Drugs for Disorders of the Respiratory System

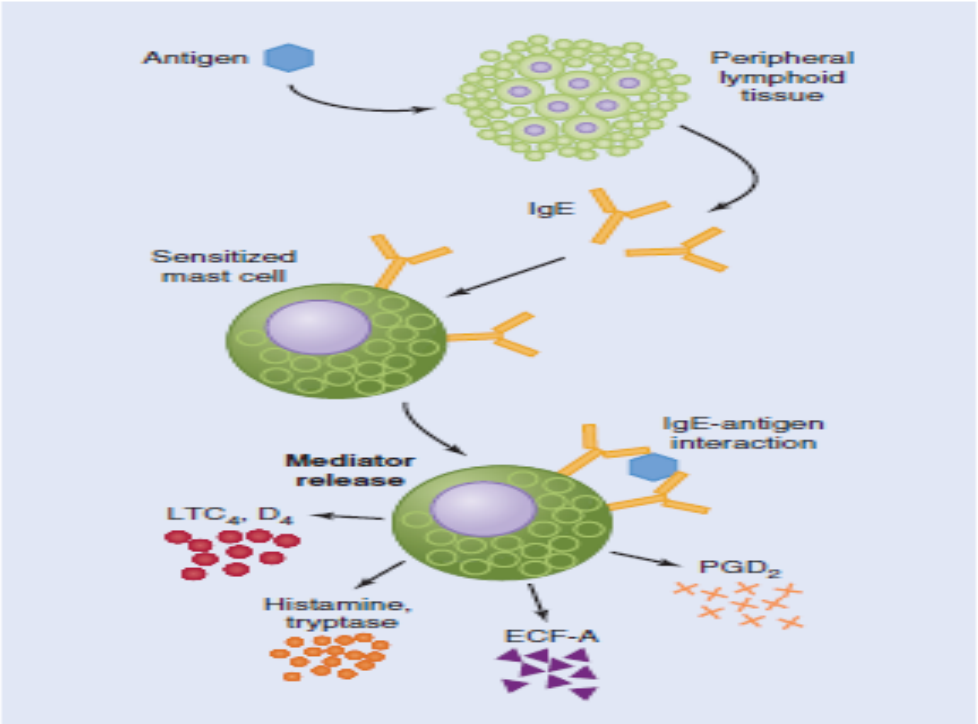
1-Drugs used for treatment of asthma

A. Pathophysiology of asthma

The immediate cause of asthmatic bronchoconstriction is the release of several mediators from IgE-sensitized mast cells and other cells involved in immunologic responses. These mediators include the leukotrienes LTC4 and LTD4. In addition, chemotactic mediators such as LTB4 attract inflammatory cells to the airways. Finally, several cytokines and some enzymes are released, leading to chronic inflammation.

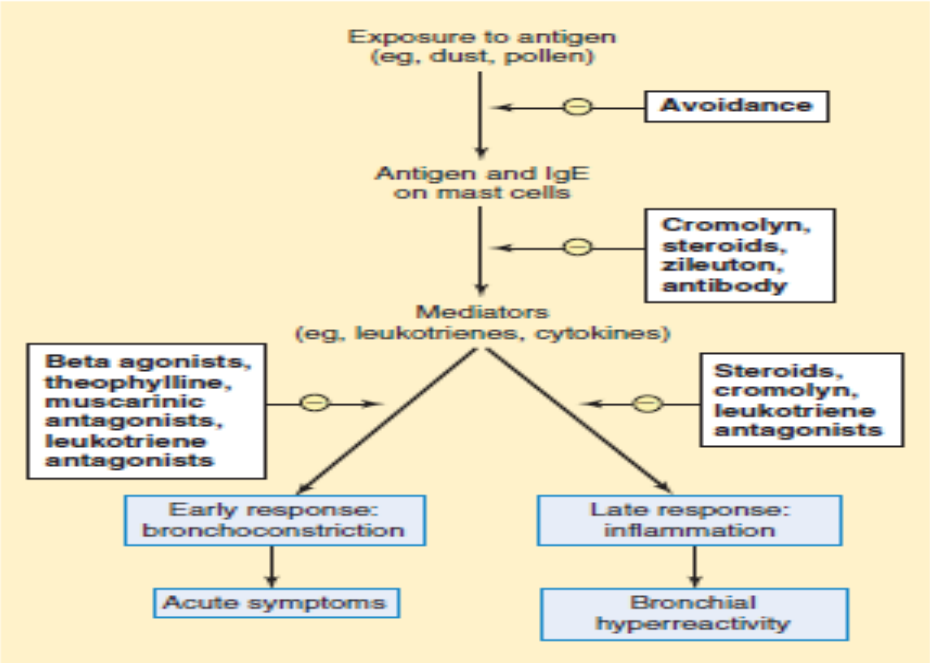
Chronic inflammation leads to marked bronchial hyperreactivity to various inhaled substances, including antigens, histamine, muscarinic agonists, and irritants such as sulfur dioxide (SO2) and cold air.

COPD is often triggered by upper respiratory infection (like asthma) but occurs in older patients (usually long-term smokers) and is poorly reversible with bronchodilators.



B. Goals of therapy

Acute bronchospasm is treated with **bronchodilators** like β2 agonists, muscarinic antagonists, and theophylline derivatives. Long-term asthma management focuses on **controlling airway inflammation** using corticosteroids, **supported** by long-acting β2 agonists to enhance their effects. Anti-IgE antibodies show promise for chronic therapy, while leukotriene antagonists, effective for both bronchoconstriction and inflammation, are primarily used for prophylaxis.



C. B2-adrenergic agonists

Inhaled B2-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 B~2 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 receive a SABA inhaler for use as needed. B2 agonists **have no anti-inflammatory effects,** and they should not be used as monotherapy for patients with persistent asthma. However, monotherapy with SABAs may be appropriate for patients with mild, intermittent asthma or exercise-induced bronchospasm. Direct acting B~2-selective agonists include *a/buterol* and *levalbuterol* These agents provide significant bronchodilation with little of the undesired effect of a or a1 stimulation.

Adverse effects, such as tachycardia, hyperglycemia, hypokalemia, hypomagnesemia, and B2- mediated skeletal muscle tremors are minimized **with inhaled delivery** versus systemic administration.

2. Long-term control: *Salmeterol* and *formoterol* are long-acting B2 agonists (LABAs) and chemical analogs of *albuterol*.

Salmeterol and *formoterol* have a long duration of action, providing bronchodilation for at least 12 hours. Use of LABA **monotherapy** is contraindicated, and LABAs should be used only in combination with an asthma **controller medication,** such as an inhaled corticosteroid (ICS).

ICS remain the long-term controllers of choice in asthma, and LABAs are considered to be useful adjunctive therapy for attaining control in moderate to severe asthma. Some LABAs are available as a combination product with an ICS . Although both LABAs are usually used on a scheduled basis to control asthma, adults and adolescents with moderate persistent asthma can use the *ICS/formoterol* combination for relief of acute symptoms. **Adverse effects** of LABAs are similar to quick-acting B2 agonists.

D. Corticosteroids

ICS are the drugs of choice for long-term control in patients with persistent asthma. Corticosteroids inhibit the release of arachidonic acid through inhibition of phospholipase A2 and inhibit the expression of COX-2. thereby producing direct anti-inflammatory properties in the airways.

To be effective in controlling inflammation, these agents must be used regularly. Treatment of exacerbations or severe persistent asthma may require the addition of a short course of oral or intravenous corticosteroids.

Actions on lung

ICS therapy 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.

Adverse effects: Oral or parenteral corticosteroids have a variety of

potentially serious adverse effects, whereas ICS, particularly if used with a spacer, have few systemic effects. ICS deposition on the oral and laryngeal mucosa can cause 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. Due to the potential for serious adverse effects, chronic maintenance with oral corticosteroids should be reserved for patients who are not controlled on an ICS.

Alternative drugs used to treat asthma

These drugs are useful for treatment of asthma in patients who are poorly controlled by conventional therapy or experience adverse effects secondary to corticosteroid treatment. These drugs should be used in conjunction with ICS therapy for most patients.

A. Leukotriene modifiers

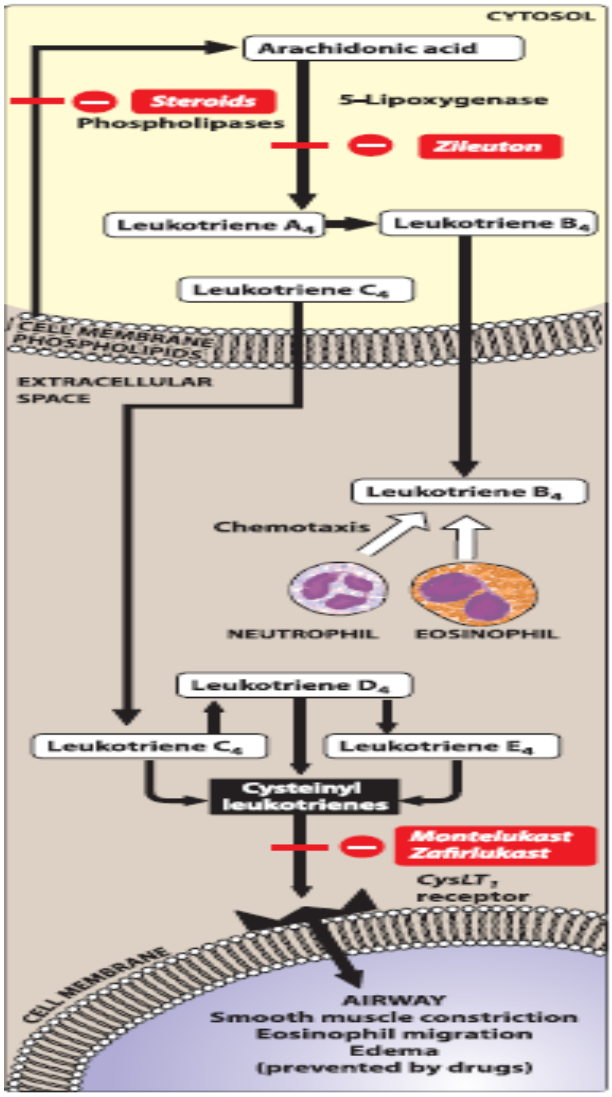
Leukotrienes (LT) B4 and the cysteinyl leukotrienes, LTC4, LTD4 , and LTE4 , are products of the 5-lipoxygenase pathway of arachidonic acid metabolism and part of the inflammatory cascade.

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. *Zafirlukast* and *montelukast* are selective antagonists of the cysteinyl leukotriene-1 receptor, and they block the effects of cysteinyl leukotrienes . These agents 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.

Adverse effects: Elevations in serum hepatic enzymes may occur with these drugs, requiring periodic monitoring and discontinuation when enzymes exceed three to five times the upper limit of normal. Other effects include headache and dyspepsia. *Zafirlukast* is an inhibitor of cytochrome P450 (CYP) isoenzymes 2C8, 2C9, and 3A4, and *zileuton* inhibits CYP1

A2. Coadministration with drugs that are substrates of these isoenzymes may result in increased effects and/or toxicity.



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 and is available as a nebulized solution. Because *cromolyn* is not a bronchodilator, it is not useful in managing an acute asthma attack. Due to its short duration of action, this agent requires dosing three or four times daily, which affects adherence and limits its use.

Adverse effects are minor and include cough, irritation, and unpleasant taste.

C. Cholinergic antagonists

The anticholinergic agents block vagally mediated contraction of airway smooth muscle and mucus secretion .

Inhaled *ipratropium* , a short-acting quaternary derivative of *atropine*, is not recommended for the routine treatment of acute bronchospasm in asthma, as its onset is much slower than that of inhaled SABAs. However, it may be useful in patients who are unable to tolerate a SABA or patients with asthma-COPD overlap syndrome. *lpratropium* also offers additional benefit when used with a SABA for the treatment of acute asthma exacerbations in the emergency department. *Tiotropium* , a long-acting anticholinergic agent, can be used as an add-on treatment in adult patients with severe asthma and a history of exacerbations. Adverse effects such as xerostomia and bitter taste are related to local anticholinergic effects.

D. Theophylline

Theophylline is a bronchodilator that relieves airflow obstruction in chronic asthma and decreases asthma 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 B2 agonists and corticosteroids due to its narrow therapeutic window, adverse effect profile, and potential for drug interactions. Overdose may cause seizures or potentially fatal arrhythmias. *Theophylline* is metabolized in the liver and is a CYP1 A2 and 3A4 substrate. It is subject to numerous drug interactions. Serum concentration monitoring should be performed when *theophylline* is used chronically.

E. Monoclonal antibodies

Omalizumab is a monoclonal antibody that selectively binds to human immunoglobulin E (lgE). This leads to decreased binding of lgE to its receptor on the surface of mast cells and basophils. Reduction in surface-bound lgE limits the release of mediators of the allergic response. The monoclonal antibodies *mepolizumab*, *benralizumab* , and *reslizumab* are interleukin-5 (IL-5) antagonists. IL-5 is the major cytokine involved in recruitment, activation, and survival of eosinophils in eosinophilic asthma. These agents are indicated for the treatment of severe persistent asthma in patients who are poorly controlled with conventional therapy. Their use is limited by the high cost, route of administration (IV for *reslizumab* and subcutaneous for others), and adverse effect profile.

Adverse effects include serious anaphylactic reactions (rare), arthralgias, fever, rash, and increased risk of infections. New malignancies have been reported.

2-Drugs used to treat allergic rhinitis

Rhinitis is nasal mucosa inflammation causing sneezing, itchy eyes/nose, runny nose, and congestion, often triggered by allergens. Mast cell mediators like histamine and leukotrienes worsen symptoms. Preferred treatments include antihistamines and intranasal corticosteroids.

- **Antihistamines:**
    - Oral: Second-generation (e.g., fexofenadine, loratadine) are preferred for prevention with fewer side effects than first-generation options.

- Topical: Intranasal and ophthalmic forms (e.g., olopatadine, azelastine) offer targeted relief with minimal side effects.
- Combination: Antihistamines with decongestants are used for congestion or partial symptom control with corticosteroids.

- **Corticosteroid**

Intranasal corticosteroids (e.g., beclomethasone, fluticasone, mometasone) are the most effective treatment for allergic rhinitis, improving symptoms like sneezing, itching, and congestion. They act within 3 to 36 hours, with minimal systemic absorption. Side effects are localized (e.g., nasal irritation, nosebleeds). Proper administration avoids systemic absorption and targets the nasal tissue effectively. Full benefits for chronic rhinitis may take 1–2 weeks.

α-Adrenergic agonists (nasal decongestants)

like phenylephrine and oxymetazoline reduce nasal congestion by constricting arterioles. Intranasal forms act quickly with minimal systemic effects but should not be used for more than 3 days to avoid rebound congestion. Oral forms have longer action but may cause systemic effects like elevated blood pressure and heart rate. Long-term use, whether intranasal or oral, is not recommended.

3-Drugs used to treat cough

Coughing is a key respiratory defense often caused by irritants, infections, or chronic conditions. It may be beneficial in clearing bacterial infections and should not always be suppressed. Identifying the cause is crucial to determine if antitussive treatment is appropriate, with priority given to addressing the underlying cause.

- **Codeine**: An opioid that reduces cough sensitivity and mucosal secretions at low doses but carries risks of constipation, fatigue, dysphoria, and addiction, limiting its use.
- **Dextromethorphan**: A non-analgesic morphine derivative effective for cough suppression with fewer side effects and low addiction risk at low doses but is prone to abuse at high doses.
- **Guaifenesin**: An expectorant often combined with codeine or dextromethorphan in cough products.
- **Benzonatate**: A non-opioid that suppresses cough by anesthetizing respiratory stretch receptors; adverse effects include dizziness and oral numbness, particularly if capsules are broken or chewed.