**College of Pharmacy**

**Fourth year. Clinical Pharmacy**

**Respiratory disorders**

**Asthma**

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** that vary over time and in intensity, together with variable expiratory airflow limitation.

**Pathophysiology**

1-There is a **variable degree of airflow obstruction**. In acute inflammation, inhaled allergens in allergic patients **cause activation of inflammatory cells (mast cells, neutrophils and macrophages)**

2-After rapid activation, **inflammatory cells release proinflammatory mediators such as histamine** and eicosanoids that induce **contraction of airway smooth muscle (bronchospasm), mucus secretion, edema, and exudation of plasma in the airways**.

**Clinical presentation**

**A-Chronic asthma**

**Signs and symptoms** include episodes of **shortness of breath, chest tightness, dry coughing** (particularly at **night**), **wheezing, or a whistling** sound when breathing. These often occur with exercise but may occur spontaneously or in association with known allergens.

**B-Acute severe asthma**

1-Uncontrolled asthma can progress to an **acute state**. Patients may be anxious in acute distress and **complain of severe dyspnea, shortness of breath, chest tightness, or burning**. They may **be able to say only a few words** with each breath. **Symptoms are unresponsive to usual measures (ie, SABAs).**

2-Signs include **dry, hacking cough; tachypnea; tachycardia; pallor or cyanosis;** and **hyperinflated** **chest** with **intercostal and supraclavicular retractions.**

**Diagnosis**

**A-Chronic asthma**

1-Diagnosis is made primarily by **history** and confirmatory spirometry.

2-**Spirometry demonstrates obstruction** (forced expiratory volume in 1 second [FEV1]/forced vital capacity [FVC] **<80%)** with **reversibility after inhaled β2-agonist** administration.

**B-Acute severe asthma**

1-**Peak expiratory flows (PEF) and FEV1 are <40%** of normal predicted values. Pulse oximetry reveals decreased arterial oxygen **and O2 saturations**.

2-Arterial blood gases may reveal **metabolic acidosis** and low partial pressure of oxygen (PaO2).

**Treatment**

**Goals of Treatment**: The GINA long-term goals for asthma management include:

(1) achieve good control of symptoms and maintain normal activity levels.

(2) 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 providing rapid treatment.

**Nonpharmacologic Therapy**

1-**Patient education** is mandatory to improve medication adherence, self-management skills, and use of healthcare services.

2-Routine PEF monitoring is generally recommended only **for patients with severe asthma or poor symptom perception.**

3-**Avoidance of known allergenic triggers** can improve symptoms, and reduce medication use. Smokers should be encouraged to quit.

4-**In acute asthma exacerbations, initiate oxygen therapy**.

5-Correct **dehydration if present**.

**Pharmacologic Therapy**

**General Approach**

1-Figure 1 summarizes GINA recommendations for **initial treatment** in adults and adolescents with asthma (**further reading**).



**Figure 1: GINA recommendations for initial treatment in adults and adolescents**

2-Despite the addition of inhaled corticosteroid-short acting β2 agonist (**ICS-SABA**) reliever in track 2, **GINA track 1 with as-needed ICS- formoterol remains the preferred treatment for adults and adolescents** (2).

[Single Maintenance and Reliever Therapy (**SMART**) also called Maintenance and Reliever Therapy (**MART**) in GINA guidelines: SMART therapy with ICS-formoterol **significantly reduces the risk of severe exacerbation** compared with using a SABA reliever, with similar symptom control] (2).

3-Depending on the inflammatory phenotype (e.g. allergic asthma, eosinophilic asthma) and other clinical features, add-on treatment for severe asthma include **long acting muscarinic antagonist** (LAMA), **leukotriene receptor antagonists** (LTRA), and **biologic agents** (2).

**4-Low-dose maintenance oral corticosteroid** (OCS) should be considered only as a last resort if no other options are available, because of their long-term side effects (2).

5-Once good asthma control has been achieved and maintained **for 2-3 months**, consider **stepping down gradually** to find the patient's lowest treatment that controls both symptoms and exacerbations (2).

6-The **primary therapy of acute exacerbations includes** inhaled **SABAs** and (depending on severity) **systemic corticosteroids**, inhaled **ipratropium**, intravenous (IV) **magnesium** sulfate, and **oxygen**. Treatments are typically administered concurrently to facilitate rapid improvement.

**β2-Agonists**

1- SABAs (eg, albuterol) **are the treatment of first choice for managing acute severe asthma**. A SABA is also indicated for **as needed** treatment of intermittent episodes of bronchospasm (e.g., exercise induced bronchospasm).

**2-Aerosol administration** enhances bronchoselectivity and provides more rapid response **than systemic administration**.

3-Two **long-acting β2-agonists** (**LABAs**), **formoterol** and **salmeterol**, provide bronchodilation for 12 hours or longer and **are dosed twice daily**. When **combined with an ICS, formoterol may be dosed on a daily and as needed basis** (thus, more frequently than twice daily).

**Corticosteroids**

1-**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.

2-**Response to ICS is delayed**.

3-**Systemic toxicity of ICS is minimal with low-to-moderate doses**, but risk of systemic effects increases with high doses (e.g., growth suppression in children, osteoporosis, cataracts, dermal thinning, adrenal insufficiency).

4-**Local adverse effects include** dose-dependent oropharyngeal candidiasis and dysphonia, which can be **reduced by using a spacer device.**

5-**Systemic corticosteroids** are indicated in all patients **with acute severe asthma** not responding completely to initial inhaled β2-agonist administration and should be administered within 1 hour of presentation.

6-**IV therapy offers no advantage over oral administration** except in patients unable to take oral medications.

**Anticholinergics**

1-Anticholinergics **reverse cholinergic mediated bronchoconstriction** and are effective bronchodilators in asthma.

2-**Ipratropium bromide** is useful **as adjunctive therapy in acute severe asthma not completely responsive to SABA alone.**

3-Patients with persistent asthma who are **intolerant to short acting β2agonists** may be **prescribed ipratropium for rescue inhaler use**.

4-**Tiotropium bromide** is a **long acting inhaled anticholinergics** with a duration of 24 hours. Tiotropium may be considered an **add on therapy in patients whose asthma is not well controlled with ICS and LABA combination therapy.**

**Leukotriene Modifiers**

1-**Zafirlukast** and **montelukast** are oral leukotriene receptor antagonists (LTRA) that reduce the proinflammatory and bronchoconstriction effects of leukotriene D4.

2**-They are less effective than ICS**, and they are **less effective than LABAs when added to ICS**. They are **not used** to treat acute exacerbations and must be taken on a regular basis, even during symptom-free periods.

3-Use of **montelukast and zafirlukast has fallen out of favor due to increased observance of unusual adverse effects and modest therapeutic efficacy.**

4-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.

5-There have been reports of fatal **hepatic failure associated with zafirlukast**.

6-**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**

1-**These agents target the IgE pathway (Omalizumab)** **or (IL-4, IL-13) (Dupilumab), and IL-5 pathways** (**Mepolizumab, Benralizumab and reslizumab**).

**A-Omalizumab** is approved for treatment of allergic asthma.

B-**Mepolizumab, Benralizumab, Dupilumab and reslizumab** are indicated for patients with an “**eosinophilic phenotype”.**

**Magnesium Sulfate**

1-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.

2-For patients with **severe asthma exacerbations**, a single 2 g IV infusion may reduce hospital admissions

3-**Adverse effects include** hypotension, facial flushing, sweating, depressed deep tendon reflexes, hypothermia, and CNS and respiratory depression.

**Methylxanthines**

1-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.

2-Theophylline is available for oral and IV administration. Theophylline dosing requires **monitoring of serum concentrations** for both efficacy and toxicity, including seizures and death.

3-In addition, theophylline is eliminated primarily by metabolism via the hepatic CYP P450 microsomal enzymes, **and drug interactions affecting metabolism significantly affect blood concentrations.**

**Evaluation of therapeutic outcomes**

1-All patients on inhaled drugs should have **their inhalation technique evaluated monthly initially and then every 3–6 months.**

2-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.**

**Reference**

**1-Joseph T. DiPiro, Robert L. Pharmacotherapy: A Pathophysiologic Approach,**

**12th Edition. 2023.**

**2-GINA guideline. 2023.**

**Further reading**

**Table 1: Initial asthma-treatment recommended options for adults and adolescents (2).**

