

Bronchial Asthma

Summary

Asthma is a respiratory disease that is characterized by chronic airway inflammation and manifests with variable respiratory symptoms and expiratory airflow limitation. **Allergic asthma** usually develops in childhood and is triggered by **allergens** such as pollen, dust mites, and certain foods. **Nonallergic asthma** typically develops in patients aged > 40 years; triggers include cold air, medications (e.g., aspirin), exercise, and viral infections. Typical clinical features of asthma include **dyspnea**, **end-expiratory wheezing**, and **persistent dry cough that worsens at night** and/or **on exposure to triggers**. Symptoms remit in response to antiasthmatic medications or resolve spontaneously upon removal of the trigger. **Diagnosis** is confirmed in individuals who present with asthma symptoms that vary in severity and demonstrate variable expiratory airflow limitation on **pulmonary function testing (PFT)**, e.g., $\downarrow$ FEV_1 and $\downarrow$ FEV_1/FVC ratio. Additional tests may be utilized to identify asthma triggers and comorbidities that increase the risk of acute exacerbations. **Treatment** regimens differ based on the severity of asthma but primarily consist of an **inhaled corticosteroid (ICS)** combined with a **long-acting beta agonist (LABA)**, e.g., **budesonide/formoterol**. **Systemic glucocorticoids** are usually reserved for the treatment of acute asthma exacerbations but may also be used in patients with severe persistent asthma. Avoidance of asthma triggers and management of comorbidities (e.g., rhinosinusitis) are important to achieve symptomatic control and minimize the risk of exacerbations. Frequent follow-up is essential for monitoring response to therapy and for stepwise adjustment of treatment regimens.

"Acute asthma exacerbations" and "Exercise-induced bronchoconstriction" are discussed separately.

FEEDBACK

Definition:

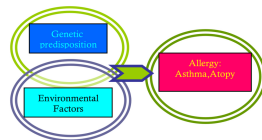
- Asthma is a **reversible obstructive lung disease**, which is the main difference between this disorder and chronic obstructive pulmonary disease (COPD).
- Asthma is a disease characterized by inflammatory hyperreactivity of the respiratory tree to various stimuli, resulting in reversible airway obstruction. **A combination of mucosal inflammation, bronchial musculature constriction, and excessive secretion of viscous mucus-causing mucous plugs will produce bronchial obstruction.**

Epidemiology:

- **Prevalence**
 - 5–10% of the US population
 - More common in Black than in White individuals
 - For unknown reasons, the prevalence of asthma has been increasing over the past 20 years. [1]
- **Sex:** differs depending on age of onset
 - $\sigma > \rho$ in patients < 18 years
 - $\rho > \sigma$ in patients > 18 years
- **Age of onset**
 - Allergic asthma: typically in **childhood**
 - Nonallergic asthma: typically > **40 years**

Etiology:

- A. Inheritance & genetic factors in asthma**
- More than **22 loci on 15 autosomal chromosomes** are linked to asthma, e.g. **IL-4 gene clusters on chromosome 5**
 - 1. **Multi-factorial inheritance:** so:
 - If **One parent** is affected $\rightarrow$ **25%** risk of asthma
 - If **Both parents** are affected $\rightarrow$ risk is **50%**
 - Monozygotic twins are highly concordant regarding liability to **bronchospasm on exercise**. Dizygotic twins are less concordant
 - 2. **Genetic variations in receptors** for asthma medications results in variations in response. (i.e. polymorphism in drugs receptors)
- B. Environmental factors**
1. **Infectious causes:** the **most important are Viruses**: by common respiratory viruses e.g. **RSV** (the most common and important virus), **the more the severe is the injury the more likely the asthma persists.**
 - A. in early life: **RSV + Parainfluenza**
 - B. In older ages: **Rhinoviruses + Influenza**
 - **Mechanism:** **vagal stimulation** or **IgE response**: e.g. **RSV IgE**
 - RSV unmask asthma in predisposed patient (if 1st episode triggered by RSV)
 2. **Allergen exposure:** leads to sensitization to the same allergen and to other irritant exposures.
 - Perennial exposure is a major factor for degree of severity.
 - Allergen elimination $\rightarrow$ control of asthma
 3. **Tobacco smoke**
 4. **Air pollutants (ozone, sulfur dioxide).**
 5. **Dry and cold air**
 6. **Strong odors**
 - some of these triggers only produce bronchospasm without inflammation
- C. Autonomic Factors**
- **Vagal stimulation** $\rightarrow$ **Broncho-constriction**
 - **Histamine & Leukotrienes** $\rightarrow$ **Broncho-constriction (directly or by vagal stimulation)**
 - **Adenosine (locally produced in airways)** $\rightarrow$ **Broncho-constriction**
 - **VIP** $\rightarrow$ **Broncho-dilation**
 - **Catecholamines** $\rightarrow$ **Broncho-dilation**
- D. Endocrine Factors**
- **Menses & pregnancy** : may $\uparrow$ **severity of asthma**
 - Asthma may **start with menopause**
 - **Thyroidosis** may worsen asthma
 - Asthma may **improve or subside at puberty**
- E. Psychological factors**
- Asthma may be triggered with **laughing or crying**
 - Asthma may lead to **behavioral & emotional problems**



Pathophysiology:

Common underlying pathophysiology

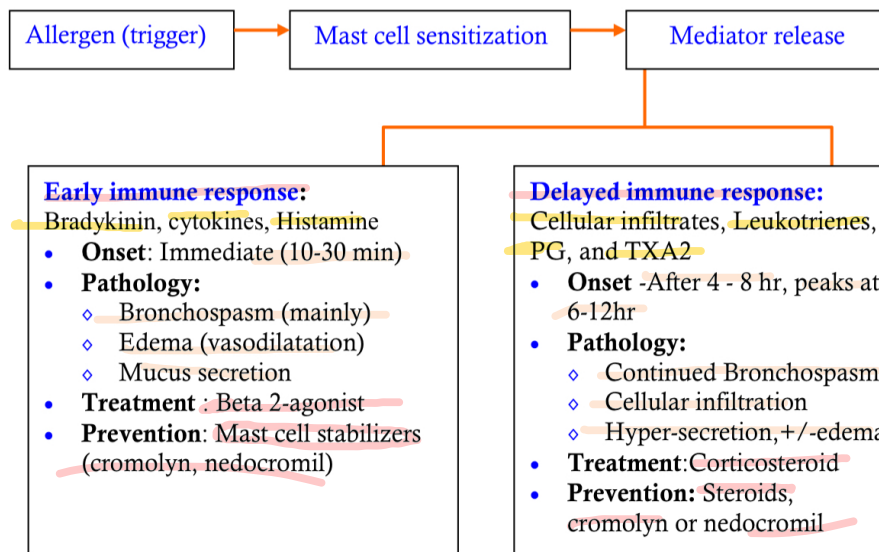
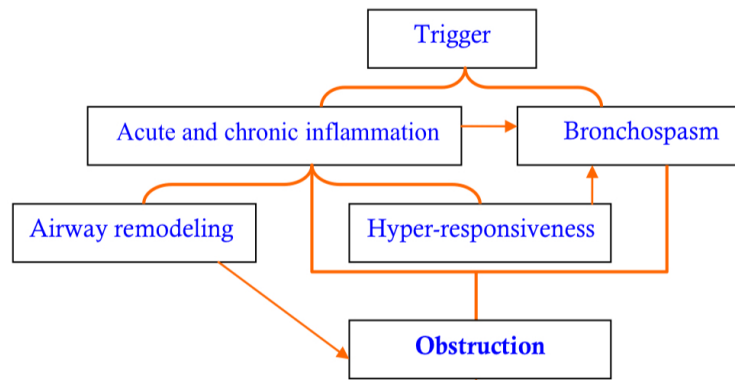
Asthma is an inflammatory disease driven by T-helper type 2 cells (Th2-cell) that manifests in individuals with a genetic predisposition. It consists of the following three pathophysiologic processes:

1. **Bronchial hyperresponsiveness**
2. **Bronchial inflammation**
 - Symptoms are primarily caused by inflammation of the **terminal bronchioles**, which are lined with **smooth muscle** but lack the **cartilage** found in larger airways.
 - Overexpression of Th2-cells $\rightarrow$ inhalation of antigen results in production of cytokines (IL-3, IL-4, IL-5, IL-13) $\rightarrow$ activation of eosinophils and induction of cellular response (B-cell **IgE** production) $\rightarrow$ **bronchial submucosal edema** and **smooth muscle contraction** $\rightarrow$ **bronchioles collapse** [4][5]
3. **Endobronchial obstruction** caused by:
 - Increased parasympathetic tone
 - **Reversible bronchospasm**
 - **Increased mucus production**
 - **Mucosal edema and leukocyte infiltration into the mucosa with hyperplasia of goblet cells**
 - Hypertrophy of smooth muscle cells

Type-specific pathophysiology

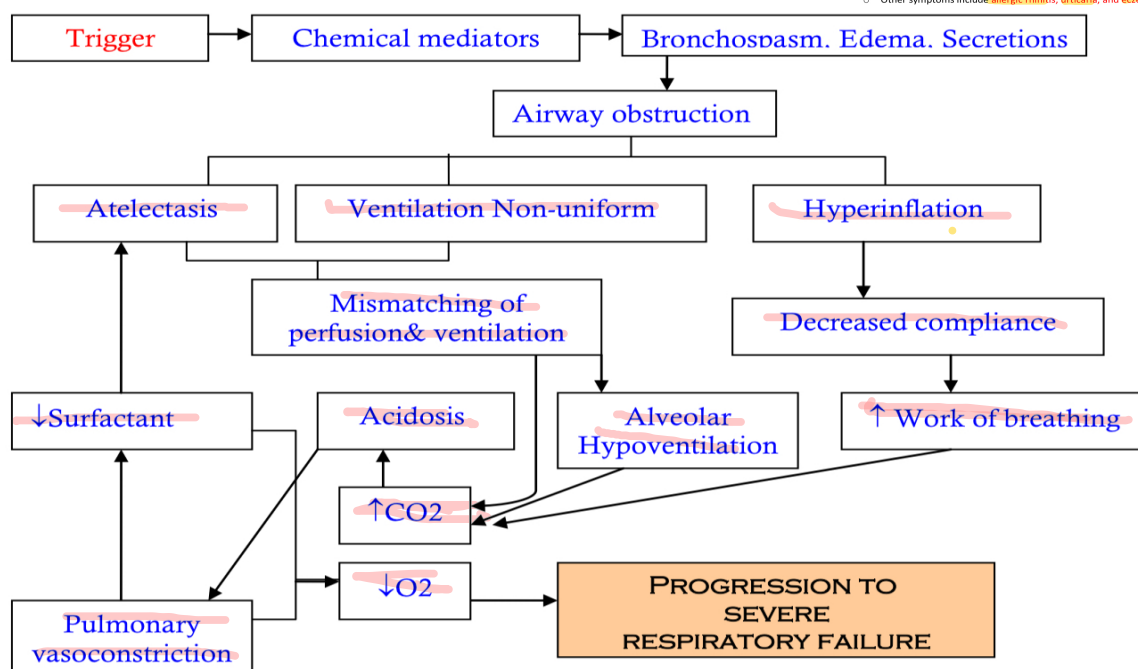
- **Allergic asthma**
 - **IgE-mediated type 1 hypersensitivity** to a specific allergen
 - Characterized by **mast cell degranulation** and **release of histamine** after a prior phase of sensitization
- **Nonallergic asthma**
 - **Irritant asthma:** irritant enters lung $\rightarrow$ $\uparrow$ **release of neutrophils** $\rightarrow$ **submucosal edema** $\rightarrow$ **airway obstruction**
 - **Aspirin-exacerbated respiratory disease** is characterized by the Samter triad:
 - **Inhibition of COX-1** $\rightarrow$ $\downarrow$ **PGE₂** $\rightarrow$ $\uparrow$ **leukotrienes** and **inflammation** $\rightarrow$ **submucosal edema** $\rightarrow$ **airway obstruction**
 - **Chronic rhinosinusitis with nasal polyps**
 - **Asthma symptoms**

ASTHMA PATHOGENESIS



TYPE OF ASTHMA	EXTRINSIC	INTRINSIC
ENVIRONMENTAL ALLERGEN	Yes	No
SERUM IgE	High	Normal
SKIN TESTS	Positive	Negative

- There are 2 types of asthma. Many patients have features of both types:
- A. **Intrinsic or idiosyncratic asthma:**
- A bronchial reaction occurs **secondary to nonimmunologic stimuli**, such as **infection**, irritating inhalant, **cold air**, **exercise**, and **emotional upset**.
- B. **Extrinsic (allergic, atopic) asthma:**
- Specific immunoglobulins (IgE class type 1) are produced, and **total serum IgE concentration is elevated**.
 - There is a **positive family history of allergic disease**.
 - Extrinsic asthma is precipitated **by allergens**.
 - Other symptoms include **allergic rhinitis**, **urticaria**, and **eczema**.



Clinical Findings:

CLINICAL ASPECTS OF ASTHMA

ONSET:

- Acute:
 - ◊ develops in few minutes
 - ◊ due to bronchospasm of large airways
 - ◊ examples: pollens, smoke, drugs,--
- Insidious:
 - ◊ develops over days
 - ◊ due to inflammation, & ↑ mucus, +/- spasm
 - ◊ examples: viral infections



CLINICAL MANIFESTATIONS

- According to severity of attack, we may have: *Tachypnea, retraction, wheezing, cough, accessory muscle use,----*
 1. Wheezing +/- cough or cough alone (night cough)
 2. Dyspnea: (shortness of breathing); difficult walking or talking
 3. Abdominal pain, vomiting.
 4. Palpable liver & spleen (overinflation)
 5. Low grade fever (work of breathing)
 6. Profuse sweating
 7. Pulsus paradoxus (drop in systolic BP during inspiration)
- In chronic asthma:
 - ◊ Barrel-shaped chest deformity
 - ◊ Harrison sulcus
 - ◊ **Rarely** digital clubbing: usually late manifestation in older ages, if seen in children other diagnoses are possible like **cystic fibrosis**
- Subtle symptoms: fatigue, ↓ physical activity, sleepiness
- Auscultation: wheezing, rhonchi, rales, ↓ air entry (unilateral or regional)

CLINICAL DIAGNOSIS OF ASTHMA:

- **The presence of any of these is suggestive of asthma**
 1. Recurrent episodes of wheezing (≥ 3 attacks), +/- cough → highly suggestive
 2. Clinical improvement after therapy with drugs that are specific for asthma,
 3. Positive family history of asthma or atopy
 4. Episodes are caused by specific environmental triggers e.g. allergen exposure, exercise, viral infection → environmental history is essential in dx and ttt
 5. Symptoms worsen at night & early morning
- Normal chest exam does not exclude asthma
- **Consider asthma if any of the following signs or symptoms are present:**
 1. Frequent episodes of wheezing: > once a month
 2. Activity-induced cough or wheeze
 3. Cough particularly at night during periods without viral infections
 4. Absence of seasonal variation in wheeze
 5. Symptoms that persist after age 3
 6. Symptoms occur or worsen in the presence of:
 - ◊ Animals with fur
 - ◊ Aerosol chemicals
 - ◊ Changes in temperature
 - ◊ Domestic dust mites
 - ◊ Drugs (aspirin, beta blockers)
 - ◊ Exercise
 - ◊ Pollen
 - ◊ Respiratory (viral) infections
 - ◊ Smoke
 - ◊ Strong emotional expression
 7. The child's colds repeatedly "go to the chest" or take more than 10 days to clear up
 8. Symptoms improve when asthma medication is given

Diagnosis:

1. **Eosinophilia** in the blood or sputum
2. **IgE serum level:** may be increased
3. **Allergy skin testing & RAST** to determine specific allergen
4. **Chest X-RAY:**
 - ◊ Findings: Variable: often normal, hyperinflation, atelectasis, peribronchial thickening, pneumothorax
 - ◊ Indications:
 - A. In the first attack of asthma to R/O other diagnosis
 - B. In recurrent attacks IF:
 1. Patient is febrile
 2. H.R > 160/min
 3. Tachypnea > 60/min
 4. Suspicion of pneumothorax
 5. Localized findings on chest exam, e.g. localized breathing or ↓ air entry
5. **Blood Gases:**
 - ◊ Hypoxia (low PaO₂)
 - ◊ PaCO₂: Early low → normal → high.
6. **Pulmonary function tests:**
 - A. **Lung volumes:**
 - ◊ Decreased VC & FVC
 - ◊ Increased TLC, RV, & FRC
 - B. **Airway flow:**
 - ◊ Decreased PEF (PFR), FEV₁, FEF_{25-75%}

- Increased IgE levels suggest an **allergic etiology**. IgE levels may also help guide therapy such as the use of the anti-IgE medication **omalizumab**. Increased IgE levels are also associated with allergic **bronchopulmonary aspergillosis**.

NOTE:

Spirometry:

- ◊ Airflow limitation
 1. Low FEV₁
 2. FEV₁/FVC ratio < 0.8
 - ◊ Bronchodilator response (inhaled β_2 -agonist) ↑ FEV₁ $\geq 12\%$ *
 - ◊ Exercise challenge ↓ FEV₁ $\geq 15\%$ *
- Peak flow** morning-to-afternoon variation $\geq 20\%$ *
- * Main criteria consistent with asthma

- Decrease in FEV₁ of more than 20% with the use of methacholine or histamine.
- When the patient is asymptomatic, the most accurate test of reactive airway disease is a 20% decrease in FEV₁ with the use of methacholine (provocative challenge test).
- Acetylcholine and histamine provoke bronchoconstriction and an increase in bronchial secretions. **Methacholine is an artificial form of acetylcholine used in diagnostic testing.**
- Increase in the diffusion capacity of the lung for carbon monoxide (DLCO).

Asthma Diagnosis:

- FEV₁ ↑ 12% with albuterol.
- FEV₁ ↓ 20% with methacholine.

	Asthma
FVC	Normal/↓
FEV ₁	↓
FEV ₁ /FVC	↓
Bronchodilator response	Reversible
Chest x-ray	Normal
DLCO	Normal/↑

في علاجها بالصفحة السابعة



Acute asthma exacerbation:

- Causes of acute exacerbations of symptoms include:
 - o Infection and cold air. Respiratory infections are the most common stimuli to cause asthma exacerbation; studies have documented that viruses (respiratory syncytial virus in young children, rhinoviruses in adults) are the major causes.
 - o Allergens such as pollen, dust mites, cockroaches, and cat dander.
 - o Emotional stress or exercise.
 - o Catamenial (related to menstrual cycle).
 - o Aspirin, NSAIDs, beta blockers, histamine, any nebulized medication, tobacco smoke.
 - o Gastroesophageal reflux disease (GERD).

❖ N.B:

1. Exercise-induced bronchoconstriction (EIB) occurs in response to mast cell degranulation triggered by the passage of high volumes of dry, cold air.
 - Beta agonists and mast cell stabilizers are important in the management of EIB.
 - Short-acting beta-adrenergic agonists such as albuterol, used 10-20 minutes prior to exercise, are typically sufficient to prevent symptoms. They are considered first-line therapy if used only intermittently (less than daily).
 - An antileukotriene agent can be used 15-20 minutes prior to exercise for those unable to tolerate beta agonists.
 - A combination of beta agonists and antileukotriene agents may also be used in high-performance athletes.
2. Comorbid gastroesophageal reflux disease (GERD) is common in patients with asthma and can exacerbate asthma symptoms through microaspiration of gastric contents, leading to an increase in vagal tone and bronchial reactivity.
 - Proton-pump inhibitor (PPI) therapy has been shown to improve both asthma symptoms and peak expiratory flow rate in asthma patients with evidence of comorbid GERD, and a PPI trial (esomeprazole) should be initiated in this patient.
3. Aspirin-exacerbated respiratory disease (AERD) is a pseudoallergic reaction to nonsteroidal anti-inflammatory drugs (NSAIDs).
 - Pseudoallergic reactions are not IgE-mediated but typically occur in patients with comorbid asthma, chronic rhinosinusitis with nasal polyposis, or chronic urticaria.
 - About 10%-20% of patients with asthma may develop AERD.
 - AERD pathogenesis involves increased production of pro-inflammatory leukotrienes and decreased production of anti-inflammatory prostaglandins. The breakdown of arachidonic acid to prostaglandins is mediated by the cyclooxygenase (COX1, COX2) pathway and is inhibited by aspirin. Instead, arachidonic acid is diverted to the production of leukotrienes via the 5-lipoxygenase pathway.
 - Treatment includes management of the patient's underlying asthma and chronic rhinosinusitis, avoidance of NSAIDs, and desensitization if NSAID use is required. The use of leukotriene inhibitors (zileuton) and leukotriene receptor antagonists (montelukast) can also improve respiratory and nasal symptoms.

4. Nonselective beta blockers (propranolol, nadolol, sotalol, timolol) act on B_1 and B_2 receptors and often trigger bronchoconstriction in patients with underlying asthma.

- Cardioselective beta blockers (metoprolol, atenolol, bisoprolol, nebivolol) act predominantly on B_1 receptors and are generally considered safe in patients with mild-to-moderate asthma.
- However, all beta blockers can trigger bronchoconstriction, especially when administered in large doses.

■ **Presentation:**

- In a **mild** attack, slight tachypnea (increased respiratory rate), prolonged expirations, and mild, diffuse wheezing are seen.
- Asthma can present exclusively as a cough.
- In a **severe** attack, use of accessory muscles of respiration, diminished breath sounds, loud wheezing, hyper-resonance (increased vocal fremitus), unable to speak in full sentences, and intercostal retraction are noted.
- Poor prognostic factors** include fatigue, diaphoresis, inaudible breath sounds, decreased wheezing, cyanosis, and bradycardia.

■ **Diagnostic Tests:**

- The best initial test in an acute exacerbation: **peak expiratory flow (PEF) or arterial blood gas (ABG)**. Peak flow can be used by the patient to determine function.
- Chest x-ray is most often normal in asthma.** Chest x-ray is used to:
 - Exclude pneumonia as a cause of exacerbation.
 - Exclude other diseases such as pneumothorax or CHF in cases that are not clear.
- The **most accurate diagnostic test is pulmonary function testing (PFTs)**.
- Spirometry will show a **decrease in the ratio of forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC)**. The FEV1 decreases more than the FVC.

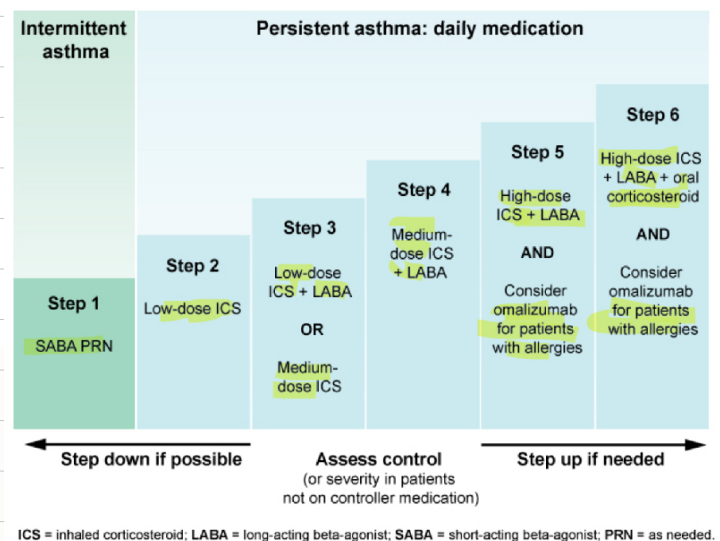
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- The pharmacologic management of asthma is guided by a **stepwise approach**.
- In patients with **newly diagnosed** asthma or **intermittent asthma** managed with only an as-needed short-acting beta-2 agonist (SABA) (albuterol).
- The need for controller medication therapy (and level of controller therapy) is assessed by categorizing symptoms into 1 of 4 levels of asthma severity: **intermittent, mild persistent, moderate persistent, and severe persistent**.

Asthma severity for patients not on controller medication

Asthma severity	Symptom frequency/ SABA use	Nighttime awakenings	Indicated therapy initiation
Intermittent	≤2 days a week	≤2 times a month	Step 1
Mild persistent	>2 days a week but not daily	3-4 times a month	Step 2
Moderate persistent	Daily	>1 time a week but not nightly	Step 3
Severe persistent	Throughout the day	4-7 times a week	Step 4 or 5

SABA = short-acting beta-2 agonist.



- The factors that define severity are frequency of daytime symptoms (can be assessed as frequency of SABA use if already prescribed) and frequency of nighttime awakenings:

A. Step 1:

- Always start the treatment of asthma with an inhaled short-acting beta agonist (SABA) as needed.

Examples of SABA are:

- o Albuterol.
- o Pirbuterol.
- o Levalbuterol.

B. Step 2:

- Add a long-term control agent to a SABA.

- Low-dose inhaled corticosteroids (ICS) are the best initial long-term control agent.

- Example of ICS are: Beclomethasone, budesonide, flunisolide, fluticasone, mometasone, triamcinolone.

- The most common adverse effect of inhaled corticosteroid therapy is oropharyngeal thrush (oral candidiasis) and dysphonia.

- Alternate long-term control agents include:

- o Cromolyn and nedocromil to inhibit mast cell mediator release and eosinophil recruitment.
- o Theophylline.
- o Leukotriene modifiers: montelukast, zafirlukast (competitive leukotrienes receptors antagonist), or zileuton (inhibit 5-lipoxygenase). Zafirlukast is hepatotoxic and has been associated with Churg-Strauss syndrome.

C. Step 3:

- Add a long-acting beta agonist (LABA) to a SABA and ICS, or increase the dose of the ICS (medium dose).

- LABA medications are salmeterol or formoterol.

- Never use LABA first or alone!

D. Step 4:

- Increase the dose of the ICS (medium dose) in addition to the LABA and SABA.

E. Step 5:

- Increase the dose of the ICS to maximum.

- Omalizumab may be added to the SABA, LABA, and ICS in those who have an increased IgE level.

F. Step 6:

- Oral corticosteroids such as prednisone are added when all the other therapies are not sufficient to control symptoms.

- Influenza and pneumococcal vaccine are given in all asthma patients.

❖ Adverse Effects of Systemic Corticosteroids:

- They should be used as a last resort because of very harsh adverse effects such as:

- Osteoporosis.
- Cataracts.
- Adrenal suppression and fat redistribution.
- Hyperlipidemia, hyperglycemia, acne, and hirsutism (particularly in women).
- Thinning of skin, striae, and easy bruising.

- High-dose inhaled steroids rarely lead to the adverse effects associated with prednisone.

❖ Anticholinergics:

- Anticholinergic drugs (ipratropium bromide and tiotropium) have particular benefit in patients with heart disease, in whom the use of β -adrenergic agonists and theophylline may be dangerous.
- Their major disadvantages are that they take significant time to achieve maximal bronchodilation (~90 min) and they are only of medium potency.
- Anticholinergic agents will dilate bronchi and decrease secretions.
- They are very effective in COPD.

❖ Acute Asthma Exacerbation:

- The severity of an asthma exacerbation is quantified by:
 - Decreased peak expiratory flow (PEF).
- ABG:
 - Acute asthma exacerbation causes increased respiratory drive and hyperventilation, leading to decreased partial pressure of carbon dioxide (PaCO_2).
 - Hyperventilation results in a decrease in the PaCO_2 and a primary respiratory alkalosis, which is the typical presentation in an acute asthma exacerbation.
- The PEF is an approximation of the FVC. There is no precise "normal" value. It is based predominantly on height and age, not on weight.
- The PEF is used in acute assessment by seeing how much difference there is from the patient's usual PEF when the patient is stable.
- Chest x-ray is used to see if there is an infection leading to the exacerbation. In addition, asthma predisposes to pneumothorax.

■ Treatment:

- Oxygen.
 - Albuterol.
 - Steroids.
 - Ipratropium.
 - The best initial therapy is oxygen combined with inhaled short-acting beta agonists such as albuterol and a bolus of steroids.
 - Corticosteroids need 4 to 6 hours to begin to work, so give them right away.
 - Epinephrine injections are no more effective than albuterol and have more adverse systemic effects.
 - Ipratropium should be used but does not work as rapidly as albuterol.
 - Magnesium helps relieve bronchospasm. Magnesium is used only in an acute, severe asthma exacerbation not responsive to several rounds of albuterol while waiting for steroids to take effect.
 - Magnesium is not as effective as albuterol, ipratropium, or steroids, but it does help.
- The following are not effective in acute exacerbations:
 - Theophylline.
 - Cromolyn and nedocromil (best with extrinsic allergies like hay fever).
 - Leukotriene modifiers.
 - Omalizumab.
 - LABAs (salmeterol, formoterol, olodaterol, vilanterol).
 - If the patient does not respond to oxygen, albuterol, and steroids or develops respiratory acidosis (increased pCO_2), the patient may have to undergo endotracheal intubation for mechanical ventilation. These patients should be placed in the intensive care unit.

PHARMACOTHERAPY FOR ASTHMA BASED ON DISEASE CLASSIFICATION

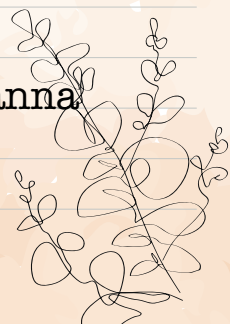
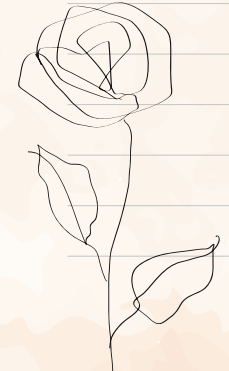
CLASSIFICATION	LONG-TERM CONTROLLERS	QUICK-RELIEVERS
Mild intermittent: -Daytime symp=<2/d -Nocturnal symp=2/mo -PEF =>80%, variability <20%	NO anti-inflammatory medications	Short-acting beta2 agonist as needed
Mild persistent: -Daytime >2/d -Nocturnal > 2/mo -PEF =>80%, variab 20-30%	-Low-dose inhaled corticosteroid or -cromolyn sodium (Intal) or -nedocromil (Tilade) or -leukotriene modifiers (=>2yr old)	Short-acting beta2 agonist as needed
Moderate persistent: -Daytime daily -Night >1/week -PEF>60 - <80%,variab >30%	-Low - Medium-dose ICS plus a long-acting bronchodilator (long-acting beta2 agonist) if needed -medium dose ICS +/- antileukotr	Short-acting beta2 agonist as needed
Severe persistent: -Continuous symp -Frequent night symp -PEF =<60%,variability >30%	High-dose inhaled corticosteroid plus a long-acting bronchodilator and systemic corticosteroid if needed	Short-acting beta2 agonist as needed



Clinical notes:

❖ N.B:

1. Beta-2 agonists like **albuterol** reduce serum potassium levels by driving potassium into cells.
 - In some patients, clinically significant hypokalemia can result, causing **muscle weakness, arrhythmias, and EKG changes.**
 - Other common side effects of beta-2 agonists include tremor, headache and palpitations. Obtaining a serum electrolyte panel would be helpful to confirm and assess the severity of patient's hypokalemia.
2. Acute asthma exacerbation causes increased respiratory drive and hyperventilation, leading to decreased partial pressure of carbon dioxide (PaCO_2).
 - Hyperventilation results in a decrease in the PaCO_2 and a **primary respiratory alkalosis**, which is the typical presentation in an acute asthma exacerbation.
 - An elevated or even normal PaCO_2 suggests an inability to meet increased respiratory demands (likely due to respiratory muscle fatigue) and impending respiratory failure.
 - Other clinical signs or symptoms of impending respiratory failure include:
 - Markedly decreased breath sounds.
 - Absent wheezing.
 - Decreased mental status.
 - Marked hypoxia with cyanosis.
 - Endotracheal intubation and mechanical ventilation are indicated in patients with severe asthma unresponsive to maximal medical therapy and who have signs of impending respiratory arrest.
3. Theophylline has a **narrow therapeutic index**, and toxicity can occur from accumulation by reduced clearance or decreased metabolism due to saturation of metabolic pathways.
 - Theophylline is **metabolized predominantly by the cytochrome oxidase system in the liver.** Inhibition of these enzymes by concurrent illness (cirrhosis, cholestasis, respiratory infections with fever) or drugs (**cimetidine, ciprofloxacin, erythromycin, clarithromycin, verapamil**) can raise serum concentration and cause toxicity.
 - Symptoms of toxicity usually manifest as **central nervous system stimulation** (headache, insomnia, **seizures**), **gastrointestinal disturbances** (nausea, vomiting), and **cardiac toxicity (arrhythmia).**
- **Children under 5 years of age**
 - Asthma in patients under 5 years of age is challenging to diagnose and is often underdiagnosed, as children in this age group are not typically able to adequately perform the spirometric maneuvers.
 - Regimens containing glucocorticoids are preferred as initial therapy in infants and young children.^[20]
 - Young children (< 5 years) may require nebulizers because of difficulty using inhalers. ^[3]



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