



Bleeding disorders

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Investigation of the bleeding patient

Investigation of a patient with a bleeding predisposition should follow a formula to prevent unnecessarily expensive, complex and time consuming testing, and to give the greatest opportunity for correct and early diagnosis without the need for repetitive testing. Investigation should only proceed after an adequate clinical history and examination.

Bleeding from any site should be considered first according to its usual causes before assuming it is pathological. Epistaxes are frequent in childhood due to explorative fingers, and dysfunctional uterine bleeding is frequent at the start and end of reproductive life, even in the absence of a haemostatic disorder.

The frequency, nature and predictability of bleeding must be considered in association with family history. Both the personal and family history should be objectively scrutinised and supportive evidence sought where available.

A positive response to the screening questionnaire should be considered in the following context:

- Age of onset of first symptoms (eg. paediatric vs. adult)
- Sites and degree of bleeding (eg. mucosal vs. joint/muscle, haemorrhage vs. bruising)
- Whether bleeding is spontaneous or inducible (eg. in response to trauma, or occurring in protected sites without tissue invasion)
- Reproducibility and predictability of bleeding in response to haemostatic challenges (ie. always vs. sometimes)
- Seriousness of the consequences of bleeding episodes (complicated by anaemia or transfusion)

Routine questionnaire

- Epistaxis and gum bleeding
- Menorrhagia and pregnancy related bleeding (ante and postpartum haemorrhage)
- Bruising and petechiae
- Bleeding with surgical episodes and dental extraction
- Bleeding from any other mucosal surface (haematuria, haemoptysis, malaena, rectal bleeding)

Direct enquiry should be made about prescription and non-prescription medications, herbal therapies and alternative or complementary medicines. Self-initiated medicines may not always be admitted to by the patient or recognised as a problem.

Examples of drugs and herbs which may contribute to a bleeding phenotype

- Platelet inhibition has been reported with ginkgo biloba, garlic, ginger, horse chestnut, turmeric
- Epilim may reduce fibrinogen levels
- Prednisolone increases cutaneous fragility
- Quinine and heparin can cause thrombocytopenia

The Initial Screen

A small number of tests (FBE and film, coagulation profile, PFA-100®, von Willebrand Disease Screen (VWS) and Blood Group) are sufficient to provide numerical and qualitative data about platelets and plasma proteins and will guide second layer investigation. Liver and renal function are also informative but are expected to be normal in most patients under review. Iron studies may indicate that progressive and continuous blood loss is occurring. Each test has individual value and contributes cumulatively to diagnose or exclude a bleeding disorder. **They should not be interpreted in isolation and labels should not be applied to patients unless test results are reproducible and consistent with the clinical picture.**

Limitations of initial screening tests

Platelets

Platelets may be normal in number and appearance, yet functionally impaired, as in aspirin and clopidogrel therapy.

High platelet counts when associated with a Myeloproliferative Neoplasm are not protective and increase the risk of bleeding. Acquired von Willebrand disease may occur in these conditions in addition to platelet dysfunction.

Thrombocytopenia does not always imply haemostatic compromise. Most patients with Immune Thrombocytopenia do not bleed and many are discovered incidentally.

Coagulation Profile (APTT, PT, Fibrinogen and TCT)

The APTT is subject to marked pre-analytical variability and may be erroneously prolonged or shortened in the absence of a bleeding disorder due to collection or handling of the specimen.

APTT reagents are variably sensitive to mild coagulation factor deficiencies (factors FVIII, FIX, FXI and FXII) which may be missed when the APTT is within the normal range.

The APTT may also be prolonged by inhibitors that are associated with thrombosis rather than bleeding, particularly a lupus anticoagulant.

PFA-100®

Tests of platelet function such as the PFA-100® can only be performed when the platelet count is adequate (generally $>100 \times 10^9/L$). An abnormal PFA-100® result is informative but not diagnostic of the specific platelet disorder (including VWD). Von Willebrand Disease may be missed by the PFA-100® in up to 15 percent of mild type 1 patients.

If an hereditary platelet disorder is suspected, drug and herbal therapies should be ceased for 10 days prior to testing if safe to do so.

Von Willebrand Disease Screen

Von Willebrand factor and FVIII are acute phase reactants and testing on multiple occasions may be required to demonstrate the true level nadir. Interpretation of a von Willebrand screen (VWS) is complex and requires knowledge of the personal and family history of bleeding, as well as of the patient Blood Group.

There is well recognised imprecision in some components of the VWS as demonstrated by External Quality Assurance Programs. Subsequently some patients are missed or misclassified.

Interpreting results

PFA-100®

This test reproduces the physiological environment by inducing shear stress on whole blood which is forced through a small aperture in a disc impregnated with platelet agonists. Once activated the platelets aggregate and block the aperture. It is analogous to the skin bleeding time but has greater reproducibility than this outdated test.

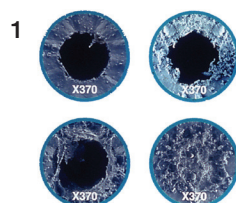


Figure 1: PFA-100® Occlusion Process (courtesy of Siemens Healthcare Diagnostics)

The negative predictive value of this assay is high. If normal, significant platelet dysfunction is unlikely. Mid range levels are of unclear clinical significance. Marked prolongation of closure times always indicates significant platelet dysfunction but does not define the abnormality. A differential response between adrenaline and ADP cartridges helps to distinguish an aspirin response from other causes, and the test is sometimes used to assess aspirin therapy or patient compliance to therapy.

Von Willebrand Disease Screen

Von Willebrand factor (VWF) is a protein that mediates interaction between platelets, and between platelets and the subendothelial matrix eg. through interaction with collagen. It is a molecular chaperone for FVIII, protecting this pivotal cofactor from premature degradation. A VWS combines tests for FVIII activity, quantitation of VWF protein (VWF Ag) and one or more tests of VWF function (ristocetin cofactor assay collagen binding assay).

Factors affecting levels of FVIII and VWF

- Physiological stressors
- Blood Group (lowest in Blood Group O)
- Ethnicity (lower in Caucasians)
- Genetic polymorphisms
- Hormone status
- Liver disease
- Assay limitations

Von Willebrand disease

Von Willebrand disease is the most common hereditary bleeding disorder with a gene frequency that may be as high as 1:100 – 1:200 people. The disorder is divided into 3 groups based on deficiency (type 1: partial, type 3: complete), or dysfunction (type 2). Types 2 and 3 are easily diagnosed and give consistently abnormal results by both VWS and PFA-100®. The diagnosis of type 1 is difficult and controversial, but type 1 accounts for 70-80 percent of patients affected. Levels above 30 percent for VWF or the functional assays should always be interpreted with the guidance of a clinical haematologist with expertise in this field. Management of these patients will rely less on their absolute levels and more on their clinical phenotype (bleeding behaviour) which is influenced by a range of genetic factors, not just those related to the von Willebrand gene itself.

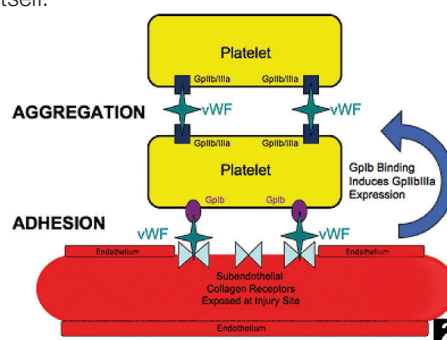


Figure 2: Diagram of the roles of von Willebrand factor in platelet adhesion to the damaged wall of the blood vessel and subsequent platelet aggregation.

Reference: <http://www.orthosupersite.com/view.aspx?rid=26898>

Type 1 VWD

Very low levels

- Highly heritable
- Often associated with bleeding
- Frequently caused by dominant VWF gene mutations

Low normal levels

- Very low heritability
- Rarely segregate with bleeding symptoms
- Rarely exhibit VWF locus linkage



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Dr Maxwell is a University of Melbourne graduate who completed combined fellowships with the College of Physicians and the College of Pathologists in 1997.

She trained initially at the Austin and Repatriation Medical Centres and later the Alfred Hospital where she developed a keen interest in coagulation and transfusion medicine.

Dr Maxwell is a current member of the Victorian Blood User Group, the National Blood Transfusion Committee, The Australian Red Cross Blood Service Advisory Committee and the Serious Transfusion Incident Reporting Working Group (DHS Victoria). She has been an active member of many committees for the RCPA and ANZSBT.

Dr Maxwell was appointed Medical Director at Melbourne Pathology in September 2009.

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