Heritable Bleeding Disorders - Diagnosis UHL Haematology Guideline	University Hospitals of Leicester NHS NHS Trust **Trust Reference Number:C8/2020**

1. Introduction and Who Guideline applies to

This guideline is for use by haematology staff working in UHL and within the haemophilia unit. It provides guidance for specialty trainess and specialist nurses in particular.

2. Guideline Standards and Procedures

The following heritable bleeding disorders are managed in the UHL comprehensive care centre:

Haemophiia A

Haemophilia B

Von Wilebrand disease

FXI deficiency

Platelet function disorders

Hypo-/a-/dys-fibrinogenaemia

Rare coagulation factor deficiencies (II, V, VII, X, XIII)

N.B. FXII deficiency is not a bleeding disorder

Diagnostic testing for bleeding disorders should be carried out by specialist staff with experience in managing such disorders. Testing should follow and careful history +- relevant examination.

When should a diagnosis of a bleeding disorder be suspected?

- a family history of haemophilia A is often the reason for referral but 30- 50% of new cases have no prior family history.
- when a bleeding disorder is not known in the family, bleeding disorders may be suspected in the following circumstances:
- abnormal bleeding from the umbilical stump (although delayed bleeding tends to occur in FXIII deficiency)
- bleeding following circumcision or unusual bruises or haematomas in infant boys, once ambulatory/mobile (sometimes leading to wrongful suspicion of child abuse)

- abnormal unexplained bruising or underuse of a limb once crawling/walking
- intracranial hemorrhage after birth (including cephalhaematoma) or in infancy
- abnormal or excessive bleeding following a haemostatic challenge such as tooth extraction.
- abnormal or excessive bleeding following surgical intervention or trauma.
- unexplained bleeding symptoms in females including post partum haemorrhage and menorrhagia could be related to low factor levels.
- acquired disorders, such as acquired haemophilia A or acquired Von Willebrand disease may be present in later life and usually present with excessive bruising.

Careful sampling is essential when testing for bleeding disorders. The following are important considerations:

- incorrect specimen collection, transportation or storage or presence of anticoagulant medication that may interfere with the assay e.g. blood tests taken at GP practices would not be suitable for detailed assessment of haemostasis
- an abnormal haematocrit may lead to an incorrect blood to citrate ratio in the test tube
- blood test tubes should be stored at 4-25ºC and expiry checked on every use.
- any samples filled below the fill indicator line will be rejected as insufficient – one must allow the tube to fill until the vacuum is exhausted and blood flow ceases.
- filling tubes from other tubes or combining two partially filled citrate tubes may introduce error and should be avoided
- immediately after draw samples should be gently inverted in the tube 3 to 4 times. Inverted not shaken, Mr Bond!
- a visual check should be performed on the sample prior to patient departure and any uncertainty regarding the samples addressed at the time to avoid the patient attending for a repeat.
- transport to the laboratory should be prompt and at room temperature.

N.B. These tests should be requested by, or under advice from, the haematology team.

Factor assays - notes

Two factor VIII assays are available and should be performed for patients in whom there is a low FVIII level or where there is a borderline low result with bleeding disorder symptoms. These two tests are a “one-stage assay” and a “chromogenic assay”. There may be assay discrepancy because patients with certain genetic mutations in the FVIII gene causing mild haemophilia A may be missed using the one-stage APTT based FVIII assay. In some cases the one-stage assay result may be several times higher than the chromogenic assay. In general, the results of the chromogenic reflect the clinical phenotype in haemophilia A better compared with the one-stage assay. There are also

some genotypes causing inverse assay discrepancy, with lower one-stage than chromogenic assay results in mild haemophilia A. These individuals may have normal chromogenic results which correlates with a normal bleeding phenotype. Thus, mild haemophilia A may be challenging to identify correctly in the laboratory, if only one of the assay principles are used.

If patients have received clotting factor concentrates this should be stated on the request form, long with dose and timing of last dose

For FIX a one-stage assay is used

Available in-house tests for Von Willebrand disease include: VWF antigen, VWF activity measures (RCof and CBA), VWF platelet binding assessment (RIPA). Send away tests include: FVIII binding assay, VWF multimer analysis. For diagnostic testing, request “Von Willebrnand Screen”.

All other coagulation factor assays are available on-site apart from FXIII (send away). A factor XIII screen is available upon request.

Standard fibrinogen assays are “activity” based. A fibrinogen antigen test may be requested when dysfibrinogenaemia is suspected.

Platelet function testing

Platelet function testing may be requested to investigate for acquired or inherited bleeding disorders.

Initial coagulation testing and Von Willebrand screening should be taken in advance of platelet function testing

For light transmission aggregometry (current “gold standard” for platelet function testing), the patient should weight at least 30kg to allow for the large blood draw. Exceptions may be made for selective testing in extraordinary circumstances only

Platelet function testing must be arranged with the laboratory and nursing staff in the haemostasis unit

Key points for diagnostic testing:

Testing for a bleeding disorder should involve a careful history, appropriate blood tests and careful interpretation when considering possible diagnosis.

Individuals with a suspected bleeding disorder and a prolonged APTT should have all intrinsic pathway factor assays performed (FVIII, FIX, FXI and FXII)

VWF levels should always be checked when a low FVIII is found

All new cases with suspected haemophilia A should have both one stage and chromogenic assays FVIII assays in order to ensure correct classification of severity.

Performing a chromogenic FVIII level should be considered in an individual with a significant bleeding history but normal APTT to rule out mild haemophilia with discrepant levels.

As FVIII is an acute phase reactant and rises in other situations such as pregnancy and stress, repeat testing may be needed in individuals who have borderline results.

Always consider the age-appropriate normal range:

- Haemophilia A and VWD cannot be excluded in children under 6months of age due to the natural elevation of these factors in early life
- Haemophilia B may be over-diagnosed in early life as a result of naturally reduced levels during this period.

Some bleeding disorders will not be detected by a “routine” coagulation screen (PT, APTT, Fibrinogen, FBC). These include mild Von Willebrand disease, platelet function disorders, FXIII deficiency).

Genetic diagnosis

The causative variant can be established for most families with haemophilia. This has significantly improved the quality of information that can be offered to families by allowing assessment of the risk of inhibitor formation in affected males, precise carrier detection and improved prenatal diagnosis. All children with haemophilia should have their genotype established as soon as possible after diagnosis. All females who are pregnant and are confirmed or possible carriers of haemophilia must be referred to the Obstetric Haematology clinic without delay.

Genetic testing may provide help where there is doubt about whether the conition is acquired or inherited.

Genetic testing is not carried out as standard of care for Von Willebrand disease and should be performed is selected cases in which there is a definable potential benefit.

Genetic testing for platelet function disorders and rare coagulation factor deficiencies should only be performed on selected individuals on a case by case basis.

Where possible a detailed family history should be taken and maintained in order to trace familial disorders and provide safety and benefit for future generations.

3. Education and Training

None

4. Monitoring Compliance

What will be measured to monitor compliance	How will compliance be monitored	Monitoring Lead	Frequency	Reporting arrangements
N/a				

5. Supporting References (maximum of 3)

References 1. Laboratory SOP: PR2605 – Intrinsic Coagulation Factor Assays (F8, 9, 11, 12, IAS & Refact8) on the CS-2500

2. Laboratory SOP: PR2606 – Factor VIII Chromogenic Assay (Siemens) (F8C) on the CS-2500

3. Diagnosis of Haemophilia and Other Bleeding Disorders A laboratory manual. Second Edition Steve Kitchen, Angus McCraw, Marión Echenagucia Published by the World Federation of Haemophilia 2010

4. Nordic Haemophilia Council guidelines for the diagnosis and treatment of haemophilia. http://nordhaemophilia.org/library/Files/PDFskjol/NordicGuidelinesCongenitalHaemophilia_2017.pdf

6. Key Words

Hemophilia, von Willebrand disease, bleeding disorders

CONTACT AND REVIEW DETAILS	
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Details of Changes made during review:	