

BY DR MOHAMED ABDELRAHMAN

Definition

Asthma is defined by the Global Initiative for Asthma (GINA) as a heterogeneous disease usually characterized by chronic airway inflammation. It is defined by a history of respiratory symptoms such as wheezing, shortness of breath, chest tightness, and cough

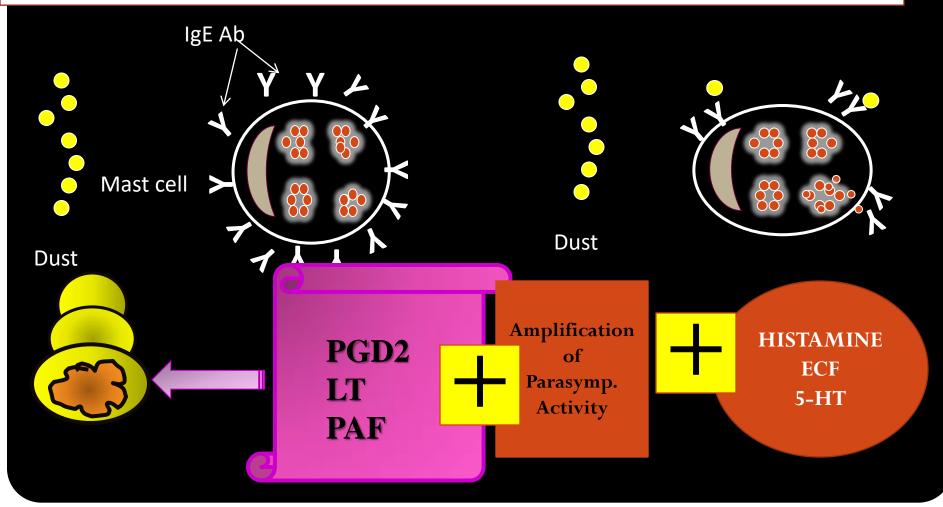
Pathophysiology

- There is a variable degree of airflow obstruction. In acute inflammation, inhaled allergens in allergic patients cause activation of cells bearing immunoglobulin E (IgE) antibodies.
- After rapid activation, airway mast cells and macrophages release pro-inflammatory mediators such as histamine and eicosanoids that induce contraction of airway smooth muscle, mucus secretion, edema, and exudation of plasma in the airways.
- Mast cell degranulation results in release of mediators such as histamine. Histamine can induce smooth muscle constriction and bronchospasm and may contribute to mucosal edema and mucus secretion.

- Alveolar macrophages release inflammatory mediators. Neutrophils also release mediators that contribute to airway inflammation.
 Producing bronchospasm, mucus secretion, and airway edema.
- The exudative inflammatory process and sloughing of epithelial cells into the airway lumen impair mucociliary transport.

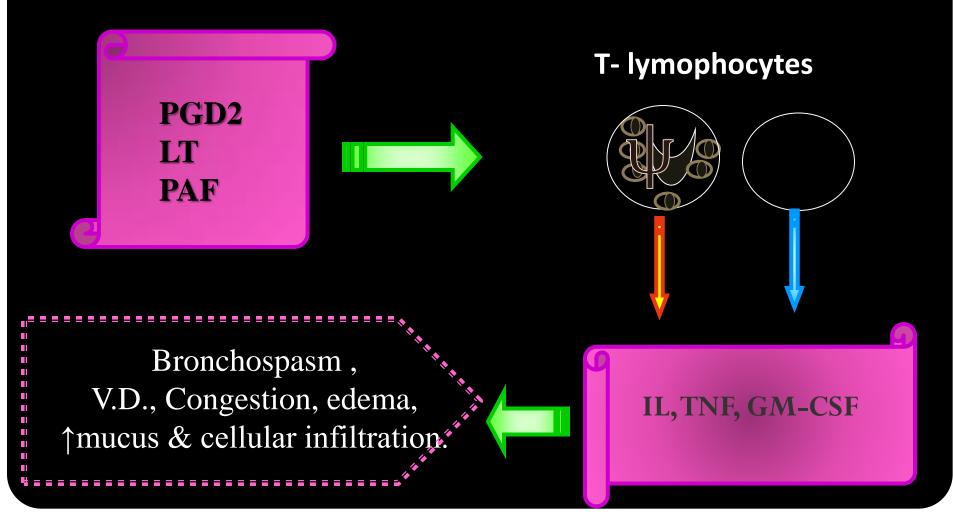
Patho- physiology:

Early phase of Bronchospasm→ reach its maximum at about 20 min.



Patho-physiology:

Late phase of inflammation \rightarrow about 6- 12 hours later



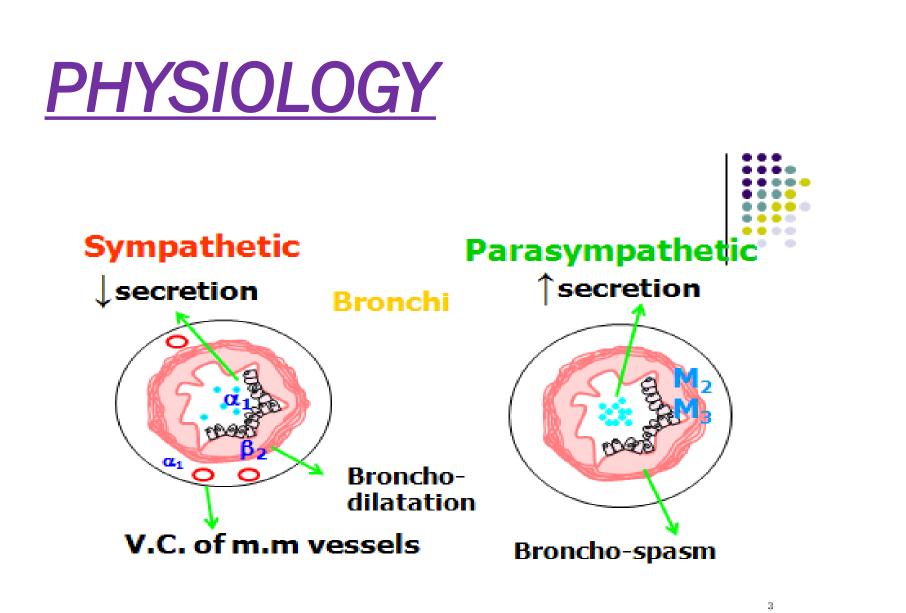


Allergens - pollen, house dust, mites, animal fur, foods Respiratory infections Exercise Emotional stress Cold air Pollution - indoor and outdoor





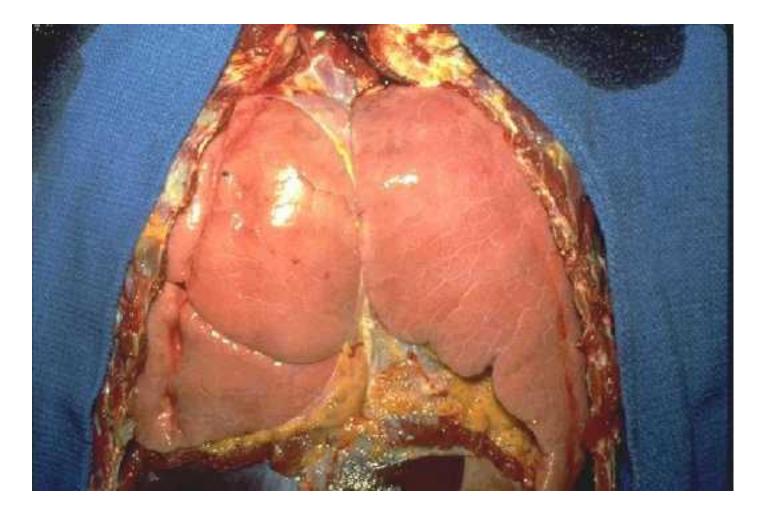
Drugs - NSAIDs, beta-blockers, Parasympathomimetics,...



The bronchial tone is controlled by:

- - β -receptor stimulation: ++ Aden.Cy. \rightarrow + c-AMP \rightarrow bronchodilation
- Methyl xanthenes: → -- PDE → + c-AMP → bronchodilation &→ block adenosine R→+ c-AMP → bronchodilation
- M-receptor stimulation: →+PLC→+IC Ca → bronchoconstriction
- IT-receptor stimulation: →+PLC→+IC Ca→
 bronchoconstriction
- PG F2a stim. →+PLC→+IC Ca → bronchoconstriction.

Lung Hyperinflation in Asthma



Types of asthma

- Allergic (extrinsic) asthma: Allergic history, common, childhood
- Intrinsic asthma: Respiratory viral infections
- Exercise-induced asthma: Cold air inhalation
- Occupational asthma: Exposure to dust & fumes in work
- Drug-induced asthma: Aspirin & NSAIDs (COX inhibitors)
 - β-Blockers (non-selective)
 - Parasympathomimetics
 - Histamine & histamine releasers
 - morphine &other narcotics
 - ACE inhibitors.

DIAGNOSIS OF BRONCHIAL ASTHMA

Patient History:

- Family history of allergy
- Occupation & Smoking
- Relation to exercise and Drugs
- Known Triggers
- Previous Trt.

<u>SYMPTOMS</u> Episodic/variable:

- Wheeze
- Breathlessness
- Chest tightness
- Cough
- Mucus production

FEV1(forced expiratory volume)

- FEV1 is the volume of air that can forcibly be blown out in first 1 second, after full inspiration.
- Average values for FEV1 in healthy people depend mainly on sex and age, according to the diagram. Values of between 80% and 120% of the average value are considered normal. Predicted normal values for FEV1 can be calculated and depend on age, sex, height, mass and ethnicity as well as the research study that they are based on.
- FVC(forced vital capacity) is the amount of air that can be forcibly
 Exhaled from your lungs after taking the
 Deepest breath possible.



The FEV1/FVC

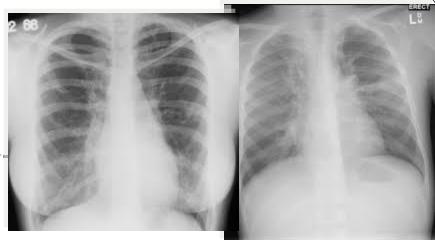
- The FEV1/FVC ratio, also called <u>Tiffeneau-Pinelli index</u>,
- is a calculated ratio used in the diagnosis of obstructive and restrictive lung disease.
- It represents the proportion of a person's vital capacity that they are able to expire in the first second of forced expiration (FEV1) to the full, forced vital capacity (FVC).
- The result of this ratio is expressed as FEV1%.
- Normal values are approximately 75%.Predicted normal values can be calculated online and depend on age, sex, height, and ethnicity as well as the research study that they are based upon.

Peak expiratory flow (PEF)

- Peak expiratory flow (PEF)
- Normal values for peak expiratory flow (PEF), shown on EU scale.
- Peak expiratory flow (PEF) is the maximal flow (or speed) achieved during the maximally forced expiration initiated at full inspiration, measured in liters per minute or in liters per second.
- Tidal volume (TV)
- Tidal volume is the amount of air inhaled or exhaled normally at rest.
- Total lung capacity (TLC)
- Total lung capacity (TLC) is the maximum volume of air present in the lungs

Investigations:

- CXR
- Esinophilic Count
- Total IG-E & Allergen specific IG-
- Skin and Blood Allergy test.
 - <u>In special cases</u> : CT Chest



- Histamine bronchial challenge
- Bronchoscopy plus biopsy/lavage
- <u>Pulmonary Function tests</u>: PEF & FEV₁[%] &VC.
 - > 20% diurnal variation on ≥ 3 days in a week for 2 weeks on Peak Expiratory Flow (PEF) diary.
 - FEV1 \geq 15% increase after short acting β -agonist (eg salbutamol 400 mcgs by MDI/spacer or 2.5 milligrams by nebuliser).
 - FEV1 ≥ 15% increase after 14 DAY Prednisolone trial (30mg/day).
 - $FEV1 \ge 15\%$ decrease after strenuous exercise (running).

GRADING OF ASTHMA					
	Mild intermittent	Mild persistent	Moderate persistent	severe persistent	
Frequency of symptoms	<twice a<br="">week</twice>	>twice a week but <once a="" day<="" th=""><th>Daily</th><th>Throughout the day</th></once>	Daily	Throughout the day	
SABA for symptoms control	<2 days/ week	>2 days/ week	Daily	Several times/ day	
Night time awakening	Not >twice a month	>twice a month, 3-4 times/month	>once a week	7/week	

Treatment

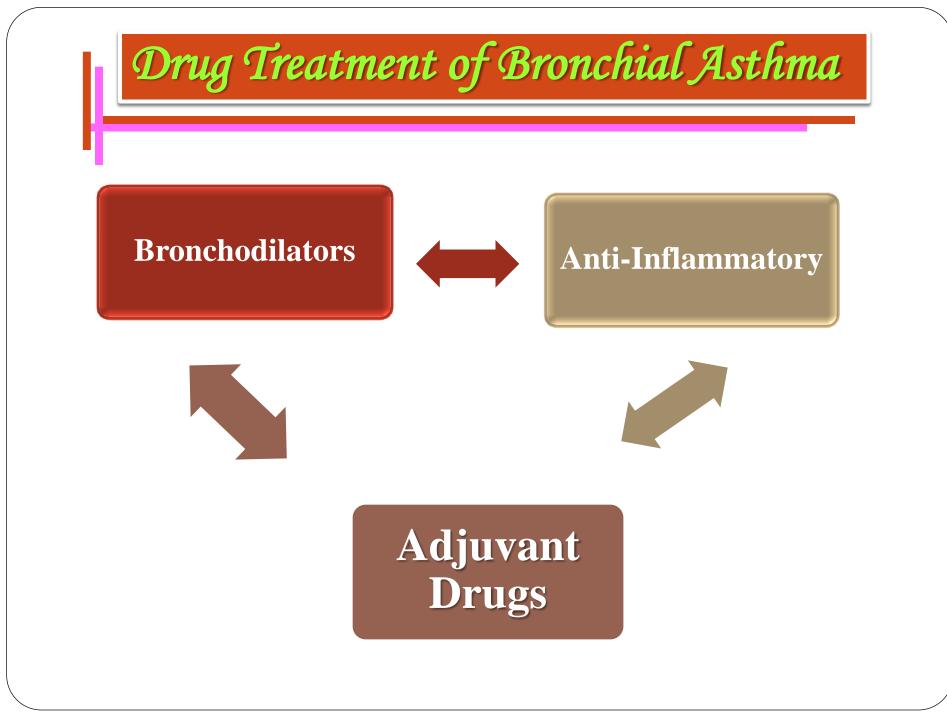
• Goals of Treatment:

The GINA long-term goals for asthma management include:

- achieve good control of symptoms and maintain normal activity levels.
- minimize future risk of exacerbations, and side effects.
- For acute severe asthma, the primary goal is prevention of life-threatening asthma by early recognition of signs of deterioration and early intervention.

Nonpharmacologic Therapy

- **Patient education** is mandatory to improve medication adherence
- Routine PEF monitoring is generally recommended only for patients with severe asthma or poor symptom perception.
- Avoidance of known allergenic triggers
- In acute asthma exacerbations, initiate oxygen therapy to achieve an arterial oxygen saturation of 93%–95% in adolescents and adults and 94%– 98% in school-aged children and pregnant women or those with cardiac disease.
- Correct **dehydration if present**.





Sympathomimetic β₂-Agonists e.g. Salbutamol.
 Parasympatholytics e.g. Ipratropium.
 Methyl- xanthines e.g. Theophylline.

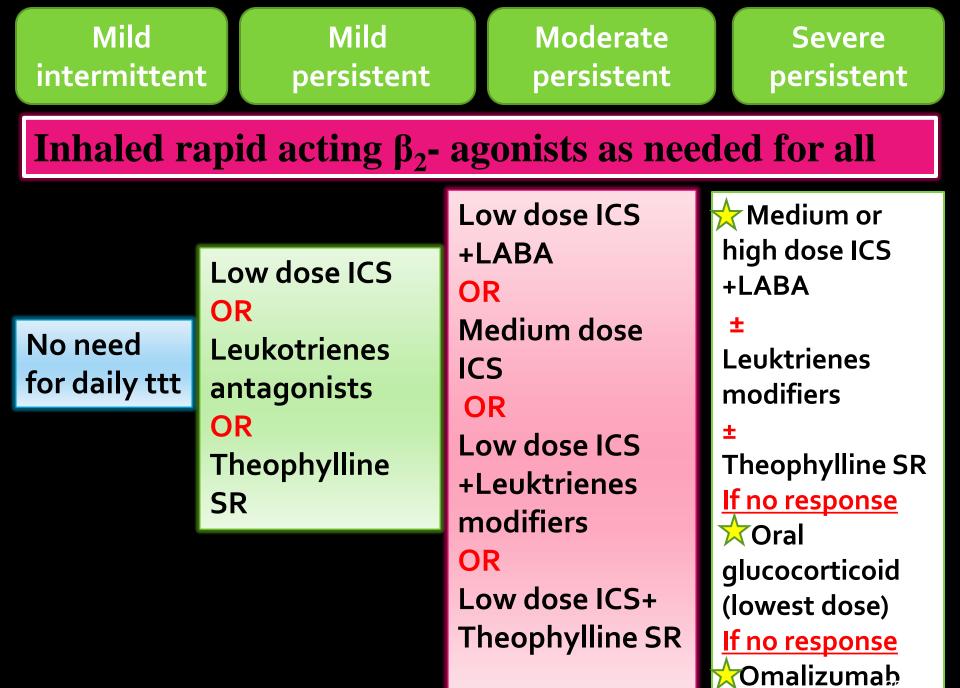
GINA Recommendations for Initial Controller Treatment in Adults and Adolescents

Symptom Presentation	Preferred Treatment (Evidence Level)
Symptoms or need for SABA less than 2×/mo; no waking due to asthma in last month; and no risk factors for exacerbations, including in prior year	No controller (D)
Infrequent symptoms, but patient has one or more risk factors for exacerbation (eg, low lung function, use of OCS in prior year, intensive care treatment for asthma ever)	Low-dose ICS (D)
Symptoms or need for SABA between 2×/mo and 2×/week, or patient wakes due to asthma more than once/mo	Low-dose ICS (D)
Symptoms or need for SABA $> 2 \times$ /week	Low-dose ICSª (A)
Troublesome symptoms most days or waking $\geq 1 \times$ /week, esp. if any risk factors exist	Medium/high-dose ICS or low-dose ICS/LABA ^b (A)
Symptoms consistent with severely uncontrolled asthma, or with an acute exacerbation	OCS short course AND start of high-dose ICS or moderate-dose ICS/ LABA ^b (D)

GINA Stepwise Approach to Control Symptoms and Minimize Future Risk

Step	Preferred Option (Evidence Level)	Other Recommended Options (Evidence Level)
1	As-needed SABA (A)	Consider low-dose ICS, in addition to as-needed SABA, for patients at risk for exacerbations (B)
2	Low-dose ICS plus as-needed SABA (A)	LTRA (A)
		Low-dose ICS/LABA (A)
		ICS started with symptoms of allergic asthma, for seasonal treatment only (D)
3	Low-dose ICS/LABA, plus as-needed SABA for adults/adolescents	Medium-dose ICS for adults/adolescents (A)
	OR low-dose ICS/formoterol as both maintenance and reliever (A)	Low-dose ICS plus LTRA (A) or low-dose, sustained-release theophylline (B)
	For children 6–11 years of age, moderate- dose ICS, plus as-needed SABA	

1	Medium-dose ICS/LABA, plus as-needed SABA for adults/adolescents (B) OR medium-dose ICS/formoterol as both maintenance and reliever (A) For children 6–11 years of age, refer child to asthma specialist	Add-on therapy with tiotropium for adults with exacerbation history (A) Sublingual allergen immunotherapy in adults with allergic rhinitis and house dust mite sensitization if FEV ₁ is >70% predicted
5	Referral to specialist and consideration of add-on treatment if asthma remains uncontrolled	Add-on anticholinergic (B): tiotropium if ≥12 years of age
		Add-on anti-IgE (A): omalizumab (subcutaneous) for moderate-to-severe allergic asthma if ≥6 years of age
		Add-on anti-interleukin-5 therapy (A): mepolizumab if ≥12 years (subcutaneous); reslizumab if ≥18 years) (intravenous)
		Add-on anti-interleukin 5 receptor (A): benralizumab if ≥12 years (subcutaneous)
		Sputum-guided treatment adjusted by eosinophilia > 3% (0.03) (A)
		Bronchial thermoplasty in some adults with severe asthma (B)
		Add-on low-dose OCS (≤7.5 mg/day prednisone equivalent) (B)



β2-Agonists

- SABAs are the most effective bronchodilators. Aerosol administration enhances bronchoselectivity and provides more rapid response and greater protection against provocations (eg, exercise, allergen challenges) than systemic administration.
- Albuterol and other inhaled SABAs are indicated for intermittent episodes of bronchospasm and are the treatment of choice for acute severe asthma and Exercise-induced bronchospasm (EIB).
- Two long-acting β2-agonists (LABAs), formoterol and salmeterol, provide bronchodilation for 12 hours or longer.

- Combination treatment with ICS/LABA provides greater asthma control than increasing the dose of ICS alone while reducing the frequency exacerbations. A SABA should be continued for acute exacerbations.
- Three ultra-LABAs (indacaterol, olodaterol, and vilanterol) have a 24-hour bronchodilator duration of effect. Products containing indacaterol and olodaterol are currently only indicated for chronic obstructive pulmonary disease (COPD) but are being evaluated for asthma.

Corticosteroids

- ICS are the preferred long-term control therapy for persistent asthma because of potency and consistent effectiveness; they are the only therapy shown to reduce risk of dying from asthma.
- After asthma is controlled, many patients can reduce the ICS dose and maintain control.
- Response to ICS is delayed; symptoms improve in most patients within the first 1–2 weeks and reach maximum improvement in 4–8 weeks. Maximum improvement in FEV1 and PEF rates may require 3–6 weeks.

- Systemic toxicity of ICS is minimal with low-tomoderate doses, but risk of systemic effects increases with high doses (eg, growth suppression in children, osteoporosis, cataracts, dermal thinning, adrenal insufficiency).
- Local adverse effects include dose-dependent oropharyngeal candidiasis and dysphonia, which can be reduced by using a spacer device.
- Systemic corticosteroids are indicated in all patients with acute severe asthma not responding completely to initial inhaled β2agonist administration and should be administered within 1 hour of presentation.

- IV therapy offers no advantage over oral administration except in patients unable to take oral medications.
- Adults are treated effectively with 5–7 days of oral prednisone (or equivalent), but children may require only 3–5 days. Dexamethasone for 1–2 days is an option for children and has the benefit of less vomiting. Continue full doses until the PEF reaches 70% of predicted normal or personal best.
- Because short-term (1–2 weeks), high-dose corticosteroids (1–2 mg/kg/day of oral prednisone) do not produce serious toxicities, the ideal strategy is to use systemic corticosteroids in a short "burst" and then maintain the patient on appropriate long-term control therapy with ICS.

Anticholinergics

- 1-Ipratropium bromide and tiotropium bromide produce bronchodilation only in cholinergicmediated bronchoconstriction. Anticholinergics are effective bronchodilators but are not as effective as β2-agonists.
- Ipratropium bromide is approved by the FDA for maintenance treatment of bronchospasm associated with COPD but is not currently approved for treatment of asthma.
- Tiotropium bromide is also approved for oncedaily maintenance treatment of COPD and is also indicated for the long-term, once-daily, maintenance treatment of asthma in patients ≥6 years of age.

- Time to reach maximum broncho-dilation from aerosolized ipratropium is longer than from aerosolized SABAs (30–60 minutes vs. 5–10 minutes).
- Ipratropium bromide has a duration of action of 4–8 hours; tiotropium bromide has a duration of 24 hours.
- In acute asthma exacerbations, inhaled ipratropium bromide produces a further improvement in lung function of 10%–15% over inhaled β2-agonists alone.

- Inhaled ipratropium bromide should only be considered as adjunctive therapy in acute severe asthma not completely responsive to β2-agonists alone.
- Tiotropium may be considered as add-on therapy in patients whose asthma is not well controlled with a medium-to-high dose of ICS and LABA combination therapy.

Leukotriene Modifiers

- Zafirlukast and montelukast are oral leukotriene receptor antagonists (LTRA) that reduce the proinflammatory and bronchoconstriction effects of leukotriene D4.
- They are less effective than low-dose ICS, and they are less effective than LABAs when added to ICS for moderate persistent asthma. They are not used to treat acute exacerbations and must be taken on a regular basis, even during symptom-free periods.

- In general, the LTRA are well tolerated. An idiosyncratic syndrome similar to the Churg– Strauss syndrome, with marked circulating eosinophilia, heart failure, and associated eosinophilic vasculitis, has been reported rarely; a direct causal association has not been established.
- Because of reports of adverse neuropsychiatric events especially within a few weeks of starting therapy, monitor patients for signs of irritability, aggressiveness, and sleep disturbances; suicidality has also been reported rarely.

- There have been reports of fatal hepatic failure associated with zafirlukast.
- Zileuton is a 5-lipoxygenase inhibitor; its use is limited due to potential for elevated hepatic enzymes and inhibition of metabolism of drugs metabolized by CYP3A4 (eg, theophylline, warfarin).

Biologic Agents

- -These agents target the IgE pathway or IL-4, IL-13, and IL-5 pathways. They are typically reserved for patients with moderate-to-severe persistent asthma who have been treated with dual therapy with ICS/LABA or triple therapy such as with ICS/LABA+ long-acting muscarinic antagonist (LAMA) and remain poorly controlled.
- **Omalizumab** is an anti-IgE antibody approved for treatment of allergic asthma not well controlled by oral or ICS.
- Dosage (is determined by baseline total serum IgE) and body weight (kg). It is given subcutaneously (SC).

- Because of a 0.2% incidence of anaphylaxis, observe patients for a reasonable period after injection because 70% of reactions occur within 2 hours. Some reactions have occurred up to 24 hours after injection.
- B-Mepolizumab and reslizumab are monoclonal antibodies directed against IL-5 to block activation of the IL-5 receptor on eosinophils. Benralizumab binds to IL-5 receptor of eosinophils and prevents binding of IL-5, thus mitigating downstream eosinophilic inflammation.
- Mepolizumab and benralizumab are administered SC; reslizumab is administered IV.
- Each of these drugs is indicated for patients with an "eosinophilic phenotype".
- **C-Dupilumab** targets the **IL-4α receptor**, thus blocking signaling of IL4 and IL-13, which are cytokines that promote IgE synthesis and inflammatory cell recruitment. Dupilumab is approved for patients with an **eosinophilic phenotype** and is administered SC.

Magnesium Sulfate

- Magnesium sulfate is a moderately potent bronchodilator, producing relaxation of smooth muscle by blocking calcium ion influx into smooth muscles; it may also have anti-inflammatory effects.
- For patients with severe asthma exacerbations, a single 2 g IV infusion may reduce hospital admissions
- Adverse effects include hypotension, facial flushing, sweating, depressed deep tendon reflexes, hypothermia, and CNS and respiratory depression.

Methylxanthines

- Methylxanthines are rarely used today because of the high risk of severe life-threatening
- toxicity, numerous drug interactions, and decreased efficacy compared with ICS, LABAs, and biologics.
- Theophylline is available for oral and IV administration. Theophylline dosing requires monitoring of serum concentrations for both efficacy and toxicity, including seizures and death.
- In addition, theophylline is eliminated primarily by metabolism via the hepatic CYP P450 microsomal enzymes, and drug interactions affecting metabolism significantly affect blood concentrations.

ACUTE ATTACK OF ASTHMA

Short acting β2- agonist: Salbutamol or Terbutaline by inhalation

If no response add: Aminophylline 250- 500 mg slowly IV.



3-Glucose 5% by IV infusion (for hydration &

nutrient)

SEVERE ACUTE ATTACK

5- Bronchodilators:

a) $\beta 2$ agonists e.g. Salbutamol 5mg or terbutaline 10mg inhalation by nebulizer

b) Methylthanthines e.g. Aminophylline infusion 250mg over 20 min.

c) Magnesium sulfate 2 g IV \rightarrow \uparrow peak expiratory flow rate

4- Systemic steroids:

a) Hydrocortisone sodium hemisuccinate (200mg) or methyl prednisolone IV infusion/4hrs till control of attack <u>then</u>
b) Oral Prednisolone 30- 60mg. for 2 days <u>then</u> gradual withdrawal
<u>6-Antimicrobial</u> for bacterial infections

1.What is inhaler?

 An inhaler is a medical device used for delivering medication into the body via the lungs.



2.Advantages Vs Disadvantages

• Advantages:

 Less systemic toxicity
 More rapid onset of medication
 Delivery to target of action
 Higher concentrations available in the lung



<u>Disadvantages</u>:
 1.Time and effort consuming
 2.Limitation of delivery
 device

Types of inhaler

- Metered dose inhaler
- Dry powder inhaler
- Nebulizer

Asthma Medication Delivery Devices.mp4



1.Metered-dose inhalers



Properties

A liquid propellant Inhalation technique is critical for optimal drug delivery

How to use

Without chamber



Remove the cap and shake the inhaler.

Place the inhaler in your mouth. Close your lips around it. As you breathe in, press down on the inhaler.

all



Hold your breath for a count of 10. Then slowly breathe out. Remove the cap from the MDI and shake well.
 Breathe out all the way.
 Place the mouthpiece of the inhaler between your teeth and seal your lips tightly around it.
 As you start to breathe in slowly, press down on the canister one time. 5.Keep breathing in as slowly and deeply as you can. (It should take about 5 to 7 seconds for you to completely breathe in.) 6.Hold your breath for 10 seconds (count to 10 slowly) to allow the medication to reach the airways of the lung. 7.Repeat the above steps for each puff ordered by your doctor. Wait about 1 minute between puffs.

8.Replace the cap on the MDI when finished.

9.If you are using a corticosteroid MDI, you should use a valved holding chamber as described above.

With chamber



1. Remove the cap from the MDI and chamber. Shake well. 2. Insert the MDI into the open end of the chamber (opposite the mouthpiece). 3. Breathe out completely. 4. Place the mouthpiece of the chamber between your teeth and seal your lips tightly around it.

5. Press the canister once.

 Breathe in slowly and completely through your mouth. If you hear a "horn-like" sound, you are breathing too quickly and need to slow down.

 Hold your breath for 10 seconds (count to 10 slowly) to allow the medication to reach the airways of the lung. 8.Repeat the above steps for each puff ordered by your doctor. Wait about 1 minute in between puffs.

9.Replace the cap on your MDI when finished.

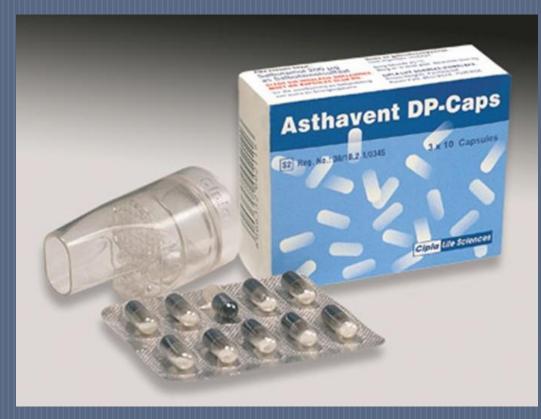
10.If you are using a corticosteroid MDI, rinse your mouth and gargle using water or mouthwash after each use. You should always use a chamber with a steroid MDI.

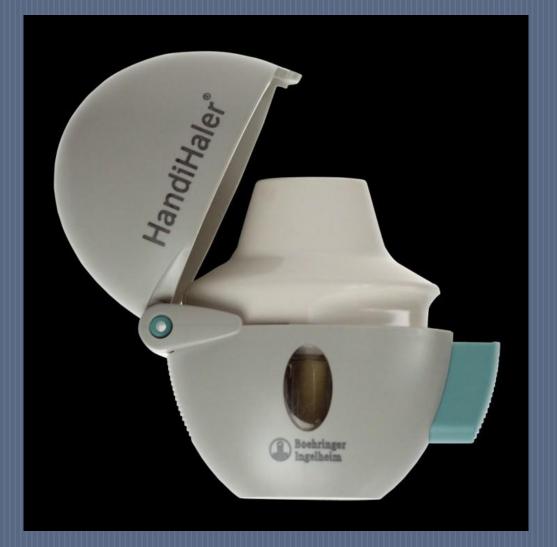
Advantages Vs Disadvantages Disdvantages Advantages •Hand-breathe coordinations Rapid application Ineffective use in poor •Handling ventilated patients Multidose Oropharyngeal deposition and local

side effects

2. Dry powder inhalers

Single dose





Handihaler



Discus inhaler

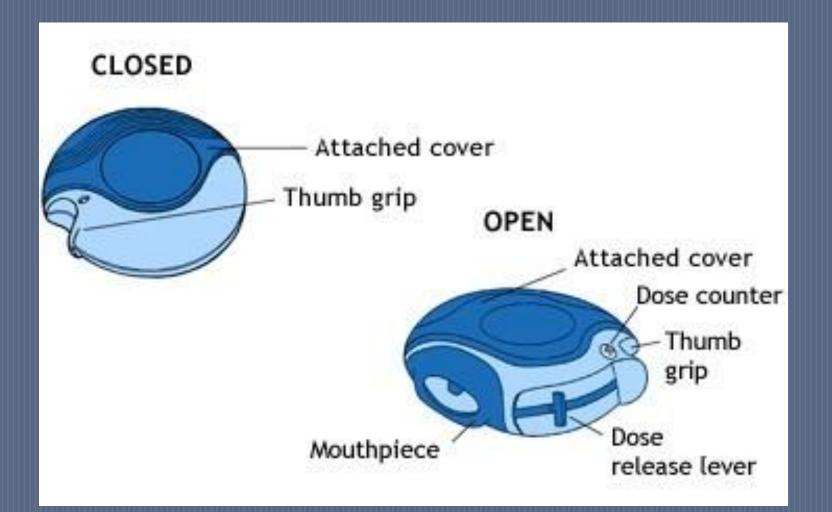


Multi dose

Turbuhaler

Properties

just dry-powder and no propulsion system.
manual mechanism to insert one dose of dry-powder drug into the mouthpiece.



How to use

1.To load a dose, hold the DPI with mouthpiece up to ensure proper loading of the medication.
2.Twist the \ grip fully in one direction as far as it will go and then fully back again. You will hear a click. The DPI is now loaded with a dose.
3.Turn your head away from the inhaler and breathe out as much air as you comfortably can.



- 4.Place the device in your mouth and breathe in as forcefully and deeply as you can.
- 5.Hold your breath for 10 seconds.
- 6.Take the DPI away from your mouth and exhale slowly.
- 7.If more than one dose is prescribed, repeat steps 1 through 5 for each dose.
- 8.When your treatment is complete, replace the white cover and twist it completely to close

Advantages Vs Disadvantages

<u>Advantages</u>
Less patient
coordination required
Spacer not necessary
Compact Portable
No propellant
Usually higher lung
deposition than a pMDI

Disadvantages •Work poorly if inhalation is not forceful enough Many patients cannot use them correctly (e.g.capsule handling problems for elderly Most types are moisture sensitive. Need to reload capsule each time

Flexhaler

- How to use
- 1. twist the brown grip back and forth for 2 times
- Check the dose counter
- Grip fully in one direction and then the other
- Take breath in and blow it
- Make tight seal around your mouthpiece by lips
- Take fast deep forceful breath
- Hold your breath for 10 seconds
- Breath through mouth and nose



Twisthaler

- Check the dose counter
- Attach the pink base and twist the White cap to remove it (prepare Medicine for inhalation.
- Take breath in and blow it out
- Tight seal with your lips aroud the mouthpiece
- Take fast deep forceful breath in
- Hold your breath for 10 seconds.



respiclick

- Check dose counter
- Make sure cap is closed before use
- Open the cap fully open to the Back until you hear click
 This prepare medicine for using.



TURBUHALER

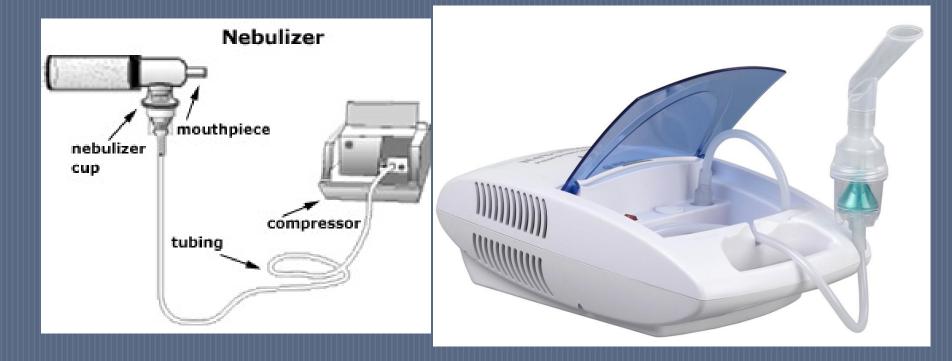




TURBUHALER

- 1. Unscrew the cap of the turbuhaler anticlockwise and lift off
- 2. Hold the turbuhaler upright. Load it by turning the coloured base of the turbuhaler to the right as far as it will go.
- 3. Then twist it back to the left until it clicks. It is now loaded.
- 4. Breathe out gently, away from turbuhaler. Hold the turbuhaler without covering the air inlets and put the tip of the mouthpiece between your lips. Be sure you make a good seal. Breathe in quickly and deeply through your mouth and hold your 72

3. Nebulizer



Properties

 The fundamental concept of nebulizer performance is the conversion of the medication solution into droplets in the respirable range of 1-5 micrometers

How to use nebulizer

- Place medication into the medicine cap
- Screw the nebulizer lid into the medicine cap
- Insert the angled mouthpiece into the nebulizer
- Attach one end of tubing to the compressor and connect the other to nebulizer
- Switch the compressor on
- Check for the airflow from the device.

Improving Compliance in Asthma

- Review inhaler technique and use of spacer
- Educate:
 - What is asthma?
 - Controller vs quick reliever medications
- Address misconceptions (mistaken beliefs)
- Consider oral therapy if patient cannot learn how to use inhalers

Evaluation of therapeutic outcomes

- 1-Basic education should include
- 2-The two key components of effective asthma control are "symptom control" and "future risk of adverse outcomes."
- .During ongoing care, measure spirometry yearly but reserve long-term PEF monitoring
- for patients with severe asthma.
- All patients on inhaled drugs should have their inhalation technique evaluated monthly initially and then every 3–6 months.
- After initiation of anti-inflammatory therapy or increase in dosage, most patients should experience decreased symptoms within 1–2 weeks and achieve maximum improvement within 4–8 weeks. Improvement in baseline FEV1 or PEF should follow a similar time course.