Learning Objectives

- Describe functions of blood vessels and platelets in controlling bleeding
- Explain three phases of coagulation and the respective factors involved
- Describe laboratory tests for evaluating hemostasis
- Describe common clinically significant disturbances of hemostasis and their clinical manifestations

Factors Concerned with Hemostasis (1 of 2)

- Integrity of small vessels
  - Small vessels are first line of defense in the body
  - Constrict on injury to facilitate closure by a clot
  - Exposure of underlying connective tissue of the endothelium activates coagulation mechanism
- Adequate number of platelets to accumulate and adhere to injury area

Factors Concerned with Hemostasis (2 of 2)

- Platelets: small fragments of cytoplasm from large precursor cells called megakaryocytes
- Average survival in the circulation is 10 days, removed by macrophages spleen
- Three important platelet functions
  - PLUG defect in the vessel wall
  - Liberate vasoconstrictors and compounds causing platelets to AGGREGATE
  - Release substances (phospholipids) that INITIATE coagulation

Hemostasis

- Arrest of bleeding caused by activation of the blood coagulation mechanism
- Factors concerned with hemostasis
  - Integrity of small blood vessels
  - Adequate numbers of platelets
  - Normal amounts of coagulation factors
  - Normal amounts of coagulation inhibitors
  - Adequate amounts of calcium ions in the blood
Blood Coagulation Process (1 of 2)
- Highly complex chain reaction
- Phase 1: Formation of thromboplastin by either interaction of
  - Intrinsic factors in blood (platelets and plasma factors)
  - Extrinsic factors from components outside circulatory system
- Phase 2: Conversion of prothrombin into thrombin
  - After thromboplastin interacts with other substances to form prothrombin activator

Blood Coagulation Process (2 of 2)
- Phase 3: Conversion of fibrinogen into fibrin by thrombin
  - Thrombin splits off a part of the fibrinogen → forms smaller molecules, fibrin monomers
  - Fibrin monomers join end-to-end into long strands of fibrin and link side to side
  - Fibrin stabilizing factor strengthens bonds between fibrin molecules to increase strength of fibrin clot
- Blood clot: end stage of clotting process
- Made up of an interlacing meshwork of fibrin threads with plasma, red cells, white cells, and platelets

A simplified concept of the blood coagulation mechanism

Disturbances of Blood Coagulation (1 of 7)
- Classification: Four categories
  - Abnormalities of small blood vessels
  - Abnormality of platelet formation
  - Deficiency of one or more plasma coagulation factors
  - Liberation of thromboplastic material into circulation

Disturbances of Blood Coagulation (2 of 7)
- Abnormality of small blood vessels
  - Abnormal bleeding resulting from failure of small blood vessels to contract after tissue injury
  - Abnormality of platelet formation
  - Thrombocytopenia
- Injury or disease of bone marrow damaging the megakaryocytes (precursors of platelets)
- Infiltration of bone marrow by leukemic cells or cancer cells that have spread to the skeletal system, crowding out the megakaryocytes

Disturbances of Blood Coagulation (3 of 7)
- Antiplatelet antibodies destroy platelets in peripheral blood
- Abnormal function of platelets despite normal count
- Petechiae
  - Small red or red-blue spots about 1-5 mm
  - Pinpoint-sized hemorrhages of small capillaries in skin or mucous membranes
  - Indicative of defective or inadequate platelets
  - Do not blanch when pressed
  - Petechiae + fever: in infections such as meningococcemia; dengue hemorrhagic disease
Disturbances of Blood Coagulation (4 of 7)

- Phase 1 usually hereditary; relatively rare except
  - Hemophilia A
  - Hemophilia B
  - von Willebrand’s disease
- Hemophilia: x-linked hereditary disease affecting males
  - Most common and best known
  - Episodes of hemorrhage in joints and internal organs after minor injury
- Hemophilia A: classic hemophilia = Factor VIII (antihemophilic factor)
- Hemophilia B: Christmas disease (after affected patient) = Factor IX (Christmas factor)

Disturbances of Blood Coagulation (5 of 7)

- von Willebrand disease: von Willebrand factor
  - Large protein molecule produced by endothelial cells required for platelets to adhere to vessel wall at site of injury
  - vWF adheres to the damaged vessel wall, forms a framework that allows platelets and coagulation factors to adhere, interact, form clot
  - Forms a complex with factor VIII and maintains normal level of factor VIII

Disturbances of Blood Coagulation (6 of 7)

- Phase 2: deficiency of prothrombin or factors required for the conversion of prothrombin into thrombin
- Causes of coagulation disturbance
  - Factors produced in liver
  - Vitamin K required for synthesis of most factors
  - Vitamin K synthesized by intestinal bacteria
  - Bile required for its absorption

Disturbances of Blood Coagulation (7 of 7)

- Administration of anticoagulant drugs
  - Inhibits synthesis of biochemically active vitamin K-dependent factors
- Inadequate synthesis of vitamin K
  - Occurs if the intestinal bacteria have been eradicated with prolonged use of antibiotics
- Inadequate absorption of vitamin K
  - Occurs in blockage of common bile duct by a gallstone or tumor, preventing bile from entering the intestine to promote absorption of vitamin
- Severe liver disease
  - Impairs synthesis of adequate amounts of coagulation factors
Causes of Thrombocytopenia

• Injury or disease of bone marrow
• Leukemic or cancer cells infiltrate bone marrow
• Antiplatelet antibody destroys platelets in peripheral blood

Liberation of Thromboplastic Material into Circulation

• Products of the following events have thromboplastic activity, liberated into circulation, result in intravascular coagulation
  – Diseases associated with shock and tissue necrosis
  – Overwhelming bacterial infections
  – Other causes of tissue necrosis

Disseminated Intravascular Coagulation Syndrome (1 of 2)

• Abnormal bleeding state
• Activation of the coagulation mechanism due to
  – Diseases associated with shock
  – Overwhelming bacterial infection
  – Extensive necrosis of tissue
• Products of tissue necrosis and other substances with thromboplastic activity are liberated into the circulation

Disseminated Intravascular Coagulation Syndrome (2 of 2)

• Clotting: platelets and plasma coagulation factors are utilized, causing the levels to drop rapidly in the blood
• Activation of fibrinolysin to defend body from widespread intravascular clotting
  – Clots are dissolved to prevent lethal obstruction of the circulatory system
• Net effect: hemorrhage

Pathogenesis of disseminated intravascular coagulation syndrome

Fibrous thrombus in small blood vessel of patient with disseminated intravascular coagulation syndrome
Laboratory Tests to Evaluate Hemostasis (1 of 2)

- To evaluate overall efficiency of coagulation process
  - Platelet count: examination of blood smear for platelet numbers
  - Bleeding time: time it takes for a small skin lesion to stop bleeding; used to evaluate the function of capillaries in the hemostatic process
  - Clotting time: time it takes for blood to clot in a test tube

Laboratory Tests to Evaluate Hemostasis (2 of 2)

- To evaluate overall efficiency of coagulation process
  - Partial thromboplastin time (PTT): time it takes for blood plasma to clot after a lipid substance is added to the plasma sample; measures time of first phase coagulation
  - Prothrombin time (PT): measures time of combined second and third phases of coagulation

Tests Measuring Phases of the Clotting Mechanism (1 of 3)

- Partial thromboplastin time: measures time it takes for blood plasma to clot after adding lipid and calcium

Tests Measuring Phases of the Clotting Mechanism (2 of 3)

- Prothrombin time: measures time it takes for blood to clot after adding thromboplastin; prolonged time indicates abnormality in second or third phases of coagulation; used to measure effects of coumadin

Tests Measuring Phases of the Clotting Mechanism (3 of 3)

- Thrombin time: bypasses the first two phases of blood coagulation, primarily measures the level of fibrinogen

Discussion (1 of 2)

- 55-year-old female admitted for a severe bacterial pneumonia (Staphylococcus aureus) with pus in the left pleural cavity. Patient was given antibiotics.
  - On physical exam:
    - Patient has severe nausea and vomiting
    - Unable to eat or drink
    - Bleeding noted per rectum and from the urinary tract after a few weeks of treatment
  - Lab results: Prolonged partial thromboplastin time (PTT) and prothrombin time (PT)
- What phase of coagulation is most likely affected? Explain
Discussion (2 of 2)

• A 10-month-old infant sustained a cut under the lower lip after a fall. The child is bleeding profusely followed by a tarry stool. The child has a history of easy bruising since birth but without previous episodes of bleeding. On physical exam, he has ecchymoses on his chest and left side with a small bruise on abdomen.
  • Lab results:
    – Normal prothrombin time (PT)
    – Prolonged partial thromboplastin time (PTT)
    – Low factor VIII and von Willebrand factor (vWF)
• What phase of coagulation is most likely affected? Explain

Intravascular Blood Clots

• Normally, blood does not clot within the vascular system
• Pathogenesis of intravascular clotting
    – 1. Slowing or stasis of blood flow
    – 2. Blood vessel wall damage
    – 3. Increased coagulability of blood
• Thrombus: an intravascular clot; can occur in any vessel or within the heart
  • Embolus: a detached clot carried into pulmonary or systemic circulation; plugs vessel of smaller caliber than diameter of clot, blocking blood flow and causing necrosis
  • Infarct: tissue necrosis from interruption in blood flow

Embolism (1 of 5)

• From blood clots, fat, air, amnionic fluid, and foreign particles
• Fat embolism
  – Following severe bone fracture that disrupts fatty bone marrow and surrounding adipose tissue
  – Emulsified fat globules sucked into veins and carried into lungs, obstructing pulmonary capillaries
  – If it reaches systemic circulation, eventually blocks small vessels in brain and other organs

Embolism (2 of 5)

• Air embolism
  – Large amount of air sucked into circulation from lung injury due to a chest wound
  – May be accidentally injected into circulation
  – Air carried into right heart chambers and prevents filling of heart by returning venous blood
  – Heart unable to pump blood and individual dies rapidly of circulatory failure

Embolism (3 of 5)

• Amnionic fluid embolism
  – Devastating complication of pregnancy
  – Amnionic fluid enters maternal circulation through a tear in fetal membranes
  – Fetal cells, hair, fat, and amniotic debris fluid block maternal pulmonary capillaries causing severe respiratory distress
  – Thromboplastic material in fluid activates coagulation mechanism leading to disseminated intravascular coagulation syndrome

Embolism (4 of 5)

• Foreign particulate matter embolism
  – Various types of particulate material
  – May be injected by substance users that crush and dissolve tablets intended for oral use
  – Material injected intravenously and is trapped within small pulmonary blood vessels
  – Symptoms of severe respiratory distress
Embolism (5 of 5)

- Septic emboli
  - Thrombi form in pelvic vein following uterine infection
  - Bacteria invade thrombi
  - Emboli from infected thrombus travel to lungs, causing pulmonary infarct
  - Bacteria in clot invade pulmonary infarct causing lung abscess

Venous Thrombosis

- Predisposing factors to clot formation in leg veins
  - Prolonged bed rest
  - Cramped position for an extended period
  - Impaired “milking action” of leg musculature that normally promotes venous return resulting in stasis of blood in veins
  - Varicose veins or any condition preventing normal emptying of veins
- Outcome
  - Leg swelling from partial blockage of venous return in leg
  - Pulmonary embolism

Pulmonary Embolism (1 of 5)

- Clinical manifestations depend on size of embolus and where it lodges in the pulmonary artery
- Large pulmonary emboli may completely block main pulmonary artery or major branches obstructing blood flow to lungs
- Lung not infarcted due to collateral blood flow from bronchial arteries (from descending aorta) that interconnect with pulmonary arteries via collateral channels
- Cyanosis and shortness of breath due to inadequate oxygenation of blood

Pulmonary Embolism (2 of 5)

- Large pulmonary emboli
  - Right side of heart becomes distended
  - Pulmonary artery becomes overdistended with blood, causing increased pulmonary pressure
  - Left ventricle unable to pump adequate blood to brain and vital organs
  - Systemic blood pressure falls and patient may go into shock

Pulmonary Embolism (3 of 5)

- Small pulmonary emboli
  - Small emboli may pass through main pulmonary arteries, becoming impacted in peripheral arteries supplying lower lobes of the lungs
  - Raises pulmonary pressure and inadequate collateral circulation
  - Affected lung segment undergoes necrosis; wedge-shaped pulmonary infarct
  - If infarct develops: dyspnea, pleuritic chest pain, cough, and expectoration of bloody sputum due to leakage of blood from infarcted lung tissue into bronchi

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Pulmonary Embolism

- Diagnosis
  - Chest X-ray: detects infarct but not the embolus
  - Radioisotope lung scans: detects abnormal pulmonary blood flow caused by embolus
  - Pulmonary angiogram (gold standard): detects blocked pulmonary artery
  - Computed tomography (CT) scan: detects pulmonary embolus indicated by obstructed flow of contrast medium, information comparable to pulmonary angiography without requiring insertion of catheter in pulmonary artery

Pulmonary Angiography

- Treatment
  - Anticoagulants: heparin initially followed by coumadin
  - Thrombolytic drugs if with massive embolus
  - Angioplasty (balloon or stent to widen vein)
  - Thrombectomy (clot extraction surgery)
  - General supportive care

Arterial Thrombosis (1 of 2)

- Stasis is not a factor due to rapid blood flow and high intravascular pressure
- Main cause: injury to vessel wall from arteriosclerosis, causing ulceration, roughening of arterial with thrombi formation
- Blocks blood flow
  - Coronary artery: myocardial infarction
  - Major leg artery: gangrene
  - Cerebral artery: stroke

Gangrene
Arterial Thrombosis (2 of 2)

- Intracardiac thrombosis
  - Clot forms
  - Within atrial appendages: heart failure
  - Surfaces of heart valves: valve injury
  - Wall of left ventricle: myocardial infarction
  - May dislodge into systemic circulation and cause infarction: spleen, kidneys, brain

Thrombosis by Increased Coagulability (1 of 2)

- Rise in coagulation factors following surgery or injury
- Estrogen in contraceptive pills stimulates synthesis of clotting factors
- Hereditary gene mutations
  - Mutation of gene that codes for factor V results in abnormal factor V Leiden: more resistant to inactivation, prolonged activity, increased coagulability
  - Mutation of gene regulating prothrombin synthesis
  - Risk for venous thrombosis increases as prothrombin level rises

Thrombosis by Increased Coagulability (2 of 2)

- Thrombosis in patients with cancer, from increased platelets and coagulation factors
  - Predisposes to both arterial and venous thromboses
  - Hypercoagulability due to rapid release of thromboplastic materials into circulation from tumor deposits
  - Platelets and coagulation factors consumed faster than can be replenished, leading to bleeding
  - Large tumors release thromboplastic material slowly but continuously; production of coagulation factors exceeds destruction leading to hypercoagulability

Edema

- Accumulation of fluid in interstitial tissues, first noted in ankles and legs
- Results from disturbance of extracellular fluid circulation between capillaries and interstitial tissues
- Pitting edema: pit or indentation formed when edematous tissue is compressed with the fingertips
- Hydrothorax: fluid accumulates in pleural cavity
- Ascites: fluid accumulates in peritoneal cavity

Pathogenesis of Edema

- Increased capillary permeability
  - Causes swelling of tissues with acute inflammation
  - Increase in capillary permeability from some systemic diseases
- Low plasma proteins
  - Excess protein loss (kidney disease)
  - Inadequate synthesis (malnutrition)
- Increased hydrostatic pressure
  - Heart failure
  - Localized venous obstruction
- Lymphatic obstruction

Factors Regulating Fluid Flow Between Capillaries and Interstitial Tissue

- Capillary hydrostatic pressure: force pushing fluid from capillaries into extracellular space
- Capillary permeability: determines ease of fluid flow through capillary endothelium
- Osmotic pressure: water-attracting property of a solution; exerted by proteins in the blood (colloid osmotic pressure) that attract fluid from interstitial space back into the capillaries
- Open lymphatic channels: collect fluid forced out of the capillaries by the hydrostatic pressure and return fluid into circulation
Shock (1 of 2)

• Low blood flow/pressure to adequately supply body with blood; potentially life-threatening; circulating blood volume < capacity of vascular system

• Categories according to pathogenesis
  – Hypovolemic shock: low blood volume
  – Cardiogenic shock: reduced cardiac output
  – Septic shock: excessive vasodilatation secondary to release of microbial toxins and inflammatory mediators
  – Anaphylactic shock: excessive vasodilatation from release of inflammatory mediators

Shock (2 of 2)

• Prognosis depends on early recognition and rapid appropriate treatment
  – Drugs that promote vasoconstriction
  – Use of intravenous fluids or blood to restore blood volume secondary to fluid loss or hemorrhage
  – Treat underlying cause