Pathophysiology of Lung Inflammation

In The Know

Asthma Airway Pathology
- Cellular infiltrates composed of:
  - Eosinophils
  - Lymphocytes
- Epithelial damage
- Vascular permeability changes
- Airway smooth muscle hypertrophy

Blood Components
- Erythrocytes (RBC)
- Leukocytes (WBC)
  - Neutrophils (40%-75%)
  - Eosinophils (1%-6%)
  - Basophils (less than 1%)
  - Monocytes (2%-10%)
  - Lymphocytes (20%-45%)

Neutrophils
- Contain granules in the cytoplasm
- Released from marrow and migrate to extravascular tissue
- Activated by chemoattractants at the site of injury
- Ingest bacteria (phagocytosis) then release enzymes (cytotoxins)

Basophils
- Contain granules in the cytoplasm
- Migrate to extravascular tissue from marrow
- Similar to mast cells
- Phagocytic properties
- Stimulated by antigens bound to IgE

Eosinophils
- Contain granules in cytoplasm
- Migrate to extravascular tissue from marrow
- Do not ingest bacteria but are cytotoxic
Monocytes
- Larger than leukocytes
- Mature into macrophages (antigen presenting cells APC’s) once released from marrow
- Migrate to tissue (liver, lymph nodes, lungs)
- Actively phagocytic, ingest particulate matter
- Ingest, process, and present antigens (B- and T-lymphocytes)

Lymphocytes
- Two types:
  - B-cells
    - Produced in bone marrow
    - Contain immunoglobulins on their surface
    - When stimulated by cytokine IL-4 produce IgE antibodies specific to the antigen
  - T-cells
    - Produced by bone marrow but mature in the thymus
    - Take part in cell mediated response, independent of antibodies after being presented with the antigen

Lymphocytes T-Cells & NK Cells
- Two types of T-Cells:
  - T-helper
    - Secrete specialized factors (cytokines, etc.) that activate other white blood cells
  - T-killer
    - Directly kill tumor cells, viral-infected cells, and sometimes parasites
  - Natural Killer cells
    - Kill like T-Killer but need no antigen presentation
    - Activated by antigen-antibody complex

Dendritic Cells
- Extremely efficient (APC’s)
- Recently discovered
- Originate in bone marrow
- Capture antigen and take it to lymph tissue
- Bind high amounts of HIV
  - Reservoir of virus presented to T-Helper cells

Chemical Mediators
- Histamine (Vasoactive amine)
  - Stored in mast cells, leukocytes (basophils and eosinophils), and platelets
  - Release (degranulation) is stimulated by complement components C3a and C5a, and lysosomal proteins released from neutrophils
- Cysteinyl Leukotrienes
  - Synthesized from arachidonic acid, especially in neutrophils
  - Produced from the lipoxygenase pathway
  - Can cause bronchospasm, have vasoactive properties

Chemical Mediators
- Stimulate receptor cells in the airways
- Bronchoconstriction
- Broncial hyperreeractivity
- Mucous obstruction
- Edema
- Microvascular leakage
Chemical Mediators

- Lysosomal compounds:
  - Released from neutrophils
  - Cationic proteins (increase vascular permeability)
  - Neutral proteases (may activate complement)
- Prostaglandins:
  - Long chain fatty acids derived from arachidonic acid
  - Produced from cyclooxygenase pathway
  - Potentiate increase in vascular permeability caused by other compounds

- 5-hydroxytryptamine (Serotonin)
  - Vasoactive amine like histamine
  - Stored in mast cells in high concentration
  - Potent vasoconstrictor
- Lymphokines
  - Chemical messengers released by lymphocytes
  - Have vasoactive and chemotactic properties

Leukotrienes

- Produced from arachidonic acid using lipoxygenase
  - Limited to cells of lung, blood vessels, epicardium
- Slow-reacting substance (SRS)
  - Noted for prolonged smooth muscle contraction
  - SRS-A found to be LTC4, LTD4, and LTE4
- Potent constrictors of bronchial smooth muscle
  - 1000-10,000x more potent than histamine or prostaglandin
  - Probable role in asthma

Leukotriene Formation

- LTC4, LTD4, LTE4 (SRS-A)
- LTC4 & LTD4 (most potent)
  - Smooth muscle contraction, increase vascular permeability
  - LTE4 (10% as potent as LTD4)
  - All bind to receptor CysLT1
- LTB4
  - Chemotactic for neutrophils and eosinophils

Leukotriene Development Path
Cytokines

- Protein mediators synthesized by parenchymal, inflammatory cells, T-cells
  - Interleukins (IL)
  - Interferons (IFN)
  - Tumor necrosis factor (TNF)
  - IL-4 induces expressions of adhesion molecules (CAM’s) and inflammatory cells (eosinophils)
- Pro-inflammatory properties

Plasma Factors

- The plasma contains four enzymatic cascade components:
  - Complement system
  - Kinins
  - Coagulation factors
  - Fibrinolytic system
- All are inter-related
- Produce inflammatory mediators

Plasma Factors

- Complement system
- Series of serum proteins that circulate in the blood
- Cascade of enzymatic proteins activated by:
  - Tissue necrosis
  - Infection (activated by antigen-antibody complexes)
  - Products of kinin, fibrinolytic and coagulation systems

Once activated has four major functions
- Destroying bacterial invaders (creates holes in them)
- Recruiting phagocytic cells
- Opsonization
  - Facilitating ingestion of pathogens by phagocytes
  - Mediating vascular responses
- Products of complement activation:
  - C5a
    - Chemotactic for neutrophils
    - Increase vascular permeability
    - Release histamine from mast cells
  - C567
    - Chemotactic for neutrophils
  - C56789
    - Cytolytic activity
  - C4b, 2a, 3b
    - Opsonization of bacteria (facilitates phagocytosis by macrophages

Products of complement activation
- C3a
  - Similar to C5a but less active
- C567
- C56789
- C4b, 2a, 3b
Complement Pathway

Plasma Factors (Kinins)
- Kinin system (interacts with Fibrinolytic system)
  - Peptides of 9-11 amino acids
  - Bradykinin
    - The most important vascular permeability factor
    - Chemical mediator for pain
    - Activated by coagulation factor XII

Plasma Factors (Fibrinolytic)
- Fibrinolytic system (interacts with Kinin system)
  - Plasmin
    - Responsible for lysis of fibrin
    - May effect local vascular permeability
    - Chemotactic for PMN’s

Plasma Factors (Coagulation)
- Coagulation system
  - Responsible for conversion of soluble fibrinogen into fibrin (component of exudate)

Plasma Factors (Coagulation)
- Coagulation Factor XII (Hageman factor)
  - Activated by proteolytic enzymes of bacterial origin
  - Activates the coagulation, kinin, and fibrinolytic systems

Pathway
Inflammation Pathway