196 – GUIDELINES FOR THE EMERGENCY TREATMENT AND MANAGEMENT OF PATIENTS WITH HAEMOPHILIA & BLEEDING DISORDERS

Broad Recommendations / Summary
This document provides the clinician with the appropriate information to safely, effectively and promptly manage the emergency treatment and management of patients with haemophilia and bleeding disorders presenting to Hull and East Yorkshire Hospitals NHS Trust. This guideline applies to all medical staff in all specialities.

1 PURPOSE / LEGAL REQUIREMENTS / BACKGROUND

This document details the optimum management for patients with inherited disorders of haemostasis who present acutely to Hull and East Yorkshire Hospitals NHS Trust.

2 POLICY / PROCEDURE / GUIDELINE DETAILS

This guideline will be available on the intranet. Any training needs identified can be discussed with the authors. Teaching sessions can be organised at departmental level or trust wide if necessary.

Rationale for the recommendations:
The need for such a guideline within the Trust has arisen to ensure patients presenting with bleeding disorders to A&E, AAU, wards and clinic areas are treated promptly and safely. It also ensures staff in these departments are fully aware of the correct way to manage patients with bleeding disorders.

Haemophilia A and B
Haemophilia A and B are X-linked recessive congenital bleeding disorders caused by deficiencies of either factor VIII (Haemophilia A) or factor IX (Haemophilia B), usually related to mutations within the clotting factor gene. Haemophilia A and B are diseases that typically affect males, while females are carriers (WFH 2005). It is possible for females to be symptomatic carriers who require treatment as a mild haemophilia patient.

Haemophiliacs can present with sudden, significant bleeding episodes such as intracranial, joint, muscle and gastrointestinal haemorrhages. Patients with haemophilia can suffer complications following bleeding episodes, including haemophilic arthropathy, synovitis, pseudotumours, inhibitor formation and transfusion-related infections**.** In the last 40 years haemophilia has become a condition that is readily treatable with infusions of clotting factor concentrates (latterly recombinant factor concentrates) helping to prevent the above complications (UKHCDO 2003).

The level of residual factor VIII (FVIII) or IX (FIX) is predictive of clinical severity in terms of bleeding, with severely affected patients experiencing recurrent, significant bleeding episodes (Table 1).

Table 1: Definition of severe, moderate and mild haemophilia

Severity	Clotting Factor Level activity (IU/ml)	Bleeding Episodes
Severe	<0.01	Spontaneous bleeding predominately in joints/ muscles.
Moderate	0.01 -0.05	Occasionally spontaneous bleeding. Severe bleeding with trauma/surgery.
Mild	0.05 - 0.40	Severe bleeding with trauma /surgery.

Management of bleeding episodes in Haemophilia

1. CONTACT THE ON-CALL HAEMATOLOGY SPECIALIST REGISTRAR or CONSULTANT TO DISCUSS ALL ADMISSIONS.

2. The general principle for managing haemophiliacs is that acute bleeds should be treated early. This means immediately for life threatening bleeds and within 30 minutes for serious bleeds (WFH 2005, UKHCDO 2009). For serious bleeds the maximum time to assessment should not exceed 15 minutes (UKHCDO 2009).

3. In the case of head injury an urgent CT is needed as well as elevation of the FVIII or FIX level to 1.0u/ml. Do not delay FVIII/IX administration whilst waiting for imaging.

Bleeds should be treated with factor replacement therapy at the earliest moment. The factor VIII or IX level should be increased with clotting factor concentrate infusions according to the schedule in Table 2.

The degree of bleeding provoked by trauma is often underestimated – particularly in non-severe bleeding disorders – adequate prompt treatment is therefore essential (Standard 1 - UKHCDO – 2009).

Minor bleeds in patients with mild haemophilia should be treated with DDAVP, if they are known to respond to this treatment agent, in preference to coagulation factor concentrates whenever possible (UKHCDO 2003). However, major life threatening bleeds and head injuries must be treated with factor concentrate.

All patients with haemophilia are registered with a Haemophilia Centre and given a Bleeding Disorders Information Card (previously known as a green card) that they are advised to carry with them at all times. This contains information about diagnosis, severity, inhibitor status, type of product used and contact information for their haemophilia team. A list of locally registered haemophilia patients and their treatment is available in the Haematology Clinic, Queen's centre / Ward 31, Castle Hill Hospital and in the Haematology Laboratory at Hull Royal Infirmary. All patients with severe haemophilia also have a detailed list containing the above information in their medical notes. Products are not interchangeable and patients MUST be given their current product except on the advice of a haematologist.

All invasive procedures should take place at a centre directly served by a haemophilia team (WFH 2005, Bolton-Maggs 2004). Pregnant women with severe, rare coagulation disorders (or those who carry the condition or already have one affected child) should be managed by an obstetric unit within a hospital that has a haemophilia centre (Bolton-Maggs 2004).

Table 2: Target factor VIII or IX levels following therapy with clotting factor concentrates:

Types of Haemorrhage	Haemophilia A		Haemophilia B	
	Desired Level	Duration (days)	Desired Level	Duration (days)
Joint	0.4 – 0.6u/ml	1-2, maybe longer if response is inadequate.	0.4 – 0.6u/ml	1- 2 days, may be longer if response is inadequate.
Muscle (except iliopsoas)	0.4 – 0.6u/ml	2 - 3, sometimes longer if response is inadequate.	0.4 – 0.6u/ml	2 - 3, may be longer if response is inadequate.
Iliopsoas • Initial, then • maintenance	0.8 – 1u/ml 0.3 – 0.6u/ml	1- 2 3 – 5 sometimes longer as secondary prophylaxis during physiotherapy.	0.8 – 1u/ml 0.3 – 0.6u/ml	1 – 2 3 – 5 sometimes longer as secondary prophylaxis during physiotherapy
CNS/Head • Initial, then • maintenance	0.8 -1u/ml 0.5u/ml	1 - 7 8 - 21	0.8 -1u/ml 0.5u/ml	1 - 7 8 - 21
Throat / Neck • Initial, then • Maintenance	0.8 -1u/ml 0.5u/ml	1 - 7 8 - 14	0.8 -1u/ml 0.5u/ml	1 - 7 8 - 14
Gastrointestinal • Initial, then • Maintenance	0.8 -1u/ml 0.5u/ml	1 - 6 7 - 14	0.8 -1u/ml 0.5u/ml	1 - 6 7 -14
Renal	0.5u/ml	3 - 5	0.5u/ml	3 - 5
Deep Laceration	0.5u/ml	5 - 7	0.5u/ml	5 - 7
Surgery (major) • Pre- op • Post-op	0.8 – 1u/ml 0.8 – 1u/ml 0.6 – 0.8u/ml 0.4 – 0.6u/ml	1 - 3 4 - 6 7 - 14	0.8 – 1u/ml 0.8 – 1u/ml 0.6 – 0.8u/ml 0.4 – 0.6u/ml	1 - 3 4 - 6 7 - 14

Administration of Clotting Factor Concentrates to Haemophiliacs

Wherever possible, haemophiliacs should receive recombinant products. **Children in particular should not be given plasma derived factor concentrates.** This prevents transfusion-transmitted infections that can still be associated with pooled plasma-derived clotting factor concentrates. **Cryoprecipitate is not to be used** and virally inactivated fresh frozen plasma FFP (Octaplas® or methylene-blue-treated FFP) should only be used for single factor deficiencies where no specific concentrates exists (FV and FX deficiencies).

The dose of FVIII or FIX to be administered is calculated according to the principles described below. A pre-infusion and 20 minute post-infusion level FVIII/FIX should be done (2 blue top tubes sent to Haematology Laboratory) to assess the response to the administered clotting factor concentrate. If the bleeding does not resolve as expected after treatment then the clotting factor levels should be reviewed and consideration given to the presence of an inhibitor. The preparation time of FVIII administered should be written on the sample request form.

Haemophilia A (FVIII)

Each unit of FVIII per kilogram of body weight infused intravenously will raise the FVIII level by 0.02u/ml. The half-life is between 8-12 hours. Calculate the dosage by multiplying the patient's weight in kilograms by the desired factor level rise multiplied by 0.5.

Example: In order to calculate the amount of FVIII required to elevate the FVIII level from <0.01u/mL to 0.80u/ml in a 50kg man the following calculation is used: -
50kg x 80(desired u/ml rise) x 0.5 = 2,000units of FVIII.

Haemophilia B (FIX)

Each unit of FIX per kilogram of body weight infused intravenously will raise the FIX level by 0.01u/ml. The half-life of FIX is about 18-24 hours. Calculate the dosage by multiplying the patient's weight by the desired factor level rise.
Example: In order to calculate the amount of FIX required to elevate the FIX level from <0.01u/ml to 0.80u/ml in a 50kg man the following calculation is used: -
50kg x 80(desired u/ml rise) = 4,000units of FIX.

Clotting Factor Concentrates Commonly Used.

Please refer to the product insert for information on reconstitution. The filters included in the packaging must be used to reduce the possibility of infusional reactions.

Table 3 lists the coagulation factors the trust has in stock and whether they are plasma derived or recombinant products. These products are not interchangeable and patients should be kept on the same products where possible. Products are stored in the transfusion laboratory, Hull Royal Infirmary and are available on request from transfusion.

Table 3: Clotting factor concentrates held within Hull and East Yorkshire Hospitals NHS Trust:

Product name and available doses	***Description***
Advate 250iu Advate 500iu Advate 1000iu	Recombinant factor VIII
Helixate (NexGen) 500iu Helixate (NexGen) 1000iu.	Recombinant factor VIII
Refacto AF 250iu Refacto AF 500iu Refacto AF 1000iu	Recombinant factor VIII
Benefix 1000iu	Recombinant FIX
FEIBA 1000iu	Plasma derived anti-inhibitor clotting factors.
FXI (named patients only)	Plasma derived FXI.
Wilate 500iu Wilate 1000iu	Plasma derived FVIII/Von Willebrand protein.
Novo 7 (1.2mg) Novo 7 (2.4mg) Novo 7 (4.8mg)	Recombinant factor VIIa
Beriplex 250iu Beriplex 500iu Beriplex 1000iu	Plasma derived prothrombin complex concentrate

General Principles of care:

1. Remember that patients with haemophilia and bleeding disorders are often very knowledgeable about their condition and its management and can provide useful history.
2. Locate bleeding disorder information card/green card to facilitate immediate appropriate treatment and prevent unnecessary investigations. (If the card is unavailable ask the haematology laboratory if the patient's treatment history is known to them). Severe haemophiliacs also have a list of diagnosis, treatment etc in the front of their medical notes.

3. Patients should not be taking (or given) any drugs that affect platelet functions – i.e. Non steroidal anti-inflammatory drugs/ aspirin.
4. Intramuscular injections, difficult phlebotomy and arterial punctures should be avoided.
5. Treat veins with care – only cut down if a medical emergency necessitates it.
6. "First Aid" treatment for suspected bleeds is R.I.C.E (Rest, Ice, Compression and Elevation). Ice packs should be applied for 10 minutes hourly. Skin should be protected by covering ice pack with a towel.

See appendix for algorithm.

Risk of transmission of variant Creutzfeldt Jacob Disease (vCJD)

All patients who received UK-sourced pooled factor concentrates (including plasma-derived factor VIII/IX/XI) between 1980 and 1999 and a proportion of patients treated between 1999 and 2001 are currently considered to be at increased risk of vCJD due to the possibility of transmission of this infection by blood products.

Patients at increased risk of vCJD due to exposure to implicated clotting factors have been notified of this risk and of precautions they are required to take with respect to surgery and endoscopy. Guidelines pertaining to infection control procedures in patients at risk of vCJD are available via the intranet on the "infection prevention and control webpage".

All patients at risk of vCJD have an alert on Lorenzo. Patients previously treated with pooled-plasma products may also have been exposed to hepatitis B, C or HIV, details of such exposure will be documented in the case notes.

Von Willebrand Disease.

Von Willebrand disease (vWD) is the commonest inherited bleeding disorder (Pasi et al 2004)and is caused by either a quantitative or qualitative defect of the Von Willebrand factor (vWF) (Saddler 1994). vWD usually presents as a mild to moderate bleeding disorder with easy bruising or mucosal bleeding. Occasionally there is a complete deficiency of vWF and the bleeding symptoms are usually severe and present in childhood (Laffan et al 2004).

The bleeding history of a vWD sufferer is variable. Common bleeding events include epistaxis, cutaneous haemorrhage, bruising, prolonged bleeding of trivial wounds, mouth bleeds, gastrointestinal bleeds, prolonged postoperative bleeding, haemorrhage following dental extractions and menorrhagia (Dean et al 2000).

vWD is classified into 3 major categories (Table 4), one of which, type 2 is sub classified into 4 variants (Table 5). **These are important for determining treatment regimes.**

Table 4: Primary classification of vWD

Sub classification	Type of von Willebrand Factor (vWF) deficiency	vWF protein function
Type 1	Quantitative partial deficiency	Normal
Type 2	Qualitative functional deficiency	Abnormal
Type 3	Quantitative complete deficiency	Undetectable

Table 5: Secondary classification of vWD

Subtype	Platelet associated function	Factor VIII binding capacity	High molecular weight vWF
2A	Decreased	Normal	Absent
2B	Increased affinity for glycoprotein 1b	Normal	Usually reduced/absent

2M	Decreased	Normal	Normal and occasionally ultra large forms
2N	Normal	Markedly reduced	Normal

Management of bleeding episodes in Von Willebrand Disease

Always contact the Specialist Registrar or Consultant Haematologist on call prior to treating any patients with vWD.

Table 6: Management of bleeds in Von Willebrand disease

Bleeding site	Treatment options
Oral bleeds	Tranexamic acid / DDVAP.
Epistaxis	Tranexamic acid / DDAVP / vWF containing concentrate
Prior to dental extraction	DDAVP / Tranexamic acid / vWF containing concentrate
Menorrhagia	Combined contraceptive pill DDAVP Tranexamic acid Intrauterine device Contraceptive implant (only with DDAVP cover)
Surgery	vWF containing concentrate / DDAVP Close pre and peri-operative collaboration between surgeon and haematologists required.
Peripartum	vWF containing concentrate. DDAVP (caution with use antenatally)

R.I.C.E therapy should be implemented (when appropriate)

DDAVP

Desmopressin (DDAVP, Octim®) is a synthetic analogue of the peptide vasopressin. The administration of DDAVP can significantly increase the amount of circulating FVIII and VWF and is a valuable treatment for vWD and mild haemophilia. DDAVP is given as a subcutaneous injection at a dose of 0.3micrograms/kg.

For example: If a patient weighed 65kg:
65kg x 0.3micrograms = 19.5micrograms.

Some patients use an intranasal formulation (Octim®) for the treatment of minor bleeding episodes at home. (Ideally patients should receive a test dose of DDAVP prior to the therapeutic use of this drug.)

The side effects of DDAVP include headache, flushing, tachycardia, abdominal pain, sweating and hyponatraemia.

DDAVP should be avoided in patients with **heart disease** or who take diuretics. **Care should be taken to prevent fluid overload and always inform the patients to restrict fluid intake to about 1 litre for 24 hrs post DDAVP.**

All patients with vWD will be given a Bleeding Disorders Information Card to carry. If a patient has been proved to respond to DDAVP and it is not contraindicated then it is the

treatment of choice as it is potentially safer and prevents blood borne virus transmission (Pasi et al 2004).

DDAVP SHOULD NOT BE GIVEN TO PATIENTS UNDER 2 YEARS OLD BECAUSE OF THE RISK OF HYPONATRAEMIA AND POSSIBLE SEIZURES.

Blood products
A concentrate containing vWF is the treatment of choice when DDAVP is not likely to be effective or is contraindicated. Types 2A, 2B, 2M vWD often need to be treated with FVIII/vWF concentrate due to poor responses to DDAVP. Platelets can shorten bleeding in the patient with vWD and should be considered if there has been a poor response to replacement vWF.

Cryoprecipitate is not virally inactivated and should not be used.

Tranexamic acid
Tranexamic acid is an antifibrinolytic that inhibits the natural degradation of fibrin and stabilises clots (UKHCDO 2003). It is particularly useful for the treatment of gastrointestinal bleeds and can be given intravenously (IV), orally or as a mouthwash for oral bleeds. The dose should be reduced in patients with renal impairment /failure.

The doses of tranexamic acid are: -
15 – 25miligrams/kg, oral, tds
0.5 – 1gram, IV, tds
10 millilitres of a 5% solution qds used as a mouthwash.

The common side effects are nausea, vomiting, abdominal pain and a prothrombotic state (avoid in patients with known or previous thromboembolism).

Tranexamic acid should not be given with FEIBA or used as treatment for haematuria (risk of uteteric obstruction).

Tranexamic acid mouthwash is not commercially available therefore pharmacy need to make it up within the aseptic unit and it is therefore better if pharmacy get prior notice.

Factor XI deficiency
This is a bleeding disorder of mild to moderate severity where the bleeding symptoms often do not correlate with the level of residual factor XI. Treatment options for bleeding episodes include local measures such as R.I.C.E and tranexamic acid, virally inactivated plasma or factor XI concentrate (available on a named patient basis).

All decisions regarding treatment of bleeding episodes in Factor XI deficiency should be made by the on call Haematology Specialist Registrar or Consultant.

Contact Details for the Haemophilia Team

- Dr David Allsup, Consultant, 01482 461294
- Dr Simone Green, Consultant 01482 461297
- Specialist Registrar, via switchboard bleep 633
- Nurse Specialists, Queens Centre for Oncology and Haematology CHH, 461403, 07810753456 (limited signal whilst in the Queens Centre), bleep 946, 526 and 517
- Beverley Barnett, BMS Coagulation, 607770
- Robert Elshaw, Transfusion, 607791 / 607731
- Ward 31 CHH 01482 461025/461131 (Ward used for bleeding disorder admissions – to be arranged via Consultant Haematologist)

3 PROCESS FOR MONITORING COMPLIANCE

The process for monitoring compliance with this guideline is detailed in Appendix 2.

4 REFERENCES

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- United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) – (2009) Emergency and out of hours care for patient's with bleeding disorders – Standards of care for assessment and treatment. Advisory committee April 2009.

5 APPENDICES

- Appendix 1 - Bleeding algorithm
- Appendix 2 – Monitoring overview

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Appendix 1

ALGORITHM

BLEEDING PATIENT

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If intracranial bleed suspected discuss with Haematologist/ treat/Urgent CT scan and normalise deficient clotting factor to 100iu/dl. ← **ASSESS** → **READ BLEEDING DISORDERS INFORMATION CARD**

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TAKE HISTORY
EXAMINE PATIENT

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IMPLEMENT R.I.C.E

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CONTACT HAEMATOLOGISTS ON-CALL

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TAKE PRE-LEVELS
GIVE FVIII/FIX AS INDICATED BY BLEED/ DIRECTED BY HAEMATOLOGIST

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TAKE POST INFUSION LEVELS 30 MINUTES AFTER INFUSION INFUSION

APPENDIX 2

MONITORING OVERVIEW

Element to be monitored	Lead	Tool	Frequency	Reporting arrangements	Acting on recommendations and Lead(s)	Change in practice and lessons to be shared
Compliance will be audited yearly through the Audit to evaluate the time to assessment & treatment in patients with bleeding disorders to A&E	Phillipa Woods	Audit Tool	Annual Audit	The findings will be logged in the re-audit and reported to the haemophilia team at MDT meetings	From the results of the audit the lead person will identify an action plan if necessary which the whole team will be responsible for implementing. Re-audit will allow follow up of these actions.	Lessons will be shared locally and externally through Haemophilia Nurses Association and other national and international network groups. The unit is subject to triennial audit by the regional Comprehensive Care Centre in Sheffield.