

Guidelines for the management of asthma in adults: Evidence and recommendations

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Abstract

The multidisciplinary experts in Thailand developed an asthma management recommendation that was relevant to low-middle income countries (LMICS). Population level consideration about asthma management is emphasized. The healthcare systems, access to and availability of treatments as well as the asthma populations vary from country to country in LMICS. The feasibility in clinical practice for implementation is also a major issue. For these reasons, the practice guidelines that are relevant to local contexts are essential to improve better asthma control. Furthermore, integrative and collaboration between asthma experts and the public health sector to implement and discriminate such guidelines will help to achieve these challenging goals. The topics covered include the current asthma situation in Thailand and the Asia-Pacific region, the definition of asthma, asthma diagnosis, assessment of asthma patients, asthma treatment – both pharmacological and non-pharmacological, management of asthma exacerbation, management of asthma comorbidities, treatment of asthma in special conditions, severe and uncontrolled asthma, Thai alternative medicine and asthma, and asthma and coronavirus disease-19 (COVID-19).

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The state of asthma in Thailand

There are currently at least 300 million people who suffer from asthma worldwide, and the prevalence rate has been increasing in Latin America, Europe, Africa, and Asia. In Thailand, the prevalence of asthma in adults is approximately 3%.¹ Data from a survey in Thai adult asthma patients found that 17% had been admitted in the past year, 7% of whom were admitted to the intensive care unit. The mortality rate of adult asthma patients admitted to tertiary care hospitals was 2.17%.² Additionally, 35% of asthma patients had visited the emergency department, and 44% had been absent from school or work due to an asthma attack.³

The direct cost for adult Thai asthma patients is 1,032 USD per year, which is equal to 19.14% of the gross domestic product (GDP) per capita. This is less than the direct and indirect cost for adult asthma patients in the US due to regional differences in treatment costs.⁴ Although up-to-date clinical guidelines for asthma treatment exist, most patients still suffer from inadequate asthma control and their usage of inhaled corticosteroids (ICS) is often limited or irregular. In Thailand, 62% of asthma patients report good control, but the actual rate according to the GINA guidelines is only 8%, indicating that Thai asthma patients likely underestimate the severity of their condition.⁵ The rate of ICS use in asthma control increased from 6.7% in 2000 to 57% in 2011.⁶ However, only 58% of patients use ICS on a daily basis. This can lead to asthma attacks, which can impact patients' quality of life, work/school attendance, exercise habits, mental health, mood, and social life.³

The Thai Clinical Practice Guidelines for Diagnosis and Management of Asthma in Adult Patients were first issued in 1997 and revised in 2004 and 2008 based on the Global Initiative for Asthma (GINA) guidelines with some modifications for their adaptation in Thailand. This 2020 version of the Thai clinical practice guidelines was developed as a short evidence-based summary by multidisciplinary experts involved in the management of asthma in Thailand. These experts include pulmonologists, allergy and immunology physicians, and emergency physicians. The guidelines were developed with the specific aim maximizing their practical effectiveness in Thailand, in which public health resources are limited.

Asthma definition

Asthma is a disease of airway inflammation resulting in expiratory airflow obstruction from airway smooth muscle contraction. Its clinical course characterized by intermittent attacks, which can be recurrent. Common symptoms of asthma are wheezing respiration, shortness of breath, chest tightness, and cough. These symptoms may vary and depend on asthma duration and severity.

Characteristics of asthma

Asthma symptoms and airway obstruction depend on disease duration and severity. There are various stimuli that can exacerbate the condition including exercise, allergens, irritants, weather, or viral respiratory tract infection.

Airway obstruction in asthma may improve spontaneously or with bronchodilators. Asthma symptoms vary, and asthma-free periods may last for several weeks or months. However, severe asthma attacks can be fatal. Generally, asthma is related to airway hyperresponsiveness from both direct and indirect stimuli resulting in chronic airway inflammation. Such inflammation is always present in asthma patients regardless of symptoms or lung function.

Clinical characteristics of asthma

The clinical characteristics of asthma can vary widely depending its causes. Currently, asthma is categorized by population characteristics, clinical features, and pathophysiology. However, there is no evidence of any correlation between pathology and clinical characteristics/response to treatment. Further in-depth research is required to understand these issues. Clinical characteristics of asthma can be categorized into five types as follows and are shown in **table 1**:

1. Asthma from allergy: This condition can be diagnosed easily, as onset occurs during childhood and the patient often has a family history of allergy such as eczema, allergic rhinitis, or food/drug allergies. Pre-treatment sputum examination will show evidence of eosinophilic inflammation. These patients usually response to ICS.
2. Asthma without allergy: Airway inflammation is caused by neutrophils, eosinophils, or low white blood cell count. These patients usually respond to ICS on a short-term basis.
3. Adult asthma: commonly found in women and not related to allergy. Patients may not respond to ICS or may require a high dosage. Adult asthma may be occupation related.
4. Asthma with permanent airway obstruction: permanent airway obstruction caused by long-term asthma or partially reversible airway obstruction, which results in structural airway changes.
5. Asthma in obesity: found in obese patients who have respiratory symptoms with eosinophilic airway inflammation.

Table 1. Asthma phenotypes, key diagnosis and potential treatments

Asthma phenotypes	Key diagnosis	Potential treatments
Asthma from allergy	The evidence of allergic sensitization (skin prick test or serum specific IgE) and association of asthma symptoms	ICS containing regimens, immunologic treatments, anti-IgE and immunotherapy Allergen avoidance
Asthma without allergy	Lack of evidence of allergic sensitization	ICS containing regimens
Adult asthma	Late onset or adult-onset asthma	ICS containing regimens
Asthma with permanent airway obstruction	The present of irreversible airflow limitation from spirometry either FEV ₁ /FVC ratio or absence of bronchodilator reversibility	ICS, LAMA, bronchial thermoplasty
Asthma in obesity	The increased BMI	ICS, weight reduction

Abbreviations: ICS; inhaled corticosteroids, IgE; immunoglobulin E, LAMA; long-acting antimuscarinics, FEV₁; forced expiratory volume in 1 second, FVC; forced vital capacity

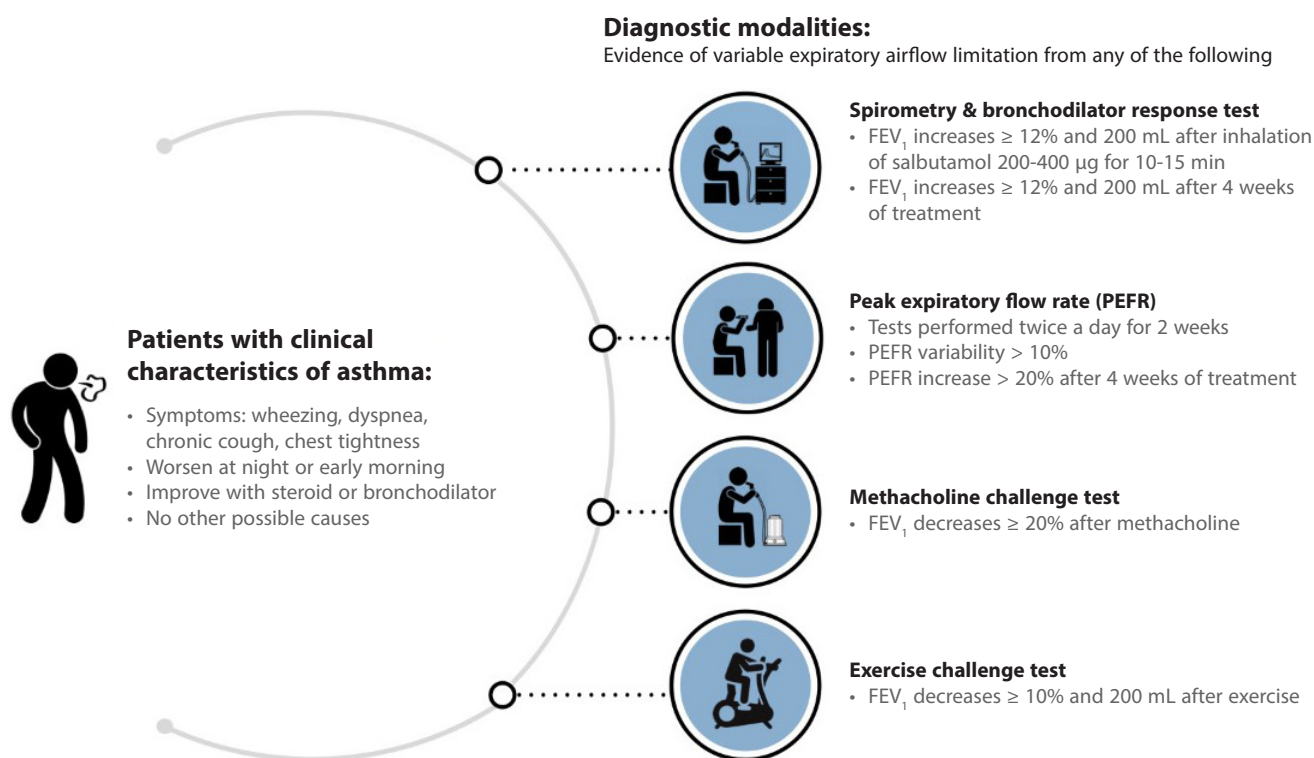


Figure 1. Diagnosis of asthma is based on history of typical asthma characteristics and evidence of expiratory airflow limitation.

Diagnosis of asthma

Diagnosis of asthma is based on the following two items:

1. Asthma symptoms: wheezing, dyspnea, cough, or chest tightness. These symptoms worsen during the night or early morning. Severity of symptoms varies overtime and worsen by precipitating factors include infection such as common cold, allergens, irritants such exposure to air pollution and tobacco smoke, medications, primarily the non-steroidal anti-inflammatory agents (NSAIDs) and beta-blockers and non-specific manner such as exercise and hyperventilation.⁷⁻⁹

Note there should be no other possible causes of these symptoms, and they should improve with ICS or bronchodilator treatment.

2. Evidence of variable expiratory airflow limitation based on a pulmonary function test (**Figure 1**).

Pulmonary function test

A pulmonary function test is performed to ascertain evidence of variable expiratory airflow limitation. The following three types of pulmonary function test can be used (criteria for variable expiratory airflow limitation are also provided):

1. Spirometry

- 1.1 evidence of airway obstruction with severity assessment: FEV₁/FVC less than 0.75-0.80.
- 1.2 bronchodilator reversibility: FEV₁ increases by 200 ml and 12% or over from baseline. This test can be performed before or after treatment. The pre-treatment test is performed after 15 minutes of inhalation of a short-acting bronchodilator such as salbutamol (200-400 micrograms), while the post-treatment test is performed using controller medication over a period of 4 weeks.¹⁰

2. Peak expiratory flow (PEF)^{11,12}

- 2.1 An increase in PEF of greater than 60 L/min or 20% after inhalation of a short-acting bronchodilator. Note that PEF has less validity than spirometry.
- 2.2 PEF variability: measurement of PEF twice a day for 1-2 weeks without any treatment.
- 2.3 An increase in PEF greater than 20% after 4 weeks of treatment with an asthma controller.

3. Airway hyperresponsiveness (AHR)

In patients with a history and physical examination compatible with asthma but normal spirometry, the methacholine challenge test may be performed. The diagnostic criterion is a required methacholine concentration of less than 4 mg/mL (PC₂₀).¹³ This test should be performed in specialized health care facilities.

Assessment of Asthma Patients

Evolution of asthma assessment

Various sets of asthma guidelines have been developed and revised over the past several decades. The first international guidelines were developed at the GINA workshop in 1993 as a result of a collaboration between the National Heart Lung and Blood Institute, US National Institute of Health (NIH), and World Health Organization (WHO) and were first published in 1995. There are currently several other sets of guidelines in use including the Expert Panel Report (EPR) by the US National Asthma Education and Prevention Program Coordinating Committee, the British Thoracic Society Guidelines (BTS), the Canadian Asthma Guidelines by the Canadian Thoracic Society, and the 2019 Thai Asthma Guideline in Adults by the Thai Asthma Council (TAC).¹⁴⁻¹⁷ All current guidelines focus on asthma control assessment rather than asthma severity assessment. This was not always the case. The 1995 GINA guidelines, for example, categorized asthma by severity, and in 2006, they assessed asthma severity by frequency of daytime asthma symptoms, frequency of nighttime asthma symptoms, and FEV₁ or PEFr and then divided severity of asthma into four categories as follows:

- Level 1: Intermittent asthma
- Level 2: Mild persistent asthma
- Level 3: Moderate persistent asthma
- Level 4: Severe persistent asthma

Treatments were to be provided based on the severity of asthma. However, subsequent evidence has shown that symptoms of asthma are not related to FEV₁. Thus, in 2003, GINA

changed its categorization of asthma to be based on control level. In the 2006 guidelines, asthma was categorized into three groups by control level plus future risk factors (based on daytime symptoms, nighttime symptoms, reliever use, FEV₁ or PEFr, and history of an asthma attack in the past year), as follows:

1. Controlled asthma
2. Partly controlled asthma
3. Uncontrolled asthma

However, the Thai Asthma Council (TAC) recommends classification into two broad categories according to level of control, i.e., uncontrolled asthma and well controlled asthma, as show in **Figure 2**.

Asthma control is defined by the patient's clinical characteristics that are improved by treatment and consists of two components:

1. Current asthma control – evaluated by symptoms and limitations to physical activity that impact quality of life.
2. Risk of future adverse events – includes loss of asthma control, asthma exacerbation, accelerated decline in lung function, and treatment side effects.

Asthma management is aimed at achieving asthma control as assessed by the components listed above. Current symptom control is focused on the past 4 weeks, and future risk is particularly concerned with asthma exacerbation, as shown in **Figure 2**.

Asthma Management Goal

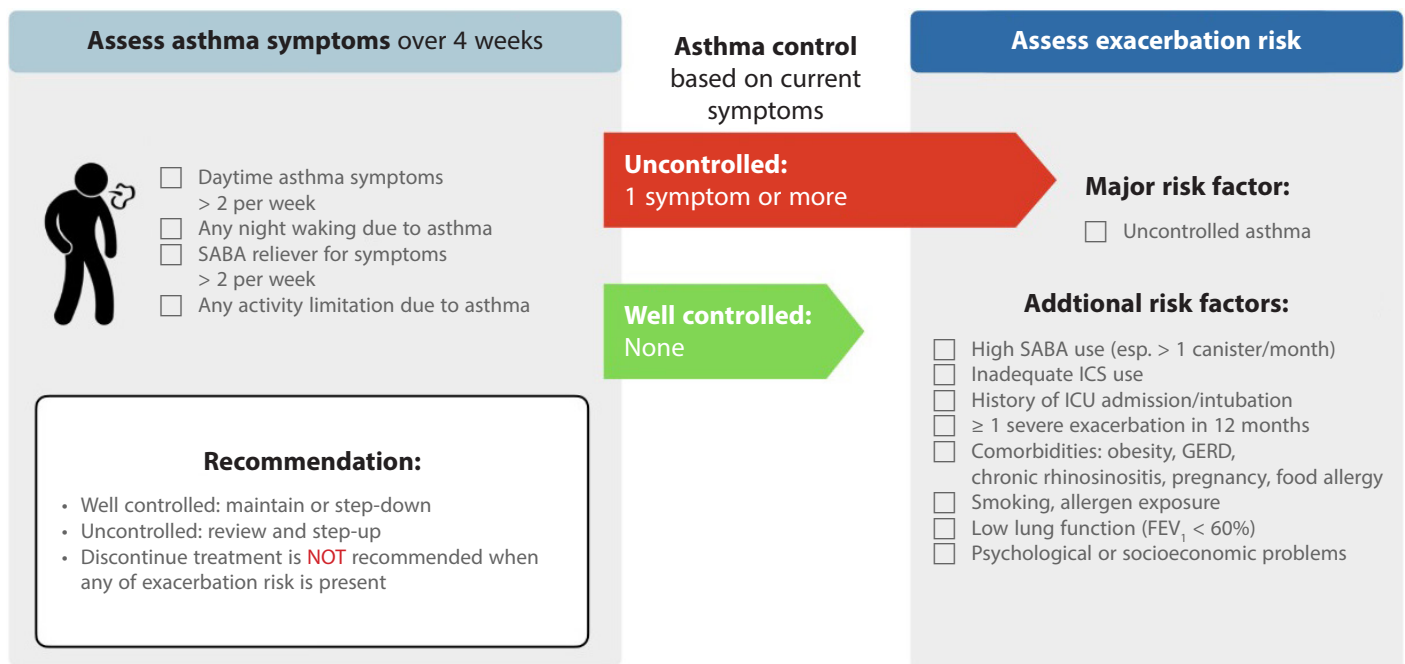


Figure 2. Asthma management goals and asthma control. Assessment of asthma control consists of examining asthma symptoms and exacerbation risk.

Asthma severity is an indicator of asthma control after external factors are excluded such as misdiagnosis, poor medication compliance, incorrect inhalation technique, and comorbid diseases. Asthma severity indicates the intensity of treatment required to control asthma and underlying disease activity. Severe asthma is defined by a need for a high-intensity treatment to control asthma at all times or uncontrolled asthma even with high-intensity treatment. Asthma treatment depends on severity in treatment-naïve patients or control in treatment-experienced patients.¹⁸

Factors used to assess asthma severity may be similar to those used to assess control such as symptoms, pulmonary function tests, asthma exacerbation, or asthma treatments. It can often be difficult for clinicians to assess asthma severity or control based on clinical manifestations or responsiveness to treatment. In other words, asthma control may be assessed based on asthma severity or whether symptoms improve/resolve with treatment. From a research perspective, the outcomes of asthma treatment may include not only asthma symptoms but also pulmonary function tests, quality of life, inflammatory biomarkers, or healthcare utilization such as asthma exacerbation or unscheduled visits.^{12,19–21}

In clinical practice, assessment for asthma control may be easier than assessment for asthma severity, as asthma severity is dynamic and may be affected by treatment. In addition, most asthma patients have likely received prior treatment, and previous ICS or ICS/LABA use may affect asthma control status.^{22,23} This means that physicians must review previous treatments before determining patients' level of control. The Thai Asthma Council (TAC) recommends the three-pronged AAR approach to asthma control listed below and shown in **Figure 3**.

A: assess asthma: assess diagnosis, symptoms, risk factors, and inhaled medications.

A: adjust treatment: adjust medication treatment, non-pharmacological treatment, treatment of other asthma-precipitating factors, and the patient's lifestyle.

R: review response: a review of treatment response, pulmonary function, and side effects from treatment.

Most asthma patients underestimate their asthma severity and overestimate their control status. A previous study from nine Asia-Pacific countries, including Australia, China, Hong Kong, India, Malaysia, Singapore, South Korea, Taiwan, and Thailand, found that only 8% of Thai asthma patients had been able to control their asthma symptoms over the previous 4 weeks.⁵ In addition, only about one-third of Thai asthma patients who reported good asthma control had actually achieved good control as defined by the GINA guidelines.³

Overall asthma control consists of symptom control and reduction of future risk.²³ The 2020 GINA strategy categorizes current clinical control of asthma into three levels (well controlled, partly controlled, and uncontrolled) and future risk of poor asthma outcomes into three categories (risk factors of exacerbation, risk of fixed airflow obstruction, and risk of medication side effects), as show in **Figure 2**.⁷ The Thai Asthma Council (TAC) recommends a more simplified classification of asthma symptoms as either well controlled or uncontrolled, placing the greatest importance on uncontrolled symptoms as they carry a risk of asthma exacerbation.

Asthma Management Process

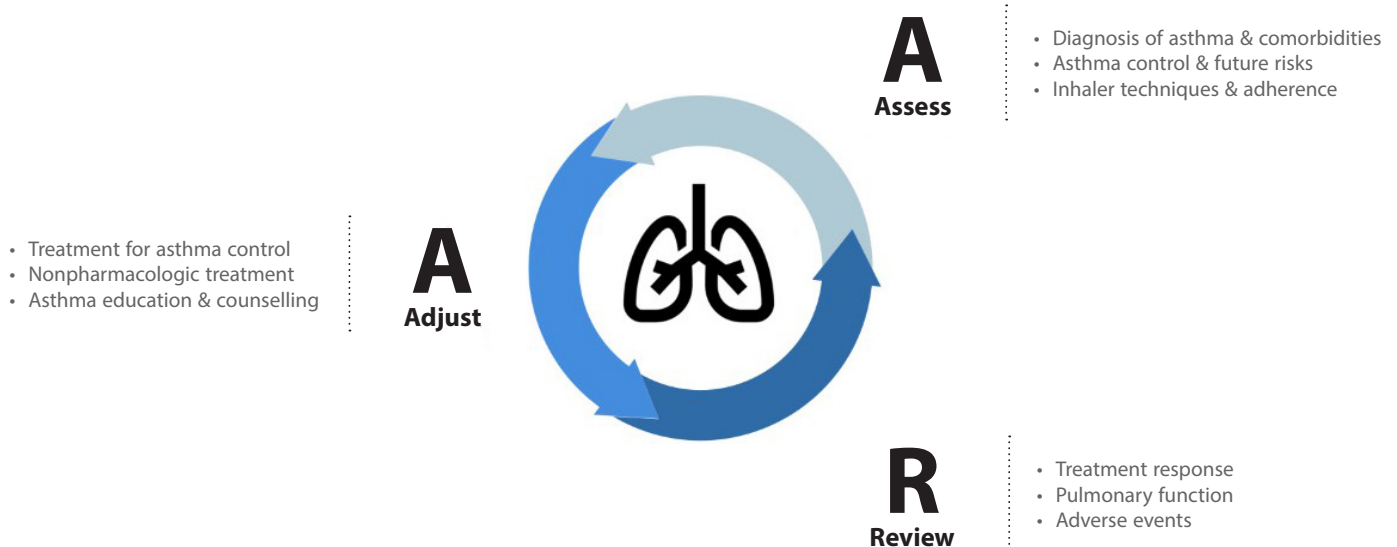


Figure 3. The three dimensions of asthma management based on the Thai Asthma Council (TAC)'s AAR method. A: Assess the diagnosis of asthma and comorbidities, asthma control, and inhaler technique and adherence; A: Adjust both pharmacologic and non-pharmacologic treatment including asthma education and counseling; R: Review treatment response and adverse events including pulmonary function.

Table 2. Comparison between the Asthma Control Test (ACT) and Asthma Control Questionnaire-7 (ACQ-7) as composite scores for assessing asthma control in clinical practice

Factors	ACT	ACQ-7
Duration of assessment	4 weeks	1 week
Score	5-point scale (total of 5-25)	7-point scale (total of 0-6)
Interpretation	ACT ≥ 20 (well-controlled asthma) 16 ≤ ACT ≤ 19 (partly controlled asthma) ACT ≤ 15 (poorly controlled asthma)	ACQ ≤ 0.75 (well-controlled asthma) ACQ ≥ 1.5 (not well-controlled asthma)
Items	5 items	ACQ-5 (5 items), ACQ-7 (7 items)
Limits daily activities	✓	✓
Shortness of breath	✓	✓
Disrupts sleep	✓	✓
SABA use	✓	✓
Effect of global control	✓	✓
Frequency of wheeze	-	✓
pre-bronchodilator FEV ₁	-	✓

Abbreviations: SABA; short-acting β₂ agonists; FEV₁; forced expiratory volume in 1 second.

Objective asthma assessment using a questionnaire is simple and practical. There have been several questionnaires developed to assess asthma control or quality of life such as:

1. The Composite Scores of Asthma Control, i.e., the Asthma Control Test (ACT score), Asthma Control Questionnaire (ACQ), and Asthma Therapy Assessment Questionnaire (ATAQ). The total numeric score is the summation of all question scores, as shown in **Table 2**.
2. The Asthma-Related Quality of Life Questionnaire, i.e., the Mini Asthma-Related Quality of Life Questionnaire (mini-AQLQ)

Type 2 asthma biomarkers for asthma control

In the past decades, biomarkers have been used to assess asthma control, particularly those measured using noninvasive techniques. Biomarkers can be detected based on respiratory factors such as induced sputum cell counts and fractional concentration of exhaled nitric oxide (FeNO) or from blood tests that measure serum eosinophils or serum periostin.^{24,25}

The FeNO test is widely used and is considered the standard method of asthma biomarker detection. However, a previous study in Thai asthma patients found that exhaled FeNO was not related to asthma control based on ACT score.²⁶ At present, type 2 inflammatory biomarkers are used to determine asthma phenotype in severe cases using precision medication in order to select targeted treatments.

Asthma treatment

Pharmacological treatment of asthma

One aim of asthma treatment is asthma control, which is defined as current symptom control (no asthma symptoms either during the day or at night, no short-acting bronchodilator use, no asthma exacerbation, ability to engage in normal daily activities including exercise, and normal pulmonary function) and prevention of future risk (asthma exacerbation, deaths from asthma, the decline of pulmonary function resulting in airway remodeling, and side effects from treatment).⁷ The principles of asthma treatment are as follows:

- A new asthmatic patient should be treated according to asthma severity (**Figure 4**)
- All asthmatic patients should have regular asthma control medication and reliever medication as needed.
- Inhaled corticosteroids (ICS) are a mainstay treatment to control asthma. The patient should start with a low dose, which can be adjusted based on severity (**Figure 4**).
- If low-dose inhaled corticosteroid treatment is not ineffective, the dosage can be increased (high dose) or other medications can be used such as long-acting β₂-agonists, LABA, or leukotriene receptor antagonists (LTRA). An inhaled ICS/LABA in the same device is recommended as it has the highest efficacy. LTRA is an alternative treatment.
- ICS/LABA with formoterol formula is a rapid-acting LABA which can be used as controller and reliever in the same device (maintenance and reliever therapy).

Recommendations for Initial Treatment

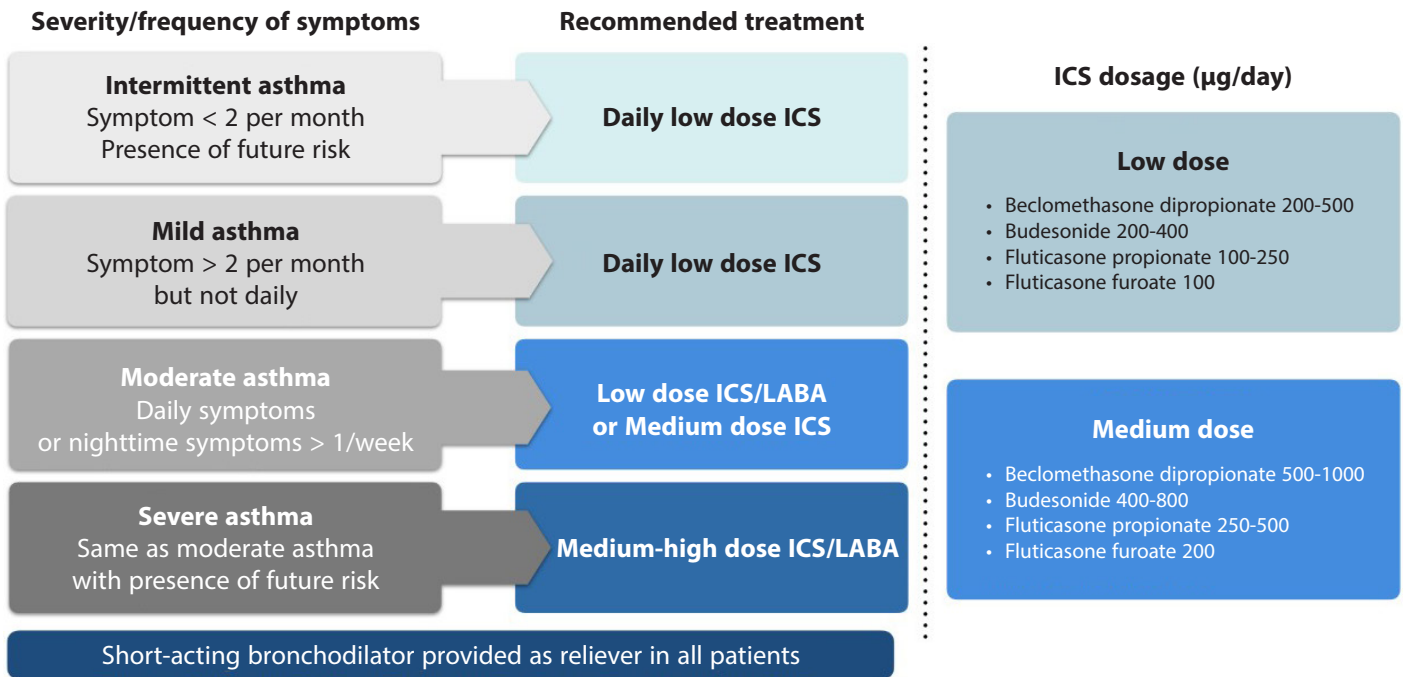


Figure 4. Initial treatment options for newly-diagnosed asthmatic patients. The recommendation of initial treatment is based on the severity and/or frequency of symptoms

Abbreviations: ICS: inhaled corticosteroid; LABA: long-acting β2 agonists

Adjustment for previously treated patients

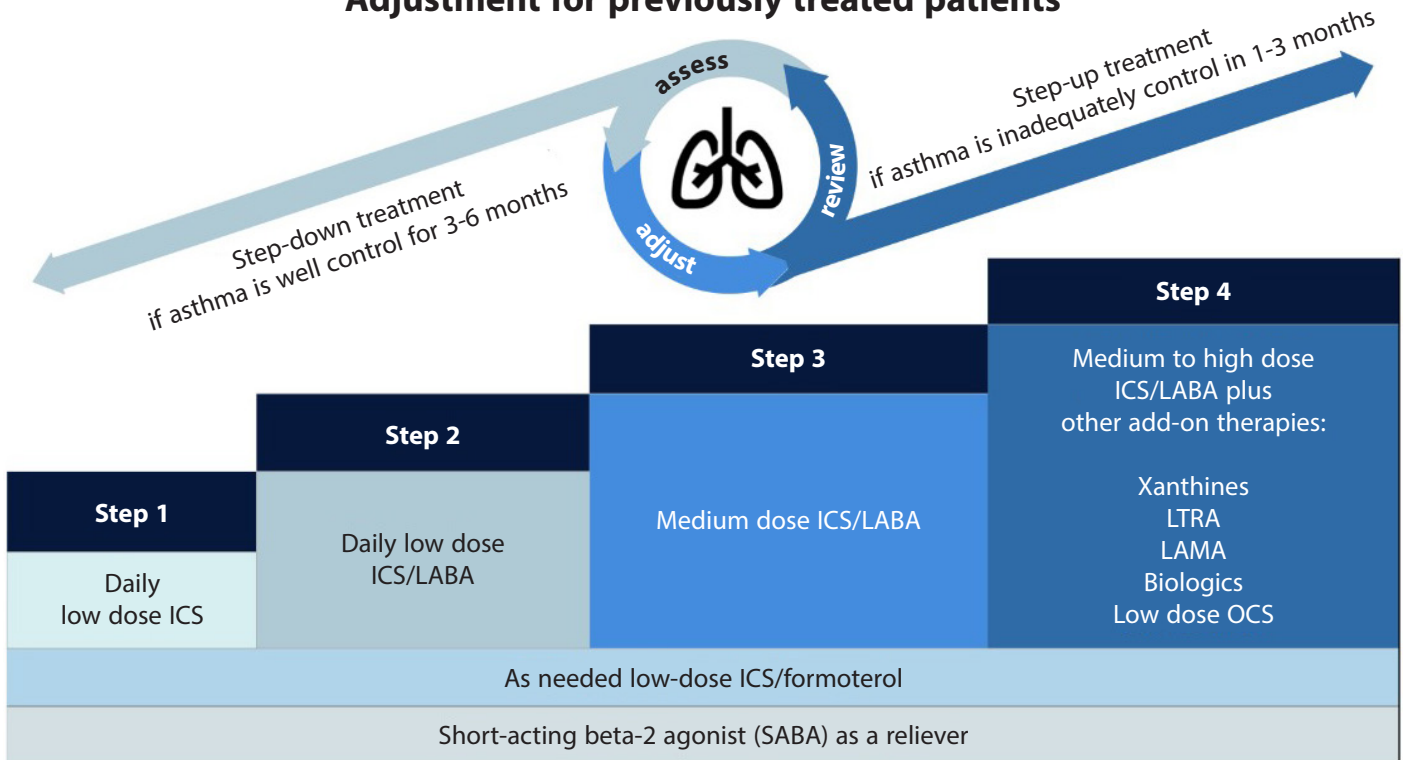


Figure 5. Stepwise treatment of asthma. The step-up and step-down treatment recommendations in previously treated asthmatic patients should be based on the level of asthma control.

Abbreviations: ICS: inhaled corticosteroid; LABA: long-acting β2 agonists; SABA: SABA: short-acting β2 agonists; LTRA: leukotriene receptor antagonist; LAMA: long-acting muscarinic antagonist; OCS: oral corticosteroid

- Dosage of controllers and relievers in previously treated asthma patients should be increased at 1-3 months if asthma remains inadequately controlled. Step-down therapy can be initiated after 3-6 months of well asthma control, as shown in **Figure 5**.
- In patients with severe, uncontrolled asthma despite taking a high dosage of ICS/LABA, referral to an asthma specialist is recommended. Additional medications, such as sustained-release xanthine, LTRA, long-acting muscarinic antagonists (LAMA): tiotropium bromide, low-dose prednisolone, or biologic agents (omalizumab, mepolizumab, benralizumab, and dupilumab) may be prescribed, but referral to a specialists should still be considered, as treatment depends on asthma phenotype.

Additional factors associated with uncontrolled asthma should be explored including misdiagnosis, improper technique in using the medication device, poor compliance, surveillance and treatment of comorbid diseases, and allergen avoidance including that of irritants and smoking.

Choice of medication can be made based on pharmacology, efficacy, safety, patient satisfaction, and price. However, factors associated with uncontrolled asthma should be evaluated prior to medication adjustment, as mentioned above. For those who have received prior treatment, medication adjustment can be performed as shown in **Figure 5**. During each step, short acting bronchodilator as a reliever as needed or low dose ICS/formoterol for dyspnea should be considered.

Step 1 Controller

For patients with controlled asthma, an inhaled short-acting bronchodilator as needed or low-dose ICS/formoterol can be used.^{27,28} Daily low-dose inhaled corticosteroids should be considered. In asymptomatic or mild asthma with risk factors for asthma exacerbation, intermittent ICS/formoterol may be used in conjunction with alternative treatment with LTRA.²⁹⁻³⁴

Step 2 Controller

For uncontrolled asthma (based on asthma assessment or presence of risk factors for asthma exacerbation), low-dose inhaled corticosteroids combined with LABA is recommended.

Step 3 Controller

In cases in which asthma remains uncontrolled after Step 2, medium-dose ICS/LABA combined with an inhaled short-acting bronchodilator as needed or ICS/formoterol is recommended.^{22,35-40}

Step 4 Controller

In cases in which asthma remains uncontrolled after Step 3 resulting in daily daytime and nighttime asthma with decreasing pulmonary function, medium- to high-dose ICS/LABA can be combined with other medications, such as sustained-release xanthine, LTRA, long-acting muscarinic antagonists (LAMA; tiotropium bromide), low-dose prednisolone

(≤ 7.5 mg prednisolone/day), or biologic agents (omalizumab, mepolizumab, or benralizumab). Referral to an asthma specialist is also required.

Non-pharmacological Therapies

Smoking cessation

Smoking, vaping, and exposure to second-hand smoke can cause severe and uncontrolled asthma. Several studies have shown that individuals who are exposed to cigarette or electronic cigarette smoke have an increased risk of asthma. Asthma patients who are current smokers should be encouraged to quit smoking as soon as possible.⁴¹⁻⁴³ At every visit, smokers should be given smoking cessation treatment.

Exercise

There is evidence that exercise can improve asthma control, increase maximum exercise ability, increase endurance, improve pulmonary function, reduce dyspnea symptoms, improve quality of life, and reduce dependence on healthcare services by reducing asthma exacerbation, antibiotic use, oral corticosteroid use, and emergency room visits.⁴⁴⁻⁴⁶ Recommended exercises include swimming, running, biking, or Tai Chi. Patients with severe, uncontrolled asthma should engage in an appropriate exercise 5-7 times/week for 20-30 minutes/time, for at least 6-8 weeks.

Breathing training

Breathing training can reduce the patient's respiratory rate, reduce breathing volume, increase abdominal and lateral chest muscle use, encourage nasal breathing, and provide relaxation. In addition, studies have found that breathing training can reduce dyspnea symptoms, improve quality of life, and reduce emotional stress.^{47,48} Such training is thus recommended for asthma patients with symptoms of dyspnea or poor quality of life.

Environmental control

Control of the home and workplace environment, such as ensuring good ventilation, avoidance of carpet, insecticides, incense, and dust mites, cleaning of bed linen, and restriction of indoor pets, is recommended to reduce asthma stimuli. History taking with regard to workplace details and occupation is necessary in patients with adult-onset asthma. Avoidance of occupational causes of asthma, NSAIDs, and beta-blockers is crucial in these patients.⁴⁹⁻⁵¹

Weight reduction

Weight reduction by more than 10% of baseline is recommended, as it can improve both asthma control and pulmonary function.⁵²

Vaccination

Influenza vaccination is recommended annually in asthma patients. The 13 serotype pneumococcal vaccine may be considered in these individuals due to no obvious benefits.^{53,54}

Bronchial thermoplasty

Bronchial thermoplasty reduces airway remodeling inhibiting fibroblast and is recommended in patients with uncontrolled asthma or frequent asthma attacks despite having undergone level 5 treatment. Bronchial thermoplasty can reduce the risk of acute asthma attack by 31.4-46.2%, reduce oral corticosteroid use and emergency room visits by 46.0-53.6%, and improve quality of life.⁵¹⁻⁵⁹ The beneficial effects of bronchial thermoplasty may last for 3-5 years. Studies from Thailand have found bronchial thermoplasty to reduce the risk of asthma attack by 50%, which is comparable with the findings of previous studies conducted in Western countries. Oral corticosteroids and risk of asthma attack are also significantly reduced. Bronchial thermoplasty improves quality of life. Previous studies have found that all patients previously treated with anti-IgE therapy have been able to discontinue the treatment after receiving bronchial thermoplasty.

Asthma patient education⁶⁰⁻⁶²

Asthma patients should be educated in the following areas as shown in **table 3**.

Table 3. The key information for asthma patient education

1. General asthma knowledge: causes, symptoms, diagnosis, and clinical course.
2. Principles of asthma treatments – both pharmacological and non-pharmacological.
3. Reliever and control medications: types of medications and their side effects.
4. The importance of regular hospital visits and good medication compliance according to their treatment plan whether or not they are experiencing symptoms.
5. Self-monitoring of exacerbation warning signs and symptoms that require medical attention.
6. Initial treatment in the event of an asthma attack according to the patient's individual asthma action plan.
7. Correct inhaler device usage.
8. Common treatment goals between healthcare providers and patients/caregivers. Physicians should assess and plan based on patient treatment expectations and concerns.
9. Treatment and behavior modifications aimed at improving comorbid diseases such as allergic rhinitis.
10. Avoidance of allergens, smoke, air pollution (e.g., mask wearing), and avoidance of outdoor activities when air quality is poor.
11. Non-competitive exercise that does not cause asthma attacks such as biking, swimming, or Yoga.
12. Avoiding close contact with persons who have respiratory tract infections. Regular annual influenza vaccination is encouraged.

Asthma Action Plan⁷

The WHO and GINA strategies recommend a written asthma action plan (WAPP) and use of a peak flow meter in asthma patients who are on daily medication. In 2015, an Asthma Care application was developed for use with Thai asthma patients to help patients and healthcare providers develop common goals.⁶² A WAPP is a helpful tool that has been shown to significantly reduce hospitalization and absence from school in children with asthma.⁶³

Advantages of the Asthma Action Plan⁶³

1. Daily reminder of medications.
2. Indications of airway obstruction before chest discomfort or breathlessness occurs.
3. Treatment during an asthma exacerbation. Asthma patients can assess themselves during asthma exacerbation and choose the appropriate medications at the correct doses without a hospital visit.
4. A media among physicians, patients, and caregivers at home, work, or school.
5. Patients are made aware of their symptoms and appropriate activities.

Advice on inhaling devices⁶⁴⁻⁶⁶

1. Use of the appropriate inhaling device provides better medication administration, which improves asthma control.
2. The choice of inhaling device should be individualized based on simplicity, inhalation force, price, and efficacy of medication delivery.
3. Considerations regarding individual inhaling devices are as follows:
 - 3.1 A pressurized metered dose inhaler (pMDI) requires push-inhalation skill. A spacer can be used to improve medication administration in cases of poor push-inhalation skill if used with other inhaling devices.
 - 3.2 Dry powder inhaler (DPI) technique varies by device (Turbohaler™, Accuhaler™, Ellipta™, Breezhaler™, or Handihaler™). Physicians should determine whether the patient is able to use the device correctly. Currently, there are videos available to educate patients in the usage of these devices.
 - 3.3 Peak inspiratory flow rate of less than 30 L/min is contraindicated for DPI device use.
4. Physicians should avoid prescribing multiple inhaling devices to one patient to avoid confusion regarding proper use.
5. Physicians should intermittently confirm that the patient is using the device correctly.

Management of asthma exacerbation

Acute asthma exacerbation constitutes a severe asthma attack. These patients must undergo asthma severity evaluation along with prompt treatment after diagnosis. Additionally, close monitoring and systematic evaluation of treatment outcomes are necessary and should serve as the basis for emergency room discharge or hospital admission. Proper management of acute asthma exacerbation can reduce relapse rate, hospitalizations, and mortality.

Evaluation

Asthma patients with acute asthma exacerbation presenting at the emergency room must first be evaluated to determine severity (Table 4). This is particularly important in those patients who require resuscitation or intubation due to drowsiness, cyanosis, or air hunger. Following this, history should be taken regarding risk factors, and physical examination should be performed to determine the proper treatment plan.

Table 4. Severity evaluation by physical examination and initial investigation in acute asthma exacerbation

Evaluation	Mild to moderate	Severe
Consciousness	Good	Agitated, confused, drowsy, or comatose
Speech ability	Full sentences	Unable to speak in full sentences
Pulse rate, bpm	100-120	> 120
Respiration, (/min)	≤ 30	> 30
Accessory muscle use	No	Yes
Oxygen saturation (room air)	90-95%	< 90%
Peak Expiratory Flow (PEF)	> 50% (predicted or best)	≤ 50% (predicted or best)

Risk factors for acute asthma exacerbation that may lead to a severe condition or death include history of acute asthma exacerbation that required intubation and respirator, history of emergency room visit and having required hospitalization within the past year, current or recent use of oral corticosteroids, use of more than one inhaler/month of a short-acting bronchodilator, presence of psychological symptoms or psychosocial problems, use of hypnotics, non-compliance with treatment/incorporation to treatment, or history of food allergy.⁶⁷⁻⁶⁹

Oxygen therapy

Supplementary oxygen therapy is needed if finger oxygen saturation (SpO₂) is 93% or lower. Oxygen saturation should be continuously monitored and kept at over 93%.⁶⁹⁻⁷¹

Inhaled short-acting β₂-agonists (SABAs)

SABAs should be given to all patients with acute asthma exacerbation. Response to this treatment should occur after 15-20 minutes and can be used as an indicator for repeated/continuous SABA administration, hospital admission, or emergency room discharge. Guidelines for SABA administration are as follows:

- In mild to moderate cases, SABAs, such as salbutamol (2.5-5 mg) by nebulization or salbutamol (400-1,000 micrograms; 4-10 puffs) via pMDI with a spacer, should be administered. Evaluation for response should be performed at 15-20 minutes after treatment. If there is no clinical improvement or only slight improvement not meeting the discharge criteria, SABAs can be administered every 20 minutes during the first hour of treatment for a total of 3 doses.^{70,71}
- In severe cases, a combination of a SABAs and short-acting anticholinergics or antimuscarinics (SAMAs) should be given. This treatment can more effectively reduce the risk of hospital admission and improve pulmonary function than SABAs alone.^{72,73}

Systemic corticosteroids

Systemic corticosteroids should be given in all asthma patients with severe acute asthma exacerbation or risk factors for severe acute asthma exacerbation (Figure 2). The first dose of an inhaled bronchodilator should be administered immediately and corticosteroid treatment should continue until emergency room discharge. Intravenous systemic corticosteroids, such as dexamethasone (4-5 mg) or hydrocortisone (100 mg), can be administered every 6-8 hours. In mild cases, oral prednisolone (30-50 mg/day or 0.5-1 mg/kg/day) is justified. All patients who receive systemic corticosteroids at the emergency room should be given oral prednisolone to take for 5-7 days after hospital or emergency room discharge. Time to systemic corticosteroid treatment at the emergency room and continuation of treatment after discharge are significantly related with reduction of hospital admission and acute asthma exacerbation relapse.⁷⁴⁻⁷⁷

Inhaled corticosteroids

Inhaled corticosteroids can be administered to patients who have not undergone previous treatment with systemic corticosteroids. A high dose of inhaled corticosteroids within the first hour of an emergency room visit is justified and can reduce hospital admission after discharge as well as reduce the risk of severe acute asthma exacerbation.^{78,79} These medications can be administered in the emergency room if the patient has no history previous use. For those who have previously used inhaled corticosteroids, the dosage should be increased.

Treatment evaluation

All patients should be evaluated and monitored continuously for consciousness, vital signs, and SpO₂. If patients are drowsy, have unstable vital signs, and/or experience a reduction in SpO₂, appropriate treatment should be promptly administered. For mild conditions, inhaled SABAs with a spacer or nebulizer should be given, and continuous systematic evaluation should be performed. Peak expiratory flow (PEF; % predicted or % personal best) is the best and most precise indicator for treatment response. PEF should be measured before the first dose of SABA treatment and 15-20 minutes after treatment. These PEF values are indicators of the need for future/continuous SABA treatment or emergency room discharge. If PEF and clinical symptoms improve, emergency room discharge is justified.^{80,81} A follow-up appointment at the outpatient department is required for continuous care after an emergency room visit.

Additional medications and treatments

Antibiotics should be considered only in patients with evidence of bacterial infection such as high-grade fever, green sputum, or pneumonia. Use of cough suppressants or medications that cause dry sputum should be avoided. Central nervous system suppressants and hypnotics should also not be used, as this can result in respiratory suppression. Intravenous or nebulized magnesium sulfate can be considered severe cases that do not fully respond to treatment.^{82,83} Intravenous aminophylline is not recommended.⁸⁴ Noninvasive ventilation or NIV is also not recommended in patients suffering from acute asthma exacerbation at the emergency room due to indications for such treatment being unclear and it providing no benefit in terms of intubation rate reduction.⁸⁵

Management of asthma comorbidities

Respiratory and non-respiratory diseases/disorders are known to be associated with asthma and may affect asthma control. Common diseases/disorders include chronic rhinitis or chronic sinusitis, gastroesophageal reflux disease, obesity, obstructive sleep apnea, and depression and anxiety disorders.

Chronic rhinitis or chronic sinusitis and asthma

Asthma and rhinosinusitis have related pathogenesises. Comorbid chronic rhinosinusitis is associated with poor asthma control and increases in CRS symptoms, which negatively affect outcomes. A previous study aimed at characterizing patients with severe asthma showed that 54% of severe patients had a history of rhinosinusitis versus 33 to 37% of those with non-severe asthma. In addition, multiple studies have shown that treatment of chronic rhinosinusitis can improve asthma symptoms.⁸⁶

There is strong epidemiologic, pathophysiologic, and clinical evidence elucidating an holistic picture of rhinitis and asthma. Hence, the concept of united airway disease (UAD) has been purposed for a decade. Interactions between the lower and the upper airways are well known and have been extensively studied. Two major UAD phenotypes are allergic (atopic or extrinsic) and nonallergic (nonatopic or intrinsic) UAD.⁸⁷

The global prevalence of UAD in terms of allergic rhinitis coexisting asthma varied from region to region.⁸⁸ Epidemiological study has shown that 80% of asthmatics have coexisting rhinitis, and 30% of rhinitis patients have asthma.

The differences in prevalence of allergic diseases are underlying by several factor such as infection exposure, the immunization, and life-style factors. In Asia Pacific Region, prevalence of allergic rhinitis varied from 13.1 to 39.7%. The highest prevalence was noted in Taiwan (39.8%), China (27.6%), Japan (15%) and Thailand (13.1%).⁸⁹

Allergic rhinitis (AR) is common among the Thai population and is diagnosed in approximately 40% of children and 26% of adolescents.⁹⁰ Allergic rhinitis and asthma share a common inflammatory response, including mediators, cytokines, and chemokines released from mast cells and basophils.⁹¹ Up to 70% of asthmatics suffer from rhinitis, and significant correlations between asthma and rhinitis severities have been found.⁹²

Clinical studies have shown that the pharmacologic treatment of rhinitis is capable of improving the outcomes of asthma and vice versa. However, systemic treatment approaches such as specific immunotherapy and type-2 biologic agents lead to improved outcomes for asthma and allergic rhinitis.

Treatment with second-generation H1-antihistamines, typically used for controlling classic symptoms of AR, may also have a beneficial effect on asthma symptoms.⁸⁷ Intranasal corticosteroid treatment has been shown to significantly reduce asthma symptoms and reliever usage.⁹⁴

Sublingual immunotherapy (SLIT) in asthma patients with concomitant AR has been shown to reduce asthma symptoms and exacerbation when the patient's dosage of inhaled corticosteroids has been reduced.⁹⁵

Gastroesophageal reflux disease and asthma

Gastroesophageal reflux disease (GERD) occurs when acid refluxes into the esophagus from the stomach. Previous studies have demonstrated a connection between nocturnal GERD and asthma. Asthma prevalence was higher and nocturnal asthma symptoms were more common in nocturnal GERD patients compared to those with non-nocturnal GERD.⁹⁶ However, screening all uncontrolled asthma patients for GERD is not currently recommended. The underlying physiology involves microaspiration associated with vagally mediated esophagobronchial reflex. Current evidence supports empirical GERD treatment in asthmatic patients with symptomatic GERD. Further investigation, such as 24-h pH monitoring, may be later considered if reflux symptoms do not resolve after treatment. Treatment options include anti-reflux medications such as proton pump inhibitors and motility agents. Previous studies have found improvement in PEF, FEV₁, reflux symptom score, daytime asthma symptoms score, and night time asthmatic score with these treatments.⁹⁷⁻¹⁰⁰ Some studies have found that GERD treatment improved daytime and nighttime asthma symptom scores – but not pulmonary function – in asthmatic patients with GERD.¹⁰¹ On the other hand, other studies have shown improvement in parametric pulmonary function but not daytime or night time symptom scores.⁹⁸

Obesity and asthma

Asthma is prevalent in the overweight and obese population.¹⁰² One previous study found 37% of severe asthmatic patients to be obese.¹⁰³ Underlying pathophysiology and mechanistic pathways include increased systemic inflammation involving leptin, IL-5, IL-13, IL-17, chemokine C-C motif ligand (CCL17), C-reactive protein (CRP), and interferon (IFN)- γ ; metabolic dysregulation associated with increased systemic inflammation; increased adipose tissue related to the adiponectin effect, and issues involving the microbiome.¹⁰⁴⁻¹⁰⁷ A pulmonary function test will usually reveal a reduction in forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV₁) without significant difference in FEV₁/FVC.¹⁰³ Reductions in expiratory reserve volume (ERV) and functional residual capacity (FRC) are also frequently observed, the former of which is linearly correlated with BMI.¹⁰⁸ Being overweight or obese may also affect the small airway due to smooth muscle dysfunction associated with airway hyper-responsiveness.¹⁰⁹ Obesity itself also increases the risk of obstructive sleep apnea (OSA) and GERD. Weight reduction is strongly recommended in asthma patients with obesity as a comorbidity. A previous study found that 5-10% weight reduction in these patients can improve asthma control, quality of life, and pulmonary function.¹¹⁰ Standard asthma therapy, including inhaled corticosteroids, is the cornerstone treatment for asthma in obese patients. However, a previous study demonstrated that treatment response may be lower in overweight/obese asthmatic patients.¹¹¹

Obstructive sleep apnea and asthma

OSA is characterized by repetitive upper airway obstruction during sleep associated with intermittent oxygen desaturation and/or arousal. Many studies have shown OSA and asthma to be affected by underlying physiology including nerve reflex stimulation, intermittent hypoxia, vascular endothelial growth factors, and leptin-mediated pathways.¹¹² Previous studies showed a higher prevalence of OSA in asthmatic patients compared to healthy controls, particularly in patients with uncontrolled asthma, indicating an association between OSA and asthma control.^{113,114} Studies have also found a higher prevalence of asthma in OSA patients compared to that observed in the normal population.¹¹⁵ The first-line treatment for OSA is continuous positive airway pressure (CPAP). There is evidence supporting the use of CPAP in asthmatic patients with coexisting OSA, as it may reduce days of asthma, nocturnal asthma attacks, and nighttime symptom scores, as well as improve ACT score, mean PEFr, %FEV₁, and quality of life.¹¹²

Depression and anxiety disorders and asthma

If asthmatic patients suffer from psychological disorders, these disorders may be exacerbated by insufficient control of asthma symptoms. Studies have found a higher rate of depression in severe asthmatic patients than in the general population. Clinicians should thus observe asthma patients for symptoms/family history of psychological problems and refer patients with possible mental disorders to a psychiatrist for diagnosis and treatment.¹¹⁶

Treatment of asthma in special conditions

Exercise-induced bronchoconstriction

Exercise may aggravate asthma symptoms, which may occur within a few minutes after finishing exercise. There are various techniques to reduce exercise-induced bronchoconstriction including pre-exercise warm-up and SABA or formoterol-budesonide inhalation. Good asthma control through regular ICS use may also improve this condition.¹¹⁷

Asthma in pregnancy

In pregnant women, asthma is equally likely to worsen, stabilize, or improve. Asthma can be used both postpartum and during pregnancy, as uncontrolled asthma during pregnancy carries a greater risk than the side effects from medications. As lowering medication dosage may cause acute asthma exacerbation, it is generally recommended that the patient's normal dosage be maintained during pregnancy. In cases of acute asthma exacerbation, standard treatment regimens are justified. During the delivery period, regional anesthesia is preferable to general anesthesia if anesthesia is needed.¹¹⁸

Aspirin-exacerbated respiratory disease (AERD)

AERD, also known as NSAID-exacerbated respiratory disease (NERD), is an inflammatory respiratory disease with three dominant characters: chronic sinusitis with nasal polyps, asthma, and hypersensitivity to aspirin or non-selective cyclooxygenase (COX) inhibitor non-steroidal anti-inflammatory drugs (NSAIDs).¹¹⁹ The mechanisms of this disease are unknown. It is postulated that AERD may be associated with abnormal metabolism of arachidonic acid, resulting in lower prostaglandin E2 and increases in leukotriene E4 and cysteinyl leukotriene. This induces white blood cell (particularly eosinophil) migration to both the upper and lower airway. This phenomenon may result in airway inflammation and can occur at any time, even absent aspirin or NSAIDs.¹²⁰ Symptoms of airway hyperresponsiveness after aspirin or non-selective COX inhibitor NSAID administration include nasal congestion, runny nose, dyspnea, and asthma attack.^{121,122} The prevalence of AERD is higher in patients with severe asthma than in the overall asthmatic population (14% vs 7%).¹²³ Patients may also have anosmia, recurrent episodes of sinusitis, and asthma exacerbation despite treatment with medications or sinus/ nasal polyp surgery.¹²⁴ In summary, AERD patients tend to have more severe, unresponsive airway inflammation than the general asthmatic population despite standard treatment. Diagnosis of AERD is based on compatible history and physical examination. An oral, bronchial, or intranasal aspirin challenge test can be performed for confirmation of the condition.¹²⁰

Treatment of AERD consists of avoidance of aspirin or non-selective COX inhibitor NSAIDs. AERD patients can safely use selective COX-2 inhibitor NSAIDs or acetaminophen (500 mg).^{120,125} Treatment of asthma in AERD patients consists of inhaled corticosteroids and other standard asthma treatments. Antileukotriene can be used as an additional treatment, as it has been shown to reduce symptoms and improve quality of life.^{126,127} Intranasal steroids are recommended

as in treatment of sinusitis. Sinus and nasal polyp surgery can be performed if indicated. However, nasal polyps may reoccur soon after the surgery. In such cases or in patients whose asthma remains uncontrolled despite standard treatment, referral to a specialist for aspirin desensitization or biologic treatment is recommended.

Aspirin desensitization is performed by administering aspirin in gradually increasing doses up to 325 mg under the care of specialists, after which 325-650 mg of aspirin is administered twice daily on a continuous basis.¹²⁰ High doses of aspirin may cause gastrointestinal side effects such as abdominal pain or upper gastrointestinal bleeding. Some studies have found that 300 mg/day of aspirin can be effective in controlling of symptoms with few gastrointestinal side effects.^{128,129} The mechanisms of aspirin desensitization in controlling AERD are unknown but may be related to decreases in leukotriene E4.¹²²

Currently, biologic treatment for asthma or sinusitis with nasal polyps with favorable outcomes in AERD patients include anti-IgE (omalizumab), anti-IL5 (mepolizumab, reslizumab), anti-IL5 receptor (benralizumab), and anti-IL 4 receptor α (dupilumab).^{130,131} However, biologic medications are expensive and target-based and should thus be used cautiously with consideration of indications and clinical characteristics specific to the individual patient.

Asthma and surgery

Prior to surgery, asthma patients should be evaluated for asthma control and to determine the appropriate type of anesthesia and surgical procedure. Patients' best FEV₁ should be 80% or over. General anesthesia with intubation and surgery on the airway, thorax, or abdomen carries a risk of airway constriction.¹³²

Smoking cessation should occur at least two months prior to surgery, and the patient should exhibit normal pulmonary function. If pulmonary function is lower than normal, administration of 1 mg/kg/day of oral prednisolone (maximum of 40 mg) for 5 days prior to surgery should be considered. If the preoperative period is less than 5 days, intravenous corticosteroids with a short-acting inhaled bronchodilator can be substituted.¹³³ For patients previously treated with high-dose corticosteroids for a long duration or oral corticosteroids for more than 2 weeks in the past 6 months, intravenous hydrocortisone should be given to reduce the risk of adrenal crisis.¹³⁴

Severe and uncontrolled asthma

Severe asthma is different from uncontrolled asthma. Severe asthma is asthma that is difficult to control even with high-dose medications and control of risk factors. Despite treatment, asthma symptoms are still frequent and severe.^{7,135} Uncontrolled asthma, however, is defined by symptoms that are unable to be controlled by medication or severe symptoms with triggers such as exercise, allergens, or upper respiratory tract infection. Uncontrolled asthma patients may have frequent nocturnal symptoms, or acute exacerbation more than twice per year and may require unscheduled visits or oral corticosteroids multiple times per year due to dyspnea.

Such patients are considered to have severe, uncontrolled asthma. Note that uncontrolled asthma may be mild and that only a small portion of severe patients have uncontrolled asthma. The percentage of asthma patients with severe and uncontrolled asthma is 3.7% and 17%, respectively.¹³⁶

Importance of severe asthma

Severe asthma results in frequent dyspnea and leads to disturbance of daily life, sleep, work, and school. Additionally, severe patients may require frequent use of oral corticosteroids, which cause long-term side effects and complications such as obesity, diabetes, osteoporosis, cataract, hypertension, depression, and suppression of the pituitary-adrenal axis.^{137,138} Severe asthma also affects various other aspects of a patient's life including family, social life, work, and vacation/leisure time. Severe asthma may also cause a heavy economic burden due to both the direct and indirect cost of care. Patients may incur direct costs due to medication, hospital visits (some of which may be unscheduled, requiring additional medical personnel), and treatment of long-term side effects from medications (such as oral corticosteroids), as well as indirect costs due to the patient or their caregivers needing to be absent from work.

Diagnosis of severe asthma

Severe, uncontrolled asthma is defined by presence of severe asthma at all times and/or frequent asthma attacks despite receiving step-4 and step-5 treatment based on GINA guidelines.¹³⁷ Asthma symptoms in these patients are still severe, even after having been treated with inhaled corticosteroids at moderate or high doses with a combination of long-acting bronchodilators and other oral medications.¹³⁹ This condition is caused by the asthma itself and not patient non-compliance.

Differential diagnoses

There are several conditions that mimic asthma including chronic obstructive pulmonary disease (COPD), obesity, heart disease, insufficient exercise, laryngeal diseases causing chronic cough, upper respiratory tract disease, gastroesophageal reflux disease (GERD), and antihypertensive medications.^{87,140-145} COPD is the most common disease that may be mistaken for severe asthma as it causes wheezing. Other conditions that cause wheezing include laryngeal diseases or upper airway obstruction.¹⁴⁶

Situations in which the patient should be referred to a specialist for severe asthma¹⁴⁷

- Inability to diagnose or differentially diagnose the condition
- Frequent emergency room visits
- Frequent or regular oral corticosteroid use
- Suspected occupational asthma
- Suspected severe food allergy or anaphylaxis
- Suspected heart disease or infection
- Suspected COPD
- Symptoms of or suspected comorbid disease causing difficulty in diagnosis

Laboratory investigations for diagnosis and differential diagnosis of severe asthma¹⁴⁷

Spirometry is a crucial laboratory test as it shows pulmonary function before and after bronchodilator use and can detect airway constriction. If asthma symptoms are present but the first pulmonary function test does not show bronchodilator reversibility (increase in FEV₁ < 200 mL or < 12% from the baseline prebronchodilator level), repeat spirometry should be performed. A flow-volume curve is also needed to evaluate upper airway obstruction.

If spirometry is not feasible, a home peak flow meter should be used to identify variability. Bronchial provocation testing should be considered if the above tests are all normal but severe asthma is still suspected.

Additionally, in asthma patients with clinical features of chronic respiratory obstruction, it may be worthwhile to perform a pulmonary function test at baseline and subsequent follow-up visits to evaluate severity. Referral to a specialist is justified if the diagnosis is uncertain or spirometry is not possible.

Common causes of severe asthma

1. Incorrect inhaler technique
2. Non- or poor compliance
3. Comorbid diseases that cause dyspnea such as obesity, depression, upper respiratory airway diseases, laryngeal diseases, gastroesophageal reflux disease (GERD), chronic obstructive pulmonary disease (COPD), cardiac diseases, or spinal diseases
4. Risk factors for uncontrolled asthma such as poor environmental conditions, smoking, allergens in the home or workplace, or use of medications associated with asthma, i.e., beta blockers or nonsteroidal anti-inflammatory drugs (NSAIDs) including aspirin.¹⁴⁸
5. Ineffective response to short-acting of bronchodilators.¹⁴⁹ Use of more than 3 canister/year of short-acting β₂-agonists as bronchodilator relievers may be an indicator for acute severe asthma and is associated with risk for exacerbation requiring an emergency room visit or hospital admission.^{150,151}
6. Psychological problems or socioeconomic status associated with undertreatment substandard treatment.¹⁵²
7. Medications, particularly oral corticosteroids, causing long term side effects and/or poor patient compliance.

Evaluation and appropriate treatment

Patients with severe asthma should be evaluated to determine whether they are receiving appropriate treatment, their treatments are specific to their individual needs, they have treatment plans in place if their symptoms improve or become more severe, and they have learned how to use their inhalers correctly. Physicians should also recheck patients' inhaler technique regularly during the outpatient visits and attempt to determine causes of non-compliance. ICS-formoterol maintenance and relievers may be appropriate if the patient has frequent asthma attacks, as they may prevent severe asthma attack¹⁵³ and the dosage can be adjusted by the patient.^{30,32} Comorbid diseases associated with asthma, such as allergic rhinitis or sinusitis, should also be treated. Steps should be taken

if the physician observes avoidance of medications associated with asthma exacerbation, and evidence of depression or other psychological symptoms should be managed by referral to a specialist.

Non-pharmacological treatments should be considered at each visit including smoking cessation, exercise, healthy diet, weight reduction, influenza vaccination, and avoidance of allergens. Additional medications such as tiotropium bromide (soft mist inhaler), leukotriene modifiers, high-dose inhaled corticosteroids administered according to asthma guidelines may be justified if severe asthma persists after all environmental causes are eliminated.¹⁴⁷

Follow-up at 3-6 months

During follow-up visits, physicians should evaluate asthma severity, inhaler device technique, medication side effects, pulmonary function, and patient satisfaction. If the patient still has severe asthma after correcting possible environmental factors, biologics may be justified. Which biologics are appropriate depends on the patient's clinical features or asthma phenotype.

Asthma phenotypes

The type-2 asthma phenotype is associated with good response to several medications (e.g., corticosteroids).¹⁵⁴⁻¹⁵⁷ However, there is limited evidence regarding the effectiveness of non-type 2 treatments, including biologics, in type-2 low asthma patients. Other factors need to be considered prior to biologic treatment including comorbid diseases, psychosocial status, and availability of biologics. Biologic agents tend to be more accessible in clinical research facilities than in other settings, and there is more clinical data regarding their use in severe asthma in such facilities.

Type-2 Asthma Phenotype

The majority of severe asthma patients have been found to have the type-2 phenotype. Clinical features of this phenotype are presence of allergy, young asthma onset, non-obesity, presence of eosinophils in blood of 150 cells/μL or over and in sputum of 2% or over, and FeNO of 20 ppb or over.⁷ The epithelial origin cytokines or alarmins include IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) are responsible to allergens, viral, and bacterial infection. These cytokines are associated with activation of innate lymphoid cell type-2 and T helper-2 lymphocytes in patients with type-2 asthma phenotype.¹⁵⁸

The indication for type 2 biologics for severe asthma have been addressed. Firstly, omalizumab as anti-IgE is indicated in patients with allergic asthma by evidence of allergen sensitization with high serum IgE. In addition, omalizumab is also indicated in chronic spontaneous urticaria. Furthermore, anti-IL5 (mepolizumab and reslizumab) and anti-IL5R (benralizumab) are indicated in severe eosinophilic asthma with high blood eosinophilia and history of asthma exacerbation. Lastly, anti-IL4R (dupilumab) is indicated in corticosteroid dependent asthma with high blood eosinophilia or high FeNO. Meanwhile, omalizumab, benralizumab and dupilumab was approved for being added on asthma treatment in Thailand.

Table 5. Registered and available biologics for severe asthma.

Generic name	Brand name	Action	Administration	Frequency (weeks)	Patient age (years)	Side effects
Omalizumab	Xolair	Anti-IgE	SC	2-4	6	Pain at injection site, anaphylaxis (few)
Mepolizumab	Nucala	Anti-IL5	SC	4	12	Pain at injection site
Reslizumab	Cinqair	Anti-IL5	IV	4	6	Pain at the injection site
Benralizumab	Fasenra	Anti-IL5R	SC	4-8	12	Pain at injection site
Dupilumab	Dupixent	Anti-IL4R	SC	2	12	Pain at the injection site, red eyes, increase blood eosinophils
Tezepelumab	NA in Thailand	Anti-TSLP	SC	2-4	NA	Pain at the injection site

Abbreviations: SC (subcutaneous), IV (intravenous), Anti-IL5 (anti-interleukin 5), Anti-IL5R (anti-interleukin 5 receptor), Anti-IL4R (anti-interleukin 4 receptor), NA: not available

Patients with the type-2 asthma phenotype can be treated with the biologics, as show in **Table 4**.^{154–157,159–162}

For patients with the non-type-2 phenotype, non-pharmacological treatment, such as bronchial thermoplasty, should be given.¹⁶³

Follow-up in severe asthma

Standard follow-up examinations for asthma, medication administration, and medication side effects should be performed every 1-3 months in patients with severe asthma.

Severe, uncontrolled asthma is defined as asthma that remains uncontrolled even after step-4 and step-5 treatment according to the GINA strategy and control for risk factors and occurrence of asthma attack when stepping down therapy. Prevalence of severe, uncontrolled asthma is 3-10% in asthma patients. Severe asthma has physical, psychosocial, and economic impacts on patients. Treatment of these patients should be performed with great care. First, the diagnosis of asthma should be definite. Then, risk factors for severe asthma should be evaluated. Quality of life should also be considered, as well as prevention of future severe asthma. Referral to a specialist should be considered if symptoms remain uncontrolled, i.e., if symptoms continue or the patient experiences frequent asthma attacks despite high-dose inhaled corticosteroid treatment. Differential diagnoses should be performed. Asthma phenotype may be a crucial factor in determining whether to administer medication in addition to inhaled corticosteroids. Choices for additional treatment include tiotropium bromide, leukotrienes receptor antagonist, or biologic agents. Oral corticosteroids should be avoided due to the possibility of long-term side effects. The clinical efficacy of additional medications should be evaluated in patients with severe asthma, as well as their clinical status after withdrawal of medications. Alternative treatments should be considered at every visit. A multidisciplinary team is needed for these patients, and referral to specialists is warranted in selected cases. Clinical research facilities and severe asthma patient groups may facilitate better clinical treatment of severe asthma.

Thai Alternative Medicine in Asthma

Complementary and alternative medicine (CAM), such as acupuncture and herbal medicine, is popular in many regions. There is some evidence to support the use of acupuncture as an alternative therapy for asthma. However, the mechanisms underlying its effects are not fully understood. The WHO listed asthma as an indication for acupuncture and the National Institutes of Health have since recommended acupuncture as an adjunctive treatment for asthma.¹⁶⁴ Traditional herbal medicine is widely used in Asia (including Thailand). Zingiber cassumunar Roxb. (known as phlai in Thai) has been used as a traditional medicine in Thailand for treatment of asthma and allergy-related diseases. Previous studies have shown that the bioactive components of phlai exhibit anti-inflammatory, smooth muscle relaxant, antihistamine, and mucin-lowering secretion properties.^{165–169} Phlai also inhibits 5-lipoxygenase enzyme and is a cysteinyl leukotriene receptor antagonist.¹⁷⁰ A preliminary study on the effect of treatment with Phlai capsules on bronchial hyperresponsiveness in asthmatic patients found that it tended to decrease BHR and significantly improved symptom scores without side effects.¹⁷⁰

Asthma and coronavirus disease-19 (COVID-19)

The outbreak of the novel coronavirus in 2019 has increased morbidities and mortalities globally. Primary infection is of the respiratory tracts and may cause pneumonia and respiratory failure leading to fatality.^{171,172} Epidemiological studies have shown that asthma and respiratory allergies are uncommon underlying diseases in COVID-19 patients,^{162–164} despite viral infection being a common cause of asthma exacerbation.^{173–175} However, increased susceptibility to COVID-19 is related to higher expression of angiotensin-2 (ACE-2) receptors in the respiratory system, and a previous study found ACE-2 expression in airway epithelium obtained from patients with asthma compared to healthy subjects. The use of inhaled corticosteroids reduces ACE-2 receptor expression in asthma in a dose-dependent manner.¹⁷⁶ Since the expression levels of ACE2 and TMPRSS2 gene were similar in asthma and healthy subjects. There was no subgroup analysis regarding allergic and non-allergic asthma phenotypes.

However, respiratory allergies, allergen exposures, high IgE and allergen sensitization were associated with a decrease in ACE2 expression in the nasal and bronchial epithelium of asthma patients. In addition, low ACE2 expression was not associated with non-atopic asthma. Hence, the reduced ACE2 expression is protective factors in patients with respiratory allergies for reduced COVID-19 severity.¹⁷⁷

Thus, although there is no conclusive evidence that asthma patients are at greater risk of COVID-19, patients should be assiduous in continuing their regular controller treatments, including inhaled corticosteroids, long-term oral corticosteroids, and biologics, during the COVID-19 pandemic.

The management of asthma exacerbation during the COVID-19 pandemic is challenging. Asthma may be exacerbated as a result of respiratory viral or bacterial infection. The common viral causes of exacerbation are rhinovirus, human coronavirus, and adenovirus.^{178,179} Nebulization is key to bronchodilator drug delivery in acute respiratory emergency (e.g., asthma and COPD exacerbation). However, as SARS-CoV2 spreads through droplets containing the virus produced by coughing and sneezing, concerns have been raised regarding the possibility of airborne spread of viral particles during nebulization and aerosol-generating procedures (AGPs).¹⁸⁰⁻¹⁸³ Hence, some asthma guidelines recommend refraining from nebulization both in patients with and those without clinically suspected COVID-19.¹⁸⁴⁻¹⁸⁷ Instead a metered-dose inhaler (MDI) with spacer, which exhibits similar efficacy to nebulization, should be used according to these recommendations.¹⁸⁸ However, the risk of aerosol spread of viruses from nebulization is debated, and other asthma guidelines state that nebulization does not spread viral droplets.^{28,189-194} Currently, the risk of SARS-CoV-2 infection among healthcare providers from nebulization and aerosol-generating procedures (AGPs) has only been extrapolated from previous epidemiological studies of severe acute respiratory syndrome (SARS) and has not yet been examined systematically.¹⁹⁵ However, high-risk patients who are critically ill, elderly and disabled patients who cannot use MDI, or patients who do not cooperate with treatment may require specific methods of drug delivery during exacerbation. The role of systemic corticosteroids in severe COVID-19 has not been established. However, in patients with asthma exacerbation, systemic corticosteroids are necessary whether or not there is clinical suspicion of COVID-19.¹⁹⁶

The perspectives of guidelines for the management of asthma in adults: Evidence and Recommendations by Thai Asthma Council (TAC)

Asthma is a common respiratory disease in Thailand. However, the burden of uncontrolled asthma in Thailand is high and associated with increased healthcare cost utilization. Thai Asthma Council (TAC) asthma recommendation emphasizes holistic care for asthma including confirmation of the diagnosis, setting asthma management goals, initiating an asthma management process, and determining a treatment plan, as shown in **Figure 1-5**.

The perspectives of this guideline and recommendation are conveniences and being practical in the context of health care limited resource setting and primary healthcare sectors. The recommendation focusing on the regular use of ICS in mild asthma who are less symptomatic and escalation level of asthma medications together with integrative approach for improving asthma outcomes. Apart from medications, the TAC guideline focuses on non-pharmacological therapies including patient education for maximizing asthma outcomes. Lastly, TAC asthma recommendation provides asthma management schema during COVID-19 pandemic in setting of stable asthma and asthma exacerbation. Again, herbal use in asthma and alternative medicine are progressively interesting issue for chronic medical diseases including asthma particularly in Thailand.

The difference of TAC recommendation from Global Initiative for asthma (GINA) is that the choice of initial controller and preferred reliever medications. The limitation of available asthma medication in Thailand is key issue and limitation for following the guideline. The TAC committee believed that despite of robust evidence and complexity of approach for diagnosis and asthma treatment. The simplicity and applicability of guideline are pivotal for implementation in Thailand. Meanwhile, the asthma control situation in Thailand is very poor include symptoms control and asthma exacerbation despite of the available ICS containing treatment of asthma.³

The asthma control in Asia Pacific region is unacceptably low. However, many countries in this region have shared the common the barriers for achieving the asthma treatment in terms of medication accessibility as well as the perception regarding clinicians and patients on asthma. The findings are similar other regions, current levels of asthma control in the Asia-Pacific region fall markedly short of goals specified in international guidelines for asthma management. The ICS users was low as 13.6%. However, the reliance on rapid reliver bronchodilator was 56.3%. Absence from school and work in the previous year was reported by 36.5% of children and 26.5% of adults in this region.¹⁹⁷

Despite the epidemiological survey demonstrates a universal acceptance of coexistent asthma and allergic rhinitis. The high disease burden has been reported. It highlights the need for increased healthcare practitioner communication and awareness regarding the disease management. This is aimed to improve appropriate treatment and management of these co-existent conditions in this region.¹⁹⁸

For these reasons, the local recommendations, and guidelines for improving management of asthma are needed in Asia Pacific region. According to the contexts of problems and barrier to overcome have been shared in several countries. The geographical similarities, the healthcare system, socioeconomic and cultural perspectives are also needed to address.

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Thai clinical practice guidelines for the diagnosis and management of asthma in adult patients were first issued in 1997. This is an updated version of those guidelines edited by multidisciplinary experts in Thailand and organized by the Thai Asthma Council (TAC)

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