Platelet Destruction Disorders

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LSUHSC – NO
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Learning Objectives

- Platelet biology; mechanisms of hemostasis
- Identify Thrombocytopenia by lab values; clinical signs and symptoms
- Identify causes and pathophysiology of thrombocytopenia caused by increased platelet destruction:
  1. ITP
  2. TMA (Thrombotic microangiopathies)
     a. TTP
     b. HUS
     c. HELLP
     d. DIC
  3. HIT/T
  4. Other drug related thrombocytopenia
- Describe treatments for Platelet Destruction Disorders

1. A 65-y.o. male with metastatic pancreatic carcinoma shows elevated PT and PTT, platelets 15 K and elevated D-Dimer. On peripheral smear, what you would see?

A. Howell-Jolly bodies
B. Plasmodium vivax
C. Macro-ovalocytes
D. Schistocytes
E. Target cells

2. A 30-y.o. female presents with blurred vision & confusion, Temp 40 C; petechiae on limbs. Platelets 28 K. The PT & PTT normal. CBC shows fragmented RBCs. BUN 40 mg/dL. What is the most likely diagnosis?

A. ITP
B. TTP
C. HUS
D. Hemophilia A
E. DIC

- We will revisit these questions at the end!

Blood Hemostasis

- The regulated process of maintaining the vascular system
- Repairing vascular injury, and limiting blood loss
- Avoiding vessel occlusion (thrombosis) and inadequate perfusion of vital organs

1) Damage → Local Vasoconstriction
2) Primary: Hemostatic plug (platelets)
3) Secondary: Thrombus (clotting factors)
4) Fibrinolysis: Degradation of blood clot

Primary Hemostasis

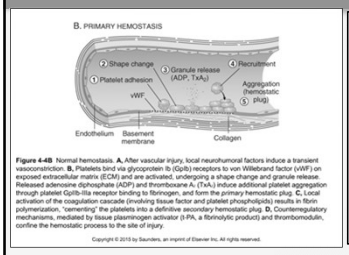
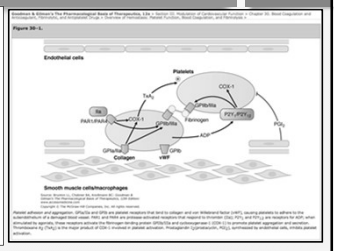


Figure 4-4B Normal hemostasis. **A,** After vascular injury, local neurohumoral factors induce a transient vasoconstriction. **B,** Platelets bind via glycoprotein Ib (GpIb) receptors to von Willebrand factor (vWF) on exposed extracellular matrix (ECM) and are activated, undergoing a shape change and granule release. Released adenosine diphosphate (ADP) and thromboxane A$_2$ (TxA_2) induce additional platelet aggregation through platelet GpIIb-IIIa receptor binding to fibrinogen, and form the primary hemostatic plug. **C,** Local activation of the coagulation cascade (involving tissue factor and platelet phospholipids) results in fibrin polymerization, "cementing" the platelets into a definitive secondary hemostatic plug. **D,** Counterregulatory mechanisms, mediated by tissue plasminogen activator (t-PA, a fibrinolytic product) and thrombomodulin, confine the hemostatic process to the site of injury.



Primary Hemostasis

1. Sub-endothelial matrix proteins (collagen and vWF) are exposed
2. Platelet adhesion and activation
   a. Platelets adhere to collagen and vWF thru GPIa/IIa and GPIb respectively
   b. Platelet granule release begins and platelets begin shape change
3. Platelet granule release
   a. ADP binds the P2Y1/12 receptors activating GPIIb/IIIa to bind fibrinogen which links platelets
   b. Thromboxane A2 (TXA_2) is released and production increased by action of COX-1
   c. Calcium release - important for coagulation cascade
4. Formation of the platelet plug

Just to be complete - Secondary Hemostasis

- Sequential proteolytic cascade leading to thrombin activation and deposition of fibrin fibers to stabilize the hemostatic platelet plug
- Thrombin (Factor II) plays a central role in the clotting cascade
- Vitamin K is an important cofactor in the maturation of clotting factors

Secondary Hemostasis

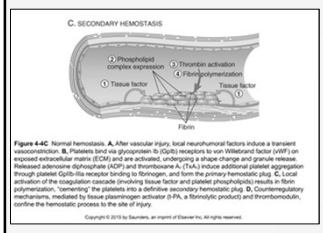
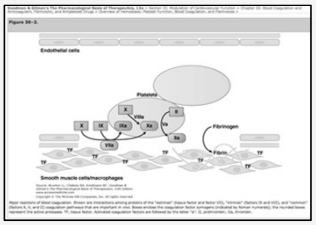
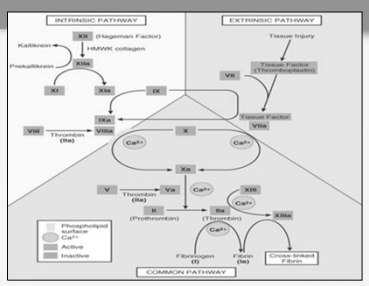


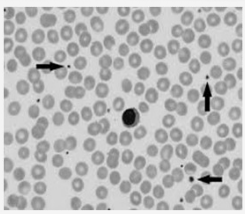
Figure 4-4C Normal hemostasis. **A,** After vascular injury, local neurohumoral factors induce a transient vasoconstriction. **B,** Platelets bind via glycoprotein Ib (GpIb) receptors to von Willebrand factor (vWF) on exposed extracellular matrix (ECM) and are activated, undergoing a shape change and granule release. Released adenosine diphosphate (ADP) and thromboxane A$_2$ (TxA_2) induce additional platelet aggregation through platelet GpIIb-IIIa receptor binding to fibrinogen, and form the primary hemostatic plug. **C,** Local activation of the coagulation cascade (involving tissue factor and platelet phospholipids) results in fibrin polymerization, "cementing" the platelets into a definitive secondary hemostatic plug. **D,** Counterregulatory mechanisms, mediated by tissue plasminogen activator (t-PA, a fibrinolytic product) and thrombomodulin, confine the hemostatic process to the site of injury.



Secondary Hemostasis



Platelets (Thrombocytes)



- Small (2-4 um) anucleated cytoplasmic fragments derived from megakaryocytes in bone marrow
- Resting discoid forms in the circulation for 9-12 days
- When activated (exposure to breached endothelium, become spiky
- 150 - 450 × 10 ^{3}/mL (150-450) K
- Mean Platelet Volume (MPV)

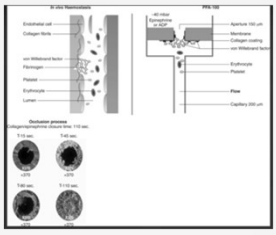
Platelets

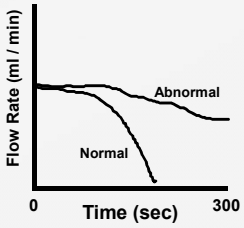
- Granules
  1. Alpha granules (α-granules)
     - Larger and more abundant
     - vWF, platelet factor 4, fibrinogen, factor V
  2. Dense granules (δ-granules)
     - ~10-fold fewer
     - Small molecules: ADP, ATP, serotonin, calcium, magnesium
- Membrane glycoproteins
  - GPIIb-IIIa: fibrinogen receptor
  - GPIb-IX-V: von Willebrand factor receptor
  - GPIa-IIa, GPVI: collagen receptors
- Phospholipid membrane bilayer

Platelet Function Tests

- ~~Bleeding Time~~
- Platelet Aggregation Assays
  - Light transmission aggregometry (LTA)
  - Impedance aggregation
- Shear-based assay
  - PFA 100/200
- Assays measuring release
  - Ligand-binding ELISA –urine, serum, citrated plasma
- Platelet activation assays
  - Flow cytometry

Primary Hemostasis test - PFA 100 (aperture occlusion)





Secondary Hemostasis Tests

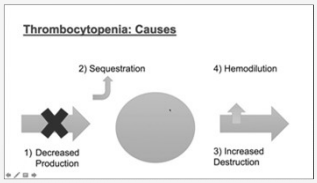
- Prothrombin time (PT):
  - Tests extrinsic and common coagulation pathways
- Partial thromboplastin time (PTT):
  - Tests intrinsic and common coagulation pathways

Thrombocytopenia (low platelets)

- Platelets count < 100K
- Platelet count < 50K - variable risk
- Platelet count < 20K- transfusion appropriate
- Platelet count < 10K - spontaneous hemorrhage
- Platelet dysfunction = mucus membrane bleeding
  - Epistaxis
  - Gingival
  - Vaginal bleeding
  - Petechiae, purpura

Bleeding Disorders Due to Thrombocytopenia

- 4 major categories:
  1. Decreased platelet production
  2. Decreased platelet survival
  3. Sequestration
     - Hypersplenism
  4. Dilution
     - Transfusion



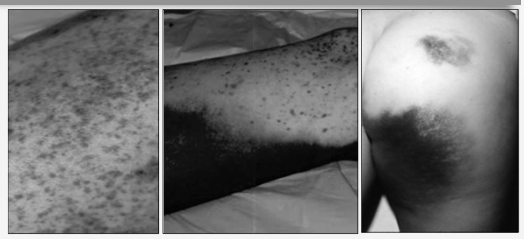
Decreased Platelet Production

- Drug-induced
- Infections
- Nutritional deficiencies (B12; Folate)
- Bone marrow failure or ineffective hematopoiesis (aplastic anemia; MDS)
- Bone marrow replacement (leukemia; metastatic carcinoma)

Decreased Platelet Survival ***

- Immunologic destruction
  - Primary autoimmune:
    - Immune thrombocytopenic purpura (ITP)
  - Secondary autoimmune:
    - Systemic lupus erythematosus
    - Posttransfusion
    - HIIT/T
- Nonimmunologic destruction
  - Disseminated intravascular coagulation
  - Thrombotic microangiopathies

Manifestations of bleeding



Petechiae | Ecchymosis (bruise) | Hematoma

AG1

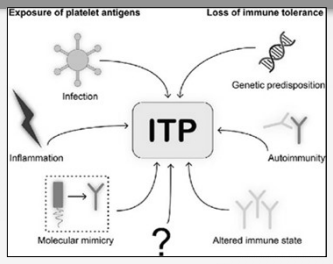
Platelet destruction *

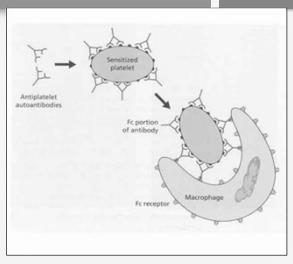
- Antibodies (Autoimmune)
- Mechanical
- Drug induced

1. Immune/Idiopathic Thrombocytopenic Purpura (ITP)

- Acquired ***autoimmune*** disorder –Antibodies against platelet membrane glycoproteins
  - Medications
  - Viral infections –chicken pox, Hep C, AIDS
  - Pregnancy
  - Autoimmune disorders
  - Lymphomas and leukemias
  - Idiopathic
- Clinical findings – Thrombocytopenia; often giant platelets with normal bone marrow
- Diagnosis of exclusion – PT and PTT usually normal; bleeding time/PFA prolonged

Model for pathogenesis of ITP

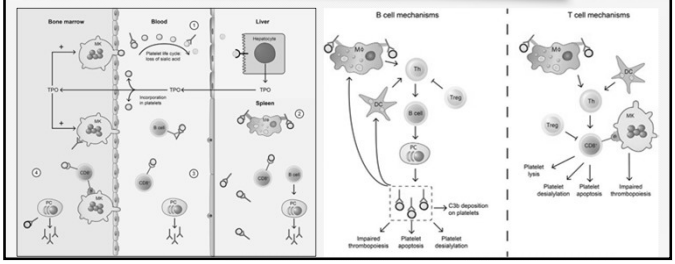




Slide 22

AG1 Athas, Grace, 4/23/20

Proposed mechanisms of ITP/Immune function effects



ITP – Acute Form

- Children 2-6 yrs. old
- Associated with prior viral illness (<3 wks.)
- Resolution > 1-2 months, often quite longer
- Spontaneous resolution in 90%
- Many children will not require treatment and may not be treated even if count <20K if not bleeding
- Treatment rarely necessary if plts > 50K

"wet purpura" - suggests need for treatment

ITP – Chronic Form

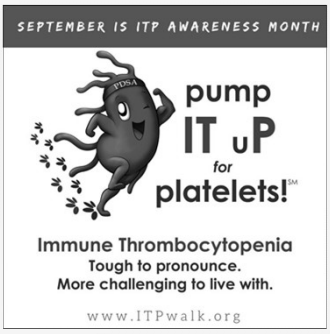
- Adults
- Associated with autoimmune disorder (SLE, HIV)
- Resolution is rare
- Thrombocytopenia < 20 K
- Mucosal bleeding

Signs and symptoms of ITP

- Large bruises
- Petechiae
- Nosebleeds
- Bleeding mouth/gums
- Heavy menstruation
- Hematuria
- Blood in stool or vomitus
- Intracranial hemorrhage

Treatment of ITP

- Steroids –reduce the rate of platelet destruction
- Other immunosuppressive drugs (eg, rituximab)
- IVIG – Intravenous Immuno(gamma) globulin
- Rh Immune globulin (RhoGAM) – Spleen removes Ab coated RBCs from circulation rather than plt (in RH + people)
- Splenectomy
- Stop suspected medicine if possible
- Treat infection
- Thrombopoiesis-stimulating drugs offer a new treatment option
- Plt (if life threatening bleeding with other RX on board) - but will be destroyed



•MORE ALPHABET SOUP!

2. Thrombotic microangiopathies (TMA) or Microangiopathic Hemolytic Anemias (MAHA)

a. TTP
b. HUS
c. HELLP
d. DIC

MICROANGOPATHIC HEMOLYTIC ANEMIA

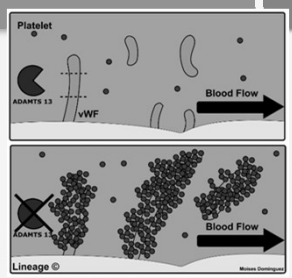
Deposition of fibrin strands within the microcirculation damages (cuts) red blood cells resulting in formation of schistocytes and fragments

a. Thrombocytic Thrombocytopenic Purpura (TTP)

- Life threatening multisystem disorder –rarely genetic; most often acquired
- Deficient activity of vWF-cleaving proteinase (ADAMTS-13)
  - "***A*** ***D***isintegrin ***A***nd ***M***etalloproteinase with ***T***hrombo***s***pondin-like domains"
- Most cases have no known cause (idiopathic) – now know there is an antibody made to ADAMTS-13

TTP mechanism

- Normally, endothelial cells produce ultra-large von Willebrand factor (vWF) multimers which the enzyme cleaves
- With deficiency
  - LARGE vWF multimers are in circulation
  - They bind platelets and cause microthrombi in circulation
- Can be enhanced by other factors (drugs, hypertension, post-partum) that damage endothelial cells



Clinical findings in TTP

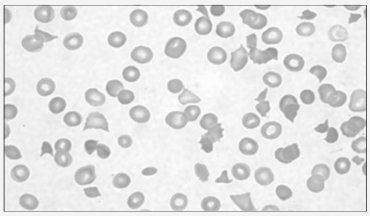
- Occurs at any age; peaks in third decade
- More common in females (60%)
- Defined by a **clinical pentad**:
  - Fever
  - Microangiopathic hemolytic anemia
  - Thrombocytopenia
  - Renal abnormalities
  - Neurological changes (confusion, mental status change)
- Entire pentad not usually seen at presentation

Lab findings in TTP

- Schistocytes -Intravascular hemolysis – peripheral smear
- Platelets < 20K
- Increased reticulocyte count
- Increased indirect bilirubin
- Increased LDH
- Decreased haptoglobin
- Decreased ADAMTS 13 ***
- Positive inhibitor screen
- Titer for antibody

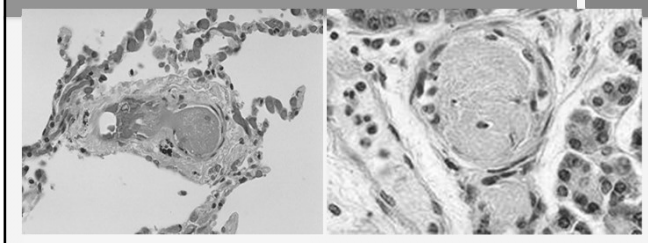
Testing Algorithm

TTP Blood Smear



- Schistocytes
- Lack of platelets

Microthrombi in circulation



Fibrin and platelet microthrombi form in the microcirculation throughout the body particularly in kidneys and brain

TTP RED CELL FRAGMENTATION

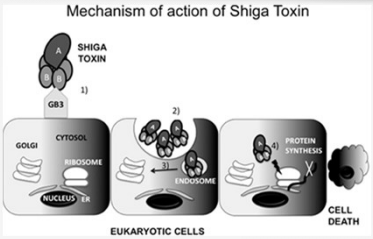
TTP Treatment

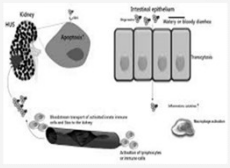
- High mortality rate if untreated (>90%)
- Plasma exchange is lifesaving
  - removes the IgG autoantibody against the enzyme
  - Replaces ADAMTS 13
- Concomitant immunosuppressive therapy often given (steroids, Rituximab)
- Case reports of success with other immunosuppressive/ Mabs - no big studies – works for some, not for all, lots of side effects
- Mortality < 20% if disease is promptly diagnosed and treated

b. HEMOLYTIC UREMIC SYNDROME (HUS)

- Microangiopathic syndrome similar to TTP, but kidneys are the main organ affected
- Damage to endothelial cells
- Often associated with GI prodrome, usually diarrhea, due to infection with toxin producing *E. coli* H7:0157
  - May occur in epidemics (contaminated food)
  - Bacterial toxin injures endothelium, causing microangiopathy and renal failure
- Often self-limited, but susceptible patients (children, elderly) may have life-threatening disease

Shiga and Shiga-like toxins – mech of action





HUS

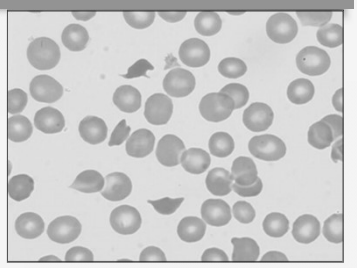
- Prodromal gastroenteritis (83%) - Fever (56%), bloody diarrhea (50%) for 2-7 days before the onset of renal failure
- Irritability, lethargy
- Seizures (20%)
- Acute renal failure (97%)
- Anuria (55%)
- Physical findings may include the following:
- Hypertension (47%)
- Edema, fluid overload (69%)
- Pallor, often severe
- One of the most common causes of acute renal failure in children
- Characterized by:
  - Acute renal failure (uremia)
  - Microangiopathic hemolytic anemia
  - Fever
  - Thrombocytopenia
- Neurologic changes usually not present (vs. TTP)

Lab studies

- Urinalysis: Benign mild proteinuria; red blood cells (RBCs) and RBC casts may be present
- Blood urea nitrogen (BUN), serum creatinine, and serum electrolyte levels
- Severe anemia may be present. Perform peripheral smear for schistocytes
- Bilirubin levels may be elevated. Lactate dehydrogenase (LDH) levels may be elevated. Haptoglobin levels may be decreased.
- aPTT, fibrinogen degradation product (FDP), and D-dimer values.
- Bilirubin levels may be elevated. Lactate dehydrogenase (LDH) levels may be elevated. Haptoglobin levels may be decreased.
- Stool culture: Obtain a sample for stool culture. Evaluate especially for *E coli* 0157:H7 and *Shigella* bacteria.
- ADAMTS-13 activity: ADAMTS-13 activity is often severely deficient (< 10% of normal) in patients with classic thrombotic thrombocytopenic purpura (TTP), but can be seen in patients with severe sepsis (especially in association with disseminated intravascular coagulation or multiorgan failure) and in patients with severe liver disease.
- On complement serology testing, a decrease in both complement factor B (CFB) and CH50 may offer important support for the diagnosis of atypical HUS.ref36] In diarrhea-associated HUS, a lowered concentration of C3 (< 0.825 g/L) at the time of initial presentation is associated with a more severe clinical course.[25]

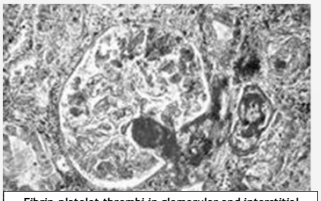
HUS – peripheral smear MAHA

A



HUS

Toxins attach to glomerular endothelial cells causing release of large mulitmer vWF molecules. Multimers promote platelet aggregation in renal glomeruli



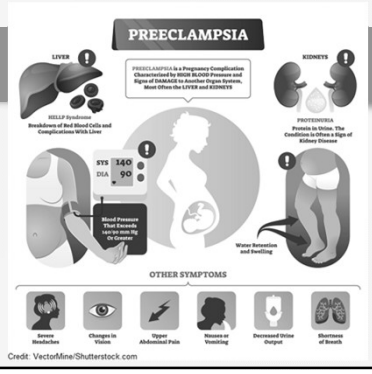
Fibrin-platelet thrombi in glomerular and interstitial vessels. Masson- trichrome staining fibrin red

HUS Treatment

- Dialysis, transfusions and supportive care
  - reduced mortality rate from 50% to 5-10%
- Plasma exchange
- Monoclonal Abs in atypical HUS-inhibit complement-mediated thrombotic microangiopathy
- No clear consensus on the use of antibiotics
- Residual renal impairment of some degree in 50% of patients

C. HELLP SYNDROME (Hemolysis, Elevated Liver enzymes, Low Platelets)

- Obstetric disease similar to TTP
  - Associated with pregnancy or delivery (significant number develop within 24-48 hours of delivery)
- Pathophysiology of HELLP syndrome is ill-defined
- Occurs in 0.1%-0.6% of all pregnancies and in 4%-12% of patients with **preeclampsia**



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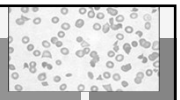
Laboratory studies



- **CBC: Thrombocytopenia, anemia with possible reticulocytosis**
- **Peripheral smear: Schistocytes (MAHA)**
- **Serum aspartate aminotransferase/alanine aminotransferase (AST/ALT) levels: Elevated secondary to liver dysfunction**
- **Lactate dehydrogenase (LDH; LD): Elevated secondary to liver dysfunction or hemolysis**

Diagnostic

- Coagulation studies: Normal prothrombin time, 50% may have prolonged activated partial thromboplastin time
- CMP: Elevated blood urea nitrogen (BUN)/creatinine with acute renal failure
- Bilirubin: Increased secondary to hemolysis
- Haptoglobin: Decreased - hemolysis
- Fibrinogen: Low due to increased coagulation
- D-dimer: Increased due to fibrinolysis/DIC

HELLP

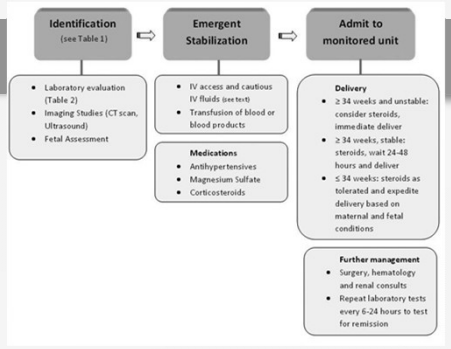
- Most common presenting symptom is RUQ abdominal pain
- Nausea and vomiting
- Headache and visual disturbances
- Jaundice
- Most recover within a few days after delivery
- Complications include hepatic rupture, seizures, blindness and DIC
- Small subset develop severe persistent multisystem disease that requires plasma exchange

Neonatal complications of HELLP syndrome

- Prematurity
- Intrauterine growth retardation (39%)
- Thrombocytopenia (one third of neonates born to patients with HELLP; 4% of these infants will have intraventricular hemorrhage

HELLP Treatment

- Blood transfusions to **treat** anemia and low platelet levels.
- Magnesium sulfate to prevent seizures.
- Antihypertensive medication to control blood pressure.
- Corticosteroid medication to helps baby's lungs mature in case an early delivery is needed



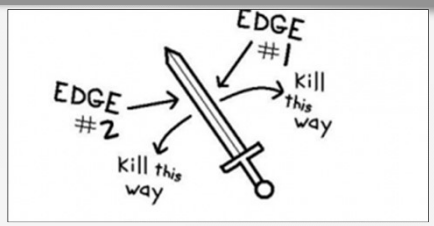
d. Disseminated Intravascular Coagulation (DIC)

- Life threatening condition with complex pathophysiology
- Release of Tissue Factor OR Exposure to Endotoxin OR Exposure to pro-coagulants (from cancer cells) OR ENDOTHELIAL DAMAGE
- Blood coagulation system is activated overwhelming normal hemostatic control mechanisms
- Coagulation cascade is ignited to such a degree that coagulation factors and platelets are consumed
- Secondary fibrinolysis due to activation of plasmin(digests fibrin)
- Prothrombotic and antithrombotic derangement

DIC

- Results from generation of TISSUE FACTOR within the blood (endothelial damage) TRIGGERS
- Production of THROMBIN. Excess thrombin leads to ↑ **thrombi in microcirculation AND**
- **Secondary activation of the FIBRINOLYTIC SYSTEM**
- *****
- **CLOTS forming in the small vessels use up all the coagulation factors →**
- CONSUMPTION COAGULOPATHY with PARADOXICAL HYPOCOAGULABLE STATE
- PLASMIN production is increased leading to FIBRINOLYSIS
- ↑ **FDPS AND D-DIMERS**

DIC



Pathophysiology of DIC

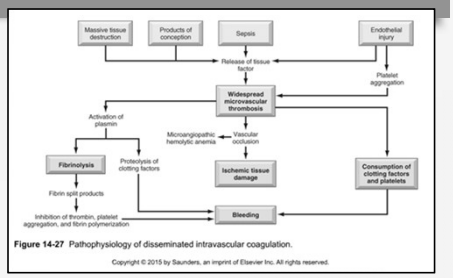


Figure 14-27 Pathophysiology of disseminated intravascular coagulation.

Triggers of DIC

Vascular Damage leading to release of Tissue Factor

- BACTERIAL SEPSIS
  - Gram negative organisms (Meningococcus)
  - Gram positive organisms (Pneumococcus)
- METABOLIC STRESS
  - Acidosis
  - Shock

Release of Tissue Factor from injured or pathologic tissue

- OBSTETRICAL COMPLICATIONS
  - Placental abruption
  - Retained placenta or fetus
  - Placenta previa
  - Amniotic fluid embolus
  - Preeclampsia/Eclampsia
- MALIGNANCIES
  - Acute Promyelocytic Leukemia
  - Solid tumors, Mucin-secreting adenomas
- SEVERE BURNS

Neutrophil Extracellular Traps (NETs) – DIC due to sepsis

- **Identified in 2004**
- **Extracellular webs of extruded neutrophil DNA and immunoreactive enzymes**
- **Decorated with neutrophil granular proteins: neutrophil elastase, MPO, calgranulin, cathepsin G**
- **Last-ditch effort by neutrophils to contain infections to primary site**
- **NETs contain a variety of substances that promote clotting**
- **They likely contribute to activation of clotting and DIC, in patients with sepsis**

NETosis Pathway (FYI)

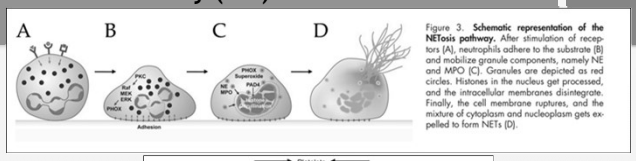
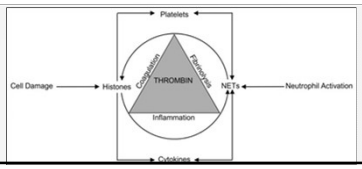
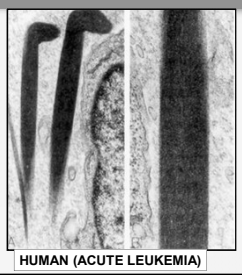


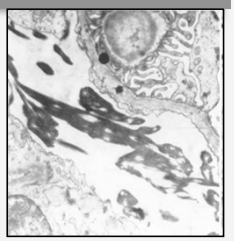
Figure 3. **Schematic representation of the NETosis pathway.** After stimulation of receptors (A), neutrophils adhere to the substrate (B) and mobilize granule components, namely NE and MPO (C). Granules are depicted as red circles. Histones in the nucleus get processed, and the intracellular membranes disintegrate. Finally, the cell membrane ruptures, and the mixture of cytoplasm and nucleoplasm gets expelled to form NETs (D).



DIC –soluble fibrin in the blood



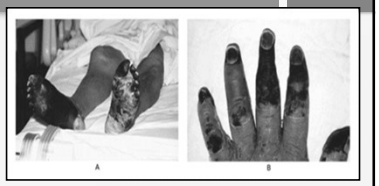
HUMAN (ACUTE LEUKEMIA)



MONKEY (E. COLI INJECTION)

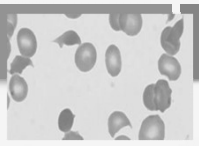
DIC –Purpura Fulminans

- Tissue necrosis and multiple organ failure, most often seen in severe sepsis. Contributing factors (mainly cytokine-mediated):
  - Tissue hypoperfusion (shock)
  - Endothelial injury
  - Intravascular fibrin formation



NEJM (2001) 344; 1593

DIC - Labs



- **Evidence of fibrinogen and platelet consumption**
  - **Thrombocytopenia**
  - **Decreased fibrinogen**
- **Combined with evidence of ▲ fibrinolytic activity**
  - Very high levels of **D-dimers** and **fibrin split products (FDPs)**
  - Plasmin formed for fibrinolysis degrades and inactivates
    - factor V, causing **increased PT**
    - factor VIII, causing **increased aPTT**

Platelets	Low
Fibrinogen	Low
D-Dimer	Increased
PT/PTT	Increased
FVIII	Decreased
MAHA	Schistocytes

DIC treatment

- Treat underlying cause
- Supportive care (maintain BP, etc.)
- Replacement therapy for bleeding (FFP, cryoprecipitate, and/or platelet transfusions)
- Antifibrinolytic agents
- Heparin (especially if thrombosis dominates picture)
- Overall, the clinical picture (bleeding vs thrombosis) should direct therapy but caution should be exercised as transfusions or anticoagulation can quickly flip the balance

Comparisons of HUS, TTP, & DIC

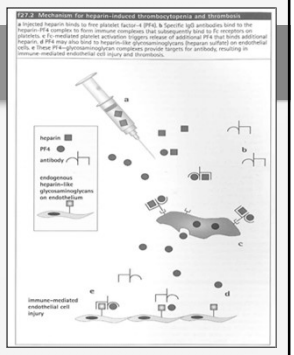
	HUS	TTP	DIC
Age	Children	Adults	Adults
CBC	Anemia & ▼ platelets	Anemia & ▼ platelets	Anemia & ▼ platelets
Peripheral Smear	MAHA	MAHA	MAHA
Clinical	Predominantly Renal	Predominantly CNS	Reflects under-lying disease
Treatment	Supportive	Plasmapheresis Steroids	Heparin & Blood Comp.
Prognosis	Good	Poor	Generally Poor

3. Heparin-Induced Thrombocytopenia

- Heparin
- Type II –MOST COMMON
  - Autoimmune
  - Antibody made to the complex of heparin and platelet factor 4 (PF4)
  - Occurs day 4-14 of heparin therapy –see platelets drop by 50%
  - Activates platelets and causes thrombosis
  - More common in unfractionated heparin therapy

(HIT)

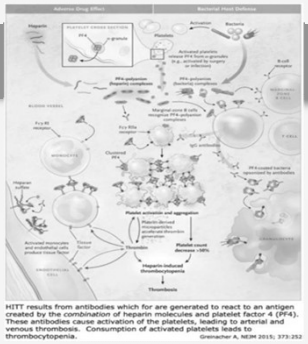
- Injected heparin binds platelet factor 4
- IgG antibodies form against heparin-platelet factor 4 (PF4) complex
- React with platelet Fc receptors
  - Thrombocytopenia
  - Platelet Activation
- Usually takes about 5-10 days unless recent history of HIT in which case it may be immediate on re-exposure
- Patients must have heparin therapy withheld because major consequence is actually thrombosis.



HIT – Lab Tests

- Enzyme-linked immunosorbent assay (ELISA) (screening)
  - Detects all circulating antibodies that bind heparin-PF4 complex including antibodies that do not cause HIT (non-platelet activating)
  - Therefore, those with a positive ELISA are tested further with a functional assay
- Serotonin release assay (SRA) (confirmation)
  - Donor platelets and patient serum are mixed with heparin
  - High serotonin release, diagnosis of HIT is confirmed
  - Gold standard but tedious
- Heparin-induced platelet agglutination (HIPA) assay
  - Washed donor platelets mixed with patient serum → macroscopic agglutination of platelets = HIT

HIIT/T



HITT results from antibodies which for are generated to react to an antigen created by the combination of heparin molecules and platelet factor 4 (PF4). These antibodies cause activation of the platelets, leading to arterial and venous thrombosis. Consumption of activated platelets leads to thrombocytopenia. Greinacher A, NEJM 2015; 373:252

Heparin

Unfractionated

Unfractionated Heparin (UFH): Pros and Cons

- Pros:
  - Rapid onset and clearance, titratable, monitoring readily available, rapidly reversed with protamine
  - Preferred for anticoagulation during procedures
- Cons:
  - Narrow window of adequate anticoagulation without bleeding
  - Highly variable dose-response
  - Hematologic side effects (including HIT)
  - Not easily used in outpatient setting/no oral formulation
  - Reduced ability to inactivate thrombin bound to fibrin or factor Xa bound to activated platelets within a thrombus →Potential extension of thrombus

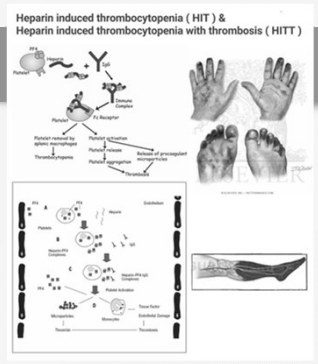
Low Molecular Weight

Low Molecular Weight Heparins (LMWHs): Pros and Cons

- Pros:
  - Does not require routine monitoring
  - Subcutaneous administration and predictable dose response allows for easier dosing and outpatient use
  - Lower risk of HIT and osteoporosis than UFH
  - Preferred agent for pregnancy, malignancy
- Cons:
  - Prolonged half-life in patients with renal failure, challenging dosing at extremes of body weight
  - Generic availability challenging because of biologic status
  - If monitoring is required, anti-factor Xa activity testing with a rapid turnaround time may be less widely available
  - No oral LMWH

Complications

- Deep venous thrombosis
- Pulmonary embolism
- Myocardial infarction
- Occlusion of limb arteries (possibly resulting in amputation)
- Transient ischemic attack and stroke
- Skin necrosis
- End-organ damage (eg, adrenal, bowel, spleen, gallbladder, or hepatic infarction; renal failure)
- Death



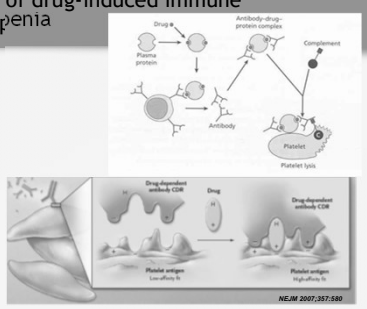
4 TS Score for clinical diagnosis

- Thrombocytopenia
- Timing of thrombocytopenia relative to heparin exposure
- Thrombosis or other sequelae of HIT
- Likelihood of other causes of thrombocytopenia

4. Drug- Induced Inactivation of Platelets

- Most common
  - Quinidine / quinine, sulfonamides. Phenytoin, ASA
- Less common
  - Chronic EtOH, NSAID's (indomethacin), valproic acid
- Development of antiplatelet antibodies
- Thrombocytopenia often severe, sudden onset
- Treatment
  - Steroids
  - DDAVP / platelet transfusions for severe hemorrhage

Pathogenesis of drug-induced immune thrombocytopenia



Therapeutic Drug-induced platelet dysfunction –for treatment of thrombotic conditions

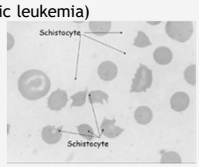
- Aspirin: irreversibly inhibits cyclooxygenase, blocks thromboxane synthesis
- Clopidogrel (Plavix®): blocks ADP receptor
  - Prasugrel, ticagrelor have similar mechanism
- Abciximab, eptifibatide, tirofiban: block IIb-IIIa receptor, prevent aggregation

1. A 65-y.o. male with metastatic pancreatic carcinoma shows elevated PT and PTT, platelets 15 K and elevated D-Dimer. On peripheral smear, what you would see?

A. Howell-Jolly bodies
B. Plasmodium vivax
C. Macro-ovalocytes
D. Schistocytes
E. Target cells

Answer D (schistocytes)

- Fragmented RBCs
- Also called helmet cells or schistocytes
- Pt has DIC with fibrin strands in small BVs that slice up the RBCs
- Schistocytes also present in TTP and HUS; also present in artificial heart valves; also seen in APML (acute promyelocytic leukemia)



2. A 30-y.o. female presents with blurred vision & confusion, Temp 40 C; petechiae on limbs. Platelets 28 K. The PT & PTT normal. CBC shows fragmented RBCs. BUN 40 mg/dL. What is the most likely diagnosis?

A. ITP
B. TTP
C. HUS
D. Hemophilia A
E. DIC

Answer B (TTP)

- Pentad of TTP
  - Thrombocytopenia
  - Fever
  - Renal disease
  - CNS disease
  - MAHA- microangiopathic hemolytic anemia
- Peripheral blood smear shows helmet cells and schistocytes