduction in bleeding.
- Complete cessation in 60%

INTRA-ARTICULAR INJECTIONS

Aim To increase factor concentration to 40 - 60%.
Give a single follow-up dose at 24 hours.

TREATMENT REGIMEN

FVIII 30 u/kg preoperatively → 20 u/kg at 24 hours.

FIX 40 u/kg preoperatively → 30 u/kg at 24 hours.

HAEMATURIA

No treatment if painless. Increase oral fluids.
If continuous - trial of steroids.
If painful with clots give factor replacement therapy.

Aim To increase factor level to 30 - 40%.

TREATMENT REGIMEN

Prednisone 1 mg/kg for 72 hours.

If the patient fails to respond proceed to

FVIII 20 u/kg daily for 3 doses then review.

FIX 30 u/kg daily for 3 doses then review.

Avoid Tranexamic Acid

MILD HAEMOPHILIA

Non-blood product treatment with DDAVP is used for minor bleeds and minor surgical procedures in mild to moderate haemophilia A.

TREATMENT REGIMEN

0.3 µg/kg I.V. or subcutaneously. Intranasal dose is 300 µg adults and 150 µg children.

Repeat up to 3 doses within 24 hour period then at intervals > 48 hours.

Tranexamic Acid 1 g tds, orally.

DDAVP

DDAVP (Minirin or Octostim), a synthetic analogue of the antidiuretic hormone Vasopressin, is an established non-transfusional form of therapy that can release factor VIII:C and von Willebrand factor from endothelial storage sites. VWF levels increase 3 - 4 fold and FVIII:C, the coagulant activity of the factor VIII complex, increases 3 - 5 times. DDAVP will also shorten the bleeding time.

The DDAVP effect on factor VIII parameters lasts for 6 - 8 hours. Patients may become progressively unresponsive to DDAVP with repeated daily or twice daily doses over 2 - 3 days. Responsiveness to DDAVP will return when the drug has been discontinued for two days.

USE IN HAEMOPHILIA A

DDAVP is especially useful in patients with mild haemophilia who have a baseline FVIII:C >10%. A three fold rise in factor VIII:C after DDAVP enables a factor VIII target level of at least 30% to be achieved which is sufficient for normal haemostasis in minor surgical procedures. In both mild and more moderately severe haemophiliacs the use of DDAVP may be useful as an adjuvant therapy with factor VIII concentrate to achieve adequate haemostasis. 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.

Dosage and Administration

DDAVP can be administered subcutaneously or intravenously. Peak levels of factor VIII occur 90 - 120 minutes after subcutaneous administration and 30 - 45 minutes after intravenous administration.

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 or Amicar (amino-caproic acid); 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.

Blood samples should be considered before and 30 - 60 minutes (if i.v. administration) after the DDAVP infusion so that the factor VIII result will be known before surgery. The peak effect following intravenous use, has variously been reported to occur within 60 minutes of infusion. For subcutaneous injection, blood samples are usually taken at two hours.

The critical haemostatic level for surgery or dentistry should be judged by the same criteria as if the patient were being managed with blood products except that the level may sometimes continue to rise for about an hour after the infusion rather than beginning to fall immediately. If a sufficient level has not been reached to cover the intended surgical procedure a supplementary dose of factor VIII should be added.

The dose detailed above can be repeated at 12 hourly intervals though it is important to repeat factor VIII assays as the response may fall off with repeated injections and to remember that there may be some refractoriness within 48 hours of the last dose.

The intranasal preparation is not reliable because of variable absorption but can be very useful when levels are not critical.

Precautions

Rapid infusion can result in very severe headache, flushing, palpitations and other pressor effects.

Avoid fluid overload, especially in young children, and do not routinely leave intravenous infusion going after surgery. If repeated doses are given, monitoring of patient weight and plasma sodium is strongly recommended.

Side Effects:

- vasomotor reactions including flushing (50% of subjects)
- headache, especially if lying down
- ADH-like effects with fluid retention and hyponatraemia.
- local stinging sensations
- may occasionally precipitate vascular accidents such as myocardial infarction in at risk patients.

Contraindications:

- Hyponatraemia.
- Avoid using in children under two years of age.
- Closed head injury.
- Myocardial infarction or stroke.
- Caution when using in patients >70 years or younger if there is a history of arteriovascular disease.

FACTOR VIII CONCENTRATE IN MILD HAEMOPHILIA

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. In the majority of mildly deficient factor VIII patient, especially those who are previously untreated (PUPS), recombinant factor VIII is the product of choice.

MANAGING PATIENTS WITH INHIBITORS

Alloantibodies to factor VIII occur in 10 - 15% of patients with classical haemophilia (usually <10% FVIII level) and usually within the first 25 treatment exposure days. Inhibitors do not occur after 200 treatment exposure days. Factor IX antibodies are extremely rare.

INFORMATION REQUIRED

Titre of the factor VIII inhibitor at the time of therapy.

- ≤ 5 BU can be treated with neutralizing doses of Factor VIII
- $5 \leq 20$ BU may respond to neutralising doses of Factor VIII
- 20 BU/ml unresponsive to FVIII concentrate.

Is the patient known to have an inhibitor of the low or high responder type?

- Majority of patient (>75%) are high responders.
- A low responder antibody remains <5 BU/ml.

Severity and site of bleeding.

MANAGING ACUTE BLEEDS

Discuss with the Regional Haematologist for individual treatment plan.

FVIIa (Novo Seven) is the recommended initial therapy.

Use only at the direction of a specialist haematologist involved with haemophilia care.

FEIBA can be considered as an alternative.

Consider assessing the response to non-activated prothrombin complex concentrate (Prothrombinex). Few patients show response to this treatment and it should not be used in a newly diagnosed case. However some established cases do gain some benefit from this treatment for a minor bleed.

MINOR BLEEDS

Recombinant Factor VIIa (Novo Seven)

TREATMENT REGIMEN

Conservative measures and pain relief should be considered for very minor bleeds.

rFVIIa: Recommended initial dose of 90 μ g/kg followed by a second dose at 2 hours.

Further doses may be required if there is evidence of continuing bleeding.

Prothrombinex for patients previously shown to respond to this treatment.

TREATMENT REGIMEN

Prothrombinex 50 - 100 u/kg for 3 doses then review.

MAJOR BLEEDS**TREATMENT REGIMEN**

Recombinant factor VIIa (Novoseven)

Recommended dose of 90 µg/kg given 2 hourly initially, with frequency reduction to 3 hourly and then 4 hourly as indicated by clinical progress until bleeding ceases.

FEIBA

Factor Eight Inhibitor Bypassing Activity is an activated prothrombin complex concentrate available as FEIBA TM-4 (specific activity 0.7 - 2.5 units/mg) prepared from pooled human plasma and high heat treated (60°C for 10 hours and 80°C for 1 hour during production). FEIBA has been used to treat joint, muscle and soft tissue bleeding in patients with both high and low responder inhibitor titres where the antibody is ≥ 5 BU. It has also been used for life threatening bleeds and surgery.

Dosage schedules, independent of inhibitor titre, are between 50 - 100 u/kg repeated 6 - 12 hourly for patients with haemophilia. Lower doses given more frequently by intermittent infusion may be preferable in some circumstances. Doses of 20-60 units FEIBA/kg of body weight are given up to 8 hourly in non-haemophilia patients with spontaneous inhibitors. The total daily dose of FEIBA should not exceed 200 u/kg body weight per day.

Efficacy rates reported in clinical trials are 80-90%.

TREATMENT REGIMEN**Joint, Muscle and Soft Tissue Haemorrhage**

Minor-moderate bleeds 50-75 u/kg 12 hourly.

Major muscle bleeds 100 u/kg 12 hourly.

Mucous Membrane Bleeding

50 U/kg 6 hourly with dose escalation to 100 u/kg if required.

CNS or Life Threatening Bleeds

100 u/kg 12 hourly. More frequent administration of lower doses at 2 - 4 hourly intervals should be considered in this setting.

Surgery

50-100 u/kg 6 hourly (up to maximum dose 200 u/kg per day).

LOW LEVEL INHIBITOR

Neutralising doses of Human FVIII C can be used in a patient with an inhibitor of less than 2.0 Bethesda units. The neutralising dose is usually 2-3 times the standard dose regimen.

Continuous infusion or intermittent dosing can be used.

Give initial test dose of approximately 100units. Have adrenaline and hydrocortisone near at hand.

TREATMENT REGIMEN

Initial bolus of 5,000 units of factor VIII followed by 500 - 1000 units hourly by continuous infusion (adults). Pro-rata reduction according to body weight in children.

Intermittent therapy is usually 25-100u/kg, depending on the indication.

Measure factor VIII level 3 hours after starting therapy.

Measurable factor VIII levels (>2 - 3%) should encourage continuation of therapy with the expectation that levels will continue to rise.

If levels are not measurable (0 - <1%) higher doses and continued infusion is unlikely to be effective.

When infusions are continued, maintain high levels and do not reduce infusion rate by more than 25% per day.

Monitor factor VIII levels daily. When factor VIII level starts to fall subsequent increases in the infusion rate are usually ineffective.

A reactive increase in antibody (anamnestic response) usually begins at 3 - 7 days peaking at 14 days. This will result in resistance to the infusion regime. Thrombocytopenia may occur.

Immune Tolerance Therapy (ITT)

AIM To suppress inhibitor by high dose repeated infusion of factor VIII concentrate.

There are a number of different regimen reported for ITT.

These generally use 50 - 200 u/kg once daily as the starting dosage.

There are no data for continuous infusion but, if the child is in hospital, it is theoretically advantageous to give the first dose as a bolus and then divide the daily dose as a continuous infusion to increase the time of antigen exposure to the T lymphocytes. Continuous infusion with or without recombinant FVIIa may be necessary to facilitate insertion of a portacath.

The best predictor of a successful outcome of ITT is a starting inhibitor titre ≤ 10 BU. Dosage of 50 - 100 u/kg/day initially seems to be most cost effective although German experts have recommended higher dosages. At present there is no evidence to show that the type of product used for ITT is an important variable.

The peak inhibitor titre and its duration may influence response. If the peak inhibitor titre is ≤ 50 BU, and the duration of the inhibitor < 5 years, there is a predicted 90% or greater success rate with ITT. If the peak inhibitor titre is greater than 50 BU and duration greater than 5 years, the response rate is less than 50%.

Product choice will be either recombinant or plasma derived factor VIII depending on the individual meeting access criteria for recombinant therapy. At present there is no difference in outcomes between patients treated with recombinant or plasma derived factor VIII.

The Medical Advisory Committee of the NZ Haemophilia Foundation prepared the following algorithm.

<p>ELIGIBLE PATIENT</p> <p>STARTING FVIII at a dose of up to 200 u/kg/day <i>(protocols using either 100u/kg or 200u/kg have been used)</i></p> <p>Measure inhibitor titres (BU) every 2 to 4 weeks</p> <p style="text-align: center;">↓</p>		
<p>Review at 3 months Is the inhibitor titre <2.0 BU?</p>		
<p>Yes</p> <p>reduce to 50 u/kg/day measure inhibitor monthly</p>	<p>No</p> <p>Repeat x 1 If already repeated this once i.e. 6 months of 100 u/kg/day and BU >2.0, refer to Medical Advisory Panel for review.</p> <p>Likely to <u>exit</u> tolerance programme if very poor response.</p> <p>If signs of falling titres then to continue on tolerance programme reducing to 50 u/kg/day with monthly BU. Review by Panel at 12 months before going to low dose tolerance (equivalent to prophylaxis).</p>	
<p>Review at 6 months is the inhibitor titre <2.0?</p>		
<p>Yes</p> <p>reduce to 25 u/kg/day for a further 8 weeks</p>		
<p>Titre remains <2.0 BU</p> <p>prophylaxis of 20 - 25 u/kg/day 3 times a week</p>	<p>No</p> <p>continue with 50 u/kg/day for a further 6 months If titre >2.0</p> <p>If inhibitor titre remains >2.0 BU refer to Medical Advisory Panel</p>	

- Following initiation of I.T.T., weekly inhibitor assays are recommended to define the anamnestic response. This is useful to document the peak titre and the rate of fall in inhibitor titre of I.T.T. Inhibitor assays should be performed at a minimum of each month during the first three months and subsequently at a minimum of three monthly for the first 12 months.
- All dosage changes should be accompanied by recovery studies whenever possible.
- Transient rises in inhibitors can occur with an intercurrent inflammatory stimulus such as infection, other illness or a significant bleed.

Access Criteria:

- Applications for I.T.T. are made to the Tolerisation Advisory Committee through the Chairperson of the Medical Advisory Committee of the N Z Haemophilia Foundation.
- The patient must be under the direct care of a Regional Haemophilia Centre.
- Treatment must be approved by the Medical Advisory Committee
- Progress will be reviewed by the Medical Advisory Committee at least every 6 months.

Assessment

- In assessing priority for this therapy preference will be given to children ≤ 5 years, with a low titre (10 BU or less) and a short duration of inhibitor.
- The inhibitor titre must be confirmed on at least two occasions ≥ 7 days apart. A titre ≥ 5 BU defines a high responding inhibitor.
- It is important to ensure that patients with transient low titre inhibitors are not entered into an I.T.T. programme. These inhibitors are usually $< 1 - 2$ BU.
- Factors to be considered in assessing suitability for entry into an I.T.T. programme include
 - the duration of the inhibitor.
 - maximal inhibitor titre.
 - titre immediately prior to initiation of I.T.T.
 - consideration of concomitant conditions especially where these may significantly limit life expectancy.
 - psychosocial assessment of patient and family to determine ability to cope with I.T.T. programme.
 - agreed cooperation and acceptance of I.T.T. therapy requirements by patient and/or parent/guardian. Written informed consent prepared.
 - acceptance by the patient (and/or family) for placement of an intravenous access device, the need for ongoing catheter maintenance, good infection control practice and replacement of the indwelling device if needed.
- Patients may be refused entry on any of the following criteria
 - inhibitor duration.
 - other morbidity.
 - patient/family's ability to comply with the regimen.

OUTCOME

At least six months of high dose therapy is needed for the inhibitor (BU) to fall to ≤ 2.0 . Further therapy (six months or longer) may be necessary for complete suppression.

The criteria for successful immune tolerisation

- Absent or barely detectable inhibitory activity.
- Evidence of factor VIII recovery (30 minutes) post infusion.
- Factor VIII half-life ≥ 4 hours by fall off study.

Long term prophylaxis

- Following successful I.T.T., prophylaxis will be continued indefinitely (lifelong) to prevent inhibitor recurrence.
- Repeat recovery studies and antibody titres:-
 - three months after starting prophylactic dosing.
 - six monthly for two years.
 - annually beyond two years.

FAILURE OF I.T.T.

If by 12 months successful I.T.T. has not been achieved, the patient should be referred to the Medical Advisory Committee for careful review.

If at 12 months the inhibitor titre is equal to or greater than the starting titre, the I.T.T. programme would usually be regarded as having failed and the patient withdrawn from the programme.

Continued prophylaxis may be recommended by the Tolerisation Advisory Committee on an individual basis. Failure to comply with recommended treatment and support protocols may also be a reason for ceasing the I.T.T.

The Tolerisation Advisory Committee may therefore discontinue the I.T.T. regimen after 12 months based on the following:-

- persistently elevated inhibitor level with little evidence of response.
- other morbidity.
- patient/family's level of compliance unacceptable.

INTRAVENOUS GAMMAGLOBULIN (INTRAGRAM) (another potential inhibitor therapy)

1g/kg intravenously daily for two days, particularly consider for factor VIII autoantibodies.

IMMUNOSUPPRESSION:

Disappointing for alloantibodies; used in the management of autoantibodies.

Prednisone 1 mg/kg for three weeks, then taper.

Cyclophosphamide 2 -3 mg/kg orally initially then reducing to 0.75 - 1 mg/kg for 3-6 months. Alternatively, cyclophosphamide may be administered by the intravenous route initially as bolus injections of 1- 2 g on a weekly schedule.

OBSTETRIC MANAGEMENT OF CARRIER WOMEN

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.

MANAGEMENT OF MOTHER

Pre-pregnancy

- pre-pregnancy counselling should be offered to all potential carriers.
- establish carrier status.
- determine factor VIII/IX gene abnormality.
- assay clotting factor (VIII/IX) level

Discuss each case with regional Haematologist

North Island - Contacts

Paul Ockelford,

Tel 0274 939 252; Fax (09) 571 4057; e-mail: pao@dml.co.nz or

Paul Harper

Tel 021 774 516 ; e-mail paulh@adhb.govt.nz

South Island - Contact

Mark Smith, Haematology Dept., Christchurch Hospital -

Tel (03) 364 0381; Fax (03) 364 0750; e-mail: @chhlth.govt.nz

On diagnosis of pregnancy

For all pregnancies, actively enquire about a family history of bleeding disorder - specifically ask about haemophilia A (factor VIII deficiency) and haemophilia B (factor IX deficiency, Christmas disease.)

Plan management with obstetrician and haematologist.

For carrier mothers:

Management depends on the parents' attitude to haemophilia and termination of pregnancy, guided by genetic counselling, and whether the mother is informative on DNA testing:

Parents *wising to terminate pregnancy* if fetus has severe haemophilia and mother informative on DNA testing:

Either

- perform chorionic villus sampling at 11 - 13 weeks and proceed to gene testing on males.

Or

- determine sex of fetus by intravaginal ultrasound at 14 - 16 weeks. If male, proceed to amniocentesis and gene testing.

Parents *not wishing to terminate but would like to know whether fetus is affected* and mother informative on DNA testing:

- as above but ensure the parents are aware of the risks of CVS.

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 $\geq 50\%$ for procedures such as CVS, amniocentesis, or termination.
- **Factor VIII deficiency:** recombinant factor VIII for procedures other than termination. DDAVP is acceptable for terminations.
- **Factor IX deficiency:** high-purity factor IX concentrates (avoid prothrombinex - thrombogenic)
- **Discuss delivery plan.** 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.
- 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 haemophilia A carrier, monitor factor VIII level daily after birth if <50% before pregnancy (acute phase protein and level falls post delivery). Give DDAVP or recombinant factor VIII if levels <50% for-
 - ⇒ 3 days if normal vaginal delivery
 - ⇒ 5 days if caesarean section
- For haemophilia B carrier, give replacement only if level noted to be < 50% - no need to monitor daily

Potential new case 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 - 36 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. 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 deficiency it is essential that the results are **sensitively communicated to the parents by experienced staff**.

Confirm diagnosis with a further factor VIII/IX level.

Follow newborn closely for a minimum of 7 days after birth through daily phone contact from Haemophilia Centre or GP and frequent midwife visits. Educate parents regarding symptoms of ICH - poor feeding, irritability, listlessness, full fontanelle, convulsions, pallor, etc.

The role of CT scanning in all newborns with haemophilia is controversial. We recommend the following

- A CT scan (in preference to ultrasound) of head should be performed if clinical suspicion of ICH.
- A CT head scan is recommended in all high risk deliveries.
- The need for a CT scan in all other cases depends on the clinical circumstances. We recommend that all cases are discussed with a specialist centre.
- If confirmed ICH, treat according to National Guidelines for intracranial haemorrhage.
- Suggest factor VIII/IX level is measured on females born to carrier mothers to detect the occasional carrier female with low levels at risk of symptomatic bleeding.
- Assay factor VIII/IX levels in newborns **without a family history** of haemophilia if coagulation screen shows prolonged APTT, particularly

if significant or unusual haemorrhage occurs 'spontaneously' e.g. subgaleal haemorrhage, large cephalhaematoma, unusual pattern of bruising

if excessive bleeding occurs with procedures e.g. venepuncture, vitamin K injection, or circumcision. Do not be dissuaded from considering haemophilia if haemorrhage is a presenting feature of a newborn's illness, even if:

⇒ coagulation screen suggests DIC

⇒ thrombocytopenia coexists with prolonged APTT

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.

MINOR BLEEDS

Most patients with type I vonWillebrand disease can be managed with DDAVP (see above for treatment protocol). DDAVP increases factor VIII levels to a similar or greater extent than in patients with mild haemophilia and shortens or normalises the skin bleeding time and platelet function assay. 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 250 units of factor VIII and approximately 500 units of von Willebrand cofactor activity). These plasma concentrates vary somewhat in terms of their content of high molecular weight multimers.

Recombinant factor VIII products are not suitable.

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 concentration and not von Willebrand factor level is used in dosage schedules and to monitor treatment. In major surgery it is advisable to supplement the factor VIII levels with ristocetin cofactor assays if possible and/or monitor platelet activity with the PFA-100.

A recommended dosage schedule is as follows:

DOSES OF FVIII-vWF CONCENTRATES FOR vWF PATIENTS UNRESPONSIVE TO DDAVP:

TYPE OF BLEEDING	DOSE (IU/KG) OF FVIII	NUMBER OF INFUSIONS	OBJECTIVE
Major Surgery	20-40	once a day or every other day	maintain FVIII >50% until healing is complete
Minor Surgery	15	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	

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.

PREGNANCY

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

- Because of the increase in factor VIII levels in pregnancy it may be difficult to exclude a diagnosis of von Willebrand disease in pregnancy.
- In most patients, if the factor VIII levels are going to normalise, this will occur by 34 - 36 weeks gestation.
- After delivery the factor VIII levels fall rapidly.
- The risk of per-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.

Management in Pregnancy

- A careful personal and family bleeding history is important.
- In patients with suspected vWD test at 34 - 36 weeks (or earlier if preterm delivery is likely).
- Request von Willebrand screen (record blood group).

- *Remember: normal levels do not exclude a diagnosis of vWD.*
- Avoid epidural anaesthesia (see below).

Treatment Options

These include either DDAVP or plasma derived factor VIII (CSL Biostate). Do not use recombinant factor VIII, plasma, or cryoprecipitate.

MANAGEMENT AT DELIVERY

- If the Factor VIIIc parameters are normal at 34 - 36 weeks manage expectantly but with a high index of suspicion for postpartum haemorrhage.
- If the Factor VIII levels are unusual or fail to normalise (e.g. $\leq 50\%$) consider prophylaxis:-

Either

- DDAVP (0.3 $\mu\text{g}/\text{kg}$) given following clamping of umbilical cord.
CAUTION: DDAVP is an antidiuretic agent and can cause hyponatraemia. Care with I.V. fluid replacement

Or

- Plasma derived factor VIII (CSL Biostate 250 units/reconstituted bottle). This should be used if there is a history of significant bleeding with a previous delivery.
- Approximately 3 - 4 bottles administered by slow I.V. push.

POST PARTUM HAEMORRHAGE

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

- DDAVP (0.3 $\mu\text{g}/\text{kg}$) by I.V. infusion (diluted in crystalloid over 20 minutes).
- *CAUTION: DDAVP is an antidiuretic agent and can cause hyponatraemia. Care with I.V. fluid replacement*

If bleeding is significant plasma derived factor VIII (CSL Biostate - 3 - 4 bottles by slow I.V. push) should be given.

SPINAL - EPIDURAL ANAESTHESIA FOR LABOUR AND DELIVERY

The majority of patients with type I von Willebrand disease show normalisation of 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.

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 potential issue relates to medico-legal risk.

If the anaesthetist is conversant with the risks, and following full discussion with the patient, it may be acceptable to proceed with epidural or 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 DDAVP at the time of the needle/catheter insertion (particularly if a traumatic tap occurs) and possibly at the time of removal of the catheter. 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 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.

Platelet Disorders

CONGENITAL PLATELET FUNCTION DEFECTS:

Platelet disorders can be treated with DDAVP, platelet transfusion or recombinant factor VIIa.

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. A therapeutic trial is indicated where possible to determine if an individual patient is DDAVP responsive.

In cases of more severe bleeding a platelet transfusion may be required. 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.

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. This shortening of bleeding time to below 10 minutes is still present in a majority of patients even after four hours. There are no controlled trials that show that DDAVP stops spontaneous bleeding or prevents excessive blood loss after surgery.

Hepatic Cirrhosis

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. Check bleeding time response. There are no controlled trials to establish the efficacy of DDAVP in arresting blood loss in cirrhotic patients with a prolongation of the bleeding time.

Myeloproliferative Disorders

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

DNA DIAGNOSIS OF HAEMOPHILIA A & B

The use of genotypic diagnosis of haemophilia A and B, in conjunction with conventional assays, is now a routine part of the modern management of haemophilia. Accurate carrier detection and prenatal diagnosis are essential elements in any genetic diagnostic service.

All individuals with haemophilia and their families should have access to specialised genetic services. Genetic counselling should be available before, during, and after genetic analysis for all potentially affected individuals and those at risk of being carriers.

Patients and families should be advised to make initial enquiries via their local Haemophilia Centre followed by referral to a specialist haematologist at Auckland, Wellington or Christchurch Centres, or direct referral to the Genetics Services. Patients can self-refer to the Genetics Services. It is important that genetic testing is only undertaken in a centre where there is ready access to genetic counselling services. Close collaboration between the genetics services and the Haemophilia centre is encouraged.

PRIOR TO TESTING

The patient should be provided with information on the following:-

- The inheritance patterns of the condition
- The nature and implications of the inherited disorder
- The options open to the family/whanau

The patient should understand the following:-

- That they have a choice whether or not they have the test (freedom from coercion)
- The purpose of the test and what it involves
- The potential benefits, risks and degree of uncertainty of the test, including any implications for other family/ whanau members

CONSENT

Informed consent for testing is conducted in the wider context of genetic counselling. Signed consent must be obtained before testing.

PRETEST ASSESSMENT

The following points related to testing should be considered in the pre-test discussion and follow-up.

- Establish that a bleeding disorder is present in the family and determine its type and severity
- Establish a pedigree/family tree
- Assess understanding, expectations, beliefs and wishes.
- Acknowledge the implications of individual and family experiences, values and culture.
- Address personal and relationship concerns related to testing
- Provide the opportunity for 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

The following specific information related to Haemophilia should be discussed:-

- The potential clinical effects of being a carrier or affected person
- Current treatment and implications of the condition
- The mode of inheritance and the individual's genetic risk.
- The rationale for identifying the genetic defect
- The means by which carrier status is assessed
- What is involved in genetic testing: sample collection; transfer/storage of data; research projects on stored material; insurance issues; risk of error.
- What will happen to any information collected
- What will happen to the DNA sample collected

It is the responsibility of the clinician dealing with the particular case, and not the laboratory, to ensure that informed consent is obtained.

RECORDS

It is recommended that Haemophilia Centres develop family genetic records of patients with haemophilia and other inherited bleeding disorders.

It is recommended that these notes should

- be a separate genetic file
- be kept within the Haemophilia Centre
- contain the family pedigree. The pedigree should be compiled in a standardised way for all haemophilia families.
- contain the results of all relevant genetic tests, (factor assays and molecular genetic tests).
- contain informed written consent for genetic studies, sharing of appropriate family information and inclusion on a register.
- contain copies of all pedigree related correspondence
- be kept confidential and only accessed by authorised staff of the Haemophilia Centre.

It is recommended that a haemophilia genetic register is also established in each centre. This comprises a list of people affected by, or at risk of genetic disease, linked as families.

A register can

- Allow regular contact with families,
- Allow planned follow-up in order to offer counselling to at-risk family members at appropriate ages.
- Allow recall of families in the light of genetic research developments.

Note: It is usually regarded as the family's responsibility to contact affected relatives and alert them to the offer of genetic testing. In those cases where the individual is unwilling to transmit the information but gives consent for the information to be shared, the haemophilia centre should approach the relatives through their GP.

It is recommended that a post consultation letter is sent to all families indicating the genetic risks, options available and the offer of genetic counselling to other at-risk relatives. The letter should include a recommendation to contact the haemophilia/genetic centre in the event of a pregnancy, preferably as soon as a pregnancy is confirmed.

DIAGNOSTIC TESTS

The Medical Advisory Committee of the Haemophilia Foundation endorses the recommendations of the National Health Committee for molecular genetic testing in New Zealand. Testing should only be carried out in appropriately accredited laboratories.

GENETIC TESTING LABORATORIES

LabPlus,
Auckland City Hospital
Private Bag 110031,
Auckland

Tel: 09 307 4949

Canterbury Health Laboratories
Corner Hagley Ave and Tuam Street
P O Box 151
Christchurch, New Zealand

Dr Paul Harper
paulh@adhb.govt.nz
Dr Paul Ockelford
PAO@dml.co.nz
Dr Neil van De Water
neilV@adhb.govt.nz

Dr Mark Smith,
mark.smith@cdhb.govt.nz
Tel: 03 364 0381

The genetic defect in all kindreds with haemophilia B have been identified at the Auckland laboratory, therefore it is most appropriate to send requests for Haemophilia B genetic testing to Auckland.

Genetic testing for Haemophilia A is performed in both Auckland and Christchurch.

INDIVIDUALS WITH HAEMOPHILIA

In families in whom the genetic defect is not known genetic testing has been prioritised. In the propositus there is no clinical benefit knowing the underlying genetic defect, except for predicting the risk of inhibitor development. Testing is far more important for the identification of carriers in at risk family members. Therefore priority has been given to testing families where there are females of child-bearing age who are potential carriers. Over time it is planned to genotype all cases in New Zealand, however there is no specific funding allocated for this.

CARRIER DETECTION

Carrier detection by genotype testing should be offered to all potential adult female carriers. Phenotypic testing is recommended for all potential carriers in childhood before invasive procedures.

Informed consent should be obtained before testing and appropriate counselling offered as outlined above.

Samples

For carrier detection in a patient with known molecular defect, one 10 ml tube (CPD anticoagulant) of blood is required for Auckland Lab or EDTA anticoagulant for Christchurch lab. It is important that the request includes family details so it is possible to identify which kindred the carrier is related to. A family tree is helpful.

For carrier detection by RFLP analysis, one 10 ml tube (CPD anticoagulant) of blood (Auckland) or EDTA anticoagulant (Christchurch) is required from each family member. Samples from the suspect female, her mother, a relative with haemophilia (e.g. brother,

uncle, cousin) and ideally her father, although in most circumstances this may not be required. The blood samples can be sent at room temperature via conventional postage courier services. Samples should be sent to arrive not later than Thursday of any week. For more detailed instructions request the sheet titled 'Blood samples for DNA analysis' from the Haemophilia Centre, Auckland Hospital.

TESTING CHILDREN

An area of particular difficulty revolves around testing female children who are potential carriers of haemophilia. This area is surrounded by potential ethical conflict and a distinction must be drawn between tests performed solely for future reproductive choice and those done to directly benefit the child in the immediate future. In testing children, the primary concern should be the best interest of the child. Therefore genetic testing should only be performed if the results will significantly influence management. Carrying out genetic tests for haemophilia carrier status is rarely likely to affect management during childhood.

Phenotypic testing

Phenotypic testing of girls who are potential carriers is acceptable as the results may influence management. Clearly in some cases the coagulation results may confirm carrier status. Phenotypic testing should be performed when easy peripheral venepuncture is possible usually when the child is more than one year of age. Carrier detection based on coagulation activity alone is often inconclusive and there is a considerable risk of an incorrect diagnosis in up to 15% of cases.

Genotypic testing

Genotypic testing for carrier status is not recommended in young children. Testing should only be offered when the individual is able to understand the issues concerned and give informed consent. It is recommended that testing should be discussed and offered before the girl is old enough to have children.

Although parents have a right to consent for their children to have genetic tests this should only be performed after fully informed discussion with the parents. In these cases discussion with a medical geneticist is recommended. In difficult cases advice may be sought from the local ethics committee.

GUIDELINE

Routine genotypic testing of all individuals with haemophilia is not recommended.

Identifying the genotype in families with potential carriers of child-bearing age is recommended.

Carrier detection

Phenotypic testing of potential carriers is recommended in girls older than one year old.

Genotypic testing in childhood is not recommended.

Genotypic testing should be offered to all potential carriers able to give informed consent.

PRENATAL DIAGNOSIS

It is good practice to address issues related to the genetics of inherited bleeding disorders before the first pregnancy so that individuals and families are not faced with large amounts of information and potentially difficult decisions in a short period of time during early pregnancy. In addition, laboratories should not be asked to provide results under time pressure if this can be avoided. It is the case, however, that some known or potential carriers of bleeding disorders unavoidably present during pregnancy and in these cases the relevant issues must be addressed urgently.

Counselling

If possible genetic counselling should be performed before pregnancy. If this is not possible then genetic counselling should take place as early as possible in the pregnancy. Counselling regarding antenatal diagnosis should cover all options available to the pregnant woman and, if appropriate her partner, and the risks and benefits of each approach should be discussed and compared.

Pre-test counselling is given by a combination of appropriate Haemophilia Centre, Genetic Services and fetal medicine staff.

The individual should be informed about the procedures, how they will be performed, the possibility of not obtaining an adequate sample, non-diagnostic results and potential side effects for both mother and fetus. It should be agreed with the couple which tests will be performed and in what order. It should be agreed whether tests unrelated to the bleeding disorder will be performed, for example karyotype testing. An indication should be given about how long the tests will take to be performed.

A crucial part of pretest counselling is a discussion of what options would be taken by the woman with each possible test outcome and the potential effects of these decisions should be explored.

The haemostatic cover for the procedure, if required, should be discussed along with issues related to maternal and fetal exposure to blood products if relevant.

Communication of results

It should be agreed in advance by whom, how and where the results of the antenatal diagnosis tests will be given. Once the results are known the options available to the woman should be discussed.

Chorionic villus sampling

The details of the procedure, including potential risks, should be discussed with the mother. Written information about the technique should be provided and written informed consent obtained.

Some women may need haemostatic cover, such as DDAVP or recombinant coagulation factor concentrates, for the procedure depending on their diagnosis and level of coagulation factor.

Chorionic villus sampling is performed at 11-13 weeks.

It is important to have already established in advance which linkage markers are to be used before this process is performed. Chorionic villus sampling can be performed at most major hospitals. Patients out of the Auckland area can travel to Auckland for the sampling or could have the Chorionic villus sampling performed at an institute closer to

home and the chorionic villi sent at 4°C via express courier to arrive the same day in Auckland.

Prenatal diagnosis requests should be co-ordinated through the Auckland Hospital Haemophilia Centre (contact Dr Neil van De Water. Neilv@adhb.govt.nz) or Christchurch Haemophilia Centre (contact Dr mark Smith. Mark.smith@cdhb.govt.nz) The results from a prenatal study will be available within 7 days from tissue sampling.

Laboratory testing

Initially fetal sexing should be established. If the fetus is female no further tests are done apart from exclusion of maternal contamination. If the fetus is male tests are performed to establish whether the affected gene has been inherited. This may be done by direct mutation analysis, gene tracking techniques or a combination.

AMNIOCENTESIS

Cells as a source of DNA can also be obtained from amniotic fluid. This method carries a lower miscarriage risk and so is preferred to CVS after 15 weeks gestation. The miscarriage rate is about 0.5% with skilled operators. The main disadvantage of amniocentesis compared to CVS is that a termination, if necessary, will occur later in pregnancy.

TESTING PRIOR TO PREGNANCY

Pre-implantation genetic diagnostic testing

Pre-implantation diagnostic testing (PGD) is not yet available in New Zealand. The Minister of Health has approved the introduction of PGD. The National Ethics committee on assisted reproduction has produced guidelines for PGD.

PGD is available in Australian centres at Monash IVF, Melbourne and Sydney IVF, but has not been used in Haemophilia. The total cost of each cycle is approximately \$13,000. Most centres quote a success rate of approximately 20% for each cycle.

Sex Selection

Sex selection of sperm by centrifugation (Microsort) is offered commercially in the U.S. It is largely marketed to allow couples to select the sex of a second or third child to 'balance' their families. However the literature produced by the company states that the process can be used to select females in families with x-linked diseases. The quoted success rate for selecting females is around 90%, however there are very few peer reviewed studies confirming this rate of success. The process is not funded. The quoted cost is approximately US\$2,500. If considered, it is important that the limitations of this technique are discussed with the family.

LABORATORY REQUIREMENTS

Regular meetings of clinical and laboratory staff from the genetics and coagulation laboratories are essential to review the genetics service, to identify any problems and to ensure the quality of the service.

Laboratory Database

Accurate and readily accessible records of all stored samples and patient / family studies must be kept for all families with inherited bleeding disorders. Such records should include the results of genetic and phenotypic studies.

Laboratory Reports

Laboratory reports should be timely, accurate and concise. The clinical question being asked should always be restated in the text. Reports should include the following:

- a brief summary section
- the family pedigree including name and date of birth of each individual together with the determined genotype
- an interpretative section

When reporting gene-linkage analysis, the polymorphic markers used, haemophilia-associated alleles and other alleles identified should be clearly indicated. A key to any nomenclature used should be included.

Any further tests required or information needed that allow further investigation should be detailed.

Any factors unknown to the laboratory and which may, if present, affect interpretation of genetic data should be indicated (e.g. non-paternity, mosaicism). All reports should be signed and dated by the individual carrying out the laboratory tests, and appropriately authorised, for example by the scientific head of the laboratory.

PRODUCT INFORMATION

RECOMBINANT FACTOR VIII

Recombinant Factor VIII is available either as Kogenate, Recombinate or Refacto. Current usage of recombinant products for factor VIII includes

- Previously untreated patients (PUPs) of undefined age for on-demand therapy.
- PUPs about to commence a prophylaxis regimen
- previously treated children and young adults to age 18 years, who are virally negative, for prophylaxis and on-demand therapy

KOGENATE SF

250unit, 500unit and 1000units vials reconstituted in 2.5mls water.

Obtained from : Bayer N.Z. Ltd (Jill Porter)

Ph: (09) 443 3093

Fax: (09) 443 3094

email: jill.porter@bayer.co.nz .

RECOMBINATE

Available as 250units, 500units and 1000units.
Reconstituted with 10 ml sterile water.

Obtained from: Baxter Healthcare Ltd (Melissa Boyes)

Ph: (09) 574 2378

Fax: (09) 574 2532

Email: melissa_boyes@baxter.com

REFACTO

Available as 250units, 500units, 1000units
Reconstituted with 4ml sterile water

Obtained from: Warwick Jeffery, Wyeth NZ Ltd.

Ph: 0800 734 076

Mobile 021 778 841

Fax: (09) 573 0235

Email: Jefferw3@wyeth.com

PLASMA DERIVED FACTOR VIII

BIOSTATE - CSL FVIII

Plasma derived (N.Z. source) dried factor VIII fraction.
Used for classical haemophilia patients who are not eligible for recombinant therapy.

Von Willebrand disease (vWD)
250 units/vial reconstituted with 5 ml sterile water. Final concentration 50u/ml.

Obtained from : NZ Blood Service.

RECOMBINANT FACTOR IX

BENEFIX

Access to this product is on the same basis as access to recombinant FVIII.
Caution when starting patients on Benefix, as the recoveries may be lower than expected in comparison with plasma derived Factor IX.

Available as 250units, 500units, and 1000units

Obtained from: Warwick Jeffery, Wyeth NZ Ltd.
Ph: 0800 734 076
Mobile 021 778 841
Fax: (09) 573 0235
Email: Jefferw3@wyeth.com

PLASMA DERIVED FACTOR IX

MONO FIX – VF

- The plasma derived Factor IX product of choice for patients with Factor IX deficiency who are ineligible for recombinant therapy.
- Dosing every 24 hours, but consider 12 hourly intervals in major surgery depending on factor responses. Can be administered by continuous intravenous infusion for surgery.
- Indicated for prevention and control of bleeding in patients with haemophilia B (PUPS).
- Haemophilia B patients undergoing surgery
- Not indicated for treatment of patients with FVIII inhibitors nor for patients with deficiencies of II, VII, X.
- Product contains 100 iu Heparin per vial.

500 units vial reconstituted with 10ml sterile water. Final concentration 50 u/ml.
Obtained from: NZ Blood Service

PROTHROMBINEX-HT (PTX) CSL

Non-activated prothrombin complex concentrate (PCC).

- Factor IX (Haemophilia B) deficiency.
- Non-life-threatening bleeds in patients with FVIII inhibitors.
- Plasma derived (NZ source plasma)

500 units FIX/vial reconstituted with 20 ml sterile water.

Final FIX concentration 25 units/ml.

Each vial also contains approximately 550 units FII ; 600 units Factor X.

Obtained from: NZ Blood Service.

RECOMBINANT ACTIVATED FACTOR VII (NOVOSEVEN)

Preferred product for surgery in patients with inhibitors.

Available as 1.2mg (60KIU), 2.4mg and 4.8mg vials

Obtained from

Novo Nordisk, Auckland (Matthew Luttrell)

Ph: (09) 579 0653 Toll Free 0800 733 737

Fax: (09) 579 0654

FEIBA TM-4

Factor VIII Inhibitor Bypassing Activity (activated PCC). Used as an alternative to recombinant FVIIa

Reconstituted with 500/1000 FEIBA units/vial 20 ml sterile water.

Final concentration 250 FEIBA u/ml.

Obtained from:

Baxter – Melissa Boyes

Ph: (09) 574 2378

Fax: (09) 574 2532

Email: melissa_boyes@baxter.com

FXIII CONCENTRATE

Fibrogammin P (Behring)

Factor XIII deficiency

250 FXIII units/vial. Reconstituted in 4 mls sterile water.

Obtained From:

NZ Blood Service

DDAVP - DESMOPRESSIN

Synthetic antidiuretic hormone.

Arginine Vasopressin

Von Willebrand disease, mild Haemophilia.

Available as **Minirin** 4ug/ml IV preparation:

Octostim - Subcutaneous DDAVP is available as 15ug/ml ampoules.

Dosage 0.3 ug/kg gives peak concentrations at 2-3 hours post injection.

Intranasal preparation

The concentrated nasal atomiser spray (2.5ml/bottle) is rapidly absorbed from the nasal mucosa. Each precompression metered dose spray delivers 150 ug/spray. Treatment consists of one spray to each nostril of 300 µg.

In haemophilia A patients, the increase in plasma concentration of VIII:C after 300 µg DDAVP by spray is comparable with that obtained with a 0.2 - 0.3 µg/kg I.V. dosage.

No tachyphylaxis if used once daily. Long shelf life at 4°C

Obtained from:

Fisons Pharmaceuticals

P. O. Box 31-213 Milford, Auckland 9

Ph. (09) 444 3540

TRANEXAMIC ACID

Anti-fibrinolytic treatment.

This is a synthetic derivative of the aminoacid lysine. Tranexamic acid, 4 - (aminomethyl) cyclohexanecarboxylic acid has antifibrinolytic activity in humans by binding reversibly to plasminogen, therefore blocking the binding of plasminogen to fibrin and its consequent activation to plasmin. Tranexamic acid is approximately 10 times more potent than aminocaproic acid (Amicar). 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.

Adult dose. 1g. 6-8 hourly oral for 5 to 14 days

Uses

Primary menorrhagia.

Recommended when organic uterine lesions have been excluded and when combined hormonal preparations are either unacceptable, contraindicated or ineffective. Oral Tranexamic acid, 10 -15 mg. per kilogram body weight, this usually approximates to 1g 8 hourly, from the onset of menstrual bleeding until bleeding stops. Anticipated 40 - 50% reduction in blood loss.

Oral bleeding in congenital and acquired coagulation disorders.

The oral mucosa and saliva are rich in plasminogen activators.

Tranexamic acid mouth rinse. Use 10mls (500mg/5mls) orally 6hourly, and hold in mouth for minimum of five minutes. This is effective in the prevention of oral bleeding in patients with haemophilia, and in patients who require dental extraction while on long term oral anticoagulant therapy.

This mouth rinse has a short expiry, approximately one week, and must be made up immediately prior to use.

Bleeding in patients with thrombocytopenia.

Tranexamic acid is useful in reducing or controlling mucosal bleeding and bleeding with dental extraction in patients with low platelet counts without affecting the platelet count.

Reducing blood loss during cardiac surgery.

Tranexamic consistently reduces blood loss by 30 - 40% when compared with placebo in patients undergoing cardiac surgery. Tranexamic acid dose 10 mg. per kilogram given intravenously preoperatively followed by 1 mg. per kilogram per hour perioperatively.

Side Effects:

Dose dependent side effects are predominantly gastrointestinal tract including nausea, vomiting, abdominal pain and diarrhoea. Theoretical risk of thrombotic side effects. Caution in liver disease.

APROTININ

Extracted from bovine lung. Inhibits the action of serine proteases such as plasma kallikrein. Inhibition of kallikrein by Aprotinin indirectly inhibits the formation of activated factor XII. Mechanism of action therefore involves inhibition of both coagulation and fibrinolysis but does not impact on platelet function.

Uses

Used to reduce blood loss in patients undergoing cardiac surgery. Dosing involves an initial slow preoperative intravenous bolus (500,000 KIU - 1 million KIU) followed by a continuous infusion or 4 - 6 hourly IV bolus 0.2 - 0.5 million KIU . Cardiac surgery bleeding reduced 60 - 80% using this regimen. Aprotinin has also been used in association with severe obstetric and gynaecological haemorrhage.

Side effects

Side effects include hypersensitivity reactions but these usually are seen in association with a repeat exposure to Aprotinin with 6 months of the initial exposure. Possible concern over the extraction from bovine lung in relation to vCJD.

CONJUGATED OESTROGENS: (EG PREMARIN)

Conjugated oestrogens shorten prolonged bleeding times and reduce or stop bleeding in patients with chronic renal failure. Mechanism of effect unknown. Administered either intravenously or orally 0.6 mg/kg per day (approximately 50mg) for four to five days. Anticipated 50% reduction in bleeding time for 7-14 days.

Can be used in uraemic patients together with DDAVP. DDAVP provides an immediate short duration of effect (days).

Conjugated oestrogens are well tolerated in this setting with minimal side effects. The short duration of treatment (\leq five days) avoids adverse effects due to oestrogenic hormonal activity.

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