Asthma

Asthma is a chronic inflammatory condition characterized by reversible obstruction to airflow in the lower airways. It is common and occurs at all ages. Patients typically present with intermittent or persistent wheezing, cough, and dyspnea. Diagnosis is usually confirmed with pulmonary function testing that shows a reversible obstructive pattern. Treatment varies based on the severity and includes bronchodilators and inhaled corticosteroids for control of inflammation.

Definition, Epidemiology, Etiology, and Pathophysiology

Definition

Asthma is a chronic syndrome of increased inflammation of the lower airways and hyperresponsiveness to a wide range of triggers. It is characterized by varying degrees of obstruction to airflow and symptoms of wheezing and dyspnea which may reverse spontaneously or with treatment.
Epidemiology

- Prevalence: 5–10% of the population in the US
- Peak age at presentation: 3 years
- Male-to-female ratio is 2:1 in childhood and 1:1 in adulthood
- Some cases of childhood asthma may resolve in adolescence or adulthood
- Progression to more severe disease and death is uncommon.

Etiology

- Asthma is caused by a combination of genetic and environmental factors.
  - Asthma risk factors: certain factors that predispose to the development of asthma (table 1)
  - Asthma triggers: environmental factors that exacerbate the symptoms in a patient with established asthma:
    - Allergens
    - Exercise
    - Hyperventilation
    - Cold air
    - Drugs (beta-blockers and aspirin)
    - Stress
    - Upper respiratory tract infections
    - Paints and fumes
    - Irritant gasses
    - Premenstrual hormones
    - Thyrotoxicosis
    - Hypothyroidism
    - Air pollution
- Nonatopic (intrinsic) asthma:
  - Comprises about 10% of asthma cases
  - Allergen skin testing is negative and serum IgE is normal
  - Commonly presents in adults
  - Symptoms are more severe and persistent
  - Patients are sensitive to aspirin

<table>
<thead>
<tr>
<th>Endogenous Risk Factors</th>
<th>Environmental Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Atopic rhinitis (major risk factor)</td>
<td>• Indoor allergens such as house dust mites, animal fur</td>
</tr>
<tr>
<td>• Atopic dermatitis (major risk factor)</td>
<td>• Outdoor allergens such as pollens</td>
</tr>
<tr>
<td>• Airway hyperresponsiveness</td>
<td>• Occupational exposures (cleaning liquid aerosols, chemicals, animal antigens)</td>
</tr>
<tr>
<td>• Genetic predisposition</td>
<td>• Environmental tobacco smoke</td>
</tr>
<tr>
<td>• Early childhood infections</td>
<td>• Respiratory infections</td>
</tr>
<tr>
<td>• Obesity (especially in women)</td>
<td>• Air pollution (sulfur dioxide, ozone, diesel particles)</td>
</tr>
<tr>
<td>• Lower maternal age</td>
<td>• Diet</td>
</tr>
<tr>
<td>• Short duration of breastfeeding</td>
<td>• Mold</td>
</tr>
<tr>
<td>• Prematurity and low birth weight</td>
<td>• Acetaminophen</td>
</tr>
</tbody>
</table>

Table 1: Asthma risk factors

Pathophysiology

Asthma is associated with specific inflammation of the lower airways that ultimately leads to the pathologic obstruction of airflow and structural changes (image 1 and 2).
### Endogenous and exogenous risk factors

#### Chronic eosinophilic inflammation of lower airways with involvement of:

<table>
<thead>
<tr>
<th>Inflammatory cells</th>
<th>Structural cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eosinophils</td>
<td>Epithelial cells</td>
</tr>
<tr>
<td>T-helper 2 cells</td>
<td>Smooth muscle cells</td>
</tr>
<tr>
<td>Mast cells</td>
<td>Endothelial cells</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>Fibroblasts</td>
</tr>
<tr>
<td>Basophils</td>
<td>Nerves</td>
</tr>
<tr>
<td>Platelets</td>
<td></td>
</tr>
</tbody>
</table>

#### Mediators (e.g., histamine, chemokines, growth factors, etc.)

#### Effects:
- Bronchospasm
- Plasma exudation
- Mucus hypersecretion and plug formation
- Airway hyperresponsiveness
- Vasodilation and angiogenesis
- Thickening of basement membrane
- Airway wall edema

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Image 1: Fundamentals of the pathophysiology of asthma. By Lecturio
Clinical Features, Diagnosis, and Differential Diagnosis

<table>
<thead>
<tr>
<th>Component</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intermittent</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
</tr>
<tr>
<td>Symptoms</td>
<td>≤ 2 days/week</td>
</tr>
<tr>
<td>SABA use</td>
<td>≤ 2 days/week</td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>≤ 2/month</td>
</tr>
<tr>
<td>Activity limitation</td>
<td>None</td>
</tr>
<tr>
<td>Lung function</td>
<td>FEV1 &gt; 80%</td>
</tr>
</tbody>
</table>

Table 2: Classification of asthma based on severity

Symptoms

- Recurrent wheezing, dyspnea, coughing, difficulty with inspiration, and/or thick sputum difficult to expectorate
- Cough-variant asthma seen especially in children: may only have a recurrent nonproductive cough
- Worse at night and during early morning hours
- May be intermittent and resolve spontaneously or with treatment
Signs

- Asymptomatic when under control
- Expiratory ± inspiratory generalized wheezing and rhonchi
- Hyperinflation

Diagnosis

- Apparent by symptoms and signs
- Confirmed by tests showing airflow limitation, reversibility, diurnal variation, and/or airway hyperresponsiveness
- Lung function test showing airflow limitation:
  - Reduced FEV1
  - Reduced FEV1/FVC ratio
  - Reduced peak expiratory flow
- Lung function tests showing reversibility: an increase in FEV1 by > 12% or 200 mL
  - 15 minutes after short-acting beta2-agonist therapy, or
  - 2–4 weeks after daily oral corticosteroid therapy
- Lung function tests showing diurnal variation by peak expiratory flow measurements twice daily
- Lung function tests showing flow-volume loops with an obstructive pattern and a reduced maximum expiratory flow (image 3)
- Airway hyperresponsiveness:
  - > 20% reduction in FEV1 with methacholine or histamine challenge or exercise testing
  - Rarely used when lung function tests are nondiagnostic
- Hematologic tests: not usually helpful
- Chest X-ray: may show hyperinflation and help to rule out pneumothorax or pneumonia during exacerbations
- Skin tests: not helpful in the diagnosis of asthma; positive tests may allow the implementation of allergen avoidance measures.
- Exhaled nitric oxide: may be useful in assessing the adequacy of treatment with inhaled corticosteroids (ICS) (appropriate ICS use reduces exhaled nitric oxide levels which reflects the control of eosinophilic airway inflammation)

Differential diagnosis

- Upper airway obstruction by tumor or laryngeal edema:
  - Causes stridor rather than wheezing
  - Flow-volume loop shows a limitation in flow in both inspiratory and expiratory curves
  - Bronchoscopy confirms diagnosis
- Foreign-body aspiration shows localized wheezing
- Left ventricular failure: wheezing is accompanied by crackles
- Vocal cord dysfunction
- Eosinophilic pneumonia and eosinophilic granulomatosis with polyangiitis may present with wheezing.
- Chronic obstructive pulmonary disease shows wheezing without significant reversibility
Video gallery

Asthma: Signs and Symptoms by Carlo Raj, MD
Asthma: Differential Diagnosis by Carlo Raj, MD
Asthma: Diagnosis by Carlo Raj, MD

Treatment

- Goals of asthma therapy:
  - Minimize chronic symptoms
  - Minimize exacerbations
  - No emergency visits
  - No limitations in daily activities or exercise
  - Minimal relief use of beta-agonists
  - Near-normal peak expiratory flow
  - No significant diurnal variation (< 20%)
  - Minimize drug side effects
- Most of the treatment of asthma is based on drug therapy.
- Asthma drugs are mainly of 2 types:
  - Bronchodilators: relax airway smooth muscles and provide symptomatic treatment
  - Controllers: control the inflammatory nature of the disease

Types of medications
Bronchodilators

- **Beta2-adrenergic agonists:**
  - Most effective bronchodilator
  - Primary effect: prevent and reverse airway constriction by relaxing smooth muscles through increasing intracellular cAMP
  - Minor reduction of airway inflammation by inhibiting mast cells and platelet exudation
  - No reduction in airway hyperresponsiveness
  - Short-acting beta2-agonists (SABA)
    - Such as albuterol or terbutaline
    - Increased use shows poor control of asthma
    - Also used to prevent exercise-induced asthma
  - Long-acting beta2-agonists (LABA)
    - Such as salmeterol or formoterol
    - Added to ICS as combination inhalers to control symptoms
  - Side effects include palpitations and tremor
- **Anticholinergics:**
  - Such as ipratropium bromide (short-acting muscarinic antagonists (SAMAs)) or tiotropium bromide (long-acting muscarinic antagonists (LAMAs))
  - Prevent nerve-induced bronchoconstriction and mucus secretion
  - Less effective than beta2-agonists
  - SAMAs are used in acute attacks of asthma, while LAMAs may be added if chronic symptoms are not controlled with ICS-LABA
- **Theophylline:**
  - Has fallen out of favor
  - Relaxes airway smooth muscles through the inhibition of phosphodiesterases
  - May be used as an additional bronchodilator in acute or chronic settings
  - Side effects include nausea, vomiting, headaches, palpitations, arrhythmias, and seizures.
  - Serum concentrations increase with inhibitors of CYP450 such as erythromycin.

Controllers

- **Inhaled corticosteroids:**
  - Most effective controllers
  - Reduce the number and activity of eosinophils, mast cells, and T lymphocytes
  - Reduce inflammatory proteins such as cytokines, chemokines, enzymes
  - Chronic use reduces airway hyperresponsiveness.
  - Rapidly improve symptoms and exacerbations
  - Side effects include: hoarseness, oral candidiasis, negligible systemic side effects
  - Examples: Beclomethasone, budesonide, fluticasone
- **Systemic corticosteroids:**
  - Such as hydrocortisone or methylprednisolone as IV therapy and
Prednisone or prednisolone as oral therapy
- Used in both acute severe asthma and as maintenance therapy
- Side effects include obesity, bruising, diabetes, hypertension, osteoporosis, cataract, proximal myopathy, and depression

- Antileukotrienes:
  - Relatively effective
  - Such as montelukast and zafirlukast
  - Inhibit the inflammation and bronchoconstriction caused by cysteinyl-leukotrienes through blocking cys-LT1-receptors

- Cromones:
  - Less commonly used and not available in the US
  - Effective in preventing asthma induced by triggers such as exercise, allergens, and sulfur dioxide

- Anti-IgE
- Anti-IL-5
- Immunotherapy: not recommended by most guidelines due to the potential for anaphylaxis
- Nonpharmacologic treatment such as yoga or breathing techniques should not replace conventional pharmacological therapy
- Bronchial thermoplasty: ablates bronchial smooth muscles through the application of heat; rarely indicated in highly selective patients who are unresponsive to maximum pharmacologic therapy and do not exhibit an inflammatory component

Treatment of chronic asthma
- Patient education: avoiding triggers, stopping tobacco smoke, appropriate technique, and the difference between rescuer and controller therapy
- Stepwise therapy is recommended based on asthma severity (table 3 and image 4)
- Step-up treatment is used to control symptoms.
- Once controlled for 3 months, step down is recommended to minimize drug dose

Diagnosis and treatment of acute severe asthma
- Diagnosis:
  - Symptoms: Increasing symptoms of dyspnea, difficulty completing sentences, cyanosis
  - Signs: Tachypnea and increased ventilation, tachycardia (bradycardia with impending cardiovascular collapse), hyperinflation, severely reduced peak expiratory flow (rarely measured), absent breath sounds (silent chest),
  - Laboratory:
    - Hypoxemia and reduced pCO2
    - Normal-high pCO2 indicates impending respiratory failure
- Prevention: ICS-LABA combination inhalers are the most effective.
- Treatment:
  - Oxygen therapy
  - Inhaled therapy:
    - High dose of SABA via nebulizer or spacer
    - Nebulized anticholinergics if no response to beta2-
agonists
- IV therapy if poor response to inhaler therapy:
  - IV beta2-agonists
  - Slow infusion of aminophylline with blood level monitoring
  - Magnesium sulfate
- Endotracheal intubation and mechanical ventilation in case of respiratory failure

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Classification</th>
</tr>
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<tbody>
<tr>
<td>SABA use</td>
<td>Intermittent</td>
</tr>
<tr>
<td>Exacerbation requiring oral corticosteroid use</td>
<td>Persistent</td>
</tr>
<tr>
<td>Recommended action for treatment</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>SABA use</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 2 days/week</td>
<td>Intermittent</td>
</tr>
<tr>
<td>&gt; 2 days/week</td>
<td>Persistent</td>
</tr>
<tr>
<td>Daily</td>
<td>Persistent</td>
</tr>
<tr>
<td>Several times/day</td>
<td>Persistent</td>
</tr>
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</table>

Table 3: Recommended treatment based on disease severity

Image 4: Step-up ladder approach in the management of asthma in adults. Note: LABA is added to ICS and is not used as the sole therapy. *Alternatives include sustained-release theophylline, leukotriene modifier, and long-acting oral beta2-agonist. ICS: inhaled corticosteroids; LABA: long-acting beta2-agonist; OCS: oral corticosteroids; SABA: short-acting beta2-agonist; Own work (with modification from Harrison’s Internal Medicine 2018; reference 2 below)

Video gallery

Asthma: Risk Factors & Prevention by Carlo Raj, MD
Asthma: Treatment by Carlo Raj, MD

Subtypes of Asthma

Refractory asthma
- 5% of patients
- Poor control of symptoms despite maximum inhaler therapy
Patients may either have persistent symptoms with poor lung function or near-normal lung function with severe exacerbations
- Must exclude poor compliance with ICS (exhaled nitric oxide may help in the diagnosis)
- Exclude exposure to asthma triggers
- Require maintenance therapy with oral corticosteroids

Brittle asthma
- Associated with normal lung functions with severe and life-threatening exacerbations that do not respond to therapy with corticosteroids or bronchodilators.
- Type 2 patients respond to subcutaneous epinephrine which suggests a localized anaphylactic reaction due to allergy to specific foods or other allergens

Aspirin-sensitive asthma
- In up to 5% of patients
- Associated with severe asthma, nasal polyps, adult-onset
- Responds to usual therapies including ICS

Asthma in pregnancy
- During pregnancy, one-third of patients with asthma improve, one-third get worse, and one-third stay unchanged.
- Poor control of asthma is associated with adverse effects during pregnancy.
- Safe medications during pregnancy include SABA, ICS, and theophylline.
- If oral corticosteroids are needed, prednisone is preferred.
- Asthma medications are not contraindicated during breastfeeding.

Corticosteroid-resistant asthma
- Very rare subtype

References

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