

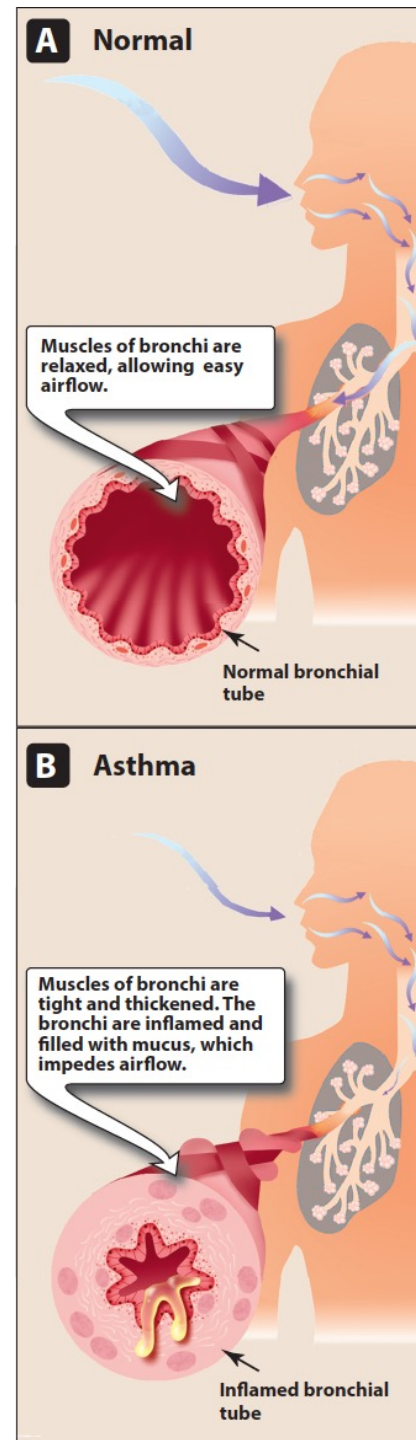
Drugs for Disorders of the Respiratory System

Part 1

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Asthma

- Asthma is a chronic inflammatory disease of the airways characterized by episodes of acute bronchoconstriction causing shortness of breath, cough, chest tightness, wheezing, and rapid respiration.
- **Pathophysiology:** Airflow obstruction in asthma is due to bronchoconstriction that results from contraction of bronchial smooth muscle, inflammation of the bronchial wall, and increased secretion of mucus.
- Asthma attacks may be triggered by exposure to allergens, exercise, stress, and respiratory infections.
- Unlike COPD, cystic fibrosis, and bronchiectasis, asthma is usually not a progressive disease (that is, it does not inevitably lead to incapacitated airways).
- However, if untreated, asthma may cause airway remodeling, resulting in increased severity and incidence of asthma exacerbations and/or death.

Asthma

- **Goals of therapy:** are to decrease the intensity and frequency of asthma symptoms and the degree to which the patient is limited by these symptoms.
- All patients need to have a “quick-relief” medication to treat acute asthma symptoms.
- Drug therapy for longterm control of asthma is designed to reverse and prevent airway inflammation.

CLASSIFICATION	BRONCHO-CONSTRICTIVE EPISODES	RESULTS OF PEAK FLOW OR SPIROMETRY	LONG-TERM CONTROL	QUICK RELIEF OF SYMPTOMS
Intermittent	Less than 2 days per week	Near normal*	No daily medication	Short-acting β_2 agonist
Mild persistent	More than 2 days per week, not daily	Near normal*	Low-dose ICS	Short-acting β_2 agonist
Moderate persistent	Daily	60% to 80% of normal	Low-dose ICS + LABA OR Medium-dose ICS	Short-acting β_2 agonist
Severe persistent	Continual	Less than 60% of normal	Medium-dose ICS + LABA OR High-dose ICS + LABA	Short-acting β_2 agonist

β2-Adrenergic agonists

- Inhaled β2-adrenergic agonists directly relax airway smooth muscle.
- They are used for the quick relief of asthma symptoms, as well as adjunctive therapy for long-term control of the disease.

1. Quick relief: Short-acting β2 agonists (SABAs) have a rapid onset of action (5 to 30 minutes) and provide relief for 4 to 6 hours. They are used for symptomatic treatment of bronchospasm, providing quick relief of acute bronchoconstriction.

- All patients with asthma should be prescribed a SABA inhaler.
- β2 agonists have no anti-inflammatory effects, and they should never be used as the sole therapeutic agents for patients with persistent asthma. However, monotherapy with SABAs may be appropriate for patients with intermittent asthma or exercise-induced bronchospasm.
- Direct acting β2-selective agonists include *albuterol and levalbuterol*. These agents provide significant bronchodilation with little of the undesired effect of α or β1 stimulation.

β₂-Adrenergic agonists

2. Long-term control: *Salmeterol and formoterol* are long-acting β₂ agonists (LABAs) and chemical analogs of albuterol.

- Salmeterol and formoterol have a long duration of action, providing bronchodilation for at least 12 hours.
- Neither salmeterol nor formoterol should be used for quick relief of an acute asthma attack. Use of LABA monotherapy is contraindicated, and LABAs should be used only in combination with an asthma controller medication.
- Inhaled corticosteroids (ICS) remain the long-term controllers of choice in asthma, and LABAs are considered to be useful adjunctive therapy for attaining asthma control.
- Some LABAs are available as a combination product with an ICS (Figure 29.1).

Inhaled Corticosteroids (ICS)

- ICS are the drugs of choice for long-term control in patients with any degree of persistent asthma.
- ICS inhibit the release of arachidonic acid through phospholipase A2 inhibition, thereby producing direct anti-inflammatory properties in the airways.
- No other medications are as effective as ICS in the long-term control of asthma in children and adults.
- To be effective in controlling inflammation, ICS must be used regularly. Severe persistent asthma may require the addition of a short course of oral glucocorticoid treatment.
- **Actions on lung:** ICS directly targets underlying airway inflammation by decreasing the inflammatory cascade (eosinophils, macrophages, and T lymphocytes), reversing mucosal edema, decreasing the permeability of capillaries, and inhibiting the release of leukotrienes.
- After several months of regular use, ICS reduce the hyperresponsiveness of the airway smooth muscle to a variety of bronchoconstrictor stimuli, such as allergens, irritants, cold air, and exercise.

Inhaled Corticosteroids (ICS)

- Routes of administration

a. Inhalation: The development of ICS has markedly reduced the need for systemic corticosteroid treatment to achieve asthma control. However, as with all inhaled medications, appropriate inhalation technique is critical to the success of therapy.

b. Oral/systemic: Patients with a severe exacerbation of asthma (status asthmaticus) may require intravenous *methylprednisolone* or *oral prednisone* to reduce airway inflammation.

- Due to the increased incidence of adverse effects with oral therapy, chronic maintenance with systemic administration of corticosteroids should be reserved for patients who are not controlled on an ICS.
- **Adverse effects:** ICS deposition on the oral and laryngeal mucosa can cause adverse effects, such as oropharyngeal candidiasis (due to local immune suppression) and hoarseness. Patients should be instructed to rinse the mouth in a “swish-and-spit” method with water following use of the inhaler to decrease the chance of these adverse events.
- If used with a spacer, ICS have few systemic effects.

Alternative Drugs Used To Treat Asthma

A. Leukotriene modifiers

- Leukotrienes (LT) B₄ and the cysteinyl leukotrienes, LTC₄, LTD₄, and LTE₄, are products of the 5-lipoxygenase pathway of arachidonic acid metabolism and part of the inflammatory cascade.
- 5-Lipoxygenase is found in cells of myeloid origin, such as mast cells, basophils, eosinophils, and neutrophils. LTB₄ is a potent chemoattractant for neutrophils and eosinophils, whereas the **cysteinyl leukotrienes** constrict bronchiolar smooth muscle, increase endothelial permeability, and promote mucus secretion.
- **Zileuton** is a selective and specific inhibitor of 5-lipoxygenase, preventing the formation of both LTB₄ and the cysteinyl leukotrienes.
- Because **zafirlukast and montelukast** are selective antagonists of the cysteinyl leukotriene-1 receptor, they block the effects of cysteinyl leukotrienes.
- All three drugs are approved for the prevention of asthma symptoms. They should not be used in situations where immediate bronchodilation is required.
- Leukotriene receptor antagonists have also shown efficacy for the prevention of exercise induced bronchospasm.

Alternative Drugs Used To Treat Asthma

B. Cromolyn

- Cromolyn is a prophylactic anti-inflammatory agent that inhibits mast cell degranulation and release of histamine.
- It is an alternative therapy for mild persistent asthma. However, it is not useful in managing an acute asthma attack, because it is not a bronchodilator.
- Cromolyn is available as a nebulized solution for use in asthma. Due to its short duration of action, this agent requires dosing three or four times daily, which affects adherence and limits its use.

C. Cholinergic antagonists

- The anticholinergic agents block vagally mediated contraction of airway smooth muscle and mucus secretion.
- *Inhaled ipratropium*, a quaternary derivative of atropine, is not recommended for the routine treatment of acute bronchospasm in asthma, as its onset is much slower than inhaled SABAs. However, it may be useful in patients who are unable to tolerate a SABA or patients with concomitant COPD.
- Ipratropium also offers additional benefit when used with a SABA for the treatment of acute asthma exacerbations in the emergency department.

Alternative Drugs Used To Treat Asthma

D. Theophylline

- Theophylline is a bronchodilator that relieves airflow obstruction in chronic asthma and decreases its symptoms.
- It may also possess anti-inflammatory activity, although the mechanism of action is unclear.
- Previously, the mainstay of asthma therapy, theophylline has been largely replaced with β 2 agonists and corticosteroids due to its narrow therapeutic window, adverse effect profile, and potential for drug interactions.

E. Omalizumab

- Omalizumab is a recombinant DNA-derived monoclonal antibody that selectively binds to human immunoglobulin E (IgE). This leads to decreased binding of IgE to its receptor on the surface of mast cells and basophils. Reduction in surface-bound IgE limits the release of mediators of the allergic response.
- Omalizumab is indicated for the treatment of moderate to severe persistent asthma in patients who are poorly controlled with conventional therapy.
- Its use is limited by the high cost, route of administration (subcutaneous), and adverse effect profile.

Thank You!

