

TREATMENT OF ASTHMA

Chronic Asthma

Treatment goals are to:

- (a) Prevent chronic and troublesome symptoms,
- (b) Require infrequent use (2 or fewer days/week) of SAB for quick relief of symptoms,
- (c) Prevent exacerbations of asthma and the need for emergency department visits or hospitalizations,
- (d) Provide optimal pharmacotherapy with minimal or no adverse effects.

Pharmacologic Therapy

B2-Adrenergic Agonists

Mechanism of action

B2-Agonists relax airway smooth muscle by directly stimulating β_2 -adrenergic receptors in the airway. They also increase mucociliary clearance and stabilize mast cell membranes. The early-phase response to antigen in an asthma exacerbation is blocked by pretreatment with inhaled SABAs. Short-acting β_2 -agonists have significantly better bronchodilating activity in acute asthma than theophylline or anticholinergic agents.

Adverse effects

Adverse effects of β_2 -agonists include tachycardia, tremor, and hypokalemia, which are usually not troublesome with inhaled dosage forms. Oral β_2 -agonists have increased adverse effects and are not used in the treatment of asthma. Inhaled β_2 -agonists are classified as either short- or **longacting based on duration of action.**

Short-Acting Inhaled β_2 -Agonists

Value: Are the drugs of choice for treating acute asthma and symptoms of chronic asthma as well as preventing exercise-induced bronchospasm. Inhaled SABAs have an onset of action of less than 5 minutes and a duration of action of 4 to 6 hours.

Scheduled chronic daily dosing of SABAs is not recommended for two reasons. **First**, the need to use an inhaled SABA is one key indicator of uncontrolled asthma. Therefore, patients are educated to record SABA use. **Second**, scheduled SABA use decreases the duration of bronchodilation provided by the SABA.

Long-Acting Inhaled β 2-Agonists

Indication, onset, duration

Salmeterol and formoterol are LABAs that provide up to 12 hours of bronchodilation after a single dose. Because of the long duration of bronchodilation, these agents are useful for patients experiencing nocturnal symptoms. Salmeterol is a partial agonist with an onset of action of approximately 30 minutes. Formoterol is a full agonist that has an onset of action similar to that of albuterol, but it is not currently approved for the treatment of acute bronchospasm.

Value

LABAs are indicated for chronic treatment of asthma as add-on therapy for patients not controlled on low to medium doses of ICS. Adding an LABA is at **least as effective** in improving symptoms and decreasing asthma exacerbations as doubling the dose of an ICS or adding an LTRA to ICS. Adding an LABA to ICS therapy also **reduces the amount of ICS** necessary for asthma control.

Add on only reason

Although both formoterol and salmeterol are effective as add-on therapy for moderate persistent asthma, neither agent should be used as monotherapy for chronic asthma. There may be an increased risk of severe asthma exacerbations and asthma-related deaths when LABAs are used alone. The labeling for all drugs containing LABAs includes a black box warning against their use without an ICS.

Salmeterol and formoterol are available in fixed-ratio combination products containing fluticasone, budesonide, or mometasone. Combination products may increase adherence because of the need for fewer inhalers and inhalations.

Corticosteroids

Corticosteroids are the most potent anti-inflammatory agents available for the treatment of asthma and are available in inhaled, oral, and injectable dosage forms. Corticosteroids also improve the response to β 2-agonists.

Inhaled Corticosteroids

Value

ICS are the preferred therapy for all forms of persistent asthma in all age groups. ICS are more effective than LTRA and theophylline in improving lung function and preventing emergency department visits and hospitalizations due to asthma

exacerbations. The **primary advantage** of using ICS compared with systemic corticosteroids is the targeted drug delivery to the lungs, which decreases the risk of systemic adverse effects. Product selection is based on preference for dosage form, delivery device, and cost.

Frequency, smoking effect, Onset

The ICS are more effective when given twice daily rather than once daily. Cigarette smoking decreases the response to ICS, and smokers require higher doses of ICS than nonsmokers. Although some beneficial effect is seen within 12 hours of administration of an ICS, 2 weeks of therapy is necessary to see significant clinical effects. Longer treatment may be necessary to realize the full effects on airway inflammation.

Side effects and management, drug interaction, response rate

For most delivery devices, the majority of the drug is deposited in the mouth and throat and swallowed. Local adverse effects of ICS include oral candidiasis, cough, and **dysphonia**. The incidence of local adverse effects can be reduced by using a VHC and by having the patient rinse the mouth with water and expectorate after using the ICS. Decreasing the dose reduces the incidence of hoarseness.

Systemic absorption occurs via the pulmonary and oral routes. Systemic adverse effects are dose dependent and rare with low to medium doses. However, high-dose ICS have been associated with adrenal suppression, decreased bone mineral density, skin thinning, cataracts, and easy bruising. Nonprogressive growth suppression in children occurs primarily in the first month of treatment and is reported with low- and medium-dose ICS. A significant drug interaction causing Cushing's syndrome and adrenal insufficiency occurs when potent inhibitors of CYP3A4 (ritonavir, itraconazole, ketoconazole) are administered with high doses of ICS. Considerable variability in response to ICS exists, with up to 40% of patients not responding to ICS.

Systemic Corticosteroids

Indication, onset, duration, route

Prednisone, prednisolone, and methylprednisolone are systemic corticosteroids used in asthma treatment. These medications are the cornerstone of treatment for acute asthma not responding to a SABA. The onset of action for systemic corticosteroids is 4 to 12 hours. For this reason, systemic corticosteroids are started early in the course of acute exacerbations. The oral route is preferred in acute asthma; there is no evidence that IV corticosteroid administration is more effective. Therapy with systemic corticosteroids

is continued until the PEF is 70% or more of the personal best measurement and asthma symptoms are resolved.

The duration of therapy usually ranges from 3 to 10 days. Tapering the corticosteroid dose in patients receiving short bursts (up to 10 days) is usually not necessary because any adrenal suppression is transient and rapidly reversible. Because of serious potential adverse effects, systemic corticosteroids are avoided as long-term controller medication for asthma, if possible. Systemic corticosteroids are only used in patients who have failed other therapies, including immunomodulators. If systemic therapy is necessary, once daily or every-other-day therapy is used with repeated attempts to decrease the dose or discontinue the drug.

Anticholinergics

Mechanism of action, onset, duration, indication

Two anticholinergic medications are available: ipratropium bromide and tiotropium bromide. Anticholinergic agents act by inhibiting the effects of acetylcholine on muscarinic receptors in the airways and protecting against cholinergic mediated bronchoconstriction. The bronchodilating effects are not as effective as SABAs in asthma. Ipratropium bromide (Atrovent) is available as an MDI and solution for nebulization. Its onset of action is approximately 30 minutes, and the duration of action is 4 to 8 hours. The addition of ipratropium bromide to SABAs during a moderate to severe asthma exacerbation improves pulmonary function and decreases hospitalization rates in both adult and pediatric patients. Combining an SABA with ipratropium is only indicated in the emergency department setting. There is no evidence to support continued use of ipratropium during hospitalization or for chronic asthma treatment.

Leukotriene Receptor Antagonists

The LTRAs are anti-inflammatory medications that either inhibit 5-lipoxygenase (zileuton) or competitively antagonize the effects of leukotriene D₄ (montelukast and zafirlukast).

These agents improve FEV₁ and decrease asthma symptoms, SABA use, and asthma exacerbations. Although these agents offer the convenience of oral administration, they are significantly less effective than low ICS doses. Combining an LTRA with an ICS or LABA is not as effective as an ICS plus an LABA. LTRA are beneficial for asthma patients with allergic rhinitis or aspirin sensitivity. Montelukast (Singulair) is generally

well tolerated with minimal need for monitoring and few drug interactions. Zileuton (Zyflo) and zafirlukast (Accolate) are not commonly used because of the risk of hepatotoxicity. Both zileuton and zafirlukast require liver function monitoring at baseline and every 3 months for the first year of use and then periodically thereafter. Zileuton and zafirlukast are metabolized through the CYP 2C9 hepatic pathway and have significant drug interactions. All three agents have reports of neuropsychiatric events, such as sleep disorders, aggressive behavior, and suicidal thoughts that need to be monitored.

Methylxanthines

Theophylline has anti-inflammatory properties and causes bronchodilation by inhibiting phosphodiesterase and antagonizing adenosine. Its use is limited because of inferior efficacy as a long-term controller medication compared with ICS, a narrow therapeutic index with potentially life threatening toxicity, and multiple clinically important drug interactions.

Classification of Asthma Severity in Children(5yrs) to Adults [Symptom Based]

| Components of Severity | Intermittent | Persistent | | |
|--|---------------|----------------------------|--------------------------|-----------------------|
| | | Mild | Moderate | Severe |
| 1.Symptoms | =<2 days/week | >2 days/week but not daily | Daily | Throughout the day |
| 2.Nighttime awakenings | =<2x/month | 3-4x/month | >1x/week but not nightly | Often 7x/week |
| *3.Using Short-acting Beta2-agonists for symptom control | =<2 days/week | >2 days/week But not daily | Daily | Several times per day |
| 4.Interference with normal activity | None | Minor Limitation | Some Limitation | Extremely Limited |

