



Chapter 122 (Ch. 114 9th Ed) – Disorders of Hemostasis

Episode Overview:

1. List 10 causes of Thrombocytopenia
2. List 6 causes of Thrombocytosis
3. Describe the presentation and treatment of HIT, ITP and TTP
4. Describe what causes an abnormal PT? What causes an abnormal PTT?
5. Describe the deficiency and management of Hemophilia A, Hemophilia B, and vWD
6. Describe the management of a major and minor bleed in hemophilia A
7. List 4 components of cryoprecipitate
8. List adjunctive therapies in DIC

Wisecracks:

1. How do you differentiate coagulation disorders from platelet disorders?
2. What is thrombocytopathy?
3. What do INR and PTT test?
4. What is DIC?

Key Concepts:

- ❑ Although hemostatic disorders are confirmed by specific patterns of laboratory test results, a careful history and focused physical examination are often the key to the diagnosis of hematologic diseases.
- ❑ All patients with bleeding disorders of unknown cause or of a significant degree should be admitted to the hospital for further evaluation.
- ❑ The frequency of hemostatic disorders seen in the ED is unknown; however, they are likely to be more common than thought. Although classic diseases such as hemophilia and DIC are uncommon, the use of antiplatelet and anticoagulation agents is common in other disease states, such as cardiovascular diseases.
- ❑ Hemophilia patients are often highly informed about their disease. Patient input should be solicited and respected, and early consultation with the patient's hematologist is encouraged. Consider early treatment with replacement factor while diagnostic testing proceeds.
- ❑ Patients with active life-threatening bleeding who are thought to have a congenital bleeding disorder can be supported with fresh frozen plasma, 15 mL/kg, while diagnostic studies are being performed.
- ❑ Platelet dysfunction is often equated with low platelet counts. Even though critical thrombocytopenia increases the risk of bleeding, particularly with trauma and surgery, dysfunction can occur at normal counts. For example, aspirin therapy and renal disease can alter platelet function without reducing blood counts.
- ❑ All evaluations of suggested ITP should include a complete blood count, peripheral smear, antinuclear antibody test, and bone marrow examination.



- ❑ TTP should be suspected in the setting of thrombocytopenia and microangiopathic hemolytic anemia and early treatment with plasma exchange therapy should be initiated even in the absence of the classic pentad. Platelet replacement should be avoided.

Rosen's in Perspective

Hemostasis = a coordinated response to vessel injury. Usually thought of as having four phases:

1. Platelet plug formation (primary hemostasis)
2. Propagation of the coagulation cascade
3. Clot development
4. Fibrinolysis of the clot

Pathology in any of these points usually results from: drugs, systemic disease (e.g. hepatic disease), or from iatrogenic causes.

- A few FYI points:
 - What role to platelets play in hemostasis?
 - Adhesion to subendothelial connective tissue (which requires vWF)
 - Release of coagulation-promoting aggregation chemicals
 - Platelet aggregation over the injury!
 - Stabilization of the hemostatic plug
 - There are 13 coagulation factors
 - What are some normal controls of coagulation?
 - *Removal and dilution of activated clotting factors through blood flow,*
 - *Alteration of platelet activity by endothelium-generated nitric oxide and prostacyclin*
 - *Removal of activated coagulation components by the reticuloendothelial system*
 - ***Regulation of the clotting cascade by anti-thrombin III, protein C, protein S, and tissue factor pathway inhibitor***
 - *Activation of the fibrinolytic system*
 - Clinical evaluation of a bleeding patient - see Box 114.5.

When it comes to a differential diagnosis of platelet disorders (see box 114.6) it comes down to:

- Thrombocytopenia = too few
- Thrombocytosis = too many
- Thrombocytopathy = too broken

[1] List 10 causes of Thrombocytopenia

Here's the approach:



1. Decreased production:
 - a. Decreased megakaryocytes secondary to drugs, toxins, or infection
 - i. Chemo drugs, thiazides, alcohol, digoxin, septria, phenytoin, ASA
 - b. Normal megakaryocytes with megaloblastic hematopoiesis or hereditary origin
 - c. Malignant infiltration of bone marrow
2. Increased destruction
 - a. Immunologic
 1. Related to collagen vascular disease, lymphoma, leukemia
 2. Drug related: e.g. Heparin induced Thrombocytopenia (HIT)
 - a. Quinine and quinidine
 - b. Heparin
 - c. LMWH
 3. ITP: Idiopathic (autoimmune) thrombocytopenic purpura
 4. Infection
 - a. Post rubella, rubeola, varicella
 5. Post-transfusion
 - b. Mechanical
 1. Disseminated intravascular coagulation (DIC)
 2. Thrombotic thrombocytopenic purpura (TTP)
 3. Hemolytic-uremic syndrome (HUS)
 4. Vasculitis
 5. Dilutional secondary to massive blood transfusion
3. Splenic Sequestration
 - a. Usually in the context of hematologic cancers (one of the few groups where platelet transfusions are helpful).
 - b. Portal HTN

[2] List 6 causes of thrombocytosis

This is a platelet count $> 600,000 / \text{mm}^3$

Most common causes = infection or iron deficiency (platelets still work normally)

1. Autonomous (primary thrombocythemia)
2. Reactive (secondary thrombocythemia)
 - a. Iron deficiency
 - b. Infection or inflammation
 - i. Kawasaki's disease
 - c. Trauma
 - d. Nonhematologic malignant disease
 - e. Postsplenectomy
 - f. Rebound from alcohol, cytotoxic drug therapy, folate or vitamin B12 deficiency



[3] Describe the presentation and treatment of HIT, ITP, and TTP

HIT: Heparin Induced Thrombocytopenia

- UFH >> LMWH
- 1% overall risk
- Typically 5-7 days post exposure but can be longer (up to 40 days!)
- Clinical presentation is thrombocytopenia / bleeding / thrombosis (yes! ½ of pts with HIT can develop arterial or venous thrombotic complications - like a pulseless limb!)
- Diagnosis:
 - > 50% reduction in platelets post initiation of heparin
- Management:
 - Stop the heparin!!! (don't forget about lines and tubes with heparin coating e.g. IV with heparin lock)
 - Xa inhibitor (ie fondaparinux) or direct thrombin inhibitors (argatroban) for thrombotic complications

ITP: Idiopathic thrombocytopenic purpura

Has two main forms: Acute and Chronic

- Autoimmune ITP = DIAGNOSIS OF EXCLUSION (make sure no drugs are to blame)
- Acute form:
 - Typically age 2 - 6 years old
 - Viral prodrome precedes platelet drop (sometimes down to 20k/mm³!)
 - Usually platelets < 20; mild bruising/lower extremity ecchymosis
 - Self limited (80% recover within 6 months while some get chronic disease)
 - Supportive care unless BLEEDING:**
 - ICH rate higher with platelets < 10
 - IVIG
 - Steroids
 - Plasmapheresis
- Chronic form:
 - Chronic form; women >> men
 - Insidious onset = easy bruising, long menses, mucosal bleeding
 - Petechiae, purpura, plt counts 30-100k /mm³
 - Must rule out associated diseases such as lymphoma, SLE
 - Low morbidity and mortality
 - Once chronic ITP dx is made, management is usually supportive +/- steroids and IVIG
 - Platelet transfusions are reserved for **life threatening bleeding.**



TTP vs HUS

| | |
|---|--|
| <p>TTP - thrombotic thrombocytopenic purpura</p> <ul style="list-style-type: none"> • Fibrin and platelet aggregates form in the circulation • Idiopathic cause • Without plasma exchange = 90% mortality rate in 1-3 months | <p>HUS - hemolytic uremic syndrome</p> <ul style="list-style-type: none"> • Autoimmune abdominal vasculitis |
| Typically Adults (10-40 yrs old) women most common | Typically Pediatric patients |
| “FAT RN” but more neuro involvement | “FAT RN” but more renal involvement |
| Platelet count: 10-40k / mm ³ | |
| Idiopathic vs Drugs (most common quinine or plavix) | After E.Coli 0157 toxin |
| Plasma exchange (plasmapheresis) +/- rituximab/steroids/ASA | Supportive care |
| Platelet transfusion only with life-threatening bleeding | |

FAT RN = Fever, Anemia, Thrombocytopenia, Renal, Neuro Symptoms

Classic pentad:

1. Microangiopathic Hemolytic Anemia (MAHA)
2. Thrombocytopenia
3. Fever
4. Renal pathology/disease (hematuria, proteinuria, ARF)
5. CNS abnormalities (headache, seizure, altered mental status, CVA, coma). Neuro symptoms are often transient, may not be present in ED

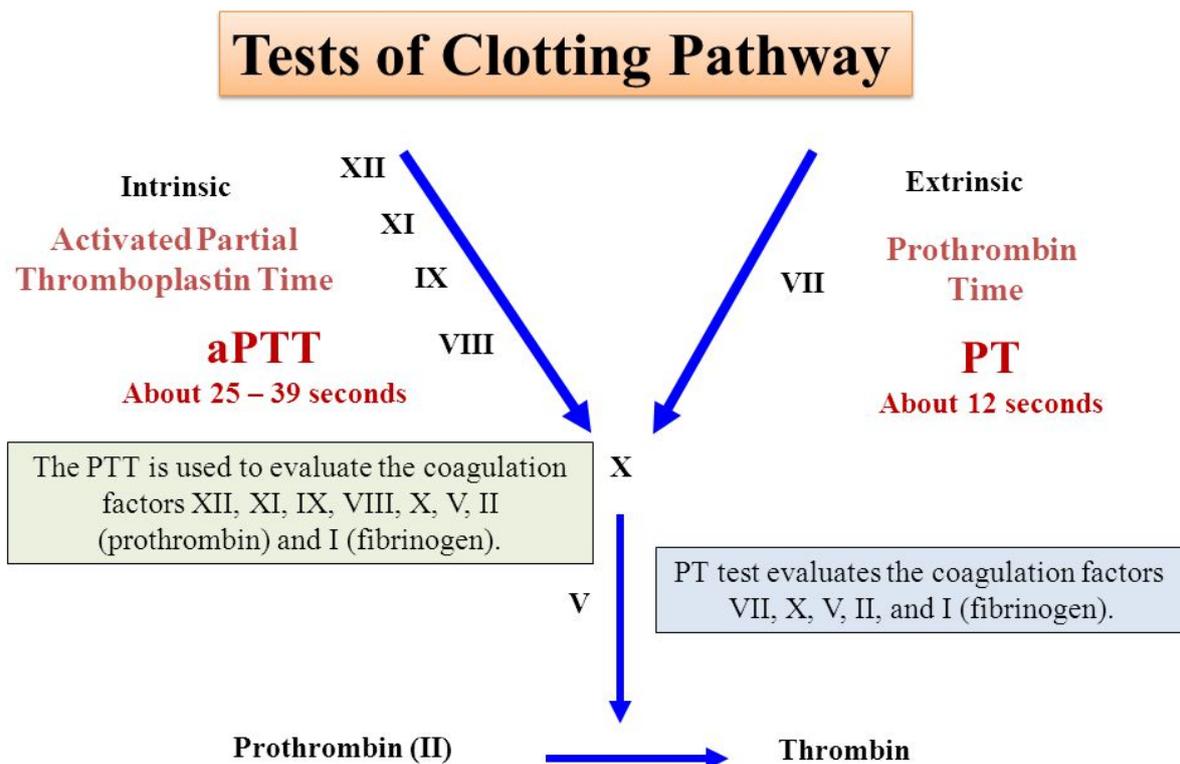
[4] Describe what causes an abnormal PT. What causes an abnormal PTT?

Now, the podcast moves on to discussing disorders of the coagulation pathway. This pathway is usually tested via the PT and PTT.

- **An abnormal PT**
 - An extrinsic pathway abnormality - mediated through a deficiency of factor VII
 - Very rare hereditary gene
 - Much more commonly acquired **vitamin K deficiency; warfarin use; or liver disease**
- **An abnormal PTT**
 - Result from inherited disorders
 - Group 1 = benign deficiencies leading to elevated PTT with NO bleeding diathesis (e.g. low Fletcher factor)



- Group 2 = serious conditions due to deficiencies in the intrinsic coagulation system
 - Factor VIII, IX, XI deficiencies = account for 99% of inherited bleeding disorders
 - *PEARL: anyone with an unknown bleeding disorder can be supported with: fresh frozen plasma @ 15 ml/kg*
 - **The most important test is assay of factor VIII and factor IX**
 - Based on the assay, a percentage of normal procoagulant activity of factor VIII is calculated
 - Btw, if you weren't already overwhelmed, factor 8 has three different activities....
 - **Hemophilia A and vWD are two forms of factor VIII deficiency**



[5] Describe the deficiency and management of Hemophilia A, Hemophilia B and vWD

| Condition | Deficiency | Management | Notes |
|---------------------|---|--|--|
| Hemophilia A | Variant form of VIII is present, that lacks a clot promoting property | 1 U of recomb. factor VIII will increase the factor level by 2% Treat Moderate bleeding with 25 | Hemophilia A can be corrected by liver transplantation! Bleeding may occur in a delayed |



| | | | |
|--|---|---|---|
| <p>Most cases are X-linked recessive</p> <p>Can be an acquired condition due to IgG antibodies postpartum/post drugs/SLE</p> | <p>Severity is related to the level of factor VIII coagulant (VIII:C)</p> <p><1% = severe 1-5% = moderate 5-10% = mild (little risk of bleeding)</p> <p>Those with levels >40% may have a normal PTT</p> | <p>U/kg of Factor VIII:C; Treat Severe bleeding with 50 U/kg.</p> <p>Desmopressin Acetate may also help: 0.3 mcg/kg/dose</p> <p>Consider prophylactic admission post trauma-related injuries.</p> | <p>fashion (8hrs to 5 days!)</p> <p>Bleeding sites: deep muscles, joints, the urinary tract, and intracranial sites are the most common.</p> |
| <p>Hemophilia B</p> <p>Less common</p> | <p>Deficiency of factor IX</p> <p>Clinically findings are indistinguishable from Hemophilia A.</p> | <p>Factor IX replacement with Factor IX concentrate or recombinant.</p> <p>PCC or FFP may also be useful.</p> | <p>Usually diagnosed after factor VIII:C returns as normal</p> <p>Same bleeding sites as Hemophilia A.</p> |
| <p>Von Willebrand's disease</p> <p>Most common hereditary bleeding disorder @1%</p> <p>Usually autosomal dominant</p> | <p>*lack of von Willebrand's factor activity (known as VIII/vWF)</p> <p>Also has decreased VIII:C and VIII:Ag activity</p> <p>****these patients have normal platelets, but in the absence of circulating VIII/vWF their adherent properties are reduced = therefore mucosal bleeding!</p> | <p>For pts with severe vWD = give factor VIII at 50 IU/Kg</p> <p>For pts with mild-mod vWD = give desmopressin; TXA may also help.</p> <p>In extenuating cases use FFP and TXA</p> <p>Cryoprecipitate is not recommended (due to risk of viral transmission)</p> | <p>Bleeding sites:</p> <ul style="list-style-type: none"> ● Mucosal ● Cutaneous ● Menorrhagia ● GI bleeding |

*= remember that the endothelium contributes to clot formation and regulation; it produces von willebrand factor, antithrombin III, heparin sulfate, prostacyclin, nitric oxide, and other inhibitors.

[6] Describe the management of a major and minor bleed in Hemophilia A

With current hemophilia home therapy, most hemophiliacs are able to manage their care and only come to the ER with severe bleeding or post-trauma.

Prehospital:

- Local pressure/compression
- Volume repletion (if available)
- Elevate the affected area
- Prevent hypothermia, hypoxia

Ideally every hemophiliac has their information with them:

- Their primary hematologist, diagnosis, factor VIII activity level, blood type, presence of antibodies.

ED treatment:

- **Replacement therapy:**
 - **Either #1 or #2**
 - **1) cryoprecipitate**



- Cryo is assumed to have ~100 U of VIII:C per bag.
 - 2) recombinant-derived factor VIII concentrates

Table 114.3 (9th Edition) – Dosage of Factor VIII (antihemophilic factor)

| Bleeding Risk | Desired Factor VIII Level (%) | Initial Dose (U/kg) |
|---------------|-------------------------------|---------------------|
| Mild | 5-10 | 12.5 |
| Moderate | 20-30 | 25 |
| Severe | >50 | 50 |

Examples of:

- **Generally no need for factor VIII**
 - Superficial laceration = local measures, suture, direct pressure. Wound reassessment in 24 hrs
 - Spontaneous epistaxis
- **Mild bleeding (12.5 U/kg)**
 - Hematuria
 - Any mucosa or tongue bites with persistent bleeding
- **Moderate bleeding (25 U/kg)**
 - Deep lacerations
 - Traumatic epistaxis or spontaneous epistaxis unresponsive to standard measures
 - Traumatic oral lacerations
 - Soft tissue hematomas
 - Early hemarthrosis (early onset joint pain = treatment and immobilization)
- **Severe bleeding (50 U/kg)**
 - Dental extractions
 - Muscle hematomas/Deep bleeding (eye, back, neck, mouth)
 - Life threatening bleeding; post head trauma (even with a normal CT head)

See table 114.2 for specific details.

In emergency therapy the present level of factor VIII is assumed to be zero. A patient will need repeat doses of factor in 8-12 hrs.

***consider adding Desmopressin Acetate @ 0.3 mcg/kg/dose for some patients!

[7] List 4 components of cryoprecipitate

Cryoprecipitate is the precipitated protein fraction from fresh frozen plasma. It contains:

- Fibrinogen – >150 mg of fibrinogen (range: 150 to 250 mg); half-life: 100 to 150 hours
- Factor VIII – >80 international units (range: 80 to 150 units); half-life: 12 hours
- Factor XIII – 50 to 75 units; half-life of 150 to 300 hours
- von Willebrand factor – 100 to 150 units; half-life: 24 hours



[8] List adjunctive therapies in DIC

1. Reverse the triggering mechanism that is causing DIC! (e.g. sepsis/triad of death in trauma; septic abortion)
2. Treat based on the major component of DIC that is present:
 - a. If bleeding:
 - i. Platelets, FFP, cryoprecipitate
 - b. If clotting:
 - i. IV heparin

Wisecracks:

[1] How do you differentiate coagulation disorders from platelet disorders

History alone can often discriminate between platelet factor abnormalities and coagulation factor abnormalities:

- PD
 - Acquired >>>> congenital
 - Petechiae
 - Purpura (not palpable)
 - Mucosal bleeding
 - More common in women
 - Capillary bleeding - ecchymosis, petechiae, epistaxis, menorrhagia, GI bleeding
 - Immediate onset, mild, continued bleeding after dental or surgery
- CD
 - Congenital >>>> acquired
 - Deep muscle hematomas
 - Hemarthroses
 - More often in men
 - Delayed onset from insult

To recap, straight from Rosen's: (**SEE box 114.7**)

The bleeding source is often an intramuscular or deep soft tissue hematoma from small arterioles. The congenital form of the disease occurs predominantly in men, often as a sex-linked inheritance. Bleeding may occur after surgery or trauma but is **delayed in onset** up to 72 hours. Epistaxis, menorrhagia, and gastrointestinal sources of bleeding are rare, **whereas hematuria and hemarthrosis** are common in severe cases. The **bleeding time is normal** except in patients with von Willebrand's disease (vWD).

[2] What is thrombocytopathy?

- Thrombocytopathy = abnormal platelet function
 - Adhesion defects
 - Classic disease is vWD



- This is actually a factor VIII problem; not a platelet problem.
- These patients have normal platelets, but they lack a normal endothelium-based factor VIII component (known as vWF) which permits normal platelet adhesion
- Release defects
 - Problems either acquired (drugs, etoh, SLE, lymphoma) or congenital that prevent platelets and the coagulation cascade from functioning
- Aggregation defects = congenital thrombasthenia

[3] What do INR and PTT test?

INR: (also called PT)

- Looks at EXTRINSIC and common pathways
- Vitamin K dependent factors (2, 7, 9, 10) *warfarin or liver disease*

PTT:

- INTRINSIC and common pathways
- All factors EXCEPT 7 and 13

How to remember?

Play Tennis Outside = PT Extrinsic

Play Table Tennis Inside = PTT INTRINSIC

[4] What is DIC?

- DIC = Disseminated Intravascular Coagulation
- An acquired coagulopathy
 - Multiple possible causes
- An out of control **coagulation and fibrinolytic cascade** (see box 114.8)
- All the platelet, coagulation factors and checks and balances get thrown off kilter =
 - Bleeding out of control
 - Clotting out of control
- Variable onset, but usually occurs rapidly
 - Clinical features:
 - Purpura, bleeding tendency, CNS/renal organ injury
- Lab diagnosis of DIC:
 - Low platelet count
 - Low Fibrinogen
 - High D-dimer
 - High PT
 - High PTT
 - High (or trending up) creatinine
 - High thrombin time
- What else to think about?



- Could this patient with coagulopathy be in severe liver disease?
 - Look for jaundice and splenomegaly with a history of liver disease!
 - Severe liver disease may need Vitamin K, cryoprecipitate
- What else is on the ddx of the bleeding patient? (box 114.9)
 - Don't forget to think about rare inherited or acquired vascular disorders
 - Inherited
 - Connective tissue disorders
 - Ehlers-Danlos, osteogenesis imperfecta, etc.
 - Blood vessel disorders:
 - Hereditary hemorrhagic telangiectasia
 - Acquired:
 - Scurvy, steroid use, HUS, hypoxemia, TTP, snakebites