

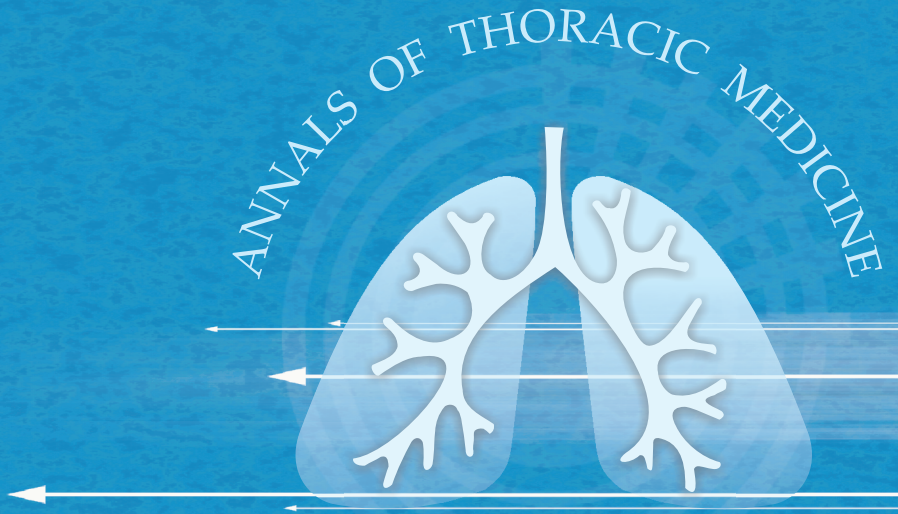
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# The Saudi initiative for asthma – 2012 update: Guidelines for the diagnosis and management of asthma in adults and children

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**Abstract:**

This an updated guidelines for the diagnosis and management of asthma, developed by the Saudi Initiative for Asthma (SINA) group, a subsidiary of the Saudi Thoracic Society. The main objective of SINA is to have updated guidelines, which are simple to understand and easy to use by non-asthma specialists, including primary care and general practice physicians. This new version includes updates of acute and chronic asthma management, with more emphasis on the use of Asthma Control Test in the management of asthma, and a new section on “difficult-to-treat asthma.” Further, the section on asthma in children was re-written to cover different aspects in this age group. The SINA panel is a group of Saudi experts with well-respected academic backgrounds and experience in the field of asthma. The guidelines are formatted based on the available evidence, local literature, and the current situation in Saudi Arabia. There was an emphasis on patient–doctor partnership in the management that also includes a self-management plan. The approach adopted by the SINA group is mainly based on disease control as it is the ultimate goal of treatment.

**Key words:**

Asthma, asthma control test, guidelines, Saudi Arabia

Asthma is a common chronic disorder of the Airways, characterized by variable reversible and recurring symptoms related to airflow obstruction, bronchial hyper-responsiveness, and underlying inflammation. It is one of the most common chronic diseases in Saudi Arabia, affecting more than 2 million Saudis.<sup>[1]</sup> Its impact is manifested in patients, their families, and the community as a whole in terms of lost work and school days, poor quality of life, frequent emergency department visits, hospitalizations, and deaths.<sup>[2-4]</sup> As part of the commitment of the Saudi Thoracic Society (STS) toward a long-term enhancement plan for promoting best practice in asthma management, the Saudi Initiative for Asthma (SINA) was developed in 2009.<sup>[5]</sup> SINA aimed to have updated guidelines, which are simple to understand and easy to use by non-asthma specialists, including primary care and general practice physicians.<sup>[6]</sup> Since the implementation of SINA, the authors have realized that there is the need to update the guidelines with special emphasis on new evidence, easy-to-use charts, with a new section on difficult-to-treat asthma (DTA), and more information related to asthma in children.<sup>[6]</sup> The updated guidelines followed the same methodology as the original guidelines.

**Epidemiology**

Asthma is one of the most common chronic illnesses in Saudi Arabia and local reports suggest that the prevalence of asthma is increasing.<sup>[7]</sup> Despite the abundance of high-caliber medical services and the availability of international guidelines, recent studies have shown that the burden of asthma might be significantly higher than previously estimated.<sup>[8,9]</sup> Poor knowledge, fear of use of new drugs, and the lack of awareness of the importance of controlling of the disease are common among primary care physicians who care for asthma patients in the Kingdom of Saudi Arabia (KSA). These are all important factors that likely contribute to the magnitude of this burden.<sup>[10]</sup> Consequently, many asthma patients continue to be under-diagnosed, under-treated, and are at a risk of acute exacerbations resulting in missing work or school, increased use of expensive acute healthcare services, and reduced quality of life.<sup>[11,12]</sup> A recent asthma control survey showed that only 5% of patients were controlled, 31% were partially controlled, and 64% were uncontrolled.<sup>[13]</sup>

Al-Fryh *et al.* investigated the changing prevalence of asthma in the KSA.<sup>[14]</sup> Two populations of school children of age group

between 8 and 16 years were studied using an internationally designed protocol in 1986 and 1995. Comparison of the data of Riyadh versus Hail (an inland desert with dry environment) and Jeddah versus Gizan (a coastal humid environment) revealed that the prevalence of asthma in similar populations increased significantly from 8% in 1986 to 23% in 1995.<sup>[15]</sup> The study also revealed that there was increased exposure to environmental factors such as tobacco smoke and indoor animals in Saudi houses, which can also play a role.

Other studies in the KSA compared the prevalence of physician-diagnosed asthma among Saudi school boys in Yanbu, an industrial city, to two non-industrial villages in a cross-sectional study.<sup>[16]</sup> The prevalence in Yanbu and in the villages of Al-Furash and Al-Gafure was 13.9% and 8%, respectively. Hijazi *et al.* conducted a study of 1020 urban and 424 rural children aged 12 years. They attempted to compare the prevalence of allergic symptoms among those living in urban and rural areas of the KSA and to investigate factors associated with any differences found.<sup>[17]</sup> The prevalence of allergic symptoms was found to be significantly greater among urban children than the rural ones and was more among Saudi children than non-Saudi children.<sup>[18]</sup> Males were more susceptible to have certain respiratory symptoms and females had more eye and skin symptoms. The educational level and occupation of the father did not influence the likelihood of having symptoms. A study by Al-Kabbaa *et al.* found that 39% of primary care physicians meet the standards of the national guidelines in management of asthma.<sup>[19]</sup> However, the overall level of awareness among physicians was low (52%). Their proficiency in general knowledge, diagnosis, classification of severity, and management was also low.

Most of the studies investigating the prevalence of asthma in various countries have focused on children below the age of 15 years or adults above the age of 18 years. There is limited knowledge concerning the prevalence of asthma in 16- to 18-year-old adolescents. A recent study conducted by the STS investigated the prevalence of asthma and associated symptoms in 16- to 18-year-old adolescents attending high schools in the city of Riyadh. This study utilized the International Study of Asthma and Allergies in Children (ISAAC) questionnaire tool. Out of 3073 students (1504 boys and 1569 girls), the prevalence of lifetime wheeze, wheeze during the past 12 months, and physician-diagnosed asthma was 25.3%, 18.5%, and 19.6%, respectively. The prevalence of exercise-induced wheezing and night coughing in the past 12 months was 20.2% and 25.7%, respectively. The prevalence of rhinitis symptoms in students with lifetime wheeze, physician-diagnosed asthma, and exercise-induced wheeze was 61.1%, 59.9%, and 57.4%, respectively. Rhinitis symptoms were significantly associated with lifetime wheeze (OR = 2.5,  $P < 0.001$ ), physician-diagnosed asthma (OR = 2.2,  $P < 0.001$ ), and exercise-induced wheeze (OR = 1.9,  $P < 0.001$ ).<sup>[20]</sup>

Although the prevalence of asthma in Saudi Arabian adults is unknown, the overall prevalence of asthma in Saudi children has been reported to range from 8% to 25%, based on studies conducted over the past three decades. The highest prevalence of physician-diagnosed asthma in Saudi Arabia was reported to be 25% in 2004.<sup>[21]</sup> Epidemiological studies in Saudi Arabia revealed an increasing prevalence of asthma in the past three decades, which may be attributed to rapid lifestyle changes related to the modernization of Saudi society, changes in

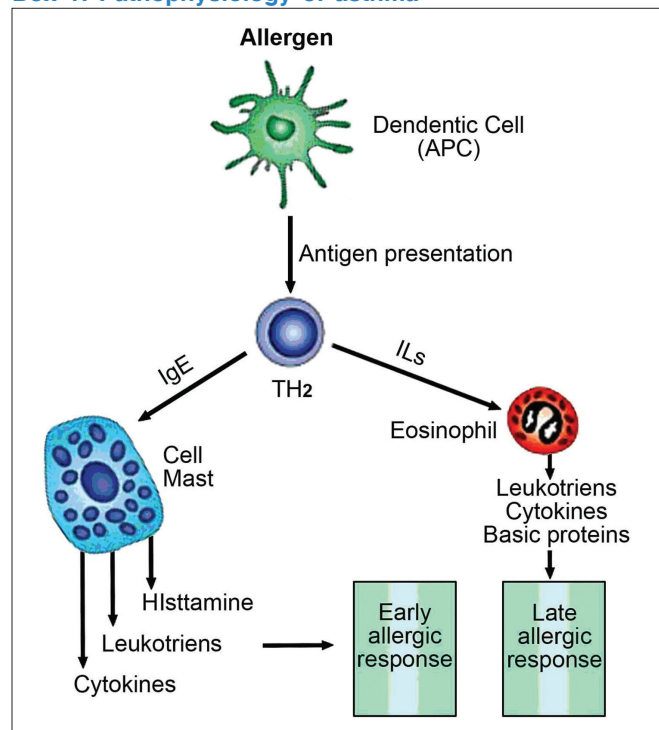
dietary habits, and exposure to environmental factors such as indoor allergens, dust, sand storms, and tobacco. Additionally, this high prevalence of asthma could be attributed to an increase in asthma awareness in the general population and among healthcare workers, allowing more individuals to be diagnosed. Other explanations have attributed the increased prevalence to the hygiene hypothesis, which proposes that there is a lack of sufficient microbial exposure early in life due to pharmacological manipulations and vaccines.<sup>[22]</sup>

## Pathophysiology of Asthma

### Airways inflammation

Asthma is a complex syndrome characterized by airway hyper-responsiveness (AH) and is caused by a multicellular inflammatory reaction that leads to airway obstruction [Box 1].<sup>[23]</sup> Recruitment and activation of mast cells, macrophages, antigen-presenting dendritic cells, neutrophils, eosinophils, and T lymphocytes result in an inflammatory and cellular infiltration of the airways.<sup>[24]</sup> Type 2 T-helper cells (Th2) have a major role in the activation of the immune cascade that leads to the release of many mediators such as interleukins (IL) IL-3, IL-4, IL-5, IL-13, and granulocyte macrophage colony stimulating factor (GM-CSF).<sup>[25,26]</sup> Some mediators such as IL-4 activate B lymphocytes to produce immunoglobulin E (IgE), while others (e.g. IL-3, IL-5, and GM-CSF) are related to eosinophilic airway inflammation. Severe asthma may present various inflammatory phenotypes, such as persistent eosinophilic bronchitis, neutrophilic infiltration of the airway, and a pauci-granulocytopenic type of inflammation.<sup>[27]</sup> Such persistent inflammation results in airway remodeling which includes increased deposition of extracellular proteins, smooth muscle hypertrophy and hyperplasia, and increased goblet cells.<sup>[28]</sup> The airway epithelium becomes fragile and thin, and

### Box 1: Pathophysiology of asthma



the epithelial basement membrane thickens. There is also increased mucus production and endothelial leakage which leads to mucosal edema. Mediator-induced abnormalities in the parasympathetic and non-adrenergic non-cholinergic nervous systems may also lead to increased bronchial hyper-responsiveness. Recent data have shown that all asthmatic patients have inflammation in the upper airways, irrespective of the presence of symptoms of rhinosinusitis. Studies have also shown that stimulation by an irritant instilled in the nose leads to eosinophilic infiltration in the lungs within a few hours later. Such co-existence of inflammation in both the upper and lower airways has led to the suggestion of the terminology “united airway disease.” In clinical practice, failure to recognize and treat rhinosinusitis may affect asthma control.<sup>[29]</sup>

### Airway hyper-responsiveness

AH to direct (histamine or methacholine) and indirect (exercise, cold air, mannitol, adenosine monophosphate, or isocapnic hyperventilation) challenges is a characteristic of asthma.<sup>[30]</sup> When asthma symptoms are present, there is a relatively good correlation between the severity of disease and the degree of AH.<sup>[31]</sup> AH is not a static feature of asthma; it may increase after sensitizing exposures and may decrease after anti-inflammatory treatments or if there is a reduction in relevant environmental exposures. Asthma has a variable component, which is related to airway inflammation, and a more refractory component that is largely attributed to underlying airway structural changes that are also known as remodeling.<sup>[32]</sup>

### Early and late responses

Following presentation of the antigen by dendritic cells in a sensitized patient, certain inflammatory cascades become activated leading to the attachment of IgE antibodies to inflammatory cells such as mast cells.<sup>[33]</sup> Cross-linking of IgE receptors leads to degranulation of inflammatory cells and liberation of various mediators which are responsible for the allergic response. The allergen-induced airway response may be immediate (early response) with a fall in expiratory flows within an hour of exposure, or may be delayed (late response) with the fall in expiratory flows being observed within 2–8 h. An increase in AH and in the variability of airway obstruction may occur within the following 2–3 days depending on the intensity of the response.<sup>[34,35]</sup>

### Airway remodeling

Structural airway changes may develop even before the disease becomes symptomatic. They can also occur in patients with allergic rhinitis, who are associated with an increased risk of developing asthma. The most prominent changes include epithelial damage, subepithelial fibrosis, increased airway vasculature, increases in extracellular matrix proteins including collagens and proteoglycans, and increased smooth muscle mass. The mucus hypersecretion observed in asthma is related to an increase in the number of secretory glands and cells such as goblet cells. These changes are generally attributed to the underlying inflammatory process, although other mechanisms may play a role.<sup>[23]</sup> It has been proposed that remodeling may be involved in the development and persistence of asthma, in the accelerated decline in pulmonary function, and in the development of a more “fixed” component of airway obstruction in some asthmatic patients, particularly severe asthmatics. Although a relationship has been found between the severity of asthma and some of the

components of airway remodeling, researchers have not yet been able to adequately distinguish severe asthma from milder forms on the basis of histological features alone.<sup>[36]</sup> Prevention of airway remodeling has not been well studied, but it is possible that sustained treatment with anti-inflammatory medications as well as the prevention of exacerbations may have a role in preventing or delaying airway remodeling.

## Methods

The SINA was initially based on two existing international guidelines, the Global Initiative for Asthma (GINA) and the National Asthma Education and Prevention Program (NAEPP).<sup>[37-40]</sup> It was customized based on reviewing the available local literature and the current setting in Saudi Arabia. Consensus among the SINA panel was followed whenever there was lack of evidence in the form of non-randomized controlled trials or non-randomized studies.<sup>[41]</sup> The following criteria are the same as those used by SINA:

- Evidence Category A: Randomized controlled trials with rich body of data
- Evidence Category B: Randomized controlled trials with limited body of data
- Evidence Category C: Non-randomized trials and observational studies
- Evidence Category D: SINA panel consensus judgment. This category is only used in cases where the provision of some guidance was deemed valuable, but the clinical literature addressing the subject was insufficient to justify placement in one of the other categories.

The task was divided among three groups that covered chronic asthma in adults, acute asthma in adults, and asthma in children. Each section was internally reviewed by at least two other members. The SINA panel conducted round-table discussions frequently and jointly reviewed it. A panel of international experts reviewed the guidelines and their recommendations were thoughtfully considered. The expected outcome will lead to safe high-quality patient care.

## Diagnosis of Asthma

The diagnosis of asthma is based on clinical assessment as there is no gold standard diagnostic test for asthma. This includes a detailed history and physical examination supplemented by spirometry, with reversibility testing, to support the diagnosis. To date, there is no single diagnostic test of asthma, although the assessment of AH is helpful in this regard.<sup>[42,43]</sup> The symptoms of wheezing, cough, shortness of breath, and chest tightness are not specific for asthma and can be seen with other pulmonary diseases. The pattern of symptoms is usually variable over time and the patient may be entirely asymptomatic between attacks.<sup>[42]</sup> Symptoms are usually worse at night, particularly in children, and could be provoked by exercise or other triggering factors. Box 2 lists the relevant questions that are commonly considered when taking history of patients. Moreover, the obstructive pattern in spirometry is not limited to asthma and occurs in others.<sup>[44,45]</sup>

Some patients, particularly children, have a cough as the main or the only symptom without wheezing or shortness of breath, which is called cough-variant asthma. In this situation, the diagnosis

may be confirmed by a positive response to asthma medications. Others may have their asthma induced by exercise only, a condition called exercise-induced asthma (EIA). Symptoms of asthma may be worsened by coexisting gastro-esophageal reflux disease (GERD), rhinosinusitis, obesity, sleep disorders, or the use of some medications such as beta blockers and nonsteroidal anti-inflammatory drugs (NSAIDs) including aspirin (ASA).<sup>[46]</sup> Asthma and rhinosinusitis commonly coexist.<sup>[47,48]</sup>

Physical examination may reveal bilateral expiratory wheezing, which may be absent between exacerbations. Examination of the upper airways is important to look for evidence of allergic rhinitis, such as mucosal swelling, nasal polyps, and postnasal dripping. Other allergic manifestations, such as atopic dermatitis and/or eczema, also support the diagnosis of allergic asthma.<sup>[49]</sup> The presence of localized wheeze, crackles, stridor, clubbing, or heart murmurs should suggest alternative diagnoses.<sup>[50,51]</sup> Therefore, there should be a careful consideration of any possible alternative diagnoses prior to commencing asthma treatment by a physician.

The Asthma Control Test (ACT) is a short, validated, self-administered questionnaire to assess asthma control [Box 3]. It

consists of five items including limitation of activity, shortness of breath, frequency of night symptoms, use of rescue medication, and rating of overall control of the disease over the past 4 weeks.<sup>[52]</sup> The score of the ACT is the sum of the five questions where each is scored from 1 (worst) to 5 (best), leading to a maximum best score of 25. A score of  $\geq 20$  indicates controlled asthma, 16–19 partially controlled asthma, and  $< 16$  uncontrolled asthma.<sup>[53]</sup>

Spirometry is necessary to detect airflow obstruction, assess severity, and demonstrate significant reversibility [Box 4]. It may help to identify other differential diagnoses, for example, large airway obstruction. However, normal spirometry, including a failure to show reversibility, does not rule out the diagnosis of asthma, as it can be normal with the patient still being symptomatic.<sup>[54]</sup> Serial peak expiratory flow (PEF) measurements may be helpful in asthma diagnosis and follow-up. Bronchoprovocation testing is another tool used by specialists to rule out asthma; however, a diagnostic therapeutic trial with inhaled steroids and bronchodilator may be useful in confirming a diagnosis.<sup>[55]</sup>

Chest X-ray is not routinely recommended unless the diagnosis is in doubt, symptoms are not typical, or suggest

**Box 2: Relevant questions in the diagnosis of asthma**

- Does the patient or his/her family have a history of asthma or other atopic conditions, such as eczema or allergic rhinitis?
- Does the patient have recurrent attacks of wheezing?
- Does the patient have a troublesome cough at night?
- Does the patient wheeze or cough after exercise?
- Does the patient experience wheezing, chest tightness, or cough after exposure to pollens, dust, feathered or furry animals, exercise, viral infection, or environmental smoke (cigarettes, burning incense “Bukhoor,” or wood)?
- Does the patient experience worsening of symptoms after taking aspirin/nonsteroidal anti-inflammatory medication or use of B-blockers?
- Does the patient’s cold “go to the chest” or take more than 10 days to clear up?
- Are symptoms improved by appropriate asthma treatment?
- Are there any features suggestive of occupational asthma?

**Box 3: Asthma control test\***

Asthma control test items					Score
1. In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, at school, or at home?					
All of the time	Most of the time	Some of the time	A little of the time	None of the time	
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	
2. During the past 4 weeks, how often have you had shortness of breath?					
More than once a day	Once a day	3–6 times a week	Once or twice a week	Not at all	
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	
3. During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness, or pain) wake you up at night, or earlier than usual in the morning?					
4 or more nights a week	2 to 3 nights a week	Once a week	Once or twice	Not at all	
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	
4. During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication such as salbutamol?					
3 or more times per day	1 or 2 times per day	2 or 3 time per week	Once a week or less	Not at all	
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	
5- How would you rate your asthma control during the past 4 weeks?					
Not controlled at all	Poorly controlled	Somewhat controlled	Well controlled	Completely controlled	
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	

\*Adapted from reference<sup>[52]</sup>

other diagnoses. Peripheral eosinophilia and elevated IgE level are supportive of the diagnosis, but are not routinely recommended. Skin testing and radioallergen sorbent test (RAST) may be helpful in identifying allergens to which the patient has been sensitized and in developing a strategy for avoiding allergen exposure.<sup>[56]</sup>

### Medications Used for the Treatment of Asthma

The objective of asthma treatment is to achieve and maintain control of the disease. Medications used to treat asthma can be classified as controllers or relievers. *Controllers* are medications taken daily on a long-term basis to keep asthma under clinical control mainly through their anti-inflammatory effects.<sup>[57]</sup> *Relievers* are medications used on an “as-needed basis” that act quickly to reverse bronchoconstriction and relieve symptoms.

#### Controller medications

##### Inhaled corticosteroids

Inhaled corticosteroids (ICS) are currently the most effective anti-inflammatory medications for the treatment of asthma.<sup>[58,59]</sup> They reduce symptoms, improve quality of life, improve lung function, decrease AH, control airway inflammation, reduce frequency and severity of exacerbations, and reduce asthma mortality. When they are discontinued, deterioration of clinical control follows within weeks to months in most patients. ICS differ in their potency and bioavailability. Most of the benefits from ICS are achieved in adults at relatively low doses [Boxes 5 and 6]. As tobacco smoking reduces the responsiveness to ICS, higher doses may be required in patients who smoke. To reach control, add-on therapy with another class of controller is preferred to increasing the dose of ICS; however, some patients with severe asthma may benefit from long-term treatments

#### Box 4: Acceptable spirometry and significant bronchodilator response<sup>[303]</sup>

- Proper instructions on how to perform the forced expiratory maneuver must be given to patients, and the highest value of three readings taken
- The degree of significant reversibility is defined as an improvement in FEV1  $\geq$  12% and  $\geq$  200 ml from the pre-bronchodilator value

#### Box 5: List of equipotent daily doses in micrograms ( $\mu$ g) of the ICS available in Saudi market for adults

Drug	Low dose	Medium dose	High dose
Beclomethasone dipropionate	200–500	>500–1000	>1000–2000
Budesonide	200–400	>400–800	>800–1600
Ciclesonide	80–160	>160–320	>320–1280
Fluticasone propionate	100–250	>250–500	>500–1000

#### Box 6: List of equipotent daily doses in micrograms ( $\mu$ g) of the ICS available in the Saudi market for children

Drug	Less than 5 years	Children above 5 years		
	Low dose	Low dose	Medium dose	High dose
Beclomethasone dipropionate	100	100–200	>200–400	>400
Budesonide	200 Nebulizer = 500	250–500	>500–1000	>1000
Ciclesonide	Not studied	80–160	>160–320	>320
Fluticasone propionate	100	100–200	>200–500	>500

with high doses of ICS.<sup>[60,61]</sup> The clinical benefits of intermittent systemic corticosteroids or ICS for children with infrequent viral-induced wheezes remain controversial. While some studies in older children have found small benefits, a study in young children found no effects on wheezing symptoms. There is no evidence to support the use of low-dose maintenance inhaled ICS for preventing transient wheezing in childhood. Though low-medium dose ICS may affect growth, this effect is clinically insignificant and may be reversible. ICS are generally safe and well tolerated. Local adverse effects can occur and include oropharyngeal candidiasis and dysphonia. With metered dose inhalers (MDI), these effects may be reduced by using spacer devices. Mouth washing after inhalation may reduce oral candidiasis. Systemic side effects are occasionally reported with high doses and long-term treatment. The small risk of adverse events from the use of ICS is well balanced by their efficacy. Some studies have shown that ciclesonide has relatively lower local and systemic side effects. To date, ciclesonide has not been approved for children by the Food and Drug Administration (FDA); its safety and effectiveness have not been established in children below 12 years.

##### Long-acting inhaled B2-agonists

Long-acting inhaled B2-agonists (LABAs), including formoterol and salmeterol, should not be used as monotherapy in asthma. In fact, studies show that it is harmful to use them alone to control asthma. When used in combination with ICS, there is an improvement in symptoms, decreased nocturnal asthma, improved lung function, decreased use of rescue rapid-onset inhaled B2-agonists, reduced number of exacerbations, and more clinical control of asthma in more patients, more rapidly, at a lower dose of ICS. Fixed combination inhalers are available in the form of fluticasone and salmeterol (Seretide) or budesonide and formoterol (Symbicort). They are considered more convenient for patients. They increase compliance, and ensure that LABA is always accompanied by ICS. Although salmeterol and formoterol provide a similar duration of bronchodilation and protection against bronchoconstriction, formoterol has a more rapid onset of action than salmeterol. Therefore, combination inhalers containing formoterol and budesonide may be used for both rescue and maintenance of control.<sup>[62]</sup> LABA provides longer protection to prevent exercise-induced bronchospasm than short-acting inhaled B2-agonists (SABA).<sup>[63]</sup> Their side effects are limited to tachycardia, tremor, headaches, muscle cramps, and sometimes hypokalemia. Regular use of LABA combined with ICS may lead to a reduction in these side effects. Further, patients rarely develop a tolerance to LABAs. The effect of LABA products has not been adequately studied in children of 5 years and below. A novel ultra LABA with a rapid onset and 24 h duration of action is expected to be in the Saudi market in the near future (e.g. indacaterol). The ultra LABA has a compliance-enhancing advantage with improved overall clinical outcomes in patients with asthma.<sup>[64-68]</sup>

### Leukotriene modifiers

Leukotriene modifier agents [leukotriene receptor antagonists (LTRAs)] reduce airway inflammation and improve asthma symptoms and lung function, but with a less consistent effect on exacerbations, especially when compared to ICS. They may be used as an alternative treatment to ICS for patients with mild asthma, especially in those who have clinical rhinitis. Some patients with aspirin-sensitive asthma respond well to the LTRA. However, when used alone as a controller, their effects are generally less than that of low-dose ICS. When added to ICS, LTRA may reduce the dose of ICS required by patients with uncontrolled asthma and may improve asthma control.<sup>[69,70]</sup> LTRA are generally well tolerated. In children, studies have shown that LTRA may be useful for reducing the number of exacerbations induced by viruses and for reducing bronchial inflammation in atopic children.<sup>[71-74]</sup> There are no clinical data to support their use under the age of 6 months.

### Theophylline

Theophylline is a weak bronchodilator with modest anti-inflammatory properties. It may provide benefits as an add-on therapy in patients who do not achieve control with ICS alone, but is less effective than LABA and LTRA. Theophylline is not recommended for use as monotherapy in asthma treatment. Recent data have shown that low-dose theophylline may have an important role in improving steroid resistance in patients with severe asthma requiring high-dose ICS through activation of certain down-regulated pathways, such as histone deacetylases.<sup>[23,75]</sup> Their side effects include gastrointestinal symptoms, cardiac arrhythmias, seizures, and even death. Nausea and vomiting are the early symptoms of toxicity. Liver disease, congestive heart failure (CHF), some quinolones, and some macrolides increase the risk of toxicity. Use of lower doses may decrease the side effects.

### Anti-IgE

Anti-IgE (omalizumab) use is indicated for patients of 12 years and above with severe allergic asthma uncontrolled on high-dose ICS and other controllers and who have an IgE level in the appropriate therapeutic range.<sup>[76,77]</sup> As this drug is expensive and requires careful monitoring, it should only be prescribed by a specialist. The side effects include pain and bruising at injection site and very rarely anaphylaxis (0.1%). According to recent data, in children of 8–10 years diagnosed with atopic asthma, anti-IgE has resulted in a significant reduction in number of days with asthma symptoms, hospital days, and use of ICS.<sup>[78]</sup>

### Oral B2-agonists

The side effect profile is much higher than that of inhaled B2-agonists. Therefore, their use is highly discouraged. Oral route is not recommended in children.

### Systemic corticosteroids

Long-term oral glucocorticosteroid therapy (excluding short courses for acute attacks of asthma for a period of 1–2 weeks) may be required to control difficult asthma despite maximum standard therapy. The dose should be reduced to the lowest possible and other controllers should be maximized to minimize the side effects. Its use is limited by the risk of significant adverse effects. Use of intramuscular long-acting steroids is highly discouraged because of the increased risk of side effects. The side effects include: osteoporosis, hypertension, diabetes,

adrenal insufficiency, obesity, cataracts, glaucoma, skin thinning, and muscle weakness. Withdrawal can elicit adrenal failure. In patients prescribed long-term systemic corticosteroids, prophylactic treatment for osteoporosis should be considered.

### Reliever medications

Relievers are medications used on an as-needed basis that act quickly to reverse bronchoconstriction and relieve symptoms.

### Rapid-onset inhaled B2-agonists

SABA, such as salbutamol, are the medications of choice for relief of symptoms of acute exacerbations of asthma and for the pretreatment of exercise-induced bronchoconstriction. The MDI with chamber is as effective as the nebulized route in treatment of acute episodes of wheeze in children.<sup>[79]</sup> Formoterol is not currently available in the market as a single inhaler; however, it can be used for symptom relief because of its rapid onset of action. When it is used for maintenance therapy, it should always be given with ICS. Regular, long-term use of SABA is not recommended.

### Anticholinergics

Anticholinergics are less effective than SABA. However, when used in combination with SABA in acute asthma, they have an additional effect. It can also be an alternative bronchodilator for patients who experience adverse effects such as tachycardia, arrhythmia, and tremor from rapid-acting B2-agonists. Their side effects include dryness of the mouth and a bitter taste. Benefits in the long-term asthma control have been established for the long-acting anticholinergic medication, tiotropium. Tiotropium, when combined with ICS, is superior to doubling the dose of ICS in poorly controlled asthmatics on low-dose ICS, similar to the effect of addition of LABA to ICS.<sup>[80]</sup>

### Theophylline

There is no evidence supporting the routine use of theophylline in treating acute asthma and its use is discouraged.

## Aerosol Devices Used in Asthma

Medication aerosol can be delivered using three devices:

### Small-volume nebulizer

It is the most popular for patients and clinicians. Small-volume nebulizers (SVNs) are predominately powered by a compressed gas (air or oxygen) to convert one or more than one drug solutions or suspensions at any concentrations and dose into aerosols. One of its main advantages is that it requires minimal patient cooperation and is therefore suitable for all ages, with normal breathing and no inspiratory pause required. One of its main disadvantages is portability and time to deliver the medication (10–25 min), in addition to the potential of contamination.

### Pressurized metered-dose inhaler (pMDI)

It is a pre-pressurized inhaler with medication and a propellant, which when actuated will give one dose of the drug for a single inspiration. pMDIs typically require slow inspiratory flow (<30 L/min). One of its main advantages is that it is premixed and the ability to provide multiple doses in a short period of time. It is also small and portable with limited contamination. Disadvantages include the need of patient training to coordinate inhalation with actuation, and if this not

done properly, there is a potential of high deposition of drug in the oropharynx. Also, because it does not have dose counter, it is difficult to determine the dose remaining in the canister. Compared to the older chlorofluorocarbon (CFC) propellant formulations, hydrofluoroalkane (HFA) formulations provide smaller particle size aerosols with less oral deposition, hence less oral side effects and greater proportion of lung deposition.

#### *Dry powder inhaler*

It is not pressurized (no propellant), and therefore requires high inspiratory flows (60–90 L/min) to disperse a full dose. In addition to its portability, advantages include that it is breath-actuated and there is a built-in dose counter. Disadvantages include an adequate inspiratory flow to disperse a full dose. If not used properly, there is fairly higher oropharyngeal impaction and exhaled humidity into mouthpiece would affect the function of the device. Therefore, it may not be suitable for very young or very old patients. The commonly available devices in Saudi Arabia are the Turbo-haler, Diskus, and Handihaler devices. HFA formulations provide smaller particle size aerosols with less oral deposition, hence less oral side effects and greater proportion of lung deposition than the older CFC propellant formulations.

#### *Breath-actuated inhalers*

These inhalers automatically release a spray of medication when the person begins to inhale. These inhalers are easy to use and improve asthma control and compliance to medications.<sup>[81-84]</sup>

### **Approach to Asthma Management**

The long-term goal of asthma therapy is to achieve and maintain asthma control by utilizing pharmacological and non-pharmacological measures [Box 7]. This should lead to utilization of the least possible dose of medications in order to minimize the risk of side effects.

#### **Non-pharmacological measures**

##### *Developing partnership with the patient*

The development of partnership between the patient and healthcare professionals leads to enhancement of knowledge, skills, and attitude toward understanding asthma and its management. Based upon agreed goals of management, a guided-written self-management plan is offered to the patient. A wide variety of plans are available which vary from patient-based to physician-based plans. This should be reflected positively on patient adherence, which is a major issue in the management. Factors leading to non-adherence may be related to poor inhaler technique, a regimen with multiple drugs, concern regarding side effects from the drugs, or the cost of medications.<sup>[85-87]</sup> Other factors include: lack of knowledge about asthma, lack of partnership in the management, inappropriate expectations, underestimation of asthma symptoms, use of unconventional therapy, and cultural issues.<sup>[88,89]</sup>

##### *Asthma education*

The goal of asthma education is to provide a patient with asthma (or the parents of a child with asthma) adequate training to enhance their knowledge and skills to be able to adjust treatment according to guided self-management (Evidence A).<sup>[90-94]</sup> In order to enhance the level of knowledge

and skills among asthmatics, education should include knowledge about asthma and skills related to the devices, as there might be misperceptions about the use of inhalers and the safety of ICS.<sup>[95-97]</sup> Asthma education should be conducted by a well-trained healthcare worker with good communication skills, who is able to create an interactive dialog in a friendly environment. With the availability of appropriate information, patients will be encouraged to continue on the management plan and reassured about the control of the disease.<sup>[98]</sup> It is essential to get the feedback from the patient in order to maintain a bidirectional rapport and an optimum environment. It has been documented that a well-structured asthma education program will improve quality of life, reduce cost, and the utilization of healthcare resources.<sup>[99-101]</sup> Asthma education should be tailored based on the available setting [Box 8].

##### *Written action plan for asthma*

It is considered an integral part of asthma management for patients and doctors. It helps to recognize the loss of control of asthma and gives clear instructions for early intervention to prevent asthma attacks. The use of an asthma action plan leads to better control in both children and adults. The asthma action plan may be based on symptoms or PEF measurements [Box 9].<sup>[102]</sup> Regular review of the asthma action plan is important as a person's level of asthma control may change over time. If a patient has an exacerbation, the patient should be assessed if he/she has effectively used their action plan.

##### *Identify and reduce exposure to risk factors*

Measures to prevent or reduce exposure to risk factors should be implemented wherever possible. There are different triggers leading to asthma exacerbations, which may include: allergens,

#### **Box 7: The long-term goals of asthma management**

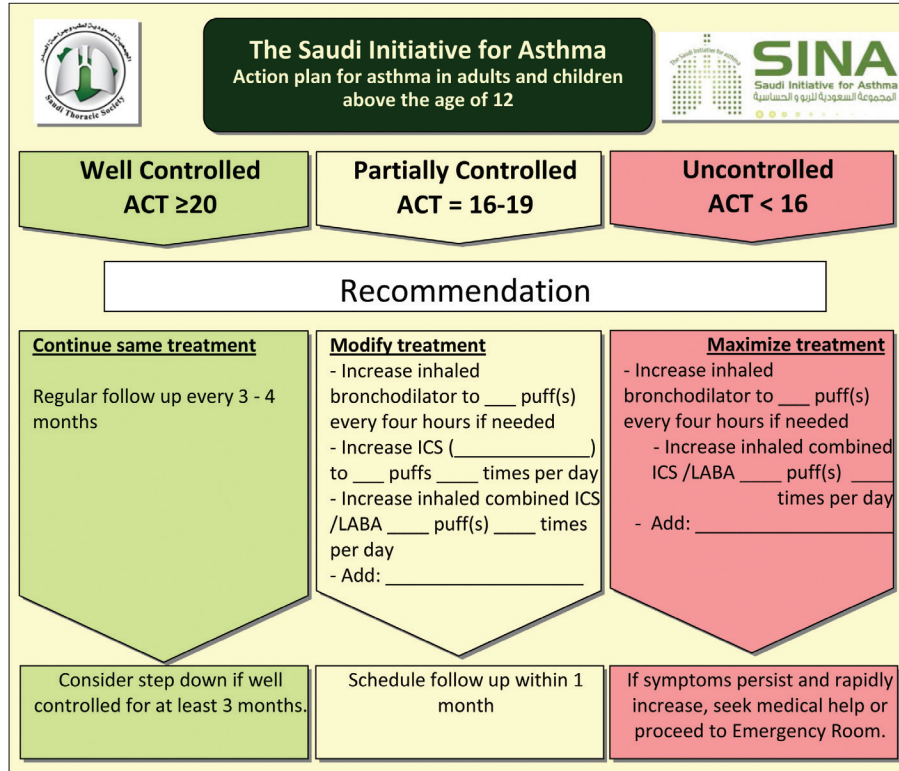
- Control asthma symptoms (cough, wheezing, or shortness of breath)
- Infrequent and minimal use ( $\leq 2$  days a week) of reliever therapy
- Maintain (near) normal pulmonary function
- Maintain normal exercise and physical activity levels
- Prevent recurrent exacerbations of asthma, and minimize the need for emergency room (ER) visits or hospitalizations
- Optimize asthma control with the minimal dose of medications
- Reduce mortality
- Optimize quality of life

#### **Box 8: Outcomes of asthma education program**

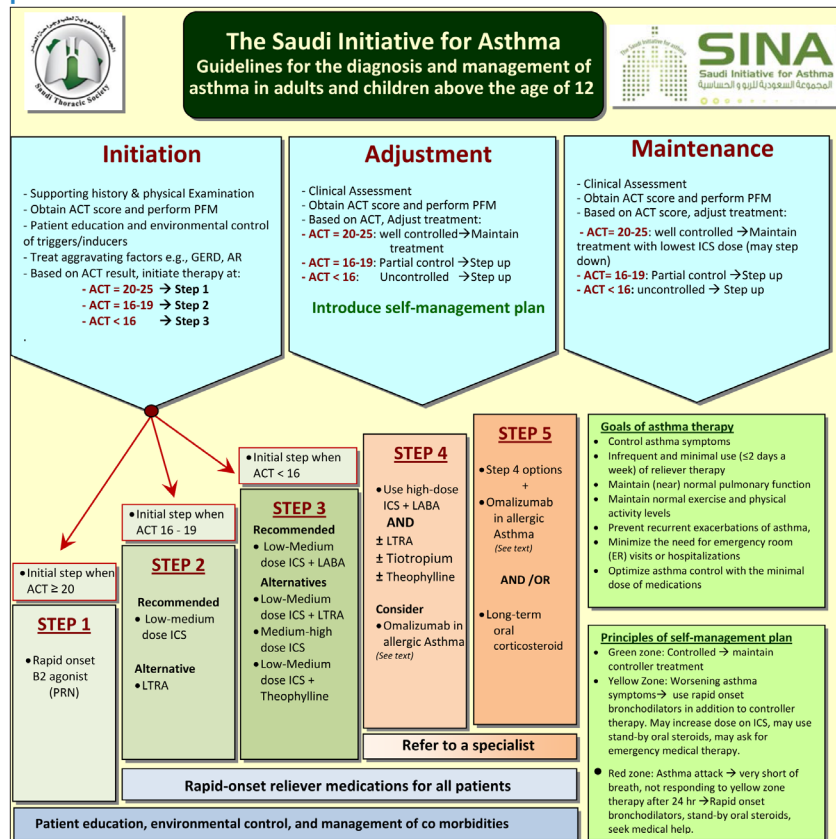
- Creation of partnership between the patient and the healthcare worker
- Understanding clinical presentation of asthma and methods of diagnosis
- Ability to differentiate between "reliever" and "controller" medications and their appropriate indications
- Recognition of potential side effects of medications and the appropriate action to minimize them
- Performance of the proper technique of different inhaler devices
- Identification of symptoms and signs that suggest worsening of asthma control and the appropriate action to be taken
- Understanding the approach for monitoring asthma control
- Recognition of the situations that need urgent medical attention
- Ability to use a written self-management plan



**Box 9: Action plan for asthma based on the Saudi initiative for asthma in adults**



**Box 10: Initiation and maintenance of asthma therapy in stable patients based on the Saudi initiative for asthma in adults**



viral infections, pollutants, drugs, and occupational agents. These factors can be classified as indoor or outdoor allergens and occupational sensitizers.

*Indoor allergens and air pollutants:* There is a wide spectrum of indoor allergens that includes domestic mites, furred animals, cockroaches, and fungi.<sup>[103,104]</sup> Most of the interventions to reduce exposure to these triggers will enhance the asthma control. The most important indoor air pollutant is related to tobacco exposure.<sup>[105]</sup> Measures to avoid tobacco exposure will lead to better asthma control and avoidance of long-term lung function impairment.

*Outdoor allergens:* Outdoor allergens such as pollens and molds are impossible to avoid completely. Exposure may be reduced by closing windows and doors, remaining indoors during dust storms and initial raining seasons, and using air conditioning if possible. It is recommended to avoid outdoor strenuous physical activities in cold weather, low humidity, or high air pollution.<sup>[106]</sup>

*Occupational exposures:* Whenever an occupational sensitizer is identified, it is advisable to keep the affected person away from that environment. The earlier the removal of this sensitizer takes place, the higher the chance of complete recovery from occupational asthma.

*Food and drugs:* Food and food additives are uncommon triggers of asthma. Avoidance cannot be recommended until it is documented by a specialist. However, certain drugs whenever identified should be avoided (e.g. beta blockers).

*Influenza vaccination*

Annual influenza vaccination is advised for individuals with severe asthma. Other asthmatics may benefit from vaccination, although it does not appear to protect from asthma exacerbations or improve asthma control (Evidence B).<sup>[107-109]</sup>

**Pharmacological measures for asthma in adults**

*Principles for optimal asthma management*

The principles of optimal asthma management should follow the assessment of asthma control. The severity index is no longer recommended by SINA to classify asthma, as it is not practical due to the change of severity over time (Evidence D).<sup>[110]</sup>

*Initiation of treatment*

The consensus among SINA panel is to simplify the approach

to initiate asthma therapy by using the ACT score [Box 10].<sup>[111]</sup> A score of  $\geq 20$  will lead to initiating treatment at step 1, 16–19 at step 2, and less than 16 at step 3 (Evidence B).<sup>[112]</sup> An alternative to this approach is the GINA approach that recommends initial treatment at step 2 for patients who are currently *not* taking long-term controller medications. If the initial symptoms are more frequent, treatment is recommended at step 3. Nevertheless, some patients have few symptoms when on SABA and an “as-needed basis” is enough. It should be noted that patients often underestimate the presence of asthma symptoms and also tend to assume their asthma is controlled when this is not the case.

*Adjustment of treatment*

The level of asthma control is categorized into: controlled, partially controlled, and uncontrolled [Box 11]. According to symptoms, relievers use pulmonary function, exacerbation, and a validated asthma questionnaire such as ACT. The SINA expert panel recommends the utilization of ACT to assess control as it is validated, practical, and simple to use (Evidence D) [Box 10].<sup>[113,114]</sup> A score of  $\geq 20$  indicates controlled asthma, 16–19 partially controlled asthma, and  $<16$  indicates uncontrolled asthma.<sup>[52,53]</sup> The clinically important change in ACT score is considered to be  $\geq 3$  units change.<sup>[115]</sup> Patients with severe obstruction on spirometry and history of asthma attacks need more monitoring to ensure better control and a prompt response to worsening asthma control.<sup>[92]</sup>

A stepwise approach to therapy is used to achieve asthma control. The steps (1–5) of care for managing asthma are shown in Box 10. Therapy is stepped up to achieve control, and stepped down for patients who have maintained control for a sufficient length of time. It is important to determine the minimal amount of medications required to maintain control and reduce the risk of side effects. As most asthma patients have concomitant rhinosinusitis that might affect their control, treatment of this condition will improve asthma control (Evidence A).<sup>[116-120]</sup> This includes nasal steroids, LTRA, and antihistamines. Coexisting sinusitis should be treated appropriately.

*Maintaining control of asthma*

Regular follow-up by a healthcare worker is essential. Depending on the level of asthma control, it is recommended to have a follow-up at every 1–3 month intervals (Evidence D).<sup>[98,121]</sup> The follow-up should include monitoring and review of the patient’s written asthma action plan, medications, patient’s

**Box 11: Assessing asthma control in adults**

Component of control	Classification of asthma control		
	Controlled	Partial control	Uncontrolled
Symptoms and/or use of rapid-onset B2-agonist for symptoms relief	None or less than twice a week	More than twice a week	Throughout the day
Nighttime awakenings	None or once a month	Two or more attacks a month	Two or more attacks a week
Effect on daily activities	None	Some limitations	Extremely limited
FEV1 or peak flow	$>80\%$ of predicted/personal best	$60-80\%$ of predicted/personal best	$<60\%$ of predicted/personal best
Asthma control test score	$\geq 20$	16–19	$<16$
Exacerbation that requires oral steroids or hospitalization	0	One exacerbation per year	Two or more exacerbations per year

Adapted with modification from the global initiative for asthma<sup>[97]</sup>

behaviors, and possible side effects of medications. Once asthma is well controlled and the control is maintained for at least 3 months, a reduction in pharmacologic therapy (a step down) is recommended to reach the minimum therapy level that can maintain a good control and minimize side effects (Evidence D). The following are recommended:

- Reduction in therapy should be gradual and closely monitored based on clinical judgment of the individual patient's response to therapy and the ACT score (Evidence D).
- If the patient is on ICS as monotherapy, the dose of ICS may be reduced by 25% every 3–6 months to the lowest dose possible that is required to maintain control (Evidence B),<sup>[122,123]</sup> and then changed to single daily dose (Evidence A).<sup>[124]</sup> It should be clearly explained to the patient that asthma control may deteriorate if treatment is abruptly discontinued.
- If the patient is on a combination of ICS and LABA, LTRA, or other controllers, then taper ICS to the lowest possible dose (Evidence B).<sup>[125,126]</sup> If control is achieved, LABA or LTRA may be discontinued or combination therapy shifted to once daily (Evidence D).<sup>[125]</sup>
- For significant side effects, consider a change in therapy, reduction in the dose or frequency of ICS (if possible), advise vigorous mouth washing after inhalation, use of spacer (concomitant with MDI devices), and/or use of appropriate local antifungal therapy for severe oral thrush.<sup>[127]</sup>
- If asthma control is not achieved at any step during therapy, the following actions are recommended:
  1. Patient's adherence and technique in using devices correctly should be assessed:
    - Medications and doses currently taken.
    - Selection of the appropriate device and appropriate prescription of spacer with MDI devices.
    - Inhaler device technique.
    - Occasions when medication is missed per week.
    - Problems and difficulties faced by the patient after taking the medications (e.g. cost, time, lack of perceived need, etc.).
    - Patient's concerns about asthma medications.
  2. Other factors that affect control should be carefully evaluated and ruled out and may indicate need for a referral to a specialist. They include:
    - Possible alternative diagnosis (e.g. presence of crackles in auscultation, restrictive pattern in spirometry, presence of stridor, or vocal cord dysfunction).
    - Unrecognized rhinosinusitis or GERD.
    - A possible environmental or occupational exposure.
    - Medication side effects (e.g. beta blockers or nonsteroidal anti-inflammatory agents).
    - Psychosocial problems such as depression.

If the above factors are ruled out, a step-up in therapy is recommended. However, in severe cases, a short course of systemic steroid may be indicated to regain asthma control.

Referral to an asthma specialist for consultation or co-management is recommended in the following situations:

- There is uncertainty regarding the diagnosis.
- There is difficulty achieving or maintaining control of asthma.

- Immunotherapy or omalizumab is being considered.
- The patient requires step 4 care or higher.
- The patient has had an exacerbation requiring a hospitalization.

## Treatment (Pharmacologic) Steps

The recommendations for treatment steps are intended to be general guidelines for assisting, not replacing, clinical decision-making.

### Who should be treated at step 1?

The symptoms are usually mild and infrequent [Box 10]. However, some patients may experience sudden, severe, and life-threatening exacerbations. It is essential to treat these exacerbations accordingly. This category is recommended to follow step 1 by considering SABA to be taken on an "as-needed basis" to treat symptoms (Evidence A).<sup>[128-130]</sup> It is usually sufficient therapy for this level. However, if treatment frequency increases to more than 2 days a week, then the patient should be treated as partially controlled asthma (see below).

### Partially controlled or uncontrolled asthma (treatment at steps 2–5)

For partially controlled asthma or uncontrolled asthma, the following general roles are recommended [Box 10]:

- Daily controller medication is needed. ICS are considered the most effective controller (Evidence A).<sup>[59,131]</sup>
- Relievers or rescue medications must be available to all patients at all steps. SABA is recommended to be taken as needed to relieve symptoms. Increasing the use of reliever treatment is usually an early sign of worsening asthma control (Evidence A).<sup>[128,132]</sup>
- Treat patients who may have seasonal asthma as having uncontrolled asthma during the season and at step 1 for the rest of the year (Evidence D).
- Patients who had two or more exacerbations requiring oral corticosteroids or hospital admissions in the past year should be treated as patients with uncontrolled asthma, even if the level of control seems to be adequate in between the exacerbations (Evidence D).

### Treatment steps for asthma control (steps 2–5)

The following medications are recommended for each step:

#### Treatment at step 2

- The preferred medication at the step 2 level is a daily ICS at a low dose (<500 µg of beclomethasone or equivalent/day) [Box 5] (Evidence A).<sup>[59,133]</sup>
- An alternative treatment is LTRA (montelukast), especially in those patients unable or unwilling to use ICS or continue to have voice hoarseness despite preventive measures (Evidence A).<sup>[134]</sup>
- Patients with mild asthma and concomitant allergic rhinitis may benefit of controlling both with LTRA (Evidence C).<sup>[119,135]</sup>

#### Treatment at step 3

- Adding an LABA to a low-medium dose ICS improves asthma control for patients whose asthma is not controlled on a low-dose ICS alone (Evidence A).<sup>[136-138]</sup> These are available in combination devices, such as fluticasone/salmeterol

(Seretide) or budesonide/formoterol (Symbicort).

- The standard strategy is to use a maintenance dose of the combination drugs twice daily and use SABA as a reliever treatment (Evidence A).<sup>[139]</sup>
- An escalating dose of combination of fluticasone/salmeterol (Seretide) achieves well-controlled asthma in 85% of patients and totally controlled asthma in 30% (Evidence A).<sup>[140]</sup>
- If a combination inhaler containing formoterol/budesonide is selected, patient may be advised to use it for both maintenance and rescue (Evidence A).<sup>[62]</sup> At this step of care, maintenance dose of budesonide/formoterol single inhaler (1–2 puffs 160/4.5 BID) is selected plus extra puffs from the same inhaler up to a total of 12 puffs per day. Those patients who require such high dose should seek medical advice to step up therapy, which may include use of short course of oral prednisone.<sup>[60]</sup>
- There was a recent warning mandate for new safety measures for the use of inhaled LABAs in asthma control.<sup>[141]</sup> Asthmatics taking inhaled LABAs without inhaled ICS faced an augmented rate of asthma exacerbations, hospitalizations, and death.<sup>[60]</sup> Based on this evidence, the Saudi FDA withdrew all LABA monotherapy medications from the Saudi market by the end of 2010.<sup>[142]</sup> Therefore, the SINA panel has limited the use of relievers to SABA.
- Alternative, but in general less-effective strategies include: the continuation of ICS as a monotherapy by increasing the dose to the medium- to high-dose range (Evidence A),<sup>[60,143]</sup> and the addition of LTRA to a low-medium dose ICS (Evidence A),<sup>[144,145]</sup> especially in patients with concomitant rhinitis.<sup>[146]</sup> The addition of sustained release theophylline to a low-medium dose ICS is a third alternative choice (Evidence B).<sup>[147]</sup>
- Tiotropium is a long-acting anticholinergic agent approved for the treatment of chronic obstructive pulmonary disease. Recent evidence has shown that when tiotropium is added to ICS, it improves symptoms and lung function in patients with inadequately controlled asthma. Its effect appeared to be at least equivalent to LABA (evidence A).<sup>[80,148,149]</sup> This evidence supports that tiotropium is an alternative to LABA when added to ICS. However, the effect on reducing exacerbations has not been shown.
- Consultation with a specialist is recommended for patients whenever there is a difficulty in achieving control (Evidence D).

#### Treatment at step 4

- Consultation with a specialist is recommended for patients who require this step of therapy (Evidence D).<sup>[150]</sup>
- At this level of care, maximizing treatment is recommended by combining high-dose ICS with LABA (Evidence A).<sup>[98,143,144,151]</sup>
- Adding LTRA to the combination of high-dose ICS and LABA is recommended for consideration (Evidence B).<sup>[152,153]</sup>
- Adding tiotropium to the combination of ICS and LABA is an alternative recommendation as it significantly improves lung function in uncontrolled cases (Evidence B).<sup>[154]</sup>
- Adding theophylline to the combination of high-dose ICS and LABA is another alternative (Evidence B).<sup>[153,155]</sup>
- Omalizumab may be recommended at this step for patients who have allergic asthma (as determined by skin test or RAST study) that is still uncontrolled (Evidence A).<sup>[143,144,151]</sup>

Special knowledge about the drug and its side effects should be available before administering omalizumab by any physician. Therefore, referral to an asthma specialist is mandatory.

#### Treatment at step 5

- Consultation with an asthma specialist is considered to be a mandatory recommendation for patients who require this step of therapy (Evidence D).
- In patients who continue to be symptomatic despite step 4 level of care, omalizumab is recommended for patients who have allergic asthma and persistent symptoms despite the maximum therapy mentioned above (Evidence A).<sup>[143,144,151]</sup>
- If the patient does not have allergic asthma or omalizumab is not available or not adequately controlling the disease, the alternative approach is to use the lowest possible dose of long-term oral corticosteroids (Evidence D).
- For patients who require long-term systemic corticosteroids, the following should be considered:
  - Use the lowest possible dose to maintain control.
  - Closely monitor the development of corticosteroid-related side effects.
  - When controlled asthma is achieved, continue attempts to reduce the dose of systemic corticosteroids. Maintaining high-dose of ICS therapy may help to reduce the dose of systemic steroid.
  - Adjustment of steroid dose at the time of stress (e.g. infection, exacerbation, surgery, etc.) is essential.
  - Strongly consider concurrent treatments with calcium supplements, vitamin D, and bone-sparing medications (e.g. bisphosphonates) in patients who have risk factors for osteoporosis or low bone mineral density (Evidence C).<sup>[156]</sup>

#### Immunotherapy

Allergen-specific immunotherapy (AIT) is the practice of administering gradually increasing quantities of an allergen product to an individual with IgE-mediated allergic disease in order to ameliorate the symptoms associated with subsequent exposure to the causative allergen. It is administered either subcutaneously or sublingually.<sup>[157-159]</sup> AIT induces clinical and immunologic tolerance, has long-term efficacy, and may prevent the progression of allergic disease. The AIT also improves the quality of life of allergic patients. Allergen immunotherapy for allergic rhinitis has been shown to reduce the risk for future development of asthma.<sup>[160-163]</sup> AIT is more effective in seasonal asthma than in perennial asthma, particularly when used against a single allergen. It may be considered if strict environmental avoidance and comprehensive pharmacologic intervention by an asthma specialist have failed to control the disease (Evidence B).<sup>[164]</sup> The AIT has been a controversial treatment for asthma; however, beneficial clinical effects have been demonstrated in randomized controlled trials including Cochrane Systematic Reviews. Overall, there was a reduction in asthma symptoms, medications, and improvement in bronchial hyper-reactivity following immunotherapy.<sup>[165,166]</sup> Allergen immunotherapy reduces allergen-specific bronchial hyper-reactivity, with some reduction in non-specific bronchial hyper-reactivity as well. In addition to concerns regarding safety and cost, there was no demonstrated consistent effect on lung function.<sup>[167-169]</sup>

## Management of Acute Asthma in Adults

Most patients who present with an acute asthma exacerbation have chronic uncontrolled asthma.<sup>[170]</sup> Many deaths have been reported in patients who have received inadequate treatment or poor education. The following should be carefully checked: Previous history of near-fatal asthma, whether the patient taking three or more medications, there is heavy use of SABA, repeated visits to emergency department, and brittle asthma. Upon presentation, a patient should be carefully assessed to determine the severity of the acute attack [Box 12] and the type of required treatment.<sup>[171,172]</sup> PEF and pulse oximetry measurements are complementary to history taking and physical examination. This section will start with a review of medications used in acute asthma. This will be followed by acute asthma management.

### Review of medications used in acute asthma

#### Oxygen

Adequate oxygenation is an essential part of therapy.<sup>[173]</sup> However, it is important to give a controlled dose of oxygen; a recent paper showed patients who received 28% oxygen did better than those who received 100% oxygen. Oxygen saturations of at least 92% are recommended as the target of treatment.

#### Rapid-onset $\beta_2$ agonist

In acute asthma, inhaled salbutamol is the preferred choice.<sup>[174,175]</sup> Repeated doses should be given at 15–30 min intervals or continuous nebulization (salbutamol at 5–10 mg/h) should be used for 1 h if there is an inadequate response to initial treatment. In patients who are able to use the inhaler devices, 6–12 puffs of MDI with a spacer are equivalent to 5 mg of salbutamol by nebulizer.

#### Ipratropium bromide

In moderate to severe acute asthma, combining ipratropium bromide with salbutamol has shown to have additional bronchodilation effect and faster improvement in lung function, compared to salbutamol alone.<sup>[176,177]</sup> A recent systematic review showed the combination therapy has an added benefit in reducing hospitalizations.<sup>[178]</sup>

#### Steroid therapy

In acute asthma, systemic steroids have been proven to reduce relapses, subsequent hospital admission, and the requirement for  $\beta_2$  agonist therapy. Oral steroids are as effective as injected steroids, provided tablets can be swallowed and retained and the patient does not become drowsy or begin to vomit.<sup>[179]</sup> Doses of prednisolone of 40–60 mg daily or parenteral steroids (intravenous hydrocortisone 100–200 mg 6–8 hourly or methylprednisolone 40–80 mg daily) are probably adequate. Systemic steroids should be given for 7–14 days. However, recent data showed that early addition of ICS to oral corticosteroids can benefit patients with acute asthma and can reduce the amount of oral steroid after hospital discharge.<sup>[180]</sup>

#### Intravenous magnesium sulfate

A single dose of IV magnesium sulfate (1–2 g) has been shown to be a safe and effective in acute asthma.<sup>[181]</sup> In a systematic review, magnesium sulfate has shown to reduce

### Box 12: Levels of severity of acute asthma exacerbations in adults

Level	Characteristics
<b>Near-fatal asthma</b>	<b>Raised PaCO<sub>2</sub> and/or requiring mechanical ventilation</b>
Life-threatening asthma	Any one of the following in a patient with severe asthma: <ul style="list-style-type: none"> <li>• PEF &lt;33% best or predicted</li> <li>• Bradycardia</li> <li>• SpO<sub>2</sub>&lt;92% (PaO<sub>2</sub>&lt;60 mmHg) on high-flow FIO<sub>2</sub></li> <li>• Cyanosis</li> <li>• Dysrhythmia</li> <li>• Hypotension</li> <li>• Normal or high PaCO<sub>2</sub></li> <li>• Exhaustion</li> <li>• Confusion</li> <li>• Silent chest</li> <li>• Coma</li> <li>• Weak respiratory effort</li> </ul>
Acute severe asthma	Any one of: <ul style="list-style-type: none"> <li>• PEF 33–50% best or predicted</li> <li>• Respiratory rate <math>\geq</math>25/min</li> <li>• Heart rate <math>\geq</math>110/min</li> <li>• Inability to complete sentences in one breath</li> </ul>
Moderate asthma exacerbation	<ul style="list-style-type: none"> <li>• Increasing symptoms</li> <li>• PEF &gt;50–75% best or predicted</li> <li>• No features of acute severe asthma</li> </ul>
Brittle asthma	<ul style="list-style-type: none"> <li>• Type 1: Wide PEF variability (&gt;40% diurnal variation for &gt;50% of the time over a period &gt;3–6 months) despite intense therapy</li> <li>• Type 2: Sudden severe attacks on a background of apparently well-controlled asthma</li> </ul>

hospitalizations in patients with severe or life-threatening asthma attack that fails to respond to initial treatment.

#### Intravenous aminophylline

Routine use of this drug in acute asthma is strongly discouraged, as there is no evidence to show benefit and the drug has high levels of toxicity and side effects.<sup>[182]</sup>

#### Antibiotics

Viral infection is the usual cause of asthma exacerbation and routine use of antibiotics is strongly discouraged.<sup>[183]</sup> Antibiotics should be used when there is associated pneumonia or bacterial bronchitis.

#### Intravenous fluid and electrolyte correction

Randomized controlled trials of fluid replacement in acute asthma showed no benefit. Hypokalemia can be caused or exacerbated by  $\beta_2$  agonist and/or steroid treatment and must be corrected.

### Assessment of Attack Severity

Management of acute asthma in adults is the extreme spectrum of uncontrolled asthma, and represents the failure to reach adequate asthma control. Treatment of acute asthma attacks requires a systematic approach similar to chronic asthma

**Box 13: Management of acute asthma in adults****Assess asthma severity by history, physical examination, oxygen saturation, and PEF**

Moderate	Severe	Life threatening
Talking phrases or full sentences	Talking words or unable to complete sentence	Unable to talk
Alert, agitated	Agitated	Confused, drowsy, or coma
Respiratory rate <30/min	Respiratory rate >30/min	Respiratory rate >30/min unless resp. failure
May or may not use of accessory muscles	Usually use of accessory muscles	Usually use of accessory muscles
Heart rate <120	Heart rate >120	Heart rate > 120 or bradycardia, silent chest
Oxygen saturation in room air >92%	Oxygen saturation in room air <92%	Oxygen saturation in room air <90% or cyanosis. Normal or high CO <sub>2</sub> , acidosis
PEF > 200 L/m or 50–75% best or predicted	PEF <200 L/m or 33–50% best or predicted	PEF <200 L/m or <33% best or predicted or unable to do it

It is important to realize that some patients might have features from more than one level of acute asthma severity. For patients' safety, he/she should be classified to the higher level and managed accordingly

**Treatment**

Moderate	Severe	Life threatening
Oxygen nasal prongs to keep SaO <sub>2</sub> >92%	Oxygen via face mask or nasal prongs to keep SaO <sub>2</sub> >92%	High-flow O <sub>2</sub> in 100% via non-rebreathe bag to keep SaO <sub>2</sub> >92%
Short-acting β <sub>2</sub> -agonist (salbutamol) can be delivered by either: <ul style="list-style-type: none"> <li>• Nebulizer: 2.5–5 mg salbutamol every 20 min for 1 h, then every 2 h according to response</li> <li>• MDI with spacer: 6–12 puffs every 20 min for 1 h, then every 2–4 h according to the response</li> </ul>	Salbutamol 2.5–5 mg plus ipratropium bromide 0.5 mg nebulized with oxygen in 3–5 ml normal saline every 10–20 min for 1 h, then every 1 h according to patient response	Salbutamol 2.5–5 mg plus ipratropium bromide 0.5 mg nebulized with oxygen in 3–5 ml normal saline every 10–20 min for 1 h, then every 1 h according to patient response or Continuous nebulization (salbutamol at 10 mg/h)
Oral prednisone 40 mg PO STAT	Hydrocortisone 200 mg IV STAT then 100–200 mg every 6 h or methylprednisone 80–125 mg IV STAT then 40 mg every 8 h or prednisone 40 mg PO daily Magnesium sulfate 1–2 g IV over 20 min if no response to initial bronchodilators CXR CBC, lytes, urea, Cr, and glucose, 12-lead ECG, ABG	Hydrocortisone 200 mg IV STAT then 100–200 mg every 6 h or methylprednisone 80–125 mg IV STAT then 40 mg every 8 h Magnesium sulfate 1–2 g IV over 20 min CXR CBC, lytes, urea, Cr, and glucose, 12-lead ECG, ABG

Assess response to treatment: Mental status, respiratory rate, heart rate, oxygen sat., and PEF every 30–60 min

management. Acute asthma management is recommended to follow these steps:

1. *Assess* severity of the attack
2. *Initiate* treatment to rapidly control the attack
3. *Evaluate* continuously the response to treatment

It is important to realize that most patients who die from an acute asthma attack had chronically uncontrolled asthma, had received inadequate treatment with inhaled steroid, and had inadequate monitoring of their asthma (Evidence C).<sup>[184–187]</sup> However, patients with mild or moderately severe asthma can develop sudden fatal attacks. The following levels of acute asthma severity should be quickly identified, as the approach to management and the prognosis vary significantly [Box 13]:

**Mild asthma exacerbation**

Patients presenting with mild asthma exacerbation are usually treated in an outpatient by stepping up in asthma management, including doubling the dose of ICS.<sup>[188]</sup> However, some cases may require short course of oral steroid.

**Moderate asthma exacerbation**

Patients with moderate asthma exacerbation are clinically stable. They are usually alert and oriented, but may be agitated. They are able to communicate and talk in full sentences. Their

respiratory rate is between 25 and 30 per minute and may be using their respiratory accessory muscles. Heart rate is <120/min and blood pressure is normal. A prolonged expiratory wheeze is usually heard clearly over lung fields. Oxygen saturation is usually normal secondary to hyperventilation. The PEF is usually in the range of 50%–75% of predicted or previously documented best. Measurement of arterial blood gases are not routinely required in this category; however, if done, it shows widened alveolar–arterial oxygen gradient and low PaCO<sub>2</sub>, secondary to increased ventilation perfusion mismatch and hyperventilation, respectively. Chest X-ray is not usually required for moderate asthma exacerbation, unless pneumonia is suspected.

**Severe asthma exacerbation**

Patients are usually agitated and unable to complete full sentences. Their respiratory rate is usually >30/min and use accessory muscles. Significant tachycardia (pulse rate >120/min) and hypoxia (SaO<sub>2</sub> <92% on room air or low-flow oxygen) are usually evident. Chest examination reveals prolonged distant wheeze secondary to severe airflow limitation and hyperinflation. The PEF is usually in the range of 33–50% of predicted. When done, arterial blood gases reveal significant hypoxemia and elevated alveolar–arterial O<sub>2</sub> gradient. PaCO<sub>2</sub> may be normal in patients with severe asthma exacerbation.

Such finding is an alarming sign, as it indicates fatigue, inadequate ventilation, and pending respiratory failure. Chest radiograph is required if complications, such as pneumothorax, or pneumonia are clinically suspected.

### Life-threatening asthma exacerbation

Patients with life-threatening asthma are severely breathless and unable to talk. They can present in extreme agitation, confusion, drowsiness, or coma. Unless already in respiratory failure, the patients usually breathe at a respiratory rate >30/min and use their accessory muscle secondary to increased work of breathing. Heart rate is usually >120/min, but at a later stage, patients can be bradycardiac. Arrhythmia is common in this category of patients secondary to hypoxia and ECG monitoring is mandatory. Oxygen saturation is usually low (<90%) and not easily corrected with O<sub>2</sub>. Arterial blood gases are mandatory in this category and usually reveal significant hypoxia and normal or high PaCO<sub>2</sub>. Respiratory acidosis might be present. PEF is usually very low (<33% of the predicted). Chest X-ray is mandatory in life-threatening asthma to rule out complications such as pneumothorax or pneumomediastinum. It is important to realize that some patients might have features from more than one level of acute asthma severity. For the patients' safety, he/she should be classified as the higher level and managed accordingly.

### Moderate asthma exacerbation

- Low-flow oxygen is recommended to maintain saturation >92%.<sup>[173,189]</sup>
- SABA is recommended to be delivered by either:<sup>[174,190]</sup>
  - Nebulizer: 2.5–5 mg salbutamol every 20 min for 1 h, then every 2 h according to response (Evidence A)<sup>[175]</sup> or
  - MDI with spacer: 6–12 puffs every 20 min for 1 h, then every 2–4 h according to the response (Evidence A).<sup>188<sup>[79,191,192]</sup></sup>
- Steroid therapy: Oral prednisolone 40 mg is recommended to be started as soon as possible.<sup>[179,193]</sup>

### Severe asthma exacerbation

- Adjusted oxygen flow is recommended to keep saturation >92% (avoids excess oxygen, see below).<sup>[189,194,195]</sup>
- Nebulized SABA (2.5–5 mg) is recommended to be repeated every 15–20 min for 1 h, then hourly according to the response.<sup>[189]</sup>
- Oxygen-driven nebulizers are preferred for nebulizing β<sub>2</sub> agonist bronchodilators because of the risk of oxygen desaturation while using air-driven compressors (Evidence A).<sup>[179,193,196,197]</sup>
- Ipratropium bromide (0.5 mg) by the nebulized route is recommended to be added to salbutamol every 4–6 h (Evidence B).<sup>[176-178,198]</sup>
- Systemic steroid (Evidence A) is recommended to be started as soon as possible in one of the following forms:<sup>[179,199]</sup>
  - IV methylprednisolone 60–80 mg STAT, or
  - IV hydrocortisone 200 mg STAT, or
  - oral prednisolone 40 mg daily which could be maintained if patient can tolerate oral intake.
- If there was no adequate response to previous measures, the following are recommended:
- Single dose of IV magnesium sulfate (1–2 g) intravenously over 20 min (Evidence B).<sup>[181]</sup>

- Chest X-Ray, serial electrolytes, urea, creatinine, glucose, 12-lead ECG, ABG

## Life-threatening Asthma

Patients in this category can progress rapidly to near-fatal asthma, respiratory failure, and death. Hence, an aggressive management approach and continuous monitoring are mandatory. The following steps are recommended for further management:

- Consult ICU service.
- Adequate O<sub>2</sub> flow to keep saturation >92%.<sup>[189]</sup>
- Deliver nebulized SABA (10 mg) continuously over 1 h (Evidence A).<sup>[200,201]</sup>
- Oxygen-driven nebulizers are preferred for nebulizing β<sub>2</sub> agonist bronchodilators because of the risk of oxygen desaturation while using air-driven compressors (Evidence A).<sup>[196,197]</sup>
- Ipratropium bromide (0.5 mg) by nebulized route every 4–6 h (Evidence B).<sup>[178]</sup>
- Systemic steroid (Evidence A) to be started as soon as possible in one of the following forms:<sup>[176,177,179,199,202,203]</sup>
  - IV methylprednisolone 40–60 mg STAT, then 40 mg every 8 h or
  - IV hydrocortisone 200 mg STAT, then 100–200 mg every 6 h.
- Single dose of IV magnesium sulfate (1–2 g) intravenously over 20 min (Evidence B).<sup>[199,203]</sup>
- Frequent clinical evaluation and serial CXR, electrolytes, BUN, creatinine, glucose, 12-lead ECG, ABGs should be implemented.

## Evaluation of the Response to Initial Treatment

Evaluation of treatment response should be done every 30–60 min, and includes patient's mental and physical status, respiratory rate, heart rate, blood pressure, O<sub>2</sub> saturation, and PEF. Response to treatment is divided into three categories [Box 14]:

*Adequate response:* It is defined as:

- Improvement of respiratory symptoms.
- Stable vital signs.
- O<sub>2</sub> saturation >92% on room air.
- PEF >60% of predicted.

If the above criteria are met and maintained for at least 4 h, the patient can be safely discharged with the following recommendations:

- Review and reverse any treatable cause of the exacerbation.
- Review inhaler technique and encourage compliance.
- Step up asthma treatment “at least step 3.”
- Prescribe oral steroid for 7–14 days.
- Ensure adequate PRN rescue treatment.
- Provide a clearly written asthma self-management action plan.
- Arrange follow-up appointment within 1 week.

*Partial response:* It is defined as:

- Minimal improvement of respiratory symptoms.
- Stable vital signs.
- O<sub>2</sub> saturation >92% on oxygen therapy.
- PEF between 33% and 60% of predicted.

**Box 14: Adjustment of acute asthma treatment**

Adequate response	Partial response	Poor response
<ul style="list-style-type: none"> <li>Improving symptoms and stable vital signs</li> <li>PEF &gt;60% of best</li> <li>Saturation &gt;92%</li> <li>Adequate response should be maintained for at least 4 h</li> <li>Continue bronchodilators for 1–4 h PRN</li> <li>Can be safely discharged</li> <li>Continue oral prednisone for 7 days</li> </ul> <p>At discharge:</p> <ul style="list-style-type: none"> <li>Ensure stable on a four hourly inhaled bronchodilator</li> <li>Prescribe combination of steroids/ long-acting <math>\beta</math>-agonist</li> <li>Review inhaler technique and encourage compliance</li> <li>Ensure adequate rescue treatment</li> <li>Provide written asthma self-management action plan</li> <li>Arrange follow-up in pulmonary clinic or family medicine clinic within few days</li> </ul>	<ul style="list-style-type: none"> <li>Minimal improvement of respiratory symptoms after 4 h of therapy</li> <li>Stable vital signs</li> <li>Saturation &gt;92% on oxygen therapy</li> <li>PEF 33–60% of the best reading of the patient</li> <li>Continue bronchodilators therapy (<math>\beta</math>2-agonist <math>\pm</math> ipratropium bromide) every 1–4 h</li> </ul> <p>At discharge:</p> <ul style="list-style-type: none"> <li>Continue oral steroid in the form of oral prednisone 40 mg daily if the patient can tolerate orally</li> <li>Observe closely for any signs of fatigue or exhaustion</li> <li>Monitor <math>O_2</math> saturation, serum electrolytes, ECG, and PEFR</li> <li>If the patient fails to show adequate response after 4 h, admit to hospital</li> </ul>	<ul style="list-style-type: none"> <li>No improvement of respiratory symptoms after 4 h of therapy</li> <li>Fatigue and acidosis</li> <li>PEF &lt;33%</li> <li>Oxygen saturation &lt;92% with high-flow oxygen</li> </ul> <p>At discharge:</p> <p>Continue bronchodilators and systemic steroids</p> <ul style="list-style-type: none"> <li>ICU admission</li> <li>Consider the following: <ul style="list-style-type: none"> <li>IV <math>\beta</math>2-agonist</li> <li>SC epinephrine</li> <li>Intubation</li> </ul> </li> </ul>

Patients who only achieved partial response after 4 h of the above-described therapy are recommended the following:

- Continue bronchodilator therapy (SABA every 1 h and/ or ipratropium bromide every 4 h), unless limited by side effects (significant arrhythmia or severe hypokalemia).
- Continue systemic steroid:
  - IV hydrocortisone 200 mg every 6–8 h, or
  - IV methylprednisolone 40 mg every 8 h, or
  - oral prednisolone 40 mg daily.
- Observe closely for any signs of fatigue or exhaustion.
- Monitor  $O_2$  saturation, serum electrolytes, electrocardiogram (ECG), and and peak expiratory flow meter (PEFR).
- If the patient fails to show adequate response after 4 h (see above), admit to hospital.

*Poor response:* It is defined as:

- No improvement of respiratory symptoms.
- Altered level of consciousness, drowsiness, or severe agitation.
- Signs of fatigue or exhaustion.
- $O_2$  saturation <92% with high-flow oxygen.
- ABGs: Respiratory acidosis and/or rising  $PaCO_2$ .
- PEFR: <33%.

Patients showing poor response after 4 h of therapy should have the following recommendations:

- Consider ICU admission.
- Deliver continuous nebulization of SABA, unless limited by side effects.
- Continue systemic steroid:
  - IV hydrocortisone 200 mg every 6–8 h or
  - IV methylprednisolone 40 mg every 8 h.

**Criteria for ICU referral**

ICU referral is recommended for patients:

- requiring ventilatory support
- developing acute severe or life-threatening asthma

- failing to respond to therapy, evidenced by:
  - deteriorating PEF
  - persisting or worsening hypoxia
  - hypercapnea
  - ABG analysis showing respiratory acidosis
  - exhaustion, shallow respiration
  - drowsiness, confusion, altered conscious state
  - respiratory arrest

**Management of Asthma in Children**

Asthma represents the commonest chronic illness of childhood.<sup>[204]</sup> According to a local survey in Saudi Arabia, the prevalence of asthma in schoolchildren has raised from 8% to 23% between 1986 and 1995.<sup>[1]</sup> It is also considered a leading cause for childhood morbidity as measured by school absences, emergency department's visits, and hospitalizations.<sup>[205]</sup> Further, the global cost of asthma goes substantially far beyond mortality and morbidity outcomes to significant socioeconomic burden, especially those related to non-medical costs.<sup>[206]</sup> From the prospective of both patient and society, the cost of not treating asthma is higher than asthma treatment.<sup>[207,208]</sup> This section represents the panel views of the Saudi Pediatric Pulmonology Group, a subsidiary of the STS, on asthma management in children.

**Asthma diagnosis in children***Clinical consideration*

Accurate diagnosis of asthma is crucial to prevent inappropriate management, and morbidities and mortalities. This may result in unnecessary or ineffective treatment due to misdiagnosis or over-diagnosis.<sup>[209,210]</sup> As the diagnosis of asthma in young children is challenging, physicians may solve any uncertainty by utilizing some terms like "reactive airway disease," a terminology that should be discouraged as it can restrain full clinical assessment.<sup>[211,212]</sup> Therefore, asthma diagnosis in



**Box 15: Diagnosis of asthma in children**

Symptom and sign	Remarks
History of multiple attacks of SOB or wheezing in a season	>3 attacks/season
Coughing	>2 weeks, during sleep, not related to upper respiratory tract infection
Wheezing	Equal at both sides of the chest, during expiratory phase, especially on forced expiration
Atopy	Eczema, environmental/food sensitization
Family history	Atopy
Breath sounds	Prolonged expiratory phase
Therapeutic trial	Trial of short-acting bronchodilator or corticosteroid therapy
Spirometry	Typically in children >6 years with bronchodilator response assessment
Chest X-ray	May be considered in infants to rule out congenital causes
Tests for hypersensitivity	Both skin testing or/and allergen-specific IgE blood testing

children is recommended to be based on a careful clinical assessment [Box 15] that would include recurrent or chronic symptoms related to airway obstruction such as wheezing, coughing, night symptoms, activity limitation, and shortness of breath. These symptoms typically result from AH or various stimuli that would be either spontaneously reversible or after receiving a bronchodilator. The diagnosis could further be supported by presence of atopy, early sensitization, and family history of atopy. Whenever possible, spirometry should be performed to show reversibility of airway obstruction after bronchodilator therapy.<sup>[212]</sup> Box 15 presents further clinical diagnostic symptoms and signs of asthma in children.

*Asthma phenotypes in children*

Based on several longitudinal studies, wheezing phenotypes have been categorized epidemiologically into transient and persistent wheeze phenotype and symptoms-based into episodic/viral induced and multi-trigger wheeze phenotypes.<sup>[213]</sup> Different responses to treatment and varied outcome may be attributed to phenotype heterogeneity, overlap, and instability over time. On the other hand, major factors that may predict persistent symptoms are allergic disease, reduced lung function, viral respiratory infection, and bacterial colonization in infancy. The Tucson Children's Respiratory Study (TCRS) described four wheezing phenotypes: Never wheezing (occurs in 51%), early transient wheezing before the age of 3 years with resolution by the age of 6 years (occurs in 20%), persistent wheezing that starts before the age of 3 years with continuation after the age of 6 years (occurs in 14%), and late-onset wheezing between 3 and 6 years of age (occurs in 15%).<sup>[213,214]</sup>

*Asthma predictive index*

For early identification of the risk of persistent asthma among children 5 years and younger, the Asthma Predictive Index (API) is one of tools used in the clinical setting. The modified Asthma Predictive Index (modified-API) is a clinical scoring tool that can be used to predict whether a child with intermittent wheezing before the age of 3 years will develop persistent asthma pattern during school-age years [Box 16].<sup>[215,216]</sup> Children with history of four or more wheezing attacks (at least one physician diagnosed) and either one major or two minor criteria at 3 years of age will have fourfold to sevenfold increase in the risk of having asthma during later childhood. The modified-API can also identify children with a low likelihood of developing later asthma when they have negative index with a negative predictive value of 57%–82%.

**Box 16: Modified asthma predicative index****History of  $\geq 4$  wheezing episodes with at least one physician diagnosed and either**

One (or more) of the major criteria	Or	Two (or more) of the minor criteria
• Parental history of asthma		• Eosinophilia ( $\geq 4\%$ )
• Skin test positive to aero-allergens		• Wheezing unrelated to colds
• Eczema (physician-diagnosed atopic dermatitis)		• Allergic sensitization to milk, egg, or peanuts

Adapted from reference<sup>[216]</sup>

**Strategy of asthma management in children**

The long-term goals of asthma management are not different from those of adults [Box 7].<sup>[208]</sup> Asthma management requires effective partnership between patients (and their caregiver) and their healthcare providers. Once established and strengthened, this relationship will impact positively asthma control. Asthma management strategy ideally should include:

- *Assessment of asthma control combined with proper pharmacotherapy:* This implies a continuous process with periodical assessment of asthma control combined with adjustments (if needed) to pharmacotherapy based on the level of control. It is strongly recommended to use asthma pharmacotherapy in a stepwise approach with the ultimate goal of achieving "optimal" control with "minimal" amount of medications and dosage.<sup>[217]</sup> Compliance to and proper use of the prescribed medications and their devices is recommended to be addressed before any modification of treatment plans. In children, it is extremely important to select the best device for optimal treatment delivery [Box 17].
- *Patient education:* Patient education is recommended to be an integral part of asthma management strategy. It should involve: basic knowledge of disease pathophysiology, identifying and avoiding triggering factors, environmental controls (especially cigarette smoke exposures), proper use of treatment devices, and recognition of worsening asthma symptoms and when to seek advice.<sup>[218,219]</sup> Asthma education can produce significant reduction in cost for asthma care, decrease emergency departments' visits and hospitalizations, and improve self-management of exacerbation.<sup>[220]</sup>
- *Action plan:* It is recommended to be provided to patients and their caregivers, and includes medications, their doses, and technique. Action plan would normally include information

for patient and caregiver on how to recognize worsening of asthma symptoms and advices of treatment modification in these situations. Finally, action plan will contain contact information of healthcare resources if help is needed.

- *Prevention:* Asthma exacerbation can be triggered by a variety of factors including: allergens, viral infection, pollutants, and drugs. Eliminating those exposures improves the control of asthma and reduces medication needs. Parents/caregivers of children with asthma should be advised not to smoke at home.<sup>[208,221]</sup>

**Outpatient management of asthma in children**

*Asthma control level*

Asthma severity has been historically used as the entry point to determine the management strategy. Earlier, asthma guidelines emphasized the assessment of severity (e.g. intermittent, mild persistent, moderate persistent, severe persistent) to decide about medication choices. However, this trend has been replaced by the concept of asthma control. The literature suggests that asthma control and severity are different concepts.<sup>[208]</sup> Asthma control is a reflection of the adequacy of management (e.g. controlled, partly controlled, uncontrolled) which may vary markedly over short period of time and should entail short-term evaluations of current asthma status, asthma burden, and medical management.<sup>[222]</sup> Focusing on asthma control may improve patient perceptions and expectations that are commonly low in children, caregivers, and clinicians. This may in turn improve symptom reporting by children and parents, and treatment decisions by clinicians.<sup>[222]</sup>

*Tools for assessment of asthma control*

Traditionally, asthma control has been estimated by physician assessment during clinic visit and/or perception of patients and their caregivers toward asthma control. The GINA criteria for asthma control [Box 18] represent a valuable means for physicians to assess disease control. On the other hand, different tools have been developed and validated to assess asthma control, utilizing patients and their caregiver perception, such as the Respiratory and Asthma Control in Kids (TRACK) and the Childhood-Asthma Control Test (C-ACT). The TRACK is a validated test for kids younger than 5 years

of age [Box 19]. It is a 5-item standardized questionnaire, with four questions that address the impairment domain and one question that addresses the risk domain of asthma control. Each item is scored from 0 to 20 points on a 5-point Likert-type scale for a total score ranging from 0 to 100. Higher scores would indicate better respiratory and asthma control; a score of less than 80 points suggests that a child’s breathing problems might not be controlled.<sup>[223]</sup>

The C-ACT is another validated test for 4–12 year old kids [Box 20]. C-ACT is a two-part questionnaire with a total of seven questions. The first part is to be answered by the patient and the second by the caregiver. The final C-ACT score is made up of the sum of the scores of the two parts, ranging from 0 (poorest asthma control) to 27 (optimal asthma control). A score of 19 points or less suggests that a child’s asthma is not well controlled.<sup>[224]</sup>

The sensitivity and specificity of TRACK at the less-than-80 cutoff are consistent with those reported for the ACT at a cutoff of 19 or less (sensitivity, 69.2% and 68%; specificity, 76.2% and 74%, respectively).<sup>[224-226]</sup> It is important to remember that these tools have limitations and interpretation of their scores should be combined with physician assessment. For instance, a recent study found that there was inconsistency between GINA and C-ACT in 26.7% of the study group when the patients were evaluated individually. This indicates that using only one method for determining the control level of asthma does not seem to be reliable and accurate.<sup>[226]</sup>

*Stepwise approach for asthma management in children*

The goal of asthma treatment is to achieve and maintain control. Treatment is recommended to be adjusted continuously based on asthma control. If current treatment failed to achieve control, then treatment is recommended to be stepped up until control is achieved. Whenever control is maintained for at least 3 months, then treatment can be stepped down. This stepwise approach is essential to maintain optimum control with lowest step to minimize cost and maximize safety. For mild intermittent symptoms, SABA is considered as the first line of treatment. The need for SABA more than 3 times a week suggests suboptimal

**Box 17: Choosing an inhaler device for children based on efficacy of drug delivery, cost-effectiveness, safety, ease of use, and convenience**

Age	Preferred device	Alternative device
<4 years	Pressurized MDI + dedicated spacer with face mask	Nebulizer with face mask
4-6 years	Pressurized MDI + dedicated spacer with mouthpiece	Nebulizer with mouthpiece
>6 years	Dry-powder inhaler, or, Breath-actuated pressurized MDI, or Pressurized MDI + dedicated spacer with mouthpiece	Nebulizer with mouthpiece

Adopted from the global initiative for asthma (208)

**Box 18: Levels of asthma control in children**

Characteristics	Controlled (all of the following)	Partly controlled (any measure present in any week)	Uncontrolled (≥3 of any features of the partly controlled asthma in any week)
Daytime symptoms	None (<2/week)	>2 days/week	>2 days/week
Limitations of activities	None	Any	Any
Nocturnal symptoms/awakening	None	Any	Any
Need for bronchodilator	≤2 days/week	>2 days/ week	>2 days/ week

Adapted from the Global Initiative for Asthma<sup>[208]</sup>

**Box 19: The test for respiratory and asthma control in kids “track” for kids <5 years of age****Test questions****Score**

1. During the past 4 weeks, how often was your child bothered by breathing problems (such as wheezing, coughing, or shortness of breath)?

Not at all	Once or twice	Once every week	2–3 times/week	≥ 4 times/week
<input type="checkbox"/> 20	<input type="checkbox"/> 15	<input type="checkbox"/> 10	<input type="checkbox"/> 5	<input type="checkbox"/> 0

2. During the past 4 weeks, how often did your child’s breathing problems (wheezing, coughing, and shortness of breath) wake him/her at night?

Not at all	Once or twice	Once every week	2–3 times/week	≥ 4 times/week
<input type="checkbox"/> 20	<input type="checkbox"/> 15	<input type="checkbox"/> 10	<input type="checkbox"/> 5	<input type="checkbox"/> 0

3. During the past 4 weeks, to what extent did your child’s breathing problems, such as wheezing, coughing, or shortness of breath, interfere with his/her ability to play, go to school, or engage in usual activities that a child should be doing at his/her age?

Not at all	Once or twice	Once every week	2–3 times/week	≥ 4 times/week
<input type="checkbox"/> 20	<input type="checkbox"/> 15	<input type="checkbox"/> 10	<input type="checkbox"/> 5	<input type="checkbox"/> 0

4. During the past 3 months, how often did you need to treat your child’s breathing problems (wheezing, coughing, or shortness of breath) with quick-relief medications?

Not at all	Once or twice	Once every week	2–3 times/week	≥ 4 times/week
<input type="checkbox"/> 20	<input type="checkbox"/> 15	<input type="checkbox"/> 10	<input type="checkbox"/> 5	<input type="checkbox"/> 0

5. In the past 12 months, how often did your child need to take oral corticosteroids for breathing problems not controlled by other medications?

Not at all	Once or twice	Once every week	2–3 times/week	≥ 4 times/week
<input type="checkbox"/> 20	<input type="checkbox"/> 15	<input type="checkbox"/> 10	<input type="checkbox"/> 5	<input type="checkbox"/> 0

Total:

Adapted from reference<sup>[223]</sup>**Box 20: The childhood asthma control test (c-act) for kids 4–12 years of age****Childhood Asthma Control Test (C-ACT) questions****Score**

By child

1. How is your asthma today?

Very bad	Bad	Good	Very good
<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3

2. How much of a problem is your asthma when you run, exercise, or play sports?

It is a big problem; I can’t do what I want to do	It’s a problem and I don’t like it	It’s a little problem but it’s okay	It’s not a problem
<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3

3. Do you cough because of your asthma?

Yes, all of the time	Yes, most of the time	Yes, some of the time	No, none of the time
<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3

4. Do you wake up during the night because of your asthma?

Yes, all of the time	Yes, most of the time	Yes, some of the time	No, none of the time
<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3

By parent

5. During the last 4 weeks, how many days did your child have any daytime asthma symptoms?

Not at all	1–3 days	4–10 days	11–18 days
<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2

6. During the last 4 weeks, how many days did your child wheeze during the day because of asthma?

Not at all	1–3 days	4–10 days	11–18 days
<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2

7. During the last 4 weeks, how many days did your child wake up during the night because of asthma?

Not at all	1–3 days	4–10 days	11–18 days
<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2

Total:

Adapted from the Global Initiative for Asthma<sup>[208]</sup>

asthma control and indicates the need for controller therapy [Boxes 10 and 21]. As ICS represent the best and first option for controller treatment, treating physicians should be familiar with dosage amount (low, medium, and high) for different ICS formulations [Box 6].

**Consideration for asthma pharmacotherapy in children***Inhaled corticosteroids*

- Inhaled corticosteroids (ICS) are considered the best option as the first-line maintenance monotherapy for childhood asthma (Evidence A).<sup>[227,228]</sup>

### Box 21: Asthma management approach based on control for children <5 years

Asthma education, Environmental control, As needed rapid acting $\beta$ 2-agonists		
Controlled on as needed rapid acting $\beta$ 2-agonists	Partly controlled on as needed rapid acting $\beta$ 2-agonists	Uncontrolled or partly controlled on low-dose ICS*
↓ Controller      ↓ options		
- No change; - continue as needed rapid acting $\beta$ 2-agonists	Preferred: Low-dose ICS Alternative: Leukotriene modifiers	Preferred: Double low-dose ICS Alternative: Low-dose ICS+ leukotriene modifiers

ICS, inhaled corticosteroids, Adapted from the Global Initiative for Asthma<sup>[208]</sup>

- The clinical benefits of intermittent systemic or ICS for children with intermittent and viral-induced wheezing remain controversial. While few studies in older children found small benefits, a study in young children found no effect. This practice should be discouraged until clear evidence-based guidelines are available on this aspect of asthma management (Evidence D).
- There are insufficient data to recommend short courses of high-dose ICS in children with mild, intermittent asthma exacerbation. Safety of this approach has not been established (Evidence B).<sup>[229,230]</sup>
- Children with frequent, severe asthma exacerbation or both are recommended to receive regular treatment with ICS (Evidence D).
- Asthmatic children when treated with ICS attain normal adult height, but at a later age. Growth retardation may be seen with all ICS when a high dose is chronically used.

#### Leukotriene modifiers

- There is insufficient evidence to recommend LTRAs as first-line monotherapy for childhood asthma. However, LTRAs represent a safe alternative option for children who cannot or will not use ICSs (Evidence B).<sup>[231,232]</sup>
- If optimal asthma control cannot be achieved on moderate doses of ICS, then escalation of therapy by the addition of LTRA represents an acceptable step (Evidence A).<sup>[232-234]</sup>
- LTRAs can reduce viral-induced asthma exacerbations in children aged 2–5 years with history of intermittent asthma (Evidence B).<sup>[235]</sup>
- LTRAs can reduce EIA in older children (Evidence B).<sup>[236]</sup>

#### Long-acting $\beta$ -agonist

- LABA should not be used as maintenance monotherapy in children (Evidence A).<sup>[237]</sup>
- If optimal asthma control was not achieved with moderate doses of ICS, then therapy is recommended to be modified by the addition of LABA “as a combination therapy with ICS” (Evidence A).<sup>[136]</sup> Alternatively, LTRA or high-dose ICS can be attempted (Evidence A).<sup>[238,239]</sup>
- Asthmatic children receiving combination treatment (ICS and LABA) may require step down of therapy by stopping LABA whenever optimum control is achieved for good time.

#### Other bronchodilators

- Inhaled anticholinergics are not recommended for long-term management of asthma in children; they are effective when combined with  $\beta$ 2-agonist for the acute management of severe exacerbations (Evidence B).<sup>[240]</sup>
- The available evidence indicates that the effect of

theophylline is less than that of low-dose ICS, and side effects are more common.

- Oral  $\beta$ 2-agonist should be avoided due to its slower onset of action and its tendency to produce more systemic side effects.

#### Devices, adjustments, and others

- Nebulizers are not superior to pMDI (when pMDI delivered is combined with valved-spacer) in both acute and chronic asthma management (Evidence A).<sup>[241]</sup>
- Use of valved-spacer, with mouthpiece when possible, is recommended when a pMDI is prescribed (Evidence B).<sup>[242]</sup>
- Breath-actuated devices (e.g. DPIs) represent an effective/simpler option for maintenance therapy in children >5 years of age (Evidence C).<sup>[243,244]</sup>
- Assessment of compliance, control of environment, and diagnosis are recommended to be revisited each time before treatment adjustments.
- Cromones (sodium cromoglycate and nedocromil sodium) are not recommended for preschool children. They have limited role in the long-term treatment of older children. Evidence showed that low-dose ICS is superior to cromones in the management of asthma.

#### Acute exacerbation management

##### Role of severity assessment during acute asthma exacerbation

Severity assessment of the acute asthma exacerbation has an important role to support the acute management decisions that includes: pharmacological interventions, need for hospitalization, and need for intensive care unit admission. The assessment of acute asthma severity in young children is important both for clinical decision-making and evaluation of treatment effectiveness.<sup>[222,245-253]</sup> This is supported by the fact that pulmonary function measurement is not feasible as more than half of pediatric asthma exacerbation presented to emergency departments are of preschool-aged children.<sup>[246]</sup> On the other hand, The Pediatric Respiratory Assessment Measure (PRAM) has been recently found to be feasible, valid, responsive, and reliable pediatric tool to determine asthma severity in children aged 2–17 years.<sup>[246]</sup> The PRAM simply represents a useful means to record clinical signs in a standardized fashion with some degree of subjectivity in the ascertainment and coding of these signs [Box 22].<sup>[222]</sup> The PRAM score is a 12-point score consisting of oxygen saturation, suprasternal retractions, scalene muscle contraction, air entry, and wheezing.<sup>[253]</sup> Measuring PRAM total score for asthmatic patients in emergency room can identify patients at risk of hospitalization [Box 23].

- Total score of 0–3: low risk (<10%) of hospital admission
- Total score of 4–7: moderate risk (10% to 50%) of hospital admission
- Total score of 8–12: high risk (>50%) of hospital admission

The initial assessment of patients is recommended to record the PRAM score at triage. The score is recommended to be checked after the initial treatment as well. Implementation of clinical pathway that utilizes PRAM score for the acute management of children with moderate to severe exacerbations will markedly decrease the rate of hospitalization without increasing the rate of return to emergency care.<sup>[254-256]</sup> Clinical pathways based on PRAM for inpatient asthma management that has been implemented in some North American hospital has

been shown to decrease the length of stay and bronchodilator use with no adverse outcomes or increased acute care encounters.<sup>[257,258]</sup> We would recommend two pathways for acute asthma management based on the utilization of PRAM score. The emergency room management [Box 24] was classified to mild (PRAM score 1–3), moderate (PRAM score 4–7), and severe.<sup>[8–12]</sup> The inpatient management was split into three phases: phase I that covers initial management [Box 25] and phases II and III that cover continuation of management till discharge [Box 26].

### Special Situations in Asthma in Adults

#### Cough-variant asthma

Patients with cough-variant asthma have chronic cough as their main, if not only, symptom.<sup>[259,260]</sup> It is particularly common in children, and is often more problematic at night. Other diagnoses to be considered are drug-induced cough caused by angiotensin-converting enzyme inhibitors, GERD, postnasal drip, eosinophilic bronchitis, and chronic sinusitis. Once the diagnosis is established, treatment should follow the same stepwise approach as for the long-term management of asthma.<sup>[261]</sup>

#### Exercise-induced asthma

Asthma-like symptoms can sometimes be triggered only by physical activities. Normally, bronchodilation occurs during exercise and lasts for a few minutes afterward. In patients with EIA, the initial bronchodilation is followed by bronchoconstriction that generally peaks within 10–15 min after completing the exercise and resolves within 60 min. EIB can be prevented by use of rapid acting B2-agonist a few minutes before exercise (Evidence A).<sup>[262]</sup> A warm-up period before exercise may reduce EIA symptoms. If this approach does not control the symptoms, patients should have maintenance therapy with ICS increased or introduced (Evidence A).<sup>(145)</sup> Regular use of LTRA may help in this condition, especially in children (Evidence B).<sup>[145,236]</sup>

#### Aspirin-induced asthma

About 10–20% of adults with asthma suffer from exacerbations

in response to aspirin or NSAIDs, which are more common in severe asthma. The majority of patients experience first symptoms during their third to fourth decade of life. Once aspirin or NSAID hypersensitivity develops, it is present for life. Characteristically, within minutes to 1–2 h following ingestion of aspirin, an acute, severe attack develops, and is usually accompanied by rhinorrhea, nasal obstruction, conjunctival irritation, and scarlet flush of the head and neck.<sup>[263]</sup> A typical history of reaction is considered adequate for diagnosis of aspirin-induced asthma. Patients known to have aspirin-induced asthma should avoid all aspirin-containing products and NSAIDs. Where an NSAID is strongly indicated, alternative analgesics such as paracetamol should be considered. Prophylactic low-dose aspirin should also be avoided; however, patients for whom aspirin is considered essential, they should be referred to an allergy specialist for aspirin desensitization. Aspirin and NSAID can be used in asthmatic patients who do not have aspirin-induced asthma.<sup>[264]</sup>

#### GERD triggered asthma

GERD is more prevalent in patients with asthma compared to the general population. The mechanisms of GERD triggered asthma include vagal mediated reflex and reflux secondary to micro-aspiration of gastric contents into the upper airways.<sup>(265)</sup> All patients with asthma should be questioned about symptoms of GERD. If symptoms are present, a trial of anti-GERD measures and therapy is recommended for 6–8 weeks; including a proton pump inhibitor may be considered (Evidence B).<sup>[266–268]</sup> Asymptomatic patients with uncontrolled asthma do not benefit from GERD therapy (Evidence A).<sup>[269]</sup>

### Asthma and Pregnancy

The course of asthma during pregnancy is unpredictable; however, one-third of pregnant asthmatics will have worsening of their asthma control.<sup>[270,271]</sup> Maintaining adequate control of asthma during pregnancy is essential for the health and well-being of both the mother and her baby. Identifying and avoiding triggering factors should be the first step of therapy for asthma during pregnancy. Treatment should

#### Box 22: The pediatric respiratory assessment measure score

Sign	0	1	2	3
Suprasternal retraction	Absent		Present	
Scalene muscle contraction	Absent		Present	
Air entry	Normal	Decreased at bases	Widespread decreased	Absent/minimal
Wheezing	Absent	Expiratory only	Inspiratory and expiratory	Audible without stethoscope/silent chest with minimal air entry
O2 saturation	≥ 95%	92–94%	<92%	

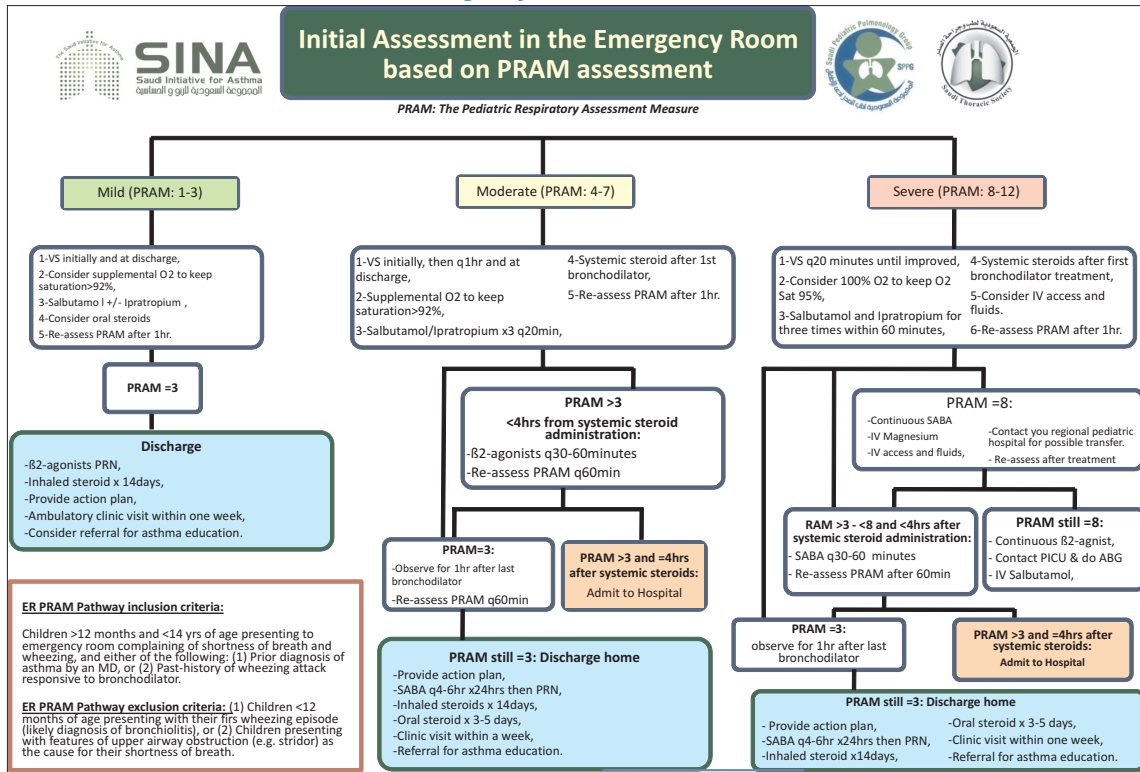
Adopted from reference no (253)

#### Box 23: Severity classification of asthma exacerbation based on PRAM score with corresponding risk of hospitalization

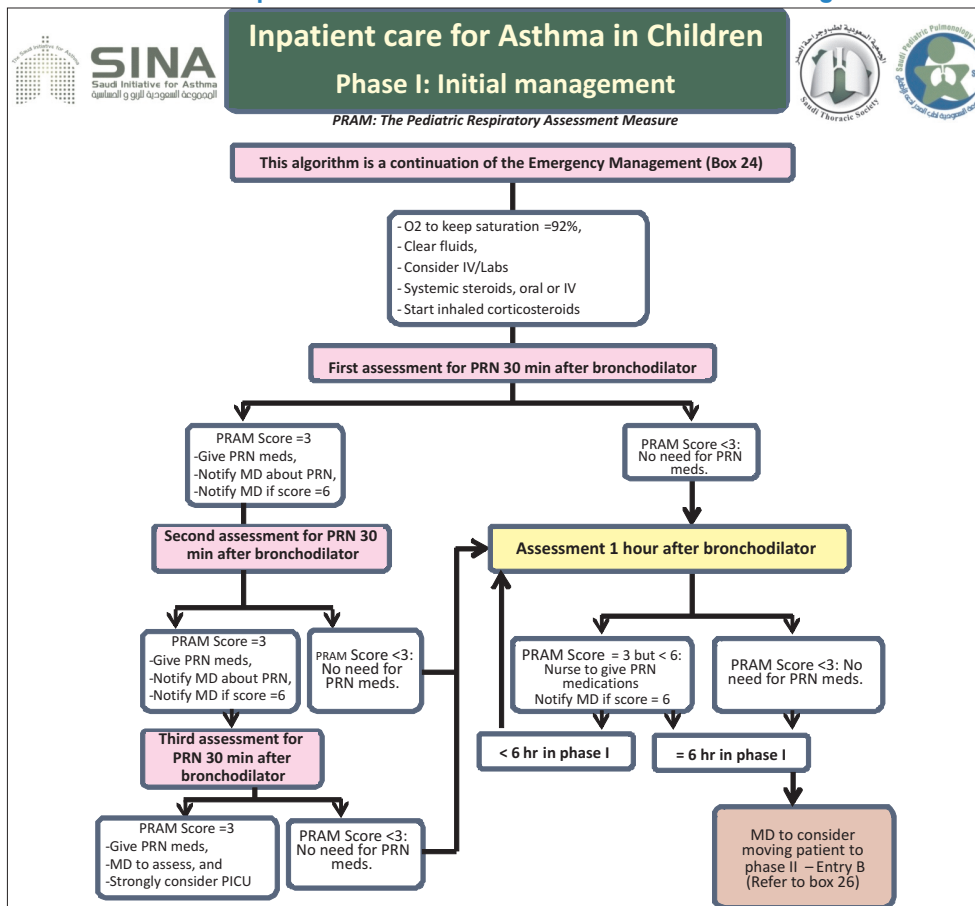
Severity of asthma exacerbation	PRAM score	Risk of hospitalization
Mild (<10% risk of hospitalization)	0-3	<10%
Moderate (10-50% risk of hospitalization)	4-7	10-50%
Severe (>50% risk of hospitalization)	8-12	>50%

Adopted from reference no (253)

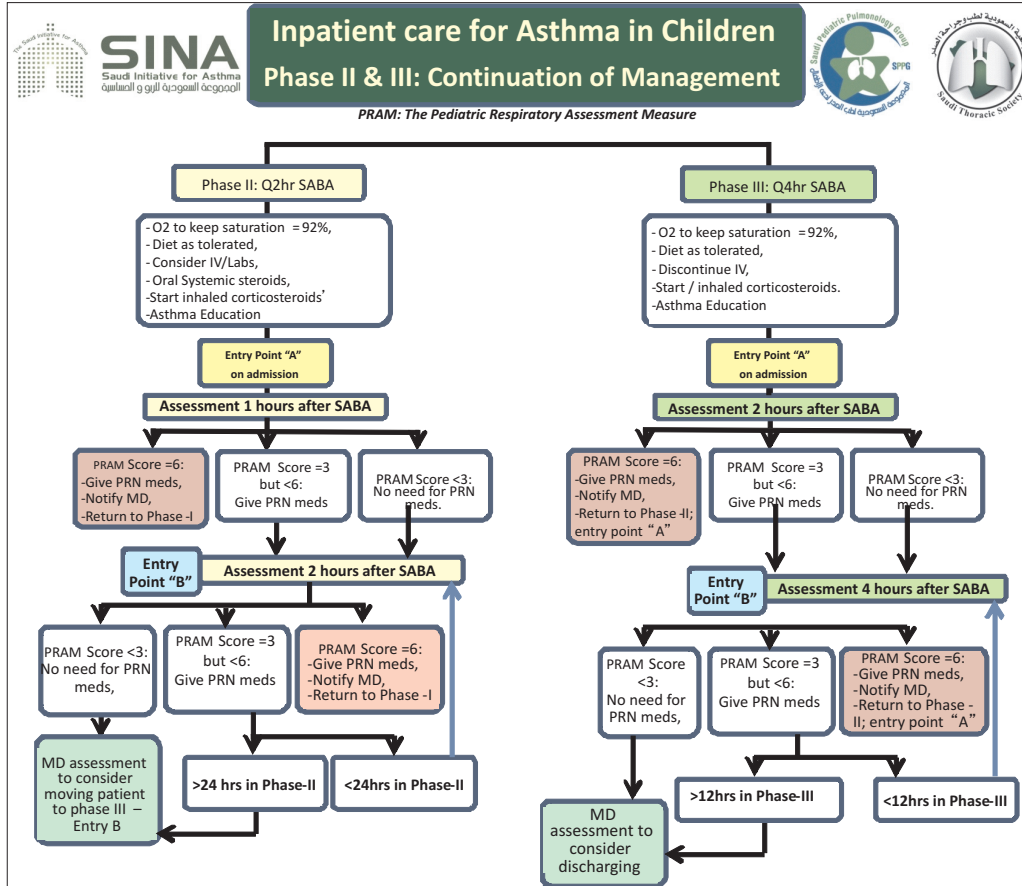
**Box 24: Initial assessment in the emergency room based on PRAM assessment**



**Box 25: Phase I of inpatient care for asthma in children: Initial management**



**Box 26: Phase II and III of inpatient care for asthma in children: Continuation of management**



take the same stepwise approach as in the non-pregnant patient. Salbutamol is the preferred SABA because it has an excellent safety profile. ICS are the preferred treatment for long-term control (Evidence B).<sup>[272]</sup> Use of ICS, theophylline, antihistamines, B2-agonists, and LTRA is generally safe, and they have not been shown to increase the risk of fetal abnormalities.<sup>[273]</sup> Prolonged use of systemic steroids may be associated with pregnancy-related complications, especially in the first trimester. Acute exacerbations during pregnancy are recommended to be treated in the same manner as in non-pregnant patients.<sup>[274]</sup>

**Treating asthma in pregnancy**

- Pregnant asthmatics are recommended to receive the same drug treatment for acute asthma as non-pregnant patients (Evidence B),<sup>[271,275]</sup> including systemic steroids if indicated (Evidence C).<sup>[275]</sup>
- Continuous fetal monitoring is recommended in severe asthma exacerbation.
- If anesthesia is required during labor, regional anesthesia is recommended whenever possible (Evidence C).<sup>[276]</sup>
- The use of prostaglandin F2α may be associated with severe bronchospasm and should be used with extreme caution (Evidence D).
- The following are recommended for pregnant asthmatics:<sup>[275,277,278]</sup>
  - If asthma is well controlled during pregnancy, acute asthma is rare in labor.

- All asthma treatments are safe in pregnancy, and asthmatics should continue their usual asthma medications during pregnancy and in labor.
- In the absence of acute severe asthma, reserve Cesarean section for the usual obstetric indications.
- Pregnant asthmatics should be encouraged to breastfeed after delivery and to use asthma medications as normal during lactation.

**Difficult to control asthma**

Difficult to control asthma (DTA) carries several names; each one points to an aspect of the disease.<sup>[279]</sup> Chronic severe asthma, steroid-dependent asthma, difficult-to-control asthma, and refractory asthma are some of these terminologies. It is simply defined as asthma in patients who require very high doses of inhaled steroids with other controller agents, or near-continuous oral steroid treatment to maintain asthma control. DTA probably accounts for 5%–10% of adult asthma, but the health cost is disproportionately high.<sup>[280]</sup> Morbidity and mortality are also higher than in regular asthma patients because of increased side effects of steroids and much more frequent exacerbations.<sup>[281,282]</sup>

Before labeling a patient as a case of DTA,<sup>[283-288]</sup> the following should be considered:

- To ensure that patient is adherent to medications with a good technique.
- Misdiagnosis where the problem is not bronchial asthma to start with, but another respiratory system pathology that is

not appropriately addressed, for example, bronchiectasis, endobronchial tumors, and vocal cord dysfunction.<sup>[286]</sup>

- Comorbidity that worsens bronchial asthma and makes it difficult to manage (e.g. chronic sinusitis, gastro-esophageal disease, sleep apnea syndrome, obesity, and CHF).<sup>[289]</sup>
- Confounding factors (e.g. non-adherence with treatment, the presence of allergens at home or work, active or passive smoking, and psychosocial problems making asthma difficult to treat).<sup>[286]</sup>

After dealing with the causes that are making asthma difficult to treat, the remaining asthma patients have a real problem of not responding to steroid therapy.<sup>[290]</sup> Patients may differ in the degree of this phenomenon of “steroid unresponsiveness.”<sup>[291]</sup> Some of these patients may have the “pseudo-steroid” resistance status which is due to other coexisting conditions.<sup>[292,293]</sup> However, a significant percentage of patients do not respond adequately to high doses of inhaled steroids but will need continuous oral therapy to show a reasonable response, and are better defined as refractory cases, that is, asthmatic patients in whom it is not possible to take off oral steroids. These patients have persistent symptoms despite high doses of inhaled steroids and other “non-steroidal” asthma therapy.

In DTA, it is strongly recommended to refer patients to a specialist of asthma. It may be difficult to achieve full control, and therefore the aim of the treatment is to reach the best possible outcome. That is, the least amount of symptoms and exacerbations.<sup>[294]</sup> After dealing with all related issues that could have made asthma difficult to control, maximum therapy is given (step 5 therapy) which may include combination therapy of high-dose steroid inhalers and LABA, LTRA, and long acting anti-muscarinic agents (LAMA).<sup>[295]</sup> Anti-IgE treatment (omalizumab) is given if the patients fulfill the criteria for this treatment.<sup>[296]</sup> If oral steroids are necessary, then it is important to try to reduce both the frequency and doses of oral steroids and only give them for short periods at a time to avoid long-term side effects.<sup>[297]</sup> New modalities of drug treatment are promising and may help to further control DTA. Mepolizumab has been shown to reduce exacerbations and improves asthma control in patients with refractory eosinophilic asthma.<sup>[298]</sup> Bronchial thermoplasty is a novel treatment modality that utilizes radiofrequency energy to alter the smooth muscles of the airways. In severe persistent asthma, it leads to improvements in various measures of asthma, including forced expiratory volume in one second (FEV<sub>1</sub>), quality of life, asthma control, and use of rescue medications.<sup>[299-302]</sup>

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