Lecture 1
Pathophysiology of Asthma
Klassen

PULMONARY/RESPIRATORY SYSTEM

**Function:** respiration (inhalation/exhalation of respiratory gases)

- Site of gas exchange (O$_2$ – for energy (ATP) production) & CO$_2$ – waste product

**Structure:** 3 segments

1. **Upper respiratory tract:** nose & nasal passages; paranasal sinuses; pharynx
2. **Respiratory airways:** voice box (larynx); trachea; bronchi/large bronchioles
3. **Lungs:** respiratory (small) bronchioles; alveolar ducts & sacs; alveoli

Gas exchange

**Alveoli:** hollow cavity (200 µm)

- Collagen & elastin (stretches upon inhalation)
- Capillary net/mesh (single layer epithelium → gasses diffuse max 2 cell distance)
- 700 million alveoli → surface area = 70 m$^2$

**Respiratory Surface:** 2 gasses are transferred in opposite directions (diffusion)

- Continuous blood flow (steep concentration gradient & saturated blood already moved on)
- Gas needs to be in FLUID (therefore moist environment in lungs)

Impaired by: pneumonia, pulmonary edema, anemia (lack of Hb to bind O$_2$)

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<th>Airways</th>
<th>Structure</th>
<th>Function</th>
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</table>
| Conducting | Trachea, L & R bronchus, bronchi | • Cartilage  
• Smooth muscle  
• Ciliated pseudostratified columnar epithelium  
• Mucus secreting goblet cells | • Conduct air to respiratory airways  
• Warm & humidify inspired air  
• NO GAS EXCHANGE |
| Bronchioles, terminal bronchioles | • No cartilage  
• Smooth muscle  
• Cuboidal epithelium  
• Mucus secreting goblet cells | |
| Respiratory bronchioles, alveoli | • Simple squamous epithelium | • Gas exchange with blood  
• O$_2$ IN / CO$_2$ OUT |

Ventilation/Perfusion (V/Q) Ratio: measures efficiency & adequacy

- V (ventilation) = air that reaches alveoli
- Q (perfusion) = blood that reaches alveoli

- Oxygen inhaled just enough to SATURATE
- Ideal V/Q = 1
- Reality V/Q = 0.8

**Low V/Q:** impaired gas exchange

- Low paO$_2$
- Bronchitis, asthma, pulmonary edema

= Perfusion, no ventilation

**High V/Q:** wasted ventilation (unoxgenated blood)

- High paO$_2$ (low paCO$_2$)
- COPD, pulmonary embolism

= Ventilation, no perfusion

**Impaired by:** pulmonary hypertension; MI

**Definition of asthma:** heterogeneous disease, usually characterized by chronic airway inflammation

- Variable & recurring symptoms
- **REVERSIBLE** airflow obstruction/bronchospasm

**Asthma risk factors:**

- Genetic burden (inheritance doubles risk)
  - Neither parent = 15-20% risk
  - One parent = 30-40% risk
  - Both parents = 80-90% risk
- History of exposure to cigarette smoke
- History of allergies/dermatitis
- Intense allergy in infancy (mold, dust mites)

**Asthma Triggers:**

- Allergens
- Irritants
- Weather changes
- URTIs
- Cold air
- Strong emotions
- Exercise
Diagnosis of asthma: based on history of characteristic sx patterns & evidence of variable airflow limitation (bronchodilator reversibility testing or other tests)
> Asthma is usually characterized by airway inflammation & hyper responsiveness, but these are not necessary/sufficient to make dx of asthma

Physical examination: often normal
> Most frequent finding: wheezing on auscultation (esp. on forced expiration)
> Wheezing may be absent during severe asthma exacerbations (“silent chest”)

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<tr>
<th>Increased % asthma sx</th>
<th>Decreased % asthma sx</th>
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<tr>
<td>• &gt; 1 type of sx</td>
<td>• Isolated cough w/ no other respiratory sx</td>
</tr>
<tr>
<td>• Sx often worse at night or early morning</td>
<td>• Chronic production of sputum</td>
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<tr>
<td>• Sx vary over time &amp; in intensity</td>
<td>• SOB associated with dizziness, light-headedness or peripheral tingling</td>
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<td>• Sx are triggered</td>
<td>• Chest pain</td>
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REVIEW – TYPE 1 HYPERSENSITIVITY

PRISH:
- Pain: release of nerve stimulating chemicals
- Redness: increased blood flow
- Immobility: multisource including swelling
- Swelling: accumulation of fluid
- Heat: blood flow from body core is warm

Not all sx may be present – depends on location
> Internal (organs) vs. external (skin)
> Pain receptors vary greatly + personal thresholds

Hypersensitivity: results when immune response is harmful to host
> Occurs when antigen recognition is exaggerated or inappropriate
> Requires presensitization (priming of immune system)

Mechanism of ACUTE PHASE:
1. Antigen presentation: MHC II + antigen presents to helper T cell → T cell differentiates becoming TH2 (cytokine mediated)
2. T cells & B cells see same antigen → co-stimulus of B & T cells → secrete cytokines (IL2 & IL4) = cell proliferation, activation & differentiation
   > B cell activation is T-cell dependent pathway
3. B cells become PLASMA CELL: antibody & cytokine production

Inappropriate pathway: B-cell isotype switching
1. IL-4 production SWITCHES antibody type → results in IgE not IgA, IgG, or IgM
2. IgE circulates with antigen specific recognition
3. IgE binds to innate cell Fc receptors on circulating mast cells & basophils → leukocyte sensitization
4. Re-exposure to antigen activates sensitized cells (IgE recognizes antigen) → degranulation → proinflammatory cytokines produced

Chemical mediators of T1 Hypersensitivity

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<tr>
<th>Pre-existing in leukocytes</th>
<th>Newly synthesized in hypersensitivity l rxns</th>
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<tr>
<td>• Histamine</td>
<td>• Leukotrienes</td>
</tr>
<tr>
<td>• Serine proteases</td>
<td>• Prostaglandins</td>
</tr>
<tr>
<td>• Chemokines (eosino- &amp; neutro- phils) used to recruit leukocytes</td>
<td>• Platelet-activating factor</td>
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<td>• Interleukins</td>
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<tr>
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<td>• Tumor necrosis factor</td>
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Mechanism of LATE PHASE:
1. Mast cells & basophils produce cytokines
2. Cytokines recruit eosinophils
3. Re-exposure and recognition – IgE binds allergen (antigen)
   > Eosinophils Fc receptors are bound to IgE antibodies
4. Eosinophil degranulates – proteolytic enzymes & proinflammatory cytokines are released

ASTHMA PATHOPHYSIOLOGY:
> Inflammation
> Bronchial hyperresponsiveness
> Mucus hypersecretion
> Airway remodeling

ASTHMATIC RESPONSE:

Early phase: BRONCHOCONSTRICTION – smooth muscle contraction in airway
> Inflammatory mediators (histamine, leukotrienes, prostaglandins)
> Peaks in 30-60 minutes

Late phase: INFLAMMATION – bronchial edema, epithelial cell lining damage, mucus hypersecretion, bronchospasm
> Eosino- & neutro- phils infiltrate airway tissues
> Peaks in 5-6 hours
GOALS OF ASTHMA MANAGEMENT
- Symptom control & maintain normal activity levels
- Risk reduction of exacerbations, fixed airflow limitation & medication side-effects

> Achieving these goals requires partnership between pt & HCPs

ROLE OF LUNG FUNCTION IN ASTHMA:
- Diagnosis: demonstrate variable expiratory airflow limitation
  > Reconsider Dx if sx & lung fxn are discordant
  - Frequent sx but normal FEV₁: cardiac disease, lack of fitness?
  - Few sx but low FEV₁: poor perception, restriction of lifestyle?
- Risk assessment: low FEV₁ is an independent predictor of exacerbation risk
- Monitoring progress: measure lung function at Dx, 3-6 months after starting txt (to identify personal best), then periodically
  > Consider long-term PEF monitoring for pts with severe asthma or impaired perception of airflow limitation
- Adjusting treatment??
  > Limited by between-visit variability of FEV₁ (15% yr-yr)

ASSESSING ASTHMA SEVERITY: assessed retrospectively from level of txt required to control sx & exacerbations
> Assess asthma severity after pt has been on controller txt for several months
> Severity is not static – may change over months or years, or as different txts become available

Categories of asthma severity:
- Mild asthma: well-controlled with Steps 1 or 2 (as-needed SABA or low dose ICS)
- Moderate asthma: well-controlled with Step 3 (low dose ICS/LABA)
- Severe asthma: requires Step 4/5 (moderate or high dose ICS/LABA ± add-on) or remains uncontrolled despite txt

ASSESSMENT OF ASTHMA
1. Asthma control
   a. Assess sx control over last 4 weeks
   b. Assess risk factors for poor outcomes (incl. low lung fxn)
2. Treatment issues
   a. Check inhaler technique & adherence
   b. Side effects
   c. Does pt have written asthma action plan?
   d. Pt’s attitudes & goals for their asthma?
3. Comorbidities – may contribute to sx & poor QOL
   > Rhinosinusitis, GERD, obesity, obstructive sleep apnea, depression, anxiety

DISTINGUISH BETWEEN UNCONTROLLED & SEVERE ASTHMA:
1. Watch pt using their inhaler. Discuss adherence & barriers to use.
2. Confirm the diagnosis of asthma.
5. Refer to a specialist or severe asthma clinic.