Hematology

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Just a Thought

Link your roots deeply into whatever task you are doing, for commitment and enthusiasm transform monotony into freshness and routine into joy and discovery.
Hematology and Immunology
Overview

Assessment of Hematological System

• CBC
  – RBC
  – WBC
  – HG
  – HCT
  – Platelets
• Reticulocyte Count
• Serum Iron
  – Ferritin
  – Transferrin
  – Total Iron Binding Capacity
• PT
• PTT
• INR
Hematologic System

• Bone Marrow
  – Production of:
    • Erythrocytes
    • Leukocytes
      – Granulocytes
      – Agranulocytes
    • Thrombocytes

Hematologic System

• Spleen (Red Pulp)
  – Stores and releases RBCs
    • 100 cc in response to SNS
  – Filtering and destruction of damaged or old erythrocytes
    • Pitting
    • Catabolizes hemoglobin / iron returned to bone marrow
  – Storage and release of platelets
  – Destruction of damaged platelets
• Spleen (white pulp)
  – Production of lymphocytes
Hematologic System

• Liver
  – Filtering of blood from GI tract
  – Conversion of bilirubin (destruction of RBCs) to bile
  – Detoxification of toxic substances that enter blood
  – Manufacturing of some clotting factors and of thrombin
  – Storage of blood
  – Storage of iron

Hematologic System

• Lymphatic system
  – Lymph
    • Composition
      – Lymphocytes, granulocytes, macrophages, enzymes, antibodies
      – Deficient in platelets and fibrinogen
    • Function
      – Returns excess interstitial fluid (hormones) to blood
      – Returns protein and fat from GI tract
  – Lymph circulation
    • Capillaries – larger than blood capillaries
    • Ducts – drain to subclavian vein
  – Lymph Nodes
    • Function – Filter / allow WBCs to phagocytose bacteria
Hematologic System

• Blood
  – Plasma – 55% of total blood volume
  – Blood Cells
    • Erythrocytes
      – Stoma – location of hemoglobin attachment / contains antigens that determine blood type
      – Reticulocytes – immature red blood cells / elevated in hemorrhage
        » 1 to 4 days to mature
    • Leukocytes

Hematologic System

• Erythrocytes
  – Function
    • Oxygen transport
    • Acid base balance
  – Types
  – Erythropoiesis
    • Secreted by kidney
    • Stimulate bone marrow
  – Destruction
    • Liver and spleen remove damaged RBCs
    • Hemoglobin / iron returned to bone marrow

• Leukocytes
  – Cytokines
    • Protein hormones
    • Synthesized by leukocytes
  – Granulocytes
    • Neutrophils
    • Eosinophils
    • Basophils
  – Agranulocytes
    • Mononuclear phagocytes
    • Lymphocytes
Hematologic System

- **Granulocytes** (polymorphic nuclei) Active phagocytes
  - Neutrophils (40-80% of WBC mass) leave blood vessels and migrate through tissues and search for microorganisms or old body cells (engulf, kill, and digest them: phagocytosis). Dies after phagocytosis producing pus.
    - Bands are immature neutrophils; increase in bands in acute infection is a shift to the left
    - Segmented neutrophils are mature
  - Eosinophils – most important during parasitic infection and allergic rx (0-5% of WBCs)
  - Basophils (0-2%) allergic rxs, no phagocytosis
- **Agranulocytes**
  - Mononuclear phagocytes (monocytes) differentiate into macrophages as they migrate into tissues; macrophages not measured in WBC count; involved in removal of mutant cancer cells
  - Lymphocytes (10-40% of WBC mass) all involved in immunity

Immune System

- **Innate (natural) Immunity**
  - Macrophages
  - Neutrophiles
  - Eosinophiles
  - Basophiles
  - Mast Cells
  - Natural killer cells
- **Aquired (adapted) Immunity**
  - B Lymphocytes
    - IgG
    - IgA
    - IgM
    - IgE
    - IgD
  - T Lymphocytes
    - T Helper cells (T4 Cells)
    - T Cytotoxic cells
    - T Memory cells
    - T Supressor cells (T8 Cells)
Immune System

- B Cells (Antibodies) (Humeral Immunity)
  - Originate in bone marrow
  - Stored in the lymph
  - Released in the blood
  - Functions
    - Neutralizing bacterial toxins and viruses
    - Promoting phagocytosis
    - Activating component of the inflammatory response

- T Cells (Cell Mediated Immunity)
  - Originate in the thymus

Coagulation
**Thrombus Formation**

A thrombosis of a coronary artery is shown here in cross section. This acute thrombosis diminishes blood flow and leads to ischemia and/or infarction, marked clinically by the sudden onset of chest pain.

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**Another Look at Thrombus**

At high magnification, the dark red thrombus is apparent in the lumen of the coronary. The yellow tan plaques of atheroma narrow this coronary significantly, and the thrombus occludes it completely.
Clot Formation

Clotting Cascade
- Intrinsic
  - Initiated by vascular injury and direct exposure to collagen
  - From initiation to a clot is 2-6 minutes
  - Measured by APTT

Extrinsic pathways
- Initiated by endothelial release of tissue factor
- From initiation to clot is 15 to 20 seconds
- Measured by Protime

A clot can be produced by activation of either the intrinsic or extrinsic pathway.

The Clotting Cascade

- The Common Pathway
  - Prothrombin is converted to thrombin
  - Thrombin permits fibrinogen to be converted to fibrin
  - Result is fibrin stable clot (red clot)
  - This fibrin stable clot is cause of STEMI MI
The Clotting Cascade

The Role of Platelets

Adhesion
Platelets

Recruitment and Activation

Aggregation
Fibrin strand

Subendothelium exposed

ADP

TXA₂
The Role of Platelets

• Platelet aggregation can be large enough to form a platelet plug or a white clot that seals a damaged vessel

• This white clot is primary culprit in unstable angina

The Role of Platelets

• Platelets release components necessary for the clotting process in the Intrinsic Pathway

• Platelets contain a fibrin stabilizing factor which is important in the final stage of the Common Pathway prior to stable clot formation
The Role of Platelets

- Platelets cross link with fibrinogen via the GP IIb/IIIa receptors to form a fibrin mesh which gives a clot more substance

Drugs Used to Alter Clotting

- Fibrinolytics
- Anticoagulants
- Antiplatelets
Fibrinolytics: Physiology

– After a clot is formed blood or tissue plasminogen activators changes plasminogen to plasmin
– Plasmin works to lyse fibrin clots and degrade circulating fibrinogen therefore producing fibrin split products
– Fibrin split products further inhibit fibrin formation
– This occurs spontaneously to produce reperfusion, however generally this falls outside window of opportunity to limit damage
– Fibrinolytics speed up this process by providing tissue plasminogen activator

Fibrinolytics

| **Streptokinase (Kabikinase, Streptase)** – bolus followed by infusion, non weight based |
| **Urokinase (Abbokinase)** – bolus followed by infusion, weight based |
| **Alteplase, tPa (Activase) (Tissue Plasminogen Activator)** – no bolus, non weight based |
| **APSAC (anisoylated plasminogen streptokinase activator complex)** |
| **(Retaplase) Retavase** – double bolus injection; non weight based |
| **Tenecteplase (TKNase)** - single bolus; weight based |
Contraindications for Fibrinolytic Therapy

• Absolute
  – Active internal bleeding
  – Suspected aortic dissection
  – Known intracranial neoplasm
  – History of any hemorrhagic CVA
  – Any cerebral vascular event within the year

• Relative
  – Prolonged or traumatic CPR > 10 minutes
  – Severe hypertension > 180 / 110
  – Chronic severe hypertension
  – History prior CVA or other intracranial pathology
  – Recent trauma or other major surgery
  – Noncompressible vascular punctures
  – Recent internal bleeding
  – Prior exposure for Streptokinase or APSAC
  – Known bleeding disorder or current INR > 2-3
Anticoagulants

- Unfractionated Heparin
- Low Molecular Weight Heparin
- Direct Thrombin Inhibitors
- Factor Xa Inhibitors
- Warfarin (Coumadin)

A Closer Look at Heparin

- Prevents conversion of prothrombin to thrombin by binding to antithrombin III
- Antithrombin III naturally inhibits thrombin; when heparin binds with it the inhibition is increased 1000 times
- Neutralizes the clotting capabilities of thrombin
- Works in the intrinsic and common pathway
- Also Inhibits platelets (thrombin is most potent platelet stimulator)
- Anticoagulation is almost instant
- ½ life relatively short
- Antidote: Protamine 1 mg per 100 units
More About Heparin

• aPTT (activated partial thromboplastin time) is used to monitor effectiveness and safety
• Goal is aPTT 1.5 Xs the control
• Weight based heparin dosing reaches goal 90% of time compared to 77% with standard therapy
• Baseline aPTT, PT/INR, platelets and CBC
• Increased bleeding can occur with renal failure
  — Heparin has dual clearance mechanism but greater effect on platelet function than LMWH

Complications of Heparin

• Bleeding
• Mild thrombocytopenia
  — Mild thrombocytopenia occurs in 10-20% of patients
• Severe thrombocytopenia occurs in 1-2% of patients
  — Platelet aggregation resulting in venous or arterial thrombosis
  — Determining patients at risk is unpredictable
  — Generally occurs 5 to 10 days after initiation of heparin
  — DC heparin if platelets fall below 100,000
  — Severe thrombocytopenia is due to an immune response (HITTS)
    • No additional heparin including line flushes
More on HIT

• Heparin – dependent platelet activating antibodies
  – Recognize a self protein (platelet factor 4: PF4) that is bound to heparin
• This results in platelet activation and increased thrombin generation

A Closer Look at Low Molecular Weight Heparin

• Low Molecular Weight Heparin (Lovenox)
  – Enoxaprin, dalteparin, tinzaparin, and nadroparin
  – Smaller in size
  – Antithrombin by inhibiting factor Xa
  – Causes less inactivation of thrombin and less inhibition of platelets and less bleeding than standard heparin
  – Does not significantly influence bleeding time
  – Anti Xa levels can be drawn 4 hours after SQ dose
  – Renal failure results in increased risk of bleeding because LMWH is renally cleared
    • Special dosing for chronic renal insufficiency with enoxaparin
Benefit of Low Molecular Weight Heparin over Unfractionated Heparin

- More predictable anticoagulant response
- Lower incidence of heparin induced thrombocytopenia
- Lower incidence of osteoporosis
- No need to monitor APTT
- Less platelet activation
- Can be self administered with Sub – Q administration
- ½ life 4-6 hours
- Protamine reverses 60% of drug effect

Administration of Enoxaparin

- Full length of 27 gauge ½ needle (prepackaged) should be injected
- Skin fold held until needle withdrawn
- Use anterolateral or posterolateral walls of abdomen
- Rotate sites frequently
- Do not massage site
- Prevention of DVT
  - 30 mg BID or 40 mg daily
  - 40 mg daily in most situations
- Venous thrombosis / DVT
  - 1mg/kg BID or 1.5 mg/kg daily depending of specific circumstances
- Unstable Angina / NSTEMI (or as adjunct in STEMI)
  - 1 mg/kg BID
  - IV dosing can be used in STEMI
- Embolism with Atrial Fib
  - 1 mg/kg BID
- Dosing adjustments are required in several renal impairment
Direct Thrombin Inhibitor

• Indicated for patients with HITTS
• Approved in Non STEMI guidelines and for PCI
• Ability to inactivate fibrin bound thrombin
• Less binding to plasma proteins, therefore more reliable anticoagulation effect
• Examples
  – Lipirudin and desirudin (hirudin)
  – Argatroban
  – Bivalirudin* (Angiomax)

Synthetic Factor Xa Inhibitor

• Fondaparinux (Arixtra)
  – Used for venous thromboembolism and PE
  – Approved for DVT prophylaxis in certain surgical patients
  – Recently approved and added to NonSTEMI Guidelines
  – Cannot be used as sole anticoagulant during PCI
• Neutralizes Factor Xa and interrupts the clotting cascade
• Does not inhibit thrombin
• No reported HIT
• Sub Q injection
• Once daily dosing (fixed dose can cover a range of body weights – lower dose for low body weight)
• Contraindicated in severe renal dysfunction
• No laboratory monitoring
• No antidote (Recombinant factor VIIa can help reverse anticoagulation effect)
A Closer Look at Coumadin

– Inhibits the synthesis of prothrombin.
– Acts indirectly through the liver by altering the synthesis of vitamin K dependent factors in the extrinsic pathway. The vitamin K dependent factors are left biologically inactive.
– It takes 4-5 days to reach a therapeutic level.
  • Can have initial transient hypercoagulable state
  • Must be overlapped with heparin

More About Coumadin

• PT (prothrombin time monitored to evaluate effectiveness and safety)
• PT – problems with standardization of anticoagulation intensity
• INR (International Normalized Ratio) – relates the patients PT to the intensity of actual coagulation.
• Dosing
  – Start with 5mg per day
  – Loading doses not recommended
  – PT / INR daily until therapeutic level reached
  – Dosage may need adjusted after 4-6 days due to individual sensitivity
  – PT / INR twice weekly for 2 weeks and weekly for two months
  – PT / INR every 4-6 weeks after dose stable
More About Coumadin

• Goal for INR of 2.0 – 3.0 is adequate in most situations
• INR of 2.5 – 3.5 is goal for mechanical prosthetic valves and prevention of recurrent MI
• Chronic condition require lifelong therapy
• Acute conditions (PE, DVT) usually require at least six months of therapy

Nursing Considerations with Coumadin

• Many many drugs interact with coumadin to alter PT
• Consistency in diet is important especially with known high vitamin K foods (green vegetables)
• Patient compliance is critical
• Antidote: Vitamin K
• Fresh frozen plasma if severe hemorrhage
• Recombinant factor VIIa is also an option for life threatening bleeding
Dabigatran

- Oral direct thrombin (factor IIa) inhibitor
  - Is a prodrug (dabigatran etexilate) that is converted in liver to active form
  - Peak plasma levels in 1.5 hours; half-life 14-17 hours
  - Eliminated mostly by kidneys (reduced dose for moderate renal failure, not recommended in severe renal failure)
  - No known reversal agent
- Predictable dose-response relationship so no lab monitoring of coagulation status needed
- Dose:
  - 110 mg PO bid (shown not inferior to warfarin) or 150 mg PO bid (shown superior to warfarin)

Dabigatran

- Study results compared to warfarin:
  - Rate of bleeding less than warfarin with 110 mg dose and about the same with 150 mg dose of dabigatran
    - One area of concern GI Bleed
  - Hemorrhagic stroke significantly lower with dabigatran
- Indicated for reduction of stroke in patients with AF at intermediate or high risk of stroke.
- Specific patient considerations
  - Can’t or won’t comply with warfarin monitoring requirements
  - Have inconsistent response to warfarin
  - Take multiple medications that can interact with warfarin
Rivaroxaban

- Oral direct factor Xa inhibitor
  - Maximum plasma level in 3 hours
  - Half-life 4-9 hours (up to 12 hrs if > 75 years old)
  - Dose 10 mg PO daily
  - Few drug interactions
  - Excreted by kidneys (contraindicated in severe renal failure)
- Predictable dose-response relationship so no lab monitoring needed
- Approved firstly in Europe and Canada for prevention of VTE after hip and knee surgery

Rivaroxaban

- ROCKET AF
  - Double-blind randomized trial
  - 14,264 patients with nonvalvular atrial fibrillation (at increased risk for stroke)
  - Rivaroxaban (at a daily dose of 20 mg) or dose-adjusted warfarin.
  - P<0.001 for noninferiority of rivaroxaban
  - no significant between-group difference in the risk of major bleeding, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group.
Antiplatelet Drugs

• GP IIb/ IIIa Inhibitors

• ADP Antagonists

• Thromboxane A₂ Inhibitor

A Closer Look at Antiplatelet Drugs: GP IIb/IIIa Inhibitors

• GP IIb/IIIa Inhibitors
  – Eptifibitide (Integrelin)
  – Tirofiban (Aggrastat)
  – Abciximab (Repro)
  – Inhibit the glycoprotein protein IIb/IIIa receptors which platelets and fibrinogen bind with to form the fibrin mesh
More about GP IIb / IIIa Inhibitors

- Glycoprotein 2b / 3a receptors are most abundant protein on the platelet surface. It is tightly packed on the platelet surface with about 80,000 receptors per platelet. Primary receptor for platelet aggregation.

- Fibrinogen links to these receptors and simultaneously binds receptors on two separate platelets. Platelet cross-linking occurs leading to platelet aggregation.

A Closer Look at ADP Inhibitors: A Type of Thienopyridine

### Clopidogrel (Plavix)
- Inhibit ADP which is released by platelets.
- ADP enhances adhesiveness and aggregation of platelets by activating GPIIb/IIIa receptors.
- Concern with Proton Pump Inhibitors
- Resistance concern

### Prasugrel (Effient)
- Inhibit ADP which is released by platelets.
  - ADP enhances adhesiveness and aggregation of platelets by activating GPIIb/IIIa receptors.
  - Greater anti-ischemic protection (compared to clopidogrel)
- Increased bleeding risk
- Not able to use with prior stroke or TIA, small body size, or advanced age
- Able to give with PPIs

Triton TIMI 38
Ticagrelor (Brillinta)

- Better anti-ischemic effect compared to clopidogrel
- No significant increase in major bleeding
- PLATO trial
- Faster onset and shorter duration than clopidogrel (known as reversible mode of action)
- BID dosing is a potential concern for compliance
- Although shorter ½ life – recommendation to be held 5 days before surgery.
- Cannot be given with more than 100 mg ASA daily.

A Closer Look at Aspirin

- ASA
  - Inhibits Thromboxane A2 which is released with vascular injury. Platelet reactivity is diminished.
  - Also inhibits the endothelium’s production of prostaglandin I₂ which decreases platelet aggregation and induces vasodilation.
  - Caution with asthma
Pathophysiology

Disseminated Intravascular Coagulation (DIC)

- A syndrome characterized by thrombus formation and hemorrhage secondary to over stimulation of the normal coagulation process and resultant consumption of clotting factors and platelets.
DIC

- **Etiology**
  - Always secondary (Massive transfusion, vascular disorders, infection, sepsis, trauma)

- **Pathophysiology**
  - Paradox
  - Bleeding after clotting
  - Results of clotting
    - Clotting causes ischemia, tissue necrosis and micro clots
  - Results of bleeding
    - Bleeding causes loss of hemoglobin and O2 carrying capacity
  - Fibrinolysis
    - Fibrin split products act as anticoagulants (interfere with platelet function and thrombin)

- **Diagnostics**
  - Platelet count < 150,000
  - PT > 40 sec
  - PTT > 70 sec
  - Thrombin time > 15 sec
  - Fibrinogen level (decrease by 50% or < 200)
  - Antithrombin III (decreased)
  - Fibrin split products (usually > 40)
  - D Dimer > 250
    - D Dimer more specific end product of fibrin degradation
  - Protamine sulfate test: Strongly positive
    - Added to plasma to see if fibrin strands form, if + there is an excessive amount of thrombin
DIC

- **Treatment**
  - Only effective treatment: Underlying Cause
  - System management
  - Heparin (PTT) – rarely if thrombosis is going to lead to mortality
  - Clotting Factors (downside)
    - Platelets
    - FFP
  - Hemostatic cofactors
    - Vit K and Folic Acid
  - Amicar **
    - Antifibrinolytic agent
    - Only if primary fibrinolysis is present; otherwise fatal
  - Thrombin gauze, ice packs, pressure dressings
  - Complications

Immune Thrombocytopenic Purpura

- **Pathophysiology:**
  - Platelets are coated with autoantibodies to platelet membrane antigens – this results in splenic sequestration – platelets are removed by phagocytosis by macrophages.
  - Life span of platelets are shortened

  - Typical autoantibody is immunoglobulin G (IgG)
  - Binds with platelet GP
Immune Thrombocytopenic Purpura

- Spleen is major organ of involvement
  - Platelet autoantibodies are formed in the white pulp
  - Mononuclear macrophages in the red pulp destroy the affected platelets

Thrombocytopenic Purpura

- Other Causes
  - Systemic lupus erythematosus
  - Acute or chronic leukemia.
  - Myelodysplastic syndrome, particularly in patients older than 60 years.
  - Post viral illness
  - HIV
  - Drug reaction
- Major Nursing Goal
  - Maintain safe environment
Thrombocytopenic Purpura

- Platelets less than 100,000 / mm$^3$
  - Petecchiae
  - Ecchymosis
  - Epitaxis
  - Bleeding gums
  - Menorrhagia
  - GI Bleeding

- Platelets less than 20,000 / mm$^3$
  - Severe GI hemorrhage
  - Severe GU hemorrhage
  - Cerebral hemorrhage

Final Thought

*Learning is a journey ……*

Each new discovery leads to a better understanding of previously learned information and opens the opportunity for unlimited future discoveries.