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**).

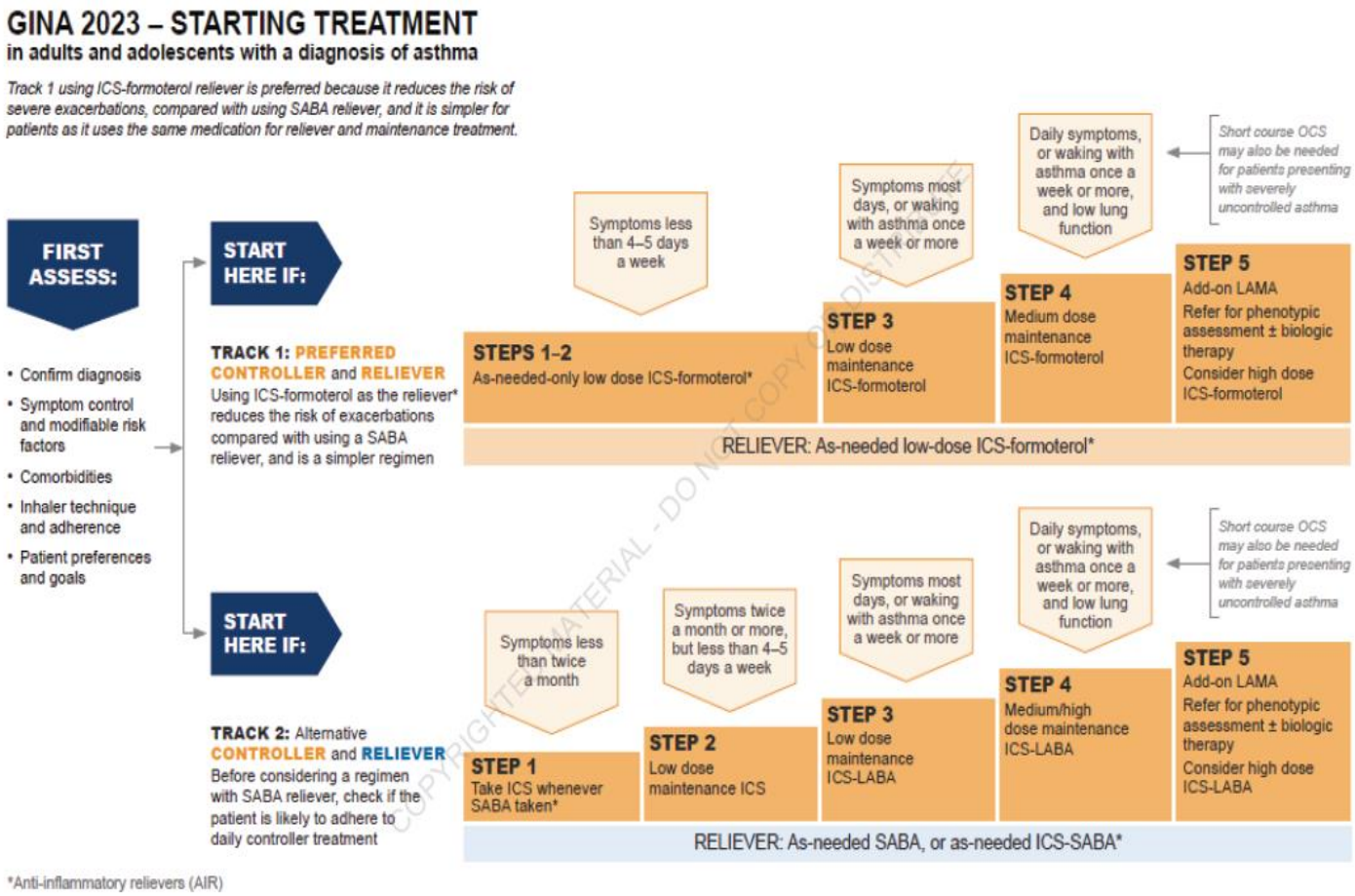

Figure 1: GINA recommendations for initial treatment in adults and adolescents

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].

Presenting symptoms	Preferred INITIAL treatment (Track 1)	Alternative INITIAL treatment (Track 2)
Infrequent asthma symptoms, e.g., less than twice a month and no risk factors for exacerbations, including no exacerbations in the last 12 months (Box 2-2B, p.38)	**As-needed low-dose ICS-formoterol** (Evidence B)	**Low-dose ICS taken whenever SABA is taken**, in combination or separate inhalers (Evidence B)
Asthma symptoms or need for reliever twice a month or more	**As-needed low-dose ICS-formoterol** (Evidence A)	**Low-dose ICS plus as-needed SABA** (Evidence A). Before choosing this option, consider likely adherence with daily ICS.
Troublesome asthma symptoms most days (e.g., 4–5 days/week); or waking due to asthma once a week or more, especially if any risk factors exist (Box 2-2B, p.38)	**Low-dose ICS-formoterol maintenance and reliever therapy** (MART) (Evidence A)	**Low-dose ICS-LABA plus as-needed SABA** (Evidence A) or plus as-needed ICS-SABA (Evidence B), **OR** Medium-dose ICS plus as-needed SABA (Evidence A) or plus as-needed ICS-SABA (Evidence B). Consider likely adherence with daily maintenance treatment.
Initial asthma presentation is with severely uncontrolled asthma, or with an acute exacerbation	**Medium-dose ICS-formoterol maintenance and reliever therapy** (MART) (Evidence D). A short course of oral corticosteroids may also be needed.	**Medium- or high-dose ICS-LABA** (Evidence D) plus as-needed SABA or plus as-needed ICS-SABA. Consider likely adherence with daily maintenance treatment. A short course of oral corticosteroids may also be needed. High-dose ICS plus as-needed SABA is another option (Evidence A) but adherence is weak compared with combination ICS-LABA.