

Therapy of Bronchial Asthma

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."
↳ either spontaneously or as a result of treatment
- This is usually a reversible process.
- Airflow limitation may later become persistent.
- Asthma is usually associated with airway hyperresponsiveness and airway inflammation, but these are not necessary or sufficient to make the diagnosis.
- Airway obstruction in asthma may become partially 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.
↳ development of new blood vessels
↳ increases mitosis in the smooth muscle → thickening of the muscular layer in the bronchi
↳ more mucous secretion..
- Tryptase (a smooth muscle mitogen) plays a role in airway remodeling.
- Airway remodeling represents an irreversible process.

Factors Contributing To Asthma Severity: تجنبهم أو خالجهم لأنه فلانهم نساء عنهم Part of the treatment

- Respiratory infection:
 - Respiratory syncytial virus (RSV), rhinovirus, influenza, parainfluenza, Mycoplasma pneumoniae, Chlamydia.
↳ like bronchiolitis in children; including wheezing & bronchial constriction .. like bronchial asthma
- Allergens:
 - Airborne pollens (grass, trees, weeds), house dust mites, animal dander, rodents, cockroaches, fungal spores.
- Exercise:
 - Particularly in cold, dry climate.
- Environment:
 - Cold air, fog, sulfur dioxide, nitrogen dioxide, tobacco smoke (including 2nd and 3rd hand), wood smoke, scented home products, cleaners, and perfumes...
↳ من الأسياء العطرة التي يحطونها في البيوت
يعني مش اللي بيخزن / اللي بيخزن الدخان
كثير لئيم
- Emotions:
 - Anxiety, stress, laughter.
- Occupational stimuli:
 - Bakers (flour dust); farmers (hay mold); spice workers; occupational cleaners, printers, (arabic gum); chemical workers; plastics, rubber, and wood workers...

Pathophysiology of Bronchial Asthma

Major characteristics of asthma include:

1. A variable degree of airflow obstruction (bronchospasm, edema, and mucous hypersecretion)
2. Bronchial hyper-responsiveness (BHR).
↳ تشبه سلك الكهرباء المعزى جزئياً
3. Airway inflammation.
↳ لو أنت بتسك سلك الكهرباء كامل ← ما بيس شياء
لو إذا جزء منه معزى بتنحرب كهرباء

→ Here there is exposure to nerve endings, result in exaggerated bronchial constriction.

Therapy of Bronchial Asthma:

Long-term goals of therapy:

1. Adequate symptom control and maintaining normal activity
2. Minimize asthma related death (obstruction/overuse of drugs)
3. Minimize exacerbations
4. Minimize persistent airflow limitations
5. Minimize drug adverse effects

* Short-term goes into eliminate the attack
↳ immediately bronchodilator

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)
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

The same thing happen in the lung ...
(oxidative stress & damage to lung tissue by the same mechanism)

⇒ in addition to hepatic toxicity in overdose but there is an interindividual variation, so it could result in toxicity in normal doses.

para-amino-benzoguinone imine; cause oxidative stress on liver
↳ Glutathione take care of this toxic metabolite, but when it deplete → liver toxicity

Asthma Medications:

1. Inhaled corticosteroids (ICS):

Beclometasone dipropionate, Budesonide, Ciclesonide, Fluticasone propionate, Mometasone furoate.

2. Short-acting inhaled β_2 -agonists (SABA):

Albuterol (salbutamol), Levalbuterol, Terbutaline.

4-6 hours تقريباً

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.

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).

6. Biologic therapy: → Monoclonal Antibodies modify the immune system, only are used in cases of allergic or resistant asthma.

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

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

C. Anti-interleukin-4R α (dupilumab)

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

long-acting
& his onset
of action

similar to
short-acting
(almost
immediate)

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.

as
baseline

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. ما نقيح وقتك

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

a. β_2 -agonists

b. corticosteroids

c. inhaled ipratropium (when response is inadequate)

d. and O_2 . \rightarrow Antimuscarinic agent
فوري جدًا

• Treatments are typically administered concurrently to facilitate rapid improvement.

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. \rightarrow بجلوا
interstitial lung disease

صعبي في مشكلة بال diffusion للأوكجين جا

Pharmacological Therapy:

- to prevent exacerbation \leftarrow
- 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. \rightarrow The combination is better to be in the same inhaler to improve adherence
 - Controller therapy: targeting both symptom control and future risk - ICS-containing relievers. \rightarrow inhibits inflammation which happened in the pathogenesis of bronchial asthma
 - Relievers: asthma inhaler taken as needed for quick relief of symptoms (rescue inhalers) - SABAs, ICS-SABA or bronchodilator
 - Anti-inflammatory reliever (AIR): contain low dose ICS and SABAs
 - Maintenance and reliever therapy (MART): ICS-formoterol every day and the same medication to relieve asthma symptoms.

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).

Reasons of starting ICS-containing medications: \rightarrow At the time of diagnosis

- Reduction of risk of severe exacerbations and ER visits or hospitalization.
- 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.
- Patients not taking ICS who experience severe exacerbations have a greater long-term decline in lung function than those who are taking ICS.
- 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.

Initial asthma treatment for adults and adolescents: > 11 years of age

- Infrequent asthma symptoms (< 2 /month) with no exacerbations: As needed low dose ICS-Formoterol.
- Asthma symptoms or need for reliever ≥ 2 /month: As needed low dose ICS-Formoterol. ما اختلفت

→ Why Formoterol?

لأنه أفضل عليه

Large Randomized Double-Blind Control Trial

→ Evidence Based Medicine

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).

جرعة منخفضة maintenance ، وجرعة إضافية لما يعبر عنه more symptoms

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.

→ depending in the severity of bronchoconstriction, because in this case ICS may not reach the site of action due to obstruction, but systemic corticosteroids can through the blood

• For all alternative treatment exist.

suppression to hypothalamic-pituitary-adrenal axis

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.

زبان كنا نضيفها لكل الرغبي Salbutamol هذا مبرر لهاي الفئة القرية

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.

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.

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.

ICS

• 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:

1. Incorrect inhaler technique. لا عرف يستعمله
2. Poor adherence.
3. Persistent exposure to allergens, tobacco smoke, air pollution, high risk medications. Aspirin/NSAIDs/Paracetamol = ما بهين جدا يدخلنا في الدار
4. Co-morbidities that may contribute to respiratory symptoms and poor quality of life.
5. Incorrect diagnosis.

Important points:

- Over use of SABA (3 or more 200-dose canisters/year) increases the risk of asthma exacerbations. → you treat the symptoms by leave the pathologic process going on
- 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.
- 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). x Medium/High Inhalers → You need! ; to prevent the risk of fungal infection in the mouth by the risk of systemic absorption of the drug.
- 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. → exacerbations من
- Inhaled short-acting anticholinergic 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. → severe و كأنه يمنع ال exacerbations whatever medication you use

ال التي غلت update

- 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. *↳ Not bronchodilator, but prevent the release of bronchoconstrictors by mast cells. [for prevention, not to terminate attack]*
- Use of theophylline is associated with low efficacy and severe adverse reactions and drug interactions.
- 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.
- 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.

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.
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.
3. Add-on anti-interleukin-4Ra 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.

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.
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.

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

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.
 - Long-term administration of β 2-agonists does NOT reduce bronchial hyperresponsiveness (BHR).
- =====

Most reasonable use: treatment of apnea in premature infants

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%. → switch إذا نقل
- Different devices for the same chemical entity may result in two-fold differences in delivery, so you should be careful when changing devices. controlled إذا صار
- 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.

systemic
absorption

← هـول الستيرويد إذا ما في

Anticholinergics:

↳ This is especially
important in chronic
bronchitis

- 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 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.
- 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 vagusmediated bronchoconstriction.

Leukotriene Receptor Antagonists (LTRA):

مخيفين للأعمال

→ Can be used as add-on
therapy..

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

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).

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