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An approach to the bleeding patient

The purpose of this newsletter is to provide an overview of the approach to the bleeding patient including the role of the laboratory in the diagnosis and management of patients with bleeding disorders.

Key words:

Bleeding, prothrombin time, activated partial thromboplastin time, correction studies, platelets

Clinical perspective of the bleeding patient

The first question that a clinician would need to answer is "Does the patient have an underlying bleeding tendency or is the bleeding in keeping with an 'external' challenge?" In this regard it is important to differentiate an acute bleeding episode from an episode of bleeding in the setting of a history of chronic bleeding. Acute bleeding may typically be related to major trauma, be surgery-related, post-partum haemorrhage or an acute bleeding diathesis as occurs in advanced disseminated intravascular coagulopathy. Symptoms more in keeping with a chronic bleeding disorder include easy bruising, a petechial rash, bleeding gums, nose bleeds, heavy menstrual bleeding and joint bleeds.

The approach to evaluating a patient with a suspected underlying bleeding disorder is no different to any other clinical condition and includes a thorough history and clinical examination followed by laboratory investigations. Here the focus is two-fold; firstly to determine the likelihood that the patient has an underlying bleeding disorder and secondly to prepare for the treatment of future bleeding episodes. A bleeding disorder in this context refers to an underlying defect in the haemostatic system that manifests as spontaneous bleeding or bleeding that is out of keeping, in terms of severity and duration, with what would be considered normal based on the nature of the injury experienced.

The history and examination generally lead one to a working diagnosis that favours a) either a primary or secondary haemostatic defect which is b) either acquired or inherited in origin (see table 1).

- Primary haemostasis defects - involve platelet and vessel wall interaction, culminating in platelet plug formation.
- Secondary haemostasis defects - involve factors involved in eventual fibrin clot formation.

The bleeding history

This is aimed at identifying the following:

- Does a bleeding tendency actually exist?
- Is primary or secondary haemostasis affected?
- Is the condition inherited or acquired?

A detailed history of the current and previous bleeding episodes is of paramount importance to guide the clinician to the most likely diagnosis.

Table 1 *Features suggestive of primary and secondary haemostasis defects*

	Primary haemostasis defects	Secondary haemostasis defects
Definition	Defects involving platelet and vessel wall interaction, culminating in platelet plug formation	Defects in factors involved in eventual fibrin clot formation
Causes	Platelets ■ Low count ■ Abnormal function Von Willebrand factor ■ Deficiency ■ Abnormal function Blood vessel abnormalities ■ Rare	Clotting factor deficiency ■ Haemophilia A – FVIII ■ Haemophilia B – FIX ■ Haemophilia C – FXI ■ Others (rare) ■ Severe vWD (FVIII markedly reduced) Fibrinogen abnormality ■ Dysfibrinogenaemias ■ Hypofibrinogenaemia
Location	Occurs mostly in high shear stress blood vessels thus mucocutaneous bleeds are common	Bleeding in low pressure areas or deep tissues
Features	Mucocutaneous bleeding ■ Gum bleeding ■ Mouth bleeds ■ Nose bleeds* ■ Menorrhagia# ■ Superficial bruising ■ GIT bleeding (uncommon) ■ Haematuria (uncommon) ■ Petechiae * Common in children in absence of bleeding disorder # Common in females in absence of bleeding disorder	Deep tissue bleeding ■ Post-surgical haemorrhage ■ Deep tissue bruising ■ Haematomas ■ Joint bleeds
	Milder episodes ■ Often manifest for first time as prolonged bleeding after tooth extraction or surgery	More severe episodes

- *At what age did the bleeding start?*
  - Was there bleeding of the umbilical stump after birth? (suggests FXIII deficiency)
  - Did the bleeding start with childhood circumcision? (typical in boys with severe haemophilia)
  - Did it coincide with minor childhood injuries sustained when starting to crawl or walk?
  - Was it first noted at the time of primary tooth loss?

- *Are the bleeding episodes spontaneous or provoked?*
  - Here one would enquire about the severity of the "insult" or injury that provoked the bleeding episode and what was required to control it.

- *Is the bleeding related to surgery?*
  - Each bleeding episode should be explored.
  - Was the bleeding immediate (suggests primary haemostatic defect) or delayed (suggests clotting factor deficiency)?
  - Was blood transfusion needed?
  - Did the surgeon describe the bleeding to be diffuse and oozing in nature (suggests bleeding diathesis) or from an isolated site (suggests a surgical bleed)?
  - In females, enquire if they bled more with some operations than others. Ask about oral contraceptive use, hormone replacement therapy or pregnancy at the time of previous surgeries. Increased hormone levels

would tend to minimise any underlying bleeding tendency.

- *In females, is there excessive menstrual bleeding?*
  - As the amount of menstrual blood loss is actually very difficult to judge, many more women perceive their menstrual bleeding to be "heavy" than those that have true menorrhagia defined as more than 80ml blood loss per menstrual cycle.
  - Gynaecological causes of menorrhagia are much more common than bleeding disorders.
  - Duration of more than 8 days, night time "flooding", the passage of clots and the development of iron deficiency increase the probability of an underlying bleeding disorder.

- *Is there a family history of bleeding?*
  - Ask probing questions.
  - A negative family history does not automatically rule out an inherited disorder.
    - More than 30% of haemophiliacs arise from a spontaneous mutation.
    - For rare autosomal recessive conditions some family members may be completely normal (e.g. Glanzmann's Thrombasthenia, deficiencies of factors II, V, VII and X, Type 2N von Willebrand disease).

- *What medication is the patient taking?*
  - Certain medications, herbal remedies as well as food supplements increase the risk of bleeding.
  - Use of such substances may precipitate bleeding in individuals with mild haemostatic defects.
  - Notably aspirin and non-steroidal anti-inflammatories impair platelet function. Special care should be taken to enquire about non-prescription cold remedies.

Whilst a thorough and detailed exploration of past bleeding episodes is generally highly informative in determining the most likely diagnosis, it should be noted that individuals with inherited conditions with a mild phenotype may be completely asymptomatic in the absence of a haemostatic challenge. Likewise, an acquired disorder can present with no prior bleeding history.

The physical examination

Special attention should be focused on examining the skin and mucosal areas for petechiae, purpura and bruising. The age of bruises, as assessed by their colour, and pattern of bruising should be documented. A person with an underlying chronic bleeding abnormality is likely to have bruises of varying ages whereas an acute episode of bleeding due to an associated once-off injury would have bruises of the same age. Any signs of joint and deep tissue bleeds must be recorded. As several platelet abnormalities form part of syndromes, a thorough physical examination is needed. Splenomegaly and lymphadenopathy may suggest an underlying haematological disorder affecting platelets.

Laboratory evaluation

Laboratory investigation is essential for confirmation of diagnosis and determining the appropriate treatment and monitoring of its effectiveness. The history and examination generally guide the order of investigations based on the most likely underlying diagnosis.

Table 2 *Laboratory investigations for suspected primary haemostasis defects*

Site of defect	Investigations	Result interpretation
Platelets	■ Bleeding time ■ Platelet aggregation studies ■ Platelet Function Analyser® closure time ■ Platelet receptor analysis by flow cytometry ■ Electron microscopy	Please see SEED newsletter No 1_2016 "Assessing platelet function – a basic introduction" for a detailed description of these tests and their interpretation.
Von Willebrand factor	■ Von Willebrand Factor Antigen assay ■ Von Willebrand Factor Activity assay ■ Factor VIII level ■ VWF Multimer analysis	Please see SEED newsletter No 11_2011 "Von Willebrand disease" for a detailed description of these tests and their interpretation.

a) Laboratory investigation of suspected primary haemostasis defects

An outline of the laboratory investigations that are available for the investigation of a primary haemostatic defect is shown in table 2.

b) Laboratory investigation of suspected secondary haemostasis defects

An outline of routine laboratory tests that are used to test for suspected disorders of secondary haemostasis is shown in table 3

Table 3 Laboratory investigations for suspected secondary haemostasis defects

Baseline Tests	Prothrombin time (PT)
	Activated partial thromboplastin time (aPTT)
	Mixing studies (if PT and/or aPTT prolonged)
	Clauss fibrinogen
	Thrombin time (TT)
Secondary tests	Individual clot-based factor assays
	Inhibitor studies (in case of FVIII or FIX deficiency)
	FXIII assay
	Clauss fibrinogen
	Thrombin time (TT)

i. Prolonged PT with normal aPTT

The PT is a baseline coagulation test that is prolonged in the case of defects in the extrinsic (FVII) or common coagulation pathways (FV, FX, FII). The aPTT will be prolonged in the case of an intrinsic pathway (FXII, FXI, FIX, FVIII) or common pathway defect. As FVII has the shortest half-life of all factors, conditions that affect multiple factors, e.g. warfarin treatment which interferes with the function of vitamin K dependent clotting factors (FII, FVII, FIX, FX), commonly manifest with a PT that is prolonged disproportionately to the aPTT (see figure 1).

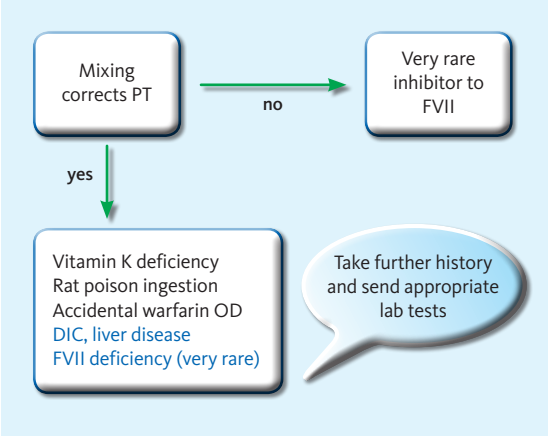

Fig. 1 *Approach to prolonged PT and normal aPTT test results. (DIC = disseminated intravascular coagulopathy, OD = overdose)*

ii. Normal PT and prolonged aPTT

In the bleeding patient, prolongation of aPTT in the face of a normal PT tends to occur because of isolated factor deficiencies. The aPTT can however also be paradoxically prolonged, i.e. the cause of the prolonged aPTT is associated with a thrombotic rather than a bleeding risk; examples are lupus anticoagulant (LAC), FXII deficiency and deficiency of the contact factors (e.g. prekallikrein).

The congenital causes of isolated aPTT prolongation include haemophilia A (FVIII deficiency), haemophilia B (FIX deficiency) and severe von Willebrand disease (vWD) (low FVIII). Acquired causes include spontaneous FVIII inhibitors, acquired vWD disorders and acquired inhibitors to FIX and FXI. With the exception of FVIII inhibitors acquired causes of prolonged aPTT are rare. The one caveat here is the presence of heparin which can cause prolongation of the aPTT in the absence of any influence on the PT. Most patients that are heparinised at therapeutic doses would however tend to have a PT greater than the upper limit of normal. The thrombin time can be used as a quick test if heparin contamination is

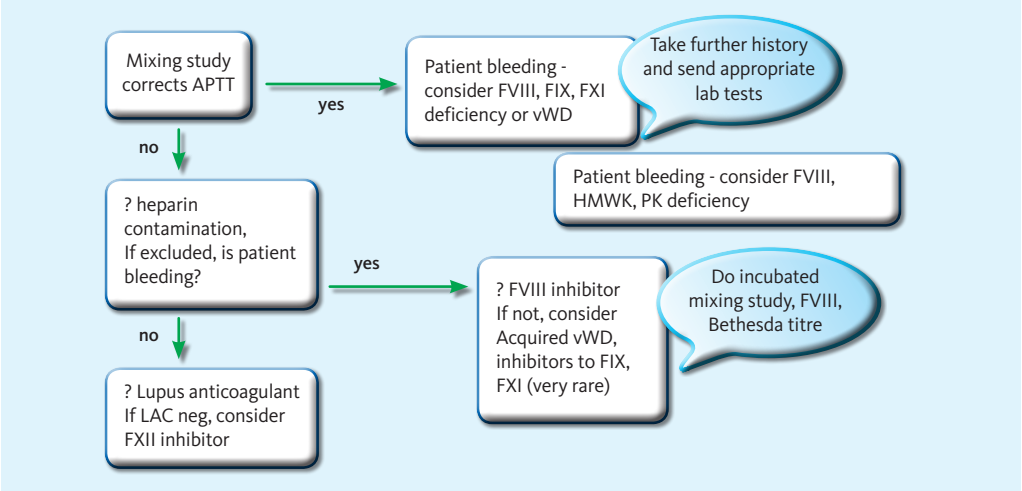

Fig. 2 *Approach to prolonged aPTT but normal PT test results.*

suspected, in which case it will be markedly prolonged. See figure 2 for a schematic outline of result interpretation.

iii Prolongation of both PT and aPTT

This is almost invariably due to an acquired condition as deficiencies of common pathway factors (FII, FV, FX) are exceedingly rare. Afibrinogenaemia or dysfibrinogenaemia severe enough to affect these basic screening tests is likewise very uncommon. The commonest causes of both PT and aPTT prolongation are established DIC, warfarin therapy, rat poison ingestion and vitamin K deficiency. Direct thrombin inhibitors as well as heparin should also be considered as a cause of prolonged PT and aPTT. See figure 3.

iv. Prolongation of neither PT nor aPTT

Normal baseline screening tests do not exclude secondary haemostasis defects. These tests are not all inclusive and therefore more specialised testing is required in patients with a definite bleeding history where baseline screening followed by directed reflex testing has not yielded any positive findings.

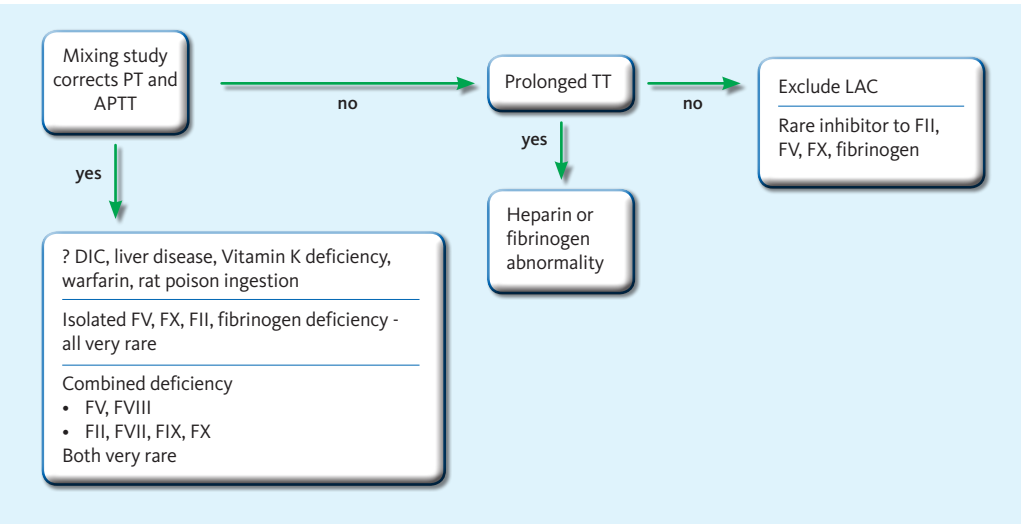

Fig. 3 *Approach to prolongation of both aPTT and PT test results.*

Congenital causes of bleeding with normal PT and aPTT include FXIII deficiency and deficiencies of the specific inhibitors of fibrinolysis (e.g. α2 antiplasmin, plasminogen activator inhibitor I). Whilst the history and physical examination generally give direction as to the more likely cause of bleeding, it is not always possible to pin-point the defect to either the primary or secondary haemostatic system. In the event of normal PT and aPTT test results, more common primary haemostatic defects (e.g. vWD and platelet disorders) should always be excluded before commencing with highly specialised testing that is not routinely available, even if the primary suspicion is that of a secondary haemostasis defect.

Abnormal laboratory findings in the absence of a bleeding history

On occasion, asymptomatic patients (i.e. absent bleeding history) may incidentally be noted to have one or more abnormal coagulation tests. A markedly prolonged aPTT occurs in FXII, prekallikrein and high molecular weight kininogen deficiency (contact pathway factor) but there is no bleeding risk at all. Individuals with FXI deficiency may be asymptomatic despite low factor levels. Mild FVII deficiency is also generally asymptomatic and patients with dysfibrinogenaemias generally do not bleed despite having markedly abnormal Clauss fibrinogen and TT test results. Prolongation of a clot based test such as the aPTT is one of the diagnostic criteria for LAC which in fact is associated with thrombosis. Patients with severe liver disease may have prolonged clotting tests but they do not usually bleed as production of functional clotting factors is somewhat offset by a concomitant reduction in the natural anticoagulant proteins (protein C, protein S and antithrombin).

Integration of clinical and laboratory data

- In the case of active bleeding, the immediate focus is to control the bleeding and therefore only an abbreviated evaluation to assess if the problem is likely to be inherited or acquired (based on the history) and to perform limited laboratory tests to look for gross abnormalities is warranted. A more detailed work-up can be done when the patient has been stabilised.
- In the event of a pre-operative evaluation because of abnormal laboratory tests, the clinician must decide if the laboratory test results correlate with an underlying bleeding tendency or are just an incidental finding.
- In the presence of a positive family history of bleeding a thorough evaluation is generally warranted in order to formulate a management plan to prevent and treat any future bleeding episodes.

Take home message

- Evaluation of bleeding patient requires careful history and physical examination.
- The laboratory workup should be tailored to the clinical presentation and pre-test probability of finding a bleeding diathesis.
- Many tests can only be performed at specialised tertiary centres but accurate diagnosis allows for rational treatment and prophylaxis for bleeding.

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