Major Components in Coagulation

1. Vessel Wall
2. Platelet
3. Coagulation factor cascade
4. Clot inhibition/lysis
The coagulation cascade of secondary hemostasis has two pathways which lead to *fibrin* formation.

*contact activation pathway* (the intrinsic pathway)  
*tissue factor pathway* (the extrinsic pathway)

It was previously thought that the coagulation cascade consisted of two pathways of equal importance joined to a common pathway. It is now known that the primary pathway for the initiation of blood coagulation is the *tissue factor* pathway.
Hemostasis

BV Injury

Neural

Contact

Blood Vessel Constriction

Platelet Aggregation

Coagulation Cascade

Primary hemostatic plug

Reduced Blood flow

Platelet Activation

Fibrin formation

Stable Hemostatic Plug

Damage/contact.

• CBC-Plt
• BT, (CT)
• PT
• PTT

Platelet study
Antibody tests
Factor Assay
HEMOSTASIS

**Primary Hemostasis**
- Blood vessel contraction
- Platelet Plug Formation

**Secondary Hemostasis**
Activation of Clotting Cascade
Deposition & Stabilization of Fibrin

**Tertiary Hemostasis**
Dissolution of Fibrin Clot
Dependent on Plasminogen Activation
Clinical Approach to Bleeding Disorders

Clinical Evaluation (who, when, where, what)

Laboratory Studies

Approach to The Patient
Tests of Hemostasis:

**Screening tests:**
- Bleeding.T - 10m. Platelet & BV function
- Prothrombin.T – Extrinsic, APTT – Intrinsic
- Thrombin.T – common path. (DIC)

**Specific tests:**
- Factor assays – hemophilia.
- Tests of thrombosis – TT, FDP,
- Platelet function studies:
  - Adhesion, Aggregation, Release tests.
- Bone Marrow study
Bleeding: Clinical Features

- Local - Vs - General, spontaneous .

- Hematoma / Joint Bleeds - Coag
- Skin / Mucosal Bleeds – PLT

- wound / surgical bleeding –
  - Immediate - PLT
  - Delayed - Coagulation
Platelet

Petechiae, Purpura

Coagulation

Hematoma, Joint bl.
Blood Coagulation & Tests

Contact activation

Intrinsic

XII, PK, XI, HK, IX, PF3, VIII

Partial thromboplastin time

Extrinsic

Tissue thromboplastin

VII

Common

PF3, X, V, prothrombin, fibrinogen

Prothrombin time

Fibrin
Coagulation Cascade:

- Intrinsic Pathway (Contact) (XII, XI, IX, VIII)
  - (APTT)
- Extrinsic Path Tissue - (VII)
  - (PT)
- Common Path (V, II)
  - (TT)
- (Factor X)
- (Thrombin)

Fibrinogen → Fibrin

(F & FDP)
# Coagulation factor disorders

- **Inherited bleeding disorders**
  - Hemophilia A and B
  - vonWillebrands disease
  - Other factor deficiencies

- **Acquired bleeding disorders**
  - Liver disease
  - Vitamin K deficiency/warfarin overdose
  - DIC
a. Factor VIII Deficiency—Hemophilia A
b. Factor IX Deficiency—Hemophilia B
c. Vitamin K Deficiency
d. Disseminated Intravascular Coagulation
e. Coagulation Disorders In Liver Disease
f. Circulating Anticoagulants
g. Inherited Prothrombotic Disorders
h. Antithrombin Deficiency
i. Deficiencies Of Proteins C And S
j. Resistance To Activated Protein C And The Factor V Leiden Mutation
k. Prothrombin Gene Mutation
Immune Thrombocytopenia

- Autoimmune Disorder
- Thrombocytopenia
- Heterogeneous
Should know:

- What is...
- Causes
- Signs & Symptoms
- Diagnosis
- Treatments
- Living with
- Key points
- Links
Factor VIII Deficiency—Hemophilia A

- Hemophilia A - Factor VIII deficiency
- Hemophilia B - Factor IX deficiency

Hemophilia A is an inherited deficiency in clotting factor VIII, which causes increased bleeding. Hemophilia B is an inherited deficiency of Factor IX.

Both X-linked recessive trait, and thus occurs in males and in homozygous females.

Both prolong the APTT (Activated Partial Thromboplastin Time)
HEMOPHILIA

Inheritance of Hemophilia
Father With Hemophilia and Mother Who Is Not a Carrier

Parents
- Father (with hemophilia) XY
- Mother (not a carrier) XX

Children
- Son (without hemophilia) XY
- Daughter (carrier) XX
- Son (without hemophilia) XY
- Daughter (carrier) XX

Parents
- Father (without hemophilia) XY
- Mother (carrier for hemophilia gene) XX

Children
- Son (without hemophilia) XY
- Daughter (carrier for hemophilia gene) XX
- Son (has hemophilia) XY
- Daughter (does not carry hemophilia gene) XX
HEMOPHILIA

Queen Victoria

May 1819 – January 1901

Haemophilia in European royalty
## Hemophilia A and B

<table>
<thead>
<tr>
<th></th>
<th>Hemophilia A</th>
<th>Hemophilia B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulation factor deficiency</td>
<td>Factor VIII</td>
<td>Factor IX</td>
</tr>
<tr>
<td>Inheritance</td>
<td>X-linked</td>
<td>X-linked</td>
</tr>
<tr>
<td></td>
<td>recessive</td>
<td>recessive</td>
</tr>
<tr>
<td>Incidence</td>
<td>1/10,000 males</td>
<td>1/100,000 males</td>
</tr>
<tr>
<td>Severity</td>
<td>Related to factor level</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;1% - Severe - spontaneous bleeding</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1-5% - Moderate - bleeding with mild injury</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5-25% - Mild - bleeding with surgery or trauma</td>
<td></td>
</tr>
<tr>
<td>Complications</td>
<td>Soft tissue bleeding</td>
<td></td>
</tr>
<tr>
<td>Severity</td>
<td>Factor VIII (or IX) level</td>
<td>Clinical Features</td>
</tr>
<tr>
<td>---------------</td>
<td>---------------------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt;1%</td>
<td>Spontaneous bleeding</td>
</tr>
<tr>
<td>Moderate</td>
<td>1-5%</td>
<td>Severe bleeding after trauma or surgery</td>
</tr>
<tr>
<td>Mild</td>
<td>5-10%</td>
<td>Moderate bleeding after trauma or surgery</td>
</tr>
<tr>
<td>Subclinical</td>
<td>10-25%</td>
<td>May not have symptoms</td>
</tr>
</tbody>
</table>
Bleeds in Hemophilia

- Minor Bleeds
  - Oral mucosa
  - Intra-articular
  - Intramuscular

- Major Bleeds
  - Retroperitoneal
  - Retropharyngeal
  - Intracranial
Acutely, bleeding in hemophiliacs can

• Compromise circulation.
• Close off airway
• Lead to compartment syndrome
• Cause neuropathy
• Cause pain
• Set up inflammatory synovitis, which can trigger more bleeding
Chronically, bleeding in hemophils can:

- Compromise joint function and lead to accelerated DJD (hemophilic arthropathy)
- Lead to pseudotumor formation
- Weaken muscles
- Lead to permanent neurologic compromise.
Other complications of hemophilia

- Inhibitor formation
- Viral (and other) Infections
- Job bias
Inhibitors in Hemophilia

• Are alloantibodies formed against Factor VIII (and less commonly FIX) in patients with congenital hemophilia
• Inactivate exogenously administered clotting factor
• Must be treated with bypassing agents which less efficacious in hemostasis
• Increase morbidity and mortality
Complications - Orthopedic

• Hemophilic arthropathy

• Surgeries
  – synovectomy - arthroscopic or isotopic
  – joint fusion - arthrodesis
  – joint replacement - arthroplasty
Complications - Viral infection

- HIV and hepatitis B and C
- Blood donation steps to improve viral safety of plasma-derived products
  1. blood donors screened
  2. donated blood tested for antibodies to hepatitis and HIV
  3. all factor concentrate products are virally inactivated and purified
Hemophilia

Clinical manifestations (hemophilia A & B indistinguishable)

Hemarthrosis (most common)
   Fixed joints
Soft tissue hematomas (e.g., muscle)
   Muscle atrophy
   Shortened tendons
Other sites of bleeding
   Urinary tract
   CNS, neck (may be life-threatening)
Prolonged bleeding after surgery or dental extractions
Treatment of hemophilia A

• Intermediate purity plasma products
  – Virucidally treated
  – May contain von Willebrand factor

• High purity (monoclonal) plasma products
  – Virucidally treated
  – No functional von Willebrand factor

• Recombinant factor VIII
  – Virus free/No apparent risk
  – No functional von Willebrand factor
Factor VIII Infusion

Pharmacokinetics of Factor VIII Infusion

![Graph showing the decrease in plasma factor VIII levels over time after repeated infusions of 1750 u each. The graph depicts the percentage of plasma factor VIII over time with markers indicating the infusion times.]
Principles of Factor Dosing

• What’s the desired clotting factor level?
• What’s the half life of the factor?
  – FVIII - 12 hours
  – FIX - 24 hours
• Clotting factor is dosed in Units
• 1 Unit is the amount of factor present in 1 ml of normal plasma
• What’s the volume of distribution and recovery?
  – 1 unit of FVIII raises plasma level by 2%
  – 1 unit of FIX raises plasma level by 1%
Dosing guidelines for hemophilia A

- One unit of F VIII increases the plasma F VIII level by 2%
- Mild bleeding
  - Target: 30%-50% dosing q8-12h; 1-3 days (15U/kg)
  - Small Hemarthrosis, mild mucosal bleed, epistaxis
- Major bleeding
  - Target: >50% dosing q8-12h; 7 days
  - Major Hemarthrosis, Large muscle bleed
- Major bleeding
  - Target: 80-100% q8-12h; 7-14 days (50U/kg)
  - CNS trauma, hemorrhage, lumbar puncture
  - Surgery
  - Retroperitoneal hemorrhage
  - GI bleeding
- Adjunctive therapy
  - amino caproic acid (Amicar), or Tranexamic acid or DDAVP
    (for mild disease only)
Adjunctive Treatment for Hemophilia

- **EACA (Amicar)**
  - Epsilon amino caproic acid
  - Inhibits fibrinolysis and increases clot stability
  - Useful in mucosal bleeding
  - Contra-indicated in upper pole urinary bleeding

- **DDAVP**
  - Causes release of pre-formed stores of FVIII/VWF from Weibel-Palade bodies in endothelial cells
  - May help in mild hemophilia A
  - Can be given as a nasal spray
  - Efficacy must be tested before-hand
Hemophilia Management - In the ER

• History
  – What kind of hemophilia?, how severe?
  – Inhibitor in the past? What was last titer? Is it gone for good?
  – What kind of factor does the patient normally take?
  – Does the patient treat himself at home?

• Physical
  – Where’s the bleed?
  – Any organ, airway, neurovascular compromise?

• Labs
  – Baseline factor level (unless pt has inhibitor)
  – Bethesda titer
Hemophilia Management - In the ER

- Give clotting factor and pain meds
- Decide if admission is necessary
Complications of therapy

• Formation of inhibitors (antibodies)
  – 10-15% of severe hemophilia A patients
  – 1-2% of severe hemophilia B patients

• Viral infections
  – Hepatitis B
  – Hepatitis C
  – HIV
  – Human parvovirus
  – Hepatitis A
  – Other
Treatment of hemophilia B

• Agent
  – High purity factor IX
  – Recombinant human factor IX

• Dose
  – Initial dose: 100U/kg
  – Subsequent: 50 U/kg every 24 hours

fresh-frozen plasma or a plasma fraction enriched in the prothrombin complex proteins
Future of Hemophilia

• Primary prophylaxis
• Gene therapy
• Inhibitor prediction/treatment
• Prevention of
  – hemophilic arthropathy
  – viral contamination of factor products
Thank You!
DISORDERS OF COAGULATION AND THROMBOSIS

a. Factor VIII Deficiency-Hemophilia A
b. Factor IX Deficiency-Hemophilia B
c. Vitamin K Deficiency
d. Disseminated Intravascular Coagulation
e. Coagulation Disorders In Liver Disease
f. Circulating Anticoagulants
g. Inherited Prothrombotic Disorders
h. Antithrombin Deficiency
i. Deficiencies Of Proteins C And S
j. Resistance To Activated Protein C And The Factor V Leiden Mutation
k. Prothrombin Gene Mutation
THE CLOTTING MECHANISM

INTRINSIC
- Collagen
  - XII
  - XI
  - IX
  - VIII

EXTRINSIC
- Tissue Thromboplastin
  - XII
  - XI
  - IX
  - VIII

X

V

PROTHROMBIN (II) → THROMBIN (III) → FIBRIN

FIBRINOGEN (I) → FIBRIN
What is DIC

- DIC is a clinic pathologic syndrome of activated coagulation that manifests with bleeding or thrombosis.

- Patients with DIC have a loss of balance between the clot-promoting and lysing systems in vivo.
What is DIC

- This syndrome can have a clinical spectrum ranging from bleeding to a prothrombotic state.
- DIC is not a specific diagnosis, and its presence always indicates another underlying disease.
- Bleeding associated with DIC usually results from excess fibrinolysis; thrombosis associated with DIC results from excess thrombin formation.
## Condition associated with DIC

### 1. Basic disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis or severe infection</td>
<td>Potentially any micro-organism, including severe acute respiratory syndrome</td>
</tr>
<tr>
<td>Trauma</td>
<td>Serious tissue injury</td>
</tr>
<tr>
<td></td>
<td>Head injury</td>
</tr>
<tr>
<td></td>
<td>Fat embolism</td>
</tr>
<tr>
<td>Organ destruction</td>
<td>Severe pancreatitis</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Solid tumours</td>
</tr>
<tr>
<td></td>
<td>Haematological malignancies (for example, acute promyelocytic leukaemia)</td>
</tr>
<tr>
<td>Obstetrical calamities</td>
<td>Placental abruption</td>
</tr>
<tr>
<td></td>
<td>Amniotic fluid embolism</td>
</tr>
<tr>
<td>Vascular abnormalities</td>
<td>Giant haemangiomas (Kasabach-Merrit syndrome)</td>
</tr>
<tr>
<td></td>
<td>Large vessel aneurysms (for example, aortic)</td>
</tr>
<tr>
<td>Hepatic failure</td>
<td></td>
</tr>
<tr>
<td>Severe toxic or immunological reactions</td>
<td>Snake bites</td>
</tr>
<tr>
<td></td>
<td>Recreational drugs</td>
</tr>
<tr>
<td></td>
<td>Severe transfusion reactions</td>
</tr>
<tr>
<td></td>
<td>Transplant rejection</td>
</tr>
</tbody>
</table>
• Infectious disease---the most common clinical condition associated with DIC;
• Severe trauma---acute DIC is often seen with serious injuries and burns caused by the release of thromboplastic material;
• Neoplasia---both solid tumor and cancer;
• Vascular disorder---large aortic aneurysms may result in local activation of coagulation;
• Obstetric accidents---includes amniotic fluid embolism and placental abruption, the fetus, the placenta, and the amniotic fluid are rich in thromboplastic substances.
DIC (DISSEMINATED INTRAVASCULAR COAGULATION)

DIC can be either an explosive and life-threatening bleeding disorder or a relatively mild or subclinical disorder. Although a long list of diseases can be complicated by DIC, it is most frequently associated with obstetric catastrophes, metastatic malignancy, massive trauma, and bacterial sepsis.

<table>
<thead>
<tr>
<th>Table 40-1</th>
<th>Etiologic Factors and Disorders Causing Disseminated Intravascular Coagulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liberation of tissue factors</td>
<td>Obstetric syndromes—abruptio placentae, amniotic fluid embolism, retained dead fetus, second trimester abortion</td>
</tr>
<tr>
<td>Hemolysis</td>
<td>Neoplasms, particularly mucinous adenocarcinomas, acute promyelocytic leukemia</td>
</tr>
<tr>
<td>Intravascular hemolysis</td>
<td>Fat embolism</td>
</tr>
<tr>
<td>Tissue damage—burns, frostbite, head injury, gunshot wounds</td>
<td>Aortic aneurysm</td>
</tr>
<tr>
<td>Endothelial damage</td>
<td>Hemolytic uremic syndrome</td>
</tr>
<tr>
<td>Acute glomerulonephritis</td>
<td>Rocky Mountain spotted fever</td>
</tr>
<tr>
<td>Vascular malformation, decreased blood flow</td>
<td>Kasabach-Merritt syndrome</td>
</tr>
<tr>
<td>Infections</td>
<td>Bacterial: staphylococci, streptococci, pneumococci, meningococci, gram-negative bacilli</td>
</tr>
<tr>
<td>Viral: arboviruses, varicella, variola, rubella</td>
<td></td>
</tr>
<tr>
<td>Parasitic: malaria, kala-azar</td>
<td></td>
</tr>
<tr>
<td>Rickettsial: Rocky Mountain spotted fever</td>
<td></td>
</tr>
<tr>
<td>Mycotic: acute histoplasmosis</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 40-2  The pathophysiology of disseminated intravascular coagulation (DIC). Shown are the interactions between coagulation and fibrinolytic pathways that result in bleeding in patients with DIC.
Hemostatic Balance

Activation of Blood Coagulation
Suppression of Physiologic Anticoagulant Pathways
Impaired Fibrinolysis
The pathophysiology of DIC

1) Activation of Blood Coagulation
   - Tissue factor/factor VIIa mediated thrombin generation
     - complex activates factor IX and X

2) Suppression of Anticoagulant
   - reduced antithrombin III levels
   - reduced activity of the protein C/protein S
   - Insufficient regulation of tissue factor activity by tissue factor pathway inhibitor (TFPI)
The pathophysiology of DIC

3) Impaired Fibrinolysis
   - relatively suppressed at time of maximal activation of coagulation due to increased plasminogen activator inhibitor type 1

4) Cytokines
   - IL-6, and IL-1 mediate coagulation activation in DIC
   - TNF-α mediates dysregulation of anticoagulant and fibrinolysis
   - IL-10 may modulate the activation of coagulation
In DIC, a systemic activation of the coagulation system simultaneously leads to thrombus formation (compromising blood supply to various organs) and exhaustion of platelets and coagulation factors (results in hemorrhage). This is a disruption of body homeostasis.

(Porth, 2001)
Hypercoagulability

1) Coagulation cascade is initiated, causing widespread fibrin formation
2) Microthrombi are deposited throughout the microcirculatory system
3) Fibrin deposits result in tissue ischemia, hypoxia, necrosis
4) Leads to multi organ dysfunction

Hypocoagulability (the hemorrhagic phase)

1) Activates the complement system
2) Byproducts of fibrinolysis (fibrin/fibrin degradation products (FDP)) further enhance bleeding by interfering with platelet aggregation, fibrin polymerization, & thrombin activity
3) Leads to Hemorrhage
Pathophysiology of disseminated intravascular coagulation.

Figure 15-6 Pathophysiology of disseminated intravascular coagulation.

- Stimulus
  - Tissue destruction
    (Extrinsic pathway)
  - Endothelial injury
    - Endotoxin
      - Factor XII activation
        (intrinsic pathway)
  - Tissue factor
    - Endotoxin
    - Endotoxin

- Thrombin generation
  - Intravascular fibrin deposition
  - Plasminogen activation
  - Platelet consumption
    - Thrombocytopenia
    - Clotting factor degradation
      - Fibrin degradation products
        (inhibit thrombin and platelet aggregation)

- Thrombosis
  - Hemolytic anemia
  - Tissue ischemia
  - Fibrinolysis

- Bleeding
Bleeding mechanisms

- Consumption of clotting factors and platelets
- Activation of secondary fibrinolytic system
- Production of fibrin degradation products
Disturbance of circulation---Shock

▲ Microthromobus → blood returning to heart ↓

DIC → bleeding → blood volume ↓

▲ Bradykinin, histamine ↑ → vasodilation → blood pressure ↓

FDP can increased to dilates vessels that cause hypotension

▲ Heart function ↓↓

↓ cardiac output ↓

↓ blood pressure ↓
Ischemic tissue damage-dysfunction of multiple organs

- Renal insufficiency
- Acute adrenal failure
- Adult respiratory distress syndrome
- Infarcted skin syndrome of purpura
The laboratory manifestations

<table>
<thead>
<tr>
<th>CBC</th>
<th>Platelets falling or low. Hb dropping. Film may show RBC fragments</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT</td>
<td>Prolonged</td>
</tr>
<tr>
<td>APTT</td>
<td>Prolonged</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>Falling or decreased</td>
</tr>
<tr>
<td>D dimer</td>
<td>Increased</td>
</tr>
<tr>
<td>FDPs</td>
<td>Increased</td>
</tr>
</tbody>
</table>
Diagnosis of DIC

• Presence of disease associated with DIC
• Appropriate clinical setting
  – Clinical evidence of thrombosis, hemorrhage or both.
• Laboratory studies
  – no single test is accurate
  – serial test are more helpful than single test
Clinical Manifestations of DIC
Microscopic findings in DIC

- Fragments
- Schistocytes
- Paucity of platelets
Disseminated intravascular coagulation

- Laboratory results:
  - Prolonged PT, APTT and TT
  - Reduced fibrinogen level
  - Increased D-Dimers
  - Thrombocytopenia: <100,000 or rapidly declining
  - Microangiopathic changes in blood film

Low levels of coagulation inhibitors: AT III, protein C
Diagnosis of DIC

• Clinical setting

• Laboratory tests

• Criteria
  – Underlying disease
  – Platelet count < 100 X 10^9/L, or rapid decline
  – PT and APTT Prolonged
  – Presence of fibrin degradation products
  – Low levels of coagulation inhibitors
  – Low fibrinogen level in severe cases
Differential Diagnosis

- Severe liver failure
- Vitamin K deficiency
- Liver disease
- Thrombotic thrombocytopenic purpura
- Congenital abnormalities of fibrinogen
Stages of DIC

- Hypercoagulable stage
- Hypocoagulable stage
- Secondary fibrinolytic stage
Acute DIC

- Almost always secondary
- Consumptive coagulopathy
- Decreases in both coagulants & anticoagulants
- Severity may relate to levels of anticoagulants
Subacute DIC

• Symptoms appear within days to weeks, clotting substances are consumed but not reduced
• Bleeding is rarely seen but the evidence of DIC can be detected by laboratory examinations
• Thrombotic manifestation is commonly seen in malignant patient
Chronic DIC

- DIC develops slowly and the illness goes through within months
- The clinical and laboratory features of chronic DIC present over periods of month and the patient is usually not critically ill
- Usually symptoms are concealed
Treatment of DIC

- Treatment of underlying disorder: Stop the triggering process
- Supportive therapy
- Other treatments
  - Plasma and platelet substitution therapy
  - Anticoagulants
  - Physiologic coagulation inhibitors
Treatment of DIC

• Platelets and Plasma
  – to treat bleeding tendency
  – to cover an invasive procedure for patients with a high risk of bleeding

• Clotting factor concentrates
  – overcomes large volumes of plasma
  – but not advocated because: 1) contains small amount of activated factors, and 2) DIC results in deficiency of multiple factors
Plasma therapy

• Indications
  – Active bleeding
  – Patient requiring invasive procedures
  – Patient at high risk for bleeding complications

• Fresh frozen plasma (FFP):
  – provides clotting factors, fibrinogen, inhibitors, and platelets in balanced amounts.
  – Usual dose is 10-15 ml/kg
Treatment of DIC

- Anticoagulants
  - low dose heparin
  - low molecular weight heparin
  - new thrombin inhibitors (ATIII independent)
  - useful for clinically overt thromboembolism or extensive deposition of fibrin
Concentrates of coagulation inhibitors

- Antithrombin concentrate
  - reduces sepsis related mortality
  - improvement of DIC and organ function
- Supportive therapeutic option in severe DIC
Coagulation Inhibitor Therapy

- Antithrombin
- Protein C concentrate
- Tissue Factor Pathway Inhibitor (TFPI)
- Heparin
Case

Female, 29 years old
Emergency admission due to placental abruption. (eight months of pregnancy), coma, petechiae, gastrointestinal bleeding, hematuria;
Laboratory tests: Hb70g/L (110 to 150)
   platelet 85*10^9/L (100 to 300*10^9/ L)
   fibrinogen 1.78g / L (2~4g/L)
   prothrombin time20.9 s (12-14)
FDPs level is increased and the D-dimer is increased

Platelet 75*10^9/L, and fibrinogen1.6g/L, 4h after the review

Diagnosis: placental abruption
Disseminated intravascular coagulation
Case

Based on the lab values, DIC is confirmed for the patient. The Platelet count is decreased, the fibrinogen level is decreased, PT and PTT levels increased and prolonged, FDPs level is increased and the D-dimer is increased (usually together, levels are 100% specificity and sensitive). If a factor assay was done one would expect the levels to show a decrease in factors VI, VIII, and IX.
Lab abnormalities along with clinical presentation is used to confirm a diagnosis of DIC.
If abnormal results are obtained for PT, PTT, platelets, and fibrinogen, then the D-dimer and FDPs levels are used to confirm DIC...FDPs abnormal in 75% and D-dimer in 95%.
Objectives

• Understand the pathophysiology of Disseminated Intravascular Coagulation (DIC)
• Identify risk factors and etiology of DIC
• Describe the signs and symptoms of DIC
• Identify treatment modalities for DIC
• Define, identify and understand Acute vs Chronic DIC
• Develop understanding of diagnosing DIC (lab interpretations)
Glossary

**Activated PTT** - aPTT tests the intrinsic and common pathways

**D-dimer** - an antigen formed as a result of plasmin lysis of cross-linked fibrin clots, documents the presence of thrombin

**Fibrin degradation product (FDP)** - degradation products increase as plasmin biodegrades fibrinogen and fibrin, levels are elevated in 85-100% of patients with DIC

**Prothrombin Time (PT)** - tests the extrinsic and common pathways

(Porth, 2004) & (Otto, 2001)
To be continued, Thank You!
DISORDERS OF COAGULATION AND THROMBOSIS - part III

Yunfeng Cheng
Zhongshan Hospital, Fudan University
VITAMIN K DEFICIENCY

Vitamin K is a fat-soluble vitamin that plays a critical role in hemostasis.

Vitamin K is converted to an active epoxide in liver microsomes and serves as a cofactor in the enzymatic carboxylation of glutamic acid residues on prothrombin complex proteins.
Vitamin K deficiency

- Source of vitamin K
  - Green vegetables
  - Synthesized by intestinal flora

- Required for synthesis
  - Factors II, VII, IX, X
  - Protein C and S

- Causes of deficiency
  - Malnutrition
  - Biliary obstruction
  - Malabsorption
  - Antibiotic therapy

- Treatment
  - Vitamin K
  - Fresh frozen plasma
VITAMIN K DEFICIENCY

- Precursor forms of factors II, VII, IX, X, protein C, and protein S (PIVKA)
- Glutamic acid
- Warfarin inhibits reductase
- Vitamin K epoxide
- Completed forms of factors II, VII, IX, X, protein C, and protein S
- Gamma carboxylated glutamic acid (gla) binds to Ca$^{2+}$
- Platelet phospholipid
VITAMIN K DEFICIENCY

The three major causes of vitamin K deficiency:

- inadequate dietary intake
- intestinal malabsorption
- loss of storage sites due to hepatocellular disease.
VITAMIN K DEFICIENCY

With vitamin K deficiency:

• Plasma levels of all the prothrombin complex proteins (factors II, VII, IX, X; proteins C and S) decrease.

• Those with the shortest half-lives, factor VII and protein C, decrease first. Because of the rapid fall in factor VII, patients with mild vitamin K deficiency may have a prolonged PT and a normal APTT.

• Later, as the levels of the other factors fall, the APTT will also become prolonged.
VITAMIN K DEFICIENCY

• Parenteral administration of 10 mg vitamin K permits normal production of prothrombin complex proteins within 8 to 10 h.

• Severe hemorrhage can be treated with fresh-frozen plasma.

• Purified prothrombin complex concentrates should be avoided because they contain trace quantities of activated forms of the prothrombin complex proteins and can cause thrombosis in patients with liver disease.
Vitamin K antagonism

- Oral anticoagulants (warfarin)
- Both PT and APTT Prolonged
- PT system chosen for monitoring
  - due to shortest half life of factor VII
- INR system
  - to standardize monitoring of oral anticoagulant therapy
- Important: INR should not be used in other clinical context
COAGULATION DISORDERS IN LIVER DISEASE

Table 40-2 Causes of Bleeding in Liver Disease

<table>
<thead>
<tr>
<th>Anatomic Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Portal hypertension</td>
</tr>
<tr>
<td>Varices</td>
</tr>
<tr>
<td>Splenomegaly and secondary thrombocytopenia</td>
</tr>
<tr>
<td>Peptic ulceration</td>
</tr>
<tr>
<td>Gastritis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hepatic Function Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased synthesis of procoagulant proteins: fibrinogen, prothrombin, factors V, VII, IX, X, XI</td>
</tr>
<tr>
<td>Decreased synthesis of coagulation inhibitors: protein C, protein S, antithrombin III</td>
</tr>
<tr>
<td>Impaired absorption and metabolism of vitamin K</td>
</tr>
<tr>
<td>Failure to clear activated coagulation proteins leading to:</td>
</tr>
<tr>
<td>Disseminated intravascular coagulation</td>
</tr>
<tr>
<td>Systemic fibrinolysis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Complications of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dilution of platelets and coagulation proteins from massive transfusions</td>
</tr>
<tr>
<td>Infusion of activated coagulation proteins in prothrombin complex concentrates</td>
</tr>
<tr>
<td>Bleeding from heparin; thrombosis from $\varepsilon$-aminocaproic acid (EACA)</td>
</tr>
</tbody>
</table>
COAGULATION DISORDERS IN LIVER DISEASE

• Causes
  – Reduced synthesis of clotting factors
  – Vitamin K mal-absorption
  – Acquired functional defect of fibrinogen
  – Failure to clear activated products of coagulation and fibrinolysis
  – Thrombocytopenia
    • hypersplenism

• Coagulation tests
  – PT and APTT Prolonged
COAGULATION DISORDERS IN LIVER DISEASE

- Treatment of Liver disease
- Vitamin K
- Fresh – frozen plasma
- Anticoagulation with heparin has been advocated to control DIC
Liver Disease

Decreased synthesis of II, VII, IX, X, XI, and fibrinogen
Prolongation of PT, aPTT and Thrombin Time

Often complicated by
Gastritis, esophageal varices, DIC

Treatment
Fresh-frozen plasma infusion
Vitamin K (usually ineffective)
von Willebrand Disease

Clinical features

- von Willebrand factor: Carrier of factor VIII, Anchors platelets to subendothelium
- Inheritance: Autosomal dominant
- Incidence: 1/10,000
- Clinical features: Mucocutaneous bleeding
Laboratory evaluation of von Willebrand disease

Classification

– Type 1 Partial quantitative deficiency
– Type 2 Qualitative deficiency
– Type 3 Total quantitative deficiency

• Diagnostic tests: vWF antigen, vWF activity
Treatment of von Willebrand disease
Varies by Classification

Cryoprecipitate
- Source of fibrinogen, factor VIII and VWF
- Only plasma fraction that consistently contains VWF multimers
- Correction of bleeding time is variable

• **DDAVP (Deamino-8-arginine vasopressin)**
  - Increases plasma VWF levels by stimulating secretion from endothelium
  - Duration of response is variable
  - Used for type 1 disease
  - Dosage 0.3 µg/kg q 12 hr IV

• **Factor VIII concentrate**
  - Virally inactivated product
  - Used for type 2 and 3
CIRCULATING ANTICOAGULANTS

Circulating anticoagulants, or inhibitors, are usually IgG antibodies that interfere with coagulation reactions.

They arise in 15 to 20% of patients with factor VIII or factor IX deficiency who have received plasma infusions.

Nonspecific (lupus-like) inhibitors prolong coagulation tests by binding to phospholipids.

lupus anticoagulant (LA), anticardiolipin antibody (ACLA)
CIRCULATING ANTICOAGULANTS

PT ↑, APTT ↑,
massive plasma or concentrate infusion
activated prothrombin complex concentrates
plasmapheresis or exchange transfusion to lower antibody titer

Women who have had more than one midtrimester abortion, especially those with SLE, should have a trial of anticoagulant therapy. Patients with a single thrombotic episode (stroke or pulmonary embolus) and no other risk factor except LA or ACLA activity should be treated.
INHERITED PROTHROMBOTIC DISORDERS

Inherited defects in the natural coagulation inhibitors (antithrombin, proteins C and S), abnormalities in the fibrinolytic system, and certain dysfibrinogenemias predispose patients to thrombosis.

Factor V Leiden

Increased risk of thrombosis.
Immune Thrombocytopenia
Introduction

Immune Thrombocytopenia (ITP)

- Autoimmune Disorder
- Thrombocytopenia (Isolated thrombocytopenia) (<100 × 10⁹/L)
- Heterogeneous
- Acquired
- Absence of any obvious initiation or underlying cause
ITP Clinical manifestations
Secondary ITP

Epidemiology

The incidence of newly diagnosed ITP in adults ranges from 1.6-3.9 per 100,000 persons per year.

Diagnostic approach

- Careful history
- Physical examination
- Complete blood count: isolated thrombocytopenia
- Should be excluded: Other autoimmune disease, Pseudo-thrombocytopenia due to EDTA, Thrombotic thrombocytopenic purpura or hemolytic uremic syndrome, Evan syndrome, aplastic anemia, Congenital thrombocytopenic disorders, Myelodysplastic syndrome, Chronic lymphocytic leukemia et al.

Three phases

- Newly diagnosed ITP: (≤ 3 months)
- Persistent ITP: (3 months ~ 1 year)
- Chronic ITP: (> 1 year)

<table>
<thead>
<tr>
<th>Basic initial evaluation</th>
<th>Additional studies of potential value</th>
<th>Studies of unproven benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient history</td>
<td>Antiphospholipid antibodies (patients with history of thrombosis or fetal loss)</td>
<td>Thrombopoietin assay</td>
</tr>
<tr>
<td>Family history</td>
<td></td>
<td>Reticulated platelets</td>
</tr>
<tr>
<td>Medication history</td>
<td>TSH or antithyroid antibodies</td>
<td>Platelet-associated immunoglobulins</td>
</tr>
<tr>
<td>Physical examination</td>
<td>ANA in children</td>
<td>Serum complement</td>
</tr>
<tr>
<td>Complete blood count</td>
<td>Pregnancy test in women of childbearing years</td>
<td>Bleeding time</td>
</tr>
<tr>
<td>Quantitative immunoglobulins</td>
<td>Viral PCR for parvovirus and CMV (selected refractory, febrile, or leukopenic patients)</td>
<td>Platelet survival studies</td>
</tr>
<tr>
<td>Blood group (Rh)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct antiglobulin test</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>H pylori</em></td>
<td>Platelet glycoprotein-specific antibodies</td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BM (in selected patients)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Blood smear

ITP

Pseudo-thrombocytopenia
Clinical presentation and natural history

- **Chronic Course**
- ~ 15% of patients remit within 1 year
- **Bleeding manifestations:** mucocutaneous bleeding is the most common, (internal bleeding or fatal intracranial hemorrhage)

<table>
<thead>
<tr>
<th>PLT&lt; 30*10^9</th>
</tr>
</thead>
<tbody>
<tr>
<td>- 3%, 0.4%/year----&lt;40 years</td>
</tr>
<tr>
<td>- 71%, 13%/year----&gt;60 years</td>
</tr>
</tbody>
</table>

Estimated annual rate of bleeding according to age group

Epitope Spread in ITP
Model of cell-mediated cytotoxicity in chronic idiopathic thrombocytopenic purpura.
Clinical presentation and natural history of ITP in children

- Peak age of presentation: 5~6 years;
- 50%~60% of children will have a febrile illness that preceded the discovery of thrombocytopenia;
- PLT < 20*10^9

- 77%: None or mild bleeding;
- 20%: Moderate bleeding;
- 3%: Severe bleeding;
- 0.1%~0.5%: Life-threatening bleeding;
- 5%~10%: develop chronic ITP (＞12 months)
<table>
<thead>
<tr>
<th>Clinical situation</th>
<th>Therapy option</th>
</tr>
</thead>
<tbody>
<tr>
<td>First line (initial treatment for newly diagnosed ITP)</td>
<td>Anti-D&lt;br&gt;Corticosteroids: dexamethasone, methylprednisolone, prednis(ol)one&lt;br&gt;IVIg</td>
</tr>
<tr>
<td>Second line</td>
<td>Azathioprine&lt;br&gt;Cyclosporin A&lt;br&gt;Cyclophosphamide&lt;br&gt;Danazol&lt;br&gt;Dapsone&lt;br&gt;Mycophenolate mofetil&lt;br&gt;Rituximab&lt;br&gt;Splenectomy&lt;br&gt;Thrombopoietin (TPO) receptor agonists&lt;br&gt;Vinca alkaloids</td>
</tr>
<tr>
<td>Treatment for patients failing first and second-line therapies</td>
<td><strong>Category A</strong>: treatment options with sufficient data&lt;br&gt;TPO receptor agonists&lt;br&gt;<strong>Category B</strong>: treatment options with minimal data and considered to have potential for considerable toxicity&lt;br&gt; Campath-1H&lt;br&gt;Combination of first- and second-line therapies&lt;br&gt;Combination chemotherapy&lt;br&gt;Hemopoietic stem cell transplantation (HSCT)</td>
</tr>
</tbody>
</table>
Management of primary ITP in adults

- Corticosteroid therapy
- IVIg and anti-Rh-D
- Splenectomy
- Anti-CD20 therapy (rituximab)
- TPO receptor agonists
- ……
Adjunctive therapy for bleeding disorders
Adjunctive drug therapy for bleeding

- Fresh frozen plasma
- Cryoprecipitate
- Epsilon-amino-caproic acid (Amicar)
- DDAVP
- Recombinant human factor VIIa (Novoseven)
Fresh frozen plasma

• Content - plasma (decreased factor V and VIII)
• Indications
  – Multiple coagulation deficiencies (liver disease, trauma)
  – DIC
  – Warfarin reversal
  – Coagulation deficiency (factor XI or VII)
• Dose (225 ml/unit)
  – 10-15 ml/kg
• Note
  – Viral screened product
  – ABO compatible
Cryoprecipitate

• Prepared from FFP

• Content
  – Factor VIII, von Willebrand factor, fibrinogen

• Indications
  – Fibrinogen deficiency
  – Uremia
  – von Willebrand disease

• Dose (1 unit = 1 bag)
  – 1-2 units/10 kg body weight
Aminocaproic acid (Amicar)

Mechanism
- Prevent activation plaminogen -> plasmin

Dose
- 100mg/kg po or IV q 6 hr

Uses
- Primary menorrhagia
- Oral bleeding
- Bleeding in patients with thrombocytopenia
- Blood loss during cardiac surgery

Side effects
- GI toxicity
- Thrombi formation
**Desmopressin (DDAVP)**

- **Mechanism**
  - Increased release of VWF from endothelium

- **Dose**
  - 0.3µg/kg IV q12 hrs
  - 150mg intranasal q12hrs

- **Uses**
  - Most patients with von Willebrand disease
  - Mild hemophilia A

- **Side effects**
  - Facial flushing and headache
  - Water retention and hyponatremia
Recombinant human factor VIIa

• Mechanism
  – Activates coagulation system through extrinsic pathway

• Approved Use
  – Factor VIII inhibitors in hemophiliacs

• Dose: (1.2 mg/vial)
  – 90 µg/kg q 2 hr
  – “Adjust as clinically indicated”
# Summary Hemostatic Disorders

<table>
<thead>
<tr>
<th>Condition</th>
<th>BT</th>
<th>Plt</th>
<th>PT</th>
<th>APTT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vascular Dis</strong></td>
<td>-</td>
<td>↑</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>PLT Disorder</strong></td>
<td>-</td>
<td>↑</td>
<td>↓</td>
<td>-</td>
</tr>
<tr>
<td><strong>Factor VIII/IX</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>↑</td>
</tr>
<tr>
<td><em>Congenital</em></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>↑</td>
</tr>
<tr>
<td><strong>Vit K / Liver</strong></td>
<td>-</td>
<td>-</td>
<td>↑</td>
<td>-↑</td>
</tr>
<tr>
<td><em>Acquired</em></td>
<td>-</td>
<td>-</td>
<td>↑</td>
<td>-↑</td>
</tr>
<tr>
<td><strong>Combined (DIC)</strong></td>
<td>↑</td>
<td>↓</td>
<td>-↑</td>
<td>↑</td>
</tr>
</tbody>
</table>
Thrombophilia
Thrombophilia

• Now considered a multicausal disease, with an interplay of acquired and genetic thrombotic risk factors

• Approximately half of venous thromboembolic episodes in patients with inherited thrombophilias occur in relation to events that are generally recognized as a predisposing states, such surgery, pregnancy, and immobilization
Inherited thrombophilic states

- Antithrombin deficiency
- Abnormalities in protein C and protein S system
  - protein C deficiency
  - protein S deficiency
  - abnormal thrombomodulin
- Resistance to activated protein C (FV Leiden, FV Cambridge)
Inherited thrombophilic states

- Hyperprothrombinemia (prothrombin variant G20210A)
- Dysfibrinogenemia
- Abnormalities in fibrinolytic system
  - hypo- or dysplasminogenemia
  - elevated plasminogen activator inhibitor
    - decreased tissue plasminogen activator
- Hyperhomocysteinemia
- Heparin cofactor II deficiency
- Elevated histidine-rich glycoprotein
- Factor XII deficiency
Clinical features of patients with inherited deficiencies of AT, PC, PS, and APC-resistance

**Venous thrombosis**
- Deep vein thrombosis of the lower limbs
- Pulmonary embolism
- Superficial thrombophlebitis
- Mesenteric vein thrombosis
- Cerebral vein thrombosis

- Frequent family history of thrombosis
- First thrombosis usually at young age (<40y)
- Frequent recurrences
- Neonatal purpura fulminans (homozygous PC or PS deficiency)
<table>
<thead>
<tr>
<th>First step</th>
<th>Second step</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AT:</strong></td>
<td><strong>AT:</strong></td>
</tr>
<tr>
<td>Heparin cofactor synthetic</td>
<td>Immunoassays, crossed</td>
</tr>
<tr>
<td>substrate-based assays</td>
<td>immunoelectrophoresis</td>
</tr>
<tr>
<td></td>
<td>DNA analysis</td>
</tr>
<tr>
<td><strong>PC:</strong></td>
<td><strong>PC:</strong></td>
</tr>
<tr>
<td>Synthetic substrate-based</td>
<td>Immunoassays, crossed</td>
</tr>
<tr>
<td>assays</td>
<td>immunoelectrophoresis</td>
</tr>
<tr>
<td>(venoms as a PC activators)</td>
<td>DNA analysis</td>
</tr>
</tbody>
</table>
## Laboratory diagnosis of inherited thrombophilia

<table>
<thead>
<tr>
<th>First step</th>
<th>Second step</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PS:</strong></td>
<td><strong>PS:</strong></td>
</tr>
<tr>
<td>Immunoassay of total PS</td>
<td>crossed immunoelectrophoresis</td>
</tr>
<tr>
<td>Immunoassay of free PS</td>
<td>DNA analysis</td>
</tr>
<tr>
<td><strong>APC-resistance:</strong></td>
<td><strong>APC-resistance:</strong></td>
</tr>
<tr>
<td>APTT-based functional assays (using FV-deficient plasma)</td>
<td>DNA analysis (mutant factor V)</td>
</tr>
</tbody>
</table>
Characteristics of AT deficiency

- Autosomal dominant inheritance
- Quantitative and qualitative defects
- Thrombotic phenomena in adolescence or even earlier
- Frequently pulmonary embolism as first clinical manifestation
Characteristics of PC deficiency

- Autosomal dominant inheritance
- Quantitative and qualitative defects
- Homozygotes die because of thrombosis in infancy
- Thrombotic phenomena in adolescence
- Skin necrosis when warfarin therapy introduced
Characteristics of PS deficiency

• Autosomal dominant inheritance
• Quantitative and qualitative defects
• Homozygotes die because of thrombosis „in utero” or in the early infancy
• Thrombotic phenomena in adolescence
• Skin necrosis when warfarin therapy introduced
### Table 40-3  Relationship between Coagulation Defect and Site of Thrombosis

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Arterial</th>
<th>Venous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V Leiden R506 Q</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Prothrombin G20210A</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Antithrombin Ⅲ</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Protein C</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Protein S</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Homocysteinemia</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Antiphospholipid antibody&lt;sup&gt;a&lt;/sup&gt;</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

<sup>a</sup>Anticardiolipin antibody—lupus anticoagulant.
Table 40-4  Prevalence of Coagulation Defects in Patients with Venous Thrombosis

<table>
<thead>
<tr>
<th>Defect</th>
<th>Prevalence, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V Leiden (Arg506 Gln)R506 Q</td>
<td>12-40</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>10-20</td>
</tr>
<tr>
<td>Prothrombin G20210A</td>
<td>6-18</td>
</tr>
<tr>
<td>Deficiencies of antithrombin III, proteins C and S</td>
<td>5-15</td>
</tr>
<tr>
<td>Antiphospholipid antibody syndrome</td>
<td>10-20</td>
</tr>
</tbody>
</table>
Thank You!
Key points

1. What is Hemophilia A
2. The treatment of Hemophilia A
3. What is Disseminated Intravascular Coagulation; The pathophysiology of DIC
4. What is immune thrombocytopenia
5. Coagulation Disorders In Liver Disease