Treatment of Bronchial Asthma
Asthma

• Asthma is a chronic disease characterized by hyperresponsive airways.
• Affecting over 25 million patients in the United States, and resulting in 2 million emergency room visits and 500,000 hospitalizations annually.
• Each of these respiratory conditions may be managed with a combination of lifestyle changes and medications.
• Drugs used to treat respiratory conditions can be delivered topically to the nasal mucosa, inhaled into the lungs, or given orally or parenterally for systemic absorption.
• Local delivery methods, such as nasal sprays or inhalers, are preferred to target affected tissues while minimizing systemic side effects.
Comparison of bronchi of normal and asthmatic individuals

A  Normal

Muscles of bronchi are relaxed, allowing easy airflow.

B  Asthma

Muscles of bronchi are tight and thickened. The bronchi are inflamed and filled with mucus, which impedes airflow.
Prefered treatment of asthma

• Asthma is a chronic inflammatory disease of the airways characterized by episodes of acute bronchoconstriction causing:

  ✓ Shortness of breath.
  ✓ Cough.
  ✓ Chest tightness.
  ✓ Wheezing.
  ✓ Rapid respiration.

  ❖ If untreated, asthma may cause airway remodeling, resulting in increased severity and incidence of asthma exacerbations and/or death.
Goals of therapy

• The goals of asthma 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.
# First-line treatment agents

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<td>Moderate persistent</td>
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<tr>
<td>Severe persistent</td>
<td>Continual</td>
<td>Less than 60% of normal</td>
<td>Medium-dose ICS + LABA OR High-dose ICS + LABA</td>
<td>Short-acting $\beta_2$ agonist</td>
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ICS = inhaled corticosteroid.LABA = long-acting $\beta_2$ agonist.

**Figure 29.3**
Guidelines for the treatment of asthma. In all asthmatic patients, quick relief is provided by a SABA as needed for symptoms. *Eighty percent or more of predicted function.
**β2-Adrenergic agonists**

- Inhaled β2-adrenergic agonists directly relax airway smooth muscle. They are used for the
  - quick relief of asthma symptoms.
  - 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 antiinflammatory** effects, and they should never be used as the sole therapeutic agents for patients with persistent asthma.

- **Monotherapy with SABAs** may be appropriate for patients with intermittent asthma or exercise-induced bronchospasm.
Direct acting β2-selective agonists

- **Albuterol** [al-BYOO-ter-all]
- **Levalbuterol** [leh-val-BYOO-ter-all].

✓ These agents provide significant bronchodilation with
✓ little of the undesired effect of α or β1 stimulation.

☐ Adverse effects are minimized with inhaled delivery versus systemic administration.

➢ These agents can cause β2-mediated skeletal muscle tremors
  ➢ Tachycardia.
  ➢ Hyperglycemia.
  ➢ Hypokalemia.
  ➢ Hypomagnesemia.
Long-term control

- **Salmeterol** [sal-MEE-ter-all] and **formoterol** [for-MOE-ter-all].
- 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.
- Adverse effects of LABAs are similar to quick-relief β2 agonists.
Corticosteroids

- ICS are the drugs of choice for long-term control in patients with any degree of persistent asthma.
- Corticosteroids 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, glucocorticoids must be used regularly.
- Severe persistent asthma may require the addition of a short course of oral glucocorticoid treatment.
Actions on lung:

• ICS do not directly affect the airway smooth muscle.

• 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.
Routes of administration of ICS

a. Inhalation:
   - The development of ICS has markedly reduced the need for systemic corticosteroid treatment to achieve asthma control.
   - 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.
   - In most cases, suppression of the hypothalamic–pituitary–adrenal cortex axis will not occur during the short course of oral prednisone “burst” typically prescribed for an asthma exacerbation
   - Prednisone dose taper is unnecessary prior to discontinuation.
   - 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.
Figure 29.6
Pharmacokinetics of inhaled glucocorticoids. GI = gastrointestinal.
Adverse effects of corticosteroids:

• Oral or parenteral glucocorticoids have a variety of potentially serious side effects whereas ICS, particularly if used with a spacer, have few systemic 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.
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, not as monotherapy.
Leukotriene modifiers

• Leukotrienes (LT) B4 and the cysteinyll 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

• cysteinyll leukotrienes constrict bronchiolar smooth muscle, increase endothelial permeability, and promote mucus secretion.
Figure 29.4
Sites of action for various respiratory medications. CysLT₁ — cysteinyI leukotriene 1.
• **Zileuton** [zye-LOO-ton] is a selective and specific inhibitor of 5-lipoxygenase, preventing the formation of both LTB4 and the cysteiny1 leukotrienes.

• **Zafirlukast** [za-FIR-loo-kast] and **montelukast** [mon-te-LOO-kast] are selective antagonists of the cysteiny1 leukotriene-1 receptor, they block the effects of cysteiny1 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.
Pharmacokinetics of Leukotriene modifiers:

- All three drugs are **orally active** and highly protein bound.
- **Food** impairs the absorption of **zafirlukast**.
- The drugs are **metabolized extensively** by the liver.
- **Zileuton** and its metabolites are excreted in urine, whereas **zafirlukast**, **montelukast**, and their metabolites undergo biliary excretion.

2. Adverse effects:

- Elevations in serum hepatic enzymes have occurred with all three agents, 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 CYP1A2.
Cromolyn

- **Cromolyn** [*KRO-moe-lin*] is a prophylactic anti-inflammatory agent that inhibits mast cell degranulation and release of histamine.
- It is an alternative therapy for mild persistent asthma.
- 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.
- Adverse effects are minor and include cough, irritation, and unpleasant taste.
Cholinergic antagonists

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

• **Inhaled ipratropium** [IP-ra-TROE-pee-um], 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.

• 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.

• Adverse effects such as xerostomia and bitter taste are related to local anticholinergic effects.
Theophylline

- **Theophylline** [thee-OFF-i-lin] 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 β2 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 CYP1A2 and 3A4 substrate.
- It is subject to numerous drug interactions.
- Serum concentration monitoring should be performed when theophylline is used chronically.
Omalizumab

- *Omalizumab* [OH-ma-LIZ-oo-mab] 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.

- Adverse effects include serious anaphylactic reaction (rare), arthralgias, fever, and rash.

- Secondary malignancies have been reported
**Intermittent Asthma**
Consult with asthma specialist if Step 3 care or higher is required. Consider consultation at Step 2.

**Step 1**
Preferred: SABA PRN
Alternative: Cromolyn or Montelukast

**Step 2**
Preferred: Medium-dose ICS
Alternative: Low-dose ICS

**Step 3**
Preferred: High-dose ICS + either LABA or Montelukast

**Step 4**
Preferred: LABA or Montelukast
Oral systemic corticosteroids

**Step 5**
Preferred: High-dose ICS + either LABA or Montelukast

**Step 6**
Step up if needed (first, check adherence, inhaler technique, and environmental control)
Assess control
Step down if possible (and asthma is well controlled at least 3 months)

**Quick-Relief Medication for All Patients**
- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms.
- With viral respiratory infection SABA every 4–6 hours up to 24 hours (longer with physician consult).
- Consider short course of oral systemic corticosteroids if exacerbation is severe or patient has history of previous severe exacerbations.
- Caution: Frequent use of SABA may indicate the need to step up treatment. See text for recommendations on initiating daily long-term-control therapy.

**Key:** Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy. ICS, inhaled corticosteroid; LABA, inhaled long-acting 2-agonist; SABA, inhaled short-acting 2-agonist.

**Notes:**
- The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- If clear benefit is not observed within 4–6 weeks and patient/family medication technique and adherence are satisfactory, consider adjusting therapy or alternative diagnosis.
- Studies on children 0–4 years of age are limited. Step 2 preferred therapy is based on Evidence A. All other recommendations are based on expert opinion and extrapolation from studies in older children.

**Figure 23-7** Stepwise approach for managing asthma in children 0 to 4 years of age. Reprinted from National Institutes of Health. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Bethesda, MD: National Heart, Lung, and Blood Institute.
Inhaler Technique

- Appropriate inhaler technique differs between metered-dose inhalers (MDIs) and dry powder inhalers (DPIs), so assessing technique regularly is critical to the success of therapy.

☐ A. Metered-dose inhalers and dry powder inhalers

- MDIs have propellants that eject the active medication from the canister.
- Patients should be instructed to inhale slowly and deeply just before and throughout actuation of the inhaler to avoid impaction of the medication onto the laryngeal mucosa, rather than the bronchial smooth muscle.
- A large fraction (typically 80% to 90%) of inhaled glucocorticoids is either deposited in the mouth and pharynx or swallowed.
- The remaining 10% to 20% of a dose of inhaled glucocorticoids that is not swallowed is deposited in the airway.
- If ICS are inappropriately inhaled, systemic absorption and adverse effects are much more likely.
- DPIs require a different inhaler technique. Patients should be instructed to inhale quickly and deeply to optimize drug delivery to the lungs.
B. Spacers

• A spacer is a large-volume chamber attached to an MDI.

• The chamber reduces the velocity of the aerosol before entering the mouth, allowing large drug particles to be deposited in the device.

• The smaller, higher-velocity drug particles are less likely to be deposited in the mouth and more likely to reach the target airway tissue.

• Spacers improve delivery of inhaled glucocorticoids and are advised for virtually all patients.

• Patients should be advised to wash and/or rinse spacers to reduce the risk of bacterial or fungal growth that may induce an asthma attack.
Large particles of aerosol are deposited in the chamber before the patient inhaled. Inhaled aerosol is enriched in small particles that more readily travel to the small airways.

Figure 29.7
Effect of a spacer on the delivery of an inhaled aerosol.
Drugs Used to Treat Chronic Obstructive Pulmonary Disease (COPD)
COPD

- COPD is a chronic, irreversible obstruction of airflow that is usually progressive.

- Symptoms include cough, excess mucus production, chest tightness, breathlessness, difficulty sleeping, and fatigue.

- Although symptoms are similar to asthma, the characteristic irreversible airflow obstruction of COPD is one of the most significant differences between the diseases.

- Smoking is the greatest risk factor for COPD and is directly linked to the progressive decline of lung function as demonstrated by forced expiratory volume in one second (FEV1).

- Smoking cessation and/or continued avoidance should be recommended regardless of stage/ severity of COPD and age of patient.
• Drug therapy for COPD is aimed at relief of symptoms and prevention of disease progression.

Unfortunately, with currently available care, many patients still experience declining lung function over time.
A. Bronchodilators

- **Inhaled bronchodilators**, including the $\beta_2$-adrenergic agonists and anticholinergic agents (ipratropium and tiotropium [tye-oh-TROEpee- um]), are the foundation of therapy for COPD.

  - These drugs increase airflow, alleviate symptoms, and decrease exacerbation rates.
  
  - The long-acting agents, LABAs and tiotropium, are preferred as first-line treatment of COPD for all patients except those who are at low risk with less symptoms.

✓ Combination of both an anticholinergic and a $\beta_2$ agonist may be helpful in patients who have inadequate response to a single inhaled bronchodilator.
B. Corticosteroids

• The addition of an ICS to a long-acting bronchodilator may improve symptoms, lung function and quality of life in COPD patients with FEV1 of less than 60% predicted.

• However, the use of an ICS is associated with an increased risk of pneumonia, and therefore, use should be restricted to these patients.

✓ Although often used for acute exacerbations, oral corticosteroids are not recommended for long-term treatment.
C. Other agents

- **Roflumilast** \( [\text{roe-FLUE-mi-last}] \) is an oral phosphodiesterase-4 inhibitor used to reduce exacerbations in patients with severe chronic bronchitis.

- Although its activity is not well defined in COPD, it is theorized to reduce inflammation by increasing levels of intracellular cAMP in lung cells.

- *Roflumilast is not a bronchodilator and is* not indicated for the relief of acute bronchospasm.

- Its use is limited by common side effects including nausea, vomiting, diarrhea, and headache.

- As in asthma, the use of **theophylline has largely** been replaced by the more effective and tolerable long-acting bronchodilators.
<table>
<thead>
<tr>
<th>PATIENT GROUP</th>
<th>RECOMMENDED FIRST CHOICE</th>
<th>ALTERNATIVE CHOICE</th>
</tr>
</thead>
</table>
| A  
Low risk  
Less symptoms | Short-acting anticholinergic when necessary or Short-acting β₂ agonist when necessary | Long-acting anticholinergic or Long-acting β₂ agonist or Short-acting β₂ agonist and short-acting anticholinergic |
| B  
Low risk  
More symptoms | Long-acting anticholinergic or Long-acting β₂ agonist | Long-acting anticholinergic and long-acting β₂ agonist |
| C  
High risk  
Less symptoms | Inhaled corticosteroid + long-acting β₂ agonist or Long-acting anticholinergic | Long-acting anticholinergic and long-acting β₂ agonist or Long-acting anticholinergic and PDE-4 inhibitor or Long-acting β₂ agonist and PDE-4 inhibitor |
| D  
High risk  
More symptoms | ICS + long-acting β₂ agonist and/or Long-acting anticholinergic | ICS + long-acting β₂ agonist and long-acting anticholinergic or ICS + long-acting β₂ agonist and PDE-4 inhibitor or Long-acting anticholinergic and long-acting β₂ agonist or Long-acting anticholinergic and PDE-4 inhibitor |

COPD = chronic obstructive pulmonary disease, ICS = inhaled corticosteroid, PDE-4 = phosphodiesterase-4
Note: Risk denotes risk of COPD exacerbations.
DRUGS USED TO TREAT ALLERGIC RHINITIS

- **Rhinitis** is an inflammation of the mucous membranes of the nose and is characterized by sneezing, itchy nose/eyes, watery rhinorrhea, nasal congestion, and sometimes, a nonproductive cough.

- An **attack** may be precipitated by **inhalation of an allergen**

- The foreign material interacts with mast cells coated with IgE generated in response to a previous allergen exposure.

- The mast cells release mediators, such as histamine, leukotrienes, and chemotactic factors that promote bronchiolar spasm and mucosal thickening from edema and cellular infiltration.

- **Antihistamines** and/or **intranasal corticosteroids** are preferred therapies for allergic rhinitis.
A. Antihistamines (H1-receptor blockers)

- Antihistamines are useful for the management of symptoms of allergic rhinitis caused by histamine release (sneezing, watery rhinorrhea, itchy eyes/nose).
- They are more effective for prevention of symptoms, rather than treatment once symptoms have begun.
- **Ophthalmic and nasal antihistamine** delivery devices are available for more targeted tissue delivery.

- **First-generation antihistamines**, such as *diphenhydramine* and *chlorpheniramine*, are usually *not preferred* due to adverse effects, such as sedation, performance impairment, and other anticholinergic effects.
- **The second-generation** antihistamines (for example, *fexofenadine*, *loratadine*, *desloratadine*, *cetirizine*, and *intranasal azelastine*) are generally better tolerated.
- Combinations of antihistamines with decongestants are effective when congestion is a feature of rhinitis.
B. Corticosteroids

- **Intranasal corticosteroids**, such as beclomethasone, budesonide, fluticasone, ciclesonide, mometasone, and triamcinolone, are the most effective medications for treatment of allergic rhinitis.
- They improve sneezing, itching, rhinorrhea, and nasal congestion.
- Systemic absorption is minimal.
- **Side effects** of intranasal corticosteroid treatment are localized: these include nasal irritation, nosebleed, sore throat, and, rarely, candidiasis.

✓ To avoid systemic absorption, patients should be instructed **not to inhale deeply** while administering these drugs because the target tissue is the nose, not the lungs or the throat.

- For patients with chronic rhinitis, improvement may not be seen until 1 to 2 weeks after starting therapy.
C. α-Adrenergic agonists

- Short-acting α-adrenergic agonists ("nasal decongestants"), such as phenylephrine, constrict dilated arterioles in the nasal mucosa and reduce airway resistance.
- Longer-acting oxymetazoline [OX-i-me-TAZoh-leen] is also available.
- When administered as an aerosol, these drugs have a rapid onset of action and show few systemic effects. Unfortunately, the α-adrenergic agonist intranasal formulations should be used no longer than 3 days due to the risk of rebound nasal congestion (rhinitis medicamentosa).
- For this reason, the α-adrenergic agents have no place in the long-term treatment of allergic rhinitis.
• Administration of oral α-adrenergic agonist formulations results in a longer duration of action but also increased systemic effects.

• As with intranasal formulations, regular use of oral α-adrenergic agonists (phenylephrine and pseudoephedrine) alone or in combination with antihistamines is not recommended.
D. Other agents

- **Intranasal cromolyn** may be useful in allergic rhinitis, particularly when administered before contact with an allergen.
- To optimize the therapeutic effect, dosing should begin at least 1 to 2 weeks prior to allergen exposure.
- A nonprescription (over-the-counter) nasal formulation of cromolyn is available.

- Although potentially inferior to other treatments, some **LT antagonists** are effective for allergic rhinitis as monotherapy or in combination with other agents.
- They may be a reasonable option in patients who also have asthma.
- An intranasal formulation of *ipratropium* is available to treat rhinorrhea associated with allergic rhinitis or the common cold. *It does not relieve sneezing or nasal congestion.*
DRUGS USED TO TREAT COUGH

• Coughing is an important defense mechanism of the respiratory system to irritants and is a common reason for patients to seek medical care.

• A troublesome cough may represent several etiologies, such as the common cold, sinusitis, and/or an underlying chronic respiratory disease.

• In some cases, cough may be an effective defense reflex against an underlying bacterial infection and should not be suppressed.

✓ Before treating cough, identification of its cause is important to ensure that antitussive treatment is appropriate.

  o The priority should always be to treat the underlying cause of cough when possible.
A. Opioids

- **Codeine** [KOE-deen], an **opioid**, *decreases the sensitivity of cough centers* in the central nervous system to peripheral stimuli and decreases mucosal secretion.
  - These therapeutic effects occur at doses lower than those required for analgesia.
  - Common side effects, such as constipation, dysphoria, and fatigue, still occur in addition, it has addictive potential.

- **Dextromethorphan** [dextro- meth-OR-fan] is a synthetic derivative of *morphine that has no* analgesic effects in antitussive doses.
  - In low doses, it *has a low addictive profile.*
  - However, it is a potential drug of abuse, since it may cause dysphoria at high doses.
• **Dextromethorphan** has a significantly safer side effect profile than **codeine** and is equally effective for cough suppression.

• **Guaifenesin** [gwy-FEN-e-sin], an expectorant, is available as a single-ingredient formulation and is also a common ingredient in combination products with **codeine** or **dextromethorphan**
B. Benzonatate

• Unlike the opioids, *benzonatate* [ben-ZOE-na-tate] *suppresses the* cough reflex through peripheral action.

• It anesthetizes the stretch receptors located in the respiratory passages, lungs, and pleura.

• Side effects include dizziness, numbness of the tongue, mouth, and throat.

➢ These localized side effects may be particularly problematic if the capsules are broken or chewed and the medication comes in direct contact with the oral mucosa.