INVESTIGATIONS

Bleeding Time or BT (Template method). BT measures the time taken for bleeding to stop spontaneously after a standard incision in the skin. A small superficial incision is made in the skin of forearm and the duration of blood flow from the incision is timed. The length and depth of the incision (usually 1mm deep and 9 mm long) is controlled by a template or automated scalpel. A sphygmomanometer is inflated to 40mm Hg to distend the capillary bed of the forearm uniformly. Normal range is between 2 to 9.0 minutes. It is not indicated in thrombocytopenia where the diagnosis is obvious. BT is usually done when a platelet disorder is suspected, but the platelet counts are normal.

The BT is prolonged in (a) thrombocytopenia (b) platelet function defects as in inherited abnormalities (Bernard-Soulier disease, Glanzmann’s disease, vonWillebrand’s disease), acquired abnormalities such as drugs (aspirin, antiinflammatory medications), uremia, myeloproliferative disorders and (c) in rare capillary wall abnormalities.

Prothrombin time (PT) measures the time taken for fibrin formation through the extrinsic pathway, requiring Factors VII, and common pathway factors X, V, II (Prothrombin) and I (Fibrinogen). Values vary in different labs, usual values being between 10-12 seconds (secs). The PT is usually prolonged if any of the clotting factors are below 10%. It is most sensitive to deficiencies of factors VII, and factor X, rather than I, II or V. Common causes are liver disease, vitamin K deficiency, oral anticoagulants, DIC.

Partial thromboplastin time (termed as PTTK or aPTT according to technical variations in methodologies), measures the time taken for fibrin formation through the intrinsic pathway, requiring Factors prekallikrein, XII, XI, IX, VIII, and common pathway factors X, V, II (Prothrombin) and I (Fibrinogen). Values vary in different labs, usual values being between 25-36 secs.

The PTTK is more sensitive to deficiencies of factors VIII, IX rather than other factors. The result shows prolongation if any of the clotting factors is below 15 to 30% of normal value. Common causes are heparin therapy, DIC, advanced liver disease, overdose of oral anticoagulants, lupus anticoagulant, hemophilia, thrombolytic therapy.

Thrombin time (TT) measures the time taken for plasma to clot after addition of thrombin. TT is prolonged if fibrinogen is deficient and below 70 to 100 mg/dl. It is also prolonged if there is an inhibitor like heparin or FDPs, or with dysfibrinogenemia. It is prolonged with heparin therapy, advanced liver disease and DIC.

INVESTIGATIONS OF DOUBTFUL VALUE

Some investigations are not sensitive, and their diagnostic value is doubtful. These are:

Finger prick Bleeding time. The method is too insensitive, and should be discarded. It is not standardized, and is often normal, even with thrombocytopenia.

Clotting time by the capillary tube method. This method is also very insensitive, and detects abnormalities only, when there is a severe coagulation factor deficiency (i.e less than 1% factor VIII or IX). Clotting time by the tube method is better, but is still much less sensitive than PT and PTTK.

Several commercial point-of-care instruments are available which detect PT and INR bedside by capillary method. Activated clotting time (ACT) is another point-of-care test, which is being used in patients on heparin therapy to monitor the dose and is based on whole blood clotting assay.

SPECIAL PRECAUTIONS FOR ABNORMAL TEST VALUES

If a test is abnormal but does not correspond to the clinical profile, the clinician should make special requests to the laboratory to repeat the tests to confirm the result.

a. An abnormal coagulogram may be due to heparin in the sample of blood. If blood is drawn from a heparinised central venous line, this is a known fallacy. Repeat counts from a peripheral vein, will give the true result.

b. Low blood counts may be due to a clot in the blood sample, as the platelets and leucocytes are consumed/bound to the clot. This is common if there is difficulty in obtaining a venous sample.

c. If the coagulation tests are abnormal (prolonged PT or PTTK or TT), the cause can be a deficiency of clotting factors or presence of inhibitors. The test should be repeated
by mixing patient’s plasma with an equal volume of normal plasma, (a 1:1 mix of patient plasma and normal plasma). If there is a factor deficiency, the test will normalize, but if the test remains abnormal, it suggests that there is an inhibitor in the patient plasma. The reason is that a 50% level of any coagulation protein will lead to a normal clotting time. Thus ‘mixing’ studies will differentiate between presence of an inhibitor or deficiency. Common causes of inhibitors are: presence of heparin, presence of FDPs, and rarely spontaneous inhibitors to clotting factors (as in Hemophilia treated with factor VIII or Inhibitors seen in Autoimmune diseases).

**VIT K DEFICIENCY**

VIT K deficiency leads to a fall in factor II, VII, IX and X. Patients with obstructive jaundice, malabsorption, very poor nutrition, those in critical care setting without Vit K supplementation and those on broad-spectrum antibiotics may be deficient in this vitamin. In early stages PT is prolonged, as factor VII has the shortest half-life and falls before the other factors with longer half lives. In severe deficiency, PTTK is also prolonged, as the levels of other factors falls. Treatment consists of Vit K. This should be given IV (not IM) if coagulopathy is present or may be given orally. If an IV preparation is not available, the subcutaneous route may be used. Vitamin K will start normalizing the derangement within 6 to 8 hours.

**LIVER DISEASE**

The liver is the sole organ for synthesis of all the clotting factors (Vit K dependent, fibrinogen, factor V), except factor VIII which is also synthesized in the endothelial cells. As the clotting factor with the shortest half life is Factor VII, this factor becomes deficient at an early stage and the PT is prolonged first. Later, the other clotting factors fall, and the PTTK or TT also get prolonged. The liver also clears the activated clotting factors, fibrin and FDPs and tissue plasminogen activator. Thus in advanced liver disease the FDPs may be raised, platelets may be low (due to hypersplenism or marrow dysfunction) and the picture is similar to DIC. One differentiating feature is that factor VIII is normal or increased in liver disease but not in DIC.

**ORAL ANTICOAGULANT OVERDOSE (WARFARIN)**

Warfarin therapy overdoses are a frequent cause of bleeding disorders. The effect of oral anticoagulants like warfarin is similar to Vit K deficiency, and approach to therapy is the same.

**HEPARIN OVERDOSE.**

The PTTK will be prolonged. The risk of bleeding is more with bolus IV doses, rather than IV continuous infusion. The half life of conventional IV heparin is about 60 minutes. For low molecular weight heparin, the half life is much longer than for conventional heparin, but PTTK is not affected.

**ACQUIRED HEMOPHILIA**

In this condition, patient develops antibodies to factor VIII (or IX) with decrease in factor levels and bleeding complications similar to that seen in classic hemophilia patients. The precipitating cause may be underlying autoimmune disease or an occult malignancy. Prolonged PTTK and failure of normal plasma to correct the PTTK indicates presence of inhibitor. Acquired haemophilia can be an unusual cause of severe and unexpected in an older individual.