The Saudi initiative for asthma – 2024 update: Guidelines for the diagnosis and management of asthma in adults and children

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Submission: 01-10-2023
Accepted: 31-10-2023
Published: 15-12-2023

Abstract:

The Saudi Initiative for Asthma 2024 (SINA-2024) is the sixth version of asthma guidelines for the diagnosis and management of asthma for adults and children that was developed by the SINA group, a subsidiary of the Saudi Thoracic Society. The main objective of the SINA is to have guidelines that are up-to-date, simple to understand, and easy to use by healthcare workers dealing with asthma patients. To facilitate achieving the goals of asthma management, the SINA Panel approach is mainly based on the assessment of symptom control and risk for both adults and children. The approach to asthma management is aligned for age groups: adults, adolescents, children aged 5–12 years, and children aged <5 years. SINA guidelines have focused more on personalized approaches reflecting a better understanding of disease heterogeneity with the integration of recommendations related to biologic agents, evidence-based updates on treatment, and the role of immunotherapy in management. The medication appendix has also been updated with the addition of recent evidence, new indications for existing medication, and new medications. The guidelines are constructed based on the available evidence, local literature, and the current situation at national and regional levels. There is also an emphasis on patient–doctor partnership in the management that also includes a self-management plan.

Keywords:

Asthma, asthma control test, guidelines, Saudi Arabia

Section 1: Introduction

Asthma is a chronic heterogeneous inflammatory disease characterized by a history of respiratory symptoms such as wheezing, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation.[1,2] Asthma is one of the most common chronic diseases in Saudi Arabia with increasing prevalence in the past decades.[3] It has a significant impact on patients, their families, the health-care system, 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.[4-6] Inadequate knowledge, lack of familiarity with new drugs, and awareness of the importance of disease control are common among primary care physicians who care for asthma patients in Saudi Arabia.[7,8] In addition to these key factors, there are other issues that influence the magnitude of the disease burden, such as socioeconomic status, number of siblings, knowledge of caregivers, and income.[9-13]

Consequently, many asthma patients are uncontrolled and continue to be under-diagnosed, under-treated, and at risk of acute attacks.[14] This was also observed among pregnant women with asthma as one study from Saudi Arabia showed that almost half of pregnant women with asthma had the intention to stop asthma medications during pregnancy.[15] The increasing prevalence of asthma in the past three decades 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, sandstorms, and tobacco. In addition, 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.

As part of its long-term commitment to promote best practices in the field of respiratory diseases, the Saudi Thoracic Society (STS) launched the Saudi Initiative for Asthma (SINA) group in 2008. The SINA Panel is a group of Saudi experts with well-respected academic backgrounds and experience in the field of asthma. Sections related to asthma in children represent the views of a panel from the Saudi Pediatric Pulmonology Association, another subsidiary of the STS.

The SINA Panel aims to have updated guidelines, which are simple to understand and easy to use. It also aims toward enhancing the multidisciplinary care of asthma patients with special attention to non-asthma specialists, including primary care and general practice physicians and other healthcare workers.[16-20] The updated 2024 edition of SINA guidelines received a comprehensive update with an emphasis on personalized approaches reflecting a better understanding of disease heterogeneity with integration of recommendations related to new medications, approved biologic agents, evidence-based updates on treatment, especially on mild asthma, and update on the role of biologics in asthma management. The SINA Panel has also reviewed the stepwise approach to provide practical clinical practice guidelines based on the best available evidence and practices. Special attention was made to managing asthma during the time of emerging acute respiratory infections such as the recent coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2. The SINA Panel stratified the guidelines based on the following age groups: adults (age above 18 years) and adolescents (age of 13–18 years); and children that were stratified into two groups: Ages of 5–12 years and ages below 5 years.[1,2]

Methods
The SINA Panel produced this clinical practice guideline for the diagnosis and management of asthma in adults and children based on the available evidence with special emphasis on local literature and the current setting in Saudi Arabia. The consensus among the SINA Panel was followed whenever there was inadequate or lack of evidence.[21] The following criteria are used to grade the evidence:

- Evidence category A: Randomized controlled trials with a rich body of data
- Evidence category B: Randomized controlled trials with a 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.

For this update, a similar approach to previous versions has been employed, whereby each section has been internally reviewed at least twice by SINA panel members. The SINA panel conducted frequent round-table discussions and virtual discussions. A panel of international experts reviewed the guidelines, and their recommendations were thoughtfully considered.

Section 2: Pathophysiology of Asthma

Asthma is a chronic inflammatory airway disease that results in a narrow airway lumen. The airway narrowing is caused by smooth muscle contraction, airway thickening, bronchospasm, and increased mucus secretion as well as bronchial wall thickening due to edema, smooth muscle hypertrophy, and subepithelial fibrosis. The pathophysiological mechanisms that underlie these changes are diverse and heterogeneous [Box 2.1]. They are driven by a variety of cell types including immune cells; mainly T-helper cells (Th2, Th17, Th1), B-cells, mast cells, eosinophils, dendritic cells, and neutrophils; as well as structural bronchial cells such as epithelial cells, myofibroblasts, and smooth muscle cells.[22] These mechanisms can be broadly classified into two major categories and further subdivided into subclasses (endotypes). Other classifications exist, but the classification that appears below is simpler and can be easily recognized by readily available biomarkers in any clinical setting. This classification is more pertinent to severe asthma and, therefore, has special implications for therapy with biologics.

Type 2 inflammation (T-helper 2 high) asthma
This is the most common type and includes 40%–70% of asthma patients. It is defined by sputum eosinophilia of $\geq 2\%$ of leukocytes in a sample. Other ways to confirm the presence of type 2 inflammation are blood eosinophilia of $\geq 150\backslash\mu l$ and Fractional exhaled nitric oxide (FeNO) ≥ 20 ppb. This eosinophil cutoff is way

below the lower normal peripheral eosinophil count. The eosinophilic count may be reduced by high-dose inhaled corticosteroids (ICS) or maintenance systemic oral corticosteroids (OCS). Eosinophils secrete mediators such as major basic protein and eosinophil cationic protein that can cause bronchial epithelial damage and subepithelial fibrosis. Those patients usually respond well to ICS especially if they have mild or moderate disease. It is further subdivided into three phenotypes:

- Early-onset allergic phenotype: This type usually starts in childhood, and it is associated with atopy. It can be triggered by allergen exposure. Allergens are taken up by dendritic cells and presented to naïve T-cells that develop into Th2 cells characterized by the secretion of type 2 cytokines: Interleukins (IL) namely, IL-4, IL-5, and IL-13. IL-4 and IL-13 are necessary for specific B-cell activation and switching into immunoglobulin E (IgE) producing cells. IgE binds to its high-affinity receptor on mast cells. Subsequent cross-linking of IgE molecules by the allergen will lead to mast cell degranulation and release of mediators such as histamine and tryptase as well as type 2 cytokines. In addition, IL-13 causes smooth muscle and goblet cell hyperplasia. This phenotype is characterized by positive allergy skin tests and increased serum-specific IgE. It usually responds to ICS and omalizumab, an anti-IgE therapy. Symptoms could also be triggered by similar triggers of the non-allergic type (see below)
- Late-onset eosinophilic phenotype: This type usually starts during adulthood. Patients typically have no allergies, but usually have more severe airway limitation and hyperresponsiveness. It is usually less responsive to ICS compared to the previous phenotype. Patients with this phenotype may develop chronic rhinosinusitis with nasal polyps (CSwNP). It is triggered by microbes (bacteria and viruses), pollutants, and irritants. IL-5 is essential for eosinophil maturation, and survival and contributes with certain other chemokines to their recruitment to the bronchial airways.[23,24] An alternative mechanism of eosinophil recruitment originates from bronchial epithelial cells that in response to non-allergenic stimuli including viral infections release alarming such as IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) that will stimulate innate lymphoid cells type 2 to release IL-5 and IL-13.[25] This phenotype is associated with a high level of blood/tissue eosinophil and/or high FeNO
- Aspirin-exacerbated respiratory disease (AERD) phenotype: This is a subset of the late-onset eosinophilic phenotype, and it is characterized by asthma, nasal polyps, and cyclooxygenase-1 (COX-1) inhibitor-induced respiratory reactions. In this phenotype, prostaglandin E2 (PGE2) and its receptor EP2 baseline levels are both severely reduced. PGE2 is essential for preventing mast cells, and eosinophils from becoming activated. Loss of homeostatic PGE2 expression eliminates the 5-lipoxygenase (5-LOX) pathway's negative feedback, which increases constitutive cysLT production. Strong COX-1 and COX-2 inhibitors include aspirin. When COX is inhibited, the 5-LOX pathway takes over as the mechanism for arachidonic acid metabolism. As a result of this inflammatory cascade, residual homeostatic PGE2 is suppressed, which leads to an excess of CysLT being produced by mast cells, eosinophils, and macrophages. Leukotriene C4 synthase (LTC4S) mediates this atypical cysLT synthesis. Most of the symptoms of AERD are caused by CysLTs, which are potent bronchoconstrictors and include leukotriene C4 (LTC4), LTD4, and LTE4.

Non-type 2 (T-helper 2 low) asthma: This can further be subdivided into 2 types

- Neutrophilic phenotype: Variably defined as neutrophils of ≥40% of leukocytes in an induced sputum sample. It is less clearly characterized and involves the release of Th1 and Th17-related cytokines and IL8, granulocyte-macrophage colony-stimulating factor that attracts neutrophils to the airways. It is triggered by infections, irritants, and tobacco smoke and may be a manifestation of the use of steroids in patients with eosinophilic inflammation. Those patients are mostly adults and do not respond to ICS as well[26]
- Pauci-granulocytic: In this form there is not as much inflammation. The airway limitation is supposedly driven by other mechanisms. It is the least common and patients usually have milder disease.[27]

Mixed type 2-high and type 2-low (granulocytic) asthma

This type has features of both eosinophilic and neutrophilic inflammation including their cytokines profile. It is less common than the two previous main types and tends to be more severe and more difficult to treat.[28]

Airway hyperresponsiveness

This is a major feature of all asthma endotypes. Its mechanisms and mediators are poorly understood. It worsens during and immediately after asthma attacks. It is usually worse in patients with severe asthma. However, it does not correlate well with markers of inflammation. Smooth muscle hypertrophy and neurohumoral factors may play a role in determining airway hyperresponsiveness (AHR).[29]

Airway remodeling

This is a major feature of asthma that starts early in the disease process and causes incomplete reversibility
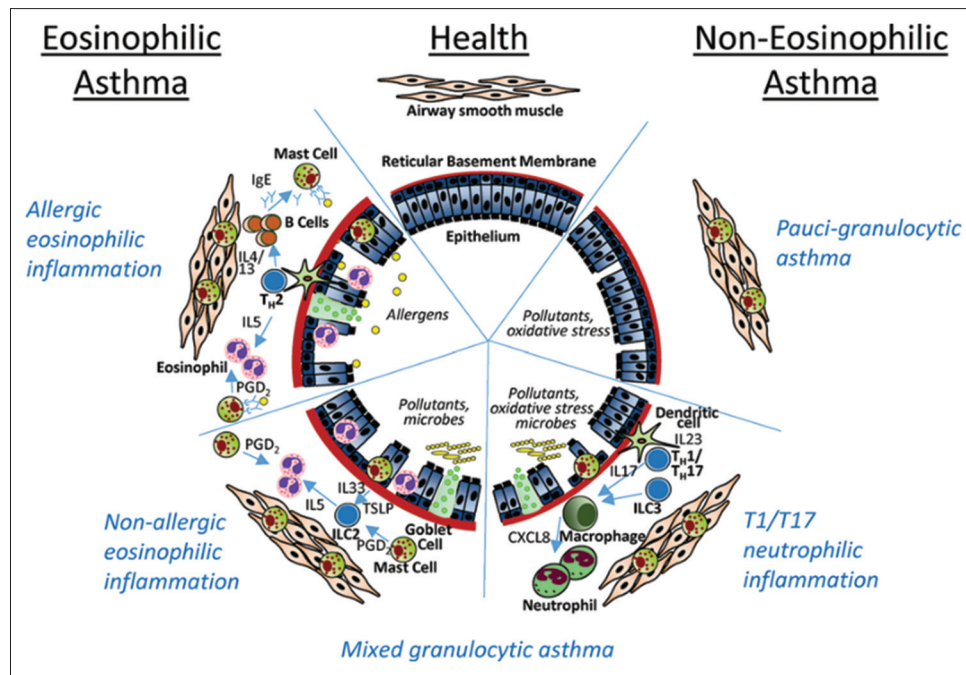
Box 2.1: Immunopathology of asthma

by bronchodilators. It is characterized by bronchial epithelial damage, thickening of the basement membrane, and muscle hypertrophy.[30,31] It is influenced by the ongoing airway inflammation and recurrent bronchoconstriction.[32]

Pathophysiology of acute asthma

The pathophysiology of acute asthma is less clear due to limited information. This is because of the difficulty in studying disease pathology and obtaining samples during exacerbations. The pathological manifestations generally depend on the trigger. At least 80% of cases of moderate to severe acute asthma are triggered by viruses, most commonly rhinovirus, but also respiratory syncytial and influenza viruses.[33] Viral infections can cause significant epithelial damage and symptoms tend to be more severe and last longer. On the other hand, allergen or irritant-triggered attacks tend to be milder and resolve more quickly. Recurrent attacks may lead to a progressive decline in lung function and increasing baseline asthma severity.[34-36]

Section 3: Diagnosis of Asthma in Adults and Adolescents

The diagnosis of asthma is based on clinical assessment by a detailed history and physical examination supported by spirometry with reversibility testing.

History

The symptoms of asthma are wheezing, cough, shortness of breath, and chest tightness but they are not specific to asthma and can be seen with other pulmonary diseases.

However, the combination of these symptoms increases the probability of asthma. The pattern of symptoms is usually variable over time and the patient may be entirely asymptomatic between attacks.[37] Symptoms are usually worse at night and can be provoked by exercise or other triggering factors such as viral infections and smoke. Asthma diagnosis can be supported by taking a detailed history including the patient's occupation, family history of asthma, other allergic disorders, smoking, and vaping. Box 3.1 lists the relevant questions that are commonly considered when taking a history where the diagnosis of asthma is under consideration. Asthma control may be worsened by coexisting symptomatic gastroesophageal reflux disease (GERD), rhinosinusitis, obesity, sleep disorders, or the use of some medications such as beta blockers and nonsteroidal anti-inflammatory drugs

Box 3.1: 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 symptoms after taking aspirin/nonsteroidal anti-inflammatory medication or use of B-blockers?

Does the patient's colds "go to the chest" or take>10 days to clear up?

Are symptoms improved by appropriate asthma treatment?

Are there any features suggestive of occupational asthma?

(NSAIDs) including aspirin.[38] Asthma and rhinosinusitis commonly coexist.[39,40]

Patients with asthma have different clinical phenotypes with specific clinical characteristics like allergic asthma which usually starts during childhood.[41] It could also be associated with CSwNP. The other phenotype is called non-allergic asthma which is not associated with a history of atopy or allergy. Other phenotypes include late-onset asthma, asthma with fixed airway obstruction, and asthma associated with obesity.

Physical examination

The physical examination of the chest may be normal in stable and controlled asthma but the presence of bilateral expiratory widespread, high-pitched, variable musical wheezing, are characteristic feature of asthma. This may be accompanied by shortness of breath or diminished oxygen saturation. The presence of wheezing indicates airway narrowing, but it is not correlated with asthma severity. Examination of the upper airways is important to look for evidence of allergic rhinitis, such as nasal mucosal swelling, nasal polyps, and postnasal dripping. Other allergic manifestations, such as atopic dermatitis, also support the diagnosis of allergic asthma.[42] The presence of a localized wheeze, crackles, stridor, clubbing, or heart murmurs should suggest alternative diagnoses.[43] Therefore, a careful consideration of any alternative diagnoses before commencing asthma treatment by a physician should be made.

Investigations

Spirometry is necessary to confirm airflow obstruction and demonstrates significant reversibility by performing a spirometry. The degree of significant reversibility is defined as an improvement in forced expiratory volume in 1 s (FEV_1) $\geq 12\%$ and ≥ 200 ml from the pre-bronchodilator value.[44] It may also help to identify other alternative diagnoses such as upper airway obstruction. However, normal spirometry or failure to show reversibility does not rule out the diagnosis of asthma, as it can be normal with the patient still being symptomatic.[45] Serial peak expiratory flow rate (PEF) measurements may be helpful in the diagnosis of asthma by showing the characteristic increased variability of <10% in twice daily PEF over 2 weeks and also for follow-up after starting treatment. A diagnostic therapeutic trial with significant reversibility after 4 weeks of ICS may be useful in confirming a diagnosis when it shows favorable reversibility.[45] Bronchoprovocation testing is another tool to rule out asthma with atypical presentation and normal spirometry, but it is not routinely required.

Chest X-ray (CXR) is not routinely recommended unless the diagnosis is in doubt when symptoms are not typical or suggest alternative diagnoses, when assessing a patient with severe asthma, or when asthma is associated with other medical conditions. Peripheral eosinophilia and elevated IgE levels are supportive of the diagnosis but are not routinely recommended unless dealing with moderate to severe asthma.[45] FeNO is an alternative method for detecting airway inflammation in eosinophilic asthma; however, it can be suppressed with the use of ICS in smokers.[46] Skin prick testing and radioallergosorbent test (RAST) are not routinely required to diagnosis asthma but may be helpful in identifying allergens to which the patient has been sensitized and in developing a strategy for avoiding allergen exposure.[47]

Section 4: Clinical Assessment in Adults and Adolescents

Principles of asthma assessment

The principles of optimal asthma management are recommended to initially consist of an assessment of asthma control.[48] Before commencing a patient on treatment, the SINA Panel recommends ensuring the following:

- Assessment of asthma control
- Assessment of risk factors for poor asthma control and fixed airway obstruction.
- Performance of pulmonary function testing (PFT) with spirometry and/or PEF to assess airflow limitations and postbronchodilator reversibility
- Documentation of current treatment and any issues related to adherence, inhaler technique, or side effects
- Utilization of a written asthma action plan
- Assessment of comorbidities such as rhinosinusitis, GERD, obesity, obstructive sleep apnea, anxiety, and exercise-induced laryngeal obstruction[49]
- Close monitoring for patients with severe asthma and a history of asthma attacks.

Assessment of asthma symptoms control

In adults and adolescents, asthma control is based on assessing asthma symptoms, use of reliever medications, and impact on daily activities. Asthma control reflects the adequacy of management by describing the clinical status of a patient as controlled, partly controlled, or uncontrolled over the past 4 weeks. The control status may vary markedly over time and is recommended to entail frequent assessment of current asthma status, asthma burden, and medical management.[50] Focusing on asthma control may improve patient perceptions and expectations that improve symptom reporting and subsequently treatment decisions by clinicians.[51] Poor asthma control is associated with increased burden of the disease, asthma attacks, and mortality.[52] Therefore, symptom control assessment should be carried out during every clinical evaluation. The SINA Panel recommends the utilization of the asthma control test (ACT).

Asthma control test

The ACT is a commonly used tool to assess asthma control.[53] It is a short, validated, self-administered questionnaire to assess asthma control in the past 4 weeks.[54] It consists of five items including limitation of activity, shortness of breath, frequency of night symptoms, use of rescue medication, and the patient's rating of overall control of asthma symptoms over the past 4 weeks.[55] The score 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. The SINA Panel recommends the utilization of asthma ACT to initiate asthma treatment in adults and adjust it at follow-up.[56-58] The clinically important significant change in ACT score is considered to be ≥3 units.[59] The level of asthma control is categorized into:

- Controlled: An ACT score of ≥20 points
- Partly controlled: An ACT score of 16–19 points
- Uncontrolled: An ACT score of <16 points.

Fractional concentration of exhaled nitric oxide

Is closely associated with type 2 inflammation and commonly elevated in eosinophilic asthma. It is suggested that FeNO <25 ppb that indicates eosinophilia is unlikely, 25–49 ppb indicates possible eosinophilia, and FeNO >50 ppb indicates that eosinophilia is likely. However. FeNO can also be elevated in non-asthma conditions such as allergic rhinitis, atopy, eczema, and eosinophilic bronchitis. It can also be reduced in smokers and neutrophilic asthma. These considerations may restrict its application to asthma diagnosis. Nevertheless, in the right clinical context with the presence of variable respiratory symptoms, elevated FeNO >50 ppb allows a valid ruling-in of an asthma diagnosis.[60] A lower level of FeNO cannot rule out asthma. The presence of a high level of FeNO is also a risk factor for future severe and frequent asthma exacerbations and a decline in lung function. FeNO ≥20 ppb is indicative of type 2 inflammation, and it is a good predictor of response to the appropriate biologic. FeNO can also aid in determining steroid responsiveness and optimizing ICS doses. A higher level of FeNO can be used as an indication of poor adherence to ICS, for which the FeNO suppression test can be used to evaluate adherence in such patients.

Assessment of risk factors for future asthma attacks

The future risk of adverse outcomes should be assessed. This is achieved by assessing future risk of attacks, fixed airflow obstruction, and adverse effects of medications.[1,2] The SINA Panel recommends assessment of risk factors for poor asthma outcomes, especially in patients experiencing attacks by assessing risk factors for:

- Independent risk factors for acute severe asthma attacks in the past 12 months or prior history of admission to an intensive care unit (ICU); especially if intubated[61,62]
- Other modifiable risk factors are recommended to be addressed, such as high usage of relievers, frequent use of OCS, low FEV_1, pregnancy, inadequate ICS, smoking and vaping, comorbidities, major psychological disorders, reduced socioeconomic status, presence of comorbidities[62]
- Risk factors for fixed airway obstruction include inadequate ICS treatment, exposure to tobacco smoke or other noxious substances, low initial FEV_1, or peripheral blood eosinophilia.[63]

Asthma severity assessment in clinical practice

There is a trend in clinical practice to retrospectively assess asthma severity based on the step of treatment required to control symptoms and attacks.[1,2,63-65] Before classifying asthma severity, it is essential to ensure that control is achieved and maintained while using a minimal level of medications over more than 3 months. Since asthma severity level could change over years or months, therefore, asthma level of severity can be classified as follows:

- Mild asthma: Controlled asthma at step 1 or 2
- Moderate asthma: Controlled asthma at step 3
- Severe asthma: Asthma that requires treatment step 4 or 5.

Assessment when control is not achieved

If asthma control is not achieved at any step during therapy, the SINA panel recommends assessing the following:

- Appropriateness of prescribed medications and doses
- Patient adherence and correct technique in using devices
- Selection of the appropriate device and appropriate spacer with a pressurized metered-dose inhaler (MDI) device
- Obstacles in taking prescribed medications (e.g., cost, time, and patients' concerns on lack of perceived need)
- Environmental exposure to allergens at home
- Assessment of comorbidities such as rhinosinusitis, CSwNP, GERD, obesity, obstructive sleep apnea, and anxiety
- Future risk of attacks and fixed airflow obstruction.

Section 5: Non-pharmacological Management in Adults and Adolescents

By utilizing pharmacological and non-pharmacological measures, the long-term goals of asthma management aim toward maintaining asthma control, minimizing exacerbations, and avoiding asthma-related death [Box 5.1]. There has been a shift in asthma treatment concepts from symptom control toward clinical remission that aims toward sustained absence of

symptoms and exacerbations, stable lung function, and no need for OCS.[66] The appropriate implementation of non-pharmacological measures also aims to the use of the least possible doses of asthma medications to minimize their side effects.

Box 5.1: Long-term goals of asthma management

Control asthma symptoms (cough, wheezing, and shortness of breath)

Infrequent and minimal use (≤2 days a week) of the reliever therapy

Maintain (near) normal pulmonary function

Maintain a normal level of exercise and physical activity

Prevent asthma exacerbations and minimize the need for emergency department visits or hospitalizations

Optimize asthma control to avoid oral corticosteroids

Achieving clinical remission of asthma

Improve quality of life and reduce the risk of adverse outcomes

Avoiding asthma-related mortality

Developing a partnership with the patient

The development of a partnership between patients and healthcare professionals leads to the enhancement of knowledge, skills, and attitudes toward a better understanding of asthma and its management. Based on the agreed goals of management, a written self-management action plan is recommended to be offered to all patients. A wide variety of plans are available. This is expected to reflect positively on patient adherence, which is a major issue in management.

Asthma education

The goal of asthma education is to provide patients with adequate training to enhance their knowledge and skills to be able to adjust treatment according to a guided self-management plan.[67-70] To enhance the level of knowledge and skills among asthma patients, it is recommended to include knowledge about asthma and skills related to prescribed inhaler devices, as there may be misperceptions about the use of inhalers and the safety of ICS [Box 5.2].[70-72] Asthma education is recommended to be conducted by a well-trained healthcare worker,

Box 5.2: Outcomes of asthma education program

Creation of patient-healthcare worker partnership

Understanding the clinical presentation of asthma and methods of diagnosis

Ability to differentiate between "reliever" and "controller" medications and their appropriate indications

Realizing the importance of persistence and adherence to asthma treatment

Recognition of potential side effects of medications and the appropriate action to minimize them

The ability to use inhaler devices correctly

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

who has good communication skills and is able to create an interactive dialogue in a friendly environment. With the availability of appropriate information, patients are expected to continue on the management plan and be reassured about the control of their asthma.[73] It is essential to get feedback from the patient to maintain a bidirectional rapport. Reproducible evidence has shown that a well-structured asthma education program improves the quality of life, reduces cost, and decreases the utilization of healthcare resources.[74,75]

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 acute asthma exacerbations, which may include: allergens, 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 dust mites, animals (mainly cats), cockroaches, and fungi (e.g., alternaria and aspergillus). Single-allergen interventions are likely to fail. However, multifaceted, tailored intensive interventions may help in improving asthma control. It may take a few months for the allergen level to become significantly lower from the implementation of the related control measures.[76] The most important indoor air pollutant is related to tobacco exposure. Measures to avoid tobacco exposure are expected to lead to better asthma control and avoidance of long-term lung function impairment
- Outdoor allergens and dust: Outdoor allergens such as pollens and molds are difficult to avoid completely; however, exposure may be reduced by closing windows and doors and using air conditioning. It is recommended to avoid strenuous outdoor physical activities in cold weather, low humidity, or high air pollution. In a single-center study in Saudi Arabia, sandstorms were shown to worsen asthma symptoms but not hospital admission in children with asthma. It is advisable to avoid going out in the storm, especially for those with uncontrolled asthma[77]
- Occupational exposures: Whenever an occupational sensitizer is identified, it is advisable to keep the affected person away from that environment.[78] 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 is not generally recommended until it is documented by a specialist.[79] However, certain drugs that could worsen asthma symptoms should be avoided (e.g., beta-blockers), whenever possible
- Vaccination: Annual influenza vaccination is strongly

recommended for individuals with asthma, especially those with severe asthma.[80-82] It usually becomes available early in the fall season. Pneumococcal vaccination and COVID-19 vaccination are also recommended as per the local guidelines.[83]

Section 6: Pharmacological Management in Adults and Adolescents

The SINA panel recommends asthma treatment to be based on the following phases:
- Initiation of treatment
- Adjustment of treatment
- Maintenance of treatment.

At each phase, the patient is recommended to have a clinical assessment that includes symptoms assessment by ACT, a physiological measurement with spirometry and FeNO, a review of current medications and patients' adherence and inhaler technique, a risk for exacerbations, and the response to treatment. Based on the clinical and physiological assessment, the patient is placed on the appropriate treatment step. The medication appendix contains more information about medications used in asthma treatment.

Saudi initiative for asthma strategies for asthma treatment in adolescents and adults

The SINA panel recommends the following strategies for asthma treatment:
- ICS is recommended for all steps as it is the most effective controller and the cornerstone of asthma treatment (Evidence A).[84-86] Uncontrolled patients on ICS may require the addition of other controllers that include a long-acting β2 agonist (LABA), a long-acting anti-muscarinic agent (LAMA), leukotriene receptor antagonists (LTRA), or biologics
- The combination of ICS/formoterol in a single inhaler is recommended to be used for regular maintenance dosing and when needed as well. This is called the maintenance and reliever therapy (MART) approach[87,88]
- The combination of ICS/non-formoterol LABA in a single inhaler is recommended for proactive regular dosing with a short-acting bronchodilator (SABA) reliever on as needed basis (with or without ICS)[89]
- A once-a-day fixed-dose combination of ICS and LABA is currently available that can be prescribed with SABA (with or without ICS) as a reliever. When compared to a twice-a-day combination, a once-a-day combination led to better adherence and a lower risk of discontinuing treatment.[90] Once-a-day single-inhaler triple therapy (SITT) is also available that contains ICS/LABA/LAMA
- Relievers are fast-acting bronchodilator medications that must be available to patients at all steps.

Increasing the use of reliever treatment should be considered as an early sign of worsening of asthma control (Evidence A).[91] The available relievers are:
- SABAs, such as salbutamol, are recommended to be taken as-needed to relieve symptoms. Using SABA alone without a controller was found to increase the risk of asthma exacerbations and asthma-related death. Patients who consumed more than three canisters of SABA per year were found to be at risk of increasing morbidity and mortality.[92] When compared with SABA alone as a reliever, fixed-dose combination (FDC) ICS/SABA led to better outcomes with a significant reduction in asthma exacerbations, hospitalization, and asthma-related death.[93] Whenever a fixed-dose ICS/SABA combination becomes available in the Saudi market, it is recommended to be prescribed on an as-needed basis to relieve symptoms (Evidence A).[94-96]
- Formoterol/ICS combination could be used as a reliever therapy on an as-needed basis for mild asthma and whenever the combination of formoterol/ICS is prescribed as maintenance therapy (MART approach) (Evidence A).[97-99] The maximum recommended dose of formoterol component is 72 µg. Exceeding this level for 2–3 days may be a warning sign of deterioration of asthma control that requires seeking medical advice.[98-100]
- Regular assessment of the adequacy of treatment, proper technique, and adherence
- Regular assessment for independent risk factors for acute asthma exacerbations in the past 12 months or prior history of admission to an ICU; especially if intubated.[61,101] Other modifiable risk factors are recommended to be addressed, such as pregnancy, inadequate ICS, smoking and vaping, comorbidities, and major psychological conditions
- Regular assessment of risk factors for fixed airway obstruction that includes inadequate ICS treatment, exposure to tobacco smoke or other noxious substances, low initial FEV_1, or peripheral blood eosinophilia[102]
- Management of comorbidities with special attention to rhinosinusitis, GERD, and Obesity. Rhinosinusitis is a condition that affects asthma control where its treatment is expected to improve asthma outcome (Evidence A).[103] Treatment includes nasal saline washes, nasal steroids, LTRA, and antihistamines. Concomitant rhinosinusitis is recommended to be treated appropriately as well.

Adherence to treatment

It is challenging to objectively assess adherence to medications during routine busy practice. It has been found that self-reported adherence and clinicians'

judgment of adherence are often overestimated.[104] In one study, only 13% of patients who received two controllers for asthma management were considered to have optimum adherence.[105] Regular ICS dosing (with or without LABA) had better asthma symptom control, a greater degree of bronchoprotection, and still maintained low systemic activity for patients with mild asthma when compared to intermittent dosing.[86,106] Therefore, healthcare professionals are recommended to regularly advise patients to be adherent to their inhalers and objectively assess patterns of prescription of relievers and controller inhalers.[107,108] Factors leading to non-adherence may be related to poor inhaler technique, a regimen with multiple drugs or devices, concern regarding side effects from the drugs, and cost of medications.[105,109-112] Other factors include a lack of knowledge about asthma, lack of partnership in its management, inappropriate expectations, underestimation of asthma symptoms, use of unconventional therapy, and cultural issues.[112,113]

Initiation of asthma treatment

Patients with asthma often underestimate the presence of symptoms and tend to assume their asthma is under control even when this is not the case.[104,105] Therefore, the consensus among the SINA Panel is to simplify the approach and supplement the initiation of asthma therapy by utilizing an objective measurement with the ACT bases on the available evidence (Evidence B).[58] The following initial steps are recommended for treatment-naïve patients based on ACT score [Box 6.1].

Start at step 1 when the ACT score is 20 points or more:
- It is recommended to use a fixed-dose combination of ICS/formoterol on an as-needed basis (Evidence A).[99,114]
- An alternative option is to use SABA together with low-dose ICS on an as-needed basis in separate inhalers (Evidence B).[95,115,116] Whenever a fixed-dose combination of ICS/SABA becomes available in the Saudi market, it is recommended to be prescribed on an as-needed basis (Evidence A).[94-96]
- Maintenance of daily low-dose ICS (with or without LABA) is recommended for patients with symptoms more than twice a week, risk factors for acute exacerbation (severe exacerbations in the past 12 months or prior history of admission to an ICU; especially if intubated) or evidence of fixed airway obstruction (Evidence B).[102,117-120] Early introduction of ICS leads to greater improvement of FEV_1.[117]

Start at step 2 when the ACT score is between 16 and 19 points:
- It is recommended to use a fixed-dose combination of low-dose ICS/LABA for patients when an ACT score of 16–19 points (Evidence A).[58] Physicians should ensure the adherence of patients to this

regimen.[106] Reliever therapy is recommended as well in the form of SABA (with or without ICS) whenever a maintenance fixed-dose combination of ICS/non-formoterol LABA or of ICS/formoterol whenever a maintenance fixed-dose ICS/formoterol combination is prescribed (MART approach).

Start at step 3 when the ACT score is <16 points:
- It is recommended to use a fixed-dose combination of medium-dose ICS/LABA as maintenance treatment for patients with an ACT score of <16 points (Evidence A).[58] Reliever therapy is recommended as well in the form of SABA (with or without ICS) whenever a maintenance fixed-dose combination of ICS/non-formoterol LABA or of ICS/formoterol whenever a maintenance fixed-dose ICS/formoterol combination is prescribed
- For patients with ACT score <16 points presenting with early signs of asthma exacerbation, it is recommended to consider adding a short course of oral steroids (Oral prednisolone 30–60 mg for 3–5 days[121] Those patients need close follow-up to adjust treatment as appropriate to achieve asthma control.
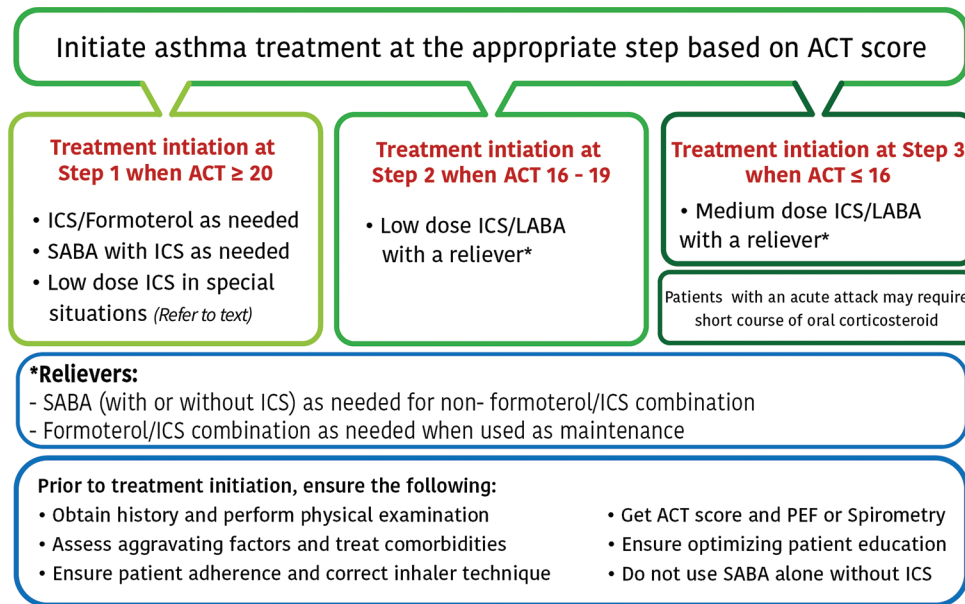
Adjustment of treatment

After initiation of asthma treatment, it is recommended to assess the patient at 1–3 month intervals as appropriate (Evidence D).[122] The SINA Panel recommends the utilization of a step-wise approach of therapy to achieve asthma control. The stepwise approach consists of five steps as shown in Box 6.2. The SINA Panel also presents a simplified chart in Box 6.3 that includes the first option for asthma management at each step; this simplified chart should be supplemented by reviewing the detailed chart in Box 6.2 and the following narrative text.

The SINA panel recommends that the stepwise approach is not meant to be compartmental; it is rather a continuum of care based on patient engagement and close monitoring of the disease (Evidence D).[123] In clinical practice, asthma severity can be retrospectively assessed based on the step of treatment required to control symptoms:[63-65,124]
- Mild asthma: controlled asthma at step 1 or 2
- Moderate asthma: controlled asthma at step 3
- Severe asthma: requires asthma management at step 4 or 5.

Reliever medications must be made available to patients at all steps. Increasing the use of reliever treatment is usually an early sign of asthma control worsening (Evidence A).[91,125] Approximately one in five patients with mild asthma who are not receiving appropriate treatment may develop at least one exacerbation in the following 12 months.[99,126,127] Reliever therapy is recommended as well in the form of SABA (with or without ICS) whenever a maintenance

Initiate asthma treatment at the appropriate step based on ACT score

Treatment intiation at Step 1 when ACT ≥ 20
- ICS/Formoterol as needed
- SABA with ICS as needed
- Low dose ICS in special situations *(Refer to text)*

Treatment intiation at Step 2 when ACT 16 – 19
- Low dose ICS/LABA with a reliever*

Treatment intiation at Step 3 when ACT ≤ 16
- Medium dose ICS/LABA with a reliever*

Patients with an acute attack may require short course of oral corticosteroid

*Relievers:
- SABA (with or without ICS) as needed for non- formoterol/ICS combination
- Formoterol/ICS combination as needed when used as maintenance

Prior to treatment initiation, ensure the following:
- Obtain history and perform physical examination
- Assess aggravating factors and treat comorbidities
- Ensure patient adherence and correct inhaler technique
- Get ACT score and PEF or Spirometry
- Ensure optimizing patient education
- Do not use SABA alone without ICS

*Saudi Initiative for Asthma 2024

Box 6.1: The SINA approach for asthma treatment dinitiation based on ACT score for adults an adolescents

Mild

Step 1
- ICS/Formoterol as needed
- SABA with ICS as needed

Step 2

Recommended
- Low-dose ICS/LABA with a reliever*

Alternatives
- Low dose ICS/LTRA with a reliever*
- Medium dose ICS with a reliever*

Moderate

Step 3

Recommended
- Medium-dose ICS/LABA with a reliever*

Alternatives
- Medium-dose ICS + LAMA in separate inhalers with a reliever*
- Medium-dose ICS/LTRA with a reliever*

Severe

Step 4

Recommended
- Add LAMA to medium dose ICS/LABA with a reliever* (Single inhaler triple therapy is preferred) ±LTRA

Step 5

Based on phenotype, Consider adding to step 4: (Refer to Box 6-3)
- Anti IgE
- Anti IL5 or anti IL5R
- Anti IL4Ra

Refer to a physician specialized in asthma

*Relievers:
- SABA (with or without ICS) as needed for non- formoterol/ICS combination
- Formoterol/ICS combination as needed when used as maintenance

At each visit, ensure patient education, environmental control, management of comorbidities, and avoid using SABA alone without ICS

Ensure patient adherence and correct inhaler technique

*Saudi Initiative for Asthma 2024

Box 6.2: The SINA pproach for asthma treatment adjustment and maintenance for adults and adolescents

Recommended Controllers | **Recommended Relievers**

Step 1
ICS/Formoterol as needed

Step 2
Low dose ICS/LABA

Step 3
Medium-dose ICS/LABA

Step 4
Add LAMA to Step 3 (SITT is preferred)

Step 5
Consider adding biologics to Step 4

- SABA as needed for non- formoterol/ICS combination
- Formoterol/ICS combination as needed when used as maintenance

ICS: Inhaled corticosteroids
LABA: Long-acting bronchodilators agent
LAMA: Long-acting anti-cholinergic agent
SABA: Short acting bronchodilator
SITT: Single inhaler triple therapy
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Note: This simplified chart represents the first recommended options. For the detailed chart, refer to box 6 – 2 and the guideline text.

*Saudi Initiative for Asthma 2024

Box 6.3: SINA 2024 simplified the approach for asthma treatment for adults and adolescents

fixed-dose combination of ICS/non-formoterol LABA or of ICS/formoterol whenever a maintenance fixed-dose ICS/formoterol combination is prescribed. The following paragraphs will describe asthma treatment at each step.

Treatment at step 1

Symptoms are usually mild and infrequent (usually < twice a week) with an ACT score of ≥20 points and no risk factors for asthma exacerbations. At this step, SABA alone on an as-needed basis is not anymore recommended.

- Recommended option: It is recommended to use ICS/formoterol on an as-needed basis (Evidence A)[98-100,114]

- Alternative option: Use SABA together with low-dose ICS on an as-needed basis from separate inhalers (Evidence B).[95,115,116] Whenever a fixed-dose combination of ICS/SABA becomes available in the Saudi Market, it is recommended to be prescribed on an as-needed basis (Evidence A)[94-96]

- Healthcare professionals are recommended to monitor the frequency of reliever usage to avoid a status of overreliance. Whenever this is observed, it

is recommended to step up therapy (Evidence D)
- Patients with seasonal asthma, who are symptomatic during the season, are recommended to be treated with low-dose ICS (with or without LABA) before the beginning of the season (Evidence D).

Treatment at step 2

- Recommended options: It is recommended to use a daily fixed-dose combination of low-dose ICS/LABA with an as-needed reliever for symptom relief (Evidence A).[87,128-130] Reliever therapy is recommended in the form of SABA (with or without ICS) whenever a maintenance fixed-dose combination of ICS/non-formoterol LABA *or* in the form of ICS/formoterol whenever a maintenance fixed-dose ICS/formoterol combination is prescribed.[131,132] Physicians should ensure the adherence of patients to this regimen[106]
- Alternative options:
  - The addition of LTRA to a low-dose ICS is another option, especially in patients with concomitant rhinitis (Evidence A)[133-135]
  - Continuation of ICS as a monotherapy by increasing the dose to the medium level is generally a less effective strategy (Evidence A).[136,137]

Treatment at step 3

- Recommended options: The fixed-dose combination of medium-dose ICS/LABA was found to improve asthma control and reduce asthma exacerbations for patients whose asthma is not controlled at step 2 (Evidence A).[87,128,129,137] Reliever therapy is recommended in the form of SABA (with or without ICS) whenever a maintenance fixed-dose combination of ICS/non-formoterol LABA or in the form of ICS/formoterol whenever a maintenance fixed-dose ICS/formoterol combination is prescribed. Physicians should ensure the adherence of patients to this regimen[106]
- Alternative options: Tiotropium is a LAMA approved for the treatment of chronic obstructive pulmonary disease (COPD).[138-140] Evidence has shown that when tiotropium is added to an ICS delivered by multiple inhalers; it improves symptoms, reduces the risk of exacerbation, and improves lung function in patients with inadequately controlled asthma. This evidence supports that tiotropium can be combined with ICS whenever LABA cannot be used.[141] Its effect appears to be at least equivalent to LABA (Evidence A)[142-144]
- Consultation with an asthma specialist is recommended whenever there is difficulty in achieving control at step 3 (Evidence D).

Available options for fixed-dose inhaled corticosteroids/long-acting β2 agonist combination at step 2 and 3

- ICS in the form of beclomethasone propionate,

budesonide, fluticasone propionate is available in combination with salmeterol. These are prescribed twice daily with SABA (with or without ICS) as a reliever
- ICS combined with formoterol can be used as maintenance and reliever without adding SABA[95,97,115,116]
- Once-a-day fixed-dose combination of ICS with vilanterol or indacaterol is also available. SABA (with or without ICS) should be utilized as a reliever. This combination leads to better adherence and a lower risk of discontinuing treatment when compared to twice a day combination[90]
- Inhaled LABA or LAMA should never be used as monotherapy in asthma management but must always be accompanied by the use of ICS, preferably in one inhaler device for the combination of ICS/LABA.[145] Asthma patients taking inhaled LABA without inhaled ICS are at an increased risk of asthma exacerbations, hospitalizations, and death[146]
- Twice a day combination:
  - If salmeterol/ICS fixed-dose combination is selected, it can achieve asthma control in a majority of patients (Evidence A).[129] Salmeterol has a slow onset of action; therefore, it should only be used for maintenance treatment with SABA (with or without ICS) as a reliever
  - If a formoterol/ICS fixed-dose combination is prescribed, it is recommended to be used as maintenance with one inhalation twice daily for step 2 or with two inhalations twice daily for step 3. Extra doses of up to 12 inhalations per day can be used as the reliever therapy from the same device (Evidence A).[95,97,115,116] Those patients who require such high doses for 2–3 days should seek medical advice to step up maintenance therapy (Evidence A).[97]
- Once-a-day combination:
  - The once-a-day combination of fluticasone furoate/vilanterol 100/25 µg in the Ellipta® device (Relvar®) can be prescribed for adults and children above 12 (Evidence A).[147,148] Vilanterol has the advantage of an onset of action within 15 min and a long half-life; however, it can only be used as a maintenance treatment while continue using SABA (with or without ICS) as a reliever
  - The once-a-day combination of mometasone furoate/indacaterol 160/150 µg in the Breezhaler® device (Atectura®) can be prescribed for adults and children above 12 years (Evidence A).[149-151] Use SABA (with or without ICS) as a reliever.

Treatment at step 4

- Recommended options: If control is not achieved after escalation to medium-dose ICS/LABA at step 3, adding

LAMA in a single inhaler is recommended (Evidence A).[152] This novel approach of SITT was found to be a safe and effective therapeutic approach.[153,154] Moreover, when compared to multiple inhalers triple therapy (MITT), SITT usage is cost-effective and is associated with better adherence.[152] The following SITT are recommended upon availability:

- Once-a-day SITT combination of fluticasone furoate/umeclidinium/vilanterol 200/62.5/25 µg (Trelegy Ellipta®) is a recommended option. Adding umeclidinium to the combination of ICS/LABA was found to be an effective treatment option with a favorable risk-benefit profile as it led to improved symptoms and FEV_1, particularly in patients with raised biomarkers of type 2 airway inflammation (Evidence A) [155] Real-world data showed that this SITT has led to lower OCS use, asthma-related exacerbations, and lower SABA usage compared to pre-treatment data.[156] SITT with a lower dose of fluticasone furoate (fluticasone furoate/umeclidinium/vilanterol 100/62.5/25 µg) could be considered as an option for a patient with lower biomarkers for type 2 airway inflammation (Evidence B).[156] It can also be considered for stepping down once control is achieved upon using higher dose SITT. Use SABA (with or without ICS) as a reliever with this combination

- Once-a-day SITT combination of mometasone furoate/indacaterol/glycopyrronium 160/150/50 µg in the Breezhaler® device (Enerzair®) is a SITT option that improves symptoms and lung function (Evidence A).[151] Further data showed that this SITT improved lung function, reduced asthma exacerbations, and provided comparable asthma control to the ICS/LABA combination.[157] SITT with a lower dose of mometasone furoate (mometasone furoate/indacaterol/glycopyrronium 80/150/50 µg) could be considered as an option for a patient with lower biomarkers for type 2 airway inflammation (Evidence D). It can also be considered for step down once control is achieved upon using higher dose SITT. Use SABA (with or without ICS) as a reliever

- Twice-a-day SITT combination of beclomethasone dipropionate/formoterol fumarate/glycopyrronium 172/5/9 µg in an MDI device (Trimbow®) is a SITT option that improves lung function and reduces exacerbation (Evidence A).[158] SITT with a lower dose beclomethasone dipropionate (beclomethasone dipropionate/formoterol fumarate/glycopyrronium 87/5/9 µg) could be considered as an option for a patient with lower biomarkers for type 2 airway inflammation (Evidence D).[158] It can also be considered for step down once control

is achieved upon using higher dose SITT. Use SABA (with or without ICS) as a reliever.

- Other considerations:
  - MITT by adding tiotropium in a separate inhaler to the combination of medium-dose ICS and LABA is another option as it significantly improves lung function in uncontrolled cases and modestly reduces asthma exacerbations (Evidence A).[159-161] However, SITT has the advantage of being cost-effective and of better adherence when compared with MITT[152]
  - Adding LTRA to the combination of medium-dose ICS and LABA can be considered but the evidence is less robust (Evidence B)[162-164]
  - High-dose ICS/LABA may be considered in some patients who are uncontrolled on medium-dose ICS/LABA.[137,165] However, it is recommended to step down whenever possible to avoid potential side effects.[136,166] An additional controller is recommended to be introduced before considering the high-dose ICS
  - If a patient is still uncontrolled at step 4, biologic therapy is recommended to be considered as described in step 5.

Treatment at step 5

Early consideration of biological therapy may lead to clinical remission and save the patient from frequent or chronic use of OCS and reduce asthma exacerbations.[66] This therapy is recommended based on appropriate indications and availability. When choosing a biological agent, several factors should be considered including the frequency of administration, cost, side effect profile, age of onset of asthma, presence of comorbid conditions such as nasal polyps, previous response, and physician experience with the treatment. Consultation with an asthma specialist is strongly recommended for patients requiring treatment at step 5 (Evidence D). The following biological agents are available for step 5. The medication Appendix contains the details of these biologic:

- Anti-IgE therapy: Omalizumab
- Anti-IL 5 therapy: Mepolizumab
- An anti-IL-5 receptor therapy: Benralizumab
- An anti-IL 4 receptor α antibody: Dupilumab
- Anti-TSLP: Tezepelumab (Not yet locally available).

Approach to selecting appropriate biologic therapy

The SINA Panel recommends assessing patients requiring biologics thorough clinical evaluation, ACT, peripheral eosinophil count, FeNO, IgE level, and RAST. Box 6.4 shows the approach for a patient requiring biologics.

Assessment of response to biologics

Biologics efficacy needs to be reassessed after 4–6 months after initiation. This can be made by comparing baseline and follow-up outcomes parameters such as ACT score, exacerbation rate, hospitalization, FEV_1, and daily OCS dose. If there is no response to biologics based on these outcomes, assessment of asthma diagnosis and ruling out coexisting conditions are needed, ensuring adherence and compliance, then consideration of a switch to a different biologic.

Combining biological therapy was tried in real life and one retrospective study.[167] It appeared that the biologics combination was well tolerated with no signal of significant side effects. In other case reports,[167,168] a cyclical method was tried in combining dupilumab twice monthly and mepolizumab monthly was able to control a patient with severe asthma. A prospective study is needed to assess the effect of such an approach.

Patient at step 5 who is not a candidate for biologics

If the patient does not have any of the biologics phenotypes, or biologics are not available or not adequately controlling the disease, the alternative approach is to use the lowest possible dose of long-term OCS (Evidence D).[65] Other alternatives are mentioned in the severe asthma section, such as long-term macrolides.

For patients who require long-term OCS, the following are recommended to be considered:
- Use the lowest possible dose to maintain control
- Closely monitor the development of corticosteroid-related side effects
- When asthma control is achieved, attempts to reduce the dose of systemic corticosteroids, preferably to every other day frequency, are recommended. Maintaining a high dose of ICS therapy may help to reduce the dose of systemic corticosteroid
- Upward adjustment of the corticosteroid dose at the time of stress (e.g., infection, asthma exacerbations, surgery, etc.) is essential
- 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 are strongly recommended.

Maintaining asthma control

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 1–3 months intervals after treatment initiation (Evidence D).[169,170] Follow-
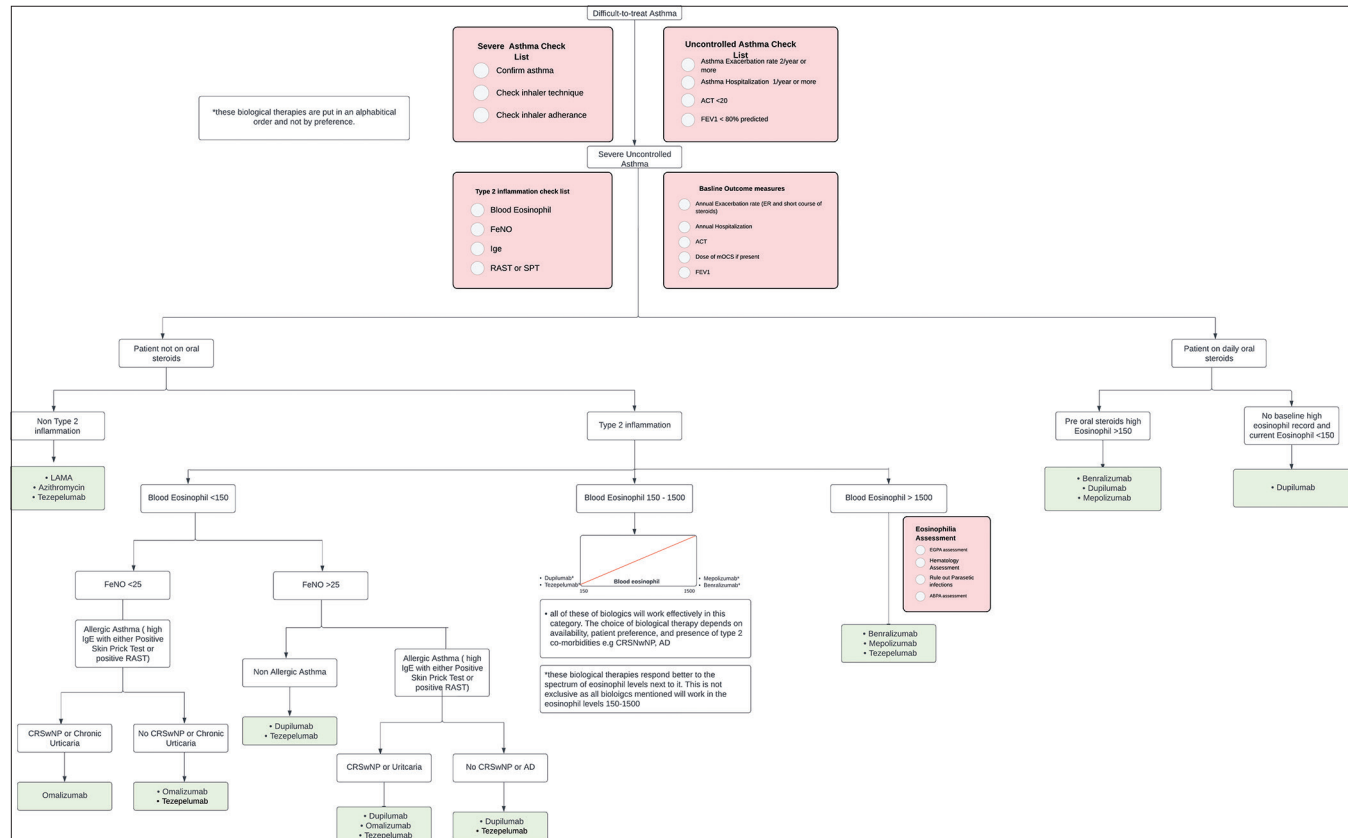
Box 6.4: Algorithm for selection of appropriate biologics for severe asthma

up is recommended to include monitoring and reviewing the patient's written asthma action plan, medication adherence, and inhaler technique, patient's behaviors, comorbidities, and possible side effects of the medications. Once asthma is controlled for at least 3 months, a step down in pharmacologic therapy is recommended at the minimum level that can maintain good control and minimize the side effects (Evidence D). The following are the general recommendations:

- Reduction in therapy is recommended to be gradual and closely monitored based on clinical judgment of the individual patient's response to therapy and ACT score (Evidence D)
- If the patient is on ICS as monotherapy at Step 1, the dose of ICS may be reduced gradually every 3–6 months to the lowest dose possible that is required to maintain control (Evidence B),[67,171,172] and then changed to a single daily dose (Evidence A).[173] It is recommended to be clearly explained to the patient that asthma control may deteriorate if treatment is abruptly discontinued[174]
- If the patient is on a combination of ICS/LABA at step 2 or 3, abrupt discontinuation of LABA is not recommended as it may lead to deterioration of the control. Therefore, initial gradual reduction of ICS to the lowest possible ICS dose before discontinuation of LABA is recommended[175]
- If the patient is on a combination of ICS and LABA, LTRA, or other controllers; start by tapering ICS to the lowest possible dose (Evidence B).[176,177] If control is achieved, LTRA may be discontinued first (Evidence D)[176]
- For significant oral side effects occur, 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[178]
- For patients with well-controlled eosinophilic asthma treated with mepolizumab for at least 18 months, extending the dosage intervals gradually between the injections up to 6–8 weeks bears the potential to save costs for the health care system without compromising asthma control[179]
- For patients with well-controlled asthma treated with omalizumab for at least 18 months, extending the dosage intervals gradually between the injections up to 3–4 weeks bears the potential to save costs for the health care system without compromising asthma control[180]
- Patients should be informed that asthma control may deteriorate if treatment is completely discontinued.[174]

Referral to an asthma specialist
Situations that require referral to an asthma specialist for consultation or co-management include:

- Uncertainty regarding the diagnosis
- Difficulty achieving or maintaining asthma control
- Immunotherapy or biological therapy is being considered
- Difficulty to achieve asthma control at step 3 or higher
- Acute asthma exacerbation requires hospitalization
- Patient request for a second opinion or further advice.

Severe asthma
There are several terms used in practice for uncontrolled asthma where each points to an aspect of the disease such as chronic severe asthma, steroid-dependent asthma, and refractory asthma are some of these terminologies.[181,182] However; it is important to distinguish between severe asthma and uncontrolled asthma. Severe asthma is defined as "Uncontrolled asthma at SINA step 4 despite adequate adherence and after addressing all comorbidities."[65] Severe asthma probably accounts for 5%–10% of adult asthma, but the healthcare cost is disproportionally high.[183] Morbidity and mortality are also higher compared to regular asthma patients because of increased side effects of treatment and more frequent exacerbations and/or hospitalizations.[184,185] Before a diagnosis of severe asthma is considered, patients must undergo a systematic assessment where the diagnosis of asthma is confirmed, and comorbidities are identified and treated.[186] Patients whose poor asthma control is related to other factors, such as poor adherence, inhaler use technique, or due to the presence of other diseases, are to be termed "difficult-to-treat asthma."[187] There are common comorbidities that need to be assessed in severe asthma such as allergic rhinoconjunctivitis, CSwNP, COPD, dysfunctional breathing, vocal cord dysfunction, anxiety/depression, obstructive sleep apnea, GERD, bronchiectasis, and allergic bronchopulmonary aspergillosis (ABPA).[188] The following are recommended items for assessment of patients with severe asthma:[189-194]

- Patient is adherent to all medications with a good inhalation technique
- Other possible misdiagnoses where the problem is not bronchial asthma but other diseases that mimic asthma symptoms, e.g., bronchiectasis, endobronchial tumors, dysfunctional breathing, vocal cord dysfunction, ABPA, or eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)[192,195]
- Comorbidities that can worsen bronchial asthma and make it difficult to manage (e. g., dysfunctional breathing, CSwNP, GERD, sleep apnoea syndrome, ABPA, obesity, and congestive heart failure[196]
- Medication overuse or side effects
- Any psychosocial contributing factors

- Other confounding factors, e.g., presence of allergens at home or work, active or passive smoking and vaping, or psychosocial problems.[192]

As it may be difficult to achieve full control in many patients with severe asthma, the aim of treatment in this situation is to reach the best possible control.[197] After dealing with all comorbidities and other confounding factors that could have made asthma difficult to control, maximum therapy is recommended, which may include combination therapy of high-dose ICS/LABA, LTRA, or LAMA and the addition of one of the available biologics as appropriate.[198-200]

A significant percentage of patients with severe asthma do not respond adequately to high-dose ICS and other controller therapy, thus, they need frequent or continuous oral steroid therapy to achieve a reasonable response.[201] Such control may be lost when oral steroid is discontinued. Patients may differ in the degree of their responsiveness to OCS.[202] Some patients may fail to improve their FEV_1 by more than 15% following treatment with OCS for 2 weeks, a condition called "corticosteroids-resistant asthma.[203,204] If OCS is necessary, then it is recommended to use the lowest possible dose and to shorten the duration as much as possible.[205] In this situation, osteoporosis prophylaxis is recommended.

For patients with severe asthma who do not qualify or respond to biologics, other modalities of treatment of severe asthma are recommended such as macrolides. Due to their role in reducing neutrophilic airway inflammation, they were shown to have a role in the management of severe asthma. A study has assessed the benefit of azithromycin at a dose of 250–500 mg 3 days/weeks as add-on therapy for 48 weeks for patients with persistent symptomatic asthma.[206] Azithromycin significantly reduced the experience of at 'least one asthma exacerbation' from 61% to 44% and improved asthma-related quality of life measures. Maintenance use of azithromycin reduces exacerbations in patients with eosinophilic, non-eosinophilic, and severe asthma.[207]

Allergen immunotherapy

The allergen immunotherapy (AIT) is a treatment modality to desensitize patients to specific allergens. It is considered for those with stable asthma and evidence of clinically relevant allergic sensitization at which the immunotherapy can be directed, especially if they have coexisting allergic rhinitis. Patients with poorly controlled asthma should not be started on immunotherapy.[208,209] Although there are insufficient data on the impact of AIT on asthma attacks and quality of life scores, it has specifically been shown to:

- Improve asthma symptoms and stepping down asthma treatment (Evidence A)[210]
- Improve AHR (Evidence B)[211]
- Decrease the progression of allergic rhinitis to asthma (Evidence B)[212]
- Decrease the chance of development of new sensitizations (Evidence B).[208]

AIT is likely to be cost-effective when appropriately used.[209] There are currently two types of AITs in clinical practice; subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT). Most studies that compared SCIT to SLIT showed a better clinical efficacy of SCIT. However, SLIT has a better safety profile than SCIT as SCIT may rarely cause anaphylaxis.[210] Patients at risk are mainly those with asthma, especially if uncontrolled. A high level of caution should be taken in patients using beta-blockers due to the risk of more serious anaphylaxis that is resistant to treatment with epinephrine.[208] Data are limited in pediatrics, but AIT has been used safely in children over 5 years of age and was shown to reduce long-term asthma medication use and improve FEV_1.[213] Although beneficial effects may be observed a few months from starting AIT, treatment with AIT needs the patient's commitment for at least 3 years to have sustained desensitization after stopping the treatment. Furthermore, AIT can be continued, but not initiated, during pregnancy. The most studied allergens' specific immunotherapy are dust mites, alternaria, grass pollens, ragweed, and cat. Anti-IgE therapy could improve tolerability to AIT in patients with moderate to severe asthma.[214] If the patient is considered a candidate for AIT, referral to an allergist is recommended to explore this option further.

Section 7: Management of Acute Asthma in Adults and Adolescents

An acute asthma attack is a challenging clinical scenario that requires a systemic approach to rapidly diagnose, evaluate the severity, and initiate therapy. The first step in managing acute asthma is early recognition to prevent the occurrence of attacks. Asthma in general has a low mortality rate compared with other chronic lung diseases.[33] Nevertheless, asthma death is still seen in clinical practice, especially among patients with poorly controlled asthma whose condition deteriorates over a period of days before the final fatal event.[215-217] The most specific marker associated with increased asthma mortality is a history of repeated hospital admissions, particularly if the patient requires intensive care treatment or ventilatory support.[218,219] Patients admitted with severe asthma attacks in Saudi Arabia were found to be younger and predominantly males and used less ICS/LABA combination.[3,220]

This section includes an assessment of the patients presented with acute asthma, initial management, and follow-up after hospital discharge. Detailed information about medications used in acute asthma can be found in the medication appendix. Box 7.1 shows the summary of the key recommendations for acute asthma management.

General assessment of acute asthma attack

The initial clinical assessment should rapidly determine whether the patient's presenting symptoms are related to an acute asthma attack and exclude alternative diagnoses or complications, such as pneumonia, pneumothorax, or atelectasis [Box 7.2]. Although most acute asthma attacks develop over a period of days, patients with brittle asthma may present with a much more dramatic deterioration.[221,222] It is important to realize that most patients who die from an acute asthma attack had chronically uncontrolled asthma, had received suboptimal treatment with ICS and other controllers, and had inadequate monitoring of their asthma.[223] Management of acute asthma is the extreme spectrum of uncontrolled asthma and represents a failure to reach adequate asthma control. Poor prognostic features of acute asthma include previous history of near-fatal asthma or hospital admission in the last year, heavy usage of relievers, patients who are not on regular ICS, a history of psychiatric or psychosocial illness, and poor adherence to asthma medications and lack of asthma action plan.[224,225]

The patient should be carefully assessed on presentation to determine the severity of the attacks [Box 7.3] and the type of treatment required [Box 7.4].[226] PEF and pulse oximetry measurements are complementary to history taking and physical examination. The major causes of death in acute asthma are cardiac arrhythmia, asphyxia, and cardiogenic shock. The risk of cardiac arrhythmia is theoretically increased by hypokalemia and QT interval prolongation related to the use of high-dose

SABA or IV aminophylline.[186,227] However, in a series of patients with near-fatal attacks, only a few arrhythmias other than sinus tachycardia and bradycardia were reported.[101,215,216,228] Hence, a more likely cause for death is probably related to the development of severe auto-PEEP leading to reduced venous return and secondary increased intracranial pressure and low cardiac output. Severe asphyxia due to severe airflow obstruction and hypoxemia are other likely causes. This is supported by the pathologic evidence of extensive airway obstruction, mucous plugging, and dynamic hyperinflation found at autopsy in patients who died of acute severe asthma.[229]

SINA Panel recommends the following steps for the management of acute asthma:
- Assess the severity of the attack
- Initiate treatment to rapidly control the attack
- Evaluate continuously the response to treatment.

The levels of acute asthma severity and the initial management are summarized in Boxes 7.3 and 7.4 respectively. It is recommended to adjust treatment intensity based on the severity of the attack and the

Box 7.1: Key recommendations of acute asthma management

Assess the severity of the attack based on the degree of dyspnoea, pulse rate, respiratory rate, peak-expiratory flow rate, and oxygen saturation

Start treatment immediately by repeated administration of salbutamol, controlled oxygen concentration, and systemic steroid
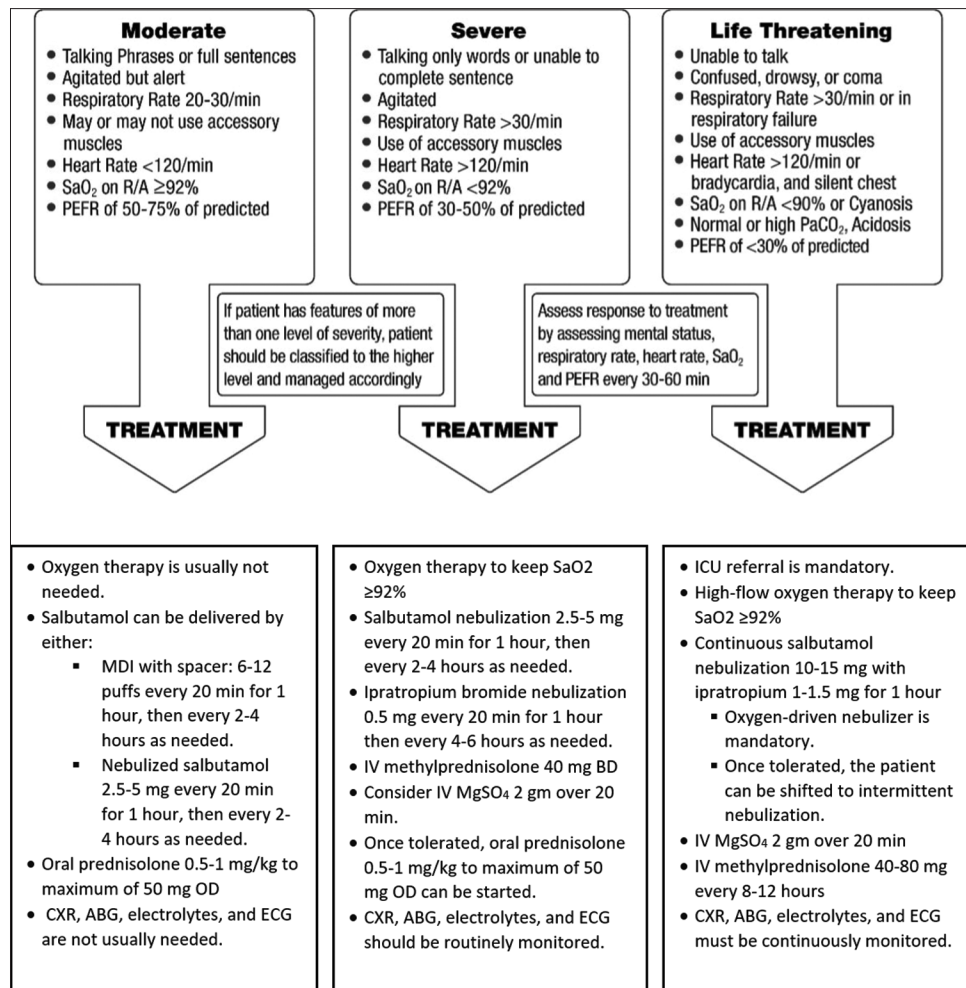
Review response to treatment after 1 h of continuous therapy

Consider other therapies (ipratropium bromide and magnesium sulfate) in managing severe attacks

Do not request routine chest X-rays or arterial blood gases routinely unless indicated

Do not prescribe routine antibiotics or sedatives unless indicated

Evaluate the need for hospital admission based on response to therapy, history of previous admission, and the ability to manage at-home

Box 7.2: Levels of severity of acute asthma in adults

Level	Characteristics
Acute moderate asthma attacks	Increasing symptoms
	PEF >50%–75% best or predicted reading
	No features of acute severe asthma
Acute severe asthma	Any one of the following
	PEF 30%–50% best or predicted reading
	Respiratory rate ≥25/min
	Heart rate ≥120/min
	Inability to complete sentences in one breath
Life-threatening asthma	Any one of the following in a patient with acute severe asthma
	SpO_2 <92% (PaO_2 <60 mmHg) on high-flow FIO_2
	PEF <30% best or predicted
	Bradycardia
	Dysrhythmia
	Cyanosis
	Hypotension
	Normal or high $PaCO_2$
	Exhaustion
	Confusion
	Silent chest
	Coma
	Weak respiratory effort
Near-fatal asthma	Raised $PaCO_2$ and/or requiring mechanical ventilation
Brittle asthma	Type 1: Wide PEF variability (>40% diurnal variation for >50% of the time over a period of >3–6 months) despite intense therapy
	Type 2: Sudden severe attacks on a background of apparently well-controlled asthma

$PaCO_2$=Partial pressure of carbon dioxide, PEF=Peak expiratory flow

Box 7.3: Initial management of acute asthma for adults and adolescents

following are the general guidelines for the treatment of acute asthma.

Assessment and management of mild-moderate acute asthma attack

Patients presenting with mild asthma attacks are usually treated in an outpatient setting by stepping up asthma management, including increasing the dose of ICS. However, some cases may require a short course of oral steroids and early outpatient department (OPD) referral. Patients with moderate acute asthma attacks are clinically stable. They are usually alert and oriented but may be agitated. They can communicate and talk in full sentences. They are tachypneic and may be using their respiratory accessory muscles. Heart rate is usually <120/min and blood pressure is normal. A prolonged expiratory wheeze is usually heard clearly over the lung fields, but examination of the chest may be relatively normal. Oxygen saturation is usually normal secondary to hyperventilation. The Peak expiratory flow meter (PEFR) is usually >50% of predicted or previously documented best. Measurement of arterial blood gases

(ABGs) is not routinely required in this setting; however, if done, it shows widened alveolar–arterial oxygen gradient and low partial pressure of carbon dioxide ($PaCO_2$), secondary to increased ventilation-perfusion mismatch and hyperventilation, respectively. CXR is not usually required for moderate asthma exacerbations unless pneumonia is suspected.

Management of moderate acute asthma attack include the following

- Oxygen saturation is usually normal in a moderate acute asthma attack, and oxygen supplementation or continuous monitoring is not routinely needed
- The standard therapy for initial care in the emergency department is inhaled SABA. It is recommended to be delivered by either:
  - MDI with spacer: 6–12 puffs every 20 min for 1 h, then every 2–4 h according to response (Evidence A).,[230,231] or
  - Nebulizer: 2.5–5 mg salbutamol every 20 min for 1 h, then every 2 h according to response (Evidence A).[232]

- Steroid therapy: Oral prednisolone 0.5–1 mg/kg to a maximum of 50 mg is recommended to be started as soon as possible and maintained for 5–7 days.[233,234]

Assessment and management of severe acute asthma attack

Patients are usually agitated and unable to complete full sentences. Their respiratory rate is usually >30/min and usage of accessory muscles is common. Significant tachycardia (pulse rate >120/min) and hypoxia (SaO_2 <92% on room air) are usually evident. Chest examination reveals prolonged wheeze secondary to severe airflow limitation and hyperinflation, more ominously the chest may be silent on auscultation in severe cases. CXR is required if complications are clinically suspected, such as pneumothorax or pneumonia. PEFR is usually in the range of 30%–50% predicted. ABG reveals significant hypoxemia and elevated alveolar–arterial oxygen gradient. $PaCO_2$ may be normal in patients with severe acute asthma attacks. Such a finding is an alarming sign, as it indicates fatigue, inadequate ventilation, and pending respiratory failure. Unlike hypoxemia, PEFR measurement has shown a good correlation with hypercapnia and is considered a useful screening tool (e.g., $PaCO_2$ >45 mmHg), making routine assessment of arterial blood gases unnecessary in most cases. In the absence of respiratory depressants, hypercapnia is rarely present when the PEF is ≥30% of normal or ≥150 L/min.[235] Thus, ABG measurements in acute severe asthma may be limited to the following situations:
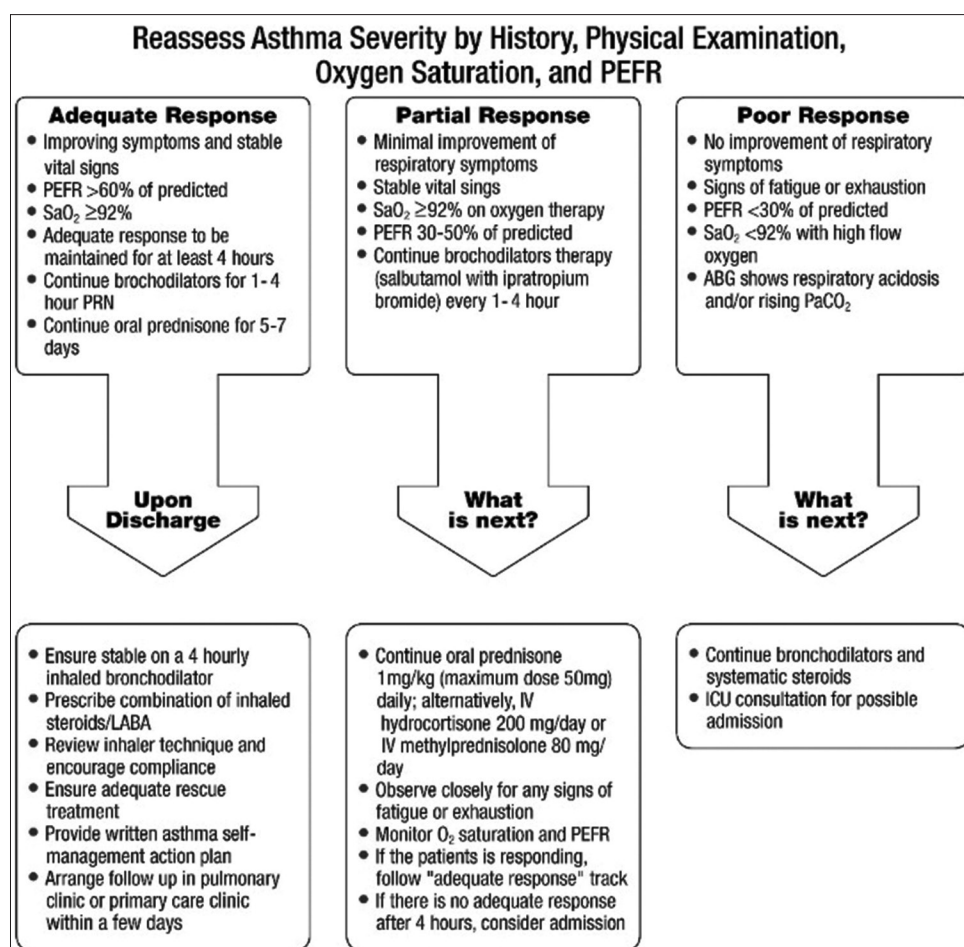
- Patients with persistent symptoms, whose PEF is <30% of normal or below 150 L/min despite initial bronchodilator therapy
- Patients who are unable to perform a peak flow measurement
- Patients whose respiratory status is deteriorating despite adequate intensive therapy
- Patients who demonstrate signs or symptoms of hypercapnia, such as depressed consciousness, inappropriately slow respiratory rate, bradycardia, or myoclonus.

The management of severe acute asthma attacks include

- Adjusted low-flow oxygen is recommended to maintain saturation ≥92%, as patients who received 28% oxygen did better than those who received 100% oxygen.[236,237] The ready availability of transcutaneous pulse oximetry allows noninvasive screening for hypoxemia among those patients. Despite the poor correlation between PEFR and oxygen saturation, it is recommended to use transcutaneous pulse oximetry among patients who are in severe distress, have a FEV_1 or PEF <50% of baseline, or are unable to perform lung function measurements

- Nebulized salbutamol (2.5–5 mg) is recommended to be administered back-to-back (repeated every 20 min for 1 h), then hourly according to response.[237] Oxygen-driven nebulizers are needed to avoid the risk of oxygen desaturation while using air-driven compressors (Evidence A)[233,234,238]
- Ipratropium bromide is recommended to be added to salbutamol at a dose of 0.5 mg every 20 min for three doses by the nebulized route, then every 4–6 h as needed (Evidence B). Alternatively, ipratropium can be administered by MDI at a dose of 4–8 puffs every 20 min, then every 4–6 h as needed.[239-242] The efficacy of adding ipratropium to SABA to treat severe acute asthma attacks has been examined in a number of trials and systematic reviews.[243] It has been shown that patients who received the combination therapy of SABA and ipratropium were less likely to be admitted to the hospital than those treated with SABA alone. This benefit pertained only to those presented with severe acute asthma attacks and not to those with mild or moderate exacerbations[244]
- Systemic glucocorticoid therapy is essential to treat the escalated airway inflammation that leads to asthma attacks, persistent airflow obstruction, and intraluminal mucus plugging.[243,245] Hence, systemic steroid is recommended to be started as soon as possible (Evidence A). The optimal dose for systemic glucocorticoids in acute asthma attacks remains unknown. SINA authors recommend starting IV methylprednisolone 40 mg twice daily in most patients present with acute severe asthma attacks. Higher doses are often chosen by some experts (60–80 mg every 6–12 h) for patients who are admitted to the ICU. If the patient can tolerate orally, oral prednisolone 0.5–1 mg/kg to a maximum of 60 mg daily is recommended[233,246]
- If there is an inadequate response to previous measures, it is recommended to administer a single dose of IV magnesium sulfate at a dose of 1–2 g over 20 min (Evidence B).[247] Intravenous (IV) magnesium sulfate has a bronchodilator response in acute asthma, possibly due to inhibition of calcium influx into airway smooth muscle cells. The best evidence for effectiveness in acute asthma attacks comes from a systematic review, which found a decrease in hospitalization days with IV magnesium compared with placebo and mild improvement in lung function[248]
- Continuous oxygen monitoring by transcutaneous pulse oximetry, blood gases (particularly in those patients with lung function <30% predicted), CXR, serum electrolytes, glucose, and 12-lead electrocardiography (ECG) should be ordered and checked.

Assessment and management of life-threatening acute asthma attack

Patients with life-threatening acute asthma attacks are severely breathless and unable to talk. They may present

Reassess Asthma Severity by History, Physical Examination, Oxygen Saturation, and PEFR

Adequate Response
- Improving symptoms and stable vital signs
- PEFR >60% of predicted
- SaO₂ ≥92%
- Adequate response to be maintained for at least 4 hours
- Continue brochodilators for 1- 4 hour PRN
- Continue oral prednisone for 5-7 days

Partial Response
- Minimal improvement of respiratory symptoms
- Stable vital sings
- SaO₂ ≥92% on oxygen therapy
- PEFR 30-50% of predicted
- Continue brochodilators therapy (salbutamol with ipratropium bromide) every 1- 4 hour

Poor Response
- No improvement of respiratory symptoms
- Signs of fatigue or exhaustion
- PEFR <30% of predicted
- SaO₂ <92% with high flow oxygen
- ABG shows respiratory acidosis and/or rising PaCO₂

Upon Discharge
- Ensure stable on a 4 hourly inhaled bronchodilator
- Prescribe combination of inhaled steroids/LABA
- Review inhaler technique and encourage compliance
- Ensure adequate rescue treatment
- Provide written asthma self-management action plan
- Arrange follow up in pulmonary clinic or primary care clinic within a few days

What is next?
- Continue oral prednisone 1mg/kg (maximum dose 50mg) daily; alternatively, IV hydrocortisone 200 mg/day or IV methylprednisolone 80 mg/day
- Observe closely for any signs of fatigue or exhaustion
- Monitor O₂ saturation and PEFR
- If the patients is responding, follow "adequate response" track
- If there is no adequate response after 4 hours, consider admission

What is next?
- Continue bronchodilators and systematic steroids
- ICU consultation for possible admission

Box 7.4: Adjustment of acute asthma treatment for adults and adolescent

in extreme agitation, confusion, drowsiness, or even coma. The patient usually breath at a respiratory rate >30/min and uses their accessory muscle secondary to increased work of breathing. Heart rate is usually >120/min, but at a later stage, patients can be bradycardic. Patients may develop different types of arrhythmias secondary to hypoxia or acidemia, and hence, ECG monitoring is recommended. Oxygen saturation is usually low (<90%) and not easily corrected with oxygen. ABGs are mandatory in this group and usually reveal significant hypoxia and normal or high $PaCO_2$. Respiratory and metabolic acidosis may be present secondary to inadequate ventilation and lactic acidosis, respectively. PEFR is usually very low (<30% of the predicted). CXR 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 mixed features from more than one level of acute asthma severity. For the patients' safety, they should be classified at a higher level of severity and managed accordingly.

The management of life-threatening acute asthma attacks includes

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.
- Consult ICU service. The intubation setting should be readily available
- Adequate oxygen flow to keep saturation ≥92%.[237] Deliver continuous nebulized salbutamol at a dose of SABA 10–15 mg with Ipratropium bromide at a dose of 1.5 mg over 1 h (Evidence A).[249] Continuous treatment was found to be safe and well tolerated and led to better improvement in pulmonary functions and reduction in hospitalization when compared to intermittent delivery (Evidence A).[250] Oxygen-driven nebulizers are mandatory due to the risk of oxygen desaturation while using air-driven compressors (Evidence A)[238]
- Once the patient showed adequate response to continuous nebulization, a shift to intermittent delivery is recommended (Evidence D)
- Systemic steroid to be started as soon as possible at a dose of methylprednisolone 60–80 mg every 8–12 h (Evidence A)[251,252]

- Single dose of IV magnesium sulfate at a dose of 2 g over 20 min (Evidence B)[246]
- Frequent clinical evaluation, CXR, electrolytes, glucose, 12-lead ECG, and ABGs are essential.

Follow-up after initial treatment and discharge planning

Close evaluation of the treatment response is essential. This includes patient's mental and physical status, respiratory rate, heart rate, blood pressure, oxygen saturation, and PEF. Response to treatment is defined as adequate, partial, or poor. Assessment of the treatment response, subsequent action, and discharge planning are illustrated in Box 7.4.

Criteria for intensive care unit referral

ICU referral is recommended for patients who are:
- Presenting or progressing to severe acute or life-threatening asthma
- Failing to respond to initial therapy, as defined by:
  - Requiring ventilatory support
  - Deteriorating lung function (FEV_1 and/or PEF)
  - Persisting or worsening hypoxia
  - Hypercapnia (either initially or subsequently)
  - ABG analysis showing respiratory acidosis
  - Exhaustion, shallow respiration, or drowsiness.

Section 8: Asthma in Special Situations

Gastro-esophageal reflux disease

GERD is more prevalent in patients with asthma, compared to the general population.[253] The mechanisms by which GERD worsens asthma include vagal mediated reflex and also reflux secondary to micro-aspiration of gastric contents into the upper and lower airways.[254] GERD induced asthma symptoms are mainly dry cough at night but can lead to asthma symptoms and it is more common with severe asthma than mild asthma. Patients with asthma should be questioned about symptoms of GERD. If GERD symptoms are present, a trial of anti-GERD measures, including a proton pump inhibitor and lifestyle modifications, is recommended for 6–8 weeks. However, if symptoms are not resolved, a referral to a gastroenterologist for further investigations like endoscopy or pH monitoring is warranted. The benefit of proton pump inhibitors is limited to patients with symptomatic GERD and night-time respiratory symptoms. On the contrary, patients with uncontrolled asthma and asymptomatic GERD are not likely to benefit from empiric GERD therapy.[255] Medical treatment for GERD for patients with asthma may provide small benefit for asthma related symptoms, modest improvement in lung function measures, and reduction of rescue medications for asthma control.[256] A recent meta-analysis does not support a recommendation for PPIs therapy as empirical treatment in asthma patients with GERD.[257]

Rhinosinusitis and nasal polyp

Most asthma patients have coexisting rhinitis and/or sinusitis and around 40% of patients with rhinitis have asthma.[258] CRSwNP is usually associated with severe and uncontrolled asthma. Asking patients about rhinitis symptoms (nasal blockage and/or nasal discharge, facial pain, or pressure and/or smell loss) and examination of the upper airways is recommended to be part of the routine management of asthma. Treatment with intranasal corticosteroids has been associated with a decrease in asthma hospitalization and emergency department visit.[259] Biologic therapy is recommended for patients with CRSwNP and severe asthma that is not controlled with the standard therapy.[260,261]

Obesity and asthma

Asthma is more common in obese than non-obese patients.[262] Studies has shown that obese asthmatics have a different pattern of inflammation when compared to non-obese asthmatics.[263] Therefore, Obese asthma patients have more symptoms, more frequent and severe exacerbations, reduced response to asthma medications, poor quality of life and more difficult to control asthma.[264] This could be in part related to reduced lung volumes, lack of fitness, and associated sleep apnea and GERD.[265] Treatment of obese asthma patients is recommended to follow same stepwise approach for asthma management; however, weight reduction, exercise and diet control are essential part of their management.[266] Patient with symptoms related to obstructive sleep apnea are recommended to visit sleep medicine specialist. For morbidly obese patient with asthma, it is recommended to discuss the risks and benefits of bariatric surgery when other measures are failed.[267,268]

Cough-variant asthma

Patients with cough-variant asthma may have chronic cough as their main or only symptom especially at night.[269,270] Perhaps cough-dominant asthma is a better term as variant implies different pathophysiology. Studies of airway inflammation in Cough variant asthma (CVA) are similar to those of asthma presenting with different combinations of symptoms. Other diagnoses to be considered are drug-induced cough caused by angiotensin-converting enzyme inhibitors, GERD, chronic upper airway cough syndrome manifesting as postnasal drip, eosinophilic bronchitis, and chronic sinusitis. Once the diagnosis is established, treatment is recommended at Step 2 or higher as appropriate.[271,272] This condition may be confused with eosinophilic bronchitis which is characterized by cough and sputum eosinophilia with normal spirometry and airway responsiveness.[273,274]

Exercise-induced bronchoconstriction

Exercise-induced bronchoconstriction (EIB) is common in inadequately controlled asthma patients. However, asthma-like symptoms can sometimes be triggered only by physical activities. Normally, bronchodilation occurs during exercise and lasts for a few minutes.[275,276] In patients with EIB, 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 using SABA or ICS/formoterol a few minutes before exercise.[277,278] A warm-up period before exercise may also reduce EIB symptoms. If this approach does not control the symptoms, the patient is recommended to have maintenance therapy at Step 2 or higher as appropriate.[135,277] Regular use of LTRA may also help in this condition, especially in children.[135,275,277]

Aspirin-exacerbated respiratory disease

AERD is a special phenotype characterized by a triad of asthma, chronic rhinosinusitis with nasal polyposis, and respiratory reactions to aspirin.[279] About 7% of adult asthma patients and 15% in those with severe asthma suffer from attacks in response to ASA or NSAIDs that inhibit COX-1.[280,281] The majority of patients experience first symptoms during their third or fourth decade of life. Once ASA or NSAID hypersensitivity develops, it persists for life. Characteristically, within minutes to 2 h following ingestion of ASA, an acute severe asthma attack develops. It is usually accompanied by rhinorrhea, nasal obstruction, conjunctival irritation, and scarlet flush of the head and neck and even severe bronchospasm and death.[282] A typical history of upper and lower respiratory reaction to aspirin or NSAIDs is very suggestive for the diagnosis, which is confirmed by aspirin challenge which is not done routinely but if indicated, it be recommended to be done in a specialized allergy center.[283] Patients known to have aspirin-induced asthma should avoid all aspirin-containing products and NSAIDs. Where an NSAID is indicated, COX-2 inhibitors or alternative analgesics such as paracetamol are recommended.[284,285] Prophylactic low-dose aspirin should also be avoided. However, referral to an allergy specialist for ASA desensitization is recommended in patients for whom aspirin is required as anti-platelet therapy.[286] Montelukast may help in the treatment of this type of asthma in some patients.[287]

Pregnancy

Almost half of the pregnant women had the desire to stop asthma medications during pregnancy as they believed that asthma medications would harm them and their babies more than asthma itself.[15] As such, a great effort should be directed towards the education of asthma in pregnancy in order to correct this misbelief.

The course of asthma during pregnancy is unpredictable; however, one-third of pregnant asthmatics may have a worsening of their asthma control.[288,289] Maintaining adequate control of asthma during pregnancy is essential for the health and wellbeing of both the mother and her baby. Poor asthma control during pregnancy increases the risk of poor outcomes for the baby such as pre-term delivery, low birth weight, and increased perinatal mortality.[290] It also increases the risk for the mother and occurrence of poor asthma control during the first trimester of pregnancy that significantly increase the risk of a congenital malformation.[291] Identifying and avoiding the indoor and outdoor triggers and providing educational resources for the patient are recommended as the first step of therapy for asthma during pregnancy. Asthma treatment is recommended to take the same stepwise approach as in the non-pregnant patient with monthly follow-up and assessment. Salbutamol is the preferred reliever due to its excellent safety profile. An ICS based regimen is the preferred treatment for long-term control.[292] Asthma medications, including ICS, SABA, LABA, and LTRA are generally safe and have not shown to increase the risk of fetal abnormalities.[293-295] However, prolonged use of OCS may be associated with pregnancy-related complications, especially in the first trimester.[289] Data about safety of biological therapy during pregnancy is lacking, however, based on SINA Panel consensus, we recommend not to initiate biologics for new patient during pregnancy. For patients already on biologics before pregnancy, counselling patient is recommended for biologics benefit/risk ratio.[296,297] For acute asthma exacerbations, it is recommended to follow the same drug treatment guidelines as non-pregnant patients including systemic steroids if indicated.[298-300] Fetal monitoring is recommended in severe asthma attack. During labor and delivery, usual controller medications should be continued and if anesthesia is required during labor, regional anesthesia is recommended whenever possible.[301] The use of prostaglandin F2α may be associated with severe bronchospasm and should be avoided if possible.[302] If asthma is well controlled during pregnancy, acute asthma is rare during labor. Pregnant asthma patients should be encouraged to breastfeed after delivery and to continue their usual asthma medications during lactation.[303]

Occupational asthma

Patients with asthma should be asked about their occupational history and exposures for possible occupation-related allergens. A simple screening test is to ask the patient if their symptoms improve when they are away from work.[304] Once identified, early detection and elimination of occupational sensitizers and removal of patients from further exposure are an essential aspect of the management. Referral to an asthma specialist for assessment and advice is recommended for patients with

suspected or confirmed occupational asthma because of the legal implications of the diagnosis.[305,306]

Asthma-chronic obstructive pulmonary disease overlap

Asthma-chronic obstructive pulmonary disease overlap (ACO) is a unique complex descriptive entity sharing features of both asthma and COPD. At this stage, there is no formal definition of ACO as there is inadequate data to describe its features, characteristics, and its optimal therapeutic intervention.[302] ACO is a term used to describe patients who have persistent airflow limitation together with clinical features that are consistent with both asthma and COPD. This is not a definition of a single disease entity, but a descriptive term for clinical use that includes several different clinical phenotypes, different inflammatory patterns, and different underlying mechanisms.[307,308] Patients with features of both asthma and COPD have a greater burden of symptoms, experience frequent exacerbations, have poor quality of life, a more rapid decline in lung function, higher mortality, and greater use of healthcare resources, compared with patients with asthma or COPD alone.[309] Spirometry is required to confirm the diagnosis of chronic airflow limitation and document persistent airflow limitation, variability and reversibility. If the initial assessment suggests the diagnosis of asthma or ACO, or there is uncertainty about the diagnosis of COPD, it is prudent to treat as asthma by starting at Step 2 or higher as appropriate and to avoid using LABA and/or LAMA as the only therapeutic option. Patients having asthma with COPD had lower morbidity and hospitalizations if they received ICS treatment; a similar benefit was seen in those with COPD plus concurrent asthma. For ACO patients, non-pharmacological measures including smoking cessation, pulmonary rehabilitation, vaccinations, and treatment of comorbidities as additive therapeutic strategies.[310]

Asthma in elderly

Most elderly patients with asthma had been previously diagnosed with asthma during childhood or early adulthood. New onset asthma above the age of 65 is uncommon and estimated to be 4%–8%. Elderly patients with asthma perceive symptoms of asthma differently than younger patients, often have comorbid conditions with similar symptoms, and have late presentation with more severe airway obstruction. Approximately 50% of deaths from asthma occur in the elderly.[311,312] The diagnosis of asthma in elderly is challenging due to the high prevalence of smoking among elderly patients and because symptoms of asthma overlap with other diseases like COPD and bronchiectasis, and congestive heart failure. Elderly patients with asthma underestimate asthma symptoms as they may contribute it to age process or associated comorbidities such as

cardiovascular disease, smoking related diseases, or medications.[312] Confirmation of asthma diagnosis in elderly is based on the presence of respiratory symptoms suggestive of asthma and the demonstration of reversible expiratory airflow obstruction on PFT testing in the absence of alternative diagnoses. The Management of asthma in elderly patients is recommended to follow the same management guidelines in adults and adolescents. Difficulties in learning inhaler technique is usually common in elderly and it is attributed to cognitive impairment, muscle weakness, arthritis or impaired vision and it is an important consideration in this patient's population when choosing the inhaler device. Multiple inhaler devices are not recommended.[313,314] MDI with holding chamber, a breath-actuated dry powder inhaler (DPI), or a nebulizer are alternative options which may improve medications delivery.[315] Elderly patients have lower inspiratory flow rates and may not be able to achieve the higher inspiratory flow rates required for some DPIs. Adverse effect of ICS are common in elderly patients such as skin bruising, risk of osteoporosis, and cataracts.[316]

Section 9: Asthma in Children

Asthma represents one of the commonest chronic illnesses of childhood with significant economic impact.[317] It is also a leading cause of childhood morbidity as measured by school absences, Emergency Department visits and hospitalizations.[318] From the perspective of both patient and society, the cost of not treating asthma is higher than the cost of asthma treatment.[319,320] This section aims toward enhancing the multidisciplinary care of asthma in children with special attention to non-asthma specialists, including primary care and general practice physicians and other healthcare workers.

Diagnosis of asthma in children

Accurate diagnosis of asthma in children is crucial to prevent inappropriate management and reducing morbidity and mortality due to under-or over-diagnosis.[321,322] Asthma diagnosis in children continues to be a clinical diagnosis. However, clinical diagnosis is notoriously inaccurate, and, although there is no one diagnostic asthma "test", every effort should be made to obtain objective evidence for the diagnosis. The more tests that are negative, the less likely is the diagnosis to be correct. Careful clinical evaluation should focus on the presence of recurrent or chronic symptoms related to airway obstruction such as physician-diagnosed wheezing, coughing, night symptoms, activity limitation, and shortness of breath. These symptoms result from pathological small airway hyperreactivity due to various stimuli, and typically would be reversible either spontaneously or after receiving an asthma therapy. The diagnosis

can be further supported by the presence of atopy, early sensitization, and a family history of atopy. Spirometry is recommended to be performed for capable children to quantify airflow limitation and to show post-bronchodilator reversibility of airway obstruction.[317] Spirometry can be performed in children aged 5 years and older. It is preferably planned when the initial diagnosis is made and after 3 months of controller therapy initiation and with subsequent follow-up assessments. Box 9.1 presents a summary of findings suggestive of the diagnosis of asthma in children.

Asthma mimickers should be suspected when any of the atypical feature is present [Box 9.2].[323] Clinical suspicion of asthma mimickers is an acceptable indication for CXR, otherwise, a routine CXR is not recommended to be part of the initial routine work up of asthma in children.[324,325]

Box 9.1: Findings suggestive of the diagnosis of asthma in children

Findings	Remarks
History of multiple attacks of SOB or wheezing in a season	>3 attacks/season, recurrent, and worse during sleep with triggers such as physical activity, laughing, crying, upper respiratory tract infections or exposure to tobacco smoke, or air pollution. Ideally, wheezing should be confirmed by a doctor
Coughing	>2 weeks, not related to URTI, recurrent, and worse during sleep with triggers such as activity, laughing, crying or exposure to tobacco smoke or air pollution. Though isolated cough, without wheeze or breathlessness, is unlikely to be due to asthma
Reduced activity	Not able to run, play, or laugh at the same intensity as other children and tires earlier during walks (wants to be carried)
Family history	Atopy (allergic rhinitis, atopic dermatitis, food allergy) and asthma in first-degree relatives
Atopy	Eczema, aeroallergen and food sensitization
Wheezing	Equal bilaterally, during expiratory phase, especially on forced expiration
Breath sounds	Prolonged expiratory phase
Therapeutic trial	Trial of inhaled corticosteroid therapy. However, many respiratory symptoms in childhood improve spontaneously that should not be confused with therapeutic response. A three-stage trial is suggested 1. Commence a trial of ICS for 6 weeks 2. Stop ICS at 6 weeks and review response. If there was no improvement, ICS-responsive asthma is unlikely that recures further evaluation 3. If symptoms recur upon stopping therapy, reintroduce ICS and adjust dose accordingly
Spirometry	Typically, in children >5 years with bronchodilator response assessment
Chest X-ray	May be considered in infants to rule out other causes
Tests for hypersensitivity	Both skin testing and/or allergen specific IgE blood testing and eosinophils count

IgE=Immunoglobulin E, SOB=Shortness of breath, URTI=Upper respiratory tract infection, ICS=Inhaled corticosteroid

Wheezing in preschool children

Wheezing and shortness of breath in preschool children are among the most common presenting symptoms in pediatric practice. Approximately one third of children have at least one episode of wheeze before their third birthday.[326,327] Uncontrolled asthma in preschool children can lead to developmental disadvantages due to the negative impact of uncontrolled asthma on their social interaction and sleep. In preschool children, asthma diagnosis and management differ from that of older children and adolescents in many ways. Early childhood wheezing can evolve to different asthma phenotypes that can have variable response to standard therapy.[328] Box 9.3 shows the differential diagnosis of wheezing in preschool children. In this age subgroup, asthma diagnosis represents a challenging clinical judgment due to the lack of objective assessment such as PFT or inflammatory biomarkers (FeNo and eosinophils count).[327] The use of the term "reactive airway disease" is discouraged as it can restrain full clinical assessment and proper management of asthmatic children in this age group.[329-331]

Phenotypes and endotypes of wheezing in children

Phenotype is defined as the observable characteristic or trait of a disease, such as developmental, clinical or epidemiological properties, whereas endotype describes its distinct pathophysiologic mechanisms at a cellular

Box 9.2: Features suggest asthma mimickers

Failure to thrive

Onset of symptoms during infancy

Very sudden onset symptoms (suggests inhaled foreign body)

Vomiting associated with respiratory symptoms

Continuous (biphasic) wheezing

Failure to respond to asthma controller medication

Clubbing

Focal auscultation signs

Symptoms that are not associated with typical triggers

Chronic sputum production

Prominent upper airway symptoms

Box 9.3: Common differential of asthma in preschool children

Congenital cardiovascular defects

Congenital structural aerodigestive defects

Functional aerodigestive disorders

Infections especially viral bronchiolitis

Obliterative bronchiolitis

Aspiration syndromes including gastroesophageal reflux, unsafe swallow, H-type fistula

Bronchopulmonary dysplasia

Cystic fibrosis

Primary ciliary dyskinesia

Foreign body inhalation

Tracheobronchomalacia

and molecular level.[332] Based on several longitudinal studies, wheezing in children has been categorized epidemiologically into transient and persistent wheeze phenotypes. It is also categorized based on symptoms into episodic/viral induced and multi-trigger wheeze phenotypes.[327,333] Major factors that may predict persistent symptoms are allergic disease, reduced lung function, viral respiratory infection, and bacterial colonization in infancy. On the other hand, advances in biomolecular and cellular techniques enabled further analysis of pooled large datasets of asthmatics which in turn resulted in further classification of asthma endotypes.[334] Two major endotype subgroups have been proposed: Th2 high and Th2 low (or non-Th2). More sophisticated clustering using combination of clinical, physiological, and biomarker parameters is an ongoing area of research.[335] Different responses to treatment and variable outcomes have been attributed to phenotype-endotype heterogeneity, overlap and instability over time. The allocation of children into these categories still remains a subject of debate, as their clinical usefulness is still under investigation.[336] However, applying the evolving understanding of asthma phenotype-endotype is believed to enhance precision medicine practice in asthma management.[337] Box 9.4 summarizes wheeze phenotype-endotype in children.[41,327,337-339]

Box 9.4: Wheezing endotypes in young children

Endo type	Characteristics
Th2-high	
Atopic, early onset	Blood/sputum eosinophilia, serum
Atopic, late onset, more severe	specific allergen IgE, high FeNO, serum periostin, high total IgE
Non-Th2	
Nonatopic	Paucigranulocytic or neutrophilic sputum, MMP-9 in BAL
Obesity related	Oxidative stress, neutrophils, increased innate immune activation; more in females; dysnaptic airway growth

FeNO=Fractional exhaled nitric oxide, MMP-9=Metalloproteinase 9, Th2=T-helper lymphocyte type-2, IgE=Immunoglobulin E, BAL=Bronchoalveolar lavage

Prediction of asthma in preschool children
SINA expert panel recommends the utilization of the modified asthma predictive index (API) for early identification of the risk for persistent asthma among preschool children. This tool is a clinical scoring instrument 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 9.5].[340,341] Preschool children with positive modified-API are at a 4–10-fold increase in the risk of having asthma later in their childhood. On other side, children with negative modified-API will have 95% chance of outgrowing their asthma later on life.[342]

Box 9.5: Positive modified asthma predictive index

History of ≥4 wheezing episodes before the age of 3 years (at least one physician diagnosed) and either

≥1 of the major criteria	or	≥2 of the minor criteria
Parental history of asthma		Eosinophilia (≥4%)
Skin test positive to aeroallergens		Wheezing unrelated to colds
Eczema (physician-diagnosed atopic dermatitis)		Allergic sensitization to milk, egg, or peanuts

Assessment of asthma in children
The long-term goals of asthma management in children are not different from those of adults [Box 5.1].[343] Asthma management requires effective partnership between patients/caregivers and their healthcare providers.[344] Once established and strengthened, this relationship will positively impact asthma management. Asthma control shall be assessed routinely by physician during every clinic visit. Assessment of a child with asthma is recommended to cover two important aspects: future risk of adverse outcomes, and symptom control.

Assessing future risk of adverse outcomes
This is achieved by assessing future risk of attacks, fixed airflow obstruction, and adverse effects of medications [Box 9.6].

Assessing symptom control
This implies a periodical assessment of asthma control combined with adjustments (if needed) of treatment based on the level of control. It is strongly recommended to use asthma treatment in a stepwise approach with the ultimate goal of achieving "optimal" control with "minimal" amount of medications and dosage.[345] Adherence to the prescribed medications and the proper use of their devices are recommended to be addressed before any modification of the treatment plan. Asthma control reflects the adequacy of management by describing the clinical status of a child as controlled, partially controlled, or uncontrolled. Focusing on asthma control may improve patient perceptions and expectations that improve symptoms reporting by children and their caregivers and subsequently treatment decisions by clinicians.[346] Assessment of asthma control is recommended to cover the domains of both physician and patient/caregiver inputs.

Patient/caregiver assessment of control
Different numerical tools have been developed and validated to objectively assess asthma control utilizing patients and their caregiver perception. However, they are recommended to be used as a complimentary tool rather than replacing physician assessment as these tools have some limitations.[347] The SINA expert panel recommends utilizing the childhood-ACT (C-ACT) [Box 9.10] for children aged 5–12 years and the respiratory and asthma control in kids (TRACK)

[Box 9.13] for children younger than 5 years of age. These questionnaires are completed by patients and/or their caregivers prior to physician evaluation based on the age of the child.

Non-pharmacological management of asthma in children

- Patient education: Patient education is recommended to be an integral part of asthma management strategy in children. It is recommended to involve the basic knowledge of the 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 the optimal time to seek advice.[348,349] Caregivers of preschool children are recommended to be educated that asthma control is an achievable target and affected children should not be prevented from engagement in age-appropriate activities. Proper asthma education can lead to a significant reduction in Emergency Department visits and hospitalizations, improve self-management of asthma attacks, and an overall reduction in the cost of asthma care [Box 9.7].[350]

Setting asthma action-plans

An action plan that documents medications, doses, and device technique is recommended to be provided to patients and their caregivers. The action plan is also recommended to include information for patients and caregivers on how to recognize worsening of asthma symptoms and advice of treatment modification in these situations [Box 9.8].

Prevention

Asthma attacks can be triggered by a variety of factors including allergens, viral infection, pollutants, and drugs. Eliminating these exposures improves the control of asthma and reduces medications need. Parents/caregivers of children with asthma should be strictly advised not to smoke or vape at home at all.[343] Breast-feeding and vitamin D supplementation may decrease the chance of developing early wheezing episodes, while probiotics benefit is still doubtful in preventing allergic disease.[351-353] A study on early-life use of probiotic supplementation did not show significant impact to prevent asthma or eczema at the age of 2 years for children at high risk.[354] School-based programs that target asthma self-management are associated with improved asthma outcomes, fewer Emergency Department visits, fewer hospitalizations, fewer days of reduced activity.[355]

Precautions during viral pandemics

During the occurrence of viral infection pandemics, precautions related to infection control measures that include handwashing, social distancing, optimizing asthma control, and minimizing use of nebulization as the mean of drug delivery to reduce the risk of droplet generation are of extreme importance. Referral to specific guidelines by local and international experts on this task is recommended. SINA expert panel has released specific advices on asthma management of adult and children during the COVID-19 pandemic.[356,357] SINA expert panel advice to continue routine care for patient with acute exacerbation of bronchial asthma and to follow the regular clinical guideline in the occasion of pandemics.

Box 9.6: Assessment of future risk of adverse outcomes of asthma in children

Risk factors	Assessment
Asthma attacks within the next few months	Uncontrolled asthma symptoms
	One or more severe asthma attacks in the previous year
	The start of the child's usual exacerbations season (especially if autumn/fall)
	Exposures to tobacco smoke; indoor or outdoor air pollution; indoor allergens, especially in combination with viral infection
	Major psychological or socioeconomic problems for a child or family
	Poor adherence manifested as underuse of ICS and/or over-use of SABAs
	Failure to attend regular follow up appointments
Fixed airflow limitation	Persistent low FEV_1 in patients with
	Severe asthma with several hospitalizations
	History of bronchiolitis
Medication side-effects	Systemic: Frequent courses of oral corticosteroids or high-dose ICS; neuropsychiatric adverse reactions after the initiation of LTRA
	Local: Moderate/high-dose or potent ICS; incorrect inhaler technique; failure to protect skin or eyes when using ICS by nebulizer or spacer with face mask. Failure to use a spacer with MDI (common in teenagers)

ICS=Inhaled corticosteroid, SABAs=Short-acting bronchodilators, FEV_1=Forced expiratory volume in 1 s, LTRA=Leukotriene receptor antagonist, MDI=Metered-dose inhaler

Box 9.7: Patient asthma-education goals and objectives

Goals	Outcome
Developing partnership and common goals	Understand asthma risk by explaining in a simplified pathophysiology term
Sharing understandable information	Acknowledge role of prevention, environmental control and, importance of avoiding triggers
Addressing relevant concerns and expectations	Recognize difference between "controller" and "reliever" treatment
Continuity and consistency in providing education	Address adverse events of medications
	Explain devices use and importance of compliance with treatment plans
	Recognize worsening asthma and explain action plan
	Define comorbid conditions and provide recommendations

Box 9.8: Components of asthma management action plan

Item	Description
Patient identification	Name, medical record number, age, and weight
List of patient's medications	Dosage, frequency, controller versus rescuer medications
Recognition of asthma control status	In simple terms and color coded
Suggested action based on asthma control status	
How to use inhalational devices	Use illustrations
When and how to seek medical advice	Access to emergency care or call center
Others	How to clean inhalers and spacer and advice on environmental control and mouth washing after ICS use

ICS=Inhaled corticosteroid

Concepts of pharmacological management of asthma in children

The SINA expert panel have the following strategies for reliever and controller therapy:

Reliever therapy

Reliever therapy is a group of medications used to rescue asthmatic patients during exacerbation to relief acute symptoms of asthma. The following are considerations for this category:
- Oral bronchodilator therapy should not be prescribed due to slower onset of action and higher side effects[358]
- LABA should not be used alone as maintenance monotherapy in children (Evidence A).[359] LABA should be used only in combination with ICS.

Controller therapy

This is a group of medications used on a regular basis to keep asthma under control and prevents future risk of adverse outcomes. The following are considerations for this category:
- ICS are considered the most effective first-line maintenance monotherapy for childhood asthma (Evidence A)[360,361]
- For significant local side effects of ICS, enforce use of MDI with spacer, consider a change in therapy, reduction in the dose or frequency of ICS (if possible), advice for a vigorous mouth washing after inhalation, and/or use of appropriate local antifungal therapy for severe oral thrush[178]
- The combination of ICS/LABA is recommended to be used regularly at Step 3 and higher
- The combination of ICS/formoterol is specified because formoterol has a fast-acting component. Hence, it is the base of MART which is an acceptable approach for Step 3 and higher in children ≥5 years
- For children ≥5 years, MART approach is

recommended to be administered as maintenance (1–2 puffs once to twice daily) and as needed for asthma symptoms (1–2 puffs every 4–6 h). The maximum number of puffs per day is 8 (total of 36 µg based on 4.5 µg/puff formoterol formulation). Children who need to use more than these amounts should be advised (and their caregivers) to contact their physician or to seek emergency department advice. MART approach was demonstrated to be associated with lower risk of acute exacerbation and to be more cost effective (Evidence B).[362-364] However, attention should be paid to the maximum daily dose allowance used with this approach
- There are insufficient data to recommend short courses of high-dose ICS in children with mild intermittent asthma attacks (Evidence B).[365] The safety of this approach has not been established
- Children with frequent or severe asthma attacks are recommended to receive regular treatment with ICS (Evidence A).[366] Doubling the dose or quintupling it at the early stages of loss of control did not result in reduction of asthma attacks or improvement in other outcomes.[243] It recommended to refer to the stepwise approach [Box 9.12 and Box 9.15]
- Chronic use of ICS for more than 3 months in pre-pubertal-aged children can suppress growth velocity which is dose dependent. However, asthmatic children when treated with low-dose ICS attain normal adult height but at a later age (Evidence A).[367,368] Any potential adverse effects of ICS needs to be weighed against the well-established benefit to control persistent asthma. More details of the use of ICS in children are available in the medication appendix
- Children commenced on LTRA should be followed during the early phase of initiation for the development of neuropsychiatric adverse drug reactions (like anxiety, irritability, aggressiveness, and sleep disturbances) which warrant cessation of therapy in almost 1 out of 6 children. Patient and/or caregiver should be educated on this potential.[369-371]

Devices

It is important to select the best device for optimal treatment delivery [Box 9.9].

- Use of valved-holding spacer, with mouthpiece when possible, is recommended when an MDI is prescribed (Evidence B).[372] Breath-actuated devices (e.g., DPIs) represent an effective and simpler option for maintenance therapy in children 5–12 years of age (Evidence C).[373,374] For more information about medications, refer to the medications appendix[372-374]
- Nebulizers are not superior to MDI delivered by spacer in both acute and chronic asthma management (Evidence A).[375]

Strategies for outpatient management of asthma in children

Management of asthma is recommended to be adjusted continuously based on asthma control. If current treatment did not achieve control, step up is recommended 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 the lowest step to maximize safety and minimize cost. SINA expert panel recommends ensuring consistency in the approach of asthma in adults, adolescents, and children. Therefore, outpatient treatment will be stratified based on age groups: 5–12 years and <5 years. It is further described in three phases: initiation, adjustment, and maintenance.

Initiation of asthma treatment in children

Prior to initiating asthma treatment in children, it is recommended to ensure availability of initial clinical assessment data, such as the status of asthma control and assessing for risk factors. It is also recommended to provide teaching of inhalers technique, and action plan.

Adjustment of asthma treatment in children

Before treatment adjustments, it is recommend to assess adherence to treatment, proper device use, control of environment and confirmation of the diagnosis especially if there is a failure to respond to therapy.[376] Adjustment of therapy is recommended after 1–3 months depending on the level of asthma control upon presentation and the C-ACT score for children aged 5–12 years or TRACK score for children aged <5 years. Based on clinical assessment and the level of asthma control, the treatment is recommended to be adjusted. If asthma control is achieved, treatment is recommended

to be maintained at the same step; however, stepping down may be considered during low seasons for asthma attacks. The need for continuation of ICS should be regularly assessed as wheeze improves in a significant portion of children.[377] For a child with uncontrolled asthma, escalation of treatment to at least the next step is recommended.

Maintenance of asthma treatment in children

It is recommended to perform a full clinical assessment including asthma control status. The child is recommended to be clinically assessed regarding medications and doses, compliance with treatment, accuracy of inhalers technique, and any related environmental factors. Based on clinical assessment and asthma control status, SINA panel recommends the following:

- Step up treatment for children who are uncontrolled based on physician assessment and complemented by a C-ACT score of ≤19 for a child aged 5–12 years or TRACK score of ≤80 for a child aged <5 years. It is recommended to rule out any modifiable factors preventing reaching optimal asthma control
- Maintain treatment for children who reached controlled status based on physician assessment complemented by a C-ACT score of ≥20 for a child aged 5–12 years or TRACK score of >80 for a child aged <5 years
- Consider stepping down treatment for children who are controlled for at least 3 months.

Reduction in therapy is recommended to be gradual and closely monitored based on clinical judgment complemented by either C-ACT score or TRACK score. Furthermore, close monitoring upon treatment stepping down is recommended for patients who have risk of asthma attack especially during seasonal variation or for those with prior acute asthma attack in the past year or history of ICU admission.

Referral to an asthma specialist

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

- Uncertainty regarding the diagnosis
- Difficulty achieving or maintaining control of asthma
- Biological therapy or Immunotherapy are being considered
- The patient requires step 4 care or higher
- The patient has had an asthma attack requiring hospitalization or 2 or more OCS in the past 12 months.

Outpatient management of asthma in children aged 5–12 years

In addition to physician evaluation of asthma control, it

Box 9.9: Choosing an inhaler device for children

Age (years)	Preferred device	Alternative device
<4	MDI + spacer with face mask	Nebulizer with face mask
4–6	MDI + spacer with mouthpiece	Nebulizer with mouthpiece
>6	Dry powder inhaler, breath actuated pressurized MDI, MDI + spacer with mouthpiece	Nebulizer with mouthpiece

MDI=Metered-dose inhaler

Box 9.10: The childhood asthma control test

is recommended that child/caregiver obtain the C-ACT score which is a validated test for children 5–12 years [Box 9.10]. 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 part 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 suggests that a child's asthma is not adequately controlled.[378]

This section describes treatment initiation, adjustment, maintenance, and step down which is mainly based on physician evaluation and assessment of disease control by obtaining C-ACT score.

Treatment initiation

It is recommended to assess asthma control status by physician assessment and/or C-CAT score for children aged ≥5 years [Box 9.11]. The following are recommended options based on asthma control level and/or C-ACT score.

- Start at Step 1 when asthma is controlled by physician assessment and/or C-ACT score is ≥20 points:
  - The recommended option is as needed ICS whenever SABA is needed[115,373,379-384]
  - For a child with intermittent viral-induced wheeze, SABA on as needed basis is recommended[385]
- Start at Step 2 when asthma is uncontrolled/partially controlled by physician assessment and/or C-ACT score is <20 points:
  - The recommended option is regular low-dose ICS for a child with more symptoms (more than twice a week) (Evidence A)[386-389]
  - For a child who cannot or will not use ICS, LTRA could be recommended though it is a less effective option (Evidence B).[390-392]
- Start at Step 3 when asthma is uncontrolled/partially controlled by physician assessment and/or C-ACT score is < 20 points with more severe symptoms:
  - The recommended option is low-dose ICS/LABA either MART of ICS/Formoterol or regular ICS/non-formoterol LABA with SABA as a reliever[393-399]
  - Other options are escalating to daily moderate-dose ICS monotherapy or adding LTRA to low-dose ICS (Evidence A)[115,400-402]
  - For a child with early signs of moderate to severe asthma exacerbation at presentation, a short course oral prednisolone is recommended to be added.[403,404]

Adjustment and maintenance of treatment

It is recommended to perform a full clinical assessment including asthma control status and obtaining C-ACT score. Patient is recommended to be clinically assessed regarding medications and doses, compliance to treatment, accuracy of inhalers technique, and any related environmental factors. Based on clinical assessment and asthma control status, SINA expert panel recommends stepping up treatment for children who are uncontrolled based on physician assessment and complemented by a C-ACT score of ≤19. It is also recommended to rule out any modifiable factors that affect achieving asthma control. For patients who achieved control status, treatment based on physician assessment is recommended to be complemented by a C-ACT score of ≥20. The following are the five recommended five steps for children aged 5–12 years which is highlighted in Box 9.12.
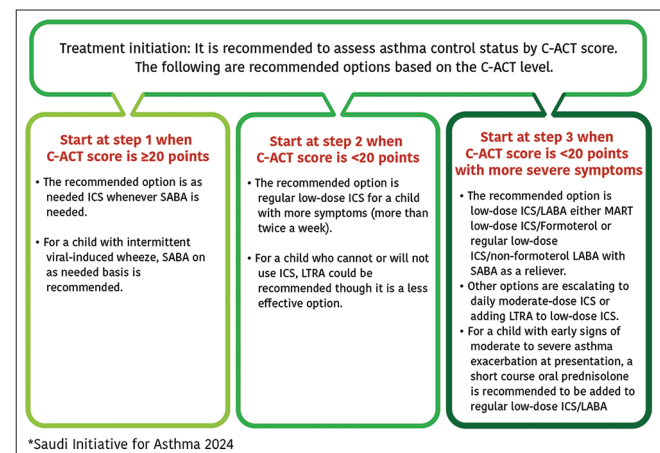
Step 1

- The recommended option is as needed ICS whenever SABA is required.[115,379-381,384,385]

Step 2

- The recommended option is low dose-ICS (step 2) (Evidence A)[360,361]
- Alternatively, either use of ICS whenever SABA is required, or daily LTRA that are less effective option at this step[115,400-402]
- For a child with intermittent viral-induced wheeze daily low-dose ICS is recommended.[383]

Step 3

- The recommended option is low-dose ICS/LABA either MART of ICS/Formoterol or regular ICS/non-formoterol LABA with SABA as a reliever[393-399,405-407]
- Other options are escalating to daily moderate-dose ICS or adding LTRA to low-dose ICS (Evidence A)[115,400-402]
- Whenever there is difficulty controlling asthma at Step 3, it is recommended to refer the child to a physician specialized in asthma for further evaluation for step 4–5 care.

Treatment initiation: It is recommended to assess asthma control status by C-ACT score. The following are recommended options based on the C-ACT level.

Start at step 1 when C-ACT score is ≥20 points
- The recommended option is as needed ICS whenever SABA is needed.
- For a child with intermittent viral-induced wheeze, SABA on as needed basis is recommended.

Start at step 2 when C-ACT score is <20 points
- The recommended option is regular low-dose ICS for a child with more symptoms (more than twice a week).
- For a child who cannot or will not use ICS, LTRA could be recommended though it is a less effective option.

Start at step 3 when C-ACT score is <20 points with more severe symptoms
- The recommended option is low-dose ICS/LABA either MART low-dose ICS/Formoterol or regular low-dose ICS/non-formoterol LABA with SABA as a reliever.
- Other options are escalating to daily moderate-dose ICS or adding LTRA to low-dose ICS.
- For a child with early signs of moderate to severe asthma exacerbation at presentation, a short course oral prednisolone is recommended to be added to regular low-dose ICS/LABA

*Saudi Initiative for Asthma 2024

Box 9.11: The SINA Approach for Asthma Treatment Initiation for children aged 5 to 12 years

Step 4

- The recommended option is medium-dose ICS/LABA either MART of ICS/Formoterol or daily of ICS/non-formoterol LABA inhaler with SABA as a reliever[393-399]
- Tiotropium or LTRA may be added to this combination if control is not achieved[408-410]
- Whenever there is difficulty controlling asthma at Step 4, it is strongly recommended to refer the child to a physician specialized in asthma for further evaluation.

Step 5

It is recommended to refer the child to a physician specialized in asthma as there are growing evidence to support biologics for children with uncontrolled asthma at Step 4. The following are SINA expert panel recommendations for biological therapy at step 5 for this age group:

- Anti-IgE therapy is a well-established therapy in children aged ≥6 years with uncontrolled asthma at Step 4 who fulfil the following criteria: severe persistent allergic asthma with frequent daytime symptoms or night-time awakenings, and who have multiple documented severe asthma attacks despite treatment at Step 4 (Evidence A)[411-414]
- Mepolizumab is an anti-IL-5 agent approved for children aged ≥6 years (Evidence A)[415,416] that is indicated when eosinophil level is ≥150 cells/uL at treatment initiation or ≥300 cells/uL at any time in the prior 12 months. The dose is 40 mg for patients 6–11 years of age subcutaneously every 4 weeks
- Dupilumab is a recombinant anti-IL-4 receptor, inhibiting the biological effects of both IL-4 and IL-13, and has been approved for the treatment of asthma in patients 6-12 years of age. Dupilumab reduces the rate of severe asthma exacerbations, improves lung function, and enhances asthma control in children with uncontrolled, moderate-to-severe asthma with evidence of type 2 inflammation as identified by blood eosinophils ≥150cells/uL or FeNO ≥20 ppb) (Evidence A).[417-420] The dose is 100 mg subcutaneously every 2 weeks or 300 mg subcutaneously every 4 weeks for children <30 Kg and 200 mg subcutaneously every 2 weeks for children ≥30 Kg
- There are other biologics that have been approved for adult asthmatic population, which is currently investigated for expanded applications in children, readers discretion advised. This line of therapeutics should be initiated by an asthma and allergy specialist.
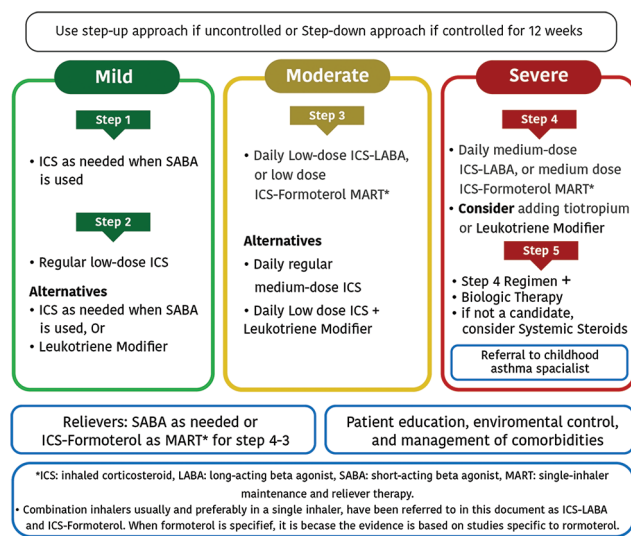
Specific immunotherapy in pediatrics

They are limited data, but it can be used for children >5 years of age and was shown to reduce long-term asthma medication use and improve FEV_1 as detailed in immunotherapy subsection.[213] It should be initiated by an asthma and allergy specialist.

Recommendations for treatment step down

SINA expert panel recommends the following concepts for stepping down treatment:

- If the patient is on ICS as monotherapy, the dose of ICS may be reduced by 25%–50% every 3 months to the lowest possible dose that is required to maintain control (Evidence B).[171-173] It should be clearly explained to the patient and/or caregiver that asthma control may deteriorate if treatment is abruptly discontinued.[174] In such a situation, an action plan that contains instruction on resuming controller therapy if asthma symptoms recurred is recommended to be provided to patients and their caregiver
- If the patient is on combination of ICS/LABA at Step 3 or 4, abrupt discontinuation of LABA may lead to deterioration of asthma control[175]
- If the patient is on a combination of ICS with LABA or LTRA, taper ICS to the lowest possible dose (Evidence B).[176-177] If control is maintained, LABA or LTRA may then be discontinued while patient on ICS (Evidence D)[176]
- For patients on long-term oral steroids, the dose is recommended to be tapered to the lowest dose and preferably to every other day (Evidence D). It is recommended to refer the child to a specialized physician in asthma management.

Outpatient management of asthma in children aged <5 years

In addition to physician evaluation, it is recommended that caregiver obtain the TRACK score which is a validated ACT for children <5 years [Box 9.13]. It is a 5-item standardized questionnaire, with four questions

Box 9.12: The SINA Approach for Outpatient management of Asthma for childern aged 5 to 12 years

that address the impairment domain and one question that address 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 <80 points suggests that a child's asthma is not controlled.[421]

This section describes treatment initiation, adjustment, maintenance, and step down which is mainly based on physician evaluation and assessment of disease control by obtaining TRACK score.

Treatment initiation

It is recommended to assess asthma control status by TRACK score for children aged <5 years [Box 9.14]. The following are recommended options based on physician assessment and TRACK score.

- Start at Step 1 when asthma is controlled by physician assessment and/or TRACK score of >80 points:
  - The recommended option is as needed SABA for a child with minimal symptoms (less than twice a week). This can be also applied for a child with intermittent viral-induced wheeze.[384,385]
- Start at Step 2 when asthma is uncontrolled/partially controlled by physician assessment and/or TRACK score is ≤80 points with mild symptoms:
  - The recommended option is regular low dose ICS for a child with more symptoms (more than twice a week) (Evidence A)[387-389,422]
  - Alternatively, LTRA for a child who cannot or will not use ICSs, though it is a less effective option.[390-392] Short course low-dose ICS at the start of URTI is another alternative option for episodic exacerbations (Evidence B).[423]
- Start at Step 3 when asthma is uncontrolled/partially controlled by physician assessment and/or TRACK score is ≤80 points pints with more severe symptoms:
  - The recommended option is regular use of double "low-dose" of ICS for a child with more persistent symptoms that is uncontrolled based on physician assessment.[424]

Adjustment and maintenance of treatment

It is recommended to perform a full clinical assessment including asthma control status and obtaining TRACK score. Patients are recommended to be clinically assessed regarding medications with doses, compliance to treatment, accuracy of inhalers technique, and any related environmental factors. Based on clinical assessment and asthma control status, SINA expert panel recommends stepping up treatment for children who are uncontrolled based on physician assessment and complemented by a TRACK score of ≤80. It is also recommended to rule out any modifiable factors preventing reaching optimal asthma control. For children achieved control status, maintain treatment based on physician assessment complemented by a TRACK score of >80.

The following are the five recommended five steps for children aged <5 years which is highlighted in Box 9.15.

Step 1

- The recommended option is as needed SABA for a child with minimal symptoms (less than twice a week). This can be also applied for a child with intermittent viral-induced wheeze.[384,385]

Step 2

- The recommended option is regular low-dose ICS (Evidence A)[383]
- Alternatively, daily LTRA for a child who cannot or will not use regular ICSs, though it is a less effective option (Evidence B).[400-402] Additionally, short course low dose ICS is recommended for URTI triggered exacerbations if regular use of ICS not applied.[360,361]

Step 3

- The recommended option is regular double the "low-dose" of ICS (Evidence A)[406]
- Alternatively, adding LTRA to low dose ICS is a less effective option[405,424]
- It is recommended to refer the patient to a physician specialized in asthma for further evaluation and options whenever management is escalated beyond step 3.

THE TEST FOR RESPIRATORY AND ASTHMA CONTROL IN KIDS (TRACK) FOR CHILDREN < 5 YEARS OF AGE					SCORE
1. During the past 4 weeks, how often was your child bothered by breathing problems (wheezing, coughing, SOB)?					
○ Not at all (20)	○ Once or twice (15)	○ Once every week (10)	○ 2-3 times/week (5)	○ ≥4 times/week (0)	
2. During the past 4 weeks, how often did your child's breathing problems, such as wheezing, coughing, or SOB, wake him/her at night?					
○ Not at all (20)	○ Once or twice (15)	○ Once every week (10)	○ 2-3 times/week (5)	○ ≥4 times/week (0)	
3. During the past 4 weeks, to what extent did your child's breathing problems, such as wheezing, coughing, or SOB, 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 (20)	○ Once or twice (15)	○ Once every week (10)	○ 2-3 times/week (5)	○ ≥4 times/week (0)	
4. During the past 3 months, how often did you need to treat your child's breathing problems (wheezing, coughing, or SOB) with quick-relief medications?					
○ Not at all (20)	○ Once or twice (15)	○ Once every week (10)	○ 2-3 times/week (5)	○ ≥4 times/week (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 (20)	○ Once or twice (15)	○ Once every week (10)	○ 2-3 times/week (5)	○ ≥4 times/week (0)	
			TRACK Score < 80 Indicates Uncontrolled Asthma	TOTAL SCORE	

**Box 9.13:** The Test for Respiratory and Asthma Control in Kids (TRACK)

Step 4
- The recommended option is adding regular LTRA to the daily double "low-dose" ICS (Evidence B)[425,426]
- There is no evidence to support the use of LABA for patients younger than 5 years
- It is strongly recommended to refer the patient to a physician specialized in asthma for further evaluation and options whenever management is escalated beyond step 3.

Step 5
- At this Step, regular use of systemic steroids shall be added to step 4 regimen, and the patient should be referred to an asthma specialist
- There is no evidence to support the use of either LABA or biologics for children <5 years.

Recommendations for treatment step down
SINA expert panel recommends the following concepts for stepping down treatment:
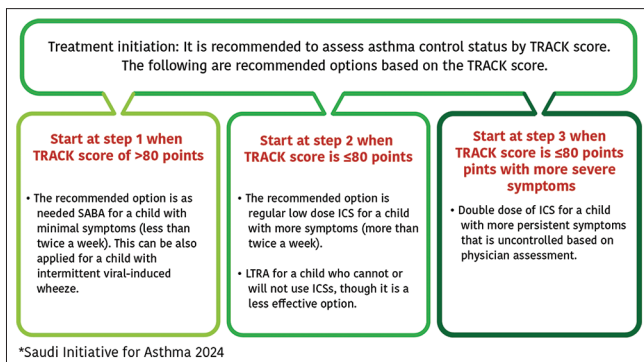
Box 9.14: The SINA Approach for Asthma Treatment Initiation for children aged less than 5 years
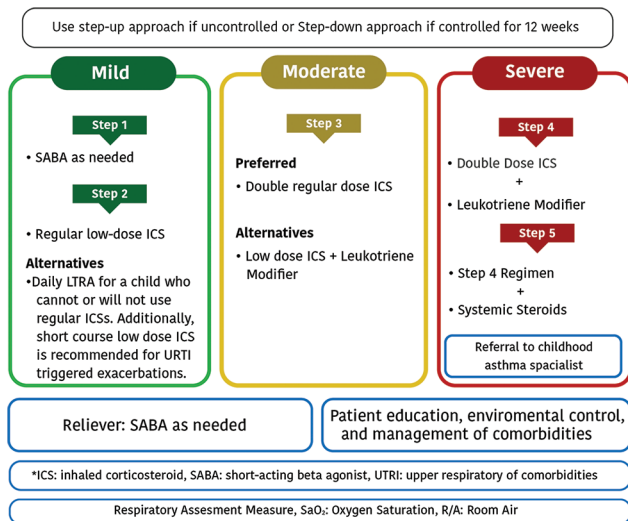
Box 9.15: The Saudi Initiative for Asthma approach for outpatient management of asthma for children aged <5 years

- If the patient is on ICS as monotherapy, the dose of ICS may be reduced by 25%–50% every 3 months to the lowest possible dose that is required to maintain control (Evidence B).[171,172] It is recommended to be clearly explained to the caregiver that asthma control may deteriorate if treatment is abruptly discontinued.[174] If asthma symptom is recurred, an action plan that contains instruction on resuming controller therapy is recommended to be provided to patients and their caregiver. Consultation with a healthcare provider is recommended if control is not achieved
- For significant side effects, consider a change in therapy, reduction in the dose or frequency of ICS (if possible), advice for a mouth washing after inhalation if possible, enforce use of MDI with spacer, and/or use of appropriate local antifungal therapy for severe oral thrush.[178]

Section 10: Management of Acute Asthma in Children

Early recognition of acute asthma
Recognition of early signs of acute asthma is essential especially for those <5 years. Early symptoms of acute asthma include (Evidence D):
- An attack of shortness of breath with wheeze or increase of shortness of breath with wheeze
- A new cough, especially at night although this is non-specific
- Impairment of daily activity
- An increased need for or poor response to SABA
- For a child <2 years, the presence of lethargy and poor feeding should raise the suspicion of acute asthma attack. However, viral bronchiolitis is a common differential diagnosis in this age group during winter season.

In a child aged 2–5 years, the combination of the above features can predict approximately 70% of acute asthma attacks with low false positive rate.[427] Moreover, URTI may frequently precede acute asthma attack in children. Clinical assessment is essential in children as the utilization of objective measures such as PFT is problematic, especially in the younger age groups.

Initial management of acute asthma at home
The SINA panel recommends management of a child with asthma to include an action plan that enables the caregiver to recognize worsening of asthma and the advice for initial treatment. The action plan is recommended to include features that mandate the need for urgent medical care that includes acute distress of the child, difficulty to complete few words in one breath, and poor response to SABA treatment at home.

In the case of acute attack, initial management at home by the caregiver is recommended to be started with salbutamol inhaler 2–4 puffs by a spacer that may be repeated every 20 min for a total of three doses. If the child improves, asthma therapy is recommended to be stepped up as per instructions in the action plan and medical advice should be sought as soon as possible.

Immediate transfer to hospital
If the child does not adequately improve within or after the initial period, urgent medical care is recommended. Box 10.1 shows the indications for immediate transfer to hospital for children with acute asthma exacerbation.

During the transfer to hospital, inhaled SABA should be provided as well as oxygen supply (to maintain saturation >94%). In addition to consideration to give the first dose of systemic corticosteroid, instant communication with specialized call center is recommended to provide the required consultations.

Assessment of asthma severity in the emergency department
Assessment of acute asthma severity in children has an important role in various components of acute asthma management such as: pharmacological interventions, need for hospitalization, and need for ICU admission. The assessment of acute asthma severity in young children is also important for clinical decision-making and evaluation of treatment effectiveness.[50,428-431] This is supported by the fact that PFT measurement is not feasible as more than half of asthma attacks in children presented to emergency departments for children <5 years.[432]

The Pediatric Respiratory Assessment Measure (PRAM) has been found to be feasible, valid, responsive and reliable tool to determine acute asthma severity in children aged 2–17 years.[432,433] The PRAM represents a useful means to record clinical signs in a standardized fashion [Box 10.2].[50] The PRAM score is a 12-point score consisting of oxygen saturation, suprasternal retractions, scalene muscle contraction, air entry, and wheezing.[430]

Clinical pathways based on PRAM for inpatient asthma management has been shown to decrease the length of stay and bronchodilator use with no adverse outcomes or increased acute care encounters.[434-436] The SINA panel recommends measuring PRAM score for asthmatic patients in emergency as it can categorize the risk of hospitalization:
- Total score of 1–3: Low risk with a chance of <10% for hospital admission
- Total score of 4–7: Moderate risk with a chance of 10%–50% for hospital admission
- Total score of 8–12: High risk with a chance of >50% for hospital admission.

Management of acute asthma in the emergency department
Management of acute asthma exacerbation in the Emergency Department should target the following goals:[437,438]
- Rapid reversal of bronchospasm
- Correction of hypoxemia if present
- Reducing the need for hospitalization
- Preventing recurrence of the attack after discharge.

After performing the necessary clinical assessment, the SINA expert recommends the utilization of PRAM as a tool to assess patients in the Emergency Department and guide further management as well. The PRAM score should be obtained at the initial assessment and after initiation of treatment as well. After initial clinical assessment and starting initial appropriate therapy, managing physician is recommended to focus on obtained history to identify risk factors for ICU admission, including:[439]
- Previous life-threatening asthma attack
- Previous ICU admission

Box 10.1: Description of indications for immediate transfer to hospital for children with acute asthma exacerbation

Indications	Description
Features of severe symptoms	Unable to speak and/or risk to choke with food or drink
	Bluish discoloration of lips and tongue (cyanosis)
	Rapid breathing >40/min for children <5 years of age
	Silent chest with evidence of increased work of breathing
Lack of response to rescuer treatment	Lack of response after 1–2 h of proper technique and dosage
Limitation to deliver acute treatment	Social, family, or environmental reasons

Box 10.2: The pediatric respiratory assessment measure score

Sign	0	1	2	3
On	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 wheeze/silent chest with minimal air entry
O_2 saturation	≥95%	92%–94%	<92%	

- Previous intubation
- Deterioration while already on systemic steroid.

In addition, managing physician is recommended to be aware of the following clinical features of severe or life-threatening asthma that require immediate medical attention:
- Child is unable to speak or drink
- Central cyanosis
- Confusion or drowsiness
- Significant subcostal or subglottic retraction
- Oxygen saturation <92%
- Silent chest on auscultation
- Tachycardia (heart rate >100 beats/min).

Implementation of clinical pathway that utilizes PRAM score for acute asthma management in children with moderate to severe asthma attacks markedly decrease the rate of hospitalization without increasing the rate of return to emergency care (Evidence B) [Box 10.3].[435,440-442] This has been supported by a study showing that PRAM score after 3 h of initial management was associated with a significant improvement in the prediction of admission rate compared to pure clinical judgment at triage.[433] Ancillary investigation that includes CXR and ABG are not routinely recommended.[439] Capillary blood gases is indicated in severe bronchial asthma that failed to respond to maximum therapy and required ICU admission. CXR is recommended in the following conditions:
- Suspected bacterial pneumonia that presents with fever >39°C and presence of focal finding of decreased breath sound and crackles
- To rule out bronchial asthma complications such as pneumothorax
- Severe disease that does not respond to maximum treatment
- Uncertainty about the diagnosis
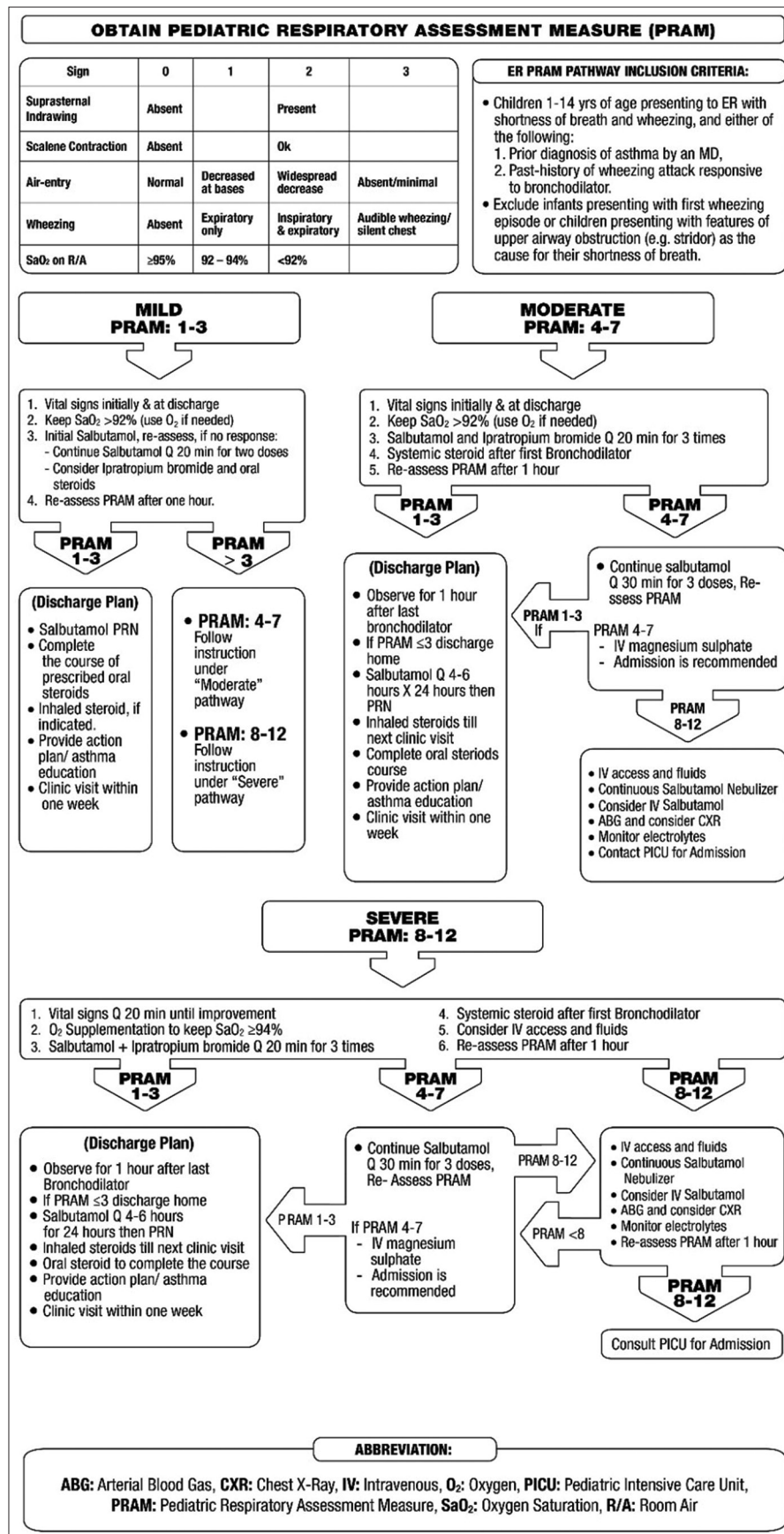- Hypoxemia apparently disproportionate to the attack severity.

Viral infection is the usual cause of asthma attacks in children and thus routine use of antibiotics is strongly discouraged.[443] Antibiotics are recommended when bacterial pneumonia is clinically suspected.[440,441]

Acute asthma management based on Pediatric Respiratory Assessment Measure

The SINA panel recommends managing asthma based on PRAM score obtained at initial assessment:
(i) Mild-PRAM score of 1–3: The initial management includes:
  - Obtain vital signs initially and at discharge
  - Prescribe appropriate oxygen dose to keep saturation ≥92%
  - Salbutamol dose based on weight:[375,444]

- Less than 20 kg: 5 puffs by MDI/spacer or 2.5 mg by nebulizer
- 20 kg or more: 10 puffs by MDI/spacer or 5 mg by nebulizer-titrate MDI dose based on response)
- In mild cases, SABA with spacer is not inferior to nebulized SABA.
  - Ipratropium bromide may be considered at a dose of 4 puffs by MDI with spacer or 250 µg by nebulizer every 20 min for the 1st h only[445]
  - Oxygen flow via facemask during the administration of nebulized drugs should not go below 6 L/min[446]
  - Consider oral steroid if there is no response to the first dose of salbutamol. Prednisolone dose is 1–2 mg/kg up to a maximum dose based on age. The maximum dose is 20 mg for children <2 years, 30 mg for children 2–5 years, and 60 mg for children 5–12 years. Dexamethasone dose of 0.6 mg/kg up to maximum dose of 16 mg[447]
  - Reassess PRAM after 1 h.
- Management after initial treatment based on PRAM score:
  - PRAM score is 1–3: The management includes:
    - The child may be discharged on salbutamol inhaler and ICS inhaler with a spacer
    - If an oral steroid course is given initially, dexamethasone is recommended for extra 1 day and prednisolone for total of 3–5 days
    - It is recommended to offer the child an action plan, education on inhalers technique, and a follow-up visit within 1 week to the appropriate clinic
    - PRAM score is 4–7: Treat as a moderate asthma attack (see below)
    - PRAM score is 8–12: Treat as a severe asthma attack (see below).
(ii) Moderate-PRAM score of 4–7: The management includes:
  - Obtain vital signs
  - Prescribe appropriate oxygen dose to keep Saturation ≥92%
  - Salbutamol dose based on weight:[444,448]
    - Less than 20 kg: 5 puffs by MDI/spacer or 2.5 mg by nebulizer
    - 20 kg or more: 10 puffs by MDI/spacer or 5 mg by nebulizer-titrate MDI dose based on response
    - Ipratropium bromide at a dose of 4 puffs or 250 µg by nebulizer every 20 min for the 1st h only[444,445,449]
  - The combination of salbutamol and ipratropium bromide has been shown to be effective in this situation (Evidence B)[444]
  - Systemic steroids after the first dose of SABA. Prednisolone dose is 1–2 mg/kg up to a maximum dose based on age. The maximum dose is 20 mg for

OBTAIN PEDIATRIC RESPIRATORY ASSESSMENT MEASURE (PRAM)

Sign	0	1	2	3
Suprasternal Indrawing	Absent		Present	
Scalene Contraction	Absent		Ok	
Air-entry	Normal	Decreased at bases	Widespread decrease	Absent/minimal
Wheezing	Absent	Expiratory only	Inspiratory & expiratory	Audible wheezing/ silent chest
SaO$_2$ on R/A	≥95%	92 – 94%	<92%	

ER PRAM PATHWAY INCLUSION CRITERIA:
- Children 1-14 yrs of age presenting to ER with shortness of breath and wheezing, and either of the following:
  1. Prior diagnosis of asthma by an MD,
  2. Past-history of wheezing attack responsive to bronchodilator.
- Exclude infants presenting with first wheezing episode or children presenting with features of upper airway obstruction (e.g. stridor) as the cause for their shortness of breath.

MILD PRAM: 1-3

1. Vital signs initially & at discharge
2. Keep SaO$_2$ >92% (use O$_2$ if needed)
3. Initial Salbutamol, re-assess, if no response:
   - Continue Salbutamol Q 20 min for two doses
   - Consider Ipratropium bromide and oral steroids
4. Re-assess PRAM after one hour.

PRAM 1-3

(Discharge Plan)
- Salbutamol PRN
- Complete the course of prescribed oral steroids
- Inhaled steroid, if indicated.
- Provide action plan/ asthma education
- Clinic visit within one week

PRAM > 3
- PRAM: 4-7 Follow instruction under "Moderate" pathway
- PRAM: 8-12 Follow instruction under "Severe" pathway

MODERATE PRAM: 4-7

1. Vital signs initially & at discharge
2. Keep SaO$_2$ >92% (use O$_2$ if needed)
3. Salbutamol and Ipratropium bromide Q 20 min for 3 times
4. Systemic steroid after first Bronchodilator
5. Re-assess PRAM after 1 hour

PRAM 1-3

(Discharge Plan)
- Observe for 1 hour after last bronchodilator
- If PRAM ≤3 discharge home
- Salbutamol Q 4-6 hours X 24 hours then PRN
- Inhaled steroids till next clinic visit
- Complete oral steriods course
- Provide action plan/ asthma education
- Clinic visit within one week

PRAM 4-7
- Continue salbutamol Q 30 min for 3 doses, Re-ssess PRAM

PRAM 1-3 If

PRAM 4-7
- IV magnesium sulphate
- Admission is recommended

PRAM 8-12
- IV access and fluids
- Continuous Salbutamol Nebulizer
- Consider IV Salbutamol
- ABG and consider CXR
- Monitor electrolytes
- Contact PICU for Admission

SEVERE PRAM: 8-12

1. Vital signs Q 20 min until improvement
2. O$_2$ Supplementation to keep SaO$_2$ ≥94%
3. Salbutamol + Ipratropium bromide Q 20 min for 3 times
4. Systemic steroid after first Bronchodilator
5. Consider IV access and fluids
6. Re-assess PRAM after 1 hour

PRAM 1-3

(Discharge Plan)
- Observe for 1 hour after last Bronchodilator
- If PRAM ≤3 discharge home
- Salbutamol Q 4-6 hours for 24 hours then PRN
- Inhaled steroids till next clinic visit
- Oral steroid to complete the course
- Provide action plan/ asthma education
- Clinic visit within one week

PRAM 4-7
- Continue Salbutamol Q 30 min for 3 doses, Re- Assess PRAM

PRAM 1-3

If PRAM 4-7
- IV magnesium sulphate
- Admission is recommended

PRAM 8-12

PRAM <8

PRAM 8-12
- IV access and fluids
- Continuous Salbutamol Nebulizer
- Consider IV Salbutamol
- ABG and consider CXR
- Monitor electrolytes
- Re-assess PRAM after 1 hour

Consult PICU for Admission

ABBREVIATION:
ABG: Arterial Blood Gas, **CXR:** Chest X-Ray, **IV:** Intravenous, **O$_2$:** Oxygen, **PICU:** Pediatric Intensive Care Unit, **PRAM:** Pediatric Respiratory Assessment Measure, **SaO$_2$:** Oxygen Saturation, **R/A:** Room Air

Box 10.3: Assessment and treatment of acute asthma in children

children <2 years, 30 mg for children 2–5 years, and 60 mg for children 5–12 years. Dexamethasone dose of 0.6 mg/kg up to maximum dose 16 mg[233,450]

- Re-assess PRAM after 1 h
- If PRAM score after 1 h is 1–3, observe for another hour.
- Management after initial treatment based on PRAM score:
  - PRAM score is 1–3:
    - The child may be discharged on salbutamol inhaler with a spacer and ICS if the patient is not already on controller treatment
    - Complete the course of oral steroids. Dexamethasone is recommended for extra 1 day and prednisolone for a total of 3–5 days; both as once daily dose
    - It is recommended to offer the child an action plan, education on inhalers techniques, and a follow-up visit within 1 week to the appropriate clinic.
  - PRAM score is 4–7: It is recommended to continue treatment with salbutamol every 30 min for three doses and to assess PRAM score every 30 min. Further evaluation is based on PRAM re-assessment:
    - If PRAM score improves to 1–3, the child can be managed as above
    - If PRAM score does not improve, IV Magnesium sulphate is recommended as a single dose of 40–50 mg/kg to a maximum of 2 g by slow IV infusion over 20–30 min. The child needs close monitoring for blood pressure and appropriate IV fluids. Admission is recommended to be considered.[451-452]
  - PRAM score is 8-12: treat as severe asthma attacks (see below).

(iii) Severe-PRAM score of 8–12: The management includes:
- Obtain vital signs every 20 min until improvement
- Prescribe appropriate oxygen dose to keep saturation ≥92%
- Salbutamol nebulizer at a dose of 2.5 mg for those weighted <20 kg or 5 mg for those weighted ≥20 kg and ipratropium bromide at a dose of 250 µg by nebulizer every 20 min for the 1st h.[444,445,449] This combination has been shown to be effective in this situation (Evidence B)[444]
- Systemic steroids after the first dose of SABA. Prednisolone dose is 1–2 mg/kg up to a maximum dose based on age. The maximum dose is 20 mg for children <2 years, 30 mg for children 2–5 years, and 60 mg for children 5–12 years. Dexamethasone dose of 0.6 mg/kg up to maximum dose 16 mg[233,450]
- Reassess PRAM after 1 h
- Consider IV access and appropriate IV fluids
- If PRAM score after 1 h is 1–3, Observe for another hour.

- Management after initial treatment based on PRAM score:
  - PRAM score is 1–3:
    - The child may be discharged on salbutamol inhaler with a spacer and ICS if the patient is not already on controller treatment
    - Complete the course of oral steroids. Dexamethasone is recommended for extra 1 day and prednisolone for total of 3–5 days; both as once daily dose[233,450]
    - It is recommended to offer the child/care giver an action plan, education on inhalers technique, and a follow-up visit within 1 week to the appropriate clinic.
  - PRAM score is 4–7: It is recommended to continue treatment with salbutamol every 30 min for three doses and to assess PRAM score every 30 min. Further evaluation is based on PRAM re-assessment:
    - If PRAM score improves to 1–3, the child can be managed as above
    - If PRAM score does not improve, IV Magnesium sulphate is recommended as a single dose of 40–50 mg/kg to a maximum of 2 g by slow IV infusion over 20–30 min. The child needs close monitoring for blood pressure and appropriate IV fluids. Admission is recommended to be considered.[451-453]
  - PRAM score is 8–12: Deterioration of clinical status despite adequate treatment in the initial period warrants special care and attention. It is recommended to:
    - Establish IV access and start on appropriate IV fluids
    - Continue nebulized salbutamol back-to-back every 20 min or use continuous salbutamol nebulization at a dose of 7.5 mg/h for those weighted <10 kg, 11.25 mg/h for those weighted 10–20 kg, or 15 mg/h for those weighted >20 kg[454,455]
    - If PRAM score does not improve, IV Magnesium sulphate is recommended as a single dose of 40–50 mg/kg to a maximum of 2 g by slow IV infusion over 20–30 min
    - If no improvement in PRAM score, start IV salbutamol at a dose of 1 µg/kg/min then titrate based on response for a maximum dose of 10 µg/kg/min)[452,453]
    - ABG, CXR and electrolyte are recommended to be obtained and the pediatrics critical care or equivalent service must be consulted.

Appendix: Medications Used in Asthma Treatment

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.[456] Relievers are medications used on an "as-needed basis" that act quickly to reverse bronchoconstriction and relieve symptoms. Multiple combinations of controllers are available.

Reliever medications

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

Fast onset inhaled β2-agonists

SABAs, such as salbutamol, have been traditionally used for relief of symptoms of acute attacks of asthma and for the pre-treatment of EIB. Use of MDI with a chamber (Spacer) is as effective as the nebulized route in treatment of acute episodes of wheeze in children.[230] Regular long-term use of SABA alone is not recommended. Formoterol is a LABA with fast-acting component that is combined with an ICS to be uses as an anti-inflammatory reliever that can be used alone on as needed basis in patients with mild asthma or as MART in more symptomatic patients.[97-99] Vilanterol is another LABA used once a day that has a fast onset of action within 15 min and long half-life; hence, the patient should be advised to only use it once a day on a regular basis and not a rescue medication.[147,148] In acute asthma, inhaled SABA is the preferred choice.[232,457] Repeated doses are recommended to be given at 15–20 min intervals. Alternatively, continuous nebulization (salbutamol at 5–10 mg/h) could be used for 1 h if there is an inadequate response to initial treatment. However, a meta-analysis of randomized controlled trials of adults with acute asthma found no significant differences between the continuous or intermittent methods in terms of pulmonary function or hospital admission; nevertheless, patients treated by continuous nebulization had fewer side effects.[458] 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. As the inhaled route has a faster onset of action and fewer adverse effects, the use of IV SABA in the initial treatment of patients with acute severe asthma is not generally recommended.[459] IV therapy should not be considered routinely and only used cautiously if the response to the inhaled drug is poor or if the patient cannot tolerate the inhaled route.

In patients with mild asthma as needed use of ICS and SABA in a single inhaler was as effective as regular use of ICS with a lower 6-month cumulative dose of the ICS.[95] In patients with uncontrolled moderate-to-severe asthma on various inhaled ICS-containing maintenance therapies, the risk of severe asthma exacerbation was significantly lower with as-needed use ICS/SABA and ICS fixed dose inhaler than with as-needed use of SABA alone.[94]

Anticholinergics

Anticholinergics are less effective than SABA in asthma. However, when used in combination with SABA in acute asthma, they provide an additional benefit.[444] They can also be an alternative bronchodilator for patients who experience adverse effects such as tachycardia, arrhythmia, and tremor from SABA. Their side effects include dryness of the mouth and a bitter taste.

In moderate to severe acute asthma, combining ipratropium bromide with salbutamol was shown to have additional bronchodilation effect and faster improvement in lung function, compared to salbutamol alone.[239,242] A systematic review showed the combination therapy has an added benefit in reducing hospitalizations.[241] Combining both agents led to reduction in hospital admission rates by 38%–57%, improvement in lung function, and substantial cost saving.[242,460,461] No evidence of benefit for length of hospital stay and other markers of response when inhaled anticholinergics are added to SABA in hospitalized asthmatic children with acute attacks.[462] The adult dosing of nebulized ipratropium bromide is 500 µg every 20 min for three doses, then as needed. Alternatively, ipratropium bromide can be administered by MDI at a dose of 4–8 puffs (80–160 µg) every 20 min, then as needed for up to 3 h.

Intravenous magnesium sulphate

In a systematic review, magnesium sulphate was shown to reduce hospitalizations in patients with severe or life-threatening asthma attacks that failed to respond to initial treatment.[463] A single dose of IV magnesium sulphate at a dose of 1–2 g over 20 min is safe and effective in acute severe asthma.[247]

Anti-inflammatory controller medications
Inhaled corticosteroids

ICS are currently the most effective anti-inflammatory medications for the treatment of asthma.[33,119,464] The available ICSs are beclomethasone dipropionate, budesonide, ciclesonide, fluticasone propionate, fluticasone furoate, mometasone furoate. They reduce symptoms, improve quality of life, improve lung function, decrease airway hyper reactivity, control airway inflammation, reduce frequency and severity of asthma attacks, and reduce asthma mortality. Early initiation of low dose ICS in asthma leads to improvement in lung functions.[117] When they are discontinued prematurely or abruptly, 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 and children at relatively low doses. Exposure to tobacco smoking or vaping, including secondary and tertiary, reduces the responsiveness to ICS. To reach control, add-on therapy with another class of controller is preferred to increase the dose of ICS.[136,465]

Local adverse effects can occur and include oropharyngeal candidiasis and dysphonia; with metered dose inhalers (MDI), these effects are reduced by using a spacer device. Mouth and throat washing after inhalation may reduce oral candidiasis. The small risk of adverse events from the use of ICS is well balanced by their efficacy.[466] Therefore, low-medium dose of ICS is generally safe and well tolerated in adults and children. Systemic side effects are occasionally reported with high doses and long-term treatment.

Special considerations for use of inhaled corticosteroids in children

Growth retardation may be seen with all ICS when a high dose ICS is chronically used. Systematic reviews showed a reduction may affect height velocity in pre-pubertal children over 12 months use of low-to-medium dose of ICS, especially during the 1st year of life.[467] Though this effect was statistically significant and sustained during adult life, it is not clear if that will be of significant clinical impact.[468,469] For instance, use of moderate-dose ICS resulted in 1.2 cm reduction in the final adult height after more than 4 years use.[470] Moreover, more studies demonstrated the negative impact of medium-to-high doses ICS on bone mineralization.[471-473] However, it is crucial to remember that long-term use of ICS is safer than frequent bursts of OCS on bone mineralization. Adequate nutrition with sufficient intake of calcium and vitamin D can blunt these effects.[474] In summary, the potential adverse effects of ICS need to be weighed against the well-established benefit to control persistent asthma. Therefore, it is important to target the lowest possible ICS dose that maintains adequate asthma control.

Leukotriene modifiers

Leukotriene modifying agents reduce airway inflammation and improve asthma symptoms and lung function, but with individual variation in response and a less consistent effect in reducing the frequency of asthma attacks, especially when compared to ICS. Currently, montelukast is available locally that 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.[475,476] LTRA are generally well tolerated, however; it is recommended to be aware of the Food and Drug Administration warning about serious behavior and mood-related changes with montelukast.[164] In children, studies have shown that LTRA may be useful for reducing the number of asthma attacks induced by viruses and for reducing bronchial inflammation in atopic children.[477-480] There are no clinical data to support their use under the age of 6 months.[164]

Other controller medications

Long-acting inhaled β2-agonists

The commonly used LABA are formoterol and salmeterol that are used twice daily. Vilanterol and indacaterol are LABA agents with a 24-h or longer duration of action.[481-487] Due to lack of anti-inflammatory effect, LABA should not be used alone as monotherapy in asthma as this can lead to increased mortality, and should be used in combination in the same device with ICS when prescribed for asthma. When used in combination with ICS, there is an improvement in symptoms, decreased nocturnal asthma, improved lung function, decreased use of SABA, reduced number of asthma attacks and better control at a lower dose of ICS. LABA provides longer protection to prevent exercise-induced bronchospasm than SABA.[488] Their side effects include tachycardia, tremor, headaches, muscle cramps, and sometimes hypokalemia. Regular use of LABA combined with ICS may lead to a reduction in their side effects. The effect of LABA has not been adequately studied in children of <5 years.

Long-acting anti-muscarinic agents

LAMA inhibits the effect of acetylcholine on muscarinic receptors, thus producing bronchodilation. LAMA agents are classically used for the treatment of COPD patients. Tiotropium bromide was the first LAMA extended for use in asthma. Its bronchodilatation duration of action of more than 24 h allows for single daily dosing.[489,490] The earlier studies on tiotropium were conducted using the Handihaler© device, while the more recent studies were conducted using the new Respimat device. To date, tiotropium is mainly available in the Saudi Market in the Handihaler device in an 18-µg capsule format while the Respimat device is not widely available. Tiotropium was shown to be an effective stepping up strategy when added to a combination of ICS/LABA, and not inferior to LABA as an add on to a medium dose ICS.[139,140,160,491,492] Adding LAMA can significantly improve lung function in uncontrolled cases and reduce attacks (Evidence A).[138,159,160] Triple therapy of ICS/LABA/LAMA in one device is available for uncontrolled asthma treatment in once and twice a day combinations (see the section on single inhaler triple therapy below). The main side effect of LAMA is dryness of mouth, although mild prostatic symptoms in men have been reported.[493]

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 or LTRA. Theophylline is not recommended for use as monotherapy in asthma treatment. Low-dose theophylline (150 mg twice daily) may have a role in improving steroid resistance in patients with severe asthma requiring high-dose ICS.[494,495] Side effects include gastrointestinal symptoms, cardiac arrhythmias, seizures, and even death. Nausea and vomiting are the early symptoms of toxicity. Liver disease and congestive heart failure may increase the risk of toxicity. The use of lower doses may decrease these side effects. Theophylline has a narrow therapeutic window, multiple drug interactions and a risk of toxicity that limits its use in treating asthma.

Oral short-acting bronchodilator

The side effect profile is much higher than that of inhaled SABA. Therefore, their use is highly discouraged in asthma management. The oral route is prohibited for children as well.

Combination therapy with inhaled corticosteroids and long-acting β2 agonist

Fixed combinations of ICS and LABA are considered more convenient for patients. Combination therapy is generally safe and results in significantly fewer asthma attacks.[132,496-499] They increase adherence 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 faster onset of action than salmeterol. Therefore, combination inhalers containing formoterol may be used for both rescue and maintenance of control.[97,132] In mild asthmatics, studies compared as-needed ICS/formoterol combination with as-needed SABA alone or in combination with daily maintenance ICS showed that as-needed ICS/formoterol was non-inferior to budesonide maintenance therapy for severe exacerbations, but was superior in real-life studies and meta-analyses, and reduced urgent healthcare utilizations and hospitalizations in mild asthma. The dose of ICS in the as-needed ICS/formoterol approach was 17% to 25% of the dose of ICS in the maintenance therapy at the expense of a small, but significant, change in asthma control score in favor of budesonide maintenance therapy. ICS are now recommended to start from Step 1 either as ICS/formoterol combination on as-needed basis or SABA with ICS in a separate inhaler every time rescue treatment is needed.[98,99,496-500] Once a day dry powder combination of ICS/LABA with fluticasone furoate and vilanterol (Relvar) is available in Ellipta® device in two strengths of 100/25 and 200/25 µg with dispensed equivalent dose of 92/22 and 184/22 µg, respectively.[147,148] The dose of fluticasone furoate of 100 µg is approximately equivalent to fluticasone propionate of 250 µg.[501] Indacaterol combination with mometasone furoate 150/160 µg is available in Breezhaler device®.[150] Such combinations have a potential adherence advantage while maintaining the same safety.

Single Inhaler Triple therapy with Inhaled Corticosteroids, Long-acting β2 Agonist, and Long-acting Anti-muscarinic Agent

Fixed combination inhalation devices are considered more convenient for patients.[502] Triple therapy of ICS/LABA/LAMA was first introduced for COPD treatment. Available triple therapy combinations for asthma management are fluticasone furoate/umeclidinium/vilanterol (Trelegy®), Beclomethasone dipropionate/Formoterol/glycopyrronium (Trimbow®), and mometasone furoate/glycopyrronium/indacaterol (Enerzair Breezhaler®).[151,155-158] In a systematic review and meta-analysis, among children (aged 6–18 years) and adults with moderate to severe asthma, triple therapy, compared with dual therapy of medium to high dose ICS/LABA, was significantly associated with 17% fewer severe asthma exacerbations and modest improvements in asthma control without significant differences in quality of life or mortality.[503] In a meta-analysis of Phase III studies, triple combination therapies with a high-dose ICS/LABA/LAMA administered were more effective than medium-dose FDC against moderate to severe exacerbation and increasing trough FEV_1.[154] Using biomarkers of type 2 airway inflammation measurement in one study showed that a higher dose of ICS reduced the rate of exacerbations.[65]

Systemic corticosteroids

Long-term oral steroid therapy (excluding short courses for acute attacks of asthma for a period of 1–2 weeks) may be required to control difficult-to-treat asthma despite maximum standard therapy when biological agents cannot be used. The dose should be reduced to the lowest possible and other controllers are recommended to be maximized to minimize the side effects from the OCS. Its use is limited by the risk of significant adverse effects. The use of intramuscular long-acting steroids is highly discouraged because of the increased risk of side effects. Side effects include osteoporosis, hypertension, diabetes, adrenal insufficiency, obesity, cataracts, glaucoma, skin thinning, and muscle weakness. Sudden withdrawal can elicit adrenal failure, therefore gradual withdrawal is recommended. In patients prescribed long-term systemic corticosteroids, prophylactic treatment for osteoporosis is recommended. If available, biologics should be used in these patients to decrease the corticosteroid burden.

Inhalation devices used in asthma

Medication aerosol can be delivered using three devices:

Box 11.1: Comparative descriptions and effects of approved biological therapies for severe asthma

	Anti-IgE	Anti-IL5[200,509-513]		Anti-IL4Rα	Anti-TSLP
	Omalizumab[514-520]	Mepolizumab[511,521-523]	Benralizumab[520,524-528]	Dupilumab[420,529-531]	Tezepelumab[532-537]
Mechanism of action	Binds to IgE and prevents it from binding to mast cells, reducing inflammation	Blocks IL-5, reducing eosinophil production and inflammation	Binds to IL-5 receptor, leading to eosinophil apoptosis, and reducing inflammation	Blocks IL-4Rα, reducing inflammation and improving airway hyperresponsiveness	Binds to TSLP and prevents it from activating immune cells such as dendritic cells, T cells, and mast cells, which can lead to a reduction in inflammation and airway hyperresponsiveness
Approved indications	Moderate to severe persistent asthma with a positive skin test or *in vitro* reactivity to a perennial aeroallergen Nasal polyps Chronic idiopathic urticaria	Severe eosinophilic asthma Rhinosinusitis with nasal polyps EGPA Hypereosinophilic syndrome	Severe eosinophilic asthma	Atopic dermatitis Severe eosinophilic asthma or with oral corticosteroid dependent asthma Chronic rhinosinusitis with nasal polyposis EoE Prurigo nodularis	Severe asthma
Asthma eligibility criteria	Severe allergic asthma (at least one positive aeroallergen on skin prick testing or an elevated specific aeroallergen IgE level) uncontrolled on high-dose ICS combined with LABA and other controllers and who have an IgE level of within therapeutic range	Severe eosinophilic asthma (blood eosinophils should be >150/µL within the last 6 weeks or >300/µL within the last 12 months before starting)	Severe eosinophilic asthma (has blood eosinophil count ≥300 cells/µL in the last 12 months)	Severe eosinophilic asthma (blood eosinophils ≥150/µL or FeNO ≥25 ppb) and oral steroids dependent severe asthma regardless of blood eosinophils count	Severe exacerbations in the last year
Age of use in asthma	6 years and above	6 years and above	12 years and above	6 years and above	12 years and above
Dose	75–375 mg based on IgE and patient weight every 2–4 weeks	12 years and older: 100 mg administered subcutaneously once every 4 weeks Aged 6–11 years: 40 mg administered subcutaneously once every 4 weeks	30 mg subcutaneously once every 4 weeks for the first 3 doses Then once every 8 weeks thereafter	600 mg SC once, then 300 mg q2 weeks	210 mg SC every 4 weeks
Outcomes based on exacerbation rates (AER)	AER reduction: 0.56/100 person-years (95% CI: 0.4–0.77)	Relative reduction in AER: 53% (95% CI: 36–65)	Relative reduction of AER (0.49, 0.37–0.64; $P<0.0001$)	AER reduction: 47.7% with dupilumab than with placebo ($P<0.001$)	AER reduction: 0.44; 95% CI: 0.37–0.53; $P<0.001$
Outcomes based on oral corticosteroids use		The median percentage reduction from baseline in the glucocorticoid dose was 50% ($P=0.007$)	Reduced the median final oral glucocorticoid doses from baseline by 75%, ($P<0.001$)	The percentage change in the glucocorticoid dose was–70.1% in the dupilumab group, ($P<0.001$)	Similar to placebo OR: 1.28; 95% CI: 0.69–2.35; $P=0.43$
Outcomes based on asthma symptoms	Decreased mean asthma symptom score (TASS score) (–0.26 [CI: –0.42––0.10]) compared with placebo	Improvement in mean ACQ5 difference 0.44 points compared to placebo	Improvement in mean ACQ6 difference 0·25, 95% CI: 0·45––0·06 compared to placebo	Improvement in mean ACQ5 difference 0.47 (95% CI: –0.76––0.18)	Improvement in mean ACQ6 difference 0.33; 95% CI: –0.46––0.20; $P<0.001$
Outcomes based on QOL	Improvement in AQLQ difference, (0.29 point [CI: 0.15–0.43])	Improvement in SGRQ difference 7.0 points compared to placebo	Improvement in AQLQ difference +0.1 (–0.08–+0.28) compared with placebo		Improvement in AQLQ difference, 0.34; 95% CI: 0.20–0.47; $P<0.001$
Outcomes based on FEV_1	Increase in FEV_1 by 120.9 mL (30.6–211.2 mL; $P=0.009$) compared to placebo	Increase in FEV_1 By 98 mL ($P=0.03$) compared to placebo	Increase in FEV_1 by 159 mL, 0.068–0.249. Compared with placebo	Increase in FEV_1 by 140 mL; $P<0.001$ compared to placebo	Increase in FEV_1 by 130 mL; 95% CI: 0.08–0.18; $P<0.001$ compared to placebo

Contd...

Box 11.1: Contd...

| | Anti-IgE | Anti-IL5[200,509-513] | | Anti-IL4Rα | Anti-TSLP |
	Omalizumab[514-520]	Mepolizumab[511,521-523]	Benralizumab[520,524-528]	Dupilumab[420,529-531]	Tezepelumab[532-537]
Predication of response	Higher blood eosinophil FeNO	Higher blood eosinophil Higher exacerbations history Adult-onset asthma Nasal polyps	Higher blood eosinophil OCS use nasal polyposis FVC <65%	Higher blood eosinophil Higher FeNO	Higher blood eosinophil Higher FeNO
Side effects	Serum sickness Unmasking hypereosinophilic conditions (EGPA) Black box warning Cardiovascular risk Anaphylaxis risk	Helminthic infection Hypersensitivity reaction Herpes zoster (rare) Headache Sore throat	Helminthic infection Hypersensitivity reaction Herpes zoster (rare) Headache Sore throat Arthralgia	Helminthic infection Hypersensitivity reaction Unmasking Hypereosinophilic conditions (EGPA) Conjunctivitis Consider completing all age-appropriate vaccinations as recommended by current immunization guidelines before initiating treatment	Pharyngitis Arthralgia Back pain Injection-site reactions
Pregnancy and breast-feeding precautions	US FDA: Not assigned There is availability of published registry which showed similar major congenital risk, live birth and lower birth weight as placebo	US FDA: Not assigned	US FDA: not assigned	US FDA: Not assigned	US FDA: Not assigned

EoE=Eosinophilic esophagitis, OR=Odds ratio, CI=Confidence interval, FDA=Food and Drug Administration, EGPA=Eosinophilic granulomatosis with polyangiitis, FeNO=Fractional exhaled nitric oxide, FVC=Forced vital capacity, OCS=Oral corticosteroid, QOL=Quality of life, AQLQ=Asthma QOL Questionnaire, SGRQ=St George's Respiratory Questionnaire, TASS=Total asthma symptom score, ACQ=Asthma Control Questionnaire, AER=Asthma exacerbation rate, LABA=Long-acting β2 agonist, TSLP=Thymic stromal lymphopoietin, IgE=Immunoglobulin E, ICS=Inhaled corticosteroid, FEV_1=Forced expiratory volume in 1 s, IL-5=Interleukin-5, IL4Rα=Interleukin 4 receptor α, SC=Subcutaneous

Small-volume nebulizer (SVN)

It is the most popular for patients and clinicians with acute asthma. Small-volume nebulizers (SVNs) are predominately powered by a compressed gas (air or oxygen) to convert one or more drug solutions or suspensions at any concentrations and dose into aerosols. SVN has the advantage of the need for minimal patient cooperation and is, therefore, suitable for all ages, with normal breathing and no inspiratory pause required. One of its main disadvantages is importability, short time to deliver the medication and potential contamination.

Pressurized metered-dose inhaler

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. An MDI typically requires slow inspiratory flow (≤30 L/min). One of its main advantages is that it is pre-mixed and has the ability to provide multiple doses in a short period of time. It is also small and portable with limited contamination. It is the preferred method in children if used with a large-volume spacer device. Disadvantages include the need of patient training to coordinate inhalation with actuation, and if this is not done properly, there is a potential of high deposition of drug in the oropharynx and poor drug delivery. Also, because it does not have a dose counter, it is difficult to determine the dose remaining in the canister.

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 an easier inhaler technique and a built-in dose counter. Disadvantages include the need for adequate inspiratory flow to disperse a full dose. If not used properly, high oropharyngeal impaction may occur, and exhaled humidity into the mouthpiece might affect the function of some devices. Therefore, it may not be suitable for very young or very old patients. The commonly available device in Saudi Arabia includes Turbohaler, Diskus, Handihaler, Easi-Breathe, Ellipta, Easyhaler, and Nexthaler devices.

Breath-actuated inhalers

These inhalers automatically release a spray of medication when the person begins to inhale. They are easy to use and improve asthma control and compliance with medications.[504-507]

Biologics in asthma treatment

The recent progress in biologics in asthma has made a

step forward toward the practice of precision medicine for asthma patients. To date, there are no head-to-head studies to compare the available biologics with each other, neither between those with different targets nor between anti-IL5 therapies themselves. In addition, due to the wide variability of the published clinical trials' inclusion criteria and analysis methodologies, it is also difficult to compare the efficacy of these therapies based on existing studies. Box 11.1 shows comparative descriptions and effects of different approved biological therapies for severe asthma.[508]

Conflicts of interest

The SINA is fully sponsored by the Saudi Thoracic Society.

References

1. Levy ML, Bacharier LB, Bateman E, Boulet LP, Brightling C, Buhl R, *et al.* Key recommendations for primary care from the 2022 Global Initiative for Asthma (GINA) update. NPJ Prim Care Respir Med 2023;33:7.
2. Venkatesan P. 2023 GINA report for asthma. Lancet Respir Med 2023;11:589.
3. Al Ghobain MO, Algazlan SS, Oreibi TM. Asthma prevalence among adults in Saudi Arabia. Saudi Med J 2018;39:179-84.
4. Mohamed Hussain S, Ayesha Farhana S, Mohammed Alnasser S. Time trends and regional variation in prevalence of asthma and associated factors in Saudi Arabia: A systematic review and meta-analysis. Biomed Res Int 2018;2018:1-9.
5. Alatawi A, Alanazi M. Barriers of asthma care among asthmatic children in Saudi Arabia: Maternal perspectives. Open J Pediatr 2020;10:302.
6. Taminskiene V, Alasevicius T, Valiulis A, Vaitkaitiene E, Stukas R, Hadjipanayis A, *et al*. Quality of life of the family of children with asthma is not related to asthma severity. Eur J Pediatr 2019;178:369-76.

7. Al-Harbi S, Al-Harbi AS, Al-Khorayyef A, Al-Qwaiee M, Al-Shamarani A, Al-Aslani W, *et al*. Awareness regarding childhood asthma in Saudi Arabia. Ann Thorac Med 2016;11:60-5.
8. Hammad MA, Alakhali KM, Manal Hattan M, Noor DA, Sulaiman SS, Kharshid AM, *et al*. Asthma in Saudi Arabia: Risk factors and pharmacotherapy. Indo Am J Pharm Res 2016;6:6814-21.
9. BinSaeed AA. Caregiver knowledge and its relationship to asthma control among children in Saudi Arabia. J Asthma 2014;51:870-5.
10. BinSaeed AA, Torchyan AA, Alsadhan AA, Almidani GM, Alsubaie AA, Aldakhail AA, *et al*. Determinants of asthma control among children in Saudi Arabia. J Asthma 2014;51:435-9.
11. Ahmed AE, Al-Jahdali H, Al-Harbi A, Khan M, Ali Y, Al Shimemeri A, *et al*. Factors associated with poor asthma control among asthmatic patient visiting emergency department. Clin Respir J 2014;8:431-6.
12. Al-Jahdali H, Anwar A, Al-Harbi A, Baharoon S, Halwani R, Al Shimemeri A, *et al*. Factors associated with patient visits to the emergency department for asthma therapy. BMC Pulm Med 2012;12:80.
13. Al-Jahdali H, Ahmed A, Al-Harbi A, Khan A, ALGamedi M, Alyami S, *et al*. The most common pulmonary diseases length of stay, and characteristics of patients admitted to pulmonary service. Ann Thorac Med 2023;18:124-31.
14. Al-Zahrani JM, Ahmad A, Al-Harbi A, Khan AM, Al-Bader B, Baharoon S, *et al*. Factors associated with poor asthma control in the outpatient clinic setting. Ann Thorac Med 2015;10:100-4.
15. Al Ghobain MO, AlNemer M, Khan M. Assessment of knowledge and education relating to asthma during pregnancy among women of childbearing age. Asthma Res Pract 2018;4:2.
16. Al-Moamary MS, Al-Hajjaj MS, Idrees MM, Zeitouni MO, Alanezi MO, Al-Jahdali HH, *et al*. The Saudi initiative for asthma. Ann Thorac Med 2009;4:216-33.
17. Al-Moamary MS, Alhaider SA, Al-Hajjaj MS, Al-Ghobain MO, Idrees MM, Zeitouni MO, *et al*. The Saudi initiative for asthma – 2012 update: Guidelines for the diagnosis and management of asthma in adults and children. Ann Thorac Med 2012;7:175-204.
18. Al-Moamary MS, Alhaider SA, Idrees MM, Al Ghobain MO, Zeitouni MO, Al-Harbi AS, *et al*. The Saudi initiative for asthma – 2016 update: Guidelines for the diagnosis and management of asthma in adults and children. Ann Thorac Med 2016;11:3-42.
19. Al-Moamary MS, Alhaider SA, Alangari AA, Al Ghobain MO, Zeitouni MO, Idrees MM, *et al*. The Saudi initiative for asthma – 2019 update: Guidelines for the diagnosis and management of asthma in adults and children. Ann Thorac Med 2019;14:3-48.
20. Al-Moamary MS, Alhaider SA, Alangari AA, Idrees MM, Zeitouni MO, Al Ghobain MO, *et al*. The Saudi initiative for asthma – 2021 update: Guidelines for the diagnosis and management of asthma in adults and children. Ann Thorac Med 2021;16:4-56.
21. Jadad AR, Moher M, Browman GP, Booker L, Sigouin C, Fuentes M, *et al*. Systematic reviews and meta-analyses on treatment of asthma: Critical evaluation. BMJ 2000;320:537-40.
22. Pavord ID, Beasley R, Agusti A, Anderson GP, Bel E, Brusselle G, *et al*. After asthma: Redefining airways diseases. Lancet 2018;391:350-400.
23. Del Giacco SR, Bakirtas A, Bel E, Custovic A, Diamant Z, Hamelmann E, *et al*. Allergy in severe asthma. Allergy 2017;72:207-20.
24. Lambrecht BN, Hammad H. The immunology of asthma. Nat Immunol 2015;16:45-56.
25. Brusselle GG, Maes T, Bracke KR. Eosinophils in the spotlight: Eosinophilic airway inflammation in nonallergic asthma. Nat Med 2013;19:977-9.
26. Amelink M, de Nijs SB, de Groot JC, van Tilburg PM, van Spiegel PI, Krouwels FH, *et al*. Three phenotypes of adult-onset asthma. Allergy 2013;68:674-80.
27. Israel E, Reddel HK. Severe and difficult-to-treat asthma in adults.

N Engl J Med 2017;377:965-76.

28. Papi A, Brightling C, Pedersen SE, Reddel HK. Asthma. Lancet 2018;391:783-800.

29. Park JA, Sharif AS, Tschumperlin DJ, Lau L, Limbrey R, Howarth P, *et al.* Tissue factor-bearing exosome secretion from human mechanically stimulated bronchial epithelial cells *in vitro* and *in vivo*. J Allergy Clin Immunol 2012;130:1375-83.

30. Brightling CE, Gupta S, Gonem S, Siddiqui S. Lung damage and airway remodelling in severe asthma. Clin Exp Allergy 2012;42:638-49.

31. Bergeron C, Al-Ramli W, Hamid Q. Remodeling in asthma. Proc Am Thorac Soc 2009;6:301-5.

32. Grainge CL, Lau LC, Ward JA, Dulay V, Lahiff G, Wilson S, *et al.* Effect of bronchoconstriction on airway remodeling in asthma. N Engl J Med 2011;364:2006-15.

33. Alangari AA. Corticosteroids in the treatment of acute asthma. Ann Thorac Med 2014;9:187-92.

34. O'Byrne PM, Pedersen S, Lamm CJ, Tan WC, Busse WW, START Investigators Group. Severe exacerbations and decline in lung function in asthma. Am J Respir Crit Care Med 2009;179:19-24.

35. O'Brian AL, Lemanske RF Jr., Evans MD, Gangnon RE, Gern JE, Jackson DJ. Recurrent severe exacerbations in early life and reduced lung function at school age. J Allergy Clin Immunol 2012;129:1162-4.

36. Russell RJ, Brightling C. Pathogenesis of asthma: Implications for precision medicine. Clin Sci (Lond) 2017;131:1723-35.

37. Bloom CI, Palmer T, Feary J, Quint JK, Cullinan P. Exacerbation patterns in adults with asthma in England. A population-based study. Am J Respir Crit Care Med 2019;199:446-53.

38. Bonsignore MR, Baiamonte P, Mazzuca E, Castrogiovanni A, Marrone O. Obstructive sleep apnea and comorbidities: A dangerous liaison. Multidiscip Respir Med 2019;14:8.

39. Price D. Asthma and allergic rhinitis: Linked in treatment and outcomes. Ann Thorac Med 2010;5:63-4.

40. Rogliani P, Sforza M, Calzetta L. The impact of comorbidities on severe asthma. Curr Opin Pulm Med 2020;26:47-55.

41. Kuruvilla ME, Lee FE, Lee GB. Understanding asthma phenotypes, endotypes, and mechanisms of disease. Clin Rev Allergy Immunol 2019;56:219-33.

42. Naclerio R, Ansotegui IJ, Bousquet J, Canonica GW, D'Amato G, Rosario N, *et al.* International expert consensus on the management of allergic rhinitis (AR) aggravated by air pollutants: Impact of air pollution on patients with AR: Current knowledge and future strategies. World Allergy Organ J 2020;13:100106.

43. Al-Mobeireek AF, Al-Sarhani A, Al-Amri S, Bamgboye E, Ahmed SS. Chronic cough at a non-teaching hospital: Are extrapulmonary causes overlooked? Respirology 2002;7:141-6.

44. Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, *et al.* Standardization of spirometry 2019 update. An official American thoracic society and European respiratory society technical statement. American journal of respiratory and critical care medicine 2019;200:e70-e88.

45. Yi F, Han L, Liu B, Zhang X, Xue Y, Luo W, *et al.* Determinants of response to bronchodilator in patients with cough variant asthma- a randomized, single-blinded, placebo-controlled study. Pulm Pharmacol Ther 2020;61:101903.

46. Song WJ, Kim HJ, Shim JS, Won HK, Kang SY, Sohn KH, *et al.* Diagnostic accuracy of fractional exhaled nitric oxide measurement in predicting cough-variant asthma and eosinophilic bronchitis in adults with chronic cough: A systematic review and meta-analysis. J Allergy Clin Immunol 2017;140:701-9.

47. Lux H, Lenz K, Budnik LT, Baur X. Performance of specific immunoglobulin E tests for diagnosing occupational asthma: A systematic review and meta-analysis. Occup Environ Med 2019;76:269-78.

48. Humbert M, Holgate S, Boulet LP, Bousquet J. Asthma control or severity: That is the question. Allergy 2007;62:95-101.

49. Halvorsen T, Walsted ES, Bucca C, Bush A, Cantarella G, Friedrich G, *et al.* Inducible laryngeal obstruction: An official joint European Respiratory Society and European Laryngological Society statement. Eur Respir J 2017;50:1-15.

50. Cope SF, Ungar WJ, Glazier RH. International differences in asthma guidelines for children. Int Arch Allergy Immunol 2009;148:265-78.

51. Apps LD, Chantrell S, Majd S, Eglinton E, Singh SJ, Murphy AC, *et al.* Patient perceptions of living with severe asthma: Challenges to effective management. J Allergy Clin Immunol Pract 2019;7:2613-21.e1.

52. Neffen H, Chahuàn M, Hernández DD, Vallejo-Perez E, Bolivar F, Sánchez MH, *et al.* Key factors associated with uncontrolled asthma – The asthma control in Latin America study. J Asthma 2020;57:113-22.

53. Vermeulen F, de Meulder I, Paesmans M, Muylle I, Bruyneel M, Ninane V. Asthma control measurement using five different questionnaires: A prospective study. Respir Med 2013;107:1314-21.

54. Schatz M, Sorkness CA, Li JT, Marcus P, Murray JJ, Nathan RA, *et al.* Asthma control test: Reliability, validity, and responsiveness in patients not previously followed by asthma specialists. J Allergy Clin Immunol 2006;117:549-56.

55. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, *et al.* Development of the asthma control test: A survey for assessing asthma control. J Allergy Clin Immunol 2004;113:59-65.

56. Lababidi H, Hijaoui A, Zarzour M. Validation of the Arabic version of the asthma control test. Ann Thorac Med 2008;3:44-7.

57. Alanezi M, Al-Jahdali HH, Al-Hajjaj MS, Zeitoni MO, Al-Tasan TH. Levels of acceptance of asthma control test questionnaire among Saudi patients attending 5 tertiary care hospitals in Saudi Arabia. Saudi Med J 2009;30:546-9.

58. Al Moamary MS, Al-Kordi AG, Al Ghobain MO, Tamim HM. Utilization and responsiveness of the asthma control test (ACT) at the initiation of therapy for patients with asthma: A randomized controlled trial. BMC Pulm Med 2012;12:14.

59. Schatz M, Kosinski M, Yarlas AS, Hanlon J, Watson ME, Jhingran P. The minimally important difference of the asthma control test. J Allergy Clin Immunol 2009;124:719-23.e1.

60. Schneider A, Brunn B, Hapfelmeier A, Schultz K, Kellerer C, Jörres RA. Diagnostic accuracy of FeNO in asthma and predictive value for inhaled corticosteroid responsiveness: A prospective, multicentre study. EClinicalMedicine 2022;50:101533.

61. Miller MK, Lee JH, Miller DP, Wenzel SE, TENOR Study Group. Recent asthma exacerbations: A key predictor of future exacerbations. Respir Med 2007;101:481-9.

62. Amnuaypattanapon K, Limjindaporn C, Srivilaithon W, Dasanadeba I. Characteristics and outcomes of treatment in status asthmaticus patients at emergency department. Asian Pac J Allergy Immunol 2019;37:87-93.

63. Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, *et al.* An official American Thoracic Society/European Respiratory Society statement: Asthma control and exacerbations: Standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med 2009;180:59-99.

64. Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, Casale TB, *et al.* A new perspective on concepts of asthma severity and control. Eur Respir J 2008;32:545-54.

65. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, *et al.* International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 2014;43:343-73.

66. Lommatzsch M, Brusselle GG, Canonica GW, Jackson DJ, Nair P, Buhl R, *et al.* Disease-modifying anti-asthmatic drugs. Lancet 2022;399:1664-8.

67. Gibson PG, Powell H. Written action plans for asthma: An evidence-based review of the key components. Thorax 2004;59:94-9.

68. Dailah H. A Self-Management Program for Adults with Asthma in Saudi Arabia. UK: University of Salford; 2020.

69. Richmond RS, Connolly M. A delineation of self-management and associated concepts. International Journal of Healthcare Management 2021;14:1576-88.

70. Elsherif OE, Al-Abdullaah AA, Aljahdali HH, Jokhdar HA, Alqahtani SH, Nahhas MA, *et al*. The burden of asthma among children and adolescents in Saudi Arabia: A national cross-sectional survey. Allergy 2022;2772:8293.

71. Al-Yami SM, Mohajer KA, Al-Jeraisy MI, Batarfi AM, Abolfotouh MA. Recurrent visits and admissions of children with asthma in central Saudi Arabia. Saudi Med J 2010;31:921-4.

72. Basyouni MH, BinDhim NF, Saini B, Williams KA. Online health information needs for patients with asthma in Saudi Arabia. J Consum Health Internet 2015;19:13-24.

73. Beydon N, Taillé C, Corvol H, Valcke J, Portal JJ, Plantier L, *et al*. Digital action plan (web app) for managing asthma exacerbations: Randomized controlled trial. J Med Internet Res 2023;25:e41490.

74. Khdour MR, Elyan SO, Hallak HO, Jarab AS, Mukattash TL, Astal A. Pharmaceutical care for adult asthma patients: A controlled intervention one-year follow-up study. Basic Clin Pharmacol Toxicol 2020;126:332-40.

75. Dardouri M, Sahli J, Ajmi T, Mtiraoui A, Bouguila J, Mallouli M. Factors associated with acute health care use in children and adolescents with asthma. Compr Child Adolesc Nurs 2021;44:122-33.

76. Gold DR, Adamkiewicz G, Arshad SH, Celedón JC, Chapman MD, Chew GL, *et al*. NIAID, NIEHS, NHLBI, and MCAN workshop report: The indoor environment and childhood asthma-implications for home environmental intervention in asthma prevention and management. J Allergy Clin Immunol 2017;140:933-49.

77. Alangari AA, Riaz M, Mahjoub MO, Malhis N, Al-Tamimi S, Al-Modaihsh A. The effect of sand storms on acute asthma in Riyadh, Saudi Arabia. Ann Thorac Med 2015;10:29-33.

78. Ronsmans S, Le Moual N, Dumas O. Update on irritant-induced occupational asthma. Curr Opin Allergy Clin Immunol 2023;23:63-9.

79. Goyal S, Gupta M, Sharma P, Beniwal V. Hypersensitivity associated with food additives. In: Microbes for Natural Food Additives. USA: Springer; 2023. p. 205-27.

80. Zeitouni MO, Al Barrak AM, Al-Moamary MS, Alharbi NS, Idrees MM, Al Shimemeri AA, *et al*. The Saudi Thoracic Society guidelines for influenza vaccinations. Ann Thorac Med 2015;10:223-30.

81. Kyung Y, Choi MH, Lee JS, Lee JH, Jo SH, Kim SH. Influencing factors for influenza vaccination among South Korean adolescents with asthma based on a nationwide cross-sectional study. Int Arch Allergy Immunol 2020;181:434-45.

82. Grohskopf LA, Alyanak E, Broder KR, Walter EB, Fry AM, Jernigan DB. Prevention and control of seasonal influenza with vaccines: Recommendations of the advisory committee on immunization practices – United States, 2019-20 influenza season. MMWR Recomm Rep 2019;68:1-21.

83. Alharbi NS, Al-Barrak AM, Al-Moamary MS, Zeitouni MO, Idrees MM, Al-Ghobain MO, *et al*. The Saudi Thoracic Society pneumococcal vaccination guidelines-2016. Ann Thorac Med 2016;11:93-102.

84. Penkalski MR, Reynaldo RF, Patterson K. A paradigm shift in pharmacotherapeutic management of asthma. Medsurg Nurs 2023;32:145-54.

85. Domingo C, Garcia G, Gemicioglu B, Van GV, Larenas-Linnemann D, Neffen H, *et al*. Consensus on mild asthma management: Results of a modified Delphi study. J Asthma 2023;60:145-57.

86. O'Byrne PM, FitzGerald JM, Bateman ED, Barnes PJ, Zheng J, Gustafson P, *et al*. Effect of a single day of increased as-needed budesonide-formoterol use on short-term risk of severe exacerbations in patients with mild asthma: A *post-hoc* analysis of the SYGMA 1 study. Lancet Respir Med 2021;9:149-58.

87. Reddel HK, Yan KY. Single maintenance and reliever therapy (SMART) of asthma. Thorax 2011;66:86-7.

88. Chapman KR, Barnes NC, Greening AP, Jones PW, Pedersen S. Single maintenance and reliever therapy (SMART) of asthma: A critical appraisal. Thorax 2010;65:747-52.

89. Scullion J. A proactive approach to asthma. Nurs Stand 2005;20:57-65.

90. Averell CM, Stanford RH, Laliberté F, Wu JW, Germain G, Duh MS. Medication adherence in patients with asthma using once-daily versus twice-daily ICS/LABAs. J Asthma 2021;58:102-11.

91. Berger WE. Levalbuterol: Pharmacologic properties and use in the treatment of pediatric and adult asthma. Ann Allergy Asthma Immunol 2003;90:583-91.

92. Nwaru BI, Ekström M, Hasvold P, Wiklund F, Telg G, Janson C. Overuse of short-acting β(2)-agonists in asthma is associated with increased risk of exacerbation and mortality: A nationwide cohort study of the global SABINA programme. Eur Respir J 2020;55:1-11.

93. Crossingham I, Turner S, Ramakrishnan S, Fries A, Gowell M, Yasmin F, *et al*. Combination fixed-dose beta agonist and steroid inhaler as required for adults or children with mild asthma. Cochrane Database Syst Rev 2021;5:CD013518.

94. Papi A, Chipps BE, Beasley R, Panettieri RA Jr., Israel E, Cooper M, *et al*. Albuterol-budesonide fixed-dose combination rescue inhaler for asthma. N Engl J Med 2022;386:2071-83.

95. Papi A, Canonica GW, Maestrelli P, Paggiaro P, Olivieri D, Pozzi E, *et al*. Rescue use of beclomethasone and albuterol in a single inhaler for mild asthma. N Engl J Med 2007;356:2040-52.

96. Israel E, Cardet JC, Carroll JK, Fuhlbrigge AL, She L, Rockhold FW, *et al*. Reliever-triggered inhaled glucocorticoid in black and Latinx adults with asthma. N Engl J Med 2022;386:1505-18.

97. O'Byrne PM, Bisgaard H, Godard PP, Pistolesi M, Palmqvist M, Zhu Y, *et al*. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. Am J Respir Crit Care Med 2005;171:129-36.

98. Bateman ED, Reddel HK, O'Byrne PM, Barnes PJ, Zhong N, Keen C, *et al*. As-needed budesonide-formoterol versus maintenance budesonide in mild asthma. N Engl J Med 2018;378:1877-87.

99. O'Byrne PM, FitzGerald JM, Bateman ED, Barnes PJ, Zhong N, Keen C, *et al*. Inhaled combined budesonide-formoterol as needed in mild asthma. N Engl J Med 2018;378:1865-76.

100. Beasley R, Holliday M, Reddel HK, Braithwaite I, Ebmeier S, Hancox RJ, *et al*. Controlled trial of budesonide-formoterol as needed for mild asthma. N Engl J Med 2019;380:2020-30.

101. Turner MO, Noertjojo K, Vedal S, Bai T, Crump S, Fitzgerald JM. Risk factors for near-fatal asthma. A case-control study in hospitalized patients with asthma. Am J Respir Crit Care Med 1998;157:1804-9.

102. Graff S, Demarche S, Henket M, Paulus V, Louis R, Schleich F. Increase in blood eosinophils during follow-up is associated with lung function decline in adult asthma. Respir Med 2019;152:60-6.

103. Pols DH, Wartna JB, Moed H, van Alphen EI, Bohnen AM, Bindels PJ. Atopic dermatitis, asthma and allergic rhinitis in general practice and the open population: A systematic review. Scand J Prim Health Care 2016;34:143-50.

104. Lee J, Tay TR, Radhakrishna N, Hore-Lacy F, Mackay A, Hoy R, *et al*. Nonadherence in the era of severe asthma biologics and thermoplasty. Eur Respir J 2018;51:1-10.

105. van Boven JF, Koponen M, Lalic S, George J, Bell JS, Hew M, *et al*. Trajectory analyses of adherence patterns in a real-life moderate to severe asthma population. J Allergy Clin Immunol Pract 2020;8:1961-9.e6.

106. Singh D, Garcia G, Maneechotesuwan K, Daley-Yates P, Irusen E, Aggarwal B, *et al*. New versus old: The impact of changing patterns of inhaled corticosteroid prescribing and dosing regimens in

asthma management. Adv Ther 2022;39:1895-914.

107. Cloutier MM, Salo PM, Akinbami LJ, Cohn RD, Wilkerson JC, Diette GB, *et al*. Clinician agreement, self-efficacy, and adherence with the guidelines for the diagnosis and management of asthma. J Allergy Clin Immunol Pract 2018;6:886-94.e4.

108. Stanford RH, Averell C, Parker ED, Blauer-Peterson C, Reinsch TK, Buikema AR. Assessment of adherence and asthma medication ratio for a once-daily and twice-daily inhaled corticosteroid/long-acting β-agonist for asthma. J Allergy Clin Immunol Pract 2019;7:1488-96.e7.

109. Noibi S, Mohy A, Gouhar R, Shaker F, Lukic T, Al-Jahdali H. Asthma control factors in the Gulf Cooperation Council (GCC) countries and the effectiveness of ICS/LABA fixed dose combinations: A dual rapid literature review. BMC Public Health 2020;20:1211.

110. Janežič A, Locatelli I, Kos M. Inhalation technique and asthma outcomes with different corticosteroid-containing inhaler devices. J Asthma 2020;57:654-62.

111. Hussain FN, Paravattil B. Assessment of educational inhaler technique interventions among community pharmacists: A systematic review. Integr Pharm Res Pract 2020;9:23-31.

112. Al-Jahdali H, Wali S, Salem G, Al-Hameed F, Almotair A, Zeitouni M, *et al*. Asthma control and predictive factors among adults in Saudi Arabia: Results from the epidemiological study on the management of asthma in asthmatic Middle East adult population study. Ann Thorac Med 2019;14:148-54.

113. Musharrafieh U, Tamim H, Houry R, AlBuhairan F. A nationwide study of asthma correlates among adolescents in Saudi Arabia. Asthma Res Pract 2020;6:3.

114. Hardy J, Baggott C, Fingleton J, Reddel HK, Hancox RJ, Harwood M, *et al*. Budesonide-formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRACTICAL): A 52-week, open-label, multicentre, superiority, randomised controlled trial. Lancet 2019;394:919-28.

115. Martinez FD, Chinchilli VM, Morgan WJ, Boehmer SJ, Lemanske RF Jr., Mauger DT, *et al*. Use of beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA): A randomised, double-blind, placebo-controlled trial. Lancet 2011;377:650-7.

116. Sumino K, Bacharier LB, Taylor J, Chadwick-Mansker K, Curtis V, Nash A, *et al*. A pragmatic trial of symptom-based inhaled corticosteroid use in African-American children with mild asthma. J Allergy Clin Immunol Pract 2020;8:176-85.e2.

117. Selroos O. Effect of disease duration on dose-response of inhaled budesonide in asthma. Respir Med 2008;102:1065-72.

118. Qazi A, Armour C, Saini B. Perspectives of general practitioners about a collaborative asthma care model in primary care. J Asthma 2021;58:1648-60.

119. Pauwels RA, Pedersen S, Busse WW, Tan WC, Chen YZ, Ohlsson SV, *et al*. Early intervention with budesonide in mild persistent asthma: A randomised, double-blind trial. Lancet 2003;361:1071-6.

120. Powell H, Gibson PG. Initial starting dose of inhaled corticosteroids in adults with asthma: A systematic review. Thorax 2004;59:1041-5.

121. Sharma S, Harish R, Dutt N, Digra KK. To evaluate the efficacy of nebulized budesonide compared to oral prednisolone in the management of moderate exacerbation of acute asthma. Int J Contemp Pediatr 2017;4:1278-83.

122. Sont JK. How do we monitor asthma control? Allergy 1999;54 Suppl 49:68-73.

123. O'Byrne PM, Jenkins C, Bateman ED. The paradoxes of asthma management: Time for a new approach? Eur Respir J 2017;50:1-12.

124. Asthma GIF. The Global Strategy for Asthma Management and Prevention; 2020. Available from: www.ginasthma.org. [Last accessed on 2023 16 Sep].

125. Fingleton J, Hardy J, Baggott C, Pilcher J, Corin A, Hancox RJ, *et al*. Description of the protocol for the PRACTICAL study: A randomised controlled trial of the efficacy and safety of

ICS/LABA reliever therapy in asthma. BMJ Open Respir Res 2017;4:e000217.

126. Reddel HK, Busse WW, Pedersen S, Tan WC, Chen YZ, Jorup C, *et al*. Should recommendations about starting inhaled corticosteroid treatment for mild asthma be based on symptom frequency: A *post-hoc* efficacy analysis of the START study. Lancet 2017;389:157-66.

127. Dusser D, Montani D, Chanez P, de Blic J, Delacourt C, Deschildre A, *et al*. Mild asthma: An expert review on epidemiology, clinical characteristics and treatment recommendations. Allergy 2007;62:591-604.

128. Pauwels RA, Löfdahl CG, Postma DS, Tattersfield AE, O'Byrne P, Barnes PJ, *et al*. Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group. N Engl J Med 1997;337:1405-11.

129. Bateman ED, Bousquet J, Keech ML, Busse WW, Clark TJ, Pedersen SE. The correlation between asthma control and health status: The GOAL study. Eur Respir J 2007;29:56-62.

130. Singh D, Oosterholt S, Pavord I, Garcia G, Abhijith Pg, Della Pasqua O. Understanding the clinical implications of individual patient characteristics and treatment choice on the risk of exacerbation in asthma patients with moderate-severe symptoms. Adv Ther 2023;40:4606-25.

131. Cates CJ, Schmidt S, Ferrer M, Sayer B, Waterson S. Inhaled steroids with and without regular salmeterol for asthma: Serious adverse events. Cochrane Database Syst Rev 2018;12:CD006922.

132. Busse WW, Bateman ED, Caplan AL, Kelly HW, O'Byrne PM, Rabe KF, *et al*. Combined analysis of asthma safety trials of long-acting β(2)-agonists. N Engl J Med 2018;378:2497-505.

133. Zeiger RS, Szefler SJ, Phillips BR, Schatz M, Martinez FD, Chinchilli VM, *et al*. Response profiles to fluticasone and montelukast in mild-to-moderate persistent childhood asthma. J Allergy Clin Immunol 2006;117:45-52.

134. Vaquerizo MJ, Casan P, Castillo J, Perpiña M, Sanchis J, Sobradillo V, *et al*. Effect of montelukast added to inhaled budesonide on control of mild to moderate asthma. Thorax 2003;58:204-10.

135. Joos S, Miksch A, Szecsenyi J, Wieseler B, Grouven U, Kaiser T, *et al*. Montelukast as add-on therapy to inhaled corticosteroids in the treatment of mild to moderate asthma: A systematic review. Thorax 2008;63:453-62.

136. Szefler SJ, Martin RJ, King TS, Boushey HA, Cherniack RM, Chinchilli VM, *et al*. Significant variability in response to inhaled corticosteroids for persistent asthma. J Allergy Clin Immunol 2002;109:410-8.

137. Powell H, Gibson PG. Inhaled corticosteroid doses in asthma: An evidence-based approach. Med J Aust 2003;178:223-5.

138. Kerstjens HA, van den Berge M. Regular treatment for moderate asthma: Guidelines hold true. Lancet Respir Med 2015;3:88-9.

139. Beeh KM, Moroni-Zentgraf P, Ablinger O, Hollaenderova Z, Unseld A, Engel M, *et al*. Tiotropium Respimat® in asthma: A double-blind, randomised, dose-ranging study in adult patients with moderate asthma. Respir Res 2014;15:61.

140. Tian JW, Chen JW, Chen R, Chen X. Tiotropium versus placebo for inadequately controlled asthma: A meta-analysis. Respir Care 2014;59:654-66.

141. Sobieraj DM, Baker WL, Nguyen E, Weeda ER, Coleman CI, White CM, *et al*. Association of inhaled corticosteroids and long-acting muscarinic antagonists with asthma control in patients with uncontrolled, persistent asthma: A systematic review and meta-analysis. JAMA 2018;319:1473-84.

142. Peters SP, Kunselman SJ, Icitovic N, Moore WC, Pascual R, Ameredes BT, *et al*. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. N Engl J Med 2010;363:1715-26.

143. Bateman ED, Kornmann O, Schmidt P, Pivovarova A, Engel M, Fabbri LM. Tiotropium is noninferior to salmeterol in maintaining

improved lung function in B16-Arg/Arg patients with asthma. J Allergy Clin Immunol 2011;128:315-22.

144. Smith LJ. Anticholinergics for patients with asthma? N Engl J Med 2010;363:1764-5.

145. Chowdhury BA, Dal Pan G. The FDA and safe use of long-acting beta-agonists in the treatment of asthma. N Engl J Med 2010;362:1169-71.

146. Koshak EA. New FDA safety warnings for LABAs: A call for asthma guidelines revisit for solo beta agonist. Ann Thorac Med 2010;5:65-6.

147. O'Byrne PM, Bleecker ER, Bateman ED, Busse WW, Woodcock A, Forth R, *et al*. Once-daily fluticasone furoate alone or combined with vilanterol in persistent asthma. Eur Respir J 2014;43:773-82.

148. Woodcock A, Bleecker ER, Lötvall J, O'Byrne PM, Bateman ED, Medley H, *et al*. Efficacy and safety of fluticasone furoate/vilanterol compared with fluticasone propionate/salmeterol combination in adult and adolescent patients with persistent asthma: A randomized trial. Chest 2013;144:1222-9.

149. Gon Y, Ishii T, Lawrence D, Nikolaev I, Wang D, Sumi K, *et al*. Once-daily, single-inhaler indacaterol/mometasone versus twice-daily salmeterol/fluticasone in Asian patients with inadequately controlled asthma: *Post hoc* pooled analysis from PALLADIUM and IRIDIUM studies. J Asthma 2022;59:1627-37.

150. van Zyl-Smit RN, Krüll M, Gessner C, Gon Y, Noga O, Richard A, *et al*. Once-daily mometasone plus indacaterol versus mometasone or twice-daily fluticasone plus salmeterol in patients with inadequately controlled asthma (PALLADIUM): A randomised, double-blind, triple-dummy, controlled phase 3 study. Lancet Respir Med 2020;8:987-99.

151. Kerstjens HAM, Maspero J, Chapman KR, van Zyl-Smit RN, Hosoe M, Tanase AM, *et al*. Once-daily, single-inhaler mometasone-indacaterol-glycopyrronium versus mometasone-indacaterol or twice-daily fluticasone-salmeterol in patients with inadequately controlled asthma (IRIDIUM): A randomised, double-blind, controlled phase 3 study. Lancet Respir Med 2020;8:1000-12.

152. Al-Moamary MS, Al-Lehebi R, Idrees MM, Zeitouni MO. When single-inhaler triple therapy is a preferred option in asthma management? Ann Thorac Med 2022;17:185-8.

153. Agusti A, Fabbri L, Lahousse L, Singh D, Papi A. Single inhaler triple therapy (SITT) in asthma: Systematic review and practice implications. Allergy 2022;77:1105-13.

154. Rogliani P, Ritondo BL, Calzetta L. Triple therapy in uncontrolled asthma: A network meta-analysis of phase III studies. Eur Respir J 2021;58:2004233.

155. Lee LA, Bailes Z, Barnes N, Boulet LP, Edwards D, Fowler A, *et al*. Efficacy and safety of once-daily single-inhaler triple therapy (FF/UMEC/VI) versus FF/VI in patients with inadequately controlled asthma (CAPTAIN): A double-blind, randomised, phase 3A trial. Lancet Respir Med 2021;9:69-84.

156. Bogart M, Germain G, Laliberté F, Mahendran M, Duh MS. Real-world impact of triple therapy with fluticasone furoate, umeclidinium, and vilanterol on asthma control among US patients with asthma. Chest 2022;162:A1930.

157. Sagara H, Barbier N, Ishii T, Yoshisue H, Nikolaev I, Hosoe M, *et al*. Efficacy of one time per day, single-inhaler indacaterol/glycopyrronium/mometasone in patients with inadequately controlled asthma: *Post hoc* analysis of IRIDIUM study in Asian population. BMJ Open Respir Res 2021;8:e000856.

158. Virchow JC, Kuna P, Paggiaro P, Papi A, Singh D, Corre S, *et al*. Single inhaler extrafine triple therapy in uncontrolled asthma (TRIMARAN and TRIGGER): Two double-blind, parallel-group, randomised, controlled phase 3 trials. Lancet 2019;394:1737-49.

159. Kerstjens HA, Disse B, Schröder-Babo W, Bantje TA, Gahlemann M, Sigmund R, *et al*. Tiotropium improves lung function in patients with severe uncontrolled asthma: A randomized controlled trial. J Allergy Clin Immunol 2011;128:308-14.

160. Kerstjens HA, Engel M, Dahl R, Paggiaro P, Beck E, Vandewalker M, *et al*. Tiotropium in asthma poorly controlled with standard combination therapy. N Engl J Med 2012;367:1198-207.

161. Rodrigo GJ, Neffen H. Efficacy and safety of tiotropium in school-age children with moderate-to-severe symptomatic asthma: A systematic review. Pediatr Allergy Immunol 2017;28:573-8.

162. American Lung Association Asthma Clinical Research Centers. Clinical trial of low-dose theophylline and montelukast in patients with poorly controlled asthma. Am J Respir Crit Care Med 2007;175:235-42.

163. Price DB, Hernandez D, Magyar P, Fiterman J, Beeh KM, James IG, *et al*. Randomised controlled trial of montelukast plus inhaled budesonide versus double dose inhaled budesonide in adult patients with asthma. Thorax 2003;58:211-6.

164. FDA U. FDA Requires Boxed Warning about Serious Mental Health Side Effects for Asthma and Allergy Drug Montelukast (Singulair); Advises Restricting Use for Allergic Rhinitis; 2020. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-boxed-warning-about-serious-mental-health-side-effects-asthma-and-allergy-drug#:~:text=We%20are%20requiring%20a%20Boxed,treated%20effectively%20with%20or%20cannot. [Last accessed on 2023 Aug 29].

165. Kearns N, Maijers I, Harper J, Beasley R, Weatherall M. inhaled corticosteroids in acute asthma: A systemic review and meta-analysis. J Allergy Clin Immunol Pract 2020;8:605-17.e6.

166. Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, *et al*. Can guideline-defined asthma control be achieved? The gaining optimal asthma control study. Am J Respir Crit Care Med 2004;170:836-44.

167. Pitlick MM, Pongdee T. Combining biologics targeting eosinophils (IL-5/IL-5R), IgE, and IL-4/IL-13 in allergic and inflammatory diseases. World Allergy Organ J 2022;15:100707.

168. Hamada S, Ogino E, Yasuba H. Cycling biologic therapy for severe asthma. Pulmonology 2022;28:65-7.

169. Al-Shimemeri A, Al-Ghadeer H, Giridhar H, Al-Jahdali M, Al-Moamary M, Khan J. Impact of an extensive Asthma education campaign for physicians on their drug prescription practices. Ann Thorac Med 2006;1:20-5.

170. Ignacio-Garcia JM, Gonzalez-Santos P. Asthma self-management education program by home monitoring of peak expiratory flow. Am J Respir Crit Care Med 1995;151:353-9.

171. Hawkins G, McMahon AD, Twaddle S, Wood SF, Ford I, Thomson NC. Stepping down inhaled corticosteroids in asthma: Randomised controlled trial. BMJ 2003;326:1115.

172. Powell H, Gibson PG. High dose versus low dose inhaled corticosteroid as initial starting dose for asthma in adults and children. Cochrane Database Syst Rev 2004;2004:CD004109.

173. Boulet LP, Drollmann A, Magyar P, Timar M, Knight A, Engelstätter R, *et al*. Comparative efficacy of once-daily ciclesonide and budesonide in the treatment of persistent asthma. Respir Med 2006;100:785-94.

174. Rank MA, Hagan JB, Park MA, Podjasek JC, Samant SA, Volcheck GW, *et al*. The risk of asthma exacerbation after stopping low-dose inhaled corticosteroids: A systematic review and meta-analysis of randomized controlled trials. J Allergy Clin Immunol 2013;131:724-9.

175. Brozek JL, Kraft M, Krishnan JA, Cloutier MM, Lazarus SC, Li JT, *et al*. Long-acting β2-agonist step-off in patients with controlled asthma. Arch Intern Med 2012;172:1365-75.

176. Masoli M, Weatherall M, Holt S, Beasley R. Budesonide once versus twice-daily administration: Meta-analysis. Respirology 2004;9:528-34.

177. Bateman ED, Fairall L, Lombardi DM, English R. Budesonide/formoterol and formoterol provide similar rapid relief in patients with acute asthma showing refractoriness to salbutamol. Respir Res 2006;7:13.

178. Randell TL, Donaghue KC, Ambler GR, Cowell CT, Fitzgerald DA, van Asperen PP. Safety of the newer inhaled

corticosteroids in childhood asthma. Paediatr Drugs 2003;5:481-504.

179. Bölke G, Tong X, Zuberbier T, Bousquet J, Bergmann KC. Extension of mepolizumab injection intervals as potential of saving costs in well controlled patients with severe eosinophilic asthma. World Allergy Organ J 2022;15:100703.

180. Domingo C, Pomares X, Navarro A, Amengual MJ, Montón C, Sogo A, *et al*. A step-down protocol for omalizumab treatment in oral corticosteroid-dependent allergic asthma patients. Br J Clin Pharmacol 2018;84:339-48.

181. Currie GP, Douglas JG, Heaney LG. Difficult to treat asthma in adults. BMJ 2009;338:b494.

182. Brożek JL, Bousquet J, Agache I, Agarwal A, Bachert C, Bosnic-Anticevich S, *et al*. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines-2016 revision. J Allergy Clin Immunol 2017;140:950-8.

183. Sullivan SD, Rasouliyan L, Russo PA, Kamath T, Chipps BE, TENOR Study Group. Extent, patterns, and burden of uncontrolled disease in severe or difficult-to-treat asthma. Allergy 2007;62:126-33.

184. Serra-Batlles J, Plaza V, Morejón E, Comella A, Brugués J. Costs of asthma according to the degree of severity. Eur Respir J 1998;12:1322-6.

185. Chen H, Blanc PD, Hayden ML, Bleecker ER, Chawla A, Lee JH, *et al*. Assessing productivity loss and activity impairment in severe or difficult-to-treat asthma. Value Health 2008;11:231-9.

186. Tiwari A, Guglani V, Jat KR. Ketamine versus aminophylline for acute asthma in children: A randomized, controlled trial. Ann Thorac Med 2016;11:283-8.

187. Asthma GIF. The Global Strategy for Asthma Management and Prevention; 2020.

188. Porsbjerg C, Ulrik C, Skjold T, Backer V, Laerum B, Lehman S, *et al*. Nordic consensus statement on the systematic assessment and management of possible severe asthma in adults. Eur Clin Respir J 2018;5:1-13.

189. Lee JH, Haselkorn T, Borish L, Rasouliyan L, Chipps BE, Wenzel SE. Risk factors associated with persistent airflow limitation in severe or difficult-to-treat asthma: Insights from the TENOR study. Chest 2007;132:1882-9.

190. Sturdy PM, Victor CR, Anderson HR, Bland JM, Butland BK, Harrison BD, *et al*. Psychological, social and health behaviour risk factors for deaths certified as asthma: A national case-control study. Thorax 2002;57:1034-9.

191. Butler C, Heaney LG. Risk factors of frequent exacerbations in difficult-to-treat asthma. Eur Respir J 2006;27:1324-5.

192. Gaga M, Papageorgiou N, Yiourgioti G, Karydi P, Liapikou A, Bitsakou H, *et al*. Risk factors and characteristics associated with severe and difficult to treat asthma phenotype: An analysis of the ENFUMOSA group of patients based on the ECRHS questionnaire. Clin Exp Allergy 2005;35:954-9.

193. Sullivan SD, Wenzel SE, Bresnahan BW, Zheng B, Lee JH, Pritchard M, *et al*. Association of control and risk of severe asthma-related events in severe or difficult-to-treat asthma patients. Allergy 2007;62:655-60.

194. Robinson DS, Campbell DA, Durham SR, Pfeffer J, Barnes PJ, Chung KF, *et al*. Systematic assessment of difficult-to-treat asthma. Eur Respir J 2003;22:478-83.

195. Natarajan S, Subramanian P. Allergic bronchopulmonary aspergillosis: A clinical review of 24 patients: Are we right in frequent serologic monitoring? Ann Thorac Med 2014;9:216-20.

196. Jani AL, Hamilos DL. Current thinking on the relationship between rhinosinusitis and asthma. J Asthma 2005;42:1-7.

197. Koczulla AR, Vogelmeier CF, Garn H, Renz H. New concepts in asthma: Clinical phenotypes and pathophysiological mechanisms. Drug Discov Today 2017;22:388-96.

198. Saji J, Arai M, Yamamoto T, Mineshita M, Miyazawa T. Efficacy of omalizumab in patients with severe asthma using the asthma health questionnaire and asthma control test. Arerugi 2014;63:1338-47.

199. Storms W, Bowdish MS, Farrar JR. Omalizumab and asthma control in patients with moderate-to-severe allergic asthma: A 6-year pragmatic data review. Allergy Asthma Proc 2012;33:172-7.

200. Bousquet J, Brusselle G, Buhl R, Busse WW, Cruz AA, Djukanovic R, *et al*. Care pathways for the selection of a biologic in severe asthma. Eur Respir J 2017;50:1-9.

201. Heaney LG, Brightling CE, Menzies-Gow A, Stevenson M, Niven RM, British Thoracic Society Difficult Asthma Network. Refractory asthma in the UK: Cross-sectional findings from a UK multicentre registry. Thorax 2010;65:787-94.

202. Adcock IM, Lane SJ, Brown CR, Peters MJ, Lee TH, Barnes PJ. Differences in binding of glucocorticoid receptor to DNA in steroid-resistant asthma. J Immunol 1995;154:3500-5.

203. Barnes PJ. Corticosteroid resistance in airway disease. Proc Am Thorac Soc 2004;1:264-8.

204. Ayres JG. Pseudo-steroid resistant asthma. Thorax 1999;54:956.

205. Campbell JD, Blough DK, Sullivan SD. Comparison of guideline-based control definitions and associations with outcomes in severe or difficult-to-treat asthma. Ann Allergy Asthma Immunol 2008;101:474-81.

206. Gibson PG, Yang IA, Upham JW, Reynolds PN, Hodge S, James AL, *et al*. Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): A randomised, double-blind, placebo-controlled trial. Lancet 2017;390:659-68.

207. Hiles SA, McDonald VM, Guilhermino M, Brusselle GG, Gibson PG. Does maintenance azithromycin reduce asthma exacerbations? An individual participant data meta-analysis. Eur Respir J 2019;54:1901381.

208. Cox L, Nelson H, Lockey R, Calabria C, Chacko T, Finegold I, *et al*. Allergen immunotherapy: A practice parameter third update. J Allergy Clin Immunol 2011;127:S1-55.

209. Dhami S, Kakourou A, Asamoah F, Agache I, Lau S, Jutel M, *et al*. Allergen immunotherapy for allergic asthma: A systematic review and meta-analysis. Allergy 2017;72:1825-48.

210. Dominguez-Ortega J, Delgado J, Blanco C, Prieto L, Arroabarren E, Cimarra M, *et al*. Specific allergen immunotherapy for the treatment of allergic asthma: A review of current evidence. J Investig Allergol Clin Immunol 2017;27:1-35.

211. Demoly P, Makatsori M, Casale TB, Calderon MA. The potential role of allergen immunotherapy in stepping down asthma treatment. J Allergy Clin Immunol Pract 2017;5:640-8.

212. Jacobsen L, Niggemann B, Dreborg S, Ferdousi HA, Halken S, Høst A, *et al*. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. Allergy 2007;62:943-8.

213. Rice JL, Diette GB, Suarez-Cuervo C, Brigham EP, Lin SY, Ramanathan M, *et al*. Allergen-specific immunotherapy in the treatment of pediatric asthma: A systematic review. Pediatrics 2018;141(5).

214. Elliott J, Kelly SE, Johnston A, Skidmore B, Gomes T, Wells GA. Allergen immunotherapy for the treatment of allergic rhinitis and/or asthma: An umbrella review. CMAJ Open 2017;5:E373-85.

215. Abramson MJ, Bailey MJ, Couper FJ, Driver JS, Drummer OH, Forbes AB, *et al*. Are asthma medications and management related to deaths from asthma? Am J Respir Crit Care Med 2001;163:12-8.

216. Omachi TA, Iribarren C, Sarkar U, Tolstykh I, Yelin EH, Katz PP, *et al*. Risk factors for death in adults with severe asthma. Ann Allergy Asthma Immunol 2008;101:130-6.

217. Plaza V, Serrano J, Picado C, Sanchis J, High Risk Asthma Research Group. Frequency and clinical characteristics of rapid-onset fatal and near-fatal asthma. Eur Respir J 2002;19:846-52.

218. Dharmage SC, Perret JL, Custovic A. Epidemiology of asthma in children and adults. Front Pediatr 2019;7:246.

219. Suruki RY, Daugherty JB, Boudiaf N, Albers FC. The frequency of asthma exacerbations and healthcare utilization in patients with asthma from the UK and USA. BMC Pulm Med 2017;17:74.

220. Alahmadi TS, Banjari MA, Alharbi AS. The prevalence of childhood asthma in Saudi Arabia. Int J Pediatr Adolesc Med 2019;6:74-7.

221. Ali F, Behbehani N, Alomair N, Taher A. Fatal and near-fatal thunderstorm asthma epidemic in a desert country. Ann Thorac Med 2019;14:155-60.

222. Serrano-Pariente J, Plaza V. Near-fatal asthma: A heterogeneous clinical entity. Curr Opin Allergy Clin Immunol 2017;17:28-35.

223. D'Amato G, Vitale C, Lanza M, Sanduzzi A, Molino A, Mormile M, *et al.* Near fatal asthma: treatment and prevention. Eur Ann Allergy Clin Immunol 2016;48:116-22.

224. Al-Dorzi HM, Al-Shammary HA, Al-Shareef SY, Tamim HM, Shammout K, Al Dawood A, *et al.* Risk factors, management and outcomes of patients admitted with near fatal asthma to a tertiary care hospital in Riyadh. Ann Thorac Med 2014;9:33-8.

225. Fergeson JE, Patel SS, Lockey RF. Acute asthma, prognosis, and treatment. J Allergy Clin Immunol 2017;139:438-47.

226. Al-Dawood KM. Pattern and risk factors associated with hospital emergency visits among schoolboys with bronchial asthma in Al-Khobar. Ann Saudi Med 2002;22:29-33.

227. Crane J, Burgess CD, Graham AN, Maling TJ. Hypokalaemic and electrocardiographic effects of aminophylline and salbutamol in obstructive airways disease. N Z Med J 1987;100:309-11.

228. Hessel PA, Mitchell I, Tough S, Green FH, Cockcroft D, Kepron W, *et al.* Risk factors for death from asthma. Prairie provinces asthma study group. Ann Allergy Asthma Immunol 1999;83:362-8.

229. Bai TR, Cooper J, Koelmeyer T, Paré PD, Weir TD. The effect of age and duration of disease on airway structure in fatal asthma. Am J Respir Crit Care Med 2000;162:663-9.

230. Cates CJ, Crilly JA, Rowe BH. Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma. Cochrane Database Syst Rev 2006:CD000052. https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD000052.pub3/full#.

231. Gates GG, Bara A, Grilly AJ, Rowe BH. Holding chamber versus nebulisers for beta-agonist treatment of acute asthma (Cochrane Review). The Cochrane Library 2003(3).

232. Rossing TH, Fanta CH, Goldstein DH, Snapper JR, McFadden ER Jr. Emergency therapy of asthma: Comparison of the acute effects of parenteral and inhaled sympathomimetics and infused aminophylline. Am Rev Respir Dis 1980;122:365-71.

233. Rowe BH, Spooner C, Ducharme FM, Bretzlaff JA, Bota GW. Early emergency department treatment of acute asthma with systemic corticosteroids. Cochrane Database Syst Rev 2001:CD002178. https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD002178/abstract.

234. Rowe BH, Spooner C, Ducharme F, Bretzlaff J, Bota G, Group CA. Early emergency department treatment of acute asthma with systemic corticosteroids. Cochrane Database of Systematic Reviews 1996;2010.

235. Vinayak AG, Kress J, Hall J. Pharmacotherapy in the emergency department, hospital floor, and intensive care unit. Lung Biol Health Dis 2005;212:351.

236. O'Driscoll BR, Howard LS, Davison AG, British Thoracic Society. BTS guideline for emergency oxygen use in adult patients. Thorax 2008;63 Suppl 6:i1-68.

237. Chien JW, Ciufo R, Novak R, Skowronski M, Nelson J, Coreno A, *et al.* Uncontrolled oxygen administration and respiratory failure in acute asthma. Chest 2000;117:728-33.

238. Douglas JG, Rafferty P, Fergusson RJ, Prescott RJ, Crompton GK, Grant IW. Nebulised salbutamol without oxygen in severe acute asthma: How effective and how safe? Thorax 1985;40:180-3.

239. Lanes SF, Garrett JE, Wentworth CE 3rd, Fitzgerald JM, Karpel JP. The effect of adding ipratropium bromide to salbutamol in the treatment of acute asthma: A pooled analysis of three trials. Chest 1998;114:365-72.

240. Chassany O, Fullerton S. Meta-analysis of the effects of ipratropium bromide in adults with acute asthma. Am J Med 2000;108:596-7.

241. Rodrigo G, Rodrigo C, Burschtin O. A meta-analysis of the effects of ipratropium bromide in adults with acute asthma. Am J Med 1999;107:363-70.

242. Stoodley RG, Aaron SD, Dales RE. The role of ipratropium bromide in the emergency management of acute asthma exacerbation: A metaanalysis of randomized clinical trials. Ann Emerg Med 1999;34:8-18.

243. Jackson DJ, Bacharier LB, Mauger DT, Boehmer S, Beigelman A, Chmiel JF, *et al.* Quintupling inhaled glucocorticoids to prevent childhood asthma exacerbations. N Engl J Med 2018;378:891-901.

244. Kirkland SW, Vandenberghe C, Voaklander B, Nikel T, Campbell S, Rowe BH. Combined inhaled beta-agonist and anticholinergic agents for emergency management in adults with asthma. Cochrane Database Syst Rev 2017;1:CD001284.

245. Menzies-Gow A, Busse WW, Castro M, Jackson DJ. Prevention and treatment of asthma exacerbations in adults. J Allergy Clin Immunol Pract 2021;9:2578-86.

246. Rowe BH, Spooner CH, Ducharme FM, Bretzlaff JA, Bota GW. Corticosteroids for preventing relapse following acute exacerbations of asthma. Cochrane Database Syst Rev 2007CD000195.

247. Camargo C, Rowe B, Bourdon C, Blitz S, Bretzlaff J, Bota G. Magnesium sulfate for treating exacerbations of acute asthma in the emergency department. Cochrane Database Syst Rev 2000;2000:CD001490.

248. Kew KM, Kirtchuk L, Michell CI. Intravenous magnesium sulfate for treating adults with acute asthma in the emergency department. Cochrane Database Syst Rev 2014CD010909.

249. Shrestha M, Bidadi K, Gourlay S, Hayes J. Continuous versus intermittent albuterol, at high and low doses, in the treatment of severe acute asthma in adults. Chest 1996;110:42-7.

250. Camargo CA Jr., Rachelefsky G, Schatz M. Managing asthma exacerbations in the emergency department: Summary of the National Asthma Education and Prevention Program Expert Panel Report 3 guidelines for the management of asthma exacerbations. Proc Am Thorac Soc 2009;6:357-66.

251. Rowe BH, Spooner C, Ducharme F, Bretzlaff J, Bota G, Group CA. Early emergency department treatment of acute asthma with systemic corticosteroids. Cochrane Database Syst Rev 1996;2010.

252. Tokuda Y, Miyagi S. Oxygen treatment for acute severe asthma. Home oxygenation would be more effective. BMJ 2001;323:1069.

253. Havemann BD, Henderson CA, El-Serag HB. The association between gastro-oesophageal reflux disease and asthma: A systematic review. Gut 2007;56:1654-64.

254. Houghton LA, Lee AS, Badri H, DeVault KR, Smith JA. Respiratory disease and the oesophagus: Reflux, reflexes and microaspiration. Nat Rev Gastroenterol Hepatol 2016;13:445-60.

255. Asano K, Suzuki H. Silent acid reflux and asthma control. N Engl J Med 2009;360:1551-3.

256. Kopsaftis Z, Yap HS, Tin KS, Hnin K, Carson-Chahhoud KV. Pharmacological and surgical interventions for the treatment of gastro-oesophageal reflux in adults and children with asthma. Cochrane Database Syst Rev 2021;5:CD001496.

257. Zheng Z, Luo Y, Li J, Gao J. Randomised trials of proton pump inhibitors for gastro-oesophageal reflux disease in patients with asthma: An updated systematic review and meta-analysis. BMJ Open 2021;11:e043860.

258. Cruz AA, Popov T, Pawankar R, Annesi-Maesano I, Fokkens W, Kemp J, *et al.* Common characteristics of upper and lower airways in rhinitis and asthma: ARIA update, in collaboration with GA(2) LEN. Allergy 2007;62 Suppl 84:1-41.

259. Corren J, Manning BE, Thompson SF, Hennessy S, Strom BL. Rhinitis therapy and the prevention of hospital care for asthma: A case-control study. J Allergy Clin Immunol 2004;113:415-9.

260. American Lung Association–Asthma Clinical Research Centers' Writing Committee, Dixon AE, Castro M, Cohen RI, Gerald LB, Holbrook JT, *et al*. Efficacy of nasal mometasone for the treatment of chronic sinonasal disease in patients with inadequately controlled asthma. J Allergy Clin Immunol 2015;135:701- 9.e5.

261. Gill AS, Alt JA, Detwiller KY, Rowan NR, Gray ST, Hellings PW, *et al*. Management paradigms for chronic rhinosinusitis in individuals with asthma: An evidence-based review with recommendations. Int Forum Allergy Rhinol 2023;13:1758-82.

262. Peters U, Dixon AE, Forno E. Obesity and asthma. J Allergy Clin Immunol 2018;141:1169-79.

263. Scott HA, Ng SH, McLoughlin RF, Valkenborghs SR, Nair P, Brown AC, *et al*. Effect of obesity on airway and systemic inflammation in adults with asthma: A systematic review and meta-analysis. Thorax 2023;78:957-65.

264. Saint-Pierre P, Bourdin A, Chanez P, Daures JP, Godard P. Are overweight asthmatics more difficult to control? Allergy 2006;61:79-84.

265. Desai AG, Togias A, Schechter C, Fisher B, Parow A, Skloot G. Peripheral airways dysfunction in obesity reflects increased bronchomotor tone. J Allergy Clin Immunol 2015;135:820-2.

266. Scott HA, Gibson PG, Garg ML, Pretto JJ, Morgan PJ, Callister R, *et al*. Dietary restriction and exercise improve airway inflammation and clinical outcomes in overweight and obese asthma: A randomized trial. Clin Exp Allergy 2013;43:36-49.

267. Moreira A, Bonini M, Garcia-Larsen V, Bonini S, Del Giacco SR, Agache I, *et al*. Weight loss interventions in asthma: EAACI evidence-based clinical practice guideline (part I). Allergy 2013;68:425-39.

268. Boulet LP, Turcotte H, Martin J, Poirier P. Effect of bariatric surgery on airway response and lung function in obese subjects with asthma. Respir Med 2012;106:651-60.

269. Cao Y, Lin SH, Zhu D, Xu F, Chen ZH, Shen HH, *et al*. WeChat public account use improves clinical control of cough-variant asthma: A randomized controlled trial. Med Sci Monit 2018;24:1524-32.

270. Achilleos A. Evidence-based evaluation and management of chronic cough. Med Clin North Am 2016;100:1033-45.

271. Morice AH, McGarvey L, Pavord I, British Thoracic Society Cough Guideline Group. Recommendations for the management of cough in adults. Thorax 2006;61 Suppl 1:i1-24.

272. Spector SL, Tan RA. Effectiveness of montelukast in the treatment of cough variant asthma. Ann Allergy Asthma Immunol 2004;93:232-6.

273. Desai D, Brightling C. Cough due to asthma, cough-variant asthma and non-asthmatic eosinophilic bronchitis. Otolaryngol Clin North Am 2010;43:123-30, x.

274. Diver S, Russell RJ, Brightling CE. Cough and eosinophilia. J Allergy Clin Immunol Pract 2019;7:1740-7.

275. Weiler JM, Brannan JD, Randolph CC, Hallstrand TS, Parsons J, Silvers W, *et al*. Exercise-induced bronchoconstriction update-2016. J Allergy Clin Immunol 2016;138:1292-5.e36.

276. Dreßler M, Friedrich T, Lasowski N, Herrmann E, Zielen S, Schulze J. Predictors and reproducibility of exercise-induced bronchoconstriction in cold air. BMC Pulm Med 2019;19:94.

277. Parsons JP, Hallstrand TS, Mastronarde JG, Kaminsky DA, Rundell KW, Hull JH, *et al*. An official American Thoracic Society clinical practice guideline: Exercise-induced bronchoconstriction. Am J Respir Crit Care Med 2013;187:1016-27.

278. Lazarinis N, Jørgensen L, Ekström T, Bjermer L, Dahlén B, Pullerits T, *et al*. Combination of budesonide/formoterol on demand improves asthma control by reducing exercise-induced bronchoconstriction. Thorax 2014;69:130-6.

279. Laidlaw TM, Boyce JA. Aspirin-exacerbated respiratory disease – New prime suspects. N Engl J Med 2016;374:484-8.

280. Rajan JP, Wineinger NE, Stevenson DD, White AA. Prevalence of aspirin-exacerbated respiratory disease among asthmatic patients: A meta-analysis of the literature. J Allergy Clin Immunol 2015;135:676- 81.e1.

281. Morales DR, Guthrie B, Lipworth BJ, Jackson C, Donnan PT, Santiago VH. NSAID-exacerbated respiratory disease: A meta-analysis evaluating prevalence, mean provocative dose of aspirin and increased asthma morbidity. Allergy 2015;70:828-35.

282. Szczeklik A, Stevenson DD. Aspirin-induced asthma: Advances in pathogenesis, diagnosis, and management. J Allergy Clin Immunol 2003;111:913-21.

283. White AA, Stevenson DD. Aspirin-exacerbated respiratory disease. N Engl J Med 2018;379:1060-70.

284. Woessner KM, Simon RA, Stevenson DD. The safety of celecoxib in patients with aspirin-sensitive asthma. Arthritis Rheum 2002;46:2201-6.

285. Morales DR, Lipworth BJ, Guthrie B, Jackson C, Donnan PT, Santiago VH. Safety risks for patients with aspirin-exacerbated respiratory disease after acute exposure to selective nonsteroidal anti-inflammatory drugs and COX-2 inhibitors: Meta-analysis of controlled clinical trials. J Allergy Clin Immunol 2014;134:40-5.

286. Cahill KN, Boyce JA. Aspirin-exacerbated respiratory disease: Mediators and mechanisms of a clinical disease. J Allergy Clin Immunol 2017;139:764-6.

287. Park JS, Jang AS, Park SW, Lee YM, Uh ST, Kim YH, *et al*. Protection of leukotriene receptor antagonist against aspirin-induced bronchospasm in asthmatics. Allergy Asthma Immunol Res 2010;2:48-54.

288. Cohen JM, Bateman BT, Huybrechts KF, Mogun H, Yland J, Schatz M, *et al*. Poorly controlled asthma during pregnancy remains common in the United States. J Allergy Clin Immunol Pract 2019;7:2672-80.e10.

289. Bonham CA, Patterson KC, Strek ME. Asthma outcomes and management during pregnancy. Chest 2018;153:515-27.

290. Murphy VE, Clifton VL, Gibson PG. Asthma exacerbations during pregnancy: Incidence and association with adverse pregnancy outcomes. Thorax 2006;61:169-76.

291. Blais L, Kettani FZ, Forget A, Beauchesne MF, Lemière C. Asthma exacerbations during the first trimester of pregnancy and congenital malformations: Revisiting the association in a large representative cohort. Thorax 2015;70:647-52.

292. Murphy VE, Gibson PG, Smith R, Clifton VL. Asthma during pregnancy: Mechanisms and treatment implications. Eur Respir J 2005;25:731-50.

293. Holland SM, Thomson KD. Acute severe asthma presenting in late pregnancy. Int J Obstet Anesth 2006;15:75-8.

294. Hanania NA, Belfort MA. Acute asthma in pregnancy. Crit Care Med 2005;33:S319-24.

295. Lim A, Stewart K, König K, George J. Systematic review of the safety of regular preventive asthma medications during pregnancy. Ann Pharmacother 2011;45:931-45.

296. Pfaller B, José Yepes-Nuñez J, Agache I, Akdis CA, Alsalamah M, Bavbek S, *et al*. Biologicals in atopic disease in pregnancy: An EAACI position paper. Allergy 2021;76:71-89.

297. Namazy J, Cabana MD, Scheuerle AE, Thorp JM Jr., Chen H, Carrigan G, *et al*. The xolair pregnancy registry (EXPECT): The safety of omalizumab use during pregnancy. J Allergy Clin Immunol 2015;135:407-12.

298. Smy L, Chan AC, Bozzo P, Koren G. Is it safe to use inhaled corticosteroids in pregnancy? Can Fam Physician 2014;60:809-12, e433-5.

299. Rahimi R, Nikfar S, Abdollahi M. Meta-analysis finds use of inhaled corticosteroids during pregnancy safe: A systematic meta-analysis review. Hum Exp Toxicol 2006;25:447-52.

300. Gluck JC, Gluck PA. The effect of pregnancy on the course of asthma. Immunol Allergy Clin North Am 2006;26:63-80.

301. Sevelsted A, Stokholm J, Bisgaard H. Risk of asthma from cesarean delivery depends on membrane rupture. J Pediatr 2016;171:38-42.e1.

302. Vallera C, Choi LO, Cha CM, Hong RW. Uterotonic medications: Oxytocin, methylergonovine, carboprost, misoprostol. Anesthesiol Clin 2017;35:207-19.

303. Arora N, Mahajan K, Jana N, Maiti TK, Mandal D, Pandey R. Successful pregnancy outcome among women with end-stage renal disease requiring haemodialysis. J Indian Med Assoc 2009;107:237-8.

304. Levy ML, Nicholson PJ. Occupational asthma case finding: A role for primary care. Br J Gen Pract 2004;54:731-3.

305. Baur X, Aasen TB, Burge PS, Heederik D, Henneberger PK, Maestrelli P, *et al.* The management of work-related asthma guidelines: A broader perspective. Eur Respir Rev 2012;21:125-39.

306. Legiest B, Nemery B. Management of work-related asthma: Guidelines and challenges. Eur Respir Rev 2012;21:79-81.

307. Chang C, Sun Y. Global strategy for asthma management and prevention: Interpretation of the updates in 2022. Chin Gen Pract 2022;25:4355.

308. Barrecheguren M, Pinto L, Mostafavi-Pour-Manshadi SM, Tan WC, Li PZ, Aaron SD, *et al.* Identification and definition of asthma-COPD overlap: The CanCOLD study. Respirology 2020;25:836-49.

309. Andersén H, Lampela P, Nevanlinna A, Säynäjäkangas O, Keistinen T. High hospital burden in overlap syndrome of asthma and COPD. Clin Respir J 2013;7:342-6.

310. Kendzerska T, Aaron SD, To T, Licskai C, Stanbrook M, Vozoris NT, *et al.* Effectiveness and safety of inhaled corticosteroids in older individuals with chronic obstructive pulmonary disease and/or asthma. A population study. Ann Am Thorac Soc 2019;16:1252-62.

311. Stupka E, deShazo R. Asthma in seniors: Part 1. Evidence for underdiagnosis, undertreatment, and increasing morbidity and mortality. Am J Med 2009;122:6-11.

312. Oraka E, Kim HJ, King ME, Callahan DB. Asthma prevalence among US elderly by age groups: Age still matters. J Asthma 2012;49:593-9.

313. Gibson PG, McDonald VM, Marks GB. Asthma in older adults. Lancet 2010;376:803-13.

314. Slavin RG, Haselkorn T, Lee JH, Zheng B, Deniz Y, Wenzel SE, *et al.* Asthma in older adults: Observations from the epidemiology and natural history of asthma: Outcomes and treatment regimens (TENOR) study. Ann Allergy Asthma Immunol 2006;96:406-14.

315. Marcus P, Oppenheimer EA, Patel PA, Katz LM, Doyle JJ. Use of nebulized inhaled corticosteroids among older adult patients: An assessment of outcomes. Ann Allergy Asthma Immunol 2006;96:736-43.

316. Reed CE. Asthma in the elderly: Diagnosis and management. J Allergy Clin Immunol 2010;126:681-7.

317. Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, *et al.* Standardization of spirometry 2019 update. An official American Thoracic Society and European Respiratory Society technical statement. Am J Respir Crit Care Med 2019;200:e70-88.

318. Naja AS, Permaul P, Phipatanakul W. Taming asthma in school-aged children: A comprehensive review. J Allergy Clin Immunol Pract 2018;6:726-35.

319. Denlinger LC, Sorkness CA, Chinchilli VM, Lemanske RF Jr. Guideline-defining asthma clinical trials of the National Heart, Lung, and Blood institute's asthma clinical research network and childhood asthma research and education network. J Allergy Clin Immunol 2007;119:3-11.

320. Ferrante G, La Grutta S. The Burden of pediatric asthma. Front Pediatr 2018;6:186.

321. Yang CL, Simons E, Foty RG, Subbarao P, To T, Dell SD. Misdiagnosis of asthma in schoolchildren. Pediatr Pulmonol 2017;52:293-302.

322. Danvers L, Lo DK, Gaillard EA. The role of objective tests to support a diagnosis of asthma in children. Paediatr Respir Rev 2020;33:52-7.

323. Kann K, Long B, Koyfman A. Clinical mimics: An emergency medicine-focused review of asthma mimics. J Emerg Med 2017;53:195-201.

324. Hederos CA, Janson S, Andersson H, Hedlin G. Chest X-ray investigation in newly discovered asthma. Pediatr Allergy Immunol 2004;15:163-5.

325. Gauthier MC, Fajt ML. Is it asthma? Recognizing asthma mimics. In: Difficult To Treat Asthma. USA: Springer; 2020. p. 25-38.

326. Alfonso J, Pérez S, Bou R, Amat A, Ruiz I, Mora A, *et al.* Asthma prevalence and risk factors in school children: The RESPIR longitudinal study. Allergol Immunopathol (Madr) 2020;48:223-31.

327. Al-Shamrani A, Bagais K, Alenazi A, Alqwaiee M, Al-Harbi AS. Wheezing in children: Approaches to diagnosis and management. Int J Pediatr Adolesc Med 2019;6:68-73.

328. Chipps BE, Bacharier LB, Harder JM. Phenotypic expressions of childhood wheezing and asthma: Implications for therapy. J Pediatr 2011;158:878-84.e1.

329. Fahy JV, O'Byrne PM. "Reactive airways disease". A lazy term of uncertain meaning that should be abandoned. Am J Respir Crit Care Med 2001;163:822-3.

330. Weinberger MI, Sirey JA, Bruce ML, Heo M, Papademetriou E, Meyers BS. Predictors of major depression six months after admission for outpatient treatment. Psychiatr Serv 2008;59:1211-5.

331. Weinberger M. Pediatric asthma and related allergic and nonallergic diseases: Patient-oriented evidence-based essentials that matter. Pediatr Health 2008;2:631-50.

332. Akdis CA, Bachert C, Cingi C, Dykewicz MS, Hellings PW, Naclerio RM, *et al.* Endotypes and phenotypes of chronic rhinosinusitis: A PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunol 2013;131:1479-90.

333. Bubshait DK, Albuali WH, Yousef AA, Obeid OE, Alkharsah KR, Hassan MI, *et al.* Clinical description of human bocavirus viremia in children with LRTI, Eastern Province, Saudi Arabia. Ann Thorac Med 2015;10:146-9.

334. Conrad LA, Cabana MD, Rastogi D. Defining pediatric asthma: Phenotypes to endotypes and beyond. Pediatr Res 2021;90:45-51.

335. McIntyre AP, Viswanathan RK. Phenotypes and endotypes in asthma. In: Precision Approaches to Heterogeneity in Asthma. USA: Springer; 2023. p. 119-42.

336. Savenije OE, Kerkhof M, Koppelman GH, Postma DS. Predicting who will have asthma at school age among preschool children. J Allergy Clin Immunol 2012;130:325-31.

337. Guilbert TW, Biagini JM, Ramsey RR, Keidel K, Curtsinger K, Kroner JW, *et al.* Treatment by biomarker-informed endotype vs guideline care in children with difficult-to-treat asthma. Ann Allergy Asthma Immunol 2022;128:535-43.e6.

338. Wan XC, Woodruff PG. Biomarkers in severe asthma. Immunol Allergy Clin North Am 2016;36:547-57.

339. Just J, Gouvis-Echraghi R, Couderc R, Guillemot-Lambert N, Saint-Pierre P. Novel severe wheezy young children phenotypes: Boys atopic multiple-trigger and girls nonatopic uncontrolled wheeze. J Allergy Clin Immunol 2012;130:103-10.e8.

340. Guilbert TW, Morgan WJ, Zeiger RS, Bacharier LB, Boehmer SJ, Krawiec M, *et al.* Atopic characteristics of children with recurrent wheezing at high risk for the development of childhood asthma. J Allergy Clin Immunol 2004;114:1282-7.

341. Castro-Rodriguez JA. The asthma predictive index: A very useful

tool for predicting asthma in young children. J Allergy Clin Immunol 2010;126:212-6.

342. Chang TS, Lemanske RF Jr., Guilbert TW, Gern JE, Coen MH, Evans MD, *et al.* Evaluation of the modified asthma predictive index in high-risk preschool children. J Allergy Clin Immunol Pract 2013;1:152-6.

343. Pedersen SE, Hurd SS, Lemanske RF Jr., Becker A, Zar HJ, Sly PD, *et al.* Global strategy for the diagnosis and management of asthma in children 5 years and younger. Pediatr Pulmonol 2011;46:1-17.

344. Yousef AA, Al-Shamrani AS, Al-Haider SA, Said YS, Al Harbi S, Al-Harbi AS. Pediatric pulmonary services in Saudi Arabia. Ann Thorac Med 2013;8:224-8.

345. Yawn BP, Brenneman SK, Allen-Ramey FC, Cabana MD, Markson LE. Assessment of asthma severity and asthma control in children. Pediatrics 2006;118:322-9.

346. Bakel LA, Hamid J, Ewusie J, Liu K, Mussa J, Straus S, *et al.* International variation in asthma and bronchiolitis guidelines. Pediatrics 2017;140:e20170092.

347. Liu AH, Zeiger R, Sorkness C, Mahr T, Ostrom N, Burgess S, *et al.* Development and cross-sectional validation of the childhood asthma control test. J Allergy Clin Immunol 2007;119:817-25.

348. Welsh EJ, Hasan M, Li P. Home-based educational interventions for children with asthma. Cochrane Database Syst Rev 2011;2011:CD008469.

349. Wolf FM, Guevara JP, Grum CM, Clark NM, Cates CJ. Educational interventions for asthma in children. Cochrane Database Syst Rev 2003:CD000326.

350. Wood MR, Bolyard D. Making education count: The nurse's role in asthma education using a medical home model of care. J Pediatr Nurs 2011;26:552-8.

351. Nurmatov U, Devereux G, Sheikh A. Nutrients and foods for the primary prevention of asthma and allergy: Systematic review and meta-analysis. J Allergy Clin Immunol 2011;127:724- 33.e1.

352. Pelucchi C, Chatenoud L, Turati F, Galeone C, Moja L, Bach JF, *et al.* Probiotics supplementation during pregnancy or infancy for the prevention of atopic dermatitis: A meta-analysis. Epidemiology 2012;23:402-14.

353. Kozyrskyj AL, Pawlowski AN. Maternal distress and childhood wheeze: Mechanisms and context. Am J Respir Crit Care Med 2013;187:1160-2.

354. Cabana MD, McKean M, Caughey AB, Fong L, Lynch S, Wong A, *et al.* Early probiotic supplementation for eczema and asthma prevention: A randomized controlled trial. Pediatrics 2017;140:e20163000.

355. Kneale D, Harris K, McDonald VM, Thomas J, Grigg J. Effectiveness of school-based self-management interventions for asthma among children and adolescents: Findings from a Cochrane systematic review and meta-analysis. Thorax 2019;74:432-8.

356. Panel SIfA. Advisory from the Saudi Initiative for Asthma during COVID-19 Riyadh, Saudi Arabia: Saudi Thoracic Society; 2020. Available from: https://saudithoracicsociety.org/wp-content/uploads/2020/04/Advisory-from-the-Saudi-Initiative-for-Asthma.pdf. [Last cited on 2023 Aug 29].

357. Al-Shamrani A, Al-Harbi AS, Alhaider SA, Alharbi S, Al-Harbi NS, Alanazi A, *et al.* Approach to childhood asthma in the era of COVID-19: The official statement endorsed by the Saudi Pediatric Pulmonology Association (SPPA). Int J Pediatr Adolesc Med 2020;7:103-6.

358. Bonner S, Matte T, Rubin M, Fagan JK, Ahern J, Evans D. Oral beta2-agonist use by preschool children with asthma in East and Central Harlem, New York. J Asthma 2006;43:31-5.

359. Lazarus SC, Boushey HA, Fahy JV, Chinchilli VM, Lemanske RF Jr., Sorkness CA, *et al.* Long-acting beta2-agonist monotherapy versus continued therapy with inhaled corticosteroids in patients with persistent asthma: A randomized controlled trial. JAMA 2001;285:2583-93.

360. Bisgaard H, Allen DB, Milanowski J, Kalev I, Willits L, Davies P. Twelve-month safety and efficacy of inhaled fluticasone propionate in children aged 1 to 3 years with recurrent wheezing. Pediatrics 2004;113:e87-94.

361. Leflein JG, Szefler SJ, Murphy KR, Fitzpatrick S, Cruz-Rivera M, Miller CJ, *et al.* Nebulized budesonide inhalation suspension compared with cromolyn sodium nebulizer solution for asthma in young children: Results of a randomized outcomes trial. Pediatrics 2002;109:866-72.

362. Goldsobel A. Association of inhaled corticosteroids and long-acting β-agonists as controller and quick relief therapy with exacerbations and symptom control in persistent asthma: A systematic review and meta-analysis. Pediatrics 2018;142 Suppl 4:S266-7.

363. Sobieraj DM, Weeda ER, Nguyen E, Coleman CI, White CM, Lazarus SC, *et al.* Association of inhaled corticosteroids and long-acting β-agonists as controller and quick relief therapy with exacerbations and symptom control in persistent asthma: A Systematic review and meta-analysis. JAMA 2018;319:1485-96.

364. Cardet JC, Papi A, Reddel HK. "As-needed" inhaled corticosteroids for patients with asthma. J Allergy Clin Immunol Pract 2023;11:726-34.

365. Dufour V, Millon L, Faucher JF, Bard E, Robinet E, Piarroux R, *et al.* Effects of a short-course of amoxicillin/clavulanic acid on systemic and mucosal immunity in healthy adult humans. Int Immunopharmacol 2005;5:917-28.

366. Adams NP, Bestall JB, Jones PW. Inhaled beclomethasone versus placebo for chronic asthma. Cochrane Database Syst Rev 2000;CD002738.

367. Zhang L, Pruteanu AI, Prietsch SO, Chauhan BF, Ducharme FM. Cochrane in context: Inhaled corticosteroids in children with persistent asthma: Effects on growth and dose-response effects on growth. Evid Based Child Health 2014;9:1047-51.

368. Pruteanu AI, Chauhan BF, Zhang L, Prietsch SO, Ducharme FM. Inhaled corticosteroids in children with persistent asthma: Dose-response effects on growth. Evid Based Child Health 2014;9:931-1046.

369. Benard B, Bastien V, Vinet B, Yang R, Krajinovic M, Ducharme FM. Neuropsychiatric adverse drug reactions in children initiated on montelukast in real-life practice. Eur Respir J 2017;50:1-11.

370. Urdaneta E. Neuropsychiatric adverse drug reactions in children initiated on montelukast in real-life practice. Eur Respir J 2017;50:1-10.

371. Glockler-Lauf SD, Finkelstein Y, Zhu J, Feldman LY, To T. Montelukast and neuropsychiatric events in children with asthma: A nested case-control study. J Pediatr 2019;209:176-82.e4.

372. Deerojanawong J, Manuyakorn W, Prapphal N, Harnruthakorn C, Sritippayawan S, Samransamruajkit R. Randomized controlled trial of salbutamol aerosol therapy via metered dose inhaler-spacer versus. Jet nebulizer in young children with wheezing. Pediatr Pulmonol 2005;39:466-72.

373. Drblik S, Lapierre G, Thivierge R, Turgeon J, Gaudreault P, Cummins-McManus B, *et al.* Comparative efficacy of terbutaline sulphate delivered by turbuhaler dry powder inhaler or pressurised metered dose inhaler with nebuhaler spacer in children during an acute asthmatic episode. Arch Dis Child 2003;88:319-23.

374. Vincken W, Levy ML, Scullion J, Usmani OS, Dekhuijzen PN, Corrigan CJ. Spacer devices for inhaled therapy: Why use them, and how? ERJ Open Res 2018;4:1-9.

375. Castro-Rodriguez JA, Rodrigo GJ. beta-agonists through metered-dose inhaler with valved holding chamber versus nebulizer for acute exacerbation of wheezing or asthma in children under 5 years of age: A systematic review with meta-analysis. J Pediatr 2004;145:172-7.

376. Halwani R, Vazquez-Tello A, Horanieh N, Dulgom S, Al-Aseri Z,

Al-Khamis N, *et al*. Risk factors hindering asthma symptom control in Saudi children and adolescents. Pediatr Int 2017;59:661-8.

377. Goksör E, Amark M, Alm B, Gustafsson PM, Wennergren G. Asthma symptoms in early childhood – What happens then? Acta Paediatr 2006;95:471-8.

378. Liu AH, Zeiger RS, Sorkness CA, Ostrom NK, Chipps BE, Rosa K, *et al*. The childhood asthma control test: Retrospective determination and clinical validation of a cut point to identify children with very poorly controlled asthma. J Allergy Clin Immunol 2010;126:267-73.e1.

379. Simons E. Use of beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA): A randomized, double-blind, placebo-controlled trial. Pediatrics 2011;128 Suppl 3:S131-2.

380. Jackson DJ, Bacharier LB. Inhaled corticosteroids for the prevention of asthma exacerbations. Ann Allergy Asthma Immunol 2021;127:524-9.

381. Rodríguez-Martínez CE, Sossa-Briceño MP, Buendia JA. As-needed use of short-Acting β(2)-agonists alone versus as-needed use of short-acting β(2)-agonists plus inhaled corticosteroids in pediatric patients with mild intermittent (step 1) asthma: A cost-effectiveness analysis. J Allergy Clin Immunol Pract 2022;10:1562-8.

382. Rodriguez-Martinez CE, Sossa-Briceño MP, Garcia-Marcos L. Use of inhaled corticosteroids on an intermittent or as-needed basis in pediatric asthma: A systematic review of the literature. J Asthma 2022;59:2189-200.

383. Ducharme FM, Lemire C, Noya FJ, Davis GM, Alos N, Leblond H, *et al*. Preemptive use of high-dose fluticasone for virus-induced wheezing in young children. N Engl J Med 2009;360:339-53.

384. Bisgaard H, Hermansen MN, Loland L, Halkjaer LB, Buchvald F. Intermittent inhaled corticosteroids in infants with episodic wheezing. N Engl J Med 2006;354:1998-2005.

385. Papi A, Nicolini G, Baraldi E, Boner AL, Cutrera R, Rossi GA, *et al*. Regular versus prn nebulized treatment in wheeze preschool children. Allergy 2009;64:1463-71.

386. Fitzpatrick AM, Jackson DJ, Mauger DT, Boehmer SJ, Phipatanakul W, Sheehan WJ, *et al*. Individualized therapy for persistent asthma in young children. J Allergy Clin Immunol 2016;138:1608-18.e12.

387. Guilbert TW, Morgan WJ, Zeiger RS, Mauger DT, Boehmer SJ, Szefler SJ, *et al*. Long-term inhaled corticosteroids in preschool children at high risk for asthma. N Engl J Med 2006;354:1985-97.

388. Nielsen KG, Bisgaard H. The effect of inhaled budesonide on symptoms, lung function, and cold air and methacholine responsiveness in 2- to 5-year-old asthmatic children. Am J Respir Crit Care Med 2000;162:1500-6.

389. Szefler SJ, Baker JW, Uryniak T, Goldman M, Silkoff PE. Comparative study of budesonide inhalation suspension and montelukast in young children with mild persistent asthma. J Allergy Clin Immunol 2007;120:1043-50.

390. Knorr B, Franchi LM, Bisgaard H, Vermeulen JH, LeSouef P, Santanello N, *et al*. Montelukast, a leukotriene receptor antagonist, for the treatment of persistent asthma in children aged 2 to 5 years. Pediatrics 2001;108:E48.

391. Bisgaard H. Leukotriene modifiers in pediatric asthma management. Pediatrics 2001;107:381-90.

392. Ducharme FM, Hicks GC. Anti-leukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma in adults and children. Cochrane Database Syst Rev 2002;CD002314.

393. O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, Runnerstrom E, Sandstrom T, Svensson K, *et al*. Low dose inhaled budesonide and formoterol in mild persistent asthma: The OPTIMA randomized trial. Am J Respir Crit Care Med 2001;164:1392-7.

394. Shrewsbury S, Pyke S, Britton M. Meta-analysis of increased dose of inhaled steroid or addition of salmeterol in symptomatic asthma (MIASMA). BMJ 2000;320:1368-73.

395. Matz J, Emmett A, Rickard K, Kalberg C. Addition of salmeterol to low-dose fluticasone versus higher-dose fluticasone: An analysis of asthma exacerbations. J Allergy Clin Immunol 2001;107:783-9.

396. Vaessen-Verberne AA, van den Berg NJ, van Nierop JC, Brackel HJ, Gerrits GP, Hop WC, *et al*. Combination therapy salmeterol/fluticasone versus doubling dose of fluticasone in children with asthma. Am J Respir Crit Care Med 2010;182:1221-7.

397. Verberne AA, Frost C, Duiverman EJ, Grol MH, Kerrebijn KF. Addition of salmeterol versus doubling the dose of beclomethasone in children with asthma. The Dutch Asthma Study Group. Am J Respir Crit Care Med 1998;158:213-9.

398. Ducharme FM, Ni Chroinin M, Greenstone I, Lasserson TJ. Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children. Cochrane Database Syst Rev 2010;CD005535.

399. Ducharme FM, Ni Chroinin M, Greenstone I, Lasserson TJ. Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma. Cochrane Database Syst Rev 2010;CD005533.

400. Knorr B, Matz J, Bernstein JA, Nguyen H, Seidenberg BC, Reiss TF, *et al*. Montelukast for chronic asthma in 6- to 14-year-old children: A randomized, double-blind trial. Pediatric montelukast study group. JAMA 1998;279:1181-6.

401. Zhou XJ, Qin Z, Lu J, Hong JG. Efficacy and safety of salmeterol/fluticasone compared with montelukast alone (or add-on therapy to fluticasone) in the treatment of bronchial asthma in children and adolescents: A systematic review and meta-analysis. Chin Med J (Engl) 2021;134:2954-61.

402. Dixon EG, King C, Lilley A, Sinha IP, Hawcutt DB. Deprescribing montelukast in children with asthma: A systematic review. BMJ Open 2022;12:e053112.

403. Harding T, Harding A. Multiple short courses of corticosteroids in children. Aust J Gen Pract 2021;50:151-6.

404. Rodriguez-Martinez CE, Sossa-Briceño MP, Castro-Rodriguez JA. Dexamethasone or prednisolone for asthma exacerbations in children: A cost-effectiveness analysis. Pediatr Pulmonol 2020;55:1617-23.

405. Chauhan BF, Ducharme FM. Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma. Cochrane Database Syst Rev 2014;2014:CD003137.

406. Ni Chroinin M, Greenstone I, Lasserson TJ, Ducharme FM. Addition of inhaled long-acting beta2-agonists to inhaled steroids as first line therapy for persistent asthma in steroid-naive adults and children. Cochrane Database Syst Rev 2009;CD005307.

407. Ni Chroinin M, Lasserson TJ, Greenstone I, Ducharme FM. Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children. Cochrane Database Syst Rev 2009;CD007949.

408. Santamaria F, Ziello C, Lorello P, Bouchè C, Borrelli M. Update on long-acting anticholinergics in children and adolescents with difficult and severe asthma. Front Pediatr 2022;10:896865.

409. Aierken A, Yu Su Fu BW, Xu P. Tiotropium as an add-on treatment to inhaled corticosteroids in children with severe and mild symptomatic asthma: Multi-center observational study for efficacy and safety analysis. Exp Ther Med 2022;24:577.

410. Antonio Buendía J, Patiño DG. Tiotropium for children and adolescents with severe asthma. J Asthma 2023;60:1009-15.

411. Kulus M, Hébert J, Garcia E, Fowler Taylor A, Fernandez Vidaurre C, Blogg M. Omalizumab in children with inadequately controlled severe allergic (IgE-mediated) asthma. Curr Med Res Opin 2010;26:1285-93.

412. Lanier B, Bridges T, Kulus M, Taylor AF, Berhane I, Vidaurre CF. Omalizumab for the treatment of exacerbations in children with inadequately controlled allergic (IgE-mediated) asthma. J Allergy

Clin Immunol 2009;124:1210-6.

413. Deschildre A, Marguet C, Langlois C, Pin I, Rittié JL, Derelle J, *et al.* Real-life long-term omalizumab therapy in children with severe allergic asthma. Eur Respir J 2015;46:856-9.

414. Licari A, Marseglia A, Caimmi S, Castagnoli R, Foiadelli T, Barberi S, *et al.* Omalizumab in children. Paediatr Drugs 2014;16:491-502.

415. Gupta A, Pouliquen I, Austin D, Price RG, Kempsford R, Steinfeld J, *et al.* Subcutaneous mepolizumab in children aged 6 to 11 years with severe eosinophilic asthma. Pediatr Pulmonol 2019;54:1957-67.

416. Gupta A, Ikeda M, Geng B, Azmi J, Price RG, Bradford ES, *et al.* Long-term safety and pharmacodynamics of mepolizumab in children with severe asthma with an eosinophilic phenotype. J Allergy Clin Immunol 2019;144:1336-42.e7.

417. Licari A, Castagnoli R, Marseglia A, Olivero F, Votto M, Ciprandi G, *et al.* Dupilumab to treat type 2 inflammatory diseases in children and adolescents. Paediatr Drugs 2020;22:295-310.

418. Bacharier LB, Maspero JF, Katelaris CH, Fiocchi AG, Gagnon R, de Mir I, *et al.* Dupilumab in children with uncontrolled moderate-to-severe asthma. N Engl J Med 2021;385:2230-40.

419. Jackson DJ, Bacharier LB, Phipatanakul W, Sher L, Domingo C, Papadopoulos N, *et al.* Dupilumab pharmacokinetics and effect on type 2 biomarkers in children with moderate-to-severe asthma. Ann Allergy Asthma Immunol 2023;131:44-51.e4.

420. Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, *et al.* Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. N Engl J Med 2018;378:2486-96.

421. Zeiger RS, Mellon M, Chipps B, Murphy KR, Schatz M, Kosinski M, *et al.* Test for respiratory and asthma control in kids (TRACK): Clinically meaningful changes in score. J Allergy Clin Immunol 2011;128:983-8.

422. O'Byrne P, Fabbri LM, Pavord ID, Papi A, Petruzzelli S, Lange P. Asthma progression and mortality: The role of inhaled corticosteroids. Eur Respir J 2019;54:1-11.

423. Zeiger RS, Mauger D, Bacharier LB, Guilbert TW, Martinez FD, Lemanske RF Jr., *et al.* Daily or intermittent budesonide in preschool children with recurrent wheezing. N Engl J Med 2011;365:1990-2001.

424. Chong JK, Chauhan BF. Addition of antileukotriene agents to inhaled corticosteroids in children with persistent asthma. Paediatr Child Health 2014;19:473-4.

425. Ducharme FM. Anti-leukotrienes as add-on therapy to inhaled glucocorticoids in patients with asthma: Systematic review of current evidence. BMJ 2002;324:1545.

426. Simons FE, Villa JR, Lee BW, Teper AM, Lyttle B, Aristizabal G, *et al.* Montelukast added to budesonide in children with persistent asthma: A randomized, double-blind, crossover study. J Pediatr 2001;138:694-8.

427. Swern AS, Tozzi CA, Knorr B, Bisgaard H. Predicting an asthma exacerbation in children 2 to 5 years of age. Ann Allergy Asthma Immunol 2008;101:626-30.

428. Ducharme FM, Chalut D, Plotnick L, Savdie C, Kudirka D, Zhang X, *et al.* The pediatric respiratory assessment measure: A valid clinical score for assessing acute asthma severity from toddlers to teenagers. J Pediatr 2008;152:476-80.e1.

429. Parkin PC, Macarthur C, Saunders NR, Diamond SA, Winders PM. Development of a clinical asthma score for use in hospitalized children between 1 and 5 years of age. J Clin Epidemiol 1996;49:821-5.

430. Chalut DS, Ducharme FM, Davis GM. The preschool respiratory assessment measure (PRAM): A responsive index of acute asthma severity. J Pediatr 2000;137:762-8.

431. Al-Muhsen S, Horanieh N, Dulgom S, Aseri ZA, Vazquez-Tello A, Halwani R, *et al.* Poor asthma education and medication compliance are associated with increased emergency department visits by asthmatic children. Ann Thorac Med 2015;10:123-31.

432. Birken CS, Parkin PC, Macarthur C. Asthma severity scores for preschoolers displayed weaknesses in reliability, validity, and responsiveness. J Clin Epidemiol 2004;57:1177-81.

433. Alnaji F, Zemek R, Barrowman N, Plint A. PRAM score as predictor of pediatric asthma hospitalization. Acad Emerg Med 2014;21:872-8.

434. Jarvis SW, Kovacs C, Badriyah T, Briggs J, Mohammed MA, Meredith P, *et al.* Development and validation of a decision tree early warning score based on routine laboratory test results for the discrimination of hospital mortality in emergency medical admissions. Resuscitation 2013;84:1494-9.

435. Johnson KB, Blaisdell CJ, Walker A, Eggleston P. Effectiveness of a clinical pathway for inpatient asthma management. Pediatrics 2000;106:1006-12.

436. Chacko J, King C, Harkness D, Messahel S, Grice J, Roe J, *et al.* Pediatric acute asthma scoring systems: A systematic review and survey of UK practice. J Am Coll Emerg Physicians Open 2020;1:1000-8.

437. Banasiak NC. Childhood asthma practice guideline part three: Update of the 2007 national guidelines for the diagnosis and treatment of asthma. The national asthma education and prevention program. J Pediatr Health Care 2009;23:59-61.

438. Al-Shamrani A, Al-Harbi AS, Bagais K, Alenazi A, Alqwaiee M. Management of asthma exacerbation in the emergency departments. Int J Pediatr Adolesc Med 2019;6:61-7.

439. Ortiz-Alvarez O, Mikrogianakis A, Canadian Paediatric Society, Acute Care Committee. Managing the paediatric patient with an acute asthma exacerbation. Paediatr Child Health 2012;17:251-62.

440. Norton SP, Pusic MV, Taha F, Heathcote S, Carleton BC. Effect of a clinical pathway on the hospitalisation rates of children with asthma: A prospective study. Arch Dis Child 2007;92:60-6.

441. Lougheed MD, Olajos-Clow JG. Asthma care pathways in the emergency department. Curr Opin Allergy Clin Immunol 2010;10:181-7.

442. Browne GJ, Giles H, McCaskill ME, Fasher BJ, Lam LT. The benefits of using clinical pathways for managing acute paediatric illness in an emergency department. J Qual Clin Pract 2001;21:50-5.

443. Graham VA, Milton AF, Knowles GK, Davies RJ. Routine antibiotics in hospital management of acute asthma. Lancet 1982;1:418-20.

444. Everard ML, Bara A, Kurian M, Elliott TM, Ducharme F, Mayowe V. Anticholinergic drugs for wheeze in children under the age of two years. Cochrane Database Syst Rev 2005;2005:CD001279.

445. Griffiths B, Ducharme FM. Combined inhaled anticholinergics and short-acting beta2-agonists for initial treatment of acute asthma in children. Cochrane Database Syst Rev 2013;CD000060.

446. Chinese College of Emergency Physicians (CCEP), Emergency Committee of PLA, Beijing Society for Emergency Medicine, Chinese Emergency Medicine. Expert consensus on nebulization therapy in pre-hospital and in-hospital emergency care. Ann Transl Med 2019;7:487.

447. Wei J, Lu Y, Han F, Zhang J, Liu L, Chen Q. Oral dexamethasone versus oral prednisone for children with acute asthma exacerbations: A systematic review and meta-analysis. Front Pediatr 2019;7:503.

448. Iramain R, Castro-Rodriguez JA, Jara A, Cardozo L, Bogado N, Morinigo R, *et al.* Salbutamol and ipratropium by inhaler is superior to nebulizer in children with severe acute asthma exacerbation: Randomized clinical trial. Pediatr Pulmonol 2019;54:372-7.

449. Griffiths B, Ducharme FM. Combined inhaled anticholinergics and short-acting beta2-agonists for initial treatment of acute asthma in children. Paediatr Respir Rev 2013;14:234-5.

450. Rowe BH, Spooner CH, Ducharme FM, Bretzlaff JA, Bota GW. Corticosteroids for preventing relapse following acute exacerbations of asthma. Cochrane Database Syst Rev 2001;CD000195.

451. Cheuk DK, Chau TC, Lee SL. A meta-analysis on intravenous magnesium sulphate for treating acute asthma. Arch Dis Child 2005;90:74-7.

452. Powell CV, Kolamunnage-Dona R, Lowe J, Boland A, Petrou S, Doull I, *et al.* MAGNEsium trial in children (MAGNETIC): A randomised, placebo-controlled trial and economic evaluation of nebulised magnesium sulphate in acute severe asthma in children. Health Technol Assess 2013;17:i-216.

453. Powell C, Kolamunnage-Dona R, Lowe J, Boland A, Petrou S, Doull I, *et al.* Magnesium sulphate in acute severe asthma in children (MAGNETIC): A randomised, placebo-controlled trial. Lancet Respir Med 2013;1:301-8.

454. Camargo CA Jr., Spooner CH, Rowe BH. Continuous versus intermittent beta-agonists in the treatment of acute asthma. Cochrane Database Syst Rev 2003;2003:CD001115.

455. Scarfone RJ, Fuchs SM, Nager AL, Shane SA. Controlled trial of oral prednisone in the emergency department treatment of children with acute asthma. Pediatrics 1993;92:513-8.

456. Creticos PS. Treatment options for initial maintenance therapy of persistent asthma: A review of inhaled corticosteroids and leukotriene receptor antagonists. Drugs 2003;63 Suppl 2:1-20.

457. McFadden ER Jr. Critical appraisal of the therapy of asthma – An idea whose time has come. Am Rev Respir Dis 1986;133:723-4.

458. Rodrigo GJ, Rodrigo C. Continuous versus intermittent beta-agonists in the treatment of acute adult asthma: A systematic review with meta-analysis. Chest 2002;122:160-5.

459. Travers AH, Rowe BH, Barker S, Jones A, Camargo CA Jr. The effectiveness of IV beta-agonists in treating patients with acute asthma in the emergency department: A meta-analysis. Chest 2002;122:1200-7.

460. Rodrigo GJ, Rodrigo C. First-line therapy for adult patients with acute asthma receiving a multiple-dose protocol of ipratropium bromide plus albuterol in the emergency department. Am J Respir Crit Care Med 2000;161:1862-8.

461. Rodrigo GJ, Rodrigo C. The role of anticholinergics in acute asthma treatment: An evidence-based evaluation. Chest 2002;121:1977-87.

462. Vézina K, Chauhan BF, Ducharme FM. Inhaled anticholinergics and short-acting beta(2)-agonists versus short-acting beta2-agonists alone for children with acute asthma in hospital. Cochrane Database Syst Rev 2014;CD010283.

463. Silverman RA, Osborn H, Runge J, Gallagher EJ, Chiang W, Feldman J, *et al.* IV magnesium sulfate in the treatment of acute severe asthma: A multicenter randomized controlled trial. Chest 2002;122:489-97.

464. Lemanske RF Jr., Sorkness CA, Mauger EA, Lazarus SC, Boushey HA, Fahy JV, *et al.* Inhaled corticosteroid reduction and elimination in patients with persistent asthma receiving salmeterol: A randomized controlled trial. JAMA 2001;285:2594-603.

465. Masoli M, Weatherall M, Holt S, Beasley R. Moderate dose inhaled corticosteroids plus salmeterol versus higher doses of inhaled corticosteroids in symptomatic asthma. Thorax 2005;60:730-4.

466. Fouda MA, Al-Kassimi FA. Budesonide and fluticasone and adrenal suppression. Ann Thorac Med 2012;7:253.

467. Pruteanu AI, Chauhan BF, Zhang L, Prietsch SO, Ducharme FM. Inhaled corticosteroids in children with persistent asthma: Dose-response effects on growth. Cochrane Database Syst Rev 2014;2014:CD009878.

468. Raissy HH, Blake K. Does use of inhaled corticosteroid for management of asthma in children make them shorter adults? Pediatr Allergy Immunol Pulmonol 2013;26:99-101.

469. Hossny E, Rosario N, Lee BW, Singh M, El-Ghoneimy D, Soh JY, *et al.* The use of inhaled corticosteroids in pediatric asthma: Update. World Allergy Organ J 2016;9:26.

470. Hoover RM, Erramouspe J, Bell EA, Cleveland KW. Effect of inhaled corticosteroids on long-term growth in pediatric patients with asthma and allergic rhinitis. Ann Pharmacother 2013;47:1175-81.

471. Kelly HW, Van Natta ML, Covar RA, Tonascia J, Green RP, Strunk RC, *et al.* Effect of long-term corticosteroid use on bone mineral density in children: A prospective longitudinal assessment in the childhood asthma management program (CAMP) study. Pediatrics 2008;122:e53-61.

472. Sidoroff VH, Ylinen MK, Kröger LM, Kröger HP, Korppi MO. Inhaled corticosteroids and bone mineral density at school age: A follow-up study after early childhood wheezing. Pediatr Pulmonol 2015;50:1-7.

473. Stelmach I, Olszowiec-Chlebna M, Jerzynska J, Grzelewski T, Stelmach W, Majak P. Inhaled corticosteroids may have a beneficial effect on bone metabolism in newly diagnosed asthmatic children. Pulm Pharmacol Ther 2011;24:414-20.

474. Altintas DU, Karakoc GB, Can S, Yilmaz M, Kendirli SG. The effects of long term use of inhaled corticosteroids on linear growth, adrenal function and bone mineral density in children. Allergol Immunopathol (Madr) 2005;33:204-9.

475. Bjermer L, Diamant Z. The use of leukotriene receptor antagonists (LTRAs) as complementary therapy in asthma. Monaldi Arch Chest Dis 2002;57:76-83.

476. Idrees MM, Al Moamary MS. Blocking leukotrienes optimize asthma control: The BLOC survey. Ann Thorac Med 2007;2:99-102.

477. Bisgaard H, Study Group on Montelukast and Respiratory Syncytial Virus. A randomized trial of montelukast in respiratory syncytial virus postbronchiolitis. Am J Respir Crit Care Med 2003;167:379-83.

478. Straub DA, Minocchieri S, Moeller A, Hamacher J, Wildhaber JH. The effect of montelukast on exhaled nitric oxide and lung function in asthmatic children 2 to 5 years old. Chest 2005;127:509-14.

479. Straub DA, Moeller A, Minocchieri S, Hamacher J, Sennhauser FH, Hall GL, *et al.* The effect of montelukast on lung function and exhaled nitric oxide in infants with early childhood asthma. Eur Respir J 2005;25:289-94.

480. Bisgaard H, Zielen S, Garcia-Garcia ML, Johnston SL, Gilles L, Menten J, *et al.* Montelukast reduces asthma exacerbations in 2- to 5-year-old children with intermittent asthma. Am J Respir Crit Care Med 2005;171:315-22.

481. Lötvall J, Bateman ED, Bleecker ER, Busse WW, Woodcock A, Follows R, *et al.* 24-h duration of the novel LABA vilanterol trifenatate in asthma patients treated with inhaled corticosteroids. Eur Respir J 2012;40:570-9.

482. Casarosa P, Kollak I, Kiechle T, Ostermann A, Schnapp A, Kiesling R, *et al.* Functional and biochemical rationales for the 24-hour-long duration of action of olodaterol. J Pharmacol Exp Ther 2011;337:600-9.

483. Pearlman DS, Greos L, LaForce C, Orevillo CJ, Owen R, Higgins M. Bronchodilator efficacy of indacaterol, a novel once-daily beta2-agonist, in patients with persistent asthma. Ann Allergy Asthma Immunol 2008;101:90-5.

484. Sugihara N, Kanada S, Haida M, Ichinose M, Adachi M, Hosoe M, *et al.* 24-h bronchodilator efficacy of single doses of indacaterol in Japanese patients with asthma: A comparison with placebo and salmeterol. Respir Med 2010;104:1629-37.

485. Cazzola M, Segreti A, Matera MG. Novel bronchodilators in asthma. Curr Opin Pulm Med 2010;16:6-12.

486. Cazzola M, Matera MG. Novel long-acting bronchodilators for COPD and asthma. Br J Pharmacol 2008;155:291-9.

487. LaForce C, Korenblat P, Osborne P, Dong F, Higgins M. 24-hour bronchodilator efficacy of single doses of indacaterol in patients with persistent asthma: Comparison with placebo and formoterol. Curr Med Res Opin 2009;25:2353-9.

488. Cates CJ, Cates MJ. Regular treatment with formoterol for chronic asthma: Serious adverse events. Cochrane Database Syst Rev 2012;4:CD006923.

489. van Noord JA, Bantje TA, Eland ME, Korducki L, Cornelissen PJ. A randomised controlled comparison of tiotropium nd ipratropium in the treatment of chronic obstructive pulmonary disease. The Dutch Tiotropium Study Group. Thorax 2000;55:289-94.

490. Maesen FP, Smeets JJ, Sledsens TJ, Wald FD, Cornelissen PJ. Tiotropium bromide, a new long-acting antimuscarinic bronchodilator: A pharmacodynamic study in patients with chronic obstructive pulmonary disease (COPD). Dutch Study Group. Eur Respir J 1995;8:1506-13.

491. Rodrigo GJ, Castro-Rodríguez JA. What is the role of tiotropium in asthma? A systematic review with meta-analysis. Chest 2015;147:388-96.

492. Fardon T, Haggart K, Lee DK, Lipworth BJ. A proof of concept study to evaluate stepping down the dose of fluticasone in combination with salmeterol and tiotropium in severe persistent asthma. Respir Med 2007;101:1218-28.

493. Gessner C, Kornmann O, Maspero J, van Zyl-Smit R, Krüll M, Salina A, *et al.* Fixed-dose combination of indacaterol/ glycopyrronium/mometasone furoate once-daily versus salmeterol/fluticasone twice-daily plus tiotropium once-daily in patients with uncontrolled asthma: A randomised, Phase IIIb, non-inferiority study (ARGON). Respir Med 2020;170:106021.

494. Elias JA, Lee CG, Zheng T, Ma B, Homer RJ, Zhu Z. New insights into the pathogenesis of asthma. J Clin Invest 2003;111:291-7.

495. Hamid Q, Tulic MK. New insights into the pathophysiology of the small airways in asthma. Ann Thorac Med 2007;2:28-33.

496. Huchon G, Magnussen H, Chuchalin A, Dymek L, Gonod FB, Bousquet J. Lung function and asthma control with beclomethasone and formoterol in a single inhaler. Respir Med 2009;103:41-9.

497. Nolte H, Pavord I, Backer V, Spector S, Shekar T, Gates D, *et al.* Dose-dependent anti-inflammatory effect of inhaled mometasone furoate/formoterol in subjects with asthma. Respir Med 2013;107:656-64.

498. Grekas N, Athanassiou K, Papataxiarchou K, Rizea Savu S, Silvestro L. Pharmacokinetic study for the establishment of bioequivalence of two inhalation treatments containing budesonide plus formoterol. J Pharm Pharmacol 2014;66:1677-85.

499. Bodzenta-Lukaszyk A, Pulka G, Dymek A, Bumbacea D, McIver T, Schwab B, *et al.* Efficacy and safety of fluticasone and formoterol in a single pressurized metered dose inhaler. Respir Med 2011;105:674-82.

500. O'Byrne PM, FitzGerald JM, Zhong N, Bateman E, Barnes PJ, Keen C, *et al.* The SYGMA programme of phase 3 trials to evaluate the efficacy and safety of budesonide/formoterol given 'as needed' in mild asthma: Study protocols for two randomised controlled trials. Trials 2017;18:12.

501. Bateman ED, O'Byrne PM, Busse WW, Lötvall J, Bleecker ER, Andersen L, *et al.* Once-daily fluticasone furoate (FF)/vilanterol reduces risk of severe exacerbations in asthma versus FF alone. Thorax 2014;69:312-9.

502. Jabbal S, Kuo CR, Lipworth B. Randomized controlled trial of triple versus dual inhaler therapy on small airways in smoking asthmatics. Clin Exp Allergy 2020;50:1140-7.

503. Kim LH, Saleh C, Whalen-Browne A, O'Byrne PM, Chu DK. Triple versus dual inhaler therapy and asthma outcomes in moderate to severe asthma: A systematic review and meta-analysis. JAMA 2021;325:2466-79.

504. Nair A, Menzies D, Barnes M, Burns P, McFarlane L, Lipworth BJ. Respirable dose delivery of fluticasone propionate from a small valved holding chamber, a compact breath actuated integrated vortex device and a metered dose inhaler. Br J Clin Pharmacol 2008;66:20-6.

505. Giraud V, Allaert FA, Roche N. Inhaler technique and asthma: Feasability and acceptability of training by pharmacists. Respir Med 2011;105:1815-22.

506. Giraud V, Allaert FA. Improved asthma control with breath-actuated pressurized metered dose inhaler (pMDI): The SYSTER survey. Eur Rev Med Pharmacol Sci 2009;13:323-30.

507. Donnell D. Inhaled corticosteroid delivery systems: Clinical role of a breath-actuated device. Eur Rev Med Pharmacol Sci 2001;5:7-16.

508. Drazen JM, Harrington D. New biologics for asthma. N Engl J Med 2018;378:2533-4.

509. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, *et al.* Mepolizumab for severe eosinophilic asthma (DREAM): A multicentre, double-blind, placebo-controlled trial. Lancet 2012;380:651-9.

510. Ortega HG, Yancey SW, Mayer B, Gunsoy NB, Keene ON, Bleecker ER, *et al.* Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: A secondary analysis of the DREAM and MENSA studies. Lancet Respir Med 2016;4:549-56.

511. Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, *et al.* Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. N Engl J Med 2014;371:1189-97.

512. FitzGerald JM, Bleecker ER, Menzies-Gow A, Zangrilli JG, Hirsch I, Metcalfe P, *et al.* Predictors of enhanced response with benralizumab for patients with severe asthma: Pooled analysis of the SIROCCO and CALIMA studies. Lancet Respir Med 2018;6:51-64.

513. Chipps BE, Newbold P, Hirsch I, Trudo F, Goldman M. Benralizumab efficacy by atopy status and serum immunoglobulin E for patients with severe, uncontrolled asthma. Ann Allergy Asthma Immunol 2018;120:504-11.e4.

514. Hanania NA, Wenzel S, Rosén K, Hsieh HJ, Mosesova S, Choy DF, *et al.* Exploring the effects of omalizumab in allergic asthma: An analysis of biomarkers in the EXTRA study. Am J Respir Crit Care Med 2013;187:804-11.

515. Normansell R, Walker S, Milan SJ, Walters EH, Nair P. Omalizumab for asthma in adults and children. Cochrane Database Syst Rev 2014;CD003559.

516. Lowe PJ, Georgiou P, Canvin J. Revision of omalizumab dosing table for dosing every 4 instead of 2 weeks for specific ranges of bodyweight and baseline IgE. Regul Toxicol Pharmacol 2015;71:68-77.

517. Agache I, Beltran J, Akdis C, Akdis M, Canelo-Aybar C, Canonica GW, *et al.* Efficacy and safety of treatment with biologicals (benralizumab, dupilumab, mepolizumab, omalizumab and reslizumab) for severe eosinophilic asthma. A systematic review for the EAACI guidelines – Recommendations on the use of biologicals in severe asthma. Allergy 2020;75:1023-42.

518. Busse WW, Humbert M, Haselkorn T, Ortiz B, Trzaskoma BL, Stephenson P, *et al.* Effect of omalizumab on lung function and eosinophil levels in adolescents with moderate-to-severe allergic asthma. Ann Allergy Asthma Immunol 2020;124:190-6.

519. Hanania NA, Alpan O, Hamilos DL, Condemi JJ, Reyes-Rivera I, Zhu J, *et al.* Omalizumab in severe allergic asthma inadequately controlled with standard therapy: A randomized trial. Ann Intern Med 2011;154:573-82.

520. Agache I, Rocha C, Beltran J, Song Y, Posso M, Solà I, *et al.* Efficacy and safety of treatment with biologicals (benralizumab, dupilumab and omalizumab) for severe allergic asthma: A systematic review for the EAACI Guidelines – Recommendations on the use of biologicals in severe asthma. Allergy 2020;75:1043-57.

521. Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P, *et al.* Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: Results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet Respir Med 2015;3:355-66.

522. Mukherjee M, Aleman Paramo F, Kjarsgaard M, Salter B, Nair G, LaVigne N, *et al.* Weight-adjusted intravenous reslizumab in severe asthma with inadequate response to fixed-dose subcutaneous mepolizumab. Am J Respir Crit Care Med

2018;197:38-46.

523. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, *et al.* Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med 2014;371:1198-207.

524. Nair P, Wenzel S, Rabe KF, Bourdin A, Lugogo NL, Kuna P, *et al.* Oral glucocorticoid-sparing effect of benralizumab in severe asthma. N Engl J Med 2017;376:2448-58.

525. Busse WW, Bleecker ER, FitzGerald JM, Ferguson GT, Barker P, Sproule S, *et al.* Long-term safety and efficacy of benralizumab in patients with severe, uncontrolled asthma: 1-year results from the BORA phase 3 extension trial. Lancet Respir Med 2019;7:46-59.

526. Chupp G, Lugogo NL, Kline JN, Ferguson GT, Hirsch I, Goldman M, *et al.* Rapid onset of effect of benralizumab on morning peak expiratory flow in severe, uncontrolled asthma. Ann Allergy Asthma Immunol 2019;122:478-85.

527. Bleecker ER, FitzGerald JM, Chanez P, Papi A, Weinstein SF, Barker P, *et al.* Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β(2)-agonists (SIROCCO): A randomised, multicentre, placebo-controlled phase 3 trial. Lancet 2016;388:2115-27.

528. Bleecker ER, Wechsler ME, FitzGerald JM, Menzies-Gow A, Wu Y, Hirsch I, *et al.* Baseline patient factors impact on the clinical efficacy of benralizumab for severe asthma. Eur Respir J 2018;52:1-13.

529. Cockcroft DW. Asthma. Can J Respir Crit Care Sleep Med 2020;4 Suppl 1:S18-20.

530. Peters MC, Wenzel SE. Intersection of biology and therapeutics: Type 2 targeted therapeutics for adult asthma. Lancet 2020;395:371-83.

531. Rabe KF, Nair P, Brusselle G, Maspero JF, Castro M, Sher L, *et al.* Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. N Engl J Med 2018;378:2475-85.

532. Corren J, Parnes JR, Wang L, Mo M, Roseti SL, Griffiths JM, *et al.* Tezepelumab in adults with uncontrolled asthma. N Engl J Med 2017;377:936-46.

533. Simpson EL, Parnes JR, She D, Crouch S, Rees W, Mo M, *et al.* Tezepelumab, an anti-thymic stromal lymphopoietin monoclonal antibody, in the treatment of moderate to severe atopic dermatitis: A randomized phase 2a clinical trial. J Am Acad Dermatol 2019;80:1013-21.

534. Wechsler ME, Colice G, Griffiths JM, Almqvist G, Skärby T, Piechowiak T, *et al.* SOURCE: A phase 3, multicentre, randomized, double-blind, placebo-controlled, parallel group trial to evaluate the efficacy and safety of tezepelumab in reducing oral corticosteroid use in adults with oral corticosteroid dependent asthma. Respir Res 2020;21:264.

535. Menzies-Gow A, Colice G, Griffiths JM, Almqvist G, Ponnarambil S, Kaur P, *et al.* NAVIGATOR: A phase 3 multicentre, randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the efficacy and safety of tezepelumab in adults and adolescents with severe, uncontrolled asthma. Respir Res 2020;21:266.

536. Tezepelumab K. NAVIGATOR Phase III Trial Met Primary Endpoint of a Statistically Significant and Clinically Meaningful Reduction in Exacerbations in a Broad Population of Patients with Severe Asthma: AstraZeneca; 2020. Available from: https://www.astrazeneca.com/media-centre/press-releases/2020/tezepelumab-navigator-phase-iii-trial-met-primary-endpoint.html. [Last accessed on 2023 Sep 19],

537. Menzies-Gow A, Corren J, Bourdin A, Chupp G, Israel E, Wechsler ME, *et al.* Tezepelumab in adults and adolescents with severe, uncontrolled asthma. N Engl J Med 2021;384:1800-9.