Notes by: Katherina Baranova

Oct. 18th - Approach to Coagulopathy: Adults

Step 1: primary or secondary hemostasis?

Primary: "platelet plug". Requires **functioning platelets** in sufficient numbers and an intact/functional vascular system.

Steps: (1) platelets adhere; (2) change shape; (3) release granules; (4) recruit other platelets; (5) aggregate to form a hemostatic plug.

Secondary: "fibrin clot". Requires functioning **clotting factors**.

Steps: (1) Tissue factor released; (2) phospholipid complex expressed; (3) thrombin activated; (4) fibrin polymerizes.

Primary Hemostasis	Secondary Hemostasis
Decreased Platelets • Decreased marrow production • Increased destruction (eg. ITP, HUS, HIT) • Sequestration by the spleen	Hereditary • Hemophilia A or B (and other rare coagulation factor deficiencies)
Dysfunctional Platelets • Hereditary – eg. vWD • Drugs – antiplatelet, ex. clopidogrel • Liver/kidney disease (TPO)	Acquired • Inhibitors of clotting factors (acquired hemophilia) • Drugs – anticoagulants, ex. warfarin • Liver disease • DIC
Vascular Disorders • Trauma/injury • Connective tissue diseases • Hereditary hemorrhagic telangiectasia • Ehlers-Danlos	

Characterize bleeding: primary usually presents with mucosal bleeds, secondary with intramuscular/intra-articular. Spontaneous bleeds vs. secondary bleeds (from trauma, surgery, etc.). Petechiae vs. ecchymosis.

Ask for family history of bleeding disorders (hemophilia has strong family hx on mother's side).

Medications? Liver disease (clotting factor deficiency)? DIC? VitK deficiency?

Step 2: INR, PTT, TT

Order lab tests as appropriate: CBC always; INR; PTT; liver function tests if liver disease is suspected; bleeding tests.

A platelet count <50 is associated with bleeding, <10 particularly so.

Start with platelet poor plasma. Incubate with appropriate substance and time until clot forms after addition of $CaCl_2$.

INR: incubate with thromboplastin (brain tissue factor and phospholipid), normalize prothrombin time (PT) to international standard. Measures **extrinsic pathway.**

- PT reference range 12-14.
- INR normal range 0.9 - 1.1 with therapeutic range 2.0 - 3.0
- Prolonged by warfarin, vitamin K deficiency, liver disease

PTT: incubate with contact activator (kaolin, silica, ellagic acid). Measures **intrinsic pathway.**

- Usually < 34 seconds
- Prolonged in hemophilia (hereditary and acquired), vitamin K deficiency, liver disease, lupus, and in heparin therapy

TT: activate with excess thrombin added to sample. Measures **common pathway.**

- Prolonged by unfractionated heparin, dabigatran, fibrinogen abnormalities

Step 3: Narrow down diagnosis

1. Normal INR, PTT
    a. Platelet Disorders
        i. von Willebrand's disease – most common inherited bleeding disorder, usually mild.
        ii. anti-platelet drugs (clopidogrel)
        iii. liver/kidney disease – less thrombopoietin
    b. Factor XIII Deficiency (rare)
    c. Blood vessel/connective tissue abnormalities

2. Isolated Prolonged PTT
    a. Factor VIII or IX Deficiency - Hereditary (hemophilia A or B), acquired deficiency or inhibitors
    b. Unfractionated heparin
    c. Factor XI (rare, also known as hemophilia C)
    d. XII Deficiency (no bleeding, no symptoms, can excessively prolong PTT)
    e. Lupus anticoagulant (no bleeding)

3. Isolated Prolonged INR
    a. Mild Vitamin K Deficiency
    b. Mild/Early Liver Disease
    c. Warfarin Therapy
    d. Factor VII Deficiency
    e. Some may even include early DIC

4. Prolonged INR and PTT
    a. Severe Vitamin K Deficiency
    b. Severe Liver Disease - liver makes all factors except VIII, C, and vWF
    c. Heparin and Warfarin overdose
    d. Factor X (very rare), V (rare), II (very rare) deficiencies
    e. Hypo- or dys- fibrinogenemia: defective clot formation due to defects in fibrin
    f. DIC

Vitamin K deficiency

Vitamin K dependent factors: II, X, IX, VII, Proteins C and S

Deficiency can develop as quickly as 4-5 days and results in decreased gamma carboxylation of these factors (also in warfarin therapy). Deficiency most often associated with malabsorption, malnutrition, broad spectrum antibiotics or biliary pathology, seen most often in hospitalized, acutely ill patients

INR is elevated (as in warfarin therapy). In severe cases, PTT and INR are elevated. Will correct when mixed with normal plasma – this indicates an absence of something, rather than an inhibitor.

Liver Disease

Liver makes all factors except VIII, C, and vWF. Particularly it makes all the vitamin K dependent factors. Liver disease also affects the platelets.

INR is elevated in mild disease. PTT +/- TT in severe disease. Will correct on mix with 1:1 normal plasma.

Other indications are abnormalities on liver function tests, hepatomegaly, possible splenomegaly (portal hypertension leading to hypersplenism), etc.

Disseminated Intravascular Coagulopathy (DIC)

A precipitating must occur – sepsis, snake bite, complications with pregnancy, trauma, burns, malignancy, etc.

There is widespread coagulation and all the clotting factors are consumed…which then leads to bleeds.

INR, PTT, TT are all elevated. Decreased fibrinogen.

Clinical features may show infection, microangiopathic hemolytic anemia, etc. Red cells may be fragmented by fibrin strands.

von Willebrand's Disease

Associated with an increased mucocutaneous bleeding tendency: bruising, bleeding from gums, bleeding from dental work/surgery, **menorrhagia**, nose bleeds, etc. The biggest health burden is in menstruating women. Treated with desmopressin or vWF concentrate.

Type 1 – usually asymptomatic, maybe minor bleeding. Quantitatively less *normal* vWF (mild/moderate).

Type 2 – same presentation as type 1, but this is a qualitative defect in vWF (abnormal factor).

Type 3 – rare, severe presentation. Can present in a similar fashion to a hemophiliac, with soft tissue bleeding and hemarthroses. Accompanying low FVIII levels.

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Hemophilia A

Most common severe, inherited bleeding disorder. Due to mutations in factor VIII gene on the X-chromosome. Severity based on levels of factor VIII. Most symptomatic individuals are male.

Individuals have mucocutaneous signs of bleeding, and bleed into their joints and soft tissues.

Very **severely** affected individuals will spontaneously bleed into muscles and joints (FVIII < 0.01 u/mL)

Moderately affected individuals (0.01 – 0.05 u/mL) bleed with mild provocation.

Mild cases (FVIII levels up to 0.05 u/mL) bleed with trauma and dental work/surgery. Treated with desmopressin.

Severe cases are treated with FVIII recombinant protein concentrates.

Hemophilia B

Inherited factor IX deficiency, also on the X chromosome, also predominantly found in males.

Clinically indistinguishable from hemophilia A and differentiated by specific factor testing.

Treated with recombinant factor IX concentrate.