General approach to the investigation of haemostasis

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Clinical reasons to investigate haemostasis

- Investigating a clinically suspected bleeding tendency
- Following up an abnormal first-line test.
- Investigation of acute haemostatic failure
The components of a general coagulation screen:

• **Structured** clinical history

• Clinical findings
  • Laboratory tests
    – FBC and peripheral blood smear
    – Prothrombin time (PT)
    – Activated Partial Thromboplastin Time (aPTT)
Just a quick revision of the basics
Present thinking on the working of this system:

A Initiation
TF complexes with factor VIIa formed at the site of tissue injury; the subsequent activation of factor X and factor IX generate small amounts of thrombin.

B Amplification
Thrombin activates platelets and cofactors (V, VII); coagulation factors and cofactors assemble on surface of activated platelets (VIIIa, Va, IXa); multiple feedback loops amplify the process.

C Propagation
Assembled complexes continue cascade on surface of activated platelets; the prothrombinase complex converts prothrombin to thrombin which then converts fibrinogen to fibrin; this is followed by clot stabilization.
Haemostasis

- Platelets
- Vessels
- Coagulation factors
- Fibrinolysis
An Approach to the patient presenting with a bleeding diathesis

• Good structured clinical history
• Good clinical examination
• Formulation of a differential diagnosis, and choosing how you are going to go about confirming/ruling out diagnoses
• Planning laboratory investigations
• Management
• In all cases comprehensive clinical evaluation:
  • patient's history
  • the family history and family tree
  • details of:
    – the site,
    – frequency
    – character (purpura, bruising, large haematomata, haemarthroses,)
Other leads that can be gained form the history

1. Age (senile purpura)
2. Past bleeding history (tooth extraction, menses, iron responsive anemia, circumcision)
3. Liver, Kidney, Thyroid disorders
4. Family history of bleeding.
5. Medications use
6. Fever and weight loss (malignancy leukemia)
7. Dietary history
8. Trauma
9. Abdominal pain and arthritic pain (H-S purpura)
Vague questions such as “Do you bruise easily?” should be avoided.

It is particularly helpful to know whether the patient has had a prior haemostatic challenge.
A negative family history of bleeding does not preclude congenital disorders such as Haemophilia
Clinical Examination

1. Petechiae (less than 2 mm)
2. Purpura (more than 2 mm and less than 20 mm)
3. Ecchymoses (more than 20 mm)
4. Their Distribution.
5. Hepatosplenomegaly
6. Lymphadenopathy
7. Evidence of underlying liver disease
Pre-analytical variables

• Ratio of plasma to anticoagulant
  – 1:9
  – Influenced by over/under filling

• Time from specimen collection until testing

• Therapy
Laboratory haemostatic evaluation

- Full blood count with smear
- PT
- aPTT
- Thrombin time
- Bleeding time
The full blood count

• White cell count

• Haemoglobin

• Platelet count
The smear

- True thrombocytopenia
- Artefactual
  - Clumping
  - Satelitism
  - Clots
- Platelet morphology
Generally Available Screening Assays of coagulation

- PT
- aPTT
The PT

- Measures EXTRINSIC pathway
- Used to calculate the INR
The aPTT

• Measures the INTRINSIC pathway
PT
• Extrinsic pathway
  – TF, FVII
• Common pathway

aPTT
• Intrinsic pathway
  – VIII, IX, XI, XII
• Common pathway

II, V, X fibrinogen
Drawbacks of the PT and APTT

- In vitro assays
- Normal biological variation
- Insensitivity to clinically important bleeding disorders
  - Mild but clinical sign
    Haemophilia A
  - vWD
  - Factor XIII defic
- Artefact due to sample collection or pathological conditions
## Drawbacks of the PT and APTT

<table>
<thead>
<tr>
<th>aPTT</th>
<th>PT</th>
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<td>• Technical variability</td>
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<tr>
<td>• Disease and or physiological variability</td>
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<td>• Detection of disorders not associated with a bleeding tendency</td>
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Different scenarios
Scenario 1.

- High PT normal aPTT
Scenario 1.

• Step 1
  – Is this result true?
    • Or is it artefactually prolonged
      – Tube underfilled
      – Specimen contaminated with IV fluid
      – Patient’s haematokrit elevated

• Step 2
  – Which conditions should I think about?
Scenario 1, Step 3

• What test next:
  – Mixing studies
    • 50/50 mix patient plasma with “normal”
    • Should correct within a few seconds
  – Factor VII assay if MS corrects
Scenario no. 2

- High PTT normal PT
Scenario 2

• Step 1
  – Is this result true?

• Step 2
  – Which conditions should I think about?
What test next

• Mixing studies
• Factor assays for Factor 8 and 9
Prolonged PT and aPTT in combination

Vitamin K deficiency

Liver disease due to:
- Malabsorption of vitamin K [a fat soluble vitamin] and which leads to decreased gamma carboxylation of the vitamin K dependent clotting factors
- Decreased synthesis of clotting factors
- An acquired dysfibrinogenemia due to changes in the sialic acid content of the fibrinogen. This is similar to the effect seen in the newborn infant - the so-called 'fetal fibrinogen'.

Direct thrombin inhibitors including Hirudin, Argatroban and Dabigatran.

DIC - due to the consumption of clotting factors

Massive blood transfusion leading to a dilutional coagulopathy

In patients receiving thrombolytic therapy, the APTT may be prolonged due to a reduction in fibrinogen levels.

In multiple clotting factor deficiencies the APTT becomes prolonged with less severe reductions in factor levels.
Normal PT and aPTT and bleeding:

- **Consider evaluating for:**
  1. Platelet disorder
  2. Mild factor deficiency
  3. Factor XIII
  4. Monoclonal gammopathy
  5. Abnormal fibrinolysis
  6. a2 anti-plasmin deficiency
  7. Vascular disorders
  8. Dysfibrinogenemia
A normal BT does not predict the safety of surgical procedures, nor does an abnormal BT predict for excessive bleeding.