Learning Objectives:
1. Recognize the immunohistopathological features of asthma, including the characteristics and types of inflammatory cells that are responsible for the pathophysiology of adult asthma.
2. Describe the clinical features and differences of early versus late response to allergen or irritant in adult asthma.
3. List important factors necessary to successfully assess asthma severity and control.
4. Identify the indications for, and types of, controlling agents required to effectively manage asthma.
5. Identify disorders that mimic adult asthma.

I. Definition: Asthma is defined as a clinical condition characterized by reversible airflow obstruction, bronchial hyper-responsiveness, and airway inflammation.
   A. The immunohistopathologic features of asthma include inflammatory cell infiltration:
      i. Eosinophils (the predominant cell type in most asthmatics)
      ii. Lymphocytes (produce immunoglobulin E (IgE) and contribute to the persistent inflammatory response)
      iii. Neutrophils (less common; seen especially in sudden-onset, fatal asthma exacerbations; occupational asthma, and patients who smoke)
      iv. Mast cell activation (release of bronchoconstricting agents and inflammatory mediators)
      v. Epithelial cell injury
   B. Airway inflammation contributes to airway hyperresponsiveness, airflow limitation, respiratory symptoms, and disease chronicity.
   C. In some patients, persistent changes in airway structure occur, including sub-basement fibrosis, mucus hypersecretion, injury to epithelial cells, smooth muscle hypertrophy, and angiogenesis (this process is called airway remodeling).
   D. Gene-by-environment interactions are important to the expression of asthma.
   E. Atopy, the genetic predisposition for the development of an IgE-mediated response to common aeroallergens, is the strongest identifiable predisposing factor for developing asthma.

Note: Viral respiratory infections are one of the most important causes of asthma exacerbation and may also contribute to the development of asthma.

II. Clinical diagnosis
   A. Recurrent wheezing, dyspnea, chest tightness and/or cough
   B. Variable airflow obstruction (determined by spirometry):
      i. Reduced FEV₁/FVC <75% (FYI, not to memorize: this ratio is age dependent: Normal is ≥ 85% age 1-20; ≥ 80% age 20-40; > 75% over age 40)
      ii. Positive bronchodilator response (improvement of FEV₁ ≥ 12% AND increase of FEV₁ ≥ 200 cc)
iii. **Normal diffusion capacity** of carbon monoxide (DLCO): obtained to differentiate from COPD

C. Bronchial hyperactivity
   i. Worsening bronchospasm on exposure to various stimuli (allergens, house, dust mite, upper respiratory infection (URI)). After an asthma attack, the airways become hypersensitive to irritants and allergens
   ii. Methacholine sensitivity (FYI, not to memorize: useful in diagnosis of cough variant asthma: asthmatics have a 20% drop in FE\textsubscript{V1} when inhaling methacholine; normals have little or no response)

III. Early and Late Response of the airways to allergen or irritant
A. Early response (bronchoconstriction): After exposure to allergen or irritants, the airways have a significant drop in airflow due to bronchoconstriction. This "early response" occurs within 30 minutes and normalizes by 2-3 hours. This is due to the release of bronchoconstricting mediators from mast cells and basophils that directly contract smooth muscle. This phase is easy to treat because the bronchoconstriction can be reversed with medications.

B. Late response (inflammation): Four to six hours later, after exposure, there is a second drop in airflow due to edema and inflammation. The inflammatory response is called the "late response" and can last for over 12 hours. This results from an influx of inflammatory cells leading to edema, mucous formation, and airway narrowing that is more difficult to treat. **Chronic inflammation** results in a variety of changes in the airway:
   i. **Bronchoconstriction**: In asthma, the dominant physiological event leading to clinical symptoms is airway narrowing and a subsequent interference with airflow.
   ii. **Airway edema/mucous production**: As the disease becomes more persistent and inflammation more progressive, other factors further limit airflow. These include edema, inflammation, mucous hypersecretion and the formation of inspissated mucous plugs, as well as structural changes including hypertrophy and hyperplasia of the airway smooth muscle.
   iii. **Airway remodeling**: in many people with asthma, airflow limitation may be only partially reversible. **Permanent structural changes can occur in the airway**: these are associated with a progressive loss of lung function that is not prevented by or fully reversible by current therapy. Airway remodeling can include thickening of the sub-basement membrane, subepithelial fibrosis, airway smooth muscle hypertrophy and hyperplasia, blood vessel proliferation and dilation, and mucous gland hyperplasia and hypersecretion. This appears to develop early in the course of asthma.

IV. Natural history of asthma: Main points: (1) asthma is hard to diagnose before age 6 years old because children have small airways and frequently wheeze without truly having asthma and (2) children with true childhood asthma generally do not “outgrow” asthma; rather, it becomes subclinical and can recur later in life.
A. FYI (not to memorize the numbers): Epidemiology: 6-8% of the population has asthma and >10% have asthma at some point in their lifetime. One parent with asthma increases the risk to 25% that their children will have asthma and both parents increase the risk to 50%; however, identical twins also only have a 50% chance that
both will have asthma. This suggests that both a genetic and an environmental component exist.

B. Longitudinal studies explain why it is difficult to diagnose asthma prior to age six.
   i. Transient early wheezers: often due to maternal smoking and/or Respiratory Syncytial Virus (RSV).
   ii. Nonatopic wheezers: Usually begins in 1st year of life, only a small percentage have asthma at age 35
   iii. Atopic wheezers
       • Usually begins 2nd - 3rd year
       • Severity (between colds) often predicts persistence in adulthood

C. Most children with true childhood asthma probably do not “outgrow it”; rather, it becomes subclinical and may recur later in life.

V. Assessing asthma severity and control: The assessment and treatment of asthma are closely linked to the concepts of the severity and control:

A. Severity: the intrinsic intensity of the disease process. Severity is measured most easily and directly in a patient not receiving long-term-control therapy. “Strike 3” = persistent asthma: **Persistent asthma is defined by children or adults using quick-reliever medications 3 or more times/week; waking up 3 or more times/month, or having obstruction on spirometry (even if asymptomatic).**

B. Control: the degree to which the manifestations of asthma (symptoms, functional impairments, and risks of exacerbation) are minimized. When asthma is not in control additional medications are added. When asthma is stable for 3-6 months, medications are reduced. Unfortunately many clinicians try to assess control by asking patients with asthma a general question such as “how is your asthma doing?” or “how is your breathing?” **Control must be assessed by a standardized questionnaire** (like the “asthma control test [ACT]”). Note the scoring and types of questions on the ACT (see last page of handout): **The lower the score, the worse the control!**

C. The goal of asthma therapy is prevent nocturnal awakenings and reduce symptoms (and use of rescue medications (i.e. short acting bronchodilators)) to ≤ 2 days a week.

VI. Subtypes of adult asthma

A. Eosinophilic asthma (classic or extrinsic asthma)
   i. FYI: Early onset (<12 years old; around 75% of asthmatics): more likely to be atopic, have a family history of asthma and a history of atopic dermatitis
   ii. FYI: Late onset (onset at 12 years old or older): less atopic but paradoxically more sputum eosinophilia and more rapid decline in lung function over time

B. Neutrophilic asthma (more common in severe, refractory asthma; obese asthmatics, asthmatics who smoke, or occupational asthma. Also seen in fatal asthma and “hyperacute asthma” where severe symptoms develop within 2 hours of an attack).

C. Non-inflammatory asthma (rare – hypertrophy of mucous gland hyperplasia and smooth muscle hypertrophy with little or no inflammation)

D. Occupational asthma (OA): causes 5-10% of all adult asthma. Worse on weekdays and improves on weekends or vacation.
   FYI (not to memorize): High molecular weight occupational asthma: usually organic material (animal proteins, flour, natural rubber latex) which causes an immunologic response. Low molecular weight chemicals: usually production of plastics and rubber (chemical combines with a protein in the body to create an antigen). Chemicals or fumes may also act as irritants and worsen asthma (non-immunologic)
E. Steroid resistant asthma: usually associated with high level of inflammation or cigarette smoke that reduces sensitivity to steroids. Rarely an aberrant glucocorticoid receptor is the cause of resistance.

VII. Diagnosis of asthma
A. Differential Diagnosis: make sure the patient does not have another diagnosis. There are many “asthma mimics” that present with dyspnea and wheezing. These include:
   i. COPD: tends to occur at an older age with a history of cigarette abuse or exposure to dust and fumes. Symptoms are often more persistent and less reversible. Tests to help differentiate COPD and asthma include chest CT scan and PFT test (diffusion capacity, DLCO, is low in COPD and normal in asthma).
   ii. Congestive heart failure (CHF): edema of the airways in CHF may lead to “cardiac asthma”. Chest x-ray (pulmonary edema) and physical exam (crackles) suggest CHF diagnosis. Echocardiogram, Chest X-ray, and serum laboratory test (FYI: brain natriuretic protein, BNP, released from ventricles) may be helpful.
   iii. Vocal cord dysfunction (VCD): subconscious movement of vocal cords towards the midline during inspiration. VCD may require an ear nose and throat (ENT) exam to diagnose.

B. Historical information:
   i. Episodic symptoms characteristically come and go over hours to days and resolve with removal of the triggering stimulus or treatment with asthma medications.
   ii. Common asthma triggers
      a. Allergens: house dust mite, cat dander, and cockroach antigen most common
      b. Exercise – usually within 10-15 minutes after brief exertion or 15 minutes into prolonged exertion and resolves over 30-60 minutes of rest (note exertional dyspnea from poor conditioning or cardiac causes usually resolve within 5 minutes of rest).
      c. Viral illness (common colds) often triggers asthma exacerbations

C. Physical findings: widespread, high pitched, polyphonic wheeze most commonly heard during expiration. During asthmatic flares, the inspiratory:expiratory ratio (I:E) is longer than 1:2 (the worse the obstruction the longer it takes to exhale (i.e., I:E of 1:4, 1:8, etc.). FYI: Unlike stridor (single high-pitched wheeze heard over neck) or bronchogenic cancer/foreign body (single pitched wheeze heard over one part of the chest), the wheeze of asthma is polyphonic (multiple different pitches).

D. Pulmonary function testing
   i. Peak expiratory flow rate (PEFR): more effort dependent than spirometry and mostly evaluates large airways. Also PEFR has more variability and less sensitive than spirometry. Change in PEFR of more than 20% within a day suggests asthma.
   ii. Spirometry
      a. Hallmark is obstruction (reduced FEV₁/FVC; often with reduced FEV₁)
      b. Reversible airflow obstruction: 12% increase and 200 ml increase in FEV₁ 15 minutes after 2-4 puffs of albuterol.

VII. Therapy of chronic asthma
A. Inhaled corticosteroids (ICS) are the preferred primary therapy for all patients with persistent asthma (Strike 3). Medications may control symptoms and prevent exacerbation but no therapy to date has been shown to modify or cure the disease
B. Second-line therapy includes: Long-acting beta agonist ("LABA"s should never be used for asthma without an inhaled corticosteroid) or leukotriene receptor antagonists (LTRA).

C. Third line agents include theophylline and cromolyn.

D. Refractory asthma may require chronic oral corticosteroids and subcutaneous anti-IgE (FYI: omilizumab)

E. **Avoidance of allergens**, desensitization with allergy injections may improve allergic rhinitis and asthma, and treatment of co-morbid conditions (allergic rhinitis, aspirin sensitivity, obstructive sleep apnea, and gastro esophageal reflux disease (GERD) may improve control of asthma.

F. Step-down therapy: when patient’s asthma is stable for 3-6 months then their controller therapy should be “stepped-down” (e.g. LABA/ICS changed to ICS alone or high dose ICS to medium or low dose therapy).

**VIII. Conclusions:**

A. Asthma is a chronic inflammatory disease and requires ongoing assessment and chronic controller medications in many patients.

B. Controller medications (ICS, LABA, and LTRA) are underutilized in the United States and are required in all patients with persistent asthma.

C. Standardized assessment of symptoms and medication use are essential in understanding how well asthma is controlled in your patient (lower ACT scores = worse control)

D. Environmental assessment and avoidance of allergens/irritants as well as assessment/treatment of contributing factors are important elements in the care of asthmatic patients.

**Key resource:**

http://www.nhlbi.nih.gov/about/naepp/
Asthma Control test

1. In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school or at home?
   - All of the time
   - Most of the time
   - Some of the time
   - A little of the time
   - None of the time

2. During the past 4 weeks, how often have you had shortness of breath?
   - More than once a day
   - Once a day
   - 3 to 6 times a week
   - Once or twice a week
   - Not at all

3. During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?
   - 4 or more nights a week
   - 2 or 3 nights a week
   - Once a week
   - Once or twice
   - Not at all

4. During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?
   - 3 or more times per day
   - 1 or 2 times per day
   - 2 or 3 times per week
   - Once a week or less
   - Not at all

5. How would you rate your asthma control during the past 4 weeks?
   - Not controlled at all
   - Poorly controlled
   - Somewhat controlled
   - Well controlled
   - Completely controlled

Well controlled ≥ 20 points
Not well, controlled 16-19 points
Very poorly controlled ≤ 15 points