Therapy of Bronchial Asthma

Yacoub Irshaid, MD, PhD, ABCP
Department of Pharmacology, Faculty of Medicine

Definition of Bronchial Asthma

The Global Initiative for Asthma (GINA) provides a practical asthma definition:

- **"Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of wheezing, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation."**

Definition of Bronchial Asthma

- **Airflow limitation may later become persistent.**
- **Asthma is usually associated with airway hyper-responsiveness and airway inflammation, but these are not necessary or sufficient to make the diagnosis.**

Definition of Bronchial Asthma

- **Airway obstruction in asthma may become irreversible, and worsen over time owing to airway remodeling.**
- **The most common cause of death from asthma is inadequate assessment of the severity of airway obstruction, and thus, inadequate therapy.**

Remodeling of the Airways

- Remodeling presents as extracellular matrix fibrosis, an increase in smooth muscle and mucous gland mass, and angiogenesis.
- Tryptase (a smooth muscle mitogen) plays a role in airway remodeling.
- Airway remodeling represents an irreversible process.

Factors Contributing To Asthma Severity

Respiratory infection:

- **Respiratory syncytial virus (RSV), rhinovirus, influenza, parainfluenza, *Mycoplasma pneumoniae, Chlamydia*.**

Allergens:

- **Airborne pollens (grass, trees, weeds), house dust mites, animal dander, rodents, cockroaches, fungal spores.**

Exercise:

- **Particularly in cold, dry climate.**

Factors Contributing To Asthma Severity

Environment:

- **Cold air, fog, sulfur dioxide, nitrogen dioxide, tobacco smoke (including 2nd and 3rd hand), wood smoke, scented home products, cleaners, and perfumes…**

Emotions:

- **Anxiety, stress, laughter.**

Factors Contributing To Asthma Severity

Occupational stimuli:

- **Bakers (flour dust); farmers (hay mold); spice workers; occupational cleaners, printers, (arabic gum); chemical workers; plastics, rubber, and wood workers…**

Therapy of Bronchial Asthma

Long-term goals of therapy:

1. **Adequate symptom control and maintaining normal activity**
2. **Minimize asthma related death**
3. **Minimize exacerbations**
4. **Minimize persistent airflow limitations**
5. **Minimize drug adverse effects**

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Non-pharmacological Intervention:

1. Cessation of smoking and environmental tobacco exposure
2. Engage in physical exercise (**be careful to prevent exercise-induced bronchoconstriction)**
3. Avoidance of exposure to allergens or irritants both occupational and domestic
4. Avoidance of drugs that make asthma worse: **NSAIDs and aspirin, oral or ophthalmic β-blockers, acetaminophen (paracetamol)**

Therapy of Bronchial Asthma

5. Healthy diet high rich in fruits and vegetables (for its general health benefits)
6. Weight reduction with twice weekly aerobic and strength exercises
7. Breathing exercises
8. Dealing with emotional stress

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Asthma Medications:

1. **Inhaled corticosteroids (ICS):** **Beclometasone dipropionate, Budesonide, Ciclesonide, Fluticasone propionate, Monetasone furoate.**
2. **Short-acting inhaled β_2-agonists (SABA):** **Albuterol (salbutamol), Levalbuterol, Terbutaline.**

Therapy of Bronchial Asthma

3. **Long-acting inhaled β_2-agonists (LABA):**

A. **Formoterol and salmeterol, provide long-lasting bronchodilation (≥ 12 hours).**

B. **ULTRA-LABA (indacaterol, vilanterol, and olodaterol), have a 24-hour duration of effect.**

Therapy of Bronchial Asthma

4. **Muscarinic antagonists:** **Duration of action of Ipratropium bromide is 4-8 hours, while that of Tiotropium bromide (LAMA) is 24 hours.**
5. **Leukotriene receptor antagonists (LTRA): (zafirlukast and montelukast).**

Therapy of Bronchial Asthma

6. **Biologic therapy:**

A. **Anti-immunoglobulin E (Anti-IgE) (omalizumab)**

B. **Anti-interleukin-5/5R (mepolizumab, rezlizumab, benralizumab)**

C. **Anti-interleukin-4Rα (dupilumab)**

D. **Anti-thymic stromal lymphopoietin (anti-TSLP) (tezepelumab)**

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Acute Severe Asthma in the Emergency Department:

1. **It is important that therapy NOT be delayed.**
2. **Lung function testing (PEF or FEV1) should be monitored before treatment, and at 1-hour after start of treatment and then periodically until response is achieved or no further improvement is evident.**

Therapy of Bronchial Asthma

3. **Oxygen saturation should be monitored closely, and oxygen therapy implemented when needed.**
4. **Arterial blood gases are reserved for patients who are poorly responsive to initial treatment or deteriorating.**

Therapy of Bronchial Asthma

5. **The primary therapy of acute exacerbations is pharmacologic, which includes:**

a. β_2-agonists

b. corticosteroids

c. inhaled ipratropium (when response is inadequate)

a. and O_2.

- **Treatments are typically administered concurrently to facilitate rapid improvement.**

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Also pay attention to the following:

1. **Correction of dehydration.**
2. **Do NOT use sedatives because anxiety may be a sign of hypoxemia, which could be worsened by central nervous system depressants.**
3. **Antibiotics are NOT indicated because viral respiratory tract infections are the primary cause of asthma exacerbations.**

- **Antibiotics should be reserved for patients who have pneumonia.**

4. **Mycoplasma and Chlamydia are infrequent causes of severe asthma exacerbations but should be considered in patients with high O_2 requirements.**

Therapy of Bronchial Asthma

Pharmacological Therapy:

1. **Maintenance treatment: prescribed for use every day or on a regular basis even when the patient does not have asthma symptoms – ICS, ICS-LABA, ICS-LABA-LAMA, as well as LTRA and biologic therapy.**
2. **Controller therapy: targeting both symptom control and future risk – ICS-containing relievers.**

Therapy of Bronchial Asthma

3. **Relievers:** asthma inhaler taken as needed for quick relief of symptoms (rescue inhalers) – SABAs, ICS-SABA
4. **Anti-inflammatory reliever (AIR):** contain low dose ICS and SABAs
5. **Maintenance and reliever therapy (MART):** ICS-formoterol every day and the same medication to relieve asthma symptoms.

Therapy of Bronchial Asthma

Initial Treatment of asthma ≥ 6 years of age:

- **ICS-containing treatment at time of diagnosis + reliever inhaler for quick relief of symptoms (budesonide-formoterol, beclomethasone-formoterol, ICS-salbutamol).**

Therapy of Bronchial Asthma

Reasons of starting ICS-containing medications:

1. **Reduction of risk of severe exacerbations and ER visits or hospitalization.**
2. **Early initiation of low-dose ICS leads to greater improvement in lung function than delayed use. If started late (after 2-4 years), higher ICS doses are needed and lower lung functions are achieved.**

Therapy of Bronchial Asthma

3. **Patients not taking ICS who experience severe exacerbations have a greater long-term decline in lung function than those who are taking ICS.**
4. **For patients with occupational asthma, early removal from exposure to sensitizing agent and early ICS-containing treatment increases the probability of resolution of symptoms and improvement of lung function and airway hyper-responsiveness.**

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Initial asthma treatment for adults and adolescents:

1. **Infrequent asthma symptoms (< 2 /month) with no exacerbations: As needed low dose ICS-Formoterol.**
2. **Asthma symptoms or need for reliever ≥ 2/month: As needed low dose ICS-Formoterol.**
3. **Troublesome asthma symptoms for days (4-5 days/ week) or waking due to asthma once a week or more: Low dose ICS-Formoterol maintenance and reliever therapy (MART).**

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4. **When initial asthma presentation is with severely uncontrolled asthma, or with an acute exacerbations: Medium dose ICS-Formoterol maintenance and reliever therapy (MART).**

- **A short course of oral corticosteroids may be needed.**

- **For all alternative treatment exist.**

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Initial asthma treatment for children aged 6-11 years:

1. **Infrequent asthma symptoms (< 2 /month) with no exacerbations: Low dose ICS taken whenever SABA is taken in combination or separate inhalers.**
2. **Asthma symptoms or need for reliever ≥ 2/month: Low dose ICS plus as needed SABA.**

Therapy of Bronchial Asthma

3. **Troublesome asthma symptoms for days (4-5 days/ week) or waking due to asthma once a week or more: Low dose ICS-LABA plus as needed SABA, Or Medium dose ICS plus as needed SABA, Or Very low dose ICS-Formoterol maintenance and reliever.**

Therapy of Bronchial Asthma

4. **Initial asthma presentation with severely uncontrolled asthma, or with an acute exacerbations: Start regular maintenance treatment with medium-dose ICS-LABA plus as needed SABA or low dose ICS-Formoterol maintenance and reliever (MART).**

- **A short course of oral corticosteroids may be needed.**

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Adjusting ongoing asthma treatment in ≥ 6 years of age:

- **Treatment of modifiable risk factors**
- **Adjustment of asthma medications up and down in a step-wise approach to achieve good symptom control and minimize future risk of exacerbations, persistent airflow limitations and medication adverse effects.**

Therapy of Bronchial Asthma

- **Once good asthma control has been maintained for 2-3 months, treatment may be stepped down in order to find the patient's minimum effective treatment.**
- **If the patient has persistent uncontrolled symptoms or exacerbations despite 2-3 months of ICS-containing treatment, correct the following problems before considering any step up in treatment:**

Therapy of Bronchial Asthma

1. **Incorrect inhaler technique.**
2. **Poor adherence.**
3. **Persistent exposure to allergens, tobacco smoke, air pollution, high risk medications.**
4. **Co-morbidities that may contribute to respiratory symptoms and poor quality of life.**
5. **Incorrect diagnosis.**

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Important points:

- **Over use of SABA (3 or more 200-dose canisters/year) increases the risk of asthma exacerbations.**
- **Rinsing of the mouth is not generally needed after as-needed doses of low dose ICS-Formoterol as there is no increase in the risk of oral thrush.**

Therapy of Bronchial Asthma

- **Budesonide-formoterol for symptom relief and before exercise → reduced exercise-produced bronchoconstriction to a similar extent as regular daily low-dose ICS with SABA (small study).**
- **GINA no longer recommends SABA-only treatment of asthma in patients ≥ 6 years of age. Although it is good for quick relief of symptoms, these patients are at increased of asthma related death.**

Therapy of Bronchial Asthma

- **Inhaled short-acting anticholionergic agents (ipratropium) are potential alternatives to SABA for routine relief of asthma symptoms but they have slower onset of action.**
- **Use of long-acting muscarinic antagonists (LAMA) in asthma without concomitant ICS is associated with an increased risk of severe exacerbations.**

Therapy of Bronchial Asthma

- **The rapid-onset LABA, Formoterol, is as effective as SABA as a reliever medication in adults and children and reduces the risk of severe exacerbations when used with ICS.**
- **Nedocromyl sodium and sodium chromoglycate have been discontinued globally, despite their favourable safety profile, because of low efficacy.**
- **Use of theophylline is associated with low efficacy and severe adverse reactions and drug interactions.**

Therapy of Bronchial Asthma

- **Add-on long-acting antimuscarinic antagonist (LAMA, tiotropium) can be prescribed as a separate inhaler in patients aged ≥ 6 years of age or in a combination triple inhaler for patients aged ≥ 18 years of age if asthma is not well controlled with medium- or high-dose ICS-LABA.**

Therapy of Bronchial Asthma

- **Add-on azithromycin (3 times a week), after specialist referral, for adult patients with persistent symptomatic asthma despite high dose ICS-LABA.**
- **Before that sputum should be checked for atypical mycobacteria.**
- **Duration of treatment 6 months.**
- **Adverse effects: long QTc interval, diarrhea, development of bacterial resistance.**

Therapy of Bronchial Asthma

Add-on biologic therapy options recommended by GINA for patients with severe uncontrolled asthma despite optimized maximal therapy:

1. **Add-on anti-immunoglobulin E (Anti-IgE) treatment omalizumab for patients aged ≥ 6 years of age with severe allergic asthma.**

Therapy of Bronchial Asthma

2. **Add-on anti-interleukin-5/5R treatment:**

- **Subcutaneous mepolizumab patients ≥ 6 years of age.**
- **Intravenous rezlizumab patients aged ≥ 18 years of age.**
- **Subcutaneous benralizumab patients ≥ 12 years of age with severe eosinophilic asthma.**

Therapy of Bronchial Asthma

3. **Add-on anti-interleukin-4Rα treatment (subcutaneous dupilumab) for patients aged ≥ 6 years of age with severe eosinophilic asthma or for adults and adolescents requiring treatment with maintenance oral corticosteroids.**
4. **Add-on anti-thymic stromal lymphopoietin (anti-TSLP) treatment (subcutaneous tezepelumab) for patients aged ≥ 12 years of age with severe asthma.**

Therapy of Bronchial Asthma

Factors contributing to poor adherence to therapy:

1. **Medication/regimen factors: difficulties using inhaler device (arthritis), multiple times per day, multiple different inhalers.**
2. **Unintentional poor adherence: misunderstanding of instructions, forgetfulness, absence of a daily routine, and cost.**

Therapy of Bronchial Asthma

3. **Intentional poor adherence: perception that treatment is not necessary, denial or anger about asthma or treatment, inappropriate expectations, concern about adverse effects, dissatisfaction with health care providers, stigmatization, cultural issues, cost.**

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- **Understanding of aerosol drug delivery is essential to optimal asthma therapy.**
- **You should be aware of this and teach patients how to use inhalers.**

Therapy of Bronchial Asthma

β_2-Agonists:

- **Inhaled β_2-agonists are effective bronchodilators.**
- **In more severely obstructed patients, they can be used by nebulization.**
- **Intravenous β_2-agonists have NO role in the management of patients with severe exacerbations.**
- **The β_2-agonists relax airway smooth muscle regardless of the mechanism of constriction.**

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- **Long-term administration of β_2-agonists does NOT reduce bronchial hyperresponsiveness (BHR).**

Therapy of Bronchial Asthma

Inhaled Corticosteroids:

- **The ICSs have high anti-inflammatory potency, approximately 1,000-fold greater than endogenous cortisol.**
- **Aerosol delivery of the preparations is remarkably variable, ranging from 10-60%.**
- **Different devices for the same chemical entity may result in two-fold differences in delivery, so you should be careful when changing devices.**

Therapy of Bronchial Asthma

- **Some of the drug will be deposited in oral mucosa and get absorbed through GIT.**
- **Therefore, mouth rinsing and spitting will reduce their oral bioavailability.**
- **Low- to medium-dose ICSs reduce BHR, improve lung function, and reduce severe exacerbations leading to reduced ED visits and hospitalizations.**
- **They do NOT reduce airway remodeling and loss of lung function seen in patients with persistent asthma.**

Some Potential Adverse Effects of inhaled corticosteroids

1. Hoarseness, dysphonia (myopathy of vocal cords)
2. Oral thrush (candida fungal infection).
3. Growth retardation
4. Myopathy.
5. Osteoporosis, fractures and aseptic necrosis of the hip.
6. Posterior sub-capsular cataract and glaucoma.
7. Adrenal axis suppression.
8. Immuno-suppression and impaired wound healing.
9. Easy bruising and skin striae.
10. Hyperglycemia and hypokalemia.
11. Hypertension.
12. Psychiatric disturbances.

Anticholinergics

- **Unlike β_2-agonists, they are NOT functional antagonists; they only reverse cholinergic-mediated bronchoconstriction (bronchial tone is maintained by parasympathetic nerves).**
- **A number of the triggers and mediators of asthma produce bronchoconstriction in part through vagal reflex mechanisms (histamine, prostaglandins, sulfur dioxide, exercise, and allergens).**

Anticholinergics

- Anticholinergics have NO effect on BHR.
- They also do NOT significantly affect mucociliary clearance or respiratory secretions.
- They have little absorption across respiratory mucosa and do NOT penetrate the blood–brain barrier, thus they have negligible systemic effects with a prolonged local effect.

Anticholinergics

- **Ipratropium bromide is only indicated as adjunctive therapy in acute severe asthma NOT completely responsive to β_2-agonists alone, which may produce further improvement in lung function.**
- **It is also important in COPD to reverse vagus-mediated bronchoconstriction.**

Leukotriene Receptor Antagonists (LTRA)

- **Two LTRAs (zafirlukast and montelukast) are available.**
- **They reduce allergen-, exercise-, cold air-, hyperventilation-, irritant-, and aspirin-induced asthma.**
- **These drugs improve pulmonary function tests (FEV1 and PEF), decrease nocturnal awakenings, decrease β_2-agonist use, and improve asthma symptoms.**

Leukotriene Receptor Antagonists (LTRA)

- **They are effective orally, and can be used once or twice a day.**
- **They may be specially useful in patients with aspirin-sensitive asthma.**

Leukotriene Receptor Antagonists (LTRA)

Adverse effects:

- **A rare idiosyncratic syndrome (eosinophilia, heart failure, and eosinophilic vasculitis) has been reported with zafirlukast and montelukast.**
- **Neuropsychiatric events (suicidal thoughts).**
- **Fatal hepatic failure (zafirlukast).**