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(قَالُوا سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا مَا عَلَّمْتَنَا ۖ إِنَّكَ أَنتَ الْعَلِيمُ الْحَكِيمُ)

اية 32 سورة البقرة

الاهداء

لن تكفي جُمل الشُّكر، وحتى لو بلغت ملء الأرض والسماء، أن تُعبِّر عن فضل أمي.

لن تستطيع كلماتي أن تصف مدى شعوري بالامتنان لصاحب الصدر الرحب والدي.

رُفقاء الدَّرب، والأهل، والخلَّان.

أُهديكم جميعًا بحثي المتواضع

Content

Abstract

Asthma is the most common respiratory disorder . Despite significant improvement in the diagnosis and management of this disorder, the majority of patient with asthma remain poorly controlled. In most patients, however, control can be achieved through the use of avoidance measures and appropriate pharmacological interventions. Inhaled corticosteroids (ICS) represent the standard of care for the majority of patients. Combination ICS/long-acting beta2-agonist inhalers are preferred for most adults who fail to achieve control with ICS therapy. Biologic therapies targeting immunoglobulin E or interleukin-5 are recent additions to the asthma treatment armamentarium and may be useful in select cases of difficult to control asthma. Allergen-specific immunotherapy represents a potentially disease-modifying therapy for many patients with asthma, but should only be prescribed by physicians with appropriate training in allergy. In addition to avoidance measures and pharmacotherapy, essential components of asthma management include: regular monitoring of asthma control using objective testing measures such as spirometry, whenever feasible; creation of written asthma action plans; assessing barriers to treatment and adherence to therapy.

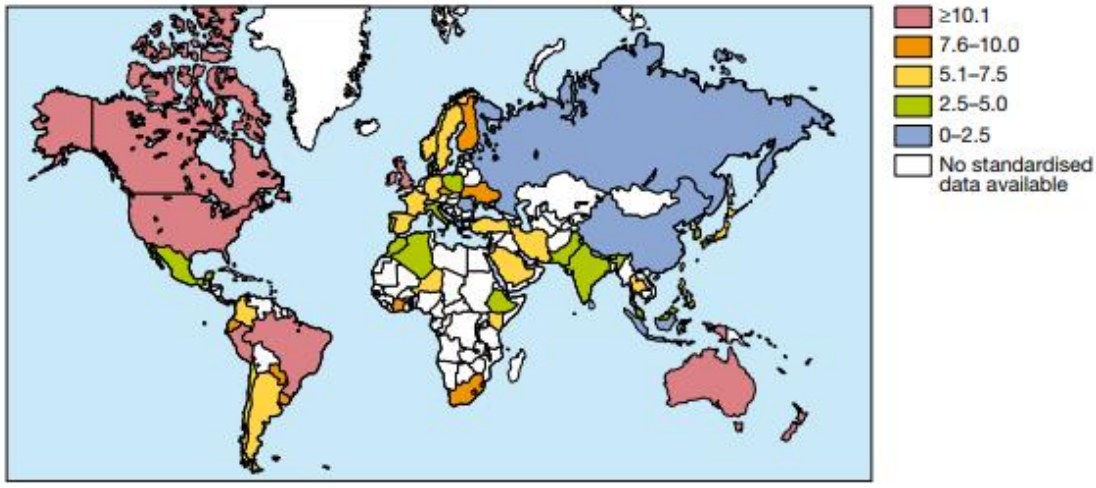
Introduction

Asthma is a common disease, affecting approximately 8–10% of the population. It is slightly more common in male children (younger than 14 years) and in female adults. There is a genetic predisposition to asthma. Prevalence, hospitalizations, and fatal asthma have all increased in the United States over the past 20 years. Each year, approximately 10 million office visits, 1.8 million emergency department visits, and more than 3500 deaths in the United States are attributed to asthma. Hospitalization rates have been highest among blacks and children, and death rates are consistently highest among blacks aged 15–24 years.[1]

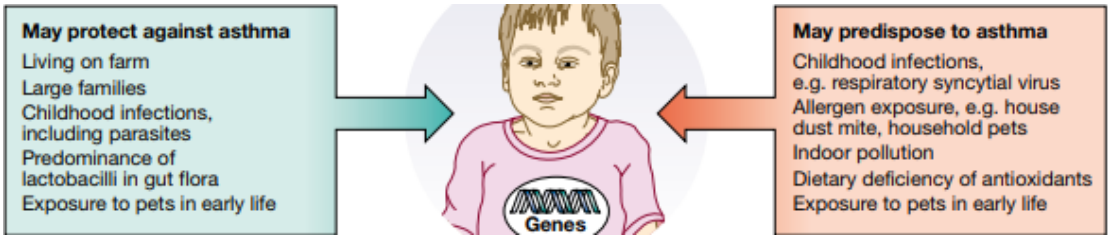
Asthma is a chronic disorder of the airways characterized by variable airway obstruction, airway hyper-responsiveness, and airway inflammation. No single histopathologic feature is pathognomonic but common findings include airway inflammatory cell infiltration with eosinophils, neutrophils, and lymphocytes (especially T cells); goblet cell hyperplasia, sometimes plugging of small airways with mucus; collagen deposition beneath the basement membrane; hypertrophy of bronchial smooth muscle; airway edema; mast cell activation; and denudation of airway epithelium. IgE plays a central role in the pathogenesis of allergic asthma. Interleukin-5 is important in promoting eosinophilic inflammation. The strongest identifiable predisposing factor for the development of asthma is atopy, but obesity is increasingly recognized as a risk factor. Exposure of sensitive patients to inhaled allergens increases airway inflammation, airway hyper-responsiveness, and symptoms.[1]

Epidemiology

The prevalence of asthma increased steadily over the latter part of the last century, first in the developed and then in the developing world. Current estimates suggest that asthma affects 300 million people world-wide and an additional 100 million persons will be diagnosed by 2025. The socio-economic impact is enormous, particularly when poor control leads to days lost from school or work, unscheduled health-care visits and hospital admissions. Although the development, course of disease and response to treatment are influenced by genetic determinants, the rapid rise in the prevalence of asthma implies that environmental factors are critically important in terms of its expression. To date, studies have explored the potential role of microbial exposure, diet, vitamins, breastfeeding, air pollution and obesity, but no clear consensus has emerged. [2]



World map showing the prevalence of clinical asthma (proportion of population (%)). Data drawn from the European Community Respiratory Health Study (ECRHS) and the International Study of Asthma and Allergies in Childhood (ISAAC).[2]



Factors implicated in the development of, or protection from, asthma.

Pathophysiology

The pathophysiology of asthma is complex and involves:

1.airway inflammation.

2. *intermittent* airflow obstruction.

3. bronchial *hyperresponsiveness*

Airway inflammation : The mechanism of inflammation in asthma may be acute, subacute, or chronic, and the presence of airway edema and mucus secretion also contributes to airflow obstruction and bronchial reactivity.[2]

Airflow obstruction : Airflow obstruction can be caused by a variety of changes, including:[2]

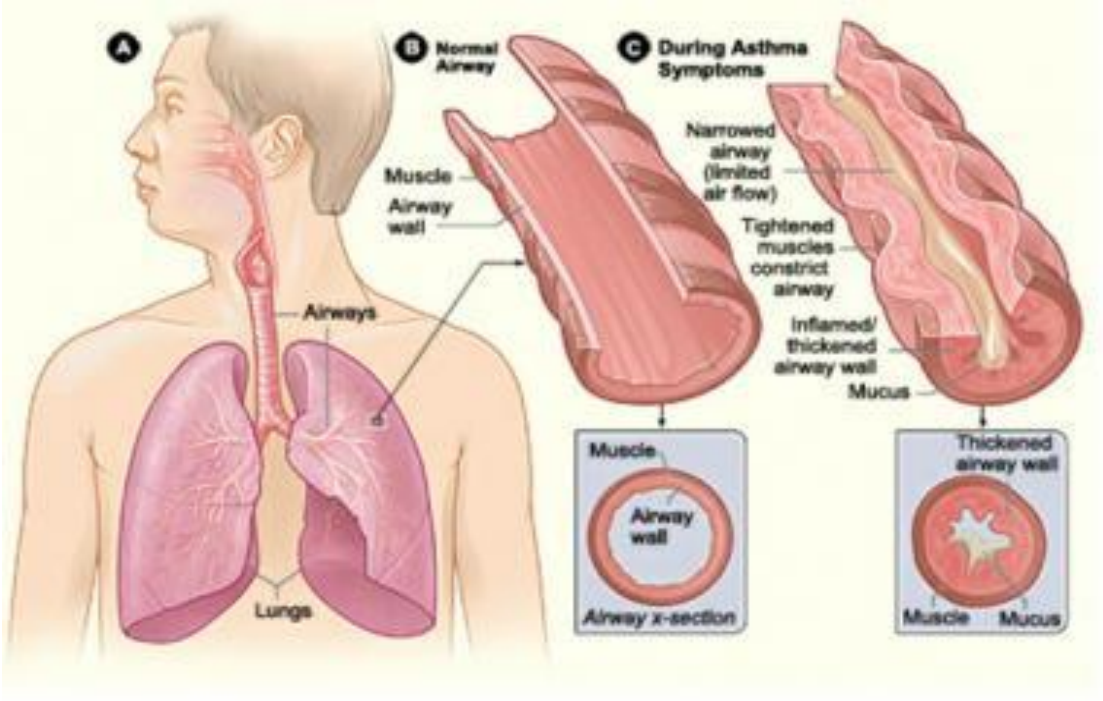
1.acute bronchoconstriction.

2. airway edema.

3. chronic mucous plug formation.

4. airway remodeling.

Airway hyperresponsiveness: bronchial hyexaggerated response to numerous exogenous and endogenous stimuli. The mechanisms involved include direct stimulation of airway smooth muscle and indirect stimulation by pharmacologically active substances from mediator-secreting cells such as mast cells or nonmyelinated sensory neurons. The degree of airway hyperresponsiveness generally correlates with the clinical severity of asthma.[2]



The relationship between atopy (a propensity to produce IgE) and asthma is well established, and in many individuals there is clear relationship between sensitisation (demonstration of skin prick reactivity or elevated serum specific IgE) and allergen exposure. Inhalation of an allergen into the airway is followed by a two-phase bronchoconstrictor response with both an early and a late-phase response . Common examples include house dust mites, pets such as cats and dogs, pests such as cockroaches, and fungi (particularly Aspergillus: allergic bronchopulmonary aspergillosis)[3]

Symptoms and Signs

Asthma is characterized by episodic wheezing, difficulty in breathing, chest tightness, and cough. Excess sputum production is common. The frequency of asthma symptoms is highly variable. Some patients have infrequent, brief attacks of asthma while others may suffer nearly continuous symptoms. Asthma symptoms may occur spontaneously or be precipitated or exacerbated by many different triggers as discussed above. Asthma symptoms are frequently worse at night; circadian variations in bronchomotor tone and bronchial reactivity reach their nadir between 3 am and 4 am, increasing symptoms of bronchoconstriction.[4]

Some physical examination findings increase the probability of asthma. Nasal mucosal swelling, increased secretions, and polyps are often seen in patients with allergic asthma. Eczema, atopic dermatitis, or other allergic skin disorders may also be present. Wheezing or a prolonged expiratory phase during normal breathing correlates well with the presence of airflow obstruction. (Wheezing during forced expiration does not.) Chest examination may be normal between exacerbations in patients with mild asthma. During severe asthma exacerbations, airflow may be too limited to produce wheezing, and the only diagnostic clue on auscultation may be globally reduced breath sounds with prolonged expiration. Hunched shoulders and use of accessory muscles of respiration suggest an increased work of breathing.[4]

Diagnosis:

1.Episodic symptoms of airflow obstruction .

2.Airflow obstruction or symptoms are at least *partially reversible*

3.Exclusion of alternative diagnoses.

1.*Spirometry with postbronchodilator response should be obtained as the primary test to establish the asthma diagnosis. a repeat spirometry 15 min after 2-4 inhalations of salbutamol(B2.agonist). A measurement of forced expiratory volume in one second (FEV1) improvement of 12% or greater from baseline represents the presence of reversible airflow obstruction,[5]

2.TheMethacholine inhalation challenge : is performed by inhalation of increasing concentrations of methacholine, which is a cholinergic agonist, until the FEV1 falls by 20% or more. which usually means that the patient has asthma **.** A negative methacholine finding is a strong indicator that the patient does not have asthma [5]

3.Exercise spirometry is the standard method for assessing patients with exercise-induced bronchospasm.[5]

An exercise challenge measures air flow limitation after a maximum exercise test. A decline in FEV1 of 10% or more is a positive result. A positive test result is highly specific for a diagnosis of asthma in children but less so in adults.(exercise indused asthma).[5]

4.Allergy skin testing : Adults with asthma often have an allergic trigger; therefore, skin tests are useful to determine the offending triggers.[5]

5.Pulse oximetry measurement is desirable in all patients with acute asthma to exclude hypoxemia.[5]

6. The chest radiograph : evaluation in most individuals with symptoms of asthma, but in most patients with asthma, chest radiography findings are normal or may indicate hyperinflation.[5]

Differential Diagnoses[6]

1.Chronic Obstructive Pulmonary Disease

.2.Bronchiectasis

3.Bronchiolitis

4.Chronic Sinusitis

5.Churg-Strauss Syndrome

6.Cystic Fibrosis

7.Foreign Body Aspiration

8.Gastroesophageal Reflux Disease

9.Heart Failure

10.Pediatric Tracheomalacia

11.Pulmonary Embolism

12.Pulmonary Eosinophilia

13.Sarcoidosis

14.Vocal Cord Dysfunction

Management Guidelines

1. Assessing and monitoring asthma severity and asthma control—Severity is the intrinsic intensity of the disease process. Control is the degree to which symptoms and limitations on activity are minimized by therapy. Responsiveness is the ease with which control is achieved with therapy. NAEPP 3 guidelines emphasize control over classifications of severity, since the latter is variable over time and in response to therapy. A measure of severity on initial presentation is helpful, however, in guiding the initiation of therapy. Control of asthma is assessed in terms of impairment (frequency and intensity of symptoms and functional limitations) and risk (the likelihood of acute exacerbations or chronic decline in lung function)[7]

Components of Severity		Classification of Asthma Severity ≥ 12 years of age			
			Persistent		
		Intermittent	Mild	Moderate	Severe
Impairment	Symptoms	≤ 2 days/week	> 2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤ 2×/month	3–4×/month	> 1×/week but not nightly	Often 7×/week
	Short-acting β_2-agonist use for symptom control (not prevention of EIB)	≤ 2 days/week	> 2 days/week but not daily, and not more than 1× on any day	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
Normal FEV_1/FVC: 8–19 yr 85%; 20–39 yr 80%; 40–59 yr 75%; 60–80 yr 70%	Lung function	• Normal FEV_1 between exacerbations • FEV_1 > 80% predicted • FEV_1/FVC normal	• FEV_1 > 80% predicted • FEV_1/FVC normal	• FEV_1 > 60% but < 80% predicted • FEV_1/FVC reduced 5%	• FEV_1 < 60% predicted • FEV_1/FVC reduced > 5%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year (see note)	≥ 2/year (see note) →		
		← Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. Relative annual risk of exacerbations may be related to FEV_1.			
Recommended Step for Initiating Treatment		Step 1	Step 2	Step 3 and consider short course of oral systemic corticosteroids	Step 4 or 5
(See Figure 9–2 for treatment steps.)		In 2–6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.			

Classifying asthma severity and initiating treatment. (Adapted from National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. National Institutes of Health Pub. No. 08-4051. Bethesda, MD, 2007.)[7]

2. Patient education designed to foster a partnership for care—Active self-management reduces urgent care visits and hospitalizations and improves perceived control of asthma. Therefore, an outpatient preventive approach that includes self-management education is an integral part of effective asthma care. All patients, but particularly those with poorly controlled symptoms or history of severe exacerbations, should have a written asthma action plan that includes instructions for daily management and measures to take in response to specific changes in status. Patients should be taught to recognize symptoms—especially patterns indicating inadequate asthma control or predicting the need for additional therapy .[7]

3. Control of environmental factors and comorbid conditions that affect asthma—Significant reduction in exposure to nonspecific airway irritants or to inhaled allergens in atopic patients may reduce symptoms and medication needs. Comorbid conditions that impair asthma management, such as rhinosinusitis, gastroesophageal reflux, obesity, and obstructive sleep apnea, should be identified and treated. This search for complicating conditions is particularly crucial in the initial evaluation of new asthma, and in patients who have difficult-to-control symptoms or frequent exacerbations.[7]

4. Pharmacotherapy for asthma—The goals of pharmacologic therapy are to minimize chronic symptoms that interfere with normal activity (including exercise), to prevent recurrent exacerbations, to reduce or eliminate the need for emergency department visits or hospitalizations, and to maintain normal or near-normal pulmonary function.[7]

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A stepwise approach to the management of asthma

Step 1: Occasional use of inhaled short-acting β2 -adrenoreceptor agonist bronchodilators For patients with mild intermittent asthma (symptoms less than once a week for 3 months and fewer than two nocturnal episodes/month), it is usually sufficient to prescribe an inhaled short-acting β2 -agonist (salbutamol or terbutaline), to be used on an as-required basis.[8]

Step 2: Introduction of regular 'preventer' therapy Regular anti-inflammatory therapy (preferably inhaled corticosteroids (ICS) such as beclometasone, budesonide, fluticasone or ciclesonide) should be started in addition to inhaled β2 -agonists taken on an as-required basis in any patient who:[8]

- has experienced an exacerbation of asthma in the last 2 years
- uses inhaled β2 -agonists three times a week or more
- reports symptoms three times a week or more
- is awakened by asthma one night per week.

For adults, a reasonable starting dose is 400 µg beclometasone dipropionate (BDP) or equivalent per day, although higher doses may be required in smokers. Alternative but much less effective preventive agents include chromones, leukotriene receptor antagonists, and theophyllines.[8]

Step 3: Add-on therapy If a patient remains poorly controlled despite regular use of ICS, a thorough review should be undertaken focusing on adherence, inhaler technique and on-going exposure to modifiable aggravating factors.[8]

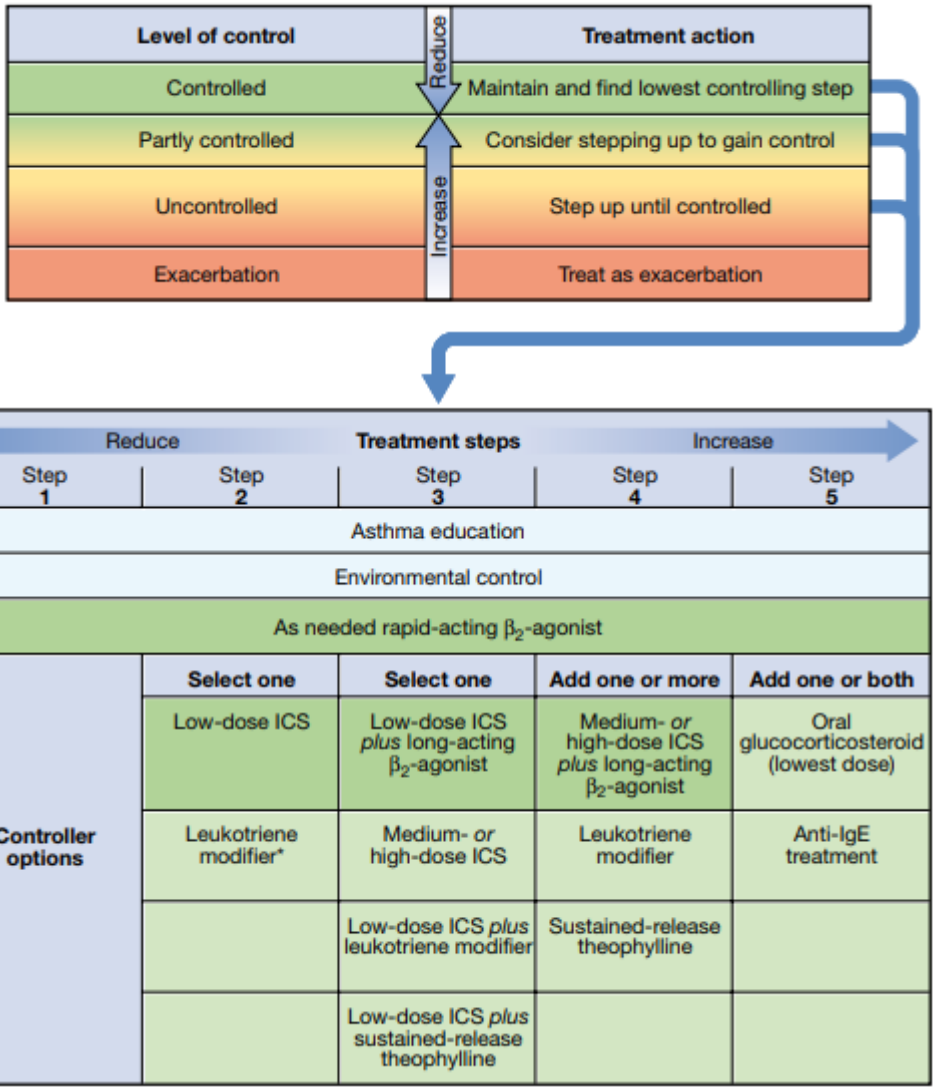
A further increase in the dose of ICS may benefit some patients, but in general, add-on therapy should be considered in adults taking 800 µg/day BDP (or equivalent). Long-acting β2 -agonists (LABAs), such as salmeterol and formoterol, with a duration of action of at least 12 hours, represent the first choice of add-on therapy.[8]

Oral leukotriene receptor antagonists (e.g. montelukast 10 mg daily) are generally less effective than LABA as add-on therapy but may facilitate a reduction in the dose of ICS and control exacerbations. Oral theophyllines may be considered in some patients but their unpredictable metabolism, propensity for drug interactions and prominent side-effect profile limit their widespread use.[8]

Step 4: Poor control on moderate dose of inhaled steroid and add-on therapy: addition of a fourth drug In adults, the dose of ICS may be increased to 2000 µg BDP/budesonide (or equivalent) daily. A nasal corticosteroid preparation should be used in patients with prominent upper airway symptoms. Oral therapy with leukotriene receptor antagonists, theophyllines or a slowrelease β2 -agonist may be considered. If the trial of add-on therapy is ineffective, it should be discontinued. Oral itraconazole should be contemplated in patients with allergic bronchopulmonary aspergillosis (ABPA).[8]

Step 5: Continuous or frequent use of oral steroids At this stage prednisolone therapy (usually administered as a single daily dose in the morning) should be prescribed in the lowest amount necessary to control symptoms.[8]

Step-down therapy Once asthma control is established, the dose of inhaled (or oral) corticosteroid should be titrated to the lowest dose at which effective control of asthma is maintained. Decreasing the dose of ICS by around 25–50% every 3 months is a reasonable strategy for most patients.[8]



Management approach based on asthma control. For children older than 5 years, adolescents and adults. (ICS = inhaled corticosteroid) *Receptor antagonist or synthesis inhibitors.[8]

Asthma Exacerbations

The course of asthma may be punctuated by exacerbations characterised by increased symptoms, deterioration in lung function, and an increase in airway inflammation. Exacerbations are most commonly precipitated by viral infections, but moulds (Alternaria and Cladosporium), pollens (particularly following thunderstorms) and air pollution are also implicated. [9]

Management of mild–moderate exacerbations The widely held view that an impending exacerbation may be avoided by doubling the dose of ICS has failed to be validated by recent studies. Short courses of 'rescue' oral corticosteroids (prednisolone 30–60 mg daily) are therefore often required to regain control of symptoms. Tapering of the dose to withdraw treatment is not necessary unless given for more than 3 weeks. Indications for 'rescue' courses include;[9]

- symptoms and PEF progressively worsening day by day
- fall of PEF below 60% of the patient's personal best recording
- onset or worsening of sleep disturbance by asthma
- persistence of morning symptoms until midday
- progressively diminishing response to an inhaled bronchodilator
- symptoms severe enough to require treatment with nebulised or injected bronchodilators.

Management of Severe exacerabation

Severe asthma **Defined as any of**:

• PEFR 33–50% predicted or best • RR ≥25

• HR ≥110B/ m • Inability to complete sentence in one breath.

Life-threatening asthma **:** Any one of:

• PEFR <33% • SaO2 <92% (NB needs ABG) • *PaO2 <8kPa*

• N ormal CO2 • Silent chest • Cyanosis

• Poor respiratory effort • Bradycardia/arrhythmia/hypotension

• Exhaustion • Confusion • Coma.

Near-fatal asthma

• Raised PaCO2, and/or

• N eeding mechanical ventilation with raised inflation pressures.

Treatment

• Oxygen. High concentrations of oxygen (humidified if possible) should be administered to maintain the oxygen saturation above 92% in adults.[9]

The presence of a high PaCO2 should not be taken as an indication to reduce oxygen concentration but as a warning sign of a severe or life-threatening attack.[9]

• High doses of inhaled bronchodilators. Short-acting β2 - agonists are the agent of first choice. In hospital they are most conveniently

administered via a nebuliser driven by oxygen but delivery of multiple doses of salbutamol via a metered-dose inhaler through a spacer device provides equivalent bronchodilatation and may be used in primary care. Ipratropium bromide should be added to salbutamol in patients with acute severe or life-threatening attacks.[9]

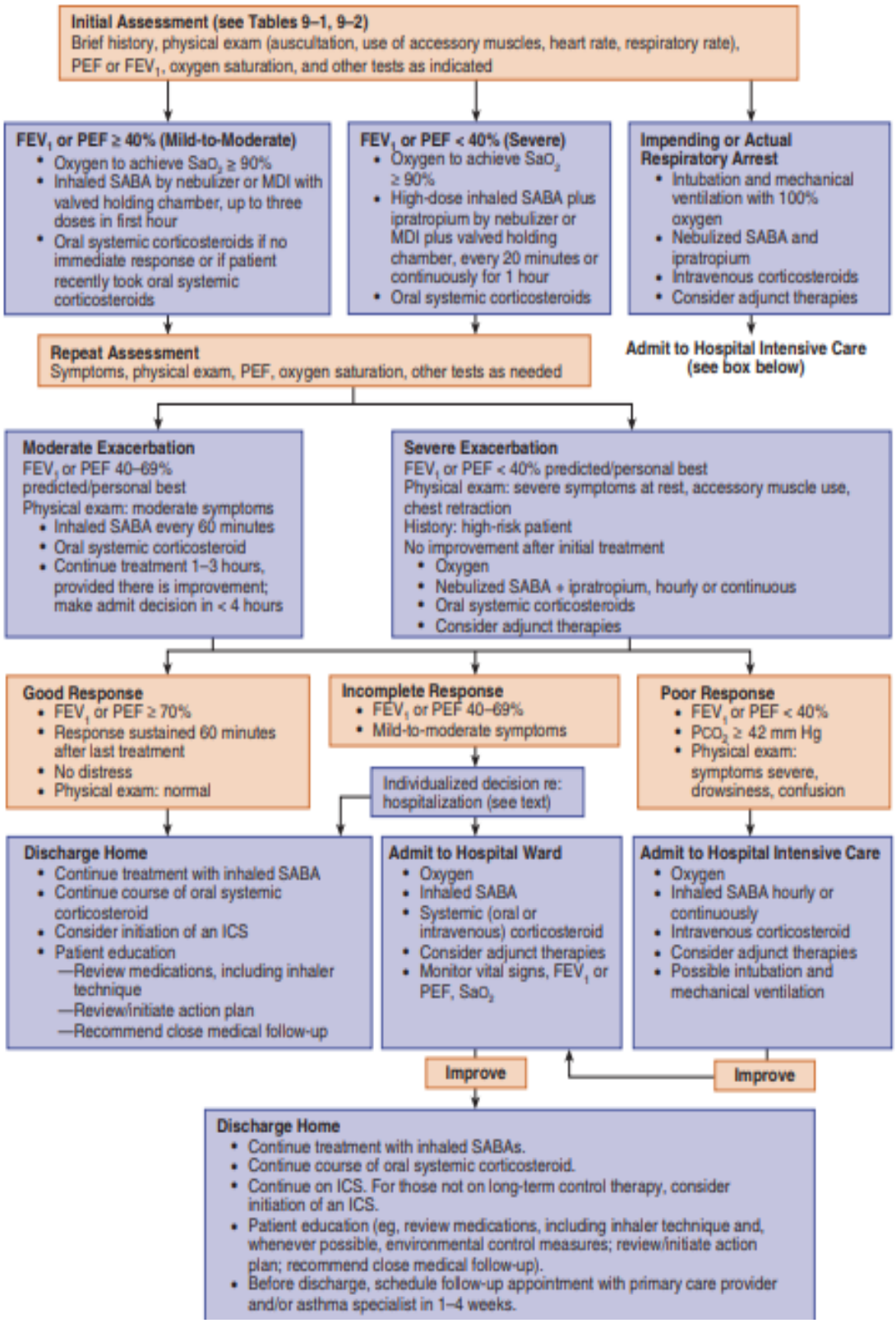
• Systemic corticosteroids. Systemic corticosteroids reduce the inflammatory response and hasten the resolution of exacerbations. They should be administered to all patients experiencing an acute severe attack. They can usually be administered orally as prednisolone, but intravenous hydrocortisone may be given in patients who are vomiting or unable to swallow.[9]

• Intravenous fluids. There are no controlled trials to support the use of intravenous fluids but many patients are dehydrated due to high insensible water loss and probably benefit from these. Potassium supplements may be necessary because repeated doses of salbutamol can lower serum potassium.[9]

• *IV magnesium sulfate—immediately if very severe and if poor* response to above therapies,1.2–2g IV infusion over 20min. *There is no evidence to support the use of NIV in the management of asthma. Hypercapnic respiratory failure in acute severe asthma is an urgent indication for endotracheal intubation.*[9]

• *IV aminophylline—some patients may respond; give if poor response* to initial therapy, in acute severe or life-threatening disease .Dose—5mg/kg loading dose over 20min, followed by continuous infusion of 0.5–

0.7mg/kg (500mg in 500mL normal saline or 0.5% glucose at 0.5 × body weight in kg/mL/h).[9]



Management of asthma exacerbations: emergency department and hospital-based treatment. (Adapted from National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. National Institutes of Health Pub. No. 08-4051. Bethesda, MD, 2007.)[9]

Conclusion

Asthma is characterized by variable airway obstruction, airway hype-responsiveness', and airway inflammation. Management of persistent asthma requires avoidance of aggravating environmental factors, use of short-acting β2-agonists for rapid relief of symptoms, and daily use of inhaled corticosteroids. Other controller medications, such as long-acting bronchodilators and biologics, may be required in moderate and severe asthma. Patients with severe asthma generally benefit from consultation with an asthma specialist for consideration of additional treatment, including injectable biologic agents.

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