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PHILIPPINE CONSENSUS REPORT ON
ASTHMA DIAGNOSIS
AND MANAGEMENT
2019
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Medical literature reports that asthma continues to be an important global health problem affecting over 300 million people of all age groups, with increasing prevalence and rising treatment costs. As one of the most common chronic conditions, asthma imposes a large burden on many countries in the developing world such as the Philippines, where limited healthcare resources are challenged by the affected population’s high healthcare utilization, impact on quality of life, loss of productivity, and increased morbidity and mortality.

The Philippine Consensus Report on Asthma Diagnosis and Management was first published in 1996 and was followed by updated versions in 2004 and in 2009. It took a decade for this current report to be developed because international asthma management guidelines such as the Global Initiative on Asthma (GINA) as well as other clinical practice guidelines that are regularly updated and easily accessed adequately filled the gap during the interim.

The Council on Asthma of the Philippine College of Chest Physicians then decided to embark on this ambitious project to re-formulate a new version of the local Asthma Consensus Report that will provide a comprehensive treatise on the clinical approach to asthma management that is intended both for generalists and specialists alike. This rejuvenated version deals with various aspects on asthma such as the definition, epidemiology, diagnosis and classification, risk factors, special considerations, as well as treatment recommendations on asthma exacerbations and chronic management. Although much of the content was adapted from the Global Initiative on Asthma clinical practice guidelines (with permission), this Report utilized the question and answer format similar to the 2004 Philippine Asthma Consensus Report. On the other hand, the chapter topics and titles featured here were lifted from the 2009 Philippine Asthma Consensus Report.

As a practice guideline update, this aims to inform local practitioners on current evidence-based practice on asthma management. As a consensus document, it not only shows which of the strategies gathered from international guidelines may be considered relevant and feasible in the local setting, but also presents some crucial caveats and innovations on treatment recommendations. Some variation is inevitable in this era of personalized medicine and is likely borne from the nuances of medical practice unique to the Filipino physician who often draws on his or her own experiences in making clinical decisions in the management of asthma patients.

The members of the Consensus Committee are solely responsible for the statements presented in this publication. They did not receive any honorarium to attend the review and deliberation meetings, and there was no remuneration given for the time they devoted in poring over scientific literature and in contributing substantively to the content of this Report. Their truly commendable efforts, commitment and cooperation were invaluable towards the successful completion of this Consensus Report.

We acknowledge the Global Initiative on Asthma (GINA) documents as major resources of this Report and we thank them for granting permission to adopt major tables and figures. Our utmost gratitude to the support staff of the Philippine College of Chest Physicians who assisted the Committee in this endeavor and to AstraZeneca, Phil. who helped in facilitating the printing of this document.

The Consensus Committee encourages the dissemination and implementation of the management strategies and recommendations of this updated Philippine Asthma Consensus Report. We hope that it can further raise awareness among our healthcare professionals on the value of adherence to high standards of asthma care, instill a desire to seek new knowledge and, for some, provide the much-needed motivation to embark on researches that may help resolve some unanswered questions on asthma. This Report may also be utilized as an additional scientific resource to assist local health authorities in formulating more up-to-date, evidence- and practice-based policies on asthma management in the Philippines.

Dina V. Diaz, M.D., FPCCP
Project Chairman
Philippine Consensus Report on Asthma Diagnosis and Management Update
Council on Asthma
Philippine College of Chest Physicians
Table A. Levels of Evidence (adapted from GINA guidelines)

<table>
<thead>
<tr>
<th>EVIDENCE LEVEL</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Evidence is from endpoints of well-designed randomized controlled trials (RCTs) or meta-analyses of relevant studies that provide a consistent pattern of findings in the population for which the recommendation is made. Category A requires substantial numbers of studies involving substantial numbers of participants.</td>
</tr>
<tr>
<td>B</td>
<td>Evidence is from endpoints of intervention studies that include only a limited number of patients, post hoc or subgroup analysis of RCTs or meta-analysis of such RCTs. In general, Category B pertains when few randomized trials exist, they are small in size, they were undertaken in a population that differs from the target population of the recommendation, or the results are somewhat inconsistent.</td>
</tr>
<tr>
<td>C</td>
<td>Evidence is from outcomes of non-randomized or uncontrolled trials or from observational studies.</td>
</tr>
<tr>
<td>D</td>
<td>This is a panel consensus judgement based on clinical experience or knowledge that does not meet the above listed criteria. This category is used only 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.</td>
</tr>
</tbody>
</table>
CHAPTER 1

Epidemiology, Definition and Diagnosis
Bronchial asthma is now recognized as one of the most important non-communicable threats to global health, social welfare and economic development in all regions of the world, especially in low-to-middle income countries. Focused and accelerated efforts are required to make asthma a lung health priority.¹

What is the burden of asthma globally and in the Philippines?

Globally, asthma is ranked 28th among the leading causes of burden of the disease and 16th among the leading causes of years lived with disability.²

Asthma was acknowledged as the most prevalent chronic respiratory disease worldwide. In 2016, the Global Burden of Disease (GBD) study estimated that there were 339.4 million people worldwide affected by asthma. This represents a 3.6% increase in age-standardized prevalence since 2006.²

The prevalence of asthma symptoms in children is 14% while in young adults aged 18 to 45-years old, it is pegged at 8.6%, according to the International Study of Asthma and Allergies in Childhood (ISAAC) undertaken between 2000 and 2003. Of the young adults who participated in the survey, only 4.5% were diagnosed to have asthma or were taking treatment for asthma.³

A World Health Survey was conducted in 2002 to determine the prevalence of asthma, involving 178,215 individuals aged 18 to 45-years old from 70 countries. Asthma was categorized as self-reported, doctor-diagnosed or based on clinical (symptoms or treatment) and the prevalence was 4.3%, 4.5% and 8.6% respectively.⁴ The same survey showed that among those with clinical/treated asthma, almost 24% were current smokers, half mostly coming from South East Asia (57.9%) reported wheezing in the past 12 months, and 20% were treatment-naïve.

In 2016, asthma, across all ages, contributed 23.7 million Disability-Adjusted Life Years (DALYs) globally. This total burden of disease has remained unchanged since 1990, despite the substantial increase in world population over that time. Hence, the age-standardized rate (329.2 DALYs per 100,000 population in 2016) has decreased by 36% since 1990. Globally, asthma ranked 28th among the leading causes of burden of disease and 27th in low- and middle-income countries (LMICs). More than half (56%) of the global burden attributable to asthma was due to 13.2 million Years Lived with Disability (YLD). This represents a small (3.0%) increase in the age-standardized rate of YLD due to asthma since 2006. In 2016, asthma ranked 16th in the leading causes of YLD globally. Worldwide, there were 10.5 million Years of Life Lost (YLL) attributed to asthma-related premature deaths. This represents an age-standardized rate of 148·5 YLL per 100,000
population, 26% lower in 2016 compared to 2006. In 2016, asthma ranked 23rd (global) and 31st (LMICs) among the leading causes of premature mortality.2

On the other hand, premature deaths measured in YLL is highest in the elderly (aged 75-79) (Figure 1.1A). The burden is similar in males and females below ages 30-34 years, but there is male predominance for asthma burden at older age groups (Figure 1.1B).

Non-communicable diseases (NCDs) are now overtaking communicable diseases as leading causes of death globally, affecting 60% among people of all ages, 80% of these deaths occurring in non-affluent countries.1

In the Philippines, the overall prevalence of asthma based on wheezing for the past 12 months was estimated at 8.7% (SE 0.4%), based on a survey involving 7,202 adults at least 20-years old from 3,744 households, 79 provinces and 17 regions using pre-validated written questionnaire used in the ISAAC Study. Males were reported to have higher prevalence at 9.4% (SE 0.5%) compared to females at 8.2% (SE 0.5%). Wheezing at any time was reported at 14.3% (SE 0.5%), with males at 14.8% (SE 0.7%) compared to 13.8% (SE 0.6%) in females. Prevalence of adult asthma in the rural area is slightly higher than in the urban area (15.3% vs 13.3%), but not statistically significant.3 Table 1.1 summarizes the asthma prevalence studies done in the Philippines.
How is asthma defined?

Based on a consensus statement considering typical asthma characteristics, asthma is a heterogeneous disease, usually characterized by chronic airway inflammation, defined by history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary in intensity over time, together with variable expiratory airflow limitation. Symptoms and airway obstruction are often reversible either spontaneously or with treatment, usually triggered by factors such as exercise, allergen or irritant exposure, weather changes or viral respiratory infections. Since asthma is affected by significant genetic and environmental factors, its pathogenesis and underlying mechanisms are still not clear. The main pathophysiological feature of asthma is episodic airway obstruction characterized by expiratory airflow limitation. The dominant pathological feature is airway inflammation, sometimes associated with airway structural changes. The predominant feature of the clinical history is episodic shortness of breath, particularly at night, often accompanied by cough. Wheezing appreciated on auscultation of the chest is the most common physical finding. The interaction of these features determines the clinical manifestations and severity of asthma. While most of asthma subsets possess the well-known inflammatory markers of the disease, not all do, and the relationship between airway inflammation, airway hyperresponsiveness, symptoms and exacerbations is not straightforward. In attempts to clinically characterize asthma (and in the process, individualize patient management), there are various underlying recognizable clusters of demographic, clinical and/or pathophysiological features known as asthma phenotypes that may be based on onset, atopic status, severity (mild/moderate/severe), triggers (nocturnal, exercise, induced cough variant, aspirin sensitive, occupational), associated conditions (smoking, COPD, obesity, Churg-Strauss Syndrome) or treatment response (steroid-sensitive/insensitive, responders to specific therapies).

How is asthma diagnosed?

Making the diagnosis of asthma is based on identifying both a characteristic pattern of respiratory symptoms such as wheezing, shortness of breath (dyspnea), chest tightness or cough, and variable expiratory airflow limitation. Practical tools for the diagnosis of asthma are recommended to reduce over or underdiagnosis of asthma.

The overall increase in asthma awareness by physicians has resulted in the overdiagnosis of asthma, which can be as high as 25-35% in developed countries. Overdiagnosis of asthma is a potential problem, resulting in unnecessary or inappropriate medication use, increased healthcare costs and mislabeling of patients. Linden Smith et al recommend greater use of objective diagnostic tests such as spirometry, peak flow diaries and bronchial provocation to establish a clinical diagnosis of asthma.

A diagnostic flowchart for clinicians is recommended in making the initial diagnosis of asthma based on clinical history and objective assessments to confirm presence of variable and reversible expiratory airflow limitation (Figure 1.3). The clinical probability of asthma increases when symptoms are more than one, especially in adults, worse at night or early morning, vary in intensity over time, and triggered by certain factors like viral infections, exercise, changes in weather, laughter or exposure to allergens or irritants like car exhaust fumes, smoke or strong smells. Presence of respiratory symptoms in childhood, history of allergic rhinitis or eczema, or family history of asthma or allergy, although non-specific, likewise increases the probability for asthma. Expiratory wheezing, when appreciated on quiet or forced breathing, is the most frequent abnormal finding for asthma. Consider other diagnosis in the following clinical conditions: 1) when cough is isolated without other respiratory symptoms; 2) when sputum production is chronic; 3) when shortness of breath is associated with lightheadedness, paresthesia, dizziness or chest pain; 4) when inspiration becomes noisy during exercise, and; 5) when there is presence of crackles or inspiratory wheezes. These are not features of asthma and the probability of asthma is less likely.

- **Clinical history.** The clinical probability of asthma increases when symptoms are more than one, especially in adults, worse at night or early morning, vary in intensity over time, and triggered by certain factors like viral infections, exercise, changes in weather, laughter or exposure to allergens or irritants like car exhaust fumes, smoke or strong smells. Presence of respiratory symptoms in childhood, history of allergic rhinitis or eczema, or family history of asthma or allergy, although non-specific, likewise increases the probability for asthma.

- **Objective assessment to confirm variability and reversibility of expiratory airflow limitation.**

  - **Airflow limitation:** confirmed at least once by a reduced FEV₁/FVC ratio (normally >0.75-0.80 in adults)³
  - **Variability:** improvement and/or deterioration in lung function within the day (diurnal variability), from day to day, from visit to visit, or seasonally, or from reversibility tests. This is defined as diurnal variability in PEF by >10% over 2 weeks; increase in FEV₁ by at least 12% AND 200 mL OR PEF by >20% from baseline after 4 weeks of anti-inflammatory treatment; fall in FEV₁ by >10% AND >200 mL from baseline after exercise; fall in FEV₁ from
What diseases may mimic asthma?

Alternative diagnoses may mimic asthma, or may co-exist with asthma. When patients fail to respond to asthma therapy, the following alternative diagnoses should be entertained:

- **Vocal Cord Dysfunction (VCD).** This is an upper aerodigestive tract respiratory disorder characterized by abnormal and inappropriate movement of the vocal cords. Many patients with this condition, with or without asthma, receive inappropriate treatment because they are misdiagnosed as just having difficult-to-control asthma. Diagnosis is often missed and can be a barrier to adequately treating patients, with uncontrolled respiratory symptoms. A finding of wheezing or stridor on auscultation of the cervical region is suggestive of vocal cord dysfunction, especially in elderly patients, and such dysfunction can be confirmed through laryngoscopy, the gold standard for its identification (i.e., inspiratory adduction of the anterior two-thirds of the vocal cords).

- **Chronic Obstructive Pulmonary Disease (COPD).** This is a differential diagnosis when patients initially present with asthma symptoms after the age of 40 years with significant history of smoking or other inhaled irritant exposure. Spirometry may distinguish asthma from COPD if lung function shows complete reversibility of the obstruction; or Asthma-COPD Overlap (ACO) may be a possibility among asthmatics who develop COPD later in life.

Other differential diagnoses in a patient with suspected asthma varies with age and are listed below:

- For young adults 12 to 39-years old:
  - Chronic upper airway cough syndrome – sneezing, itching, blocked nose, throat clearing
  - Hyperventilation dysfunctional breathing – dizziness, paresthesia, sighing
  - Bronchiectasis – productive cough, recurrent infections
  - Cystic fibrosis – excessive cough and mucous production
  - Congenital heart diseases – cardiac murmurs
  - Alpha-antitrypsin deficiency – shortness of breath, family history of early emphysema
  - Inhaled foreign body – sudden onset of symptoms
• For adults 40 years and above:
  - Hyperventilation dysfunctional breathing – dizziness, paresthesia, sighing
  - Bronchiectasis – productive cough, recurrent infections
  - Cardiac failure – dyspnea with exertion, nocturnal symptoms
  - Medication-related cough – treatment with angiotensin converting enzyme (ACE) inhibitors
  - Parenchymal lung disease – dyspnea with exertion, non-productive cough, finger clubbing
  - Pulmonary embolism – sudden onset of dyspnea, chest pain
  - Central airway obstruction – dyspnea, unresponsive to bronchodilators

References:
CHAPTER 2

Assessment and Classification of Asthma
The most important paradigm shift for asthma care is the shift to evaluating control rather than severity, which reflects the progress that has been made in the understanding of the disease and in the pharmacologic care of patients. Since 2006, the Global Initiative for Asthma (GINA) committee recommends that asthma assessment be based on asthma control (manifestations of the disease) rather than on severity (intermittent, mild persistent, moderate persistent and severe persistent). This key point of assessment was emphasized in the 2009 Philippine Consensus Report on Asthma Diagnosis and Management (PCRADM), the GINA 2014 and more recently, in the updated 2018 GINA guidelines. Assessment based on asthma control more directly reflects the effectiveness of therapeutic interventions and is more useful clinically as asthma is a variable disease.

On the other hand, classification of asthma according to severity suggests a static measure and is less helpful in guiding subsequent treatment.

How should we assess asthma?

Asthma should be assessed according to asthma control. (Evidence D)

Asthma control assessment is comprised of two parts: symptom control (previously “current clinical control”) and future risks for adverse outcome (Table 2.1). Both are important because of the close link between current level of control which is the immediate concern of the patient and the future risk especially of exacerbation or flare-ups. Lung function test is now included as an important part in the assessment of future risk.

Table 2.1. Assessment of asthma in adults, adolescents and children 6-11 years.

<table>
<thead>
<tr>
<th>1. Assess asthma control = symptom control and future risk of adverse outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Assess symptom control over the last 4 weeks</td>
</tr>
<tr>
<td>• Identify other risk factors for exacerbations, fixed airway limitation or side effects</td>
</tr>
<tr>
<td>• Measure lung function at diagnosis/start of treatment, 3-6 months after starting controller treatment, then periodically</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Assess treatment issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Document the patient’s current treatment steps</td>
</tr>
<tr>
<td>• Watch inhaler technique, assess adherence and side effects</td>
</tr>
<tr>
<td>• Check that the patient has a written asthma action plan</td>
</tr>
<tr>
<td>• Ask about patient’s attitudes and goals for their asthma and medications</td>
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</table>

<table>
<thead>
<tr>
<th>3. Assess comorbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Rhinitis, rhinosinusitis, gastroesophageal reflux, obesity, obstructive sleep apnea, depression and anxiety can contribute to symptoms and poor quality of life, and sometimes to poor asthma control.</td>
</tr>
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</table>
CHAPTER 2

What are the tools for assessing asthma symptom control?

More refined assessment tools resulted in better understanding of the behavior of an asthmatic over time and in this regard have been designed and validated to better reflect levels of control that have been used in treatment intervention studies.

A. Categorical symptom control tools

Questions answerable by yes or no are asked. The consensus-based GINA symptom control tool is an example (Table 2.2). Together with risk assessment of adverse outcomes, these may be used to guide treatment decisions. This classification correlates with assessment using numerical asthma control scores.9, 10

Table 2.2. GINA assessment of asthma control in adults, adolescents and children 6-11 years.

<table>
<thead>
<tr>
<th>A. Asthma symptom control</th>
<th>Level of asthma symptom control</th>
</tr>
</thead>
<tbody>
<tr>
<td>In the past 4 weeks, has the patient had...</td>
<td>Well controlled</td>
</tr>
<tr>
<td>Daytime asthma symptoms more than twice/week?</td>
<td>Yes</td>
</tr>
<tr>
<td>Any night waking due to asthma?</td>
<td>Yes</td>
</tr>
<tr>
<td>Reliever needed for symptoms* more than once a week?</td>
<td>Yes</td>
</tr>
<tr>
<td>Any activity limitation due to asthma?</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Well controlled asthma has none of these features, partly controlled has 1-2 of these and poorly controlled asthma has 3-4 of these features.

B. Numerical ‘asthma control’ tools

These tools, validated against healthcare provided assessment, provide scores and cut-off points to differentiate between levels of symptom control.10 These are more sensitive to change and therefore may be used to document patient progress than categorical tools.

Some examples of numerical tools are:

- Asthma Control Questionnaire (ACQ).11, 12 There are three ACQ versions and may contain 5, 6 or 7 items that give the version its name. All include 5 symptom questions, ACQ 6 adds reliever use and ACQ 7 includes a pre-bronchodilator score. The lower the number, the better the level of control.

Questions answerable by yes or no are asked. The consensus-based GINA symptom control tool is an example (Table 2.2). Together with risk assessment of adverse outcomes, these may be used to guide treatment decisions. This classification correlates with assessment using numerical asthma control scores.9, 10

Table 2.2. GINA assessment of asthma control in adults, adolescents and children 6-11 years.

<table>
<thead>
<tr>
<th>A. Asthma symptom control</th>
<th>Level of asthma symptom control</th>
</tr>
</thead>
<tbody>
<tr>
<td>In the past 4 weeks, has the patient had...</td>
<td>Well controlled</td>
</tr>
<tr>
<td>Daytime asthma symptoms more than twice/week?</td>
<td>Yes</td>
</tr>
<tr>
<td>Any night waking due to asthma?</td>
<td>Yes</td>
</tr>
<tr>
<td>Reliever needed for symptoms* more than once a week?</td>
<td>Yes</td>
</tr>
<tr>
<td>Any activity limitation due to asthma?</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Well controlled asthma has none of these features, partly controlled has 1-2 of these and poorly controlled asthma has 3-4 of these features.

B. Numerical ‘asthma control’ tools

These tools, validated against healthcare provided assessment, provide scores and cut-off points to differentiate between levels of symptom control.10 These are more sensitive to change and therefore may be used to document patient progress than categorical tools.

Some examples of numerical tools are:

- Asthma Control Questionnaire (ACQ).11, 12 There are three ACQ versions and may contain 5, 6 or 7 items that give the version its name. All include 5 symptom questions, ACQ 6 adds reliever use and ACQ 7 includes a pre-bronchodilator score. The lower the number, the better the level of control.

- Asthma Control Test (ACT).13, 14 The ACT includes four symptom/releiver questions plus a patient self-assessed level of control. In ACT, the range of score is 5-25. The higher score indicates better control.

Whichever numerical tool is used, it is important to note that respiratory symptoms may not be specific and, therefore, one needs to ascertain that the symptoms are due to asthma and are not from other comorbid conditions.

How do we assess future risk of adverse outcomes?

The second part of asthma control is to assess future risk of adverse asthma outcomes, particularly exacerbations, fixed airflow limitation and side-effects of medication (Table 2.3).5, 15

Table 2.3. Risk factors for poor asthma outcomes.

<table>
<thead>
<tr>
<th>Risk factors for developing fixed airway obstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Preterm birth, low birth weight and greater infant weight gain24</td>
</tr>
<tr>
<td>• Lack of ICS treatment25</td>
</tr>
<tr>
<td>• Exposure to tobacco smoke26, 27 or environmental chemicals28, 29</td>
</tr>
<tr>
<td>• Low initial FEV126, 27, 28, 30, 31</td>
</tr>
<tr>
<td>• High SABA use26, 27</td>
</tr>
<tr>
<td>• Elevated FENO in adults with allergic asthma26, 28, 32, 33</td>
</tr>
<tr>
<td>• Other major independent risk factors for flare-ups (exacerbations)</td>
</tr>
<tr>
<td>• Ever intubated or in intensive care unit for asthma24</td>
</tr>
<tr>
<td>• Having one or more exacerbations in the last 12 months25</td>
</tr>
</tbody>
</table>

Risk factors for medication side effects

- Systemic: frequent CSM; long-term, high-dose and/or potent ICS; also taking P450 inhibitors26, 32, 33
- Local: high-dose or potent ICS; also taking P450 inhibitors26, 32, 33
- Local: short-acting beta, agonist26, 32, 33

FEV1, forced expiratory volume in 1 second; FNO, fraction of exhaled nitric oxide; ICS, inhaled corticosteroids; OCS, oral corticosteroids; P450 inhibitors: cytochrome P450 inhibitors such as ritonavir, ketoconazole, clarithromycin; SABA, short-acting beta, agonist.

1 Independent risk factors are those that are significant after adjustment for the level of symptom control. Poor symptom control and exacerbation risk should not be simply combined numerically, as they have different causes and may need different treatment strategies.

2 Independent risk factors are those that are significant after adjustment for the level of symptom control. Poor symptom control and exacerbation risk should not be simply combined numerically, as they have different causes and may need different treatment strategies.
What is the role of lung function determination in the assessment of future risk of adverse outcomes?

Lung function does not correlate strongly with asthma symptoms in adults. When combined in numerical asthma control tools, symptoms frequency can outweigh important lung function results. However, a low initial FEV₁ is a strong independent predictor of risk of exacerbations, even after adjustment for symptom frequency.

Lung function should be assessed at diagnosis or start of treatment; after 3 to 6 months of controller treatment to assess the patient’s personal FEV₁; and periodically thereafter depending on the risk of adverse outcomes. In most adult patients, lung function can be recorded at least every 1 to 2 years. Interval lung function determinations (spirometry monitoring) are usually indicated in hard-to-control asthma and are preferably referred for specialist care.

The use of PEFR in asthma, either as part of an initial objective measure of airways caliber to be followed by a formal spirometry, or part of periodic assessment of control has long been advocated to be incorporated as a part of an asthma management plan. Its use has been evaluated in multiple studies that supports better outcome when used as part of a more comprehensive asthma program and is discussed in the pharmacological management of stable asthma and in acute asthma exacerbations or flare-ups.

How do you differentiate poorly controlled asthma and asthma exacerbations?

Poorly controlled asthma is another label that closely applies to the stable asthma condition that is characterized by more symptoms, increased use of medications and resulting in interference with activities of daily living very much akin to uncontrolled asthma. Some patients may not achieve the goals of good asthma control even with maximal therapy. There are initial steps recommended to investigate a patient with poor symptom control and/or exacerbation despite treatment (Figure 2.1). Asthma exacerbation, also termed acute asthma deterioration, is defined as a change in the stable condition that warrants a change in therapy and for both patient and the physician has an element of urgency. The patient experiences mild to severe deterioration in symptoms and is recognized by the patient’s ability to talk, presence or absence of distress by physical examination and if available the use of an objective measure of airway caliber like PEFR. Each level of severity, whether mild-to-moderate, are used to recommend the necessary steps to control/reverse the condition and prevent morbidity and/or mortality.

In situations where the line between poorly controlled asthma or actual exacerbation is hard to distinguish, previous recommendation states to err on the side of treatment as if it is an exacerbation.

**Figure 2.1. Investigating a patient with poor symptom control and/or exacerbations despite treatment.**

- **Watch patient using their inhaler**
  - Watch the patient use their inhaler(s), check against inhaler checklist.
  - Have emphatic discussion to identify poor adherence, e.g., “Many patients don’t use their inhaler as prescribed. In the last 4 weeks, how many days have you taken it?” (0 days, 1, 2, 3, etc.) and/or: “Do you find it easier to remember your inhaler in the morning or the evening?” Ask about beliefs, cost of medications, and refill frequency.

- **Discuss adherence and barriers to use**
  - Consider treatment step-up to next treatment level or alternative option on present level.
  - Use shared decision-making and balance potential benefits and risks.

- **Assess and manage comorbidities**
  - Check for risk factors or what factors such as smoking, beta-blockers or NSAIDs, or occupational or domestic allergen exposure, and address as possible Treating moderate risk factors.
  - Check for and manage comorbidities (e.g., rhinitis, obesity, GERD, obstructive sleep apnea, depression/anxiety) that may contribute to symptoms.

- **Confirm the diagnosis of asthma**
  - If no evidence variable airflow limitation or spirometry or other testing, consider having ICS dose and repeating lung function after 2-3 weeks; check patient has action plan; consider referring for challenge test.

- **Consider treatment step-up**
  - Consider treatment step-up to next treatment level or alternative option on present level.
  - Use shared decision-making and balance potential benefits and risks.

- **Refer to a specialist or severe asthma clinic**
  - If asthma is still uncontrolled after 3-6 months on high-dose ICS-LABA, or with ongoing risk factors, refer to a specialist or severe asthma clinic.
  - Refer earlier than 6 months if asthma is very severe or difficult to manage, or if doubts about diagnosis.

**Notes:**
- For clinical efficiency, the flowchart starts with the most common reasons for uncontrolled asthma (i.e., incorrect inhaler technique and poor adherence), as these can be identified in clinical practice – and often remedied – without any special resources. If symptoms and/or lung function improve when inhaler technique or adherence are addressed, this can provide confirmation of the diagnosis of asthma. However, the various steps may be carried out in a different order depending on the clinical context and available resources.
References:


A variety of risk factors, referred to as "triggers," cause asthma exacerbations. As a result, there is worsening of asthma symptoms and deterioration of asthma control, often despite existing maintenance treatment. Respiratory infections, allergens, irritants, environmental and occupational exposures are among the more common asthma triggers. Each of these factors are postulated to act through different mechanisms but has a final common pathway that includes cellular inflammation, heightened bronchial hyperresponsiveness and increased airflow obstruction.

For many of these risk factors, such as tobacco smoke, occupational agents, certain foods, additives and drugs, reducing or eliminating an affected patient’s exposure improves asthma control and reduces medication needs. For other known asthma triggers, such as allergens, respiratory infections and pollutants, avoidance measures where possible should be taken. However, because many asthma patients react to multiple factors that are ubiquitous in the environment, complete avoidance of these factors is usually impractical and very limiting to the patient. Thus, controller medications have an important role because patients are often less sensitive to these risk factors when their asthma is under good control.

This chapter discusses updates and important issues of a few of these asthma triggers.

**AEROALLERGENS**

*What is the burden imposed by allergen exposure in asthma?*

Allergenic triggers include indoor allergens, such as house dust mites (HDMs), molds, animal dander, cockroaches, and outdoor allergens, such as pollens and molds. HDMs are by far the most common Aeroallergen implicated in allergic individuals in Asian countries. Data from most of the Asian countries have reported rates of greater than 60% and even up to 80% in sensitized atopic individuals. The highest rates of HDM sensitization were reported in Singapore, Taiwan and South India, reaching almost 90%. The Philippines has one of the lowest sensitization rates at 33-47%. The most common species strongly associated with wheezing and asthma in atopic Asians is the Dermatophagoides HDM species, with a slightly lower percentage sensitized to Blomia Tropicalis. Southeast Asian countries, such as the Philippines, with stable year-round tropical climates typically do not experience wide fluctuations in environmental or indoor allergens such as dust mites and, thus, allergic disease phenotypes tend to be perennial rather than seasonal in these regions.
Dust mite population and sensitization patterns are heavily influenced not only by urbanization but by climatic conditions. However, the overall burden of dust mite sensitization in Asia is much higher than that seen in the United States and Europe, even in areas of similar climate and/or urbanization, and the question has been posed as to whether other factors such as genetics may play a role.  

Sensitization to other aeroallergens was generally lower compared to mites across the Asian population. Cockroach, followed by mold and animal dander, and subsequently grass and tree pollen, in descending order of positivity, formed the remainder of aeroallergens commonly seen in Asia. Pollen sensitization in Asia, apart from Japan, generally has less medical significance in Asia than in the West.

Because many asthmatic individuals especially children tend to be sensitized to more than one allergen, the more current approach to environmental remediation is multifaceted and targets multiple allergens.

**HOUSE DUST MITE (HDM) ALLERGENS**

Is the association of house dust mite (HDM) allergen exposure and asthma established?

Studies have found that exposure to dust mite allergens is associated with dust mite sensitization and with asthma. House dust mite allergen exposure is involved in triggers of asthma attacks and asthma outcomes such as asthmatic symptoms and a frequent requirement for medication in allergic asthmatic patients. However, the relationship of HDM exposure with visits to the emergency department has provided conflicting results. An updated review of findings from 11 studies from the scientific literature on indoor exposures and exacerbations of asthma concluded that in children sensitized to dust mites, there seems to be a causal relationship between exposure to dust mite allergen and asthma exacerbation. However, this causal relationship is not very evident in children not sensitized to dust mites and in adults, whether sensitized or non-sensitized.

Are avoidance measures directed to house dust mite (HDM) beneficial to asthma patients?

Many studies which have examined the efficacy of HDM interventions in HDM sensitized asthmatics revealed inconsistent results. A systematic review of 54 studies show that HDM interventions did not significantly decrease asthma symptoms compared to control groups.

There are measures that may show some benefit. A recent review indicated the level of evidence for these measures as follows:

- Frequent vacuum cleaning has not been proven to be sufficiently effective in reducing HDM exposure, while specific physical barriers, in particular pillow and mattress encasing, have been demonstrated to be more useful at this purpose. (Evidence B)
- Efforts could be made to restrict the presence of carpets, upholstered furniture and drapes in the environment of the dust mite allergic patients, in particular in the rooms where the patient spends the greatest amount of time, first of all in the bedroom. Although there is a lack of evidence to support this recommendation alone, these may be useful as a part of a comprehensive intervention plan.
- Humidifier use should be avoided while dehumidifiers can be used, although these do not generally filter the air as air conditioners do. (Evidence B)
- Washing sheets, pillowcases, mattress pads and blankets weekly effectively reduces mite counts. (Evidence B)
- Chemical products, so called acaricides such as benzyl benzoate and tannic acid, showed only modest effects on reducing mite allergen, therefore their use is not recommended.

The GINA guidelines acknowledge that measures should be implemented wherever possible to prevent the development of asthma and asthma symptoms and exacerbations. However, considering that mite allergens may trigger asthma symptoms, the GINA guidelines conclude that no single avoidance measure is likely to reduce exposure to mite allergens, but also that an integrated approach to avoidance cannot be widely recommended.

**MOLDS AND FUNGI**

What is the effect of indoor dampness and mold on asthma?

Published epidemiologic studies and meta-analyses show consistently that indoor dampness or mold or measured dampness was positively associated with exacerbation or severity of asthma. This causal relationship is
established with sufficient evidence in children, but less so in adults. The evidence, however, does not suggest that this relationship is restricted to those with specific sensitization to fungi or dust mites.5, 6, 11, 12, 13, 14, 15, 16

There are inexpensive measures to help discourage mold expansion, for example, reducing humidity by increasing ventilation, covering cold surfaces such as water pipes with insulation and increasing the air temperature to reduce surface humidity.17 It is often assumed that the specific causal agents for exacerbations of asthma that are associated with dampness are fungal, but this has not been confirmed. Other causal agents in dampness may include other biologic exposures such as bacteria, amoebas, dust mites that thrive in dampness or non-biologic exposures such as chemicals emitted from damp materials.13 It can therefore be challenging to isolate the health effects of fungal exposure in damp environments.

Credible research has shown that adverse health effects are associated with damp indoor environments, and governmental or professional bodies recommended that persistent dampness and mold damage in the nonindustrial workplace, including schools and residential housing, requires prevention, management and effective remediation.18, 19, 20

**FURRY ANIMALS**

What are the effects of furry animal exposure on asthma?

The health effects of furry animal exposure include development of allergen specific IgE (defined as sensitization) in susceptible individuals, often leading to manifestations of allergic diseases, such as asthma and rhinitis, if the exposure persists. Once a sensitized individual develops an allergic disease, continued exposure to the allergens is likely to exacerbate symptoms and lead to poorer outcomes.21

In an updated review, it was stated that there is sufficient evidence of a causal relationship between cat allergen exposure and exacerbation of asthma in individuals sensitized to cats.22 It also states that an association of dog allergen exposure to exacerbation of asthma in sensitized children, and also suggests associations in non-sensitized adults.5, 22

What intervention strategies can be adopted?

Avoidance is the most effective way to manage cat and dog allergy and patients should be advised to consider removing the cat or dog from the environment, if present, to improve respiratory health.21 (Evidence A)

Additional strategies include interventions aimed at reducing exposure to reservoirs and blocking pathways from reservoirs to home occupants.

Washing cats or dogs at least weekly can reduce airborne cat allergen Fel d 1 or dog allergen Can f 1; however, the clinical benefit is yet to be proven. Moreover, the effect of washing is not sustained. (Evidence B) Chemical treatments used to denature, oxidize or modify these allergens represent only temporary measures. Because the source is not removed, the allergen will re-accumulate after the treatment is applied. In addition, chemicals in the home need to be used with caution because some agents are volatile and can trigger symptoms in sensitized individuals. Long-term regular use of high-efficiency or central vacuum cleaners is associated with reduced exposure to Fel d 1 and Can f 1 in homes with cats or dogs living in them, although the health effects are uncertain.9, 21 (Evidence B)

**COCKROACH ALLERGENS**

Does cockroach allergen exposure cause exacerbation of asthma?

There is sufficient evidence of a causal relationship between cockroach allergen exposure and asthma exacerbation in individuals specifically sensitized to cockroaches, especially adults, but there is limited or suggestive evidence of such an association in children not sensitized to cockroaches.6, 23, 24

What intervention strategies can be adopted to minimize the effects of cockroach allergens?

Exposure to cockroach allergen in homes should be minimized to reduce the risk of cockroach sensitization (Evidence B) and reduce the risk of asthma morbidity in sensitized subjects.23 (Evidence C)

In general, individual interventions are not successful at eliminating exposure to cockroach contaminants, and therefore, it is necessary to use a combination of interventions depending on the specifics of the infestation. These interventions include initial removal of facilitating factors, elimination of the cockroaches and removal of reservoirs of cockroach-derived contaminants. Facilitating factors are conditions in the environment that facilitate or promote the production of contaminants by a source. For cockroaches, such factors include a means of ingress, as well as sources of water, food and shelter.24 (Evidence D)
IRRITANTS AND POLLUTANTS

OUTDOOR AIR POLLUTION

What are the effects of air pollution on asthma?

Within the past decade, a substantial body of research on the adverse effects of air pollution on asthma has been published. Air pollutants, at high concentrations, such as those noted in megacities of India and China, might have direct irritant and inflammatory effects on airway neuroreceptors and epithelium. However, other mechanisms are probably in operation in high income countries whose concentrations of air pollutants are lower.26

Air pollutants exert their detrimental effects on airways and lungs by: attenuating ciliary activity of airway epithelial cells, increasing permeability of airway epithelium leading to inflammatory changes in cells of airways and lung parenchyma, and modulating cell cycle and death of cells of respiratory system. Air pollutants show these effects by causing direct cellular injury or by inducing intracellular signaling pathways and transcription factors that are known to be sensitive to the oxidative stress.27

Specific pollutants such as ozone (O₃), nitrogen dioxide (NO₂) and particulate matter <2.5 μm in diameter (PM₂.₅) can induce airway inflammation and airway hyperresponsiveness. In addition, such pollutant exposures have been associated with oxidative stress, thought to be a feature of severe asthma.28

Can air pollution cause the development of asthma?

Increasing amounts of evidence suggest that long-term exposures to air pollution, especially traffic-related air pollution (TRAP) and its surrogate, NO₂, can contribute to new-onset asthma in both children and adults.26 The UK’s Committee on the Medical Effects of Air Pollutants found that the evidence is consistent with the possibility that outdoor air pollution might play a role in causing asthma in susceptible individuals living very close to busy roads carrying a lot of truck traffic.26

Four main mechanisms have been identified by which air pollution could contribute to asthma development: oxidative stress and damage, airway remodeling, inflammatory pathways and immunological responses and enhancement of respiratory sensitization to aeroallergens.29, 30 In humans, multiple mechanisms are likely involved, and air pollutants are likely to make only a small contribution, compared with other factors, in the development of asthma, and in only a small proportion of the population.29

Can air pollution trigger asthma exacerbations?

Air pollution that involve changes in gaseous and particulate outdoor air pollutants are associated with daily asthmatic symptoms, a decrease in lung function, emergency room (ER) visits and hospitalizations for asthma attacks.5

A recent meta-analysis provided evidence of the association between selected pollutants, namely, NO₂, PM₂.₅, O₃, carbon monoxide (CO) but not sulfur dioxide (SO₂) and particulate matter <10 μm in diameter (PM₁₀).28 In children, the association was significant for NO₂, SO₂ and PM₁₀.28

Short-term exposures to O₃, NO₂, SO₂, PM₂.₅ and TRAP may increase the risk of exacerbations of asthma symptoms.26, 32, 33 A meta-analysis using various databases has shown that acute elevation of PM concentration in the air may increase hospital admission for asthma. It was specifically noted when the concentration of PM₁₀ is increased to 10 μg/m³, the increment of asthma-related hospital admissions is nearly twice than that when the concentration of PM₂.₅ is increased to 10 μg/m³.26, 34

What avoidance measures reduce the impact of air pollution exposure on asthma?

For patients with clear association of exposure to air pollutants and increase in asthma symptoms, it is often advised to stay indoors and to limit physical exertion when air pollutant levels exceed health-based thresholds. However, there is limited evidence that these individual actions can reduce health risks. Relative contribution of indoor and outdoor-generated pollutants to personal exposures depends on multiple factors, including the type of pollutants, building structure, indoor sources and personal activities and these should be considered so that healthcare providers and their patients may tailor interventions to individual circumstances in order to maximize the net exposure reduction based on individual circumstances.35

INDOOR FUEL EXPOSURE

Indoor fuels include solid, liquid and gas fuels. Solid fuels include biomass and coal. Biomass fuel refers to any living or recently living plant and/or animal-based material that is deliberately burned by humans as fuel, such as wood, twigs, dried animal dung, charcoal, grass or agricultural crop residues.36 Stoves fueled by coal or biomass, which are major sources of indoor combustion, release respiratory irritants such as particulate matter (PM), CO, SO₂, NOₓ and organic toxins. Burning biomass fuels, mainly wood, crop residues and livestock dung, remain as the important source of exposure to a variety of toxins.37
What is the effect of indoor fuel exposure on asthma?

Studies examining biomass and adult asthma are not uniformly positive and the associations with specific fuel type are inconsistent. A population survey study from India indicates that adult women living in households using biomass and solid fuels have a significantly higher risk of asthma than those living in households using cleaner fuels (OR: 1.26; 95% CI: 1.06–1.49; \( p = .010 \)), even after controlling for the effects of a number of potentially confounding factors.

A more recent review by Desai and colleagues have estimated that exposure to solid fuel smoke exacerbates asthma with a relative risk of 1.6 (95% CI, 1.0–2.5%) in children between 5 and 14 years and 1.2 (95% CI, 1.0–1.5) in persons older than 15 years. In adults with asthma, however, there is no evidence that indoor biomass use contributes to worse morbidity and exacerbations. Existing evidence from five studies is mixed for use of other fuels and exacerbations in adults. Although there is no direct evidence to implicate indoor biomass fuel burning for exacerbation of asthma in children, there is supportive evidence by gas stove use.

It is currently unclear if prevention of chronic disease can be achieved by reducing solid fuel exposure and how much reduction in exposure is required to achieve a useful benefit. The importance of increased awareness about the health effects of solid fuel smoke inhalation still needs to be emphasized. The promotion of preventive initiatives through education, research and policy change is recommended.

TOBACCO SMOKE

What is the effect of tobacco smoke on asthma?

It has been established in several studies that the risk of developing asthma was significantly higher among current smokers and among ex-smokers compared with those who have never smoked. Their results support the hypothesis that smoking causes asthma in adulthood. In addition, they found that women may be more susceptible to the adverse effects of smoking. It is debatable whether smoking induces the development of asthma in adolescents.

Furthermore, several investigators have found that asthmatic patients who smoke are more likely to have poorer disease control compared with asthmatic non-smokers. Asthmatic smokers are at risk of developing severe symptoms, higher frequency of exacerbations and worse asthma-specific quality of life. Cigarette smoking in asthma is also associated with increased numbers of life-threatening asthma attacks and greater asthma mortality.

Airway mucosal permeability is increased in smokers, which could lead to increased clearance of inhaled corticosteroids (ICS) from the airways. Smokers also have decreased histone deacetylase activity, which is necessary for corticosteroids to fully suppress cytokine production, and can lead to corticosteroid resistance.

What is the effect of secondhand smoke (SHS) on asthma?

Secondhand smoke (SHS), also referred to as passive smoking, environmental tobacco smoke and involuntary smoking, contain irritant gases, such as ammonia, nitrogen dioxide, sulfur dioxide, hydrogen cyanide and acrolein which can contribute to the development of airway disease.

Of all forms of SHS, maternal exposure seems to have the largest impact on asthma by increasing the frequency and severity of the disease and decreasing lung function during pregnancy. Asthmatic children exposed to multiple household smokers face an increased risk for respiratory illness-related absences from school, and these effects persist during adolescence but weaken during adulthood.

What are the benefits of smoking cessation and the interventions that are needed?

Smoking cessation improves several asthma outcomes. In a prospective study by Tonnesen et al, asthmatic smokers who stopped smoking experienced a significant improvement in quality of life, decreased hyperreactivity and a reduction in their usage of rescue medications. It has also been shown that asthmatic ex-smokers exhibited significant improvement in FEV₁, asthma control, recovery to corticosteroid response and decrease in neutrophil counts in sputum compared with individuals who continued to smoke. In another study, it was demonstrated that the improvement in airway hyperresponsiveness was maintained one year after smoking cessation which was not seen in the control group.

The evidence reviewed in published articles regarding the multiple negative effects of smoking and SHS on patients with asthma pose the urgent need to emphasize the obligation of all physicians and other healthcare professionals to assist patients and those they live with to quit smoking. Specific instructions for family members, caregivers and friends of patients with asthma should include never smoking in the home, car or workplace. Simply smoking in another room of the house is not sufficient, nor are any forms of air cleaners effective in reducing SHS exposure. It has been estimated that with successful smoking cessation, a parent can add an average of 7 years to his or her life, eliminate SHS exposure to other family members and reduce tobacco-related pregnancy outcomes.
The management of asthmatic smokers should begin with emphatic recommendations to stop smoking, including having no contact with environmental smoke. It is recommended that asthmatic smokers may need specific medications for smoking cessation in a concurrent schema of behavioral techniques. A new perspective is electronic cigarettes, but many uncertainties currently exist about their utility in smoking cessation. Cross-sectional studies on adolescents on e-cigarette use is associated with increase prevalence of asthma and chronic bronchitis. Several new drugs are being introduced in the arsenal of asthma treatment, but most of them have not been tested for the asthmatic smokers. Although no single pharmacotherapy can serve as a universally successful treatment given the complexities of tobacco dependence and individuality of smokers, the clinician should emphasize clearly that people with asthma should not smoke.

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CLIMATE CHANGE AND GLOBAL WARMING

What is the effect of climate change on asthma?

Climate change poses a massive threat to respiratory health by directly promoting or aggravating respiratory diseases or by increasing exposure to risk factors for respiratory diseases. The key climatic change factors that could potentially influence respiratory disease are extreme temperature events (both hot and cold), changes in air pollution, flooding, damp housing, thunderstorms, changes in allergen disposition and consequent allergies, forest fires and dust storms. The effects of climate change may either be short or long term.

Climate change affects allergenic plants and pollen distribution worldwide. There is evidence that, during pollen season, thunderstorms can be associated with allergic asthma outbreaks in patients suffering from pollen allergy. There is a close temporal association between the arrival of a thunderstorm, a major rise in concentration of pollen grains and the onset of asthma epidemics. Thunderstorms occurring during the pollen season have been observed to induce severe asthma attacks in pollinosis patients. Associations between thunderstorms and asthma morbidity have been identified in multiple locations around the world.

Climate change will increase the frequency and intensity of floods and cyclones and thus fungal spore production, a powerful asthma and rhinitis trigger. Both diseases are caused or aggravated by components of bioaerosol from the natural environment or from indoor environments in enclosed spaces, workplaces and homes.

Climate change, coupled with air pollutant exposures, may have potentially serious adverse consequences for human health. Rising temperatures will contribute to the elevation of the concentrations of ozone (due to more sunlight and higher temperature) and particulate matter (due to wildfire, droughts, desertification, sandstorms and an increased use of coal-fired power to produce energy for cooling) at ground level.

EXERCISE-INDUCED BRONCHOCONSTRICTION (EIB)

What is the effect of exercise on asthma?

It has long been recognized that physical exercise may trigger symptoms of asthma. Exercise-induced bronchoconstriction (EIB) is acute airway narrowing that occurs as a result of exercise.

Recent clinical practice guidelines recommended to abandon the term of exercise-induced asthma (EIA) because exercise is not the cause, but only a trigger of asthma. It was suggested to use the terms EIB with asthma (EIBA), the occurrence of bronchial obstruction after exercise in asthmatic patients, and EIB without asthma (EIBWA), the occurrence of bronchial obstruction in subjects without other symptoms and signs of clinical asthma. The latter may be seen particularly in children, athletes and patients with atopy or rhinitis, or following respiratory infections.

How is exercise-induced bronchoconstriction (EIB) diagnosed?

Symptoms alone are insufficient to identify patients with EIB. In order to establish a secure diagnosis, it is important to perform objective testing to confirm dynamic changes in airway function by measuring the change in FEV\textsubscript{1} during exercise. Recent clinical practice guidelines recommended to use exercise capacity tests to objectify changes in airway function. An ECT should be performed in subjects with EIBA only when their baseline FEV\textsubscript{1} is ≥70% of normal. A diagnosis of EIB is established when there is ≥10% fall in FEV\textsubscript{1} at any two consecutive time point recordings (1, 3, 5, 10, 15, 20, 25, 30 minutes) after 6 to 8 minutes of treadmill or cyclo-ergometer exercise in ambient conditions (20-25°C; relative humidity <50%). The intensity of exercise should be enough to reach in the first 2 to 3 minutes 40-60% of the predicted maximum voluntary ventilation (estimated as baseline FEV\textsubscript{1} X 35) or 80-90% of the predicted maximal heart rate.
Other bronchoprovocative tests (BPTs) may be optional diagnostic tools for EIB, such as methacholine or histamine bronchoprovocation that directly documents bronchial hyperreactivity, or indirect tests, such as eucapnic voluntary hyperpnea (EVH), hypertonic saline challenge and mannitol inhaled powder challenge reproduce the effects of exercise on the airways and may be more accurate to diagnose EIBwA.76

**What is the treatment and prevention of exercise-induced bronchoconstriction (EIB)?**

Treatment of both EIBA and EIBwA is essentially based on reversing bronchial obstruction by using short-acting beta2-agonists (SABA).76

Because EIBA is a sign of poor asthma control, prevention essentially consists of following international guidelines to achieve asthma control.77 For all patients with EIB, use of an inhaled SABA before exercise is recommended.78 *(Strong recommendation, High-quality evidence)*

The SABA is typically administered 15 minutes before exercise. For patients who continue to have symptoms despite using an inhaled SABA before exercise, or who require an inhaled SABA daily or more frequently, daily administration of an ICS *(Strong recommendation, Moderate-quality evidence)* or a leukotriene receptor antagonist (LTRA) *(Strong recommendation, Moderate-quality evidence)* is recommended.74

In cases where the baseline lung function is below normal, an ICS is appropriate. Additional therapies are appropriate for patients who continue to have symptoms despite using an inhaled SABA before exercise or who require an inhaled SABA daily or more frequently.74

Nonpharmacological therapy for all patients with EIB, interval or combination warm-up exercise before planned exercise is recommended.74 *(Strong recommendation, Moderate-quality evidence)* For patients with EIB who exercise in cold weather, use of a device (e.g., face mask or scarf) that warms and humidifies the air during exercise is suggested.74 *(Weak recommendation, Low-quality evidence)* The potential occurrence of EIBA should not prevent asthmatic patients from an adequate practice of physical exercise, which is not associated to an increased risk of asthma developing or worsening and should instead represent part of their treatment.74

**BETA-BLOCKERS**

*Can beta-blockers be given to asthmatics?*

When indicated, cardioselective beta-blockers are preferred over non-cardioselective beta-blockers. *(Strong recommendation, High-quality evidence)*

A systematic review of literature published in 2013 concluded that the available, although limited, evidence suggests that a dose-escalating model of beta-blocker therapy to patients with asthma is well tolerated, does not induce acute bronchoconstriction, and, not least, may have beneficial effects on airway inflammation and airway hyperresponsiveness in some patients with asthma. Further studies addressing the potential role of beta-blocker therapy for asthma are clearly needed, but careful selection of the target population is warranted.79

In a recent population-based nested case control study, a cohort consisted of 35,502 people identified with active asthma and cardiovascular disease, of which 14.1% and 1.2% were prescribed cardioselective and non-selective beta-blockers, respectively, during follow-up. It was shown that cardioselective beta-blocker use was not associated with a significantly increased risk of moderate or severe asthma exacerbations and, thus, potentially could be used more widely when strongly indicated.80

**RESPIRATORY INFECTIONS**

*What is the impact of viral respiratory infections on asthma?*

In both children and adults, viral infections of the airways may be associated with the development of chronic asthma, as well as with acute exacerbations for those with existing asthma.81, 82, 83, 84, 85, 86, 87, 88, 89, 90

The most commonly involved viruses associated with asthma exacerbations include human rhinovirus (HRV), respiratory syncytial virus (RSV), influenza and parainfluenza viruses, coronavirus, enterovirus and adenovirus. Human rhinovirus represents the most frequent cause of infectious respiratory illnesses affecting adults while influenza and parainfluenza viruses affect all age groups.84, 85
Several recent studies have also shown that respiratory allergy may partner with certain viral infections to synergistically produce airway inflammation and increase cold and asthma symptoms. Environmental factors may act synergistically with viral infections and other known triggers leading to acute exacerbations.

Are there effective treatment and preventive strategies for virus-induced exacerbations?

Eradication of respiratory viruses would be the ideal approach but it is not realistic nor feasible. Virus-induced asthma exacerbations are likely to involve multiple mechanisms and, as such, a single treatment modality is unlikely to be effective in all people with asthma. For specific antiviral therapies to be implemented into clinical practice, it also may be necessary to develop accurate, affordable and rapid viral diagnostics.

Optimization of current therapies may be beneficial. Treatment with anti-inflammatory drugs such as ICS can reduce the risk of exacerbations by 40% to 50%, and this suggests that moderating inflammation may reduce the chances that a cold will precipitate bronchospasm. Exacerbations have also been prevented by combined treatment with ICS and long-acting beta2-agonists (LABAs).

Should antibiotics be routinely used in the treatment of asthma exacerbations?

Antibiotics should not be routinely used in the treatment of asthma exacerbations. However, despite guideline recommendations, antibiotics are often included in the treatment regimen for exacerbations. Current guidelines state that antibiotics should be reserved for cases in which clear signs, symptoms or laboratory test results are suggestive of bacterial infection. Bacterial infections are thought to be responsible for asthma exacerbation, however, evidence show that this is true for only a minority.

Atypical organisms, such as M. pneumoniae and Chlamydophila pneumoniae, may have possible association with asthma exacerbations. However, studies have shown inconsistent results and their role in acute exacerbations has not been definitively established. These organisms seem to be involved more with asthma persistence rather than with disease exacerbations.

It was also hypothesized that bacteria interact with respiratory cold viruses to alter outcomes of respiratory infections in asthmatic individuals, but little is known about the role of secondary bacterial infections in increasing the severity and persistence of symptoms.

The Azithromycin Against Placebo in Exacerbations of Asthma (AZALEA) randomized, double-blind, placebo-controlled, multicenter clinical trial conducted in the United Kingdom from September 2011 to April 2014 studied the effect of azithromycin in patients presenting in the emergency room for asthma exacerbation requiring a course of systemic steroids. This study conclusively showed that azithromycin treatment resulted in no statistically or clinically significant benefit. For each patient randomized, more than 10 were excluded because they had already received antibiotics.

In a recent Cochrane review of six published studies that included 681 adults and children with asthma, the authors concluded that there was very limited evidence that antibiotics may help people having asthma attacks. However, they did not find much information about important outcomes such as hospital admissions or side effects.
References:

5. Gautier C, Chapin D. Environmental triggers and avoidance in the management of asthma, J Asthma Allergy, 2017:10 47-56.


84. Busse WW, Lemanske RF Jr, Gern JE. The role of viral respiratory infections in asthma and asthma exacerbations. Lancet 2010; 376:826-34.
The goals of asthma management are to achieve good symptom control, to control exacerbations and to minimize future risk of exacerbations, fixed airflow limitation and side-effects of treatment. In this chapter, pharmacologic options for treatment of asthma will be discussed.

The pharmacologic options for treatment of asthma fall into three main categories, namely: controller medications, reliever medications and add-on therapies. Controller medications reduce airway inflammation, control symptoms and reduce future risks for exacerbations and decline in lung function and are therefore advised to be used regularly for maintenance treatment. On the other hand, reliever medications, which relieve acute bronchospasm, are “rescue” medications provided to all patients for relief in case of breakthrough symptoms including worsening asthma or exacerbations. These are also recommended for short-term exercise-induced bronchoconstriction. Reducing and, ideally, eliminating the need for reliever treatment is both an important goal in asthma management and a measure of success of asthma treatment. Add-on therapies are given for patients already on optimized controller medications with treatment of modifiable risk factor, who remained uncontrolled, with severe symptoms or persistent exacerbations.

CONTROLLERS

What are the recommended controller medications for asthma?

Inhaled corticosteroids (ICS) are the cornerstone of therapy and are currently the most effective anti-inflammatory medications for the treatment of persistent asthma. Several studies consistently demonstrate that ICS are effective in reducing symptoms, improving quality of life, decreasing frequency of flare-ups, decreasing the need for bronchodilator rescue therapy, improving lung function and reducing asthma mortality. Studies showed that ICS are relatively safe. At low to moderate doses, ICS do not frequently exhibit clinically important side-effects and provide asthmatics a good risk-benefit profile.

Are all inhaled corticosteroids (ICS) the same?

Not all ICS are the same. The available ICS differ in their: relative glucocorticoid receptor binding affinity, lipophilicity or aqueous solubility, plasma protein binding, plasma clearance and half-life. The most potent ICS is fluticasone furoate while flunisolide has the least potent attributes. Comparatively, oral prednisolone ranks even lower based on
these attributes with considerably higher incidence of side-effects. The potential advantage of a more potent ICS is that a lower dose is required to occupy the same numbers of glucocorticoid receptors in the airways, resulting in a lower daily dose with equivalent efficacy. Figure 4.1 depicts mid-range nominal therapeutic daily doses of ICS used in adult asthma plotted against potency and expressed as relative glucocorticoid receptor binding affinity. This clearly shows the exponential decline in therapeutic daily dose with increasing potency. Despite differences in potency of ICS, at recommended doses, clinical efficacy has been noted to be equipotent.

Fluticasone furoate (FF), mometasone furoate (MF), fluticasone propionate (FP), budesonide (BUD), beclometasone dipropionate (BDP), ciclesonide (CIC), flunisolide (FLU).

Figure 4.1. Relationship between glucocorticoid receptor binding affinity and mid-range nominal therapeutic daily doses of inhaled corticosteroids (ICS) ($r^2 = 0.980$).

The different ICS are listed below (Table 4.1) with the corresponding pharmacological characteristics of binding affinity, lipophilicity, aqueous solubility, plasma protein binding percentage, plasma clearance and half-life.

Table 4.1. Inhaled corticosteroid pharmacological characteristics.

<table>
<thead>
<tr>
<th>INHALED CORTICOSTEROIDS</th>
<th>Relative glucocorticoid receptor binding affinity</th>
<th>Lipophilicity</th>
<th>Aqueous solubility (mcg/mL)</th>
<th>Plasma protein binding (%)</th>
<th>Plasma clearance h$^{-1}$</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluticasone furoate (FF) DPI</td>
<td>2989</td>
<td>4.17</td>
<td>0.03</td>
<td>99.7</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Mometasone furoate DPI</td>
<td>2100</td>
<td>4.73</td>
<td>&lt;0.1</td>
<td>99.5</td>
<td>54</td>
<td>4.5</td>
</tr>
<tr>
<td>Fluticasone propionate (FP) DPI</td>
<td>1775</td>
<td>3.89</td>
<td>0.14</td>
<td>99.3</td>
<td>69</td>
<td>7.8</td>
</tr>
<tr>
<td>Beclometasone dipropionate (BDP) MDI</td>
<td>53</td>
<td>4.39 (3.27)</td>
<td>0.37 (15.5)</td>
<td>95.9</td>
<td>120</td>
<td>0.5</td>
</tr>
<tr>
<td>Ciclosonide (des-CIC) MDI</td>
<td>12 (1200)</td>
<td>3.2 (3.0)</td>
<td>0.17 (7)</td>
<td>98.7</td>
<td>228</td>
<td>0.36/3.4</td>
</tr>
<tr>
<td>Budesonide DPI</td>
<td>935</td>
<td>2.32</td>
<td>16</td>
<td>91.4</td>
<td>84</td>
<td>2.8</td>
</tr>
<tr>
<td>Triamcinolone acetonide MDI</td>
<td>233</td>
<td>1.85</td>
<td>21</td>
<td>73.2</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Flunisolide MDI</td>
<td>190</td>
<td>1.36</td>
<td>140</td>
<td>61.2</td>
<td>58</td>
<td></td>
</tr>
</tbody>
</table>

What are the recommended doses of inhaled corticosteroids (ICS)?

Doses of ICS may be classified as low, medium and high, based on clinical comparability. Table 4.2 shows low, medium and high daily doses of ICS for adults and adolescents (12 years and older). Once good symptom control has been maintained for 3 months, the ICS dose should be carefully titrated to the minimum dose, taken regularly to maintain good symptom control and minimize exacerbation risk, while reducing the potential side-effects. Those patients that need high dose of ICS must be referred to a specialist for expert assessment and advice. Additional benefits of ICS include modification of airway remodeling and prevention of an accelerated decline in lung function.
Their long term use in adequate doses has been shown to decrease exacerbations and mortality.

**Table 4.2. Low, medium and high daily doses of inhaled corticosteroids (ICS).**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>LOW</th>
<th>MEDIUM</th>
<th>HIGH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclometasone dipropionate (CFC)</td>
<td>200-500</td>
<td>&gt;500-1000</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>Beclometasone dipropionate (HFA)</td>
<td>100-200</td>
<td>&gt;200-400</td>
<td>&gt;400</td>
</tr>
<tr>
<td>Budesonide (DPI)</td>
<td>200-400</td>
<td>&gt;400-800</td>
<td>&gt;800</td>
</tr>
<tr>
<td>Ciclesonide (HFA)</td>
<td>80-160</td>
<td>&gt;160-320</td>
<td>&gt;320</td>
</tr>
<tr>
<td>Fluticasone furoate (DPI)</td>
<td>100</td>
<td>n.a.</td>
<td>200</td>
</tr>
<tr>
<td>Fluticasone propionate (DPI)</td>
<td>100-250</td>
<td>&gt;250-500</td>
<td>&gt;500</td>
</tr>
<tr>
<td>Fluticasone propionate (HFA)</td>
<td>100-250</td>
<td>&gt;250-500</td>
<td>&gt;500</td>
</tr>
<tr>
<td>Mometasone furoate</td>
<td>110-220</td>
<td>&gt;220-440</td>
<td>&gt;440</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>400-1000</td>
<td>&gt;1000-2000</td>
<td>&gt;2000</td>
</tr>
</tbody>
</table>

**How safe is long term use of inhaled corticosteroids (ICS)?**

Clinically important adverse events are rare with doses of 800 mcg/day or less. Inhaled corticosteroids given long-term use with doses greater than 800 mcg/day is likely to cause osteoporosis. Side-effects may occur at doses above 1 mg/day such as HPA suppression, cataracts, skin thinning and easy bruising, but these may be acceptable risks in a patient who would otherwise take oral corticosteroids (OCS). There are no reports of any life-threatening events.

Effects of local deposition of ICS can cause the following: dysphonia, topical candidiasis and contact hypersensitivity. Symptomatic candidiasis affects less than 5% and can be usually controlled by measures that limit oropharyngeal deposition (i.e., gargle with water, topical antifungal treatment). Inhaled corticosteroid use has been shown to increase the risk of tuberculosis (TB) in an intermediate TB burden country. Clinicians should be aware of the possibility of TB development among long-term high-dose users.

**What is the role of systemic corticosteroids?**

Systemic corticosteroids, if given early in the treatment of asthma exacerbations in the emergency room (ER) setting, were shown to be effective in reducing symptoms and decreasing rate of hospitalization. In a Cochrane database review by Rowe et al, the greatest benefit of systemic corticosteroids in reducing rate of hospital admission was observed in patients with more severe symptoms and not on any corticosteroid therapy. The usual dose of systemic corticosteroids is computed at 1-2 mg/kg/day of prednisone. Table 4.3 shows the relative potencies of commonly used corticosteroids. There was no significant added benefit from giving high-dose systemic corticosteroids (above 60-80 mg/day or 2 mg/kg/day), in terms of improving the pulmonary function, rate of admission or length of hospital stay. A systematic review of randomized controlled studies of patients with acute severe asthma compared different doses of corticosteroids with a minimum follow-up of 24 hours. Corticosteroids used in the included trials were divided into three groups as an equivalent dose of methylprednisolone over 24 h: low dose (<80 mg), medium dose (>80 mg and ≤360 mg) and high dose (>360 mg). Nine trials were included with a total patients' number of 344 adults. No differences were found among the different doses.

For patients discharged from the ER setting after effective control of symptoms, prescribing a short course of OCS was found to reduce the rate of relapse. However, courses longer than 5 days were not found to provide any additional benefit. For patients discharged from the ER setting after effective control of symptoms, prescribing a short course of OCS was found to reduce the rate of relapse. However, courses longer than 5 days were not found to provide any additional benefit.
Table 4.3. Common types of systemic corticosteroids and their relative properties.

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Potency relative to hydrocortisone</th>
<th>Relative sodium retention potency</th>
<th>Biological half-life (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>1</td>
<td>1</td>
<td>8-12</td>
</tr>
<tr>
<td>Prednisone/prednisolone</td>
<td>4</td>
<td>0.8</td>
<td>12-36</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>5</td>
<td>0.5</td>
<td>12-36</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>25</td>
<td>0</td>
<td>36-72</td>
</tr>
</tbody>
</table>

Are all long-acting beta-2-agonists (LABAs) the same?

Long-acting bronchodilators differ in their onset of action, duration of action and half-life.14 (Table 4.4) Sustained action bronchodilators such as salmeterol and formoterol are administered twice daily dosing due to its 12-hours’ duration of action. They are useful in controlling nocturnal symptoms and exercise-induced asthma. Formoterol has a rapid onset of action of about 1-3 minutes after administration and has a wide dose range, hence its usefulness as reliever. On the other hand, salmeterol is not suitable for acute relief of asthma since it has a long onset of action and is limited by the ceiling dose of 50 mcg twice a day. However, it cannot be over-emphasized that LABAs should never be used alone as it has been reported in several studies that monotherapy with LABA increases asthma related deaths.

Table 4.4. Pharmacologic characteristics of long-acting bronchodilators.

<table>
<thead>
<tr>
<th>LABA</th>
<th>Onset of action (mins)</th>
<th>Duration of action (h)</th>
<th>Half-life (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmeterol</td>
<td>10-30</td>
<td>12</td>
<td>12-15 days</td>
</tr>
<tr>
<td>Formoterol</td>
<td>1-3</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Olodaterol</td>
<td>5</td>
<td>24</td>
<td>7.5</td>
</tr>
<tr>
<td>Vilanterol</td>
<td>5.0±0.5</td>
<td>24</td>
<td>2.5</td>
</tr>
<tr>
<td>Indacaterol</td>
<td>4.0±0.2</td>
<td>24</td>
<td>&gt;30</td>
</tr>
</tbody>
</table>

Monotherapy with a LABA given on a long-term basis leads to down regulation of beta-receptors, a process associated with beta-agonist tolerance which may result in increasing doses of beta-agonist and higher prevalence of adverse events and even death. Therapy with inhaled LABA may cause cardiovascular stimulation, skeletal muscle tremor and hypokalemia. Data indicating a possible increased risk of asthma-related death associated with the use of salmeterol in a small group of individuals led to advisories from the US Food and Drug Administration (FDA) and Health Canada that LABAs are not a substitute for inhaled or oral glucocorticosteroids, and should only be used in combination with an appropriate dose of ICS.

There are no studies yet for the role of monotherapy with olodaterol, vilanterol and indacaterol in the treatment of persistent asthma.

What is the benefit of inhaled corticosteroid – long-acting beta-2-agonists (ICS-LABA) combination in achieving asthma control?

Analysis of several studies clearly show that adding a LABA to ICS is more effective than increasing the dose of ICS in terms of improving asthma control and reducing exacerbations.15

Inhaled corticosteroid – long-acting beta-2-agonists combination in clinical studies and systematic reviews consistently show improvement in symptom scores, decrease in nocturnal asthma symptoms, improvement in lung function, decrease in the use of rapid-acting inhaled beta-2-agonists, reduction in the number of exacerbations and achievement of clinical control of asthma in more patients, more rapidly, and at a lower dose of ICS than ICS given alone.
Long-acting beta$_2$-agonists, when given concomitantly with corticosteroids, can activate glucocorticoid receptors and enhance the transcription of anti-inflammatory mediators and, at the same time, provide a protective mechanism against the down-regulation of beta$_2$-receptors. Glucocorticoids and beta$_2$-agonists both inhibit proliferation of airway smooth muscle cells in vitro. The exact signal transduction process involved in this synergistic mechanism is not yet fully understood.

In the local setting, initial therapy with ICS-LABA in patients with mild persistent asthma may provide greater improvements in lung function and asthma control, improve compliance and has comparable safety to ICS alone.

The use of ICS-formoterol has an added advantage of serving both as controller and reliever when used as a single inhaler therapy in the maintenance and reliever strategy.

**RELIEVERS**

**What are the reliever medications for asthma?**

Reliever medications are usually bronchodilators that quickly relieve bronchospasm. These medications generally do not treat the underlying inflammatory process of asthma. Reliever medications for asthma are mainly short-acting sympathomimetic beta$_2$-agonists (SABAs), such as salbutamol and terbutaline and short-acting muscarinic antagonists (SAMAs), such as ipratropium.

Short-acting beta$_2$-agonists have more rapid onset of action and provide three to four times more bronchodilatation than the SAMAs and were recommended for use on an as-needed basis at the lowest dose and frequency required. Increased use, especially daily use, is a warning of deterioration of asthma control and indicates the need to reassess treatment. Failure to achieve a quick and sustained response to beta$_2$-agonist treatment during an exacerbation mandates medical attention and may indicate the need for short-term treatment with oral glucocorticosteroids.

Patients who regularly use SABAs alone without concomitant anti-inflammatory therapy are at an increased risk for asthma-related death and urgent asthma-related healthcare. As such, in the chronic management of asthma, SABA-only treatment for as-needed relief of symptoms is no longer a preferred option.

Short-acting anti-muscarinic agents are anticholinergic bronchodilators that are also quick acting medications but generally less potent than beta$_2$-agonists. For patients with moderate-severe exacerbation seen at the ER, the addition of ipratropium to a SABA was associated with fewer hospitalizations and greater improvement in PEF and FEV$_1$ compared with SABA alone.

Oral SABA or short-acting theophylline are potential alternatives to SABA for relief of asthma symptoms; however, these agents have a slower onset of action than inhaled SABA, (Evidence A) and oral SABA and theophylline have a higher risk of side-effects.

The rapid-onset LABA, formoterol, is as effective as SABA as a reliever medication in adults and children, but use of regular or frequent LABA without ICS is strongly discouraged because of the risk of exacerbations. (Evidence A)

The use of low-dose ICS-formoterol for as-needed symptom relief in mild asthma is based on a large double-blind study comparing this regimen with SABA-only treatment. (Evidence B) At present, as-needed ICS-formoterol is considered off label in most countries, including the Philippines.

Under certain circumstances, high-dose intravenous (IV) corticosteroids and OCS may also relieve acute asthma symptoms.

**ADD-ON THERAPIES**

**What is the mechanism of action of leukotriene modifiers?**

Leukotrienes are released from mast cells, basophils and eosinophils which causes airway constriction, increased mucus production, swelling and inflammation in the lungs. Leukotriene modifiers prevent the action of leukotrienes in the body. Montelukast, the only available leukotriene modifier in the Philippines, is a cysteinyi leukotriene receptor antagonist (LTRA) used for the maintenance treatment of asthma and to relieve symptoms of seasonal allergies. Montelukast acts by blocking the action of leukotriene D4 (and secondary ligands, leukotrienes C4 and E4) on the cysteinyi leukotriene receptor CysLT1 in the lungs and bronchial tubes by binding to it. This reduces the bronchoconstriction otherwise caused by the leukotriene and results in less inflammation.

A recent meta-analysis of randomized, controlled trials (RCTs) on montelukast confirms its usefulness as on montelukast confirms its usefulness as monotherapy and add-on therapy to ICS in mild-to-moderate
childhood asthma across all age groups. Inhaled corticosteroids are generally superior to montelukast for asthma management. In adults, it is mainly used as a complementary therapy in addition to ICS if ICS alone do not bring the desired effect. It is also used to prevent allergic reactions and asthma flare-ups during the administration of intravenous immunoglobulin.

Montelukast is administered orally once daily and is approved for treatment of asthma in patients two years or older. The bioavailability is similar regardless of patient age and absorption is not affected by food. No drug interactions have been documented. Side-effects in adults are similar to those found with placebo; they occurred in less than 2 percent of patients 6 to 14 years of age.

These medications are usually well-tolerated. Side-effects are uncommon but include: headache, nausea, stomach upset, pain, fever, muscle ache, fatigue, sore throat, laryngitis and liver enzyme elevation. Churg-Strauss Syndrome, a form of vascular inflammation, rarely is noted with these medications and can include vague symptoms of fever, fatigue, weight loss, vasculitis leading to kidney disease, hypotension, abdominal pain, bowel damage, heart disease, muscle aches and wasting, nervous system damage and arthritis. Liver function abnormalities have been reported with all of these agents and should be periodically monitored.

What is the role of methylxanthines in asthma treatment?

Theophylline is the most well known and most commonly used methylxanthine. At low dosages, it has an immunomodulatory, anti-inflammatory and bronchoprotective effect. Theophylline is also a nonselective inhibitor of phosphodiesterase (PDE) isoenzymes, which may account for the effects of theophylline at higher doses.

Theophylline is a relatively poor bronchodilator and adverse effects limit the dose and make it less effective than inhaled bronchodilators. Thus, it is no longer recommended for routine use in asthma.

Doxofylline, a newer generation methylxanthine, an alternative to theophylline that differs with the presence of a dioxolane group in position 7. It is thought to have a wider therapeutic window than theophylline.

In a recent pooled analysis of two double-blind, randomized, placebo-controlled trials, both doxofylline and theophylline demonstrated significantly better results on functional and clinical outcomes in asthma versus placebo. Doxofylline demonstrated a favorable safety profile superior to theophylline.

Does tiotropium have a role in asthma management?

Tiotropium has been recommended as add-on therapy for severe asthma. In the study of Rodrigo et al, tiotropium as an add-on to ICS showed statistically significant increases in PEF (22-24 L/min) and FEV, (140-150 mL). Tiotropium was observed to have decreased the rate of exacerbations (number needed to treat for benefit [NNTB], 36) and improved asthma control. The use of tiotropium in poorly controlled asthma patients despite the use of medium-to-high doses of ICS was not inferior to salmeterol. Finally, the use of tiotropium as an add-on to ICS-salmeterol combination increased pulmonary function to a clinically significant magnitude, reduced asthma exacerbations (relative risk, 0.70; 95% CI, 0.53-0.94; p value <.02; I² = 0%; NNTB, 17), and improved asthma control compared with ICS-salmeterol. Tiotropium was well tolerated, and no potential safety signals were observed.

What is the mechanism of action of omalizumab?

Omalizumab is a recombinant DNA-derived humanized IgG1k monoclonal antibody against human immunoglobulin E (IgE). It binds to free IgE with a greater affinity than high affinity IgE receptor (FcεRI) present on basophils. Thus, it reduces availability of free IgE for binding.

Omalizumab is a medication originally designed to reduce sensitivity to allergens. It has been used to try to control severe allergic asthma which does not respond to high doses of corticosteroids. Its primary use is for patients mostly with severe, persistent allergic asthma, uncontrollable with oral or injectable corticosteroids. Omalizumab is currently recommended for the treatment of patients >12 years in the U.S., administered subcutaneously once every 2 or 4 weeks. For each patient, the dosing schedule (2 vs 4 weeks between injections; and the amount of omalizumab, in milligrams for each injection) is determined according to the serum IgE level and the body weight of the patient.

In addition to omalizumab, there are other US-FDA approved biological agents in asthma, namely: mepolizumab, reslizumab and benralizumab, which are not currently available locally.
INHALER THERAPY

Inhaler or aerosolized therapy delivers medicines directly to the lumen of the airways and onto their therapeutic sites. This enables the delivery of low doses of the medicine to its site of action for a localized effect, leading to a rapid clinical response and reducing the risk for systemic side-effects.

In clinical practice, several types of inhalers are used for aerosol delivery in asthma. Each device is associated with a different approach to inhalation and, in turn, specific requirements in handling and inhalation to optimize drug delivery.

Pressurized metered-dose inhalers (pMDIs) are pressurized metal canisters containing a mixture of propellants, surfactants, preservatives and drug. They vary in the used propellants, in the combined drug formulations, in the sizes of the metering valves and in the diameters of the actuator nozzle. These differences influence the medicine’s stability, particle size, plume velocity and temperature. Pressurized metered-dose inhalers may be used with spacers, which are add-on devices that help reduce oropharyngeal deposition and increase lung deposition by increasing the distance between the pMDI mouthpiece and the back of the pharynx. Further, spacers make pMDIs easier to use by reducing or eliminating the need for coordination between actuation and inhalation and by reducing the cold Freon effect.

Dry powder inhalers (DPIs) are inhalers which contain the medicine in a powder form, which deaggregates into respirable particles when the patient inhales thru the device. Dry powder inhalers help overcome the coordination issues associated with pMDIs. However, they also suffer from inherent limitations, particularly, that the inhaler’s success depends on the generation of sufficient inspiratory flow.

Nebulizers convert solutions and suspensions into small droplets using compressed air (in the case of pneumatic or jet nebulizers) or sound waves (in the case of ultrasonic nebulizers). They are able to aerosolize high doses of drugs that are not available with DPIs or pMDIs. In addition, nebulizers may be fitted into facemasks, allowing use by patients <2-years old, the elderly and those with severe respiratory distress.

Soft mist inhalers are a new type of inhaler which utilizes the mechanical energy from a compressed spring to force the drug solution through an extremely fine nozzle system, producing a fine, slow moving mist. Although this provides advantages over pMDIs and DPIs on ease of coordination and improved lung deposition, its use in the management of asthma is currently limited as a delivery device for tiotropium as add-on therapy to the usual ICS-LABAs.

Is there a difference between pressurized metered-dose inhalers (pMDIs) and dry powder inhalers (DPIs)?

Since pMDIs and DPIs are the recommended outpatient inhalers to be used, further discussion will focus on these two inhaler types. Table 4.5 lists the general advantages and disadvantages between these two inhalers.

Table 4.5. Advantages and disadvantages between pressurized metered-dose inhalers (pMDIs) and dry powder inhalers (DPIs).

<table>
<thead>
<tr>
<th>Types</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metered-Dose Inhaler (MDI)</td>
<td>Convenient Generally inexpensive Portable Widely available for most inhaled medicines No drug preparation required Difficult to contaminate Less patient coordination required Less patient oropharyngeal deposition</td>
<td></td>
</tr>
<tr>
<td>MDI with holding chamber</td>
<td>More complex for some patients More expensive than MDI alone Less portable than MDI alone Requires moderate to high inspiratory flow Some units are single dose More expensive than MDI alone</td>
<td></td>
</tr>
<tr>
<td>Dry Powder Inhaler (DPI)</td>
<td>Less patient coordination required Convenient Portable Breath actuated</td>
<td>Patient coordination essential Patient actuation required Large oropharyngeal deposition difficult to deliver high dose</td>
</tr>
</tbody>
</table>

The effectiveness of inhaled treatments is influenced by their efficacy, i.e., their positive effects when used under optimal conditions, directly resulting from their pharmacological properties; and the way they are used, i.e., the appropriateness of prescription and patients’ adherence and ability to use inhalation devices.

Reviews of RCTs comparing inhaler devices report no difference in efficacy between devices. In 2005, the American College of Chest Physicians (ACCP) issued an evidence-based guideline on inhaler device selection for inhaler therapy. Multiple meta-analyses revealed that...
there was no significant difference between pMDIs and DPIs in an efficacy outcome in any patient group that was investigated. The guideline concluded that either device may be used provided that patients are able to use the correct technique for inhalation.38

Unfortunately, errors in inhaler technique are common. The frequency of misuse for each particular type of device varies between studies, depending on the studied population and on the criteria used to define proper technique.36, 39, 40, 41 What is certain is that poor inhaler technique is associated with poor asthma control.42, 43

These considerations place great importance in the selection of the appropriate inhaler and in the provision of adequate education and training on correct inhaler technique to the patient.

What patient factors should be considered in the choice of inhaler device?

Treatment guidelines do not provide adequate recommendations on inhaler selection. Unfortunately, determining the appropriateness of the inhaler for a particular patient is paramount to the success of inhaler therapy.37

Figure 4.2 outlines a general algorithm in the proper selection of inhalers for particular patients. A pMDI requires good actuation-inhalation coordination for optimal lung deposition, whereas a DPI requires sufficient inspiratory flow.

Not all inhalation devices are appropriate for all patients. Patients with severe airway obstruction, as well as young children and the elderly, may be unable to inhale with sufficiently fast acceleration to use DPIs; conversely, patients with cognitive or motor problems suffer from poor coordination to be able to use pMDIs correctly. When choosing the appropriate device, it could be useful for clinicians to have a means of mapping the patient’s natural inhalation profile and of assessing whether the patient is more likely to master the inhalation required of the chosen device.44

What strategies can ensure effective use of inhaler devices?

Overcoming problems with the use of inhalers starts with the prescriber choosing the most appropriate device for the individual patient, followed by educating and training the patient in the use of the chosen device (Table 4.6). Patient education and inhaler training are discussed in the chapter on Patient Education.

Table 4.6. Strategies to ensure effective use of inhaler devices.

<table>
<thead>
<tr>
<th>CHOOSE</th>
<th>CHECK</th>
<th>CORRECT</th>
<th>CONFIRM</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Choose the most appropriate inhaler device for the patient before prescribing. Consider the medication options, the available devices, patient skills and cost.</td>
<td>• Check inhaler technique at every opportunity</td>
<td>• Show the patient how to use the device correctly with a physical demonstration, e.g., using a placebo inhaler</td>
<td>• Clinicians should be able to demonstrate correct technique for each of the inhalers they prescribe</td>
</tr>
<tr>
<td>• If different options are available, encourage the patient to participate in the choice.</td>
<td>• Ask the patient to show you how they use their inhaler (don’t just ask if they know how to use it)</td>
<td>• Check technique again, paying attention to problematic steps. You may need to repeat this process 2-3 times.</td>
<td>• Pharmacists and nurses can provide highly effective inhaler skills training</td>
</tr>
<tr>
<td>• For pMDIs, use of a spacer improves delivery and (with ICS) reduced the potential for side-effects.</td>
<td>• Identify any errors using a device-specific checklist</td>
<td>• Only consider an alternative device if the patient cannot use the inhaler correctly after several repeats of training.</td>
<td></td>
</tr>
<tr>
<td>• Ensure that there are no physical barriers, e.g., arthritis, that limit use of the inhaler.</td>
<td>• Avoid use of multiple different inhaler types where possible, to avoid confusion.</td>
<td>• Re-check inhaler technique frequently. After initial training, errors often recur within 4-6 weeks.</td>
<td></td>
</tr>
</tbody>
</table>

Figure 4.2. How to choose the right inhaler. (Adapted from Laube, BL, 2011 and Lavorini F, 2015)
Although not always feasible, use of a single type of device to deliver all medications is preferable since using a variety of devices increases the likelihood of error. Using multiple types of inhalers requires the patient to master (and maintain mastery of) more than 1 inhaler technique. Such possibility of errors will need to be considered during training, retraining and education to avoid loss of disease control and stability.51, 52

**What is the role of nebulizers in asthma management?**

The role of nebulizers in asthma management should be limited in patients in severe respiratory distress or in patients in mechanical ventilation. Nebulizers offer no distinct advantage over pMDIs with spacers or holding chambers in acute asthma management. The use of nebulizers may actually be associated with problems such as a greater dose of drugs, leading to systemic side-effects, and contamination with bacteria, increasing the risk for nosocomial pneumonia.53 Further discussion on acute asthma management is provided in the chapter on Asthma Exacerbations.

An in vitro study on mechanically ventilated subjects indicate that pMDIs were associated with greater aerosol delivery than nebulizers.45 However, a retrospective observational study among mechanically ventilated patients did not indicate any significant difference between the two types of inhalers in number of days receiving ventilation, in-hospital mortality or ventilator-associated pneumonia.46

There is question that pMDIs and DPIs may not be appropriate to use among elderly due to age-related changes, and that nebulizers may be more appropriate for these patients. Unfortunately, no studies have been made on elderly patients to address this concern. Experts agree, though, that considerations on device factors (device type, complexity of use), patient factors (inspiratory capabilities, manual dexterity and hand strength, cognitive ability, comorbidities) and healthcare system factors (patient and physician education, cost reimbursement) should be made in selecting the appropriate inhaler for an elderly patient, similar to any other patient.51, 52

**References:**

28. Dolovich MB, Dhand R. Aerosol drug delivery: developments in device design and
27.
26. Impact of doxofylline compared to theophylline in asthma: A pooled analysis of
CHAPTER 5
Management of Asthma Exacerbations
Exacerbations of asthma are defined as episodes characterized by a progressive increase in symptoms of shortness of breath, cough, wheezing or chest tightness and progressive decrease in lung function, i.e., they represent a change from the patient’s usual status that is sufficient to require a change in treatment.1 These exacerbations may occur in patients as an initial presentation or in those previously diagnosed to have asthma.

An exacerbation is usually triggered by exposure to an external agent or stimuli but a few patients may develop an exacerbation without a known trigger. Although exacerbations are more common in patients with poor adherence to controller medications, i.e., poorly controlled asthma, it can also occur in patients with mild or well-controlled asthma.1

The 2018 GINA guidelines recommend the use of the term “flare-up” since it is “simpler and conveys the sense that asthma is present even when symptoms are absent.”2 For the rest of this document however, exacerbation and flare-up are used interchangeably to mean the same thing.

The goals of treatment of acute exacerbations are to rapidly relieve airflow obstruction, relieve the hypoxemia, address the underlying inflammatory pathophysiology and prevent relapse.1

How is an asthma exacerbation diagnosed?
In a patient previously diagnosed to have asthma, asthma exacerbation is diagnosed by getting a history of increase in frequency of symptoms and documenting the change in lung function measurements, either a decrease in peak expiratory flow rates (PEF) or forced expiratory volume in the first second (FEV1), compared with the patient’s previous lung function or predicted values.3

Lung function measurements are more reliable indicators of severity of exacerbation, but the frequency of symptoms may be a more sensitive measure of the onset of exacerbation than PEF.4

How is the severity of an asthma exacerbation evaluated?
A brief focused history, relevant physical examination and objective measurements should be conducted concurrently with the prompt initiation of therapy.

The history should include:
• Timing of onset and cause (if known) of the present exacerbation
• Severity of asthma symptoms, including any limiting exercise or disturbing sleep
• Any symptoms of anaphylaxis
• Any risk factors for asthma-related death (Table 5.2)
• All current reliever and controller medications, including doses and devices prescribed, adherence pattern, any recent dose changes and response to current therapy.

The physical examination should assess:
• Signs of exacerbation severity and vital signs (e.g., temperature, pulse rate, respiratory rate, blood pressure) and other signs such as level of consciousness, ability to communicate sentences, use of accessory muscles, presence or absence of wheeze
• Complicating factors (e.g., anaphylaxis, pneumonia, pneumothorax)
• Signs of alternative conditions that could explain acute breathlessness (e.g., cardiac failure, upper airway dysfunction, inhaled foreign body or pulmonary embolism)

Objective measurements should include:
• Pulse oximetry. Saturation levels <90% in children or adults signal the need for aggressive therapy
• PEF in patients older than 5 years.

Depending on the patient’s signs and symptoms, the asthma exacerbation can usually be classified as shown in Table 5.1. After classification of severity of exacerbation, appropriate treatment may be instituted.

### Table 5.1. Classification of severity of exacerbation.

<table>
<thead>
<tr>
<th>Symptom or Sign</th>
<th>Mild to Moderate</th>
<th>Severe</th>
<th>Life-threatening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conversation</td>
<td>Talks in phrases</td>
<td>Talks in words</td>
<td>Drowsy</td>
</tr>
<tr>
<td>Preferred body position</td>
<td>Prefers sitting to lying</td>
<td>Sits hunched forward</td>
<td></td>
</tr>
<tr>
<td>Mental state</td>
<td>Not agitated</td>
<td>Agitated</td>
<td>Confused</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>Increased</td>
<td>&gt;30/min</td>
<td>Silent chest</td>
</tr>
<tr>
<td>Accessory muscle use</td>
<td>Not used</td>
<td>In use</td>
<td></td>
</tr>
<tr>
<td>Pulse rate</td>
<td>100-120 bpm</td>
<td>&gt;120 bpm</td>
<td></td>
</tr>
<tr>
<td>O₂ sat (room air)</td>
<td>90-95%</td>
<td>&lt;90%</td>
<td></td>
</tr>
<tr>
<td>PEF</td>
<td>&gt;50% pred. or best</td>
<td>≤50% pred. or best</td>
<td></td>
</tr>
</tbody>
</table>

Modified from GINA 2018

### Why is it important to identify patients who are at risk for asthma-related deaths?

It is important to identify patients with risk factors for asthma-related deaths because these patients should be encouraged to seek urgent medical care regardless of severity of symptoms or early in the course of exacerbation. The presence of one or more of these risk factors listed in Table 5.2 should be quickly identifiable in the clinical notes, and these patients should be encouraged to seek urgent medical care early in the course of an exacerbation.

### Table 5.2. Risk factors for asthma-related deaths.

- A history of near-fatal asthma requiring intubation and mechanical ventilation
- Hospitalization or emergency care visit for asthma in the past year
- Currently using or having recently stopped using oral corticosteroids (a marker of event severity)
- Over-use of SABAs, especially use of more than one canister of salbutamol (or equivalent) monthly
- A history of psychiatric disease or psychosocial problems
- Poor adherence with asthma medications and/or poor adherence (or lack of) a written asthma action plan
- Food allergy in a patient with asthma

### What is the ideal first-line therapy for symptom relief in asthma exacerbations?

The ideal first-line therapy for an acute exacerbation of asthma is inhaled SABA. It should be administered frequently for patients presenting with acute asthma. Usually, SABA is administered through nebulization, however, studies show that delivery of SABA via a pMDI with spacer leads to a similar improvement in lung function as delivery via nebulizer. (Evidence A) Please note that patients with acute severe asthma were not included in these studies.5, 6
To administer pMDI doses with spacer, it is recommended to give 4 to 10 puffs every 20 minutes for the first hour. Subsequently, 4 to 10 puffs every 3 to 4 hours or 6 to 10 puffs every 1 to 2 hours can be given. If there is a good response to the initial treatment (i.e., PEF >60-80% of predicted or personal best for 3 to 4 hours), there is no need to administer additional treatment.

There have been conflicting results as to the more effective way of administering nebulized SABA, whether intermittently or continuously. One study found no significant differences in lung function or hospital admissions between the two strategies but a later review with additional studies found reduced hospitalizations and better lung function with continuous compared with intermittent nebulization, particularly in patients with worse lung function.7, 8

An earlier study in hospitalized patients found that intermittent on-demand therapy led to a significantly shorter hospital stay, fewer nebulizations and fewer palpitations when compared with 4-hourly intermittent therapy.9 Therefore, a reasonable approach to inhaled SABA in exacerbations would be to initially use continuous therapy, followed by intermittent on-demand therapy for hospitalized patients. There is no evidence to support the routine use of intravenous beta2-agonist in patients with severe asthma exacerbations.10 (Evidence A)

In the treatment of moderate-severe exacerbations in the ER, the addition of ipratropium, a short-acting anticholinergic, to SABA was associated with fewer hospitalizations and greater improvement in PEF and FEV1 compared with SABA alone.11, 12 It is, therefore, reasonable to administer the combination as initial treatment for moderate to severe exacerbations. For mild exacerbations, it may be enough to give SABA alone.

What is the first-line therapy for control of inflammation in asthma exacerbations?

Systemic corticosteroids should be utilized in all but the mildest exacerbations in adults, adolescents and children 6 to 11-years, because it has been shown to speed the resolution of exacerbations and prevent relapse.14, 15, 16 (Evidence A)

It is recommended that systemic corticosteroids should be administered within one hour of presentation. In the ER, the use of systemic corticosteroids is particularly important in situations where the initial SABA treatment fails to achieve lasting improvement in symptoms; the exacerbation developed while the patient was already taking OCS, and; the patient has a history of previous exacerbations requiring OCS.

Oral corticosteroids are as effective as intravenous systemic corticosteroids. The oral route is preferred because it is quicker, less invasive and less expensive.15, 16 Oral corticosteroids require at least 4 hours to produce a clinical improvement. Intravenous corticosteroids can be administered when patients are too dyspneic to swallow; if the patient is vomiting; or when patients require non-invasive ventilation or intubation. A treatment regimen consisting of daily doses of OCS equivalent to 50 mg prednisolone as a single morning dose, or 200 mg hydrocortisone in divided doses, are adequate for most patients. (Evidence B)

The duration of treatment may vary but 5- and 7-day courses in adults have been found to be as effective as 10- and 14-day courses respectively, and a 3-5-day course in children is usually considered sufficient.17, 18 (Evidence B) Evidence from studies in which all patients were taking maintenance ICS after discharge suggests that there is no benefit in tapering the dose of OCS, either in the short term or over several weeks.19, 20 (Evidence B)

Is there a role for inhaled corticosteroids (ICS) in the management of asthma exacerbations?

In the acute care setting, high-dose ICS given within the first hour after presentation reduces the need for hospitalization in patients not receiving systemic corticosteroids.16 (Evidence A) However, when given in addition to systemic corticosteroids, evidence is conflicting.16 (Evidence B)

Overall, ICS are well tolerated and may be given in the acute care setting, especially at home or at the out-patient department. However, cost is a significant factor, and the agent, dose and duration of treatment with ICS in the management of asthma in the acute care setting remain unclear.

There are few randomized and blinded studies examining the effect of nebulized corticosteroids as add-on therapy to systemic corticosteroids. Although most of these studies were conducted in children and the patient number is usually very small not allowing for subgroup analyses, these earlier studies found no differences in the pulmonary index scores.21, 22, 23, 24, 25
Is there a role of inhaled long-acting beta₂-agonist – inhaled corticosteroid (LABA-ICS) in the management of acute asthma?

The role of these medications in the ER or hospital is unclear. One study showed that high-dose budesonide-formoterol in patients in the ER, all of whom received prednisolone, had similar efficacy and safety profile to SABA. For exacerbations of asthma treated at home, patients already on combination formoterol and low-dose ICS (budesonide or beclomethasone) in a single inhaler, increasing doses of up to 72 mcg of formoterol in a day is effective in achieving control of symptoms (Evidence A).

What is the role of magnesium sulfate in the management of asthma exacerbations?

Intravenous magnesium sulfate can be given to adults and children who fail to respond to initial treatment and have persistent hypoxemia. When administered as a single 2 g infusion over 20 minutes, intravenous magnesium sulfate reduces hospital admissions in adults with FEV₁ <25–30% predicted at presentation (Evidence A).

What is the role of methylxanthines in the management of asthma exacerbations?

There is no role for methylxanthines, whether parenteral or oral, in the management of an asthma exacerbation because of poor efficacy and safety profile. The use of intravenous aminophylline is, in fact, associated with severe and potentially fatal side-effects, particularly in patients already treated with sustained-release theophylline. Evidence has shown that, in patients with severe asthma exacerbations, add-on treatment with aminophylline does not improve outcomes compared with SABA alone.

How should asthma exacerbations be managed at home?

All patients with asthma should be provided with guided self-management education, including monitoring of symptoms and/or lung function, a written asthma action plan and regular review by a healthcare professional.
How should asthma exacerbations be managed in the out-patient setting?

After an evaluation of the severity of exacerbation, initial therapy may be started consisting of repetitive administration of short-acting bronchodilators, i.e., SABA, early introduction of corticosteroids and controlled-flow oxygen supplementation.

Severe and life-threatening exacerbations should not be managed in the out-patient setting. These patients should immediately be transferred to an acute care facility. While waiting for transfer, a combination of inhaled SABA and ipratropium bromide either through pMDI + spacer or nebulization, O₂ inhalation and systemic corticosteroids should promptly be administered.

For mild-to-moderate exacerbations (Figure 5.2), an initial treatment at the out-patient setting should consist of SABA 4 to 10 puffs via pMDI + spacer administered every 20 minutes for one hour, prednisolone or equivalent at 1 mg/kg/day for adults, maximum of 50 mg and 1-2 mg/kg/day for children, maximum of 40 mg. Controlled oxygen, if available, should be given to achieve an oxygen saturation of 93-95% in adults and 94-95% in children.

The clinical response to the initial treatment should be evaluated after one hour. If the patient's condition is worsening, with deteriorating vital signs, transfer immediately to an acute care facility. While waiting to be transported, give a combination of inhaled SABA and ipratropium bromide, oxygen inhalation and systemic corticosteroids. If the patient partially improved after initial treatment, continue SABA 4 to 10 puffs via pMDI with spacer every four hours or 6 to 10 puffs every 1-2 hours. If, however, the patient has good response, no need for further SABA, and the patient is evaluated for discharge.

The patient may be discharged from the out-patient service department (OPD) if symptoms have improved and SABA is not needed any more, PEF 60-80%, and O₂ sat >94% at room air. Home instructions or a written action plan should include instructions on reliever medications, controller medications, OCS to be given for 5-7 days in adults and 3-5 days in children.
How should asthma exacerbations be managed in the emergency room (ER)?

Severe exacerbations of asthma are life-threatening medical emergencies and should be managed in an acute care setting such as an ER. An evaluation based on history, physical examination and objective measures should indicate whether the patient is in mild to moderate, severe or life-threatening exacerbation. (Figure 5.3)

Once the patient has arrived in the ER with a life-threatening exacerbation, initial treatments should be given concurrently to achieve rapid improvement. Combined SABA and ipratropium bromide via nebulization continuously should be started while awaiting transfer to the intensive care unit (ICU). Low flow oxygen therapy should be administered by nasal cannulae or mask to achieve oxygen saturation of 93-95% in adults (94-98% for children) and IV corticosteroids at 200 mg hydrocortisone in divided doses should be given while preparing for intubation.2

For patients in severe exacerbation seen at the ER, SABA and ipratropium may be administered via nebulization intermittently at 2.5 mcg ipratropium bromide and 2.5 mcg salbutamol every 20 minutes for three doses, or continuously every 10-15 minutes back to back for one hour. Short-acting beta2-agonist (SABA) and ipratropium can also be given via pMDI with spacer at 4 to 10 puffs every 20 minutes for one hour.

For adults with mild-to-moderate exacerbation, systemic corticosteroids should be given either through intravenous route, if the patient is too dyspneic to swallow, or by oral administration.

The patient’s clinical status and oxygen saturation should be assessed frequently, with further treatment titrated according to the patient’s response. Lung function (PEF) should be measured after one hour, and patients who deteriorate despite intensive bronchodilator and corticosteroid treatment should be re-evaluated for transfer to the intensive care unit (Figure 5.3).2
**INITIAL ASSESSMENT**  
A: airway B: breathing C: circulation  

Are any of the following present?  
Drowsiness, confusion, silent chest  

- NO  
- YES  

Further TRIAGE BY CLINICAL STATUS  
According to worst feature  

- MILD or MODERATE  
- SEVERE  

**MILD or MODERATE**  
Talks in phrases  
Not agitated  
Respiratory rate increased  
Accessory muscles not used  
O₂ saturation (on air) 90-95%  
PEF >50% predicted or best  

- Short-acting beta₂-agonists  
- Ipratropium bromide  
- Controlled O₂ to maintain saturation 93-95% (children 94-95%)  
- Oral corticosteroids  

If continuing deterioration, treat as severe and re-assess for ICU  

**SEVERE**  
Talks in words  
Sits hunched forwards  
Agitated  
Respiratory rate >30/min  
Accessory muscles being used  
O₂ saturation (on air) <90%  
PEF ≤50% predicted or best  

- Short-acting beta₂-agonists  
- Ipratropium bromide  
- Controlled O₂ to maintain saturation 93-95% (children 94-98%)  
- Oral or IV corticosteroids  
- Consider IV magnesium  
- Consider high-dose ICS  

**ASSESS CLINICAL PROGRESS FREQUENTLY**  
Measure lung function in all patients one hour after initial treatment  

- FEV₁ or PEF 60-80% of predicted or personal best and symptoms improved  
- MODERATE  
  Consider for discharge planning  

- FEV₁ or PEF <60% of predicted or personal best, or lack of clinical response  
- SEVERE  
  Continue treatment as above and re-assess frequently  

Figure 5.3. Management of asthma exacerbations at the emergency room (ER).

**What are the indications for hospitalization?**

Clinical status and lung function after one hour of bronchodilator and corticosteroid treatment are more reliable predictors of the need for hospitalization than the patient’s status on arrival.\textsuperscript{35, 36}

Based on lung function measurements, hospitalization is recommended if pre-treatment FEV₁ or PEF is <25% predicted or personal best, or post-treatment FEV₁ or PEF is <40% predicted or personal best.\textsuperscript{36}

Other factors associated with increased likelihood of need for admission include:\textsuperscript{38, 39, 40}

- Female sex, older age and non-white race
- Use of more than 8 beta₂-agonist puffs in the previous 24 hours
- Severity of the exacerbation (e.g., need for resuscitation or rapid medical intervention on arrival, respiratory rate >22 breaths/minute, O₂ saturation <95%, final PEF <50% predicted)
- Past history of severe exacerbations (e.g., intubations, asthma admissions)
- Previous unscheduled office and emergency department visits requiring use of OCS.

**When do we discharge patients after being treated in the emergency room (ER)?**

If post-treatment lung function is 40–60% predicted, discharge may be possible after considering the patient’s risk factors (Table 5.1) and availability of follow-up care. If post-treatment lung function is >60% predicted or personal best, discharge\textsuperscript{37} is recommended after considering risk factors and availability of follow-up care. Prior to discharge, instructions should be given on correct medications and inhaler skills, a written action plan should be provided, and a follow up appointment within one week from discharge should be arranged.\textsuperscript{2} (Table 5.3)
**Chapter 5**

Identify factors that may have contributed to the exacerbation and implement strategies to reduce allergen exposure, inadequate long-term treatment, problems with adherence, and/or lack of written asthma action plan, as well as unavoidable factors such as viral respiratory infections.

**Medications**

**Oral Corticosteroids (OCS)**
Prescribe at least a 5-7 days’ course of OCS for adults (prednisolone or equivalent 1 mg/kg/day to a maximum of 50 mg/day) and 3-5 days for children (1-2 mg/kg/day to a maximum of 40 mg). For patients considered at risk of poor adherence, intramuscular corticosteroids may be considered. (Evidence B)

**Reliever Medication**
Transfer patients back to as-needed rather than regular reliever medication use, based on symptomatic and objective improvement. If ipratropium bromide was used in the emergency department or hospital, it may be quickly discontinued as it is unlikely to provide ongoing benefit.

**Inhaled Corticosteroids (ICS)**
Initiate ICS prior to discharge, if not previously prescribed. Patients currently prescribed ICS-containing medication should generally have their treatment stepped up for 2-4 weeks and should be reminded about the importance of adherence with daily use.

**Risk factors that contributed to the exacerbation**

Identify factors that may have contributed to the exacerbation and implement strategies to reduce modifiable risk factors. An exacerbation severe enough to require hospitalization may follow irritant or allergen exposure, inadequate long-term treatment, problems with adherence, and/or lack of written asthma action plan, as well as unavoidable factors such as viral respiratory infections.

**Self-management skills and written asthma action plan**

- Review inhaler technique.
- Review technique with PEF if used.
- Provide a written asthma action plan or review patient’s existing plan, either at discharge or as soon as possible afterwards. Patient discharged from the emergency room with an action plan and PEF meter have better outcomes than patients discharged without these resources.
- Evaluate patient’s response to exacerbation. If it was inadequate, review the action plan and provide written guidance to assist if asthma worsens again.
- Review the patient’s use of controller treatment before and during exacerbation. Was it increased promptly and by how much? Were OCS added and if not, why not? Consider providing short-course of OCS to be on hand for subsequent exacerbations.

**Follow-up appointment**

A follow-up appointment within 2-7 days of discharge should be made with the patient’s usual healthcare provider to ensure that treatment is continued, that asthma symptoms are well controlled and that the patient’s lung function reaches their personal best (if known).

Table 5.3. Discharge management after hospital or emergency room care for asthma.

<table>
<thead>
<tr>
<th>Table 5.3. Discharge management after hospital or emergency room care for asthma.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medications</strong></td>
</tr>
<tr>
<td><strong>Oral Corticosteroids (OCS)</strong></td>
</tr>
<tr>
<td>Prescribe at least a 5-7 days’ course of OCS for adults (prednisolone or equivalent 1 mg/kg/day to a maximum of 50 mg/day) and 3-5 days for children (1-2 mg/kg/day to a maximum of 40 mg). For patients considered at risk of poor adherence, intramuscular corticosteroids may be considered. (Evidence B)</td>
</tr>
</tbody>
</table>

**Reliever Medication**
Transfer patients back to as-needed rather than regular reliever medication use, based on symptomatic and objective improvement. If ipratropium bromide was used in the emergency department or hospital, it may be quickly discontinued as it is unlikely to provide ongoing benefit.

**Inhaled Corticosteroids (ICS)**
Initiate ICS prior to discharge, if not previously prescribed. Patients currently prescribed ICS-containing medication should generally have their treatment stepped up for 2-4 weeks and should be reminded about the importance of adherence with daily use.

References:


32. FitzGerald JM. Magnesium sulfate is effective for severe acute asthma treated in the emergency department. West J Med 2000 Mar;172(2):96.
CHAPTER 6
Chronic Asthma Management
Asthma cannot be cured, but appropriate management can result in control of the disease and enable those affected to enjoy a good quality of life.\(^1\)

**What are the goals of chronic asthma management?**

The aim of asthma management is control of the disease.\(^2\) The long-term goals are:\(^3\)

- To achieve good control of symptoms and maintain normal activity levels
- To minimize future risk of exacerbations, fixed airflow limitation and side-effects.

Complete control of asthma is defined\(^2\) as:

- no daytime symptoms
- no night-time awakening due to asthma
- no need for rescue medication
- no asthma attacks
- no limitations on activity including exercise
- normal lung function (in practical terms FEV\(_1\) and/or PEF >80% predicted or best)
- minimal side-effects from medication.

Current degree of asthma control has been found to predict future risk of instability and exacerbations.\(^4\) On the other hand, an exacerbation in the past year is a strong independent predictor of future exacerbations, particularly in patients with severe or difficult-to-treat asthma.\(^5,\,6\)

Discrepancies between patient and physician understanding of asthma control have been observed in Asia.\(^7\) Patients’ asthma control targets need to evolve from quick symptomatic relief to long-term prevention. In clinical practice, patients may have different goals and may wish to balance the aims of asthma management against the potential side-effects or inconvenience of taking medication necessary to achieve perfect control.\(^3\) Healthcare providers are best positioned to address these differences in perception and goals, as well as influence patient attitudes towards treatment.

**What is control-based asthma management?**

Control-based asthma management is a continual process of adjustment of pharmacological and non-pharmacological strategies and involves a cycle of assessment, treatment modifications based on current status and review of clinical response (Figure 6.1).\(^3\)
Successful asthma management requires a system of regular objective monitoring, stepwise adjustment of medications based on clinical response and patient preference, addressing non-pharmacologic interventions and comorbidities, nurturing an excellent patient-healthcare provider partnership and self-management education planning.

In low- and middle-income countries such as the Philippines, affordability and availability are additional important considerations in the choice of medications, aside from efficacy and safety. Physicians should check the accessibility of free generic inhaled asthma medications in local health units.

What is the stepwise approach for adjusting asthma treatment in adults?

The approach to asthma treatment in Filipino adults is a 5-step continuum of care that involves a stepwise escalation or de-escalation of the number and dosing of asthma controller medications that are required to achieve and maintain control. (Figure 6.2)

After a diagnosis of asthma is made, pharmacotherapy is initiated. The choice of medications is based on the patient's current level of asthma control, the presence of future risks of adverse outcomes and the response to current asthma treatment, if any. On subsequent clinic visits, controller therapy is adjusted up or down in a stepwise fashion depending on whether the goals of asthma management are met or not.

Once good asthma control has been maintained for 2-3 months, taking a lower treatment step is done in order to find the minimum effective drug and dosing that can maintain control. On the other hand, if a patient has persisting symptoms and/or exacerbations despite 2-3 months of controller treatment, the following common problems need to be assessed and corrected before considering any step-up in treatment:

- Incorrect inhaler technique
- Poor adherence
- Persistent exposure to agents which trigger asthma
- Presence of uncontrolled comorbidities
- Incorrect diagnosis

**Figure 6.2. Stepwise approach to treatment in Filipino adults.**
STEP 1

**Preferred option:** As-needed combination low-dose ICS-formoterol

For step 1, which mostly consist of patients with mild intermittent asthma, previous local consensus report recommended the use of as-needed SABA with no maintenance controller but recent studies have raised concerns regarding such a strategy. The REALISE Asia study that included Filipino subjects has shown that 50% of patients who use a reliever inhaler as sole medication have uncontrolled asthma. Among Chinese asthmatics, only 4.9% of patients in GINA Step 1 have well-controlled asthma and 12.2% are uncontrolled. A Spanish survey reports an even higher proportion of uncontrolled asthmatics in GINA Step 1 (52.4%). In the REALISE Europe survey, 26.1% of patients in GINA Step 1 experienced exacerbations in the previous 12 months that required short course oral steroids.

Eosinophilic airway inflammation and remodeling have been demonstrated even in the mildest forms of asthma. The results of a recent post-hoc analysis of the 3-year Inhaled Steroid Treatment As Regular Therapy (START) study on mild recent-onset asthma do not support restriction of ICS to patients with symptoms on more than 2 days per week and suggest that treatment recommendations for such patients should consider both risk reduction and symptoms. (Evidence B)

Indeed, anti-inflammatory treatment with ICS has been found to reduce asthma symptoms, increase lung function, improve quality of life and reduce the risk of exacerbation and asthma-related hospitalization or death. (Evidence A) Note that the use of ICS-formoterol as symptom-driven treatment for mild asthma, as of this writing, is still off-label.

**Other options:**

Regular early low-dose ICS should be considered, in addition to as-needed SABA, to reduce the risk of exacerbation. (Evidence B) The use of ICS-SABA as reliever is off-label and currently not available in the Philippines. However, it would be a better option than SABA alone.

STEP 2

**Preferred option:** Low-dose ICS-formoterol as maintenance and reliever therapy (MART) OR regular low-dose ICS-LABA combination plus as-needed SABA

In the local setting, patients often carry the financial burden of out-of-pocket cost of treatment, and the medical care of a significant number of Filipinos is neither covered by Health Maintenance Organizations nor subsidized by their employers. Furthermore, Filipino asthmatics prioritize medications that can provide rapid relief of symptoms. To assure the delivery of anti-inflammatory therapy while providing bronchodilator efficacy for the majority of symptomatic asthmatics, the consensus is to start at Step 2, with either low doses of ICS-formoterol as maintenance and reliever therapy or low doses of a fixed dose ICS-LABA combination inhaler. (Evidence D)

Recent data has shown benefit of as-needed budesonide-formoterol in a 52-week study for mild asthma in reducing severe exacerbations by 64% compared with SABA only treatment. This is also in congruence with older studies by Zetterstrom and O’Byrne showing that budesonide-formoterol single inhaler therapy provided better asthma control than budesonide alone in patients not previously fully controlled by glucocorticoids. In patients who are not currently taking ICS, a low dose of inhaled budesonide in addition to formoterol reduced the rate of severe exacerbations and poorly controlled asthma days by more than half and the addition of formoterol resulted in improved lung function. On the other hand, Bateman et al showed that budesonide-formoterol used as needed was noninferior to twice-daily budesonide with respect to the rate of severe asthma exacerbations during 52 weeks of treatment but was inferior in controlling symptoms.

In both studies by O’Byrne and Bateman, patients in the budesonide-formoterol group had substantially lower glucocorticoid exposure than the patients on budesonide maintenance therapy. No safety signals were identified. Quite notably, the adherence level to the study medications was high in both studies (>60%).

Alternatively, the regular use of combination ICS-LABA in adolescents and adults with suboptimal asthma control on low-dose ICS monotherapy is more effective than ICS alone in reducing the risk of exacerbations requiring OCS, provides greater improvement in lung function, symptoms, use of rescue SABA and leads to fewer withdrawals due to poor asthma control than a higher dose of ICS. (Evidence A)
Access to corticosteroid inhalers has become a problem in many parts of the Philippines. Fixed dose ICS-LABA combination inhalers are more easily available, including the cheaper generic brands that are freely provided in selected local health units. Where ICS as monotherapy cannot be obtained, maintenance treatment with low-dose ICS-LABA is an alternative option. (Evidence D)

Other options:
Alternatively, daily low-dose ICS may be used regularly for mild asthma. This is based on evidence for the benefits of low-dose ICS in this population in significantly reducing the risk for asthma-related deaths, asthma-related hospitalizations, and risk of severe exacerbations.

Daily LTRA is another option although less effective for prevention of exacerbations than ICS containing therapy. (Evidence A)

STEP 3
Preferred option: Combination medium-dose ICS-LABA plus as-needed SABA OR combination ICS-formoterol as maintenance and reliever therapy (MART)

If control is suboptimal despite combination low-dose ICS-LABA, maintenance treatment may be increased to medium-dose ICS-LABA. (Evidence B)

Low-dose ICS-formoterol combination inhalers can be prescribed as both maintenance and reliever therapy (MART). This approach has been shown to result in a reduction in exacerbations and improvement in lung function and asthma symptoms in adults and adolescents at relatively low doses of ICS, compared with a fixed dose of ICS-LABA as maintenance treatment, or a higher dose of ICS combined with as-needed SABA. (Evidence A)

Other options:
Other options in Step 3 include increasing ICS from low- to medium-dose or combining a low-dose ICS with LTRA. These two approaches have been shown to be less effective than the addition of an inhaled LABA to ICS. (Evidence A)

STEP 4
Preferred option: Combination high-dose ICS-LABA plus as-needed SABA OR combination ICS-formoterol as maintenance and reliever therapy (MART)

Step 4 treatment options depend on prior selections at Step 3. As previously stated, before stepping up, the presence of common problems such as incorrect asthma diagnosis, suboptimal inhaler technique, poor adherence, continuing environmental exposure to triggers and uncontrolled comorbidities must be reviewed and addressed accordingly. Where possible, patients who are not controlled on Step 3 treatment should be referred early to an asthma specialist for investigation of alternative diagnoses and/or causes of difficult-to-treat asthma and further management.

For patients already on combination low-dose ICS-formoterol as MART, the maintenance dose may be increased if necessary. In patients with moderate to severe asthma, MART strategy was found to be more effective and less expensive than a strategy of clinician-directed titration of ICS-LABA with salbutamol as reliever therapy. (Evidence A)

Pre-defined total asthma control through stepped-up treatment with ICS-LABA (maximum of 500 μg ICS twice a day) can be achieved by about a third of patients. Combination high-dose ICS-LABA may thus be considered in adult patients with more severe asthma, but the increase in ICS dose generally provides little additional benefit, and there is an increased risk of side-effects, including adrenal suppression. A high dose is recommended only on a trial basis for 3-6 months when good asthma control cannot be achieved with medium-dose ICS plus LABA and/or a third controller (e.g., LTRA). (Evidence A)

Other options:
The long-acting muscarinic antagonist tiotropium delivered via soft-mist inhaler may be used as add-on therapy for adult or adolescent patients with a history of frequent exacerbations; it modestly improves lung function and delays the time to severe exacerbation. (Evidence A) Tiotropium is not indicated in children <12 years. Leukotriene modifiers as add-on therapy in asthma have been shown to exhibit steroid sparing effects. (Evidence B)
STEP 5

Preferred option: Referral for asthma specialist investigation and consideration of add-on treatment

Patients with persistent symptoms or exacerbations despite correct inhaler technique and good adherence to Step 4 treatment, and in whom other controller options have been considered, should be referred to a tertiary-level medical center with a severe asthma clinic or to a specialist with expertise in the management and treatment of severe asthma.3 (Evidence D)

Sputum-guided treatment based on eosinophilia (>3%) in induced sputum may be considered for patients with difficult-to-treat asthma, specifically those with persisting symptoms and/or exacerbations despite higher doses of ICS-LABA. This strategy can lead to reduced exacerbation and/or lower doses of ICS.40 (Evidence A)

Treatment options which are currently available in the local setting that may be considered in Step 5:

1. Add-on tiotropium by soft-mist inhaler, if not yet started in Step 4
2. Add-on Anti-Immunoglobulin E (anti-IgE) treatment with omalizumab for patients ≥6 years with moderate to severe allergic asthma that is uncontrolled in Step 4 treatment.44 (Evidence A)

Other add-on options in Step 5 which are not yet available in the Philippines include anti-interleukin 5 (subcutaneous mepolizumab and intravenous reslizumab) for patients ≥12 years with severe eosinophilic asthma uncontrolled by Step 4 treatment and bronchial thermoplasty. Their efficacy and safety are well covered by international guidelines.2,3

Published guideline recommendations in the evaluation and management of severe asthma can be accessed.59–60

Other options:

Add-on low-dose OCS (≤7.5 mg/day prednisone or equivalent) may be considered in adults with poor symptom control and/or frequent exacerbations despite good inhaler technique and adherence with Step 4 treatment, and after exclusion of other contributory factors.1 However, this option is often associated with significant systemic side-effects.29 (Evidence B)

Patients who are expected to be treated with systemic steroids for ≥3 months should be provided lifestyle counselling and prescription therapy for prevention of osteoporosis, if appropriate.3

Screening for tuberculosis (TB) is likewise important as the risk of TB reactivation increases 2.8- to 7.7-fold.52

How often should response to treatment be assessed and monitored?

To achieve asthma control, review of symptoms, risk factors and occurrence of exacerbations as well as response to treatment adjustments, patients should be monitored on a regular basis.2 For most controller medications, improvement begins within days of initiating treatment, but the full benefit may only be evident after 3-4 months.55 In severe and chronically under treated disease, this may take even longer.54

The frequency of healthcare visits and assessments depends upon the patient’s initial clinical severity and the patient’s training and confidence in playing a role in the ongoing control of his or her asthma, including adherence and proficiency to use the assigned inhaler. Typically, patients are seen one to three months after the initial visit, and every 3-12 months thereafter.3 After an exacerbation, follow-up should be scheduled within one week.56 (Evidence D)

What are the guidelines for the escalation of asthma treatment?

Asthma is a variable condition and patients may have more symptoms during allergen season. Periodic treatment adjustments by the clinician and/or the patient may be needed.56

The Philippine consensus has adopted these GINA 2018 recommendations:3

- **Sustained step-up (for at least 2-3 months):** some patients may fail to respond adequately to initial treatment. A step-up in treatment may be recommended if the symptoms are confirmed to be due to asthma; inhaler technique and adherence are satisfactory, and; modifiable risk factors such as smoking have been addressed (Table 6.2). Any step-up should be regarded as a therapeutic trial, and the response reviewed after 2-3 months. If there is no response, treatment should be reduced to the previous level, and alternative treatment options or referral considered.

- **Short-term step-up (for 1-2 weeks):** an occasional short-term increase in maintenance ICS dose for 1-2 weeks may be necessary; for example, during viral infections or seasonal allergen exposure. This may be initiated by the patient according to their written asthma action plan or by the healthcare provider.
• **Day-to-day adjustment**: for patients prescribed combination ICS-formoterol as MART, the patient adjusts the number of as-needed doses of ICS-formoterol from day to day according to their symptoms, while continuing the maintenance dosage.

What are the guidelines for the de-escalation of asthma treatment?

When asthma control has been achieved and maintained for at least 3 months and lung function has reached a plateau, treatment can often be successfully reduced without loss of asthma control. The appropriate time to step down therapy is when the patient currently has no respiratory infection, not travelling, not pregnant or will have minimal exposure to triggers such as weather/season change. Approach to stepping down of treatment should also be regarded as a therapeutic trial. Patients must be provided with enough information and a written action plan and instructions on how and when to resume their previous treatment if their symptoms worsen. If the patient has risk factors for exacerbations or fixed airflow limitation, close supervision by a clinician is necessary.3

Independent risk factors associated with asthma worsening or exacerbation during treatment de-escalation include reduced baseline lung function, an exacerbation that necessitated an ER visit in the past year, and early onset disease, even if otherwise well controlled.5 Patients with these risks may require more meticulous monitoring to prevent treatment failures and asthma exacerbation during step down of therapy.

The goals of stepping down are as follows:

- To establish the lowest step and dose of treatment necessary (i.e., minimum effective treatment), which minimizes the cost and maximizes the safety of treatment
- To encourage the patient to continue regular controller treatment.3

The following are some of the strategies that can be adopted in the local setting:3

- When asthma is controlled with a combination of ICS and LABA, the preferred approach is to begin by reducing the dose of inhaled steroid by approximately 50% at 3-month intervals while continuing the inhaled LABA. (Evidence B)

- When ICS monotherapy in medium to high doses is being used, a 50% reduction in dose should be attempted at 3-month intervals. (Evidence B)

- Where control is achieved at a low dose of ICS alone, in most patients, treatment may be switched to once-daily dosing. (Evidence A)

- If control is maintained, further reductions in the inhaled steroid should be attempted until a low dose is reached, at which time, the LABA may be stopped. (Evidence D)

- When asthma is controlled with ICS in combination with controllers other than LABA; the dose of inhaled steroid should be reduced by 50% until a low dose is reached, then the combination treatment can be stopped, as described above. (Evidence D)

- Controller treatment may be stopped if the patient’s asthma remains controlled on the lowest dose of controller and no recurrence of symptoms occurs for at least one year. (Evidence D)

What are the strategies to reduce the risk of asthma exacerbations?

For all asthma patients, risk factors for exacerbation need to be identified and addressed. Table 6.1 lists the modifiable conditions with their corresponding level of evidence.3
### Table 6.1. Treating modifiable risk factors to reduce exacerbations.

<table>
<thead>
<tr>
<th>Risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any patient with ≥1 risk factor for exacerbations (including poor symptom control)</td>
</tr>
<tr>
<td><strong>Treatment strategy</strong></td>
</tr>
<tr>
<td>• Ensure patient is prescribed regular ICS-containing controller</td>
</tr>
<tr>
<td>• Ensure patient has a written action plan appropriate for their health literacy</td>
</tr>
<tr>
<td>• Review patient more frequently than low-risk patients</td>
</tr>
<tr>
<td>• Check inhaler technique and adherence frequently</td>
</tr>
<tr>
<td>• Identify any modifiable risk factors</td>
</tr>
<tr>
<td><strong>Evidence</strong></td>
</tr>
<tr>
<td>A</td>
</tr>
</tbody>
</table>

| ≥1 severe exacerbation last year |
| **Treatment strategy** |
| • Consider alternative controller regimens to reduce exacerbation risk, e.g., ICS-formoterol maintenance and reliever regimen |
| • Consider stepping up treatment if no modifiable risk factors |
| • Identify any avoidable triggers for exacerbations |
| **Evidence** |
| A | A | A | C |

| Exposure to tobacco smoke |
| **Treatment strategy** |
| • Encourage smoking cessation by patient/family; provide advice and resources |
| • Consider higher dose of ICS if asthma is poorly controlled |
| **Evidence** |
| A | B |

| Low FEV1, especially if ≤60% predicted |
| **Treatment strategy** |
| • Consider trial of 3-months’ treatment of high-dose ICS and/or 2 weeks’ OCS |
| • Exclude other lung diseases, e.g., COPD |
| • Refer for expert advice if Po2 improvement |
| **Evidence** |
| B | D | D |

| Obesity |
| **Treatment strategy** |
| • Strategies for weight reduction |
| • Distinct asthma symptoms from symptoms due to deconditioning, mechanical restriction and/or sleep apnea |
| **Evidence** |
| B | D |

| Major psychological problems |
| **Treatment strategy** |
| • Arrange mental health assessment |
| • Help patient to distinguish between symptoms of anxiety and asthma; provide advice about management of panic attacks |
| **Evidence** |
| D | D |

| Major socioeconomic problems |
| **Treatment strategy** |
| • Identify most cost-effective ICS-based regimen |
| **Evidence** |
| D |

| Confirmed food allergy |
| **Treatment strategy** |
| • Appropriate food avoidance; injectable epinephrine |
| **Evidence** |
| A |

| Allergen exposure if sensitized |
| **Treatment strategy** |
| • Consider trial of simple avoidance strategies; consider cost |
| • Consider step up of controller treatment |
| • Consider adding SLIT in adult HDM-sensitive patients with AR and exacerbations despite ICS, provided FEV1 is ≥70% predicted |
| **Evidence** |
| C | D | B |

| Sputum eosinophilia (limited centers) |
| **Treatment strategy** |
| • Increase ICS dose independent of level of symptom control |
| **Evidence** |
| A |

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*ICS: inhaled corticosteroids; OCS: oral corticosteroids; FEV1: forced expiratory volume in 1 second; COPD: chronic obstructive pulmonary disease; SLIT: sublingual immunotherapy; HDM: house dust mite; AR: allergic rhinitis |

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**What is the role of immunotherapy in asthma?**

Allergen-specific immunotherapy has a role in patients with allergic asthma and allergic rhinoconjunctivitis. In patients with asthma and allergic sensitization, subcutaneous immunotherapy (SCIT) is associated with a reduction in symptom scores and medication requirements and improved allergen-specific and nonspecific airway hyperresponsiveness. Anaphylactic reactions are uncommon but may be life-threatening.

Sublingual immunotherapy (SLIT) as an add-on option may be considered for adult HDM-sensitive patients with allergic rhinitis who have exacerbations despite ICS, provided FEV1 is ≥70% predicted. In these patients, SLIT for HDM has been shown to decrease mild to moderate asthma exacerbations.

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**What is the role of vaccination among asthmatics?**

The U.S. Centers for Disease Control and Prevention (CDC) recommend annual seasonal influenza vaccination for all persons aged 6 months and older in general, and in particular for individuals with chronic pulmonary diseases including asthma. For the latter population, this vaccine aims to limit influenza-related mortality and decrease transmission of the virus.

Although there were concerns that influenza vaccination might aggravate respiratory symptoms, any such effect would be outweighed by the benefits of the vaccination. A Cochrane review did not find an increased rate of exacerbation for two weeks following vaccination.

Compared to the general population, asthmatics are at higher risk of the development of pneumococcal pneumonia and invasive pneumococcal disease. Well-designed and robust randomized clinical trials to determine the efficacy of pneumococcal vaccine in reducing mortality or morbidity from pneumococcal disease in asthmatic individuals are lacking. Nevertheless, both the 2017 Philippine Society for Microbiology and Infectious Diseases and the 2019 U.S. CDC adult immunization recommendations include pneumococcal polysaccharide and conjugate vaccination schedules for all adults age 65 years and over and for younger adults with chronic lung diseases, e.g., asthma.

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**What are the non-pharmacological interventions for asthma?**

There are other interventions, activities and strategies aside from pharmacotherapy that can help in managing asthma. These are listed and summarized in Table 6.2.
Table 6.2. Non-pharmacological interventions for asthma.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Advice/recommendation</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cessation of smoking and ETS exposure</td>
<td>• At every visit, strongly encourage people with asthma who smoke to quit. Provide access to counselling and smoking cessation programs (if available)</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>• Advise parents/carers of children with asthma not to smoke and not to allow smoking in rooms or cars that their children use</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>• Strongly encourage people with asthma to avoid environmental smoke exposure</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>• Assess smokers/ex-smokers for asthma and COPD (asthma-COPD overlap or ACO) as additional treatment strategies may be required</td>
<td>D</td>
</tr>
<tr>
<td>Physical activity</td>
<td>• Encourage people with asthma to engage in regular physical activity for its general health benefits</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>• Provide advice about prevention and management of exercise-induced bronchoconstriction</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>• Regular physical activity improves cardiopulmonary fitness, but confers no other specific benefit on lung function or asthma symptoms, with the exception of swimming in young people with asthma</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>• There is little evidence to recommend one form of physical activity over another</td>
<td>D</td>
</tr>
<tr>
<td>Avoidance of occupational exposures</td>
<td>• Ask all patients with adult-onset asthma about their work history and other exposures</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>• In management of occupational asthma, identify and eliminate occupational sensitizers as soon as possible, and remove sensitized patients from any further exposure to these agents</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>• Patients with suspected or confirmed occupational asthma should be referred for expert assessment and advice, if available</td>
<td>A</td>
</tr>
<tr>
<td>Avoidance of medications that may make asthma worse</td>
<td>• Always ask about asthma before prescribing NSAIDs, and advise patients to stop using them if asthma worsens</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>• Always ask people with asthma about concomitant medications</td>
<td>D</td>
</tr>
<tr>
<td></td>
<td>• Aspirin and NSAIDs are not generally contraindicated unless there is a history of previous reactions to these patients</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>• Decide about prescription of oral or intra-ocular beta-blockers on a case-by-case basis. Initiate treatment under close medical supervision by a specialist</td>
<td>D</td>
</tr>
<tr>
<td></td>
<td>• If cardioselective beta-blockers are indicated for acute coronary events, asthma is not an absolute contraindication, but the relative risks/benefits should be considered</td>
<td>D</td>
</tr>
<tr>
<td>Healthy diet</td>
<td>• Encourage patients with asthma to consume a diet high in fruit and vegetables for its general health benefits</td>
<td>A</td>
</tr>
</tbody>
</table>

COPD: chronic obstructive pulmonary disease; NSAID: non-steroidal anti-inflammatory drugs; HDM: house dust mite; ICS: inhaled corticosteroids; SLIT: sublingual immunotherapy; SCIT: subcutaneous immunotherapy; FEV1: forced expiratory volume in 1 second
### Table 6.2. Non-pharmacological interventions for asthma. (continued)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Advice/recommendation</th>
<th>Evidence</th>
</tr>
</thead>
</table>
| Bronchial thermoplasty                            | • For highly selected adult patients with uncontrolled asthma despite use of recommended therapeutic regimens and referral to an asthma specialist center, bronchial thermoplasty is a potential treatment option in some countries  
• Caution should be used in selecting patients for this procedure as the number of studies is small and people with chronic sinus disease, frequent chest infections or FEV1 <60% predicted were excluded | D        |

| Avoidance of outdoor allergens                    | • For sensitized patients, when pollen and mold counts are highest, closing windows and doors, remaining indoors and using air conditioning may reduce exposure to outdoor allergens | D        |

| Dealing with emotional stress                     | • Encourage patients to identify goals and strategies to deal with emotional stress that makes their asthma worse  
• There is insufficient evidence to support one stress reduction strategy over another, but relaxation strategies and breathing exercises may be helpful  
• Arrange a mental health assessment for patients with symptoms of anxiety or depression | B        |

| Avoidance of outdoor air pollutants/weather conditions | • In general, when asthma is well-controlled, there is no need for patients to modify their lifestyle to avoid unfavorable outdoor conditions (air pollutants, weather)  
• It may be helpful during unfavorable environmental conditions (very cold weather, low humidity or high air pollution) to avoid strenuous outdoor physical activity and stay indoors in a climate-controlled environment; and during viral infections to avoid polluted environments | D        |

| Avoidance of foods and food chemicals             | • Food avoidance should not be recommended unless an allergy or food chemical sensitivity has been clearly demonstrated, usually by carefully supervised oral challenges  
• For confirmed food allergy, food allergen avoidance may reduce asthma exacerbations  
• If food chemical sensitivity is confirmed, complete avoidance is not usually necessary, and sensitivity often decreases when asthma control improves | D        |

COPD: chronic obstructive pulmonary disease; NSAID: non-steroidal anti-inflammatory drugs; HDM: house dust mite; ICS: inhaled corticosteroids; SLIT: sublingual immunotherapy; SCIT: subcutaneous immunotherapy; FEV1: forced expiratory volume in 1 second

### References:

10. Philippine College of Chest Physicians (Philippine Consensus Report on Asthma Diagnosis and Management 2009


Patient education is an equally crucial factor as the other pillars of asthma control which are: (1) accurate diagnosis, level of severity assessment and asthma control monitoring; (2) control of environmental triggers and comorbid conditions affecting asthma, and; (3) highly effective pharmacologic therapy. For the past three decades, guidelines advocated for the provision of Guided or Supported Asthma Self-Management Education to patients and their caregivers because of its evidence-based effectiveness in asthma outcomes. Despite global recommendations, its impact on asthma care has not been fully realized because of its suboptimal use in clinical practice. Only one-third (1/3) of asthmatic patients have ownership of asthma action plans. Factors identified as barriers for its use or implementation include: time constraints, lack of training of the asthma education providers, lack of belief of patient's ability to self-manage and lack of confidence in completing self-management plans. A whole system approach is needed to break the barriers which would include: intensified patient education, intensified professional training and strong organizational commitment. This chapter will focus on (1) patient's Guided Asthma Self-Management Education with their families and caregivers and (2) Asthma Education Provider training. Empowering asthma patients, caregivers and asthma education providers would encourage its implementation in clinical practice.

What is Guided Self-Management Education and its impact on asthma outcomes?

Guided or Supported Self-Management Education is an individualized, dynamic, continuous, progressive, sequential and regular educational process that emphasizes on patient's involvement to take responsibility in his or her own care. It enhances self-efficacy in symptom monitoring, treatment and prevention. It is achieved through physician-caregiver-patient collaboration at all points-of-care. The family and other caregivers are oriented on the treatment plan designed by the patients with the guidance of the physician. It is tailored to the literacy level, cultural beliefs and practices of the patient. If asthma symptoms are controlled, the patient should have fewer exacerbations, a higher quality of life, lower costs, slower progression of airway remodeling from inflammation, less morbidity and lower risk of death from asthma.
What are the core components of Guided Self-Management Education program?

An asthma self-management education program integrates the four components of Guided Asthma Self-Management Education. The following core asthma information and technical skills will be taught, reviewed, refined and reinforced on every patient’s clinic visit.

1. Basic facts about asthma (natural history of disease, signs and symptoms, triggers)
2. What defines well-controlled asthma and patient’s current level of control
3. Role of medications
4. Skills (e.g., inhaler technique, use of valve holding chamber or spacer and, self monitoring [peak flow meter use or based on symptom diaries])
5. When and how to handle signs and symptoms of worsening asthma; when and where to seek care
6. Environmental exposure control measures
7. Develop an active partnership with the patient
8. Provide a written action plan

What are the components of a written asthma action plan?

The following are included in the action plan:

1. Daily management, which includes:
   a. Medicines to take daily (medication names and doses)
   b. Actions to take to control and avoid asthma triggers
2. Recognizing and handling worsening asthma
   a. Signs, symptoms and peak flow values that indicate worsening asthma
   b. Medications and dosages to take in response to worsening symptoms
   c. Signs, symptoms and peak flow values that indicate the need for urgent medical attention
   d. Emergency telephone numbers of the physician, emergency department and service to rapidly transport the patient to medical care

Regular review by a healthcare provider is a vital management skill in asthma education. Asthmatic patients should collaborate with his/her healthcare provider. The healthcare provider review includes the following components:

1. Elicit questions and concerns. Discuss and provide additional educational messages. Patient may be referred to a trained asthma education provider, if available.

2. Assess asthma control
   a. Review patient’s level of symptom control and risk factors
   b. Elicit episodes of flare-up and identified contributory factors. Evaluate if the patient’s response or actions taken were appropriate. Elicit if a written asthma action plan was used to guide the actions taken.
   c. Review symptom and/or peak expiratory flow diary, if the patient keeps one
   d. Assess comorbidities

3. Assess treatment issues
   a. Watch the patient use their inhaler. Re-checking and correcting inhaler techniques using a standardized checklist leads to improved asthma control. (Evidence A)
   b. Assess medication adherence and identify barriers
   c. Assess adherence with other interventions, e.g., smoking cessation
   d. Review the asthma action plan and update it if the level of asthma control or treatment has changed.

By modifying patient’s therapy based on home monitoring of disease severity, patients can improve control of their asthma and avoid visits to acute care facilities. PEF monitoring has been advocated as useful in detecting asthma exacerbations especially in those who have difficulty in recognizing changes in their symptoms.

In designing asthma action plans, studies are not clear if the traffic light configuration format is better than the standard instructions. Studies in adults revealed that outcomes are comparable whether the written action plan is based on symptoms or peak flow measurements. Benefits are greater when asthma action plans are based on percentage personal best peak flow than percentage predicted peak flow. (Evidence A) The 2-3 action points action plan (peak flow <80% best: increase inhaled steroids; peak flow <60% best: commence oral steroids and seek medical advice and peak flow <40% best: seek urgent medical advice) is consistently effective in reducing admissions and ER visits than the use of 1-action point or 4-action points plan.

Whether in written instructions or paper template or electronic plans, the action points in the asthma action plan should be agreed upon by the patient, caregiver and primary care physician. The asthma action plan should be regularly reviewed by the physician and updated accordingly. The family and caregiver should be oriented to the treatment plan for home education reinforcement.
Who should deliver Asthma Education?

Provision of asthma education is usually practiced by the primary care physicians or subspecialists in a clinic setting during clinic visits or hospital setting during hospitalization due to exacerbation. Current evidence supports that trained and certified asthma educators, who are neither subspecialists nor primary care physicians, are as effective in providing asthma education and improving asthma outcomes. Respiratory therapists,\(^9\) nurse practitioners,\(^1, \, 10, \, 11\) (Evidence A) clinical pharmacists\(^1, \, 9, \, 11\) (Evidence A) or community health workers\(^12\) deployed to primary care clinics, community health centers, school and office clinics and pharmacies can bridge the gap in patient care.\(^9-12\)

Healthcare providers teaching patients with asthma should have the basic skills and knowledge necessary to transmit current principles of asthma self-management and to assess individual needs and the efficacy of the teaching.\(^11, \, 13, \, 14\) Educational programs for asthma educators was developed in 2015, as a result of a collaboration between the Philippine College of Chest Physicians (PCCP) through the Asthma Council and the American College of Chest Physicians (ACCP) currently known as CHEST Philippine Delegation, produced the Handshake Project on Asthma Education, which will standardize the information provided and improve the quality of asthma education in the Philippines.

What are the effective methods of asthma information delivery?

High-impact learning is always targeted in any information delivery situation.\(^14, \, 15\) Asthmatics are envisioned to be competent to control and manage their asthma, and confident in their ability to do Guided Asthma Self-Management with their health professional.

Effective information delivery also hinges on the asthmatics’ ability to sort out questions and arrive at answers themselves rather than being told. The Socratic method has proven effective in helping learners learn. Through questions, asthmatics are able to surface and articulate their own insights, in the process often discovering the answers within themselves. The skill of using questions involves four subskills: asking questions, rephrasing questions, answering questions and deferring questions. Questions must be phrased clearly and simply, with a single focus on what is being explored. Questions must be rephrased if the original questions did not elicit response or appeared muddled and unclear. A desired default should be to ask a question in response to a question rather give an answer.

Example: “I love my cat very much but I know she gives me asthma. Should I give my cat away?” This can be answered with another question which will help the person arrive at an answer on his/her own. The following question can be asked: “What do you think is more important to you – your cat or the discomforts you feel with the asthma that she brings?”

Asthmatics learn best when they are able to connect what they know (head) with how they feel (heart) and the skills they need to do what is needed (hands). Learning should be experienced, not taught.

What are the effective strategies for asthma adherence management?

Andrew Weinstein\(^16\) proposed an approach composed of four sequential adherence management principles to enhance asthma guidelines, which could be adapted in the local clinical practice:

1. Objective adherence monitoring (e.g., self-reports, caregiver reports, canister weight, electronic monitoring devices) and asthma control monitoring (e.g., Asthma Control Questionnaire and Asthma Control Test)
2. Identification of the reasons for non-adherence
3. Delivery of an individually-tailored strategy to address each specific cause of non-adherence
4. Use of motivational interviewing (MI)\(^17, \, 18\) communication skills to enhance the delivery of each strategy.

The World Health Organization (WHO) defined three types of non-adherence: intelligent/intentional, erratic (forgetfulness) and unwitting non-adherence.\(^19\) GINA 2018\(^1\) listed factors contributing to poor adherence (Table 7.1).
Table 7.1. Poor medication adherence in asthma.

<table>
<thead>
<tr>
<th>Factors contributing to poor asthma medication adherence</th>
<th>How to identify poor adherence in clinical practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication/regimen factors</td>
<td>Ask an emphatic question</td>
</tr>
<tr>
<td>• Difficulties using inhaler devices (e.g., arthritis)</td>
<td>• Acknowledge the likelihood of incomplete adherence and encourage an open non-judgmental discussion.</td>
</tr>
<tr>
<td>• Burdensome regimen (e.g., multiple times per day)</td>
<td>Examples are:</td>
</tr>
<tr>
<td>• Multiple different inhalers</td>
<td>• “Many patients don’t use their inhaler as prescribed in the last 4 weeks, how many days a week have you been taking it - not at all, 1, 2, 3, or more days a week?”</td>
</tr>
<tr>
<td></td>
<td>• “Do you find it easier to remember your inhaler in the morning or evening?”</td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Unintentional poor adherence</td>
<td>Check medication usage</td>
</tr>
<tr>
<td>• Misunderstanding about instructions</td>
<td>• Check the date of the last controller prescription</td>
</tr>
<tr>
<td>• Forgetfulness</td>
<td>• Check the date and dose counter on the inhaler</td>
</tr>
<tr>
<td>• Absence of a daily routine</td>
<td>• In some health systems, prescribing and dispensing frequency can be monitored electronically by clinicians and/or pharmacists</td>
</tr>
<tr>
<td>• Cost</td>
<td></td>
</tr>
<tr>
<td>Intentional poor adherence</td>
<td></td>
</tr>
<tr>
<td>• Perception that treatment is not necessary</td>
<td></td>
</tr>
<tr>
<td>• Denial or anger about asthma or its treatment</td>
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<tr>
<td>• Inappropriate expectations</td>
<td></td>
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<tr>
<td>• Concerns about side-effects (real or perceived)</td>
<td></td>
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<tr>
<td>• Dissatisfaction with healthcare providers</td>
<td></td>
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<tr>
<td>• Stigmatization</td>
<td></td>
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<tr>
<td>• Cultural or religious issues</td>
<td></td>
</tr>
<tr>
<td>• Cost</td>
<td></td>
</tr>
</tbody>
</table>

Examples of successful adherence intervention

• Shared decision making for medication/dose choice
• Inhaler reminders for missed doses
• Prescribing ICS once daily versus twice daily
• Home visits for a comprehensive asthma program by an asthma nurse
References:


CHAPTER 8

Special Considerations
There are certain types of patients with asthma who may be more difficult to manage, and/or may require closer attention because of coexisting comorbid conditions, or during special circumstances such as pregnancy, menstruation, surgery and others.

**PREGNANCY AND ASTHMA**

**How common is asthma in pregnancy?**

Asthma is one of the most common chronic conditions that is found in women in the reproductive age group. It is considered as the most common respiratory condition of pregnancy complicating 4%–8% of pregnancies with increasing healthcare utilization and cost. 1, 2, 3, 4 Different regions of the world have varying data on the incidence of asthma in pregnancy. Values range from 2 to 13%, which mimics the incidence of asthma in the community. 3, 4, 5 In the Philippines, there is a lack of local data on the incidence of asthma in pregnant patients.

**What is the course of asthma during pregnancy?**

The “rule of thirds” has always been cited when the course of asthma in pregnancy is discussed, that is, one-third of patients will remain stable, one-third will have symptomatic improvement, and in one-third of pregnant patients, their asthma will deteriorate. 6 Unfortunately, it may not always be easy to predict which patients will go into which group.

Two factors seem to correlate significantly with the course of asthma during pregnancy: the severity of a patient’s asthma before she became pregnant, and the use of asthma medications. 7 It should be noted that even patients with “mild” pre-pregnancy asthma may deteriorate significantly during pregnancy. 8

Asthma exacerbations usually occur towards the second half of pregnancy. In a recent prospective cohort study, 50% of all exacerbations and losses of control were noted to occur before 20 weeks of gestation. 8 The risk appears to be increased in smokers (or ex-smokers), in those who are obese, and in those who are infected with respiratory viruses, and whose asthma is uncontrolled before their pregnancy. 9
What are the possible adverse maternal and fetal outcomes in pregnant asthmatics?

Asthma is strongly associated with preeclampsia, placental abruption and placenta previa, and obstetric hemorrhage. Pregnant women with asthma are at a significantly increased risk of a range of adverse perinatal outcomes, including low birthweight, small for gestational age (SGA), preterm labor and delivery. Evidence pointed to a direct correlation between the severity of the asthma, the higher occurrence of exacerbations, and the increase in the incidences of these adverse events on the baby. Evidence also revealed that optimal treatment of the asthma reduced these risks, including exacerbations, significantly. A recent prospective cohort study highlighted recurrent uncontrolled asthma as a greater contributor to poor perinatal outcomes than exacerbations. There were studies that implied an increased need for caesarian section delivery, however, a recent meta-analysis revealed that the increase in caesarian sections was secondary to elective caesarian sections and not emergencies. The risk of cesarean delivery was higher for patients with severe asthma as compared to those with mild asthma. There have been some published studies that showed that congenital malformations are more common in asthma patients who took OCS in the first trimester of pregnancy. Other studies, however, have found no direct correlation. Exacerbations, use of bronchodilators, or use of ICS were not associated with congenital malformation. Asthma in pregnancy has also been associated with multiple comorbid maternal conditions, such as a higher risk of developing gestational diabetes but that aggressive and optimal treatment of asthma reduced this risk significantly. There were also reports of an increased risk of pulmonary embolism and a greater frequency and severity of respiratory viral infections.

How is asthma diagnosed in pregnancy?

The usual parameters for the diagnosis of asthma in the general asthma population are, for the most part, applicable to the pregnant asthmatic patient. A problem may arise in a pregnant patient who was never previously diagnosed with asthma, and who, during her pregnancy, starts manifesting with symptoms of shortness of breath. The breathlessness associated with a progressively enlarging abdomen may be difficult to differentiate from dyspnea caused by obstructive airway disease. Spirometry is still the gold standard for the diagnosis. Peak flow variability may also be helpful. Other tests have been proposed, particularly the use of fraction of exhaled nitric oxide (FeNO), not so much in the diagnosis of asthma, but in the management. What medications can be prescribed for pregnant asthmatics?

The ultimate goal of asthma therapy in pregnant patients is to protect both the mother and the fetus by achieving good asthma control. This can be accomplished by prescribing the same medications as one would to a non-pregnant patient. Although there is a general concern about any medication use in pregnancy, the advantages of actively treating asthma in pregnancy markedly outweigh any potential risks of usual controller and reliever medications.

The pregnant asthmatic should be prescribed an ICS, the mainstay of controller therapy. Majority of the studies have declared that ICS are safe in pregnancy, and their regular use does not result in complications in the mother or the fetus. It has been shown that regular use of ICS as maintenance in achieving asthma control has led to a lower incidence of complications and adverse outcomes. If asthma is well controlled throughout pregnancy, there is little or no increased risk of adverse maternal or fetal complications. Inhaled corticosteroids reduce the risk of exacerbations of asthma during pregnancy, (Evidence A) and cessation of ICS during pregnancy is a significant risk factor for exacerbations. Some studies have suggested using the FeNO to monitor for the need to adjust the ICS dosage to reduce the risk for exacerbations.

Budesonide is the ICS with the most published human gestational safety data and is considered the preferred ICS for use in pregnant patients. There are no published studies for other ICS preparations and there are no data to show that they are not safe. Therefore, if a patient is well controlled on an ICS other than budesonide prior to getting pregnant, it may be more beneficial to just continue the current ICS rather than shift to budesonide especially if changing formulations may jeopardize asthma control.

Inhaled SABAs are the rescue medications of choice for the pregnant asthmatic. Inhaled albuterol (salbutamol) has been the most extensively studied SABA, and almost all the researches point to its very good...
safety profile. In a meta-analysis of cohort studies from 1975 to 2012, there appeared to be no increased risk of congenital malformations, caesarean section or postpartum hemorrhage in pregnant women with asthma who used inhaled bronchodilators during pregnancy.

Patients not fully controlled on ICS alone may be given LABA in combination. The safety profile of salmeterol and formoterol are expected to be the same as albuterol or salbutamol. LABAs should always be given in combination with ICS and never as monotherapy.

Theophylline is also an alternative, but not preferred, add-on treatment for moderate to severe persistent asthma but its use is limited by its many adverse side-effects and potential drug interactions, resulting in possible toxicity.

As for other medications, only montelukast and zafirlukast have been found in most studies to be safe although data on their use in pregnancy are more limited. In contrast, zileuton was associated with teratogenicity in animal studies and should be avoided. More studies are needed for omalizumab although animal studies have been reassuring and an ongoing registry showed that rates of prematurity and SGA were not unlike those seen in other studies of pregnant women with severe asthma.

Some patients with severe asthma may require regular OCS use to achieve adequate asthma control. Oral corticosteroids are also typically given as part of the discharge regimen after an acute asthma episode. Its use in pregnancy has been associated with an increased risk of preterm birth and low birth weight infants. Since these risks would be less than the potential risks of a severe asthma exacerbation, which include maternal or fetal mortality, OCS, is recommended when indicated for the management of severe asthma during pregnancy.

What is the approach to the management of asthma exacerbations in pregnancy?

Asthma exacerbations are one of the most common medical problems in pregnant women, and can have the most significant impact on fetal morbidity and mortality. From 33 to 45% of pregnant women will have exacerbations requiring immediate medical attention. Prevention of exacerbations is important since there is an increased incidence of congenital anomalies, i.e., cleft lip and palate in infants whose mothers had an exacerbation, particularly in the first trimester.

Although the treatment of asthma exacerbations is exactly the same in the pregnant and non-pregnant patients, a pregnant asthmatic in acute exacerbation will require more intensive monitoring and management. Pregnant women with acute asthma should be considered to be high-risk patients, and their management requires a close multidisciplinary collaboration and coordination of all the healthcare professionals managing the patient such as primary care physicians, pulmonologists, obstetricians and pediatricians.

All asthma patients will benefit tremendously from patient education. Pregnancy is a good time to review the patient’s basic understanding of asthma and its management, including trigger avoidance, asthma control and adequate use of devices, medication and personal action plans.

When should pregnant asthmatics be hospitalized?

Acute severe asthma in pregnancy is an emergency and should be treated vigorously in hospital. Patients in the third trimester and who are very symptomatic may have to be admitted to the hospital for close monitoring. The avoidance of maternal and fetal hypoxia is of primary importance and this requires aggressive treatment of acute exacerbations during pregnancy with SABA, oxygen and early administration of systemic corticosteroids. It is recommended that high flow oxygen be delivered immediately to maintain saturation above 95%. Continuous fetal monitoring should be performed when asthma is uncontrolled or severe, or when fetal assessment on admission is not reassuring. The cause of the exacerbation also has to be addressed.

What is the approach to the management of the pregnant asthmatic during labor and delivery?

Acute exacerbations are uncommon during labor and delivery, perhaps due to endogenous steroid production. The usual controller medications should be taken, with reliever if needed. Bronchoconstriction may be induced by hyperventilation during labor, and should be managed with SABA. Pregnant asthmatics on oral steroids at a dose exceeding prednisolone 7.5 mg per day for more than two weeks prior to delivery should receive parenteral hydrocortisone 100 mg 6-8 hourly during labor.

Although some data suggest that the risk of postpartum asthma attacks is increased in women having caesarean sections, this may be related more to the asthma severity rather than to the caesarean section, or to factors such as postoperative pain with diaphragmatic splinting, hyperventilation and atelectasis. In the absence of an acute severe asthma attack, caesarean section should be reserved for the usual obstetric indications. If asthma is required, regional blockade is preferable to general anesthesia.
**MENSTRUATION AND ASTHMA**

**What is the association of menstruation with asthma?**

Some females with asthma experience an increase in their symptoms, or worse, an increased incidence of exacerbations, during the peri-menstrual period, a condition that is known as peri-menstrual asthma. Asthma deterioration has been described in the periovulatory phase, in the middle of the preovulatory or luteal phase, and more frequently in the pre-menstrual phase, an entity defined as pre-menstrual asthma (PMA).

There is no clear definition of PMA, although it is considered to be a cyclical deterioration of asthma during the pre-menstrual (luteal) phase, sometimes including the first few days of the menstrual cycle. This is thought to be due to fluctuations in the various hormones associated with ovulation and the menstrual cycle.

**How common is pre-menstrual asthma (PMA)?**

The reports on the incidence of PMA vary, ranging from 17% to 44% likely due to the fact that some studies rely on purely subjective data from the patients while others require objective parameters such as lung function studies. The precise prevalence is difficult to determine due to a lack of explicit diagnostic criteria and appropriate epidemiological surveys. Nevertheless, there seems to be a significant percentage of asthmatic females who experience deterioration in their symptoms during the peri-menstrual phase. These patients with PMA represent a certain asthma phenotype that should be recognized, as there is an increased incidence of asthma-related ER visits, hospitalizations and intubation in this group.

**What causes pre-menstrual asthma (PMA)?**

The etiology of PMA remains unknown. The available data link the endocrine system with the influence of female sex hormones on inflammatory mediators and asthma symptoms. The significant fluctuation in the levels of many hormones, such luteinizing hormone, follicle stimulating hormone, estradiol, progesterone and testosterone, during the menstrual cycle is thought to contribute significantly to the pathogenesis of PMA.

The peri-menstrual phase is characterized by a decline in progesterone and estradiol levels which triggers mast cell degranulation at the basal layer of the endometrium which induces a local inflammatory reaction with endometrial tissue breakdown and menstruation. There is also a systemic inflammation that occurs with mast cell and eosinophil degranulation and consequent increase in inflammatory markers in tissues where hyperactive mast cells are already present, such as the lung/bronchial tissues of an asthmatic woman.

Studies have also demonstrated the changes in the female immune response throughout the respiratory cycle such as increased wheal-flare response to skin prick testing and hyperactivity to histamine of the nasal mucosa during the peak ovulatory estrogen levels of days 12-16 of the menstrual cycle.

Another study showed that an increase in bronchial hyperresponsiveness documented as a decrease in PC_{20}FEV1 in the follicular phase of the menstrual cycle in about 30% of women. This was associated with lower cAMP levels in sputum samples, which may contribute to bronchoconstriction. A link between PMA and lower testosterone levels were also noted.

Despite the studies carried out so far and the reviews published on the subject, the research results are inconclusive and the causal factors of this entity remain unknown.

**How is pre-menstrual asthma (PMA) diagnosed?**

The cyclical deterioration in PMA is defined as a worsening of asthma symptoms and/or deterioration of lung function tests, such as a decrease of ≥20–40% in the PEF. Most authors diagnose PMA on the basis of either asthma questionnaires, PEF measurements or questionnaires combined with PEF measurements.

Women with pre-menstrual asthma are older, have more severe asthma, a higher body mass index, a longer duration of asthma and a greater likelihood of aspirin sensitive asthma. They more often have dysmenorrhea, pre-menstrual syndrome, shorter menstrual cycles and longer menstrual bleeding. The patients with PMA had significantly higher depressive symptoms and water retention than other asthmatic patients.
How is pre-menstrual asthma (PMA) treated?

As in any patient with asthma, the mainstay of treatment is still regular ICS-LABA, with SABA as rescue medication. However, the hormonal imbalances that have been shown to precipitate the worsening of the symptoms have been evaluated.

A role for both exogenous estrogen and progesterone using oral contraceptives (OC) in the management of PMA was demonstrated in studies. In a prospective study on post-pubertal women with asthma, the 106 women using OC had reduced asthma symptoms, improved lung function and improved asthma control compared with those not using OC. Findings in another study showed that asthmatic patients receiving the OC had attenuated cyclical change in airway reactivity as well as reduced diurnal peak expiratory flow rate variability, which was associated with suppression of the normal luteal phase rise in sex-hormones. This stabilization of the airways may be due to regulation of the immune system, in particular, regulation of Th2-driven response by induced regulatory T cells (iTregs) reduces the severity of inflammatory response in asthma. Both estrogen and progesterone may also stimulate the function of the smooth airway muscles and inhibit the activities of Th2 responses.

The other associated comorbid conditions also have to be addressed.

Can pre-menstrual asthma (PMA) be prevented?

Since PMA is significantly associated with fluctuations in hormones during the menstrual cycle, stabilizing estradiol and progesterone/progestin levels and reducing the hormone-free intervals with OC may be considered. Although more studies are needed, reducing the hormone free intervals may result in less menstrual symptoms through the reduction of genital and systemic inflammation that is seen with hormone withdrawal.

SURGERY AND ASTHMA

What is the approach to the management of asthmatic patients undergoing surgery?

For elective surgery, patients with asthma should be evaluated at least one week prior to surgery to allow time for modification of treatment, if necessary, especially for those patients who are scheduled for procedures with a high risk of postoperative pulmonary complications. Postoperative pulmonary complications are most common following thoracic surgery, upper abdominal surgery, open aortic aneurysm repair, neurosurgery and surgery on the head and neck. Meticulous attention should be paid preoperatively to achieving good asthma control; especially for patients with more severe asthma, uncontrolled symptoms, significant exacerbation history (more than one exacerbation per year) or fixed airflow limitation. The following actions are recommended to reduce the risk of complications during surgery:

1. Before surgery, review the level of asthma control, medication use (especially OCS within the past 6 months) and pulmonary function.
2. Provide medications before surgery to improve lung function if lung function is not well controlled. A short course of OCS may be necessary.
3. For patients receiving OCS during the 6 months prior to surgery and for selected patients on long-term high-dose ICS, give 100 mg hydrocortisone every 8 hours intravenously during the surgical period, and reduce the dose rapidly within 24 hours after surgery.

For patients requiring emergency surgery, the risks of proceeding without first achieving good asthma control should be weighed against the need for immediate surgery. As stated above, patients taking long-term high-dose ICS, or those who have received OCS for more than 2 weeks during the previous 6 months, should receive hydrocortisone perioperatively as they are at risk of adrenal crisis in the context of surgery. For all patients, maintaining regular controller therapy throughout the perioperative period is important.
Vigilant monitoring of the asthmatic patient is of primary importance in preventing perioperative pulmonary complications. Proper preoperative evaluation of disease level and medical compliance with prescribed medication regimens, along with perioperative strategies for prevention of bronchospasm decrease postoperative pulmonary complications in asthmatics. Several guidelines on the management of asthma are available. One can easily refer to such publications as the Expert Panel Report 3 (EPR-3) on the diagnosis and management of asthma and the American College of Physicians report on risk assessment for and strategies to reduce perioperative pulmonary complications for patients undergoing non-cardiothoracic surgery. Also, such scoring systems as ARISCAT can serve as a guide to assess more effectively and systematically an asthmatic patient undergoing surgery.

**SINUS DISEASE (RHINITIS, SINUSITIS, NASAL POLYPS) AND ASTHMA**

**Is there a relationship between asthma and allergic rhinitis (AR), sinusitis, nasal polyps?**

The ‘united allergic airway’ is a theory that connects sinonasal disease, specifically allergic rhinitis (AR), chronic rhinosinusitis (CRS) and nasal polyps, with asthma in which seemingly disparate diseases, instead of being thought of separately, are instead viewed as arising from a common atopic entity. Literature supports the relationship but there is no direct evidence of causality. Epidemiological evidence suggests a strong relationship between AR and asthma. Allergic rhinitis can occur in more than 75% of patients with asthma, whereas asthma can affect up to 40% of patients with AR. Both diseases, which are IgE mediated, can be triggered by similar allergens, including mold, animal dander and HDMs. Temporally, AR often occurs before the onset of asthma.

Allergic rhinitis is a risk factor for asthma, and its presence is related to asthma severity. Patients with nasal symptoms appear to experience worse asthma control. This was supported by a recent cross-sectional studies looking at the relationship between nasal symptom scores and asthma symptoms. Many of the studies that have looked at the relationship between asthma control and rhinitis have been cross-sectional or retrospective. However, a prospective cohort study of patients with severe asthma showed that those with rhinitis had increased ER visits, and that the severity of rhinitis correlated with the severity of asthma as assessed by standardized questionnaires. Overall, studies suggest both children and adults with comorbid rhinitis and asthma have more frequent physician’s visits, ER visits and hospital admissions for asthma, and higher asthma-related drug expenses.

There is also a common pathophysiological relationship between AR and asthma with four mechanisms postulated to account for this relationship. First, the nose functions to warm, filter, humidify inhaled and via the numerous submucous glands located in the nasal passages, sterilize air through the release of antibacterial enzymes. With AR, nasal function may be partially or completely lost as the congestion forces the patient to become a mouth breather. This may predispose to bronchospasm caused by cooling and drying in the airways, as what occurs with obligate mouth breathing during vigorous activity. Second, during an exacerbation of AR, the inflammatory products from the upper airways may be aspirated directly into the lower airways. Third, nasal inflammation may result in local cytokine release into the bloodstream, which eventually causes bronchoconstriction in the lower airways. Fourth, a nasal-bronchial reflex may exist, where histamine and bradykinin stimulate the afferent nasal sensory nerve which sends a neural signal that travels to the central nervous system and activates the efferent vagus nerve, resulting in bronchial smooth muscle hyperreactivity.

A frequent association between bronchial hyperresponsiveness (BHR) and rhinitis has also been noted and patients suffering from AR frequently, in up to 80% of cases, manifest with BHR. A prospective study of a large group of patients with moderate-to-severe persistent AR alone, tree and HDM sensitization, rhinitis duration longer than 5 years and FEV1 of 86% or less of predicted value demonstrated a significant association with severe BHR: 6.4% of patients had severe BHR, 21.6% had mild BHR, 56.2% had borderline BHR and only 15.8% of patients had a negative methacholine test.
The etiology for the connection between asthma and AR is likely multifactorial. Although nasal blockage and aspiration of nasal contents have long been accepted as contributing factors, there is a growing body of evidence that suggests that a systemic response plays an important role in the AR-asthma relationship.57

With respect to CRS, it has been reported that around 90% of patients with mild to moderate asthma and almost 100% of those with severe asthma have radiological abnormalities of the sinuses.51 There is evidence supporting an association between rhinosinusitis and asthma, although it appears less clear whether CRS is a direct trigger for asthma or the two conditions are simply manifestations of a common underlying process.69 Possible mechanisms for this relationship include naso-pharyngo–bronchial reflexes, postnasal drip, abnormal breathing and the local production of inflammatory mediators that trigger pulmonary inflammation.70

It has been reported that 20%–60% of patients with CRS with nasal polyps have asthma.72, 73 Chronic rhinosinusitis has been associated with both more severe and more difficult to control asthma.74 Asthmatic patients have a higher rhinosinusitis severity score than non-asthmatic patients, and more presence of nasal polyps regardless of atopic status, indicative of a strong relationship between CRS with nasal severity and chronic airway inflammatory diseases.70, 74, 75

What is the impact of treatment of sinusonal disease on asthma outcomes?

Results of a meta-analysis demonstrated that intranasal corticosteroid medications used to treat AR significantly improve some asthma-specific outcome measures in patients suffering from both AR and asthma but only in patients not also receiving ICS.76 There is weak evidence that treatment of CRS may improve asthma outcomes, demonstrating only a small decrease in asthma symptoms after using mometasone but no difference in quiet breathing and the local production of inflammatory mediators that trigger pulmonary inflammation.70

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What is occupational asthma (OA) and how is it diagnosed?

Occupational asthma has been defined as a disease characterized by variable airflow limitation and/or hyperresponsiveness and/or inflammation due to causes and conditions attributable to a particular occupational environment and not to stimuli encountered outside the workplace.82

Occupational asthma refers to asthma caused by occupational exposures which can be sensitizers or irritants.82 Occupational asthma caused by workplace sensitizers are immunological and characterized by WRA appearing after a latency period. It encompasses OA caused by most high and certain low-molecular weight agents for which an allergic IgE-mediated mechanism has been proven.82 Occupational asthma caused by irritants or irritant-induced asthma occur with or without a latency period. This category includes reactive airways dysfunction syndrome which may occur after single or multiple exposures to non-specific irritants at high concentrations.83

Sensitizer-induced OA should be suspected in every adult with new-onset asthma.84 A latency period ranging from weeks to years after the first exposure to the sensitizer is observed before the initial onset of work-related symptoms. Sensitizer-induced symptoms begin variably— at the beginning of the work shift, toward its end, or even in the evening after working hours. Improvement or even remission typically occurs during weekends and holidays. Rhinitis often accompanies or precedes lower respiratory symptoms, especially when high-molecular-weight agents are the inciting factors.

A thorough clinical and occupational history must be obtained but a compatible history alone is insufficient for diagnosis and has a low positive predictive value.84, 85
Diagnostic tests can be divided into: tests that confirm asthma, tests that identify that the asthma is work-related or that the workplace as the cause of the respiratory symptoms, and tests that identify the agent causing the OA.82

The best method of confirming that the asthma is work-related is measuring lung function in relation to work exposure. This can only be done when the patient is still exposed to the suspected cause of their symptoms, so it needs to be the first confirmatory test.

Guidelines recommend serial measurement of PEF on days at and away from work which is considered the best validated method with good sensitivity and specificity in the diagnosis of WRA.84 Minimum criteria are ≥3 weeks of usual work exposure with measurements at least four times a day, or 8 work days and 3 rest days with 2-hourly measurements, with treatment being kept constant.

Both skin-prick and specific IgE measurements are highly sensitive for detecting type I sensitization to most high molecular weight agents, but are not specific for diagnosing OA.84 This is because sensitization is more common than disease. However, the presence of specific IgE in a worker with confirmed OA from workplace measurements is sufficient to identify the specific cause.

A specific inhalation challenge (SIC) (i.e., the subject inhales the agent of concern) is the best method of confirming the specific cause of OA when workplace measurements are not possible or specific IgE measurements are not available, as is the case for many low molecular weight agents. But it is not readily available and false-positive or false-negative responses can occur.82, 84, 86, 87 A supervised return to work with either a workplace challenge (for those with severe symptoms) or unsupervised PEF measurement on days at and away from work is helpful when occupational asthma is likely and SIC is negative.82

How is work-related asthma (WRA) managed?

In contrast to non-WRA, optimal management of OA consists of primary, secondary and tertiary prevention. Primary, secondary and tertiary preventive measures may reduce the incidence and severity of sensitizer-induced asthma.

Primary prevention aims to prevent sensitization to workplace agents, thus preventing disease. One way to achieve this aim would be to replace known sensitizing agents with non-sensitizers, however, this may not be readily achieved. Reduction of exposure to respiratory sensitizers may be achieved by instituting occupational hygiene measures such as containment, improved ventilation, and (as a last option) the use of personal protective equipment, as well as worker education to enhance adherence to recommended measures.85

Secondary prevention includes early identification of workers with occupational exposure to asthma-causing agents by means of medical surveillance (periodic respiratory questionnaires with or without spirometry and immunologic tests) and further investigations to confirm diagnosis and after diagnosis, removal of the affected worker from further exposure.85

Appropriate management after diagnosis, in addition to prevention of further exposure when possible, involves tertiary prevention with pharmacologic management that follows clinical-practice guidelines.85

There is less information on the prevention of irritant-induced asthma since the most straightforward cases of irritant-induced asthma are due to accidental exposure. Prevention should include occupational-hygiene measures that ensure the safety of workers in environments where there is the potential for accidental exposure to irritants. General measures include containment, good ventilation, worker education regarding safety practices, and, when other measures are not sufficient, use of fit-tested respiratory protective devices.85

WORK-EXACERBATED ASTHMA (WEA)

What is work-exacerbated asthma (WEA) and how is it recognized?

Work-exacerbated asthma (WEA), also termed work-aggravated asthma, describes a subset of work-related asthma that is worsened but not caused by work (unlike OA that is caused by work). It is defined as pre-existing or concurrent (adult new-onset) asthma that is worsened by workplace conditions or exposures.85 This can manifest as an increase in frequency and/or severity of asthma symptoms and/or increase in asthma medication required to control symptoms on work days.

For any individual, OA and WEA are not mutually exclusive, meaning that someone with OA can subsequently experience WEA, and vice versa.
The prevalence of WEA from the 12 published studies conducted in the general population or general healthcare settings ranged from 13% to 58%, with a median of 21.5%. Three of the studies had more objective criteria for WEA and had prevalence estimates of 13%, 14% and 22%, with a median of 14%.\textsuperscript{88, 90}

Patients with WEA who experience persistent work-related symptoms resemble OA cases with respect to severity of asthma and medication requirements, as well as socioeconomic factors like unemployment and loss of labor-derived income. However, compared with asthma unrelated to work, WEA is associated with more symptomatic days, a greater utilization of healthcare resources, higher direct costs and a lower quality of life.\textsuperscript{90, 91}

WEA should be considered in any patient with asthma that is worsening and/or who has work-related symptoms. The initial diagnostic step is to clarify whether the patient has asthma.

The diagnosis of WEA depends on demonstrating a relationship between work exposures and asthma exacerbations, most commonly documented by changes in symptoms (e.g., frequency, severity) or medication use temporally related to work.\textsuperscript{89, 90} In the common context of preceding asthma prior to the work exposures and/or an absence of a specific sensitizer at work, the findings of work-related worsening of asthma documented by serial PEF recordings, symptoms and medications are supportive of WEA.\textsuperscript{88}

Identification of exacerbation triggers is important both for confirming WEA and for reducing or eliminating harmful conditions to prevent future problems in the index case and co-workers. However, identification of a specific causative agent for WEA is often not possible, and mixed exposures are common. Non-work factors that can exacerbate asthma, such as viral infections and environmental allergies, should also be evaluated.\textsuperscript{90, 91}

**How is work-exacerbated asthma (WEA) managed?**

The goal of treatment is to minimize asthma exacerbations by reducing work exposures (e.g., by limiting sources of exposure, improving ventilation) and optimizing standard medical management with non-work environmental control measures and pharmacologic treatment. Avoidance or reduction of exposure can often lead to an improvement in asthma symptoms.

The patient may be able to stay at the same job with reduced exposures, depending on the severity of asthma and extent of exacerbating factors at work, but a job change to a workplace with fewer triggers may be necessary if this approach fails to adequately prevent work-related exacerbation of symptoms. Preventive strategies resemble those of disease management which are reduction of work exposures and optimization of medical management.\textsuperscript{92}

**OBESITY AND ASTHMA**

**Is there a relationship between obesity and asthma?**

Numerous studies in the last two decades have revealed that obesity is truly an independent risk factor for the development of asthma.\textsuperscript{92-96} There is a 2.3-fold increased odds of developing asthma in the future in both allergic and non-allergic obese individuals with a dose-response effect: 1.7-fold increased risk for BMI 25–29; 2.3-fold increased risk for BMI >30.\textsuperscript{92} Some authors claim that the risk for asthma is increased by up to 50% in patients who are overweight/obese.\textsuperscript{92}

Most studies have shown that females who are obese have a higher risk for developing asthma, which suggests that hormones may play a role.\textsuperscript{97} Other studies observed that the risk is the same for both males and females.\textsuperscript{98} There are fewer studies in obese children citing that boys have higher risks than girls.\textsuperscript{99}

Obese asthmatics as compared to non-obese patients generally report more symptoms and limitation of activities due to their symptoms, even if they are already on the same therapeutic regimens as the non-obese asthmatics.\textsuperscript{100} This may partly be due to the respiratory effects of the obesity itself, or, these patients may truly represent a different asthma phenotype that is less responsive to medications such as inhaled steroids and LABA.\textsuperscript{101} The mechanism behind this is not clear, but there may be a certain phenotype of obese asthmatics who have a different type of inflammation that is less responsive to glucocorticoids. This was mostly found in asthma patients who were morbidly obese.

**How are obese asthmatics managed?**

Weight loss as part of the management is important and has been documented to lessen asthma symptoms, improve quality of life, decrease BHR, reduce markers of systemic inflammation, reduce the need for medications and improve lung function parameters.\textsuperscript{102-104}
The mainstay of pharmacologic treatment is still the inhaled corticosteroid combined with a long-acting beta-agonist (ICS-LABA), with a SABA as a rescue medication. A higher dosage of ICS may be necessary as some obese patients may show a degree of resistance to corticosteroid treatment.102

GASTROESOPHAGEAL REFLUX DISEASE (GERD)-RELATED ASTHMA

Is gastroesophageal reflux disease (GERD) more common in patients with asthma?

There is evidence that GERD is more common in patients with asthma compared to the general population.105-107 Various studies have shown that this increased incidence of GERD in asthmatic range from as low as 25% to as high as 90%.105-106, 108-111

What is gastroesophageal reflux disease (GERD)-related asthma and what mechanisms are involved?

Because GERD and asthma are often encountered together, complex interactions occur during which GERD may increase asthma symptoms or asthma may trigger or worsen GERD.107 Gastroesophageal reflux disease-related asthma has been defined as asthmatic symptoms being induced or exacerbated by gastroesophageal reflux.107

Although further research is needed in order to elucidate the mechanisms that link GERD with asthma, postulated mechanisms on acid reflux-induced asthma include: vagal mediated reflex;105 increased bronchial reactivity;107 bronchoconstriction due to aspiration of gastric acid.105-107

A study by Sharifi and Ansarin utilizing impulse oscillometry (IOS) to measure airway resistance among patients who had asthma and GERD demonstrated that the distal airways were more affected than the proximal airways, and these findings suggested that the main mechanism was the reflex bronchospasm secondary to acid exposure of the distal esophagus rather than direct effect of micro-aspiration of the proximal airways.107

Asthma can also result in physiological changes that might predispose to GERD which may be related to the hyperinflation within an increased pressure gradient between thorax and abdominal cavity and flattening of the diaphragm which could impair the anti-reflux barrier and result in GERD.107

Medications taken for asthma, such as beta2-agonists, theophylline and high doses of OCS which may reduce lower esophageal sphincter pressure, may also increase acid reflux.105, 107

How is gastroesophageal reflux disease (GERD)-related asthma diagnosed?

The diagnosis of GERD as the cause of GERD-related asthma may pose a challenge.102 In patients with confirmed asthma, GERD should be considered as a possible cause of a dry cough.102 However, the most common classic symptoms of GERD such as heartburn or regurgitation may not always be manifested in patients with asthma.105-112 In addition, while there are many tests that can be done to work up patients who are suspected as having GERD, there are no diagnostic gold standards.105 Current available diagnostic tests performed for GERD such as esophagogastroduodenoscopy and esophageal pH monitoring or ambulatory esophageal reflux monitoring have uncertain sensitivity and specificity for the diagnosis of GERD-related asthma.107

For patients with asthma and symptoms suggestive of reflux, an empirical trial of anti-reflux medication, such as a proton pump inhibitor (PPI) or motility agent, may be considered.12 A good response of asthmatic symptoms to PPI treatment may permit a more confident diagnosis of GERD-related asthma.112 Failure to respond to a course of PPI should prompt a careful re-assessment of the patient, with consideration for specific investigations such as 24-hour pH monitoring or endoscopy as well as other work-up for other causative factors for the persistent asthmatic symptoms.102 There is no value in routine screening of patients with uncontrolled asthma for GERD.20 (Evidence A) Nevertheless, it is important that GERD should be assessed in asthmatic patients who also have typical symptoms of GERD, as well as in patients with non-atopic refractory or difficult asthma.102

How is gastroesophageal reflux disease (GERD)-related asthma managed?

Proton pump inhibitors are the main therapeutic regimen for GERD and this is commonly recommended for suspected GERD-related asthma. Non-pharmacologic treatment include: weight loss patients who are overweight or have had recent weight gain; head of bed elevation and avoidance of meals 2-3 hours before bedtime for patients with nocturnal GERD; avoidance of food that can trigger reflux such as alcohol and caffeine.

Some patients may respond well to PPI therapy. However, studies to date have shown only limited benefits for the treatment of symptomatic GERD on asthma outcomes and results from well-designed studies are inconsistent.
Most studies report a small increase in lung function and better asthma-related quality of life with less exacerbations, but there are studies that show no improvement in both symptoms as well as peak flow, and no change in rescue SABA days as well as frequency of exacerbations.105-106, 109, 112

In general, the benefits of PPIs in asthma appear to be limited to patients with both symptomatic reflux and night-time respiratory symptoms.20, 114, 115 But patients with poorly controlled asthma should not be treated with anti-reflux therapy unless they also have symptomatic reflux.20 (Evidence A)

Anti-reflux surgery is an option for asthmatics with well-defined reflux disease, if indicated and available, preferably done by a skilled, experienced surgeon.112

FOOD ALLERGY, ANAPHYLAXIS AND ASTHMA

What is the relationship of food allergy and anaphylaxis among asthmatics?

It has been reported that food allergy and asthma are characterized by an increasing prevalence and that food allergy and asthma often coexist.116 Food allergy in early childhood often precedes asthma at a later time point in child- or adulthood as described in the atopic march hypothesis.116, 117

Although it is known that food allergic reactions can trigger lower respiratory symptoms, food allergy generally does not present with chronic or isolated asthmatic symptoms.118 But asthmatic reactions can be part of the allergic response.20 During food allergic reactions, non-specific BHR may increase.121

Although foods are rarely important triggers of asthma exacerbation, occurring in <2% of people with asthma, coexisting asthma and food allergy often coexist.118 More severe food-induced allergic reactions (anaphylaxis) can occur, as well as for a fatal outcome from food-induced anaphylaxis.20 109, 110, 111 In addition, findings in some studies on both children and adults with asthma and concurrent food allergy showed an association with worse asthma morbidity with increased hospitalizations, ER visits and use of oral steroid than those with asthma alone.122, 123

Although any substance has the potential to cause anaphylaxis, the most common causes of IgE-mediated anaphylaxis are foods, particularly peanuts, tree nuts, shellfish and fish, cow’s milk, eggs and wheat: medications (most commonly penicillin), and natural rubber latex.125, 126 Exercise, aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), opiates and radiocontrast agents can also cause anaphylaxis from non-IgE-mediated mechanisms, and, in other cases, the cause of anaphylactic reactions is unknown (idiopathic anaphylaxis).125, 127-130

The association with asthma of food additives such as benzoates, tartrazine and monosodium glutamate is probably minimal but sulfites which is a common preservative in processed foods, dried fruits, medicines, beer and wine may trigger acute asthma (uncommon).131

How is food allergy, anaphylaxis in asthma managed?

For patients with suspected food allergy, a referral to a specialist for accurate allergy assessment diagnosis is usually necessary.20 Treatment of food allergy involves strict avoidance of the trigger food. Currently, there is no cure for food allergy and medications only manage the symptoms of disease.120

In addition to education in appropriate food avoidance strategies, patients who have a confirmed food allergy that puts them at risk for anaphylaxis must be trained and have an epinephrine auto-injector available at all times.20 123-125 It is especially important to ensure that their asthma is well controlled, that they have a written action plan, and that they understand the difference between asthma and anaphylaxis, and are assessed and seen on a regular basis. A multi-faceted approach to managing this subset of patients leads to optimal care.

ASPIRIN-EXACERBATED RESPIRATORY DISEASE (AERD)

What is aspirin-exacerbated respiratory disease (AERD)?

Aspirin-exacerbated respiratory disease (AERD), also called non-steroidal anti-inflammatory drug exacerbated respiratory disease (NERD) and previously referred to as aspirin-induced asthma, is the combination of asthma, chronic rhinosinusitis (CRS) with nasal polyposis (the “Samter’s triad”), and acute upper and lower respiratory tract reactions to ingestion of aspirin (acetylsalicylic acid or ASA) and other cyclooxygenase-1 (COX-1)-inhibiting non-steroidal anti-inflammatory drugs (NSAIDs).132

In a meta-analysis of prevalence studies, AERD occurs in approximately 7% of adult asthmatic patients and higher prevalence among severe asthmatics.136 It is a distinct subtype of asthma and polyposid sinus disease characterized by greater morbidity and healthcare costs for those affected.137 Aspirin-exacerbated respiratory disease generally occurs due to abnormalities in mediators and expression of arachidonic acid biosynthesis.138
How is aspirin-exacerbated respiratory disease (AERD) diagnosed?

The clinical presentation begins with nasal congestion and anosmia, progresses to chronic rhinosinusitis with nasal polyps that tend to re-grow rapidly after surgery and asthma and hypersensitivity to aspirin inevitably develop. Following ingestion of aspirin or NSAID, an acute asthma attack develops within minutes to 1–2 hours. It is usually accompanied by rhinorrhea, nasal obstruction, conjunctival irritation, and scarlet flush of the head and neck, and may sometimes progress to severe bronchospasm, shock, loss of consciousness and respiratory arrest. Aspirin-exacerbated respiratory disease is more likely to be associated with low lung function and severe asthma.

The diagnosis of AERD can often be made clinically when all three of the conditions that characterize AERD are present: asthma, visible nasal polyps (or even just a history of nasal polypectomy), and a history of a typical reaction to NSAID. Nocturnal nasal obstruction with sleep deprivation fatigue occurs routinely in these patients. Asthma may precede the upper airway disease or develop later. Computerized tomography (CT) or plain radiographs of the sinuses reveal complete opacification in nearly all AERD patients and normal imaging of the sinuses essentially rules out the diagnosis of AERD.

Aspirin challenge (oral, bronchial or nasal) is the gold standard for diagnosis as there are no reliable in vitro tests. History of an asthma attack following ingestion of aspirin or other NSAIDs is suggestive and sometimes diagnostic.

It should be noted that oral aspirin challenge tests must only be conducted in a specialized center with cardiopulmonary resuscitation capabilities because of the high risk of severe reactions.

How is aspirin-exacerbated respiratory disease (AERD) managed?

The management of AERD involves guideline-based treatment of the patient’s asthma and CRS, in addition to suppression of the consequences of abnormal leukotriene metabolism. Patients with AERD should avoid aspirin or NSAID-containing products and other medications that inhibit cyclooxygenase-1 (COX-1). However, this does not prevent progression of the disease. If an NSAID is indicated for other medical conditions, a COX-2 inhibitor (e.g., celecoxib or etoricoxib), or paracetamol (acetaminophen), may be considered with appropriate healthcare provider supervision and observation for at least 2 hours after administration.

Inhaled corticosteroids are the mainstay of asthma therapy in AERD, but OCS are sometimes required; LTRA may also be useful. An additional option is desensitization, which may be conducted under specialist care in a clinic or hospital. Desensitization to aspirin followed by daily aspirin treatment can significantly improve overall symptoms and quality of life, decrease formation of nasal polyps and sinus infections, reduce the need for OCS and sinus surgery, and improve nasal and asthma scores.

STRESS AND ASTHMA

Is there a relationship between stress and asthma?

There is some evidence that different stressors can worsen asthma. But many factors have to be taken into consideration: the timing, chronicity and even the quality of the stress. Acute stress may not be a significant precipitant of asthma attacks, however, chronic stress seems to play a more important role. Included as significant stressors are the following:

- **Quality of life**: studies showed an inverse relationship between the socioeconomic status and pulmonary function in children. Immigrant status and poverty also showed some correlation with increased frequency of ER visits among wheezing infants.
- **Psychosocial status of patients**: severe psychological stressors where found to significantly increase the risk of asthma if there was also chronic stress.
- **Environmental stressors**: including noise and violence.
- **Family or caregiver stressors**: presence of even minor psychiatric disorders in mothers was significantly associated with increased incidence of asthma in their children.

Several factors have been cited as contributing to the worsening of asthma due to stress. A dysfunctional hypothalamic pituitary adrenal (HPA) axis resulting in less cortisol production in asthmatic patients and/or cortisol insensitivity, along with promotion of the number of eosinophils in blood and sputum and activation of mast cells by corticotropin releasing hormone (CRH), is a proposed mechanism.

Another proposed mechanism is the occurrence of changes in the methylation and expression of genes that regulate behavioral, autonomic, neuroendocrine and immunologic responses to stress. There are “susceptibility genes” that predispose chronically stressed patients to worsening of asthma symptoms.
It has also been theorized that chronic stress may result in a new "homeostasis" with a short term parasympathetic rebound or shifts in the balance between the sympathetic and parasympathetic systems.151

**How is asthma worsened by stress managed?**

The most important mainstays in the treatment of any asthma patient are maintenance ICS and SABA used as rescue medication. Stress, however, may contribute to persistence of symptoms by reducing response to these medications. It has been theorized that chronic stress may result in down regulation of glucocorticoid receptor expression and function.153

Aside from the pharmacologic treatment, other interventions may be attempted to address the stress which may be contributing to the persistence/worsening of symptoms. Several of these interventions have been studied: written emotional disclosures,154 muscle and mental relaxation158 and relaxation breathing techniques.156 However, all these interventions should be done in conjunction with the regular medications for asthma, and not as stand-alone treatments.

**DIFFICULT-TO-TREAT ASTHMA**

Despite the efficacy of the standard treatments for asthma, many patients remain uncontrolled and a small minority of about 5% to 10% can be classified as having severe asthma. In the approach to the management of difficult-to-treat and severe asthma, referral of patients to a specialist with expertise in asthma management may be helpful for investigation and treatment. When potential reasons for a lack of treatment response have been considered and addressed, a compromise level of asthma control may need to be accepted and discussed with the patient to avoid futile over-treatment (with its attendant cost and potential side-effects).20

**(Evidence D)** The objective is then to minimize exacerbations and the need for emergency medical interventions while achieving as high a level of symptom control as is feasible. This should be achieved with as little disruption of activities and as few daily symptoms and side-effects as possible.20

**How is difficult-to-treat asthma differentiated from severe asthma?**

Difficult-to-treat or simply termed ‘difficult’ asthma is asthma that remains uncontrolled despite treatment with medium- or high-dose ICS plus a second controller or those requiring maintenance OCS.20, 157

Uncontrolled asthma in this context is defined as at least one of the following:

- Poor symptom control: ACQ >1.5, ACT <20 or not well controlled by GINA guidelines
- Frequent exacerbations: two or more bursts of systemic corticosteroids (>3 days each) in the previous year
- Serious exacerbations: at least one hospitalization, ICU stay or mechanical ventilation in the past year
- Airflow limitation: FEV1 <80% predicted (in the face of reduced FEV1/FVC) following a withhold of both short- and long-acting bronchodilators.20, 157

Patients who do not meet the criteria for uncontrolled asthma, but whose asthma worsens on tapering of corticosteroids, will also meet the definition of severe asthma.20, 157

Individuals with difficult-to-treat asthma often have ongoing modifiable factors such as poor inhaler technique, poor adherence, ongoing allergen exposure or comorbidities that interfere with achieving good asthma control.20, 157 As such, difficult asthma patients are those in whom appropriate diagnosis and/or treatment of contributory factors and comorbidities result in improvement of their current condition.20, 157

Severe asthma, on the other hand, is considered a subset of difficult-to-treat asthma and includes individuals with uncontrolled asthma despite adherence with maximal optimized therapy and treatment of contributory factors, or that worsens when high-dose treatment is decreased.20, 157

**What is the approach to the diagnosis of difficult-to-treat asthma?**

An initial step in the evaluation is to determine whether the diagnosis of asthma has been confirmed. A careful history and physical examination should be done to identify whether the pattern of signs and symptoms are typical of asthma or more likely due to an alternative diagnosis. Confirmation of the asthma diagnosis can be made through objective measures such as spirometry to assess baseline lung function and evidence of variable expiratory airflow limitation. There may be persistent airflow limitation in those with long-standing asthma and a specialist advice should be obtained if the history is suggestive of asthma but the diagnosis cannot be confirmed by spirometry.20

The next step is to assess whether modifiable risk factors that contribute to poor asthma outcomes are present. A review of treatment adherence and
Inhaler technique is required because incorrect inhaler use and poor adherence are the most common reasons for failure to achieve good asthma control. An investigation for persistent environmental exposure to tobacco smoke, allergens or toxic substances should also be done. Ongoing triggers, if present at home or at the workplace, should be addressed and removed whenever possible. The presence of comorbidities that can contribute to poor asthma control should be investigated according to clinical suspicion. Medication side-effects, local or systemic, should be evaluated as these may contribute to poor quality of life and increase the likelihood of poor adherence.20

**When should referral to a specialist or severe asthma clinic be considered?**

A referral may be done at any stage of the evaluation but it is recommended that patients presenting with “difficult asthma” have their asthma diagnosis confirmed and be evaluated and managed by an asthma specialist for more than 3 months. Referral to a specialized center where patients can undergo a systematic evaluation resulted in 30–50% of patients previously called severe asthma being initially classed as difficult-to-control.20

Indications for early referral to a specialist or severe asthma clinic are:20

- There is difficulty in confirming the diagnosis of asthma
- The patient has frequent urgent healthcare utilization
- The patient needs frequent or maintenance OCS
- Occupational asthma is suspected
- Presence of food allergy or anaphylaxis
- Clinical features that suggest coexisting or complication bronchiectasis
- Symptoms suggestive of an infective or cardiac cause
- Presence of multiple comorbidities

**What is the approach to the management of difficult-to-treat asthma?**

Addressing problems of incorrect inhaler technique and poor treatment adherence should be prioritized in patients with difficult-to-treat asthma. These factors are also found in severe asthma but in most difficult-to-treat asthma patients, adherence and health outcomes may be improved with a comprehensive adherence-promoting intervention that includes patient education and behavioral modification. It is important to ensure that the inhaler is suitable for the patient and that the inhaler technique is checked, corrected and re-checked at each clinic visit. Patient education is important and clinicians should empower patients to make informed choices about their medicines and individualized interventions to manage non-adherence should be developed.

Comorbidities, when present, such as obesity, GERD, CRS and OSA, should be managed appropriately. Non-pharmacologic management strategies deemed relevant, such as smoking cessation, physical exercise, healthy diet, weight loss, counseling, breathing exercises, mucus clearance techniques and allergen avoidance, may be implemented.20

The pharmacologic treatment of difficult-to-treat asthma both in adults and children still relies heavily on the maximal optimal use of corticosteroids and bronchodilators, and other controllers recommended for moderate-to-severe asthma. A switch to ICS-formoterol maintenance and reliever therapy or non-biologic add-on therapy to ICS such as LABA (if not already using ICS-LABA combination) or anti-muscarinic agents (i.e., tiotropium)20,20 or other controllers may be options.20

Other add-on controller medications such as theophylline and LTRAs, although suggested for severe asthma, appear in the small number of available studies to be of limited benefit. LTRAs may be helpful for patients found to be aspirin sensitive.20,20-20 (Evidence A)

A trial of high-dose ICS may be instituted since some patients may respond to higher doses of ICS than are routinely recommended for general use. (Evidence B) However, this carries the risk of systemic side-effects so stepping down slowly at 3–6 month intervals after some months dose optimization is recommended.20 (Evidence D)

**How is treatment response of difficult-to-treat asthma assessed and addressed?**

The response to treatment includes a review of the following: symptom control (symptom frequency, reliever use, night waking due to asthma, activity limitation), exacerbation frequency, medication side-effects, inhaler technique, adherence, lung function, patient satisfaction and concerns.20

If asthma is well controlled, consider stepping down treatment. If the symptoms and exacerbations remain well controlled despite stepping down treatment, the patient does not have severe asthma and optimal management should be continued.20

If asthma symptoms become uncontrolled or an exacerbation occurs when high-dose treatment is stepped down, the diagnosis of severe asthma is confirmed. The patient’s previous dose should be restored to regain good asthma control and a referral to a specialist and/or to a severe asthma clinic should be done.20
References:


43. Ediger, D, Bahcetepe, D, The prevalence and evaluation of pre-menstrual asthma, meta-analysis. Expert Rev Respir Med 2017; 11(1):57-72


References: