Acquired & Iatrogenic Coagulation Deficiencies

Faizi Ali, MD
Definitions

- **Acquired Deficiency**
  Deficiency of coagulation proteins that occur in a previously normal individual in response to another disease process and are produced by a variety of mechanisms.

- **Iatrogenic Deficiency**
  Iatros (Physician) genic (induced); Deficiency of coagulation proteins that occur as a result of treatment process for a disease by a physician.
Acquired vs. Inherited Deficiencies

Acquired Deficiencies are

- Far more common than hereditary disorders
- More complicated because usually multiple factors defective
- Bleeding often simultaneously from more than one site
- Also involve deficiencies of naturally occurring Inhibitors
Acquired Disorders

- Disseminated Intravascular Coagulation
- Liver Disease
- Vitamin K deficiency
- Heparin Induced Thrombocytopenia
- Acquired Pathologic Inhibitors
DIC

- Syndrome, not a disease, secondary to a variety of disorders, caused by release of tissue factors, resulting in uncontrolled inappropriate Coagulation and Fibrinolysis.

- Acute DIC: (Uncompensated)
  - Factors consumed faster than they are replenished.

- Chronic DIC: (Compensated)
  - Factor consumption is compensated (or overcompensated) by replenishment of factors.
Etiology

- Infections: Bacterial, viral, fungal, protozoal... etc.
- Tissue Damage: Burn, Trauma, head injury, extensive surgery... etc
- Neoplasm (Malignant): Solid tumors (pancreatic, gastric, lung, breast, etc.) & Leukemias (e.g. M3)
- Obstetric complications: Abruptio placentae, amniotic fluid embolism, septic abortion, retained placenta... etc
- Vascular Injury: Shock, Hypotension... etc
- Miscellaneous: Snake bite, Heat stroke, PNH, Any disease
DIC

- **Incidence:**
  - Occurs in approx. 1 in 1000 hospital patients.

- **Clinical Aspects**
  - About 20% cases asymptomatic and suspected only on the basis of lab data.
  - Symptoms vary due to complex interaction and simultaneous activation of coagulation and fibrinolytic system factors, causing either bleeding or thrombosis and resulting in shock.
  - Mortality rate of DIC is 50-60%.
DIC

- Lab Data
  - Thrombocytopenia, microangiopathic hemolytic anemia (e.g. schistocytes), Decreased Fibrinogen and factor VIII
  - Elevated PT, aPTT, TT, FSP/D-dimers
  - Chronic DIC has normal platelets count, normal fibrinogen, PT, PTT, but elevated FSP/D-dimers

- Treatment: Eliminating the underlying cause and supportive.
Liver Disease

- Affects all haemostatic functions
- Most haemostatic proteins, involved in coagulation (all major factors except factor VIII), fibrinolysis as well as coagulation. Inhibitors are synthesized in liver.
- Liver macrophages play a major role in removal of activated factors and products of activation such as fibrinopeptides, FDPs and plasminogen activator.
- Haemostatic functions are diminished when liver is diseased, but still preserved until 80% functional hepatic tissue lost.
Liver Disease

- Vitamin K deficiency may also be seen.
- DIC also seen due to defective clearance of activated clotting factors and fibrinolytic enzymes.
- All coag screening test including PT, PTT, TT are prolonged with N-Low fibrinogen levels. D-dimer may be normal thus differentiating from DIC.
- Acquired dysfibrinogenemia, & dys-prothrombinemia.
  - Abnormal fibrinogen molecule with high sialic acid content may be synthesized, resulting in defective clot formation.
Liver Disease...

- Defective platelet function due to increased FDPs and circulating plasmin.
- Thrombocytopenia develops due to
  - Hypersplenism: sequestration of platelets in the spleen due to portal hypertension.
  - Decreased thrombopoietin synthesis.
  - Alcohol toxicity of the bone marrow
  - Platelet consumption in DIC
Liver Disease...

- Ecchymoses and epistaxis may occur but bleeding from local GI lesions is common.
- Available treatments are sub-optimal, treatment is difficult
  - FFP: has volume constraints, possible viral infection vector
  - Platelets: offer temporary support but don’t reverse pathophysiology of portal hypertension
  - Cryoprecipitate: has fibrinogen, can’t reverse consumptive coagulopathy
Vitamin K dependent factors

Collagen

XII → XIIa

XI → XIa

IXa

IX

IXa

XI

XIa

Ca²⁺

VIII

Ca²⁺

V

X

Xa

Ca²⁺

PF3

VIII

XIIa

Tissue Factor

fIII

VII

Ca²⁺

VIIa

Xa

Ca²⁺

PF3

V

XIII

XIIIa

Thrombin

I

Fibrin

Polymer
Vitamin K dependent factors

- II, VII, IX, X, protein C, & S.
- Liver needs Vitamin K to add gamma-carboxy glutamic acid residues to these proteins, required for Ca2+ linking of factor to phospholipid surface.
- Sources of Vitamin K are green leafy vegetables in diet and synthesized by GI microorganisms, and absorbed from GI tract with bile salts.
- Very long PT, long PTT, normal TT.
Vitamin K deficiency

- GI malabsorption syndrome, e.g. sprue
- Liver disease
  - Malabsorption due to obstruction of biliary tract, (Vit. K is a fat soluble vitamin)
  - Deficiency of I, V, XIII, AT, II, VII, IX, X
  - Dysfibrinogenemia (increased sialic acid)
- Antibiotics: inhibition of γ-carboxylation
  - cephalosporins and β-lactams
  - cefamandole, cefoperazone
  - moxalactam
Vitamin K deficiency

- ICU Syndrome
  - Starvation
  - Tube feedings without supplementation
  - Sterilization of GI tract
  - Decreased GI transit time
  - Nasogastric suctioning

- Hypolipidemicians (bile acid sequestration)
  - Colestid, Questran
Treatment

- Correct underlying defect
- Administer Vitamin K
  - subcutaneous, intramuscular, intravenous
  - oral
- Fresh frozen plasma administration
Heparin Induced Thrombocytopenia (HIT)

- Complication of Heparin therapy
- More common with unfractionated heparin than low molecular weight heparin- 8 fold greater risk.
- 2 types
- Type 1: Non-immune platelet activating mechanisms, and not associated with Abs, Mild thrombocytopenia (>100K), develops several days after starting on heparin, Pt. asymptomatic, resolves w/o discontinuing heparin
HIT.....

- Type 2:
  - Immune mediated
  - starts 5-15 days after start of heparin therapy, unless there has been prior sensitization event
  - Pathogenesis: Upon exposure to exogenous heparin, multimolecular complexes composed of PF4 and heparin are formed

Heparin + PF4 $\rightarrow$ Multimolecular complexes

Formation of these multimolecular complexes results in conformational change in PF4, exposing a neoepitope which elicits an immune response usually IgG type of antibody.
HIT

- IgG binding to PF4/heparin complex triggers platelet activation and aggregation through transmembrane signaling.
- Platelet activation leads to release of phospholipids microparticles from cell membranes which initiates coagulation cascade leading to thrombosis.
- PF4/heparin immune complex bind to endothelium, leading to endothelial injury which can lead to a “thrombosis storm” associated with this syndrome.
- Moderately severe thrombocytopenia (<100K)
HIT

- Heparin must be immediately stopped, and alternative anticoagulant be used (Danaparoid, Lepirudin, Argatoban)
- Lab often called to
  - Confirm diagnosis of HIT
  - Justify continued use of alternate anticoagulant
  - Guide future exposure to heparin
- Lab Methods: 1: Functional assay
  2: Antigenic assay
HIT...

- Functional assay: Based on the ability of Pt. immunoglobulin (Abs) to activate normal platelets in the presence of heparin.
  - Source of Pt. Abs either serum or plasma.
  - Detection of platelet activation may be based on
    1: Platelet aggregation
    2: Release of granular contents (e.g., serotonin)
    3: Change in membrane properties (flow cytometry)
HIT...

- **Antigenic Assay:**
  - Measures presence of Abs capable of binding to PF4-heparin complex.
  - Detection system can be modified to detect IgG, IgM or IgA antibodies.
  - Assay usually performed in ELISA format and is more sensitive than functional assay.
Acquired Pathologic Inhibitors

- Antiphospholipid syndrome
  - Lupus anticoagulant
  - Anticardiolipin antibodies

- Not specific for single factor, bind to phospholipid in vitro, inhibiting assay

- Not associated with increased risk of bleeding

- Associated with risk of thrombosis
Prolongation of PTT

- Antibodies to factors
  - factor VIII most common target
  - factor V antibodies similar to “lupus anticoagulants”
  - others rare
Iatrogenic defects

- Surgical
  - Operations
  - Biopsies
  - Intravenous and intra-arterial catheters

- Medical
  - Starvation
  - Medications
Case History:

- 22 year old newly wed
- Presents with uncontrolled nosebleed, extensive ecchymoses, PT 42 seconds
- Normal platelet count, hemoglobin 12.2 g/dL
- Denies trauma, drug ingestion
- Physical exam otherwise unremarkable
Case History, continued:

- Married six days ago, Caribbean cruise for honeymoon
- Developed nausea, vomiting and diarrhea on cruise
- Nose bleed cut cruise short
- Admitted to Beaumont as inpatient
Case History conclusion:

- Factor deficiency due to starvation
  - dieting prior to wedding
  - nausea, vomiting, diarrhea, anorexia during cruise
- Rapid response to food and oral vitamin K with cessation of bleeding and correction of PT