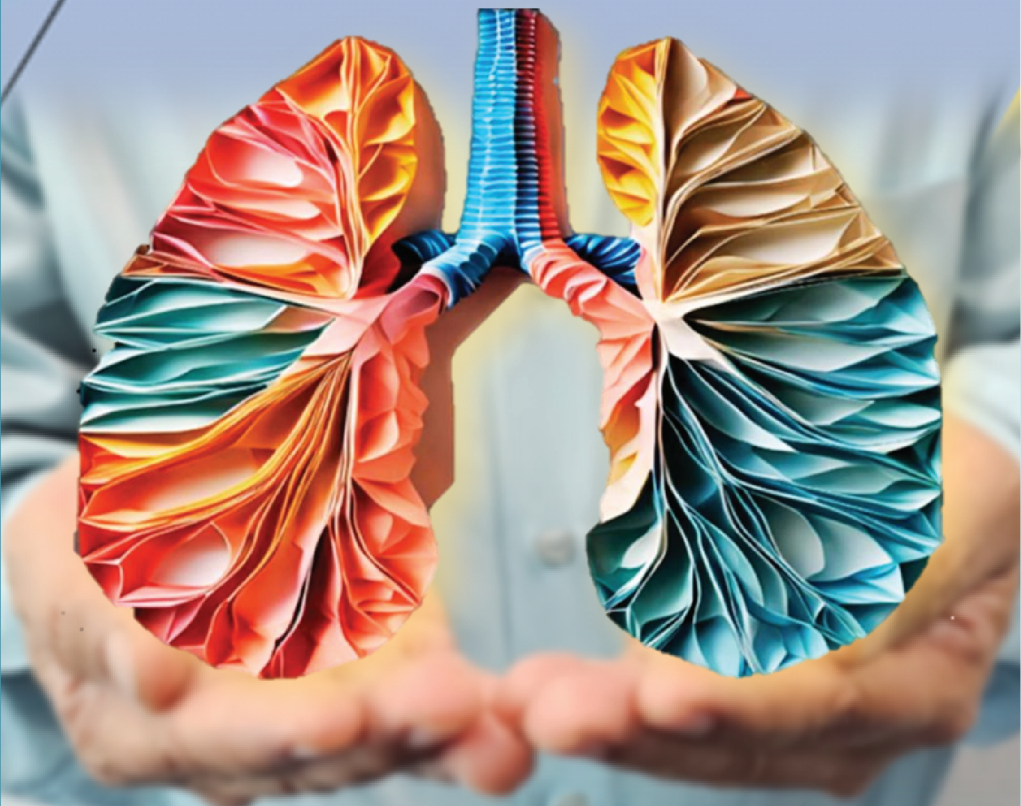
2024 MOH/P/PAK/567.24(GU)-e

Clinical Practice Guidelines

Management of Asthma in Adults

(Second Edition)



Ministry of Health Malaysia
Malaysian Thoracic Society
Academy of Medicine of Malaysia

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http://www.moh.gov.my
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STATEMENT OF INTENT

These clinical practice guidelines (CPG) are meant to be guides for clinical practice, based on the best available evidence at the time of development. The guidelines should not override the responsibility of the practitioners to make decisions appropriate to the circumstances of the individual. This should be done in consultation with the patients and their families or guardians, taking into account the management options available locally.

UPDATING THE CPG

These guidelines were issued in 2024 and will be reviewed in a minimum period of four years (2028) or sooner if new evidence warrants earlier revision. When it is due for updating, the Chairperson of the CPG or National Advisor of the related specialty will be informed about it. A discussion will be done on the need for a revision including the scope of the revised CPG. A multidisciplinary team will be formed and the latest systematic review methodology used by MaHTAS will be employed.

Every care is taken to ensure that this publication is correct in every detail at the time of publication. However, in the event of errors or omissions, corrections will be published in the web version of this document, which will be the definitive version at all time. This version can be found on the websites mentioned above.

TABLE OF CONTENTS

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LEVELS OF EVIDENCE

Level	Study design
I	Properly powered and conducted randomised controlled trial; well-conducted systematic review or meta-analysis of homogeneous randomised controlled trials
II-1	Well-designed controlled trial without randomisation
II-2	Well-designed cohort or case-control analysis study
II-3	Multiple time series, with or without the intervention; results from uncontrolled studies that yield results of large magnitude
III	Opinions of respected authorities, based on clinical experience; descriptive studies or case reports; reports of expert committees

SOURCE: *U.S. Preventive Services Task Force. U.S. Preventive Services Task Force Procedure Manual. Rockville, MD: USPSTF; 2015.*

FORMULATION OF RECOMMENDATION

- In line with the new development in CPG methodology, the CPG Unit of MaHTAS is adapting **Grading Recommendations, Assessment, Development and Evaluation (GRADE)** in its work process. The quality of body of evidence and related effect size are carefully assessed/reviewed by the CPG DG.
- Recommendations are formulated based on **certainty of evidence** and the wording used denotes the **strength of recommendations**. This takes into account:
  - quality and level of the evidence
  - balance of benefits and harms of the options
  - patient's preference and values
  - resource implications
  - relevancy and applicability to the local target population
- The more criteria being fulfilled, the more certain is the evidence leading to strong recommendations using the word "**should**" being considered. Otherwise, weak recommendations use the word "**may**" in proposing an action to be made.
- In the CPG, a yellow box ☐ highlights important message(s) in the management while a blue box ☐ contains evidence-based recommendation(s) for the particular condition.

KEY RECOMMENDATIONS

The following recommendations are highlighted by the CPG Development Group as the key recommendations that answer the main questions addressed in the CPG and should be prioritised for implementation.

Diagnosis

- Diagnosis of asthma should be made based on typical clinical history, physical examination and evidence of airway obstruction variability. Spirometry is the preferred tool to demonstrate airway obstruction variability or reversibility.

General Principles

- The assessment of asthma control should be performed before considering stepping up or down the treatment.

Patient Education

- Regular medical reviews in asthma patients are preferred over self-adjustment of medications aided by asthma action plan.

Stable Asthma

- Assessment of asthma should include:
  - evaluating current asthma symptoms control using validated tools
  - identifying future exacerbation risk factors and co-morbidities
  - checking adherence, inhaler techniques and other treatment related issues
- In the treatment of asthma:
  - inhaled short-acting β_2-agonists (SABA) should not be used as monotherapy
  - inhaled SABA may be used as reliever therapy with regular inhaled corticosteroids (ICS)
- All asthma patients should be on inhaled corticosteroids (ICS)-containing therapy.
- Asthma patients who smoke or vape should be strongly encouraged to quit at every clinic visit.

Asthma Exacerbation

- Treatment should be initiated immediately based on severity of asthma exacerbation.
- Systemic corticosteroids should be given in all patients with asthma exacerbation.
- Following asthma exacerbation, all patients should be given a follow-up plan upon discharge.

Special Groups

Severe Asthma
- Biologics should be considered as add-on treatment for severe asthma after optimising therapy. Phenotype assessment should be conducted prior to this.
- Long-term oral corticosteroids should be reserved for severe asthma when no alternative treatments are available.

Pregnancy
- Inhaled corticosteroids-containing therapy should be initiated in pregnant asthma patients and continued if already in use.

Occupational Asthma
- All working-age adults with new or worsening asthma symptoms, reappearance of childhood asthma or unexplained airflow obstruction should be asked about their occupation.

GUIDELINES DEVELOPMENT AND OBJECTIVES
GUIDELINES DEVELOPMENT

The members of the Development Group (DG) for this CPG were from the Ministry of Health (MoH), Ministry of Higher Education and private healthcare. There was active involvement of a multidisciplinary Review Committee (RC) during the process of the CPG development.

A systematic literature search was carried out using the following electronic databases: mainly Medline via Ovid and Cochrane Database of Systemic Reviews and others e.g. PubMed and Guidelines International Network (refer to **Appendix 1** for **Example of Search Strategy**). The search was limited to literature published on humans, publication from year "2017 to Current" and English language. In addition, the reference lists of all retrieved literature and guidelines were searched, and experts in the field contacted to identify relevant studies. All searches were conducted from 17 January 2023 to 5 March 2023. Literature searches were repeated for all clinical questions at the end of the CPG development process allowing any relevant papers published before 31 July 2024 to be included. Future CPG updates will consider evidence published after this cut-off date. The details of the search strategy can be obtained upon request from the CPG Secretariat.

References were also made to other CPGs on Asthma which included:

- Global Initiative for Asthma – Global Strategy for Asthma Management and Prevention (2024)
- Spanish Society of Pulmonology and Thoracic Surgery (SEPAR)] – GEMA 5.3. Spanish Guideline on the Management of Asthma (2023)
- British Thoracic Society/Scottish Intercollegiate Guidelines Network – British Guideline on the Management of Asthma (2019)

These CPGs were evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE) II prior to them being used as references.

A total of 21 clinical questions (CQ) were developed under different sections. Members of the DG were assigned individual questions within these sections (refer to **Appendix 2** for **Clinical Questions**). The DG members met 23 times throughout the development of these guidelines. All literature retrieved were appraised by at least two DG members using Critical Appraisal Skill Programme checklist, presented in evidence tables and further discussed in each DG meetings. All statements and recommendations formulated after that were agreed upon by both the DG and RC. Where evidence was insufficient, the recommendations were made by consensus of the two groups. This CPG was developed largely based on the findings of systematic reviews, meta-analyses and clinical trials, with local practices taken into consideration.

The literature used in these guidelines were graded using the U.S. Preventive Services Task Force Level of Evidence (2015), while the grading of recommendation was done using the principles of GRADE (refer to page i). The writing of the CPG follows strictly the requirement of AGREE II.

On completion, the draft of the CPG was reviewed by external reviewers. It was also posted on the MoH Malaysia official website for feedback from any interested parties. The draft was finally presented to the Technical Advisory Committee for CPG and, the HTA and CPG Council MoH Malaysia for review and approval. Details on the CPG development methodology by MaHTAS can be obtained from Manual on Development and Implementation of Evidence-based Clinical Practice Guidelines published in 2015 (available at https://www.moh.gov.my/moh/resources/CPG_MANUAL_MAHTAS.pdf).

OBJECTIVES

The objective of the CPG is to provide evidence-based recommendations on the management of asthma in adults on the following aspects:
- diagnosis
- assessment
- treatment
- follow-up

CLINICAL QUESTIONS

Refer to **Appendix 2**.

TARGET POPULATION

Inclusion Criteria
- Adults (≥18 years old) with asthma

Exclusion Criteria
- Asthma-COPD overlap syndrome
- In-patient asthma care

TARGET GROUP/USERS

This document is intended to guide healthcare professionals and relevant stakeholders involved in the management of asthma in adults. This includes:

i. doctors
ii. allied health professionals
iii. trainees and medical students
iv. patients and their advocates
v. professional societies

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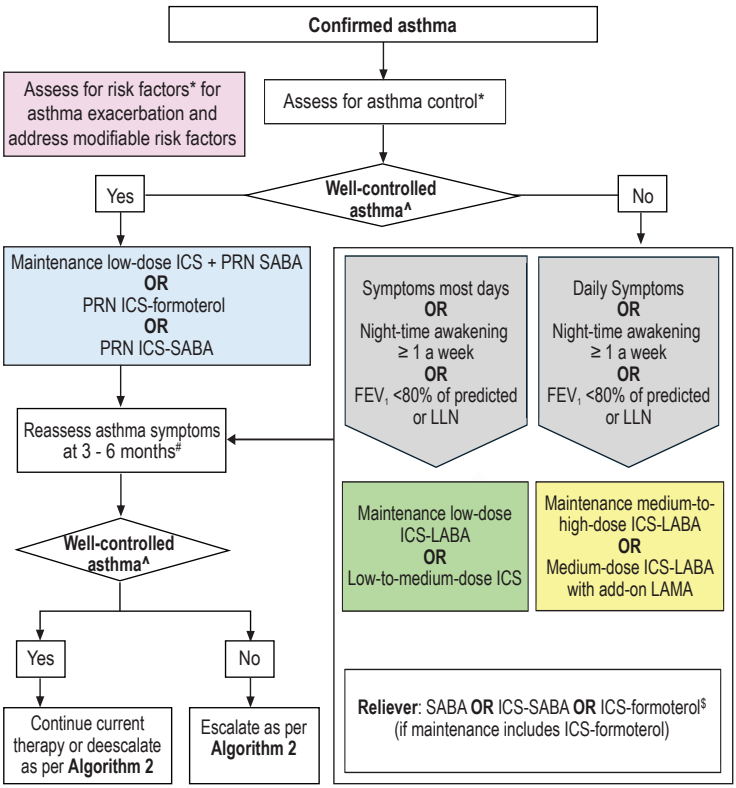
ALGORITHM 1: INITIATION OF ASTHMA TREATMENT



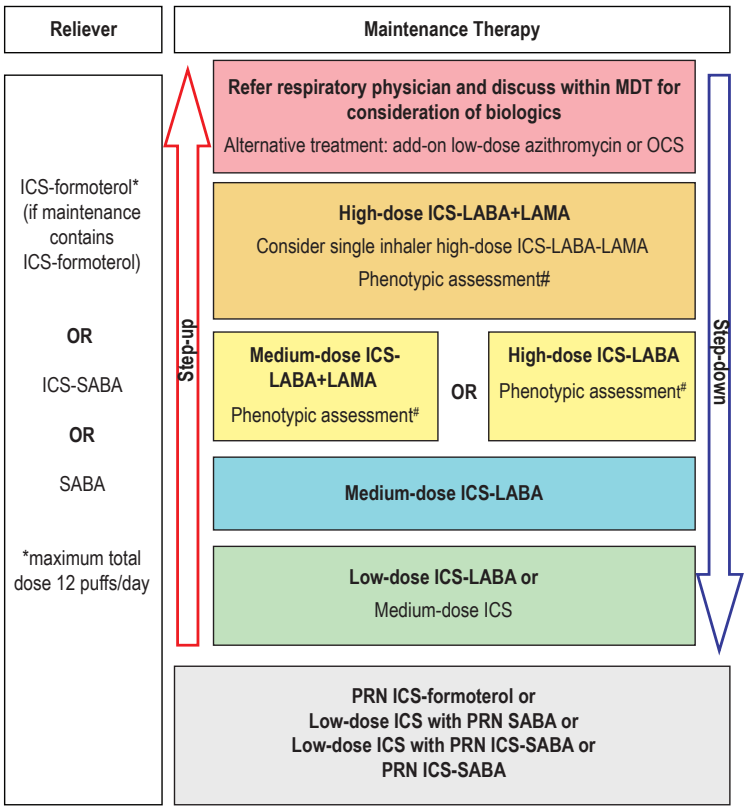
Refer to **Table 7** for ICS dosing category
LTRA may be added to maintenance therapy if the patient has concurrent allergic rhinitis.
#Inhaler technique and adherence to treatment should be assessed at every clinic/hospital visit and before escalating treatment
^Well-controlled asthma as defined by ACT ≥20 or 'NO' to all GINA questionnaire
$e.g. budesonide-formoterol or beclometasone diproprionate-formoterol

***Assess the presence of risk factors for asthma exacerbation and address them accordingly:**

- Previous history of severe asthma exacerbation requiring systemic steroids or hospitalisation within the past year (consider initiating medium dose ICS)
- Overuse of SABA (≥3 cannisters per year)
- Inadequate ICS use or not on ICS
- Poor adherence to maintenance therapy
- Incorrect inhaler technique
- Current smoker including e-cigarette or vape user
- Co-morbidities: obesity, GERD
- Pregnancy
- T2-high inflammation: high FeNO, blood eosinophilia
- Lung function: Low FEV_1 especially <60% predicted, high bronchodilator responsiveness

Abbreviations ACT=Asthma Control Test questionnaire; FeNO=fractionated nitric oxide; FEV1=forced expiratory volume in first 1 second; GERD=gastroesophageal reflux disease; ICS=inhaled corticosteroids; LABA=long-acting β-agonists; LLN=lower limit normal; PRN=as needed; SABA=short-acting β-agonists; T2=Type 2 inflammatory marker; LTRA=leukotriene receptor antagonist

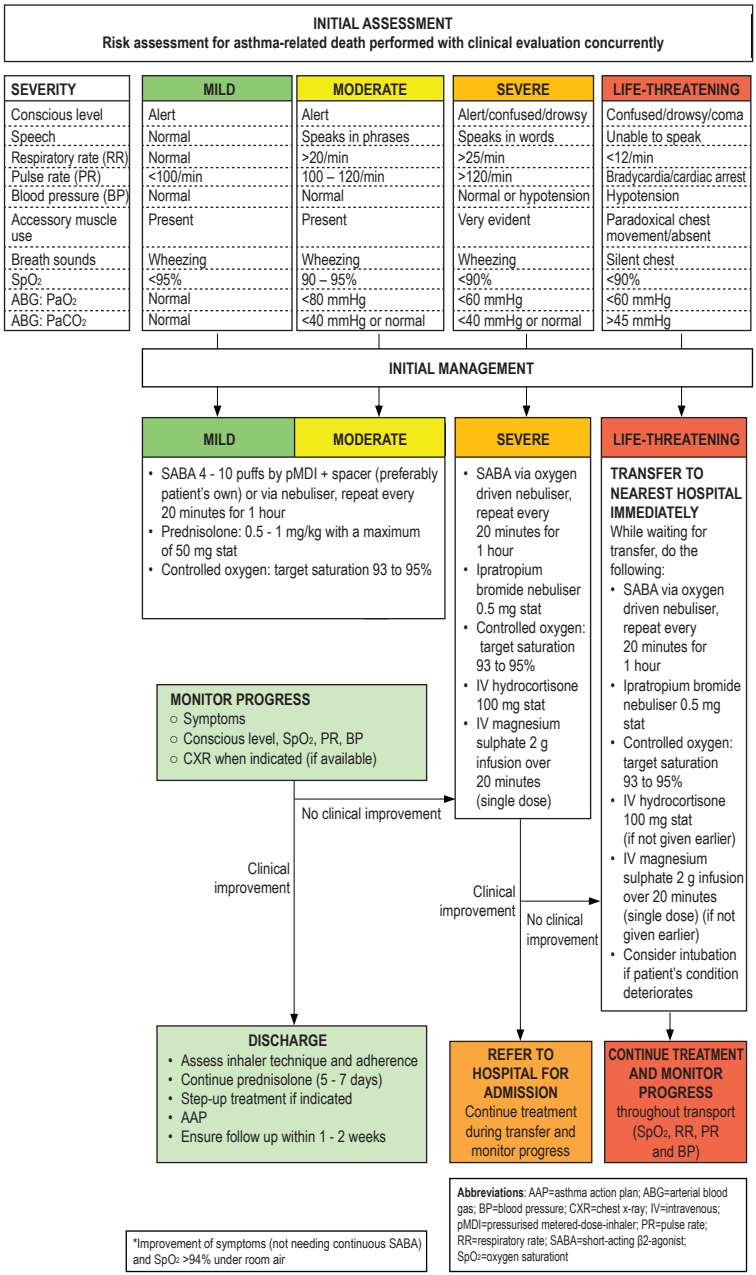
ALGORITHM 2: STEP UP AND STEP DOWN OPTIONS IN MANAGEMENT OF STABLE ASTHMA



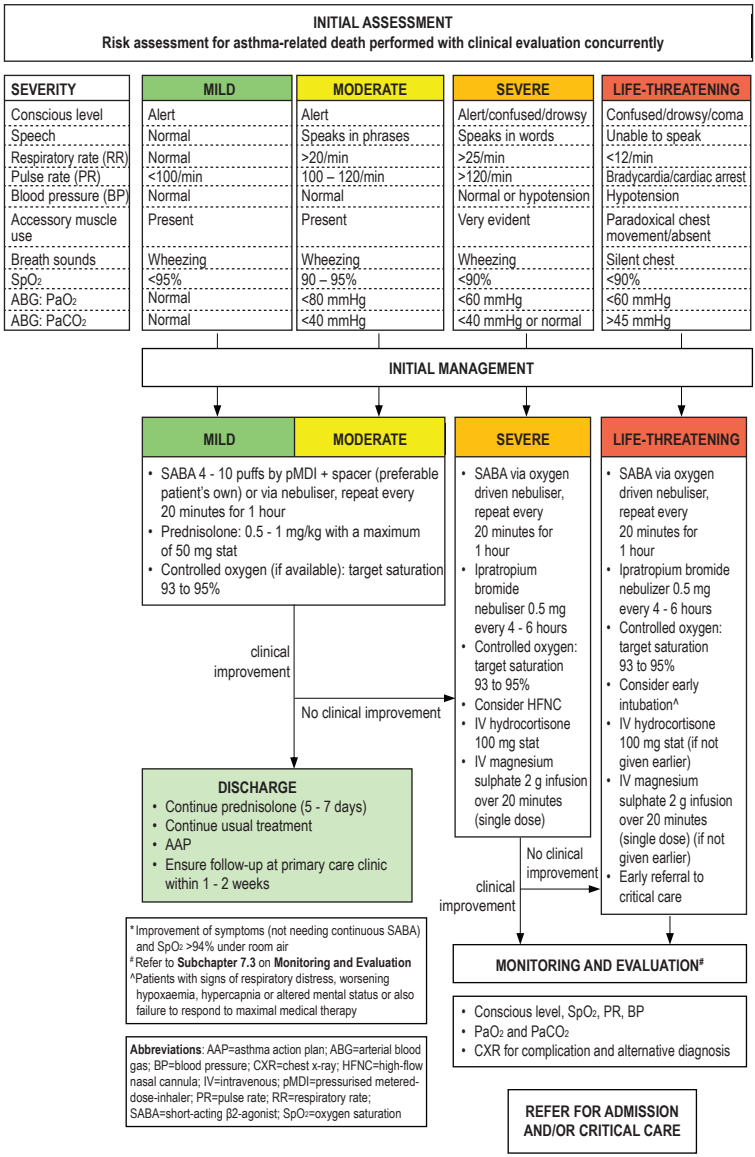
Note: LTRA may be added to maintenance therapy if the patient has concurrent allergic rhinitis.
Refer to **Table 7** for ICS dosing category
#phenotypic assessment should be done at this stage upon stepping up

Abbreviations: ICS=inhaled corticosteroids; ICS-LABA+LAMA=fixed dose combination ICS-LABA with separate inhaler LAMA; ICS-LABA-LAMA=single inhaler of ICS-LABA-LAMA; LABA=long-acting β-agonists; LAMA=long-acting muscarinic antagonists; MDT=multidisciplinary team; OCS=oral corticosteroids; PRN=as needed; SABA=short-acting β-agonists; LTRA=leukotriene receptor antagonist

ALGORITHM 3: MANAGEMENT OF ASTHMA EXACERBATION IN PRIMARY CARE



ALGORITHM 4: MANAGEMENT OF ASTHMA EXACERBATION IN EMERGENCY DEPARTMENT



1. INTRODUCTION

Asthma is a chronic inflammatory lung disease characterised by airway inflammation and narrowing, and bronchial hyperreactivity. These pathophysiological changes lead to episodic symptoms, e.g. shortness of breath, which can range from mild to severe in severity. However, asthma symptoms are often subtle and may be overlooked or misdiagnosed as other conditions, contributing to delays in proper management. Recognising and addressing this diagnostic challenge is a key focus of this CPG, which aims to improve asthma care through evidence-based recommendations.

Asthma continues to pose significant public health challenges, affecting millions globally and thousands in Malaysia. Despite advances in disease understanding and treatment, asthma remains frequently misdiagnosed or poorly managed, resulting in avoidable suffering, hospitalisations and even deaths.

The inaugural CPG for asthma in adults, introduced in 2017, was a landmark achievement in standardising asthma care. It set a strong foundation for evidence-based practice and improved patient outcomes. Since then, the rapidly evolving landscape of asthma management - including the advent of biologics for severe asthma e.g. omalizumab, benralizumab and dupilumab - has necessitated a comprehensive update. With two additional biologics currently in the pipeline, i.e. tezepelumab and mepolizumab, this updated CPG aims to provide clinicians with the latest evidence-based resource to deliver the highest standard of care for asthma patients.

The COVID-19 pandemic has underscored the need for innovative and adaptable healthcare solutions. Recognising this, the MoH is actively exploring the development of online inhaler technique tutorials, with plans for their release in the near future. These resources, once available, will complement the appendix of inhalers provided in this updated CPG. Together, they aim to enhance inhaler technique, empower patients and improve treatment adherence for better asthma management.

For those with severe asthma, the availability of cutting-edge biologic therapies has transformed the management paradigm. The CPG Development Group takes pride in the locally developed algorithm for selecting biologics in severe asthma management. Designed by the group, this tool is comprehensive and user-friendly, providing a practical resource for clinicians.

Tailored to the Malaysian context, this CPG acknowledges the challenges of local healthcare system, cultural nuances and prevalent

misconceptions about asthma. It aims to dispel myths, address gaps in understanding, and provide clear, actionable guidance for healthcare providers and patients. This updated CPG aspires to be more than just a reference - it's a tool to elevate asthma care in Malaysia. By empowering healthcare professionals with the latest knowledge and strategies, the burden of asthma can be reduced leading to transformation of the lives of those affected.

2. RISK FACTORS

- Asthma is a multifaceted respiratory disease resulting from interactions between various risk factors.
- Understanding these risk factors is crucial for effective prevention and treatment of asthma.

Refer to **Table 1** on risk factors for developing asthma.

Table 1: Risk Factors for Developing Asthma

Category	Risk Factors
Host/Genetic	• Female • Atopy • Bronchial hyperresponsiveness • Parental asthma
Environmental	• Exposure to allergens (e.g. house-dust mite, pollen, cockroach) • Tobacco smoke • Air pollution • Occupational irritants (e.g. nitrogen dioxide, carbon monoxide, sulphur dioxide, fine particulate matter)
Perinatal/ Childhood	• Younger maternal age • Maternal pre-eclampsia • Maternal tobacco consumption during pregnancy • Born via caesarean section • History of not receiving breastmilk • Lower pulmonary function of neonates
Co-morbidities	• Obesity • Allergic rhinitis • Chronic rhinosinusitis • Gastroesophageal reflux disease
Socioeconomic	• Limited access to education and/or health care

Source:

1. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2024. Updated May 2024 (Available at: www.ginasthma.org)
2. Plaza Moral V, Alobid I, Álvarez Rodríguez C, et al. GEMA 5.3. Spanish Guideline on the Management of Asthma. Open Respir Arch. 2023;5(4):100277.
3. Scottish Intercollegiate Guidelines Network & British Thoracic Society. British Guideline on the Management of Asthma. SIGN-BTS;2019

Pre-menstrual asthma refers to worsening of asthma symptoms in females in days leading up to their menstrual period. This is influenced by hormonal changes during the menstrual cycle. A meta-analysis found that risk factors for pre-menstrual asthma includes increasing age (SMD=0.42, 95% CI 0.03 to 0.82) and longer duration of asthma (SMD=0.81, 95% CI 0.41 to 1.20).[1]

3. DIAGNOSIS

Asthma is a heterogeneous disease with distinct inflammatory patterns. In Type 2 (T2)-high asthma, inflammation is driven by T2 cytokines [interleukin (IL)-4, IL-5 and IL-13], leading to eosinophilic inflammation, elevated IgE and increased fractionated exhaled nitric oxide (FeNO) levels. This phenotype is typically responsive to inhaled corticosteroids (ICS) and biologics targeting T2 pathways. In contrast, neutrophilic asthma is associated with low or absent T2 inflammation and may involve IL-17 and other non-T2 cytokines, with neutrophilic inflammation and steroid resistance often observed.

- There is no gold standard test in diagnosing asthma. The diagnosis is based on a combination of clinical history, physical examination findings and lung function test with evidence of variable and reversible airway obstruction.

A thorough history taking to identify asthma symptoms is important for accurate diagnosis. Physical examination may appear normal particularly when the patient is not experiencing an asthma exacerbation. Physical examination is important to rule out other conditions with similar symptoms. Typical clinical signs of asthma include tachypnoea, rhonchi, prolonged expiratory phase and decreased breath sounds.

Spirometry should be used to diagnose asthma whenever possible. Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) are parameters obtained from spirometry. These parameters are used to show evidence of obstructive lung disease and reversibility (refer to **Table 3**). When spirometry is not available, peak expiratory flow meter may be used instead. These tests should be performed before treatment, at 3 – 6 months after treatment and periodically (1 – 2-yearly) to establish patient's personal best FEV_1 and monitor for lung function decline. A low FEV_1 indicates underlying untreated airway inflammation and is a risk factor for future exacerbation.[2]

Peak expiratory flow rate (PEFR) can be measured using both peak flow meter and spirometry machine. Peak flow meter is used primarily for home monitoring. Whereas, spirometry is performed in a clinical setting under supervision of a healthcare provider. Whenever possible, PEFR should be recorded before treatment is initiated. It should be monitored at 1-hour post treatment and at regular intervals until a clear response has occurred or a plateau is reached.[2]

If a patient has already started on treatment, the response to the treatment (bronchodilator or corticosteroids) may aid in the diagnosis but lack of response may not exclude asthma.

FeNO is not a definitive test for diagnosing asthma. Although it tends to be high in asthma with T2 airway inflammation, it can also be elevated in non-asthmatic conditions e.g. eosinophilic bronchitis, allergic rhinitis and eczema. In patients with suspected asthma, a high FeNO level of >50 ppb predicts better response to ICS therapy than low level. However, a low FeNO level should not be used as a reason to withhold ICS treatment as in non-T2 inflammation asthma, FeNO levels are not typically elevated.[2]

Refer to **Table 2**, **Table 3** and **Figure 1**.

Table 2. Clinical Features Suggestive of Asthma

Clinical History and Symptoms	
Common symptoms	Wheeze Cough Chest tightness Shortness of breath
Symptoms variability	Episodic symptoms Diurnal symptoms Symptoms after/during exercise
Triggers	Common colds (viral infection) Allergen e.g house dust mites, pets Cold weather Irritants: • smoke • haze • strong smell i.e. perfumes, cleaning solutions • exhaust fumes
History of atopy	Allergic rhinitis Eczema
Family history of atopy	Asthma Allergic rhinitis Eczema
Physical Examination	
Respiratory examination	Use of accessory muscles Audible wheeze Rhonchi on auscultation

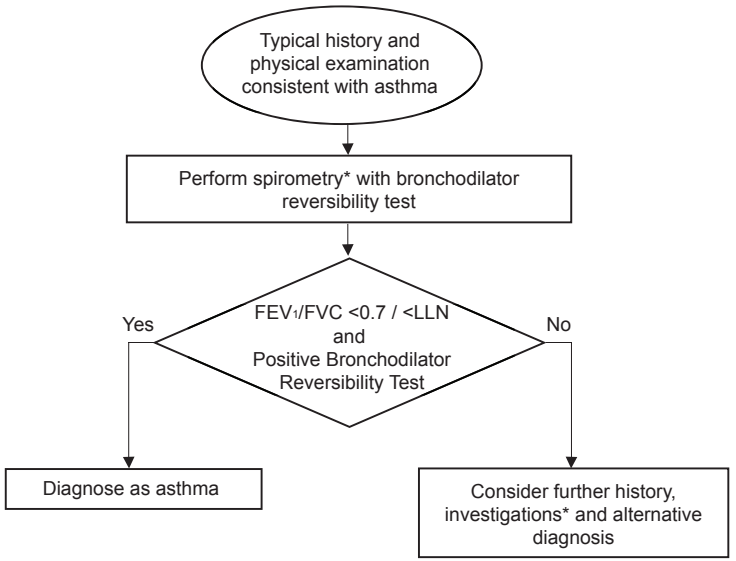
Table 3: Investigations for Asthma

Investigation	Description
Demonstration of airway obstruction	
Spirometry	A FEV_1/FVC <0.7 or <lower limit normal (LLN)
Demonstration of airway obstruction variability or reversibility	
Spirometry	An improvement in FEV_1 or FVC ≥12% AND ≥200 ml following bronchodilator treatment
	An improvement in FEV_1 or FVC ≥12% AND ≥200 ml from baseline after four weeks on ICS
Peak Expiratory Flow Rate (PEFR)	A ≥20% improvement in PEFR following bronchodilator treatment
	A ≥20% improvement in PEFR from baseline after four weeks on ICS
	Diurnal Variation • PEFR measured and recorded at least twice daily (morning and evening) over two weeks. • PEFR variability of ≥20% is suggestive of asthma. Refer to **Appendix 3** on **Peak Expiratory Flow Rate Variability** and **Appendix 4** on **Peak Expiratory Flow Normogram**.
Bronchoprovocation Test*	Methacholine challenge test • A PC20 value of ≤ 8 mg/ml is a positive test
	Mannitol challenge test • Decrease in FEV_1 of ≥15% from baseline at cumulative dose of ≤ 635 mg is a positive test
	Exercise challenge test • Decrease in FEV_1 of ≥10% from baseline
Detection of T2-high inflammation	
Blood eosinophils	Threshold for blood eosinophils is ≥150 cells/μL or >4%
IgE**	Total serum IgE >100 kU/L
	Any allergen-specific IgE >0.35 kU/L
FeNO**	Elevated FeNO level (≥50 ppb)

*Not routinely performed in clinical practice
**To be performed when resources are available

Adapted:

1. Ministry of Health, Malaysia. Management of Asthma in Adults Putrajaya: MoH; 2017.
2. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2024. Updated May 2024 (Available at: www.ginasthma.org)
3. Scottish Intercollegiate Guidelines Network & British Thoracic Society. British Guideline on the Management of Asthma. SIGN-BTS;2019



*Refer to **Table 3**.

Figure 1: Diagnosis of Asthma in Treatment Naïve Patients

For patients who are on ICS treatment, improvement of symptoms supports an asthma diagnosis. For patients on treatment who do not show airflow variability, consider repeating spirometry after withholding bronchodilator [four hours for short-acting β2-agonists (SABA), 24 - 48 hours for long-acting β_2-agonists (LABA)] or during symptoms.

Recommendation 1

- Diagnosis of asthma should be made based on typical clinical history, physical examination and evidence of airway obstruction variability.
  - Spirometry is the preferred tool to demonstrate airway obstruction variability or reversibility.

4. GENERAL PRINCIPLES

4.1. Treatment Goals

The goals of asthma management encompass both long-term objectives and patient-centred considerations.[2]

- The asthma treatment goals include:
  - achieving optimal symptom control
  - minimising risk of future exacerbations
  - reducing treatment side effects
  - preventing persistent airflow limitation
  - lowering asthma-related mortality

  It is also essential to identify and incorporate patient's personal goals for asthma management into the care plan.

Effective asthma management requires a collaborative partnership between the patients and their healthcare teams. This partnership involves agreeing on management goals and following a cyclical process of ongoing assessment, treatment adjustment and review of responses as shown in **Figure 2**.

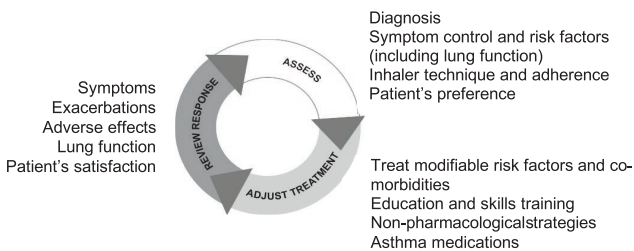


Figure 2: The Control-based Asthma Management Cycle

4.2. Initiating and Optimising Asthma Treatment

- The assessment of asthma control is mandatory before considering stepping up or down the treatment algorithm.
- Assessment of asthma should include:
  - symptom control by using a validated numerical test (e.g. ACT score), GINA or RCP questionnaire
  - future exacerbation risk
  - adherence to current therapy (insufficient use of ICS and over-reliance of SABA)
  - inhaler techniques
  - spirometry readings – FEV_1
  - FeNO (if available)
  - other medical co-morbidities e.g. allergic rhinitis, gastroesophageal reflux disease (GERD) etc.

Based on the reviewed evidence, the consensus of the CPG DG for the management of stable asthma are presented below.

Modifiable risk factors, poor adherence and incorrect inhaler techniques should be addressed and rectified prior to changing the current treatment plans. Once the assessment is completed, treatment can then be initiated (refer to **Algorithm 1**) or adjusted (refer to **Algorithm 2**). The choice of inhalers should be based on its availability, patient's preference, inhaler technique and shared decision making.

a. Treatment Initiation

The initiation of asthma treatment should be guided by the asthma control (severity and frequency of symptoms) and lung function.

For patients with well-controlled asthma (ACT score of ≥20 or 'NO' to all GINA questionnaire or RCP questionnaire) and normal lung function:

- prescribe a regular low-dose ICS and as-needed SABA as a reliever
- alternatively, as-needed ICS-formoterol or as-needed ICS-SABA (either as separate devices or a combined single device) may be prescribed

- Monotherapy with SABA is not recommended as its excessive use is associated with risk of asthma exacerbation and mortality.
  - Thus, it is vital to use ICS together with SABA or regimen without SABA [ICS-formoterol anti-inflammatory reliever (AIR)]

For patients with not well controlled asthma (ACT score of <20 or 'YES' to ≥1 GINA questionnaire or RCP questionnaire) with symptoms on most days OR night-time awakening of ≥1 night per week **OR** FEV_1 <80% of predicted or LLN, the followings are recommended.

- Prescribe either low-dose ICS-LABA or low-to-medium-dose ICS as maintenance therapy. In patients with concomitant allergic rhinitis, low-dose ICS with leukotriene receptor antagonists (LTRA) may be used.
- For reliever therapy, SABA or ICS-SABA may be used. If ICS-formoterol is used as maintenance, it can also be used as the reliever.

In those patients with not well controlled asthma (ACT score of <20 or 'YES' to ≥1 GINA questionnaire or RCP questionnaire) with daily symptoms **OR** night-time awakening of ≥1 night per week **AND** FEV_1 <80% of predicted or LLN, the followings are recommended.

- Prescribe medium-to-high-dose ICS-LABA as maintenance therapy.

- Alternatively, medium-dose ICS-LABA with add-on LAMA or LTRA (concomitant allergic rhinitis) may also be used as maintenance therapy.
- For reliever therapy, SABA or ICS-SABA may be used. If ICS-formoterol is used as maintenance, it can also be used as the reliever.

Patients on maintenance therapy, as per **Algorithm 1** on **Initiation of Asthma Treatment**, should be assessed for control at 3 - 6 months. If they are well controlled, current therapy could be continued or stepped down with regular assessments. If symptoms remain uncontrolled, management should be adjusted according to **Algorithm 2** on **Step Up and Step Down Options in Management of Stable Asthma**.

b. Treatment Step Up

Patients with initial asthma symptoms <2 per month and no risk factors for exacerbation should be prescribed on maintenance low-dose ICS [with as needed (PRN) SABA] **OR** PRN ICS-formoterol **OR** PRN ICS-SABA.

In patients who remain uncontrolled despite on low dose ICS (with PRN SABA) **OR** PRN ICS-formoterol **OR** PRN ICS-SABA, treatment may be stepped up to maintenance low-dose ICS-LABA **OR** medium-dose ICS.

In patients who remain uncontrolled despite on low-dose ICS-LABA **OR** medium-dose ICS, increasing ICS to high-dose is not recommended due to potential systemic adverse effects (AEs) which may occur with high doses and long-term use of ICS. Treatment may be stepped up to medium **OR** high-dose ICS-LABA

In patients who remain uncontrolled despite on medium **OR** high-dose ICS-LABA, a phenotypic assessment should be done. Treatment may be stepped up to either:

- medium-to-high-dose ICS-LABA with LAMA
- single inhaler high-dose ICS-LABA-LAMA if available

Early referral to respiratory physicians should be considered in patients with high-risk of exacerbation or has history of severe asthma exacerbation.

LTRA may be added to maintenance therapy if the patient has concurrent allergic rhinitis. Refer to **Subsection 6.2.1.b (iv)** on **LTRA** and **8.5.c** on **Allergic Rhinitis**.

Patients with persistent uncontrolled asthma despite on high-dose ICS-LABA-LAMA triple therapy should be referred to a respiratory physician and discuss within a multi-disciplinary team (MDT) for thorough evaluation and optimal treatment including consideration of

biologics use. Other add-on treatments e.g. low-dose azithromycin or oral corticosteroids (OCS) may be offered. An MDT for severe asthma typically includes chest physician, allergist, respiratory nurse, pharmacist and sometimes a psychologist or physiotherapist to provide comprehensive care and management.

The choice of reliever therapy depends on the patient's maintenance therapy. For those on ICS-formoterol, the preferred reliever is ICS-formoterol (maximum doses of 12 puffs/day) to avoid confusion and improve adherence. For those on ICS-LABA or ICS monotherapy as maintenance, the choice of reliever can be either SABA or ICS-SABA.

The treatment should be continued until reassessment at 3 - 6 months. Consider a short-term step up (for 1 - 2 weeks) with Asthma Action Plan (AAP) in situations with identifiable triggers e.g. during viral infection or allergen exposure.[3]

c. Treatment Step Down

If good asthma control is achieved at 3 - 6 months' re-assessment, consider stepping down treatment to find the lowest effective dose and minimal side effects. Choose an appropriate time for treatment step down (e.g. no respiratory infection, not travelling, not pregnant, etc.). Exercise caution before stepping down treatment in those with history of severe exacerbations. Ensure a follow-up for assessment of symptoms.

Recommendation 2

- The assessment of asthma control should be performed before considering stepping up or down the treatment algorithm.
- Short-acting β_2-agonist should always be taken together with inhaled corticosteroids.
- Treatment should be stepped up to achieve good asthma control.
- If good asthma control is achieved at 3 – 6 months re-assessment, consider stepping down treatment to find the lowest effective dose.

5. PATIENT EDUCATION AND SKILLS TRAINING

The main goal of education is to provide patients and their family/other carers with suitable information and training on asthma management in partnership with their healthcare providers.2 Patient education should include:

- asthma information
- guided self-management
- skills training on effective inhaler use
- adherence improvement

5.1. Asthma Information

The key topics of asthma information are provided in **Table 4**.

Table 4: Information to be Included in Asthma Education

Basic information about asthma
• Pathophysiology and symptoms • Recognising early signs of exacerbation • Treatment goal • Identifying and avoidance of asthma triggers • Impact of co-morbidities on asthma control
Pharmacotherapy
• The difference between reliever and maintenance • Dosages of medication • Information of inhalation devices and importance of correct inhaler technique • Possible drug adverse reactions
Non-pharmacotherapy
• Smoking cessation • Allergen exposure • Vaccination • Weight reduction • Pulmonary rehabilitation • Physical activity • Yoga • Breathing exercise • Dietary modifications • Vitamin D
Importance of adherence behaviours
• Medication adherence • Regular follow-up appointments

Limited asthma education, focusing solely on providing information, does not enhance health outcomes in adults with asthma unless complemented by other essential components.[3]

5.2. Guided Self-Management

Guided self-management is the active process by which healthcare providers guide and support patients to develop self-management competencies.

- It is essential for patients to understand their asthma, actively engage in shared decision-making and take charge of managing their condition.
- The components of guided asthma self-management include:
  - self-monitoring of symptoms and/or PEFR
  - AAP
  - regular medical review by healthcare providers

a. Self-monitoring of symptoms and/or PEF

Self-monitoring by either symptoms or PEF with regular medical review and an AAP has been shown to reduce both emergency department (ED) visits and hospitalisation rates compared with usual care in asthma.[3]

b. Asthma action plan

AAP contains action (decision) points which guide patients in making short-term adjustments to their treatment based on their symptoms and/or PEFR. Refer to **Appendix 5 on Asthma Action Plan**. The AAP should be completed and explained to the patient by the attending healthcare provider to ensure patients understand how to manage their asthma effectively.

Individualised AAP based on PEFR is equivalent to the plan based on symptoms in hospitalisation and ED visit.[3]

An effective AAP may contain two to four action points. In PEFR-based plans, personal best PEFR should be used for the action point. The treatment instruction should include reliever therapy, ICS and oral OCS.3 The best PEFR is the patient's known personal best under stable conditions i.e. not measured during an exacerbation. In patients without known personal best, the predicted value may be used. Refer to **Appendix 4 on Peak Expiratory Flow Nomogram**.

In an RCT on mild to moderate asthma patients, increasing a patient's ICS dose at the first sign of an exacerbation compared with maintaining stable dose of ICS showed no difference in the following outcomes:[4, level I]

- treatment failure (need for systemic corticosteroids)
- unscheduled physician visits
- unscheduled acute care, ED visit or hospital admission

However, in patients with poorer asthma control, an open label RCT found temporarily increasing ICS dose by four-fold prolonged the time to a first severe exacerbation with HR of 0.81 (95% CI 0.71 to 0.92) compared with stable dose group.[5, level I]

Increasing the dose of ICS does not benefit all patients during exacerbation. Patients are advised to seek further medical assistance if symptoms persist despite following the AAP.

c. Regular medical review by healthcare providers

Optimisation of asthma control by adjustment of medications may be conducted by either self-adjustment with the aid of an AAP or by regular medical review.[3] In a local cross-sectional study, 47.7% of patients were overprescribed with SABA, with 9% receiving prescriptions without appropriate assessment.[6, level III] Patients who are unable to manage their asthma using AAP will benefit from regular medical review.[2] Therefore, the CPG DG opines that regular medical reviews are preferred in local setting.

d. Strategies to implement guided self-management

Behaviour change techniques (BCTs) are methods used to facilitate the adoption of new desirable behaviours or the cessation of undesirable ones by targeting various psychological, social and environmental factors. BCTs can range from:

- providing information and education
- using rewards or incentives
- goal-setting
- social support
- cognitive-behavioural strategies

A network meta-analysis (NMA) found that BCTs were important elements to effective self-management. Low-intensity BCTs (≤1 per month) delivered by healthcare providers had the highest SUCRA values of 89.1% for hospitalizations and 84.2% for ED visits, suggesting they are the most likely to be effective compared to usual care.[7, level I]. Most primary studies used had an unclear risk of bias.

In an RCT on asthma patients >60 years old, tailoring interventions to screen and target specific self-management barriers compared with usual care significantly improved asthma control, medication adherence, inhaler technique and quality of life (QoL).[8, level I]

In local settings, BCTs have been shown to be useful in the management of asthma.

Recommendation 3
- Regular medical reviews in asthma patients are preferred over self-adjustment of medications aided by asthma action plan.
- Behavioural change techniques should be considered in self-management strategy of asthma.

5.3. Skills Training on Effective Use of Inhaler Device

The three main categories of inhalers are dry powder inhaler (DPI), pressurised metered-dose inhaler (pMDI) and soft-mist inhaler (SMI). They require different inhalation and operating techniques for effective use.

Inhaler technique errors are a common challenge faced by patients with asthma. Improper use can lead to inadequate medication delivery, resulting in poor asthma control and an increased risk of exacerbations.[9, level I; 10, level II-2]

Inhaler errors include failing to exhale completely to empty lungs before inhalation, not holding breath or holding it for less than 3 seconds, not tilting the head slightly back and improperly loading the dose before administering the second dose.[9, level I]

A cross-sectional study on asthma patients using pMDI found the following errors were associated with uncontrolled asthma:[10, level II-2]
- actuation before inhalation
- incorrect preparation of second dose inhalation
- exhaling into the inhaler device
- not holding the device upright

It also found that in patients using DPI, insufficient inspiratory effort was significantly associated with an increased likelihood of uncontrolled asthma and exacerbations.[10, level II-2]

The CPG DG opines that factors contributing to the above errors include lack of proper training, misunderstanding of inhaler instructions and complexity of multiple inhaler devices prescribed. Addressing these issues through education and training is essential to improve inhaler technique, enhance patient outcomes and ensure effective asthma management.

Refer to **Appendix 6** on **Inhaler Devices and Techniques**.

a. Principles of effective inhaler technique education

The following principles provide a framework for healthcare professionals to effectively educate patients on proper inhaler techniques.

- Training of healthcare professionals –
  - Healthcare professionals must be knowledgeable about inhalers including the correct technique and be able to identify any issues patients may have in using a device.[9, level I; 11, level I; 12, level I]
- Select appropriate inhaler device for the patients –
  - Consider patients' specific needs, preferences, ability to use the device correctly and availability of the device.[12, level I]
- Visual demonstration –
  - Physical and/or video demonstration by trained professionals to provide clear visual guidance of the correct inhaler technique.[13, level I; 9, level I; 12, level I]
- Teach-to-Goal (TTG) approach –
  - TTG involves cycles of demonstration and assessment of patients' inhaler techniques until they master the correct techniques. This ensures patients receive the necessary support and feedback to improve the techniques.[13, level I]
- Continuous monitoring and periodic reinforcement –
  - Regular reinforcement of inhalation instructions is necessary due to waning effect of the interventions over time.[12, level I]

b. Factors to consider when selecting an inhaler for a patient

A systematic review of nine published algorithms identified five key factors for device selection:[11, level I]

Ability to perform the required inspiratory manoeuvre

- Patients' ability to inhale –
  - slowly and deeply for pMDI and SMI
  - forcefully and deeply for DPI

  This ability depends on cognitive function and inspiratory muscle function. For patients with difficulty performing these manoeuvres and/or having cognitive impairment, a pMDI with a valved holding chamber (VHC) is recommended.

Ability to handle the device correctly

- Assess patients' ability to perform the steps of using the inhaler device, which depends on their manual dexterity and hand strength.

Sufficient inspiratory flow for DPI

- Assess inspiratory flow and effort to estimate the patient's ability to generate turbulent energy needed to disaggregate the powder into fine particles. For individuals with insufficient or suboptimal inspiratory flow and effort, a pMDI with VHC or SMI is recommended.

Availability of molecules in the device • It is important to consider which molecules are available in each type of device.
Continuity of the device • When the patients are using the inhaler correctly, it is advisable to choose the same device for any new therapy. • Using the same inhaler device for multiple-inhaler regimens improves clinical outcomes and reduced healthcare use in patients with asthma.[14, level I]
Environmental impact • The environmental impact of inhalers, including manufacturing and recycling, and pMDI propellants, should be considered when selecting devices.

5.4. Adherence Improvement

In general, adherence to inhalers in asthma is sub-optimal. This issue is common across all inhalers particularly in inhaled corticosteroids (ICS). Reliable and objective measures are needed to assess the adherence.[15, level III]

Patient-reported outcome instruments (PROs) are simple, timely and inexpensive tools that can be used in clinical practice. PROs that have been validated to assess adherence to inhaled maintenance medications in adults with asthma include:[16, level III]

- Test of Adherence to Inhalers (TAI)
- Medication Adherence Report Scale for Asthma
- Adherence Questionnaire

The 10-item TAI questionnaire has been translated into the Malay language and validated to assess inhalers adherence among Malaysian patients with asthma (refer to **Appendix 7**).[17, level III]

Records on prescribed medications from electronic health records can also be used to indirectly estimate adherence. Two of the most widely used adherence measures are the medication possession ratio and proportion of days covered.[18, level II-2]

The World Health Organization (WHO) distinguishes three types of non-adherence which are:[19, level I]

- erratic non-adherence – unintentional non-adherence due to sporadic forgetfulness (e.g. caused by a busy lifestyle)
- unwitting non-adherence – unintentional non-adherence, usually due to misunderstanding instructions or poor inhaler technique

- intelligent non-adherence – intentional non-adherence as a result of a reasoned decision to reject therapy which include lack of confidence in treatment, denial of diagnosis, embarrassment about using inhalers in social situations, peer-group pressures, concern about adverse effects and false beliefs that treatment can be stopped because symptoms have improved

Adherence improvement strategies matched to the type of non-adherence are shown below.[19, level I]

Types on non-adherence	Adherence improvement strategies
Erratic	**Reminders and/or counselling** • Caregiver support • Link to daily habits (e.g. brushing teeth) • Use daily reminders (e.g. alarm clock, text/audio/visual messages, smart inhaler) • Use motivational strategies to encourage continuous use to remain symptoms control • Discuss causes and frequency of anxiety (disease-related or not) and, counselling on coping strategies
Unwitting	**Medication plan** • Simplify medication regimen (frequency or number of devices) • Provide personalised AAP • Caregiver support – educating the caregivers on correct medication use **Inhaler technique education** • Provide written or visual inhaler instructions for home use • Physical and/or video demonstration with TTG approach
Intelligent	**Education and/or counselling** • Counselling on likelihood, severity and prevention of possible side effects • Educate on the chronic nature of the disease and long-term benefits of maintenance treatment • Apply motivational strategies for setting goals and managing expectations • Emphasise importance of following prescribed regimen for continuous effectiveness of medication • Educate on positive impact of medication use on daily life and work. • Engage in shared decision-making when selecting an inhaler

5.5. Patient Education Modality

Asthma education can be provided by any healthcare providers, including pharmacists and nurses.

In asthma patients, self-management support service provided by community pharmacists compared with usual care improved the following:[20, level I]

- symptom control (SMD=0.46, 95% CI 0.09 to 0.82)
- QoL (SMD=0.23, 95% CI 0.12 to 0.34)
- medication adherence (SMD=0.44, 95% CI 0.27 to 0.61)

In Malaysia, the Respiratory Medication Therapy Adherence Clinic (RMTAC) has been conducted by pharmacists in collaboration with other healthcare providers. This programme manages asthma by providing education, monitoring adherence and resolving medication-related problems.[3]

In a local study, compared with standard care, RMTAC significantly improved asthma control. After a 6-month intervention, 51.9% of subjects in the RMTAC group achieved well-controlled status compared with 20.9% of those in control group ($p<0.001$). The majority of RMTAC patients mastered good inhalation technique compared with control group (75.3% vs 31.9%, $p<0.001$).[21, level II-1]

Guided self-management provided by trained asthma educators in an RCT had been shown to improve patient outcomes compared with usual care in terms of:[22, level I]

- QoL based on AQLQ score (MD=0.52, 95% CI 0.19 to 0.83)
- asthma control based on ACQ score (MD= -0.68, 95% CI -0.99 to -0.38)
- asthma-related exacerbations:
  - mean number of moderate to severe exacerbations per patient (SMD= -0.25, 95%CI -0.47 to -0.03)
  - total number of exacerbations (RR=0.51, 95% CI 0.28 to 0.95)
- PEF (SMD=31.42, 95% CI 13.21 to 49.62)

6. STABLE ASTHMA

6.1. Assessment of Stable Asthma

Severity of stable asthma is categorised based on the level of treatment needed to control the symptoms. It can be categorised as below.[2]

Severity of asthma	Definition
Mild	Well controlled asthma on low-intensity treatment e.g. as needed low-dose ICS-formoterol or maintenance low-dose ICS plus as-needed SABA
Moderate	Well controlled asthma on low or medium dose ICS-LABA
Severe	Controlled asthma on high-dose ICS-LABA treatment that worsens when high-dose treatment is reduced OR Uncontrolled asthma despite adherence to maximal optimised high-dose ICS-LABA and management of contributory factors. Severe asthma is a subset type of difficult-to-treat asthma (refer to **Subchapter 8.1** for further explanation)

- In stable asthma, assessment of severity should be performed at every medical review especially before escalating (stepping-up) or de-escalating (stepping-down) treatment. The assessment should include:
  - assessment of asthma control using validated tools
  - identifying future exacerbation risk factors and co-morbidities
  - checking adherence, inhaler techniques and other treatment related issues e.g. adverse effects

a. Assessment of asthma control

The validated verified tools that can be used in assessment of asthma symptoms include Global Initiative for Asthma (GINA) Assessment (refer to **Table 5**), ACT (refer to **Appendix 8**), Asthma Control Questionnaire (ACQ) and the Royal College of Physicians '3 Questions' (RCP 3). The GINA Assessment is filled-up by the physicians while the rest are patient-reported tools. The choice of assessment tool should be the same at every medical review to ensure consistency in assessing asthma control.

The GINA questionnaire assesses symptom control based on frequency of daytime asthma symptoms, night waking, activity limitation and frequency of SABA reliever use.[2] It can be used as a quick screening tool in primary care setting to identify patients who need more detailed assessment.

Table 5: GINA Assessment of Asthma Control

In the past four weeks, has the patient had:	Yes	No	Well controlled	Partly controlled	Uncontrolled
Daytime asthma symptoms more than twice/week?			None of these	1 – 2 of these	3 – 4 of these
Any night waking due to asthma?					
SABA* reliever for symptoms more than twice/week?					
Any activity limitation due to asthma?					

*Based on SABA (as-needed ICS-formoterol reliever not included); excludes reliever taken before exercise

ACT is a validated and preferred objective assessment on degree of current control of asthma in adults for the past four weeks (refer to **Appendix 8**). The scores indicating asthma control are as follows:[2]

ACT Score	Asthma control
20 - 25	Well-controlled
16 - 19	Not well controlled
5 - 15	Very poorly controlled

Other symptom control assessment tools include the use of 5-item ACQ (ACQ-5), which is preferred over other versions primarily due to its simplicity.[2] The ACQ-5 includes five questions that focus on the core symptoms of asthma over the past one week:

- waking at night due to asthma
- waking in the morning with asthma symptoms
- activity limitation
- shortness of breath
- need for rescue inhaler use

Each question has a score from 0 to 6, with 0 indicating no symptoms and 6 indicating severe symptoms. The final score is the average of the five responses with lower scores reflecting better asthma control as shown below.

ACT Score	Asthma control
0 – 0.75	Well-controlled
0.75 – 1.50	Very poorly controlled
>1.50	Not well controlled

The RCP 3 may be used as an initial screening tool of asthma control. It consists of three questions focused on recent sleep disturbances due to asthma, daytime symptoms and limitations in daily activities caused by the condition. Responding “Yes” to any of these questions indicates suboptimal asthma control.

Different asthma assessment tools have their own unique strengths and these should be considered when selecting the most appropriate tool for each patient. **Table 6** outlines the key features of each tool, helping healthcare professionals choose the best option based on the clinical context, patient needs and asthma severity.

Table 6: Comparison of Asthma Control Assessment Tools

	GINA Questionnaire	ACT	ACQ-5	RCP
Assessor	Physician	Patient self-administered	Patient self-administered	Patient self-administered
No. of items	4 items	5 items	5 items	3 items
Recall duration	4 weeks	4 weeks	1 weeks	4 weeks

Patients with well-controlled asthma for 3 - 6 months can be considered for de-escalation of treatment. Other factors that need to be assessed before making this decision include FEV_1 percentage predicted ≥80%, post-bronchodilatation FEV_1/FVC ≥70% and absence of asthma exacerbations in the last 12 months.[23, level III]

The reduction of FeNO levels following treatment with ICS can be used to monitor effectiveness of therapy and suppression of T2 inflammation. Persistent elevation of FeNO after initiation of ICS may indicate either poor adherence to ICS or inadequate ICS dosage.

b. Assessment of future exacerbation risks

Patients with well-controlled asthma can still be at risk for future exacerbations. By identifying modifiable risk factors and evaluating the frequency of past exacerbations, healthcare providers can tailor treatment plans to prevent future exacerbations. Screening for risk

factors of future exacerbations should be conducted at every medical review.

- Risk factors for future exacerbation include:
  - previous history of severe asthma exacerbation requiring systemic corticosteroids or hospitalisation within the past year
  - overuse of SABA (≥3 cannisters per year)
  - inadequate ICS use or not on ICS
  - poor adherence to maintenance therapy
  - incorrect inhaler technique
  - current smoker, e-cigarette or vape user
  - co-morbidities: obesity, GERD, chronic rhinosinusitis, confirmed food allergy
  - pregnancy
  - type-2 inflammatory markers: high FeNO, blood eosinophilia
  - lung function: low FEV_1 especially <60% predicted, high bronchodilator responsiveness

c. Assessment of treatment adherence, inhaler techniques and medication adverse effects

Effective patient compliance relies greatly on discussing treatment goals with patients and understanding patients' treatment preferences. Inhaler techniques should be demonstrated by patients and evaluated at every medical review to correct any improper use. Healthcare providers should take time to listen to patients' feedback and experiences with their inhalers and address any issues that arise.

Although asthma medications are generally safe, adverse effects must be assessed and addressed. For example, local side effects of ICS e.g. oral thrush and dysphonia can be managed by improving inhaler technique and rinsing the mouth after each use.[2]

Recommendation 4

- Assessment of asthma should include:
  - evaluating current asthma symptoms control using validated tools
  - identifying future exacerbation risk factors and co-morbidities
  - checking adherence, inhaler techniques and other treatment related issues

6.2. Treatment

The treatment strategy for asthma involves both pharmacological and non-pharmacological interventions to effectively manage symptoms, reduce risk of exacerbations and improve QoL.

6.2.1. Pharmacological treatment

Effective pharmacological treatment is essential in asthma management. This includes using reliever therapy for relief of symptoms and maintenance therapy to reduce inflammation. Treatment should be tailored to disease severity, patient's preferences and response.

a. Reliever therapy

Reliever therapy is taken as needed for quick relief of asthma symptoms. It includes SABAs, ICS-formoterol and ICS-SABA.

i. Short-acting β_2-agonists

There is limited new evidence on safety and effectiveness of SABA monotherapy. Regular SABA monotherapy is associated with decreased in bronchodilator response and, increased in airway hyperresponsiveness and airway inflammation. Excessive SABA monotherapy use (≥3 of 200-dose canisters a year) is associated with risk of asthma exacerbation and mortality.[2]

A local study also showed that patients prescribed with ≥3 canisters of SABA/year, either as monotherapy or combination, were more likely to have severe exacerbations (OR=2.04, 95% CI 1.44 to 2.89) and less likely to have controlled asthma (OR=0.42, 95% CI 0.27 to 0.67) compared with those with 1 – 2 canisters of SABA/year.[6, level III]

In chronic asthma, a combination of short-acting muscarinic antagonists (SAMA) and SABA does not offer any additional advantage.[3]

Oral SABA is not recommended due to its higher risk of side effects compared with inhaled SABA.[2]

ii. Anti-inflammatory reliever

Anti-inflammatory reliever (AIR) is a reliever inhaler that contains both a low-dose inhaled corticosteroids (ICS) and a fast-acting bronchodilator.[2]

A Cochrane systematic review of four RCTs on mild asthma showed that as needed single combined budesonide-formoterol inhaler reduced asthma-related hospital admission or emergency department/ urgent care visit (OR=0.63, 95% CI 0.44 to 0.91) compared with regular budesonide plus as needed SABA (salbutamol or terbutaline) at 52 weeks. There were NS differences in exacerbations requiring systemic corticosteroids and annual severe exacerbation rate. However, asthma control assessed by ACQ-5 favoured regular budesonide plus as needed SABA (MD=0.12, 95% CI 0.09 to 0.15) although it did not reach minimal clinically important difference (MCID) of 0.5 points. For secondary outcome, as needed single combined budesonide-formoterol inhaler had higher FeNO level at 52 weeks (geometric mean=1.13, 95% CI 1.06 to 1.20) indicating increased airway inflammation. Safety profile

showed NS differences in any/severe AEs or mortality.[24, level I] The quality of evidence for these outcomes were mixed based on GRADE.

An RCT on patients with uncontrolled moderate to severe asthma who were on ICS maintenance therapies compared as needed pMDI budesonide-salbutamol with salbutamol alone. It showed that risk of severe exacerbation was lower in high-dose budesonide-salbutamol 160/180 µg (HR=0.74, 95% CI 0.62 to 0.89) but NS difference in moderate dose budesonide-salbutamol 80/180 µg. The percentage of patients with any AEs was similar between the groups.[25, level I]

iii. Long-acting β_2-agonists

The inhaled rapid-onset LABA i.e. formoterol is as effective as SABA as a reliever medication in asthma, but its use without ICS is strongly discouraged because of the risk of fatal and non-fatal adverse events.3 This is supported by a recommendation in SIGN-BTS guidelines where LABA should only be started in patients who are already on ICS and the ICS should be continued.[26]

Recommendation 5

- In the treatment of asthma:
  - inhaled short-acting β_2-agonists (SABA) should not be used as monotherapy
  - inhaled SABA may be used as reliever therapy with regular inhaled corticosteroids (ICS)
  - inhaled SABA overuse (≥3 canisters/year) should be avoided
  - oral SABA should not be used
  - anti-inflammatory reliever (AIR) therapy (either ICS with formoterol or ICS with SABA) may be used as a reliever therapy
  - inhaled long-acting β_2-agonists (LABA) without ICS should not be used as reliever monotherapy

b. Maintenance therapy

Maintenance is defined as medication targeting both domains of asthma symptom control and prevention of future exacerbation risk. It is intended to be used on a regular basis, even when asthma symptoms are absent.

i. Inhaled corticosteroids

Regular daily low-dose ICS is indicated for asthma patients on as needed ICS and SABA who either are unable to adhere to treatment or remain symptomatic.

It significantly reduces asthma symptoms, risk of asthma-related exacerbations, hospitalisation and death. However, patients with mild

asthma often have poor adherence to ICS, resulting in them relying on SABA alone and thus increasing risk of exacerbations.[2]

ICS dosage can be categorised into low-, medium- or high-dose as shown in **Table 7**. Different ICS within the same category may differ in potency. Switching of ICS within a category may change the asthma control. Therefore, patients need to be monitored and ICS dose adjusted accordingly.

Systemic side effects may occur with high doses and long-term use of ICS. These include easy bruising, an increased risk of osteoporosis and fragility fractures beyond the usual age-related risks, cataracts, glaucoma, and adrenal suppression.[2]

ii. Combination of ICS and long-acting β_2-agonists

Regular daily ICS-LABA is indicated for asthma patients on regular daily low-dose ICS or as-needed ICS/formoterol who remain symptomatic despite good adherence and inhaler technique.

Combination of ICS-LABA is more effective in reducing risk of exacerbations compared with a higher dose of ICS alone in asthma with sub-optimal control on low-dose ICS monotherapy.[3]

Proactive regular dosing (PRD) is a treatment strategy where medication is taken at scheduled consistent interval. It also referred to as regular maintenance dosing. A local retrospective study on patients with uncontrolled asthma despite using either as-needed budesonide-formoterol or ICS and SABA PRN, PRD of fluticasone/salmeterol was shown as an effective and safe treatment approach. It significantly improved symptom control (mean ACT scores), and reduced hospitalisations and systemic corticosteroids use.[27, level III]

A recent Cochrane systematic review found no evidence on safety concerns that would affect the choice between salmeterol/ICS and formoterol/ICS combination inhalers used for regular maintenance therapy. GRADE assessment showed low to moderate certainty of the evidence.[28, level I]

A meta-analysis demonstrated that extra-fine hydrofluoroalkane (HFA)-beclomethasone-formoterol (BDP-F) showed NS difference compared with non-extrafine ICS-LABA in pulmonary function concerning central and peripheral airways, as well as in ACT scores and exacerbation rates. Risk of bias of primary papers was generally low.[29, level I]

iii. Maintenance and reliever therapy

Maintenance and Reliever Therapy (MART) is a treatment regimen involving the daily use of an ICS-formoterol (e.g. budesonide-formoterol

or beclomethasone diproprionate-formoterol) inhaler for asthma maintenance and as-needed for symptom relief.

An NMA on single inhaler as MART and other as-needed therapies in preventing the risk of severe asthma exacerbation found the following:[30, level I]

- in mild to moderate asthma patients –
  - low-dose MART and as-needed ICS-LABA were equally effective
  - low-dose MART was significantly more effective than ICS-LABA with as-needed SABA and ICS with as-needed SABA
- in moderate to severe asthma patients –
  - low-to-medium-dose MART and high-dose ICS-LABA with as-needed SABA were equally effective
  - low-to-medium-dose MART was significantly more effective than low-to-medium-dose ICS-LABA with as-needed SABA and ICS with as-needed SABA

NS differences were found across the treatments on risk of SAEs. Overall, the quality of evidence was moderate to high based on GRADE.

Table 7: Categorisation of ICS Doses (Alone or in Combination with LABA) into Low, Medium and High Levels

Inhaled corticosteroids (alone or in combination with LABA)	Total daily ICS dose (µg)		
	Low	Medium	High
Beclometasone dipropionate (pMDI, standard particle, HFA)	200 - 500	>500 - 1000	>1000
Beclometasone dipropionate (DPI or pMDI, extrafine particle, HFA)	100 - 200	>200 - 400	>400
Budesonide (DPI, or pMDI, standard particle, HFA)	200 - 400	>400 - 800	>800
Ciclesonide (pMDI, extrafine particle, HFA)	80 - 160	>160 - 320	>320
Fluticasone furoate (DPI)	100		200
Fluticasone propionate (DPI)	100 - 250	>250 - 500	>500
Fluticasone propionate (pMDI, standard particle, HFA)	100 - 250	>250 - 500	>500
Mometasone furoate (DPI)	Depends on DPI device - refer to product information		
Mometasone furoate (pMDI, standard particle, HFA)	200 - 400		>400

Source: Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2024. Updated May 2024 (Available at: www.ginasthma.org)

iv. Leukotriene receptor antagonists

Leukotriene receptor antagonists (LTRA) as monotherapy is less effective than ICS in terms of symptom control and lung function improvement,[3] as well as exacerbations.[2]

A Cochrane systematic review of patients with suboptimal asthma control on daily ICS found:[31, level I]

- addition of LTRAs compared with using the same dose of ICS alone reduced the risk of asthma exacerbations requiring rescue OCS (RR = 0.50, 95% CI 0.29 to 0.86) and, improved lung function and asthma control. There was no increase in AEs.
- combination therapy of LTRAs and ICS compared with a higher dose of ICS alone showed NS difference in the number of participants who experienced ≥1 exacerbations requiring OCS.

Overall, the quality of evidence was low to moderate based on GRADE.

According to various guidelines, LTRA is mentioned to be particularly useful in patients with allergic asthma.[2; 26]

It is essential to advise patients, parents, and caregivers about the potential neuropsychiatric adverse effects of montelukast including new-onset nightmares, behavioural changes, and, in some cases, suicidal ideation.[32]

v. Methylxanthine

Treatment with theophylline is no longer recommended as it has limited effectiveness and often causes side effects especially at higher doses which can be life-threatening.[2; 33]

A newer immediate-released methylxanthine, doxofylline, has been shown to have better effectiveness and fewer side-effects than theophylline as stated below.

An NMA comparing doxofylline, theophylline and placebo in adolescent and adult asthmatic patients found the following:[34, level I]

- doxofylline reduced the daily asthma events (RE= -0.33, 95% CrI -0.62 to -0.04) compared with placebo
- doxofylline was more effective than theophylline in reducing daily asthma events (MD= -0.14, 95% CI -0.27 to -0.00)
- doxofylline was safer than theophylline with lower risk of AEs (RE=0.53, 95% CrI 0.27 to 0.87)

The primary papers were of mixed quality.

In a pre-post multicentre study on adults with poorly controlled asthma, oral doxofylline 400 mg three times daily was effective and well-tolerated at 1-year follow-up based on:[35, level II-3]

- improvement in FEV_1 from baseline (+16.90% ± 1.81, p<0.001)
- reduced rate of asthma events (-0.57 events/day ± 0.18, p<0.05)

The most common AEs were nausea (14.56%), headache (14.24%), insomnia (10.68%) and dyspepsia (10.03%). They were mild or moderate in severity.

vi. Long-acting muscarinic antagonists

Long-acting muscarinic antagonists (LAMAs) may be considered as add-on therapy if asthma remains uncontrolled despite medium or high-dose ICS-LABA, either in separate inhaler (tiotropium) or in a combination ('triple') inhaler (beclomethasone-formoterol-glycopyrronium; mometasone-indacaterol-glycopyrronium; fluticasone furoate-vilanterol-umeclidinium).[2] The latter is currently not registered in Malaysia.

A meta-analysis on patients with moderate to severe asthma showed that triple therapy (ICS+LABA+LAMA) compared with medium-to-high dose dual therapy (ICS+LABA):[36, level I]

- reduced risk of severe exacerbation (RR=0.83, 95% CI 0.77 to 0.90)
- improved asthma control scores (SMD= -0.06 SD units, 95% CI -0.10 to -0.02)
- showed NS difference in asthma-related quality of life (QoL), all-cause mortality, treatment-related AEs and serious AEs
- increased dry mouth and dysphonia (RR=1.65, 95% CI 1.14 to 2.38).

Overall, the quality of evidence was moderate to high based on GRADE.

This is supported by another NMA on uncontrolled asthma patients comparing treatment of medium-dose or high-dose triple therapies and medium-dose ICS-LABA where the former reduced steroid-requiring asthma exacerbations (HR=0.84, 95% CrI 0.71 to 0.99 and HR=0.69, 95% CrI 0.58 to 0.82 respectively) but not asthma-related hospitalisations. Triple therapy resulted in NS difference in all-cause or asthma-related SAEs compared with the control.[37, level I]

A retrospective cohort study on asthma patients treated with ICS-LABA showed that adding tiotropium to ICS-LABA was more effective in reducing exacerbations compared with increasing the dose of ICS in ICS-LABA therapy (HR=0.65, 95% CI 0.43 to 0.99).[38, level II-2]

However, there is insufficient evidence to support substituting LAMA for LABA as add-on therapy for patients on ICS.[2; 3]

vii. Macrolides

Macrolides is an antibacterial with immunomodulatory properties which can reduce airway hyperactivity and eosinophilic inflammation.

A Cochrane systematic review of patients with chronic asthma comparing macrolides with placebo showed:[39, level I]

- reduced exacerbations requiring ED visits and/or treatment with systemic corticosteroids (RR=0.65, 95% CI 0.53 to 0.80)
- reduced symptoms (SMD= -0.46, 95% CI -0.81 to -0.11)
- NS difference in reduction of exacerbations requiring hospitalisations
- NS difference in severe AEs (including mortality)

GRADE assessment showed low to moderate certainty of the evidence.

Long-term macrolides should be part of a comprehensive asthma management plan tailored to individual patient needs. It should only be started after consultation with a specialist.

viii. Oral corticosteroids

The use of OCS at the minimum necessary dose and for the shortest time possible may be considered as a last resort for patients with severe asthma. Refer to **Subchapter 8.1** on **Severe Asthma**.

The Thoracic Society of Australia and New Zealand position paper recommends practicing OCS stewardship in asthma to minimise the use of OCS and mitigate the harm associated with its use.[40, level III]

ix. Sublingual immunotherapy

Sublingual immunotherapy (SLIT) involves administering allergen extracts, typically in tablet or liquid drops to desensitise and decrease sensitivity to specific allergen trigger in patients with allergy. The duration varies depending on the specific allergens targeted e.g. house dust mite (HDM) or grass pollen.

A systematic review of RCTs in well-managed mild-to-moderate allergic asthma patients showed that SLIT tablets targeting HDM were effective in reducing ICS dosage (MD=81 mg, 95% CI 27 to 136) while maintaining adequate asthma control.[41, level I] The primary papers used were of mixed quality based on ROB assessment.

In cases of allergic asthma, allergen immunotherapy is advised when there is clinical evidence of IgE-mediated sensitisation to common airborne allergens. It is recommended that allergen immunotherapy be administered by experienced specialists.[33]

The role of SLIT as therapeutic options for asthma is not yet clearly established in most guidelines.

Recommendation 6
- All asthma patients should be on inhaled corticosteroids (ICS)-containing therapy.
- Combination of ICS/long-acting β_2-agonist (LABA) is preferred to high-dose ICS during stepping-up of asthma treatment.
- In moderate to severe asthma, either low-to-medium-dose maintenance and reliever therapy (MART) or high-dose ICS/LABA plus as-needed SABA may be used.
- Triple therapy (ICS/LABA/long-acting muscarinic antagonist) should be used in patients with uncontrolled asthma despite treatment with medium-to-high-dose ICS/LABA.
- Theophylline should not be used for treatment of asthma.

Refer to **Appendix 9** on **Common Medications in Asthma**.

6.2.2. Non-pharmacological treatment

Non-pharmacological treatments for asthma include a range of interventions that complement pharmacological approaches. These methods focus on reducing symptoms and improving QoL through strategies e.g. smoking cessation, allergen avoidance, dietary modification, exercise and vitamin D supplementation.

a. Smoking cessation

Smokers have higher risk of adult-onset asthma compared with non-smokers.[3] Smoking in asthma affects airway inflammation, reduces response to corticosteroid therapy and is associated with poor disease control, decline in lung function, and increased healthcare utilisation.[2; 42, level III]

Asthma patients who smoke or vape should be strongly encouraged to quit at every clinic visit. They should be provided access to counselling and smoking cessation programmes. They should also be advised to avoid environmental smoke exposure.[2] For smoking cessation, refer to the Malaysian CPG on Treatment of Tobacco Use Disorder (Second Edition).

b. Vitamin D

Vitamin D has been suggested to improve asthma control in patients with vitamin D deficiency.[2; 43, level I; 44, level] , However, a Cochrane review found that vitamin D supplementation did not significantly reduce the risk of asthma exacerbations or improve overall asthma control in mild to moderate asthma.[45, level I] Most of the primary papers used had low risk of bias.

c. Physical activity

Physical activities improve cardiopulmonary effectiveness by improving oxygen consumption, maximum heart rate and work capacity. There is limited evidence that they cause significant airway narrowing and worsening of asthma symptoms. Therefore, they should be promoted as part of the general approach to improving lifestyle and rehabilitation in people with asthma.[26]

Patients with exercise-induced bronchoconstriction (EIB) may experience symptoms if their condition is not well-controlled. However, with proper treatment, they can exercise without triggering asthma symptoms and thus avoiding physical activity is not necessary.

There is no specific type of exercise recommended exclusively for individuals with asthma.[2] A cohort study in middle-aged adults showed that lighter physical activity 3-times per week reduced current asthma (asthma attacks, need for asthma medicine or wheezing in the past 12 months) by 56% (OR=0.44, 95% CI 0.22 to 0.89) compared with vigorous physical activity. It also showed that vigorous physical activity ≤1 hour per week reduced current asthma and asthma symptoms by 43% (OR=0.57, 95% CI 0.36 to 0.91) and 8% (OR=0.92, 95% CI 0.86 to 0.98) respectively.[46, level II-2] Swimming is well tolerated among young individuals with asthma and, has been associated with increased lung function and improved cardiopulmonary fitness.[2]

Encouraging regular physical activity is important to enhance cardiopulmonary fitness leading to improved asthma control and QoL. It should be incorporated into the overall strategy for lifestyle improvement and rehabilitation, with careful consideration of the potential for EIB.[2; 26]

d. Breathing exercise

Breathing exercise programmes, which may involve techniques taught by physiotherapists in person as well as through audiovisual resources, can be offered as a complementary approach to medication. It can reduce respiratory rate, decrease breathing volume, promote the use of abdominal and lateral chest muscles, encourage nasal breathing and facilitate relaxation.[47, level III] These programmes aim to reduce asthma symptoms and improve QoL.[26]

A multicentre RCT showed that breathing exercise added to usual care was better than usual care alone in improving QoL in asthma patients at six months as measured by mini-AQLQ (MD=0.35, 95% CI 0.07 to 0.62). This effect was maintained at 12 months (MD=0.38, 95% CI 0.12 to 0.65). There was no improvement in anxiety score and although there was improvement in depression score, it did not reach clinical significance. There was NS difference in asthma-related AEs.[48, level I]

Evidence has shown that breathing exercise can alleviate dyspnoea, reduce emotional stress and enhance QoL.[2; 47, level III] However, it does not reduce the risk of asthma exacerbations or has an impact on lung function.[2]

e. Yoga

Yoga, an ancient Indian practice that includes physical postures, breathing exercises, meditation and relaxation techniques, may offer benefits for pulmonary function tests, asthma control tests and health-related QoL in patients with asthma. A meta-analysis found that yoga added to standard care conducted over a period of 8 – 10 weeks when compared with standard care alone resulted in improvement of:[49, level I]

- PEFR (SMD=0.38, CI 0.18 to 0.58)
- FEV_1 (SMD=0.96, CI 0.77 to 1.14)
- FVC (SMD=0.35, CI 0.14 to 0.55)
- overall pulmonary function (SMD=0.41, CI 0.30 to 0.53)
- health-related QoL (SMD=0.26, CI 0.18 to 0.34)

GRADE assessment indicated generally moderate quality of evidence.

Yoga may be considered as a supplementary therapy or an alternative to other types of breathing exercises.[2]

f. Pulmonary Rehabilitation

Pulmonary rehabilitation is a comprehensive multifaceted patient assessment and personalised therapy. This includes supervised exercise training, educational sessions and behaviour modification strategies. The primary goal of pulmonary rehabilitation is to improve both the physical and psychological conditions and foster long-term adherence to health-promoting behaviours.

A Cochrane systematic review showed that a pulmonary rehabilitation programme, compared with usual care, for adults with asthma resulted in improvements on:[50, level I]

- exercise performance
  - percentage predicted maximal rate of oxygen consumption with MD of 14.88% (95% CI 9.66 to 20.10) at end-intervention and 10.37% (95% CI 1.6 to 22.34) at 12 months follow-up
  - peak oxygen uptake with MD of 3.63 ml/kg/min (95% CI 1.48 to 5.77) at end-intervention and 0.69 mL/kg/min (95% CI 4.79 to 3.42) at 9 – 12 months follow-up
- asthma control
  - Asthma Control Questionnaire Score with MD -0.50 (95% CI -0.80 to -0.20) at end-intervention

GRADE assessment indicated generally low quality of evidence.

Structured pulmonary rehabilitation programmes of 4 – 12 weeks have demonstrated effectiveness in enhancing functional exercise capacity

(6-minute walk) and QoL. Referral to a pulmonary rehabilitation programme, if available, has been recommended.[2, 26]

g. Dietary modifications

The GINA guidelines advocate the consumption of a diet high in fruits and vegetables as it can significantly reduce risk of lung function decline which lead to improved asthma control and reduce risk of exacerbations.[2]

Increased dietary sodium has been linked to geographical differences in asthma mortality with high sodium intake being associated with increased bronchial hyper-responsiveness. However, reducing salt intake cannot be recommended as a strategy for asthma management due to paucity of evidence.[26]

Omega-3 found in fish oils may reduce inflammation and lessen the severity of exacerbations. However, there is insufficient evidence to support the recommendation of fish oil supplementation for asthma treatment.[26]

h. Weight reduction

Weight loss interventions, including dietary and exercise programmes, should be recommended for overweight and obese adults with asthma to enhance asthma control.[26] Refer to **Subchapter 8.5 (a)** on **Obesity**.

i. Allergen exposure

Specific recommendations for managing allergic asthma should be made after confirming sensitisations to various allergens in a patient.[2] Implementing a combination of specific measures of multifaceted allergen avoidance to decrease allergen exposure results in improved clinical outcomes.[33; 26] Examples of effective strategies involve avoiding exposure to these allergens e.g. avoidance of outdoor activities when air quality is poor/air pollution, removing pets from the home for those allergic to animal dander and addressing dampness for mold at home.[2; 33; 26]

j. Vaccination

Vaccination plays a vital role in protecting individuals against respiratory infections. Influenza and pneumococcal vaccinations are commonly available.

In a meta-analysis on children and adults with asthma, influenza vaccination reduced influenza infections as well as asthma attacks that resulted in emergency department visits and/or hospitalisations. GRADE assessment indicated generally very low quality of evidence.[51, level I]

Patients with asthma are encouraged to receive influenza vaccination.[2] The Malaysian Society of Infectious Diseases and Chemotherapy recommends influenza vaccination in all persons aged ≥18 with one or more medical problems.[52]

There is inadequate evidence to recommend the routine use of pneumococcal vaccination in patients with asthma.[2; 3] However, in asthma patients who require maintenance corticosteroids or frequently repeated systemic corticosteroids, pneumococcal vaccination is recommended.[52]

GINA guidelines advocate vaccination in adults with asthma to follow local immunisation schedule including those for respiratory syncytial virus infection.[2]

k. Medication to be used with caution

- **Aspirin and non-steroidal anti-inflammatory drugs**

Aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) are generally not contraindicated in asthma unless there is a history of adverse reactions to these medications. Patients should be asked on any previous reactions to these agents. Where NSAIDs is indicated for other medical indications, a selective COX2 inhibitors (e.g. celecoxib or etoricoxib) and paracetamol may be used as an alternative.[2; 3]

- **β-blockers**

Non-selective β-blockers including eyedrops can exacerbate asthma symptoms by inducing bronchospasm. If indicated, initiation of oral or eyedrops β-blockers should be done with caution, on a case by case basis and under close monitoring. However, cardio-selective β-blockers are not absolutely contraindicated as it has not been shown to affect FEV_1 or asthma exacerbation in mild to moderate asthma.[2; 26; 3]

Recommendation 7

- Asthma patients who smoke or vape should be strongly encouraged to quit at every clinic visit.
- Regular physical activity should be encouraged in asthma patients.
- Weight-loss interventions should be considered to improve asthma control.

7. ASTHMA EXACERBATION

Exacerbation of asthma is defined as progressive or sudden deterioration in baseline clinical status of a patient and characterised by worsening respiratory symptoms e.g. increased shortness of breath, wheezing, coughing and chest tightness.[2, 33] Exacerbations can be triggered by various factors e.g. respiratory infection, environmental pollutants or stress. Prompt recognition and treatment is important.[2]

7.1. Assessment

Assessment of an exacerbation involves a focused history and relevant physical examination with prompt initiation of treatment. A focused history should include time of onset, trigger factors, severity of symptoms, risk factors for asthma-related death, allergies and current asthma medications including doses, adherence pattern and response to treatment.[2; 3] Although the history should be detailed, it should not compromise the assessment and treatment.

The presence of any asthma-related death risk factors should be identified during exacerbations. **Table 8** shows the factors associated with increased risk of asthma-related deaths.

Table 8: Factors Associated with Increased Risk of Asthma-Related Deaths

Related to asthma exacerbation: • previous exacerbations requiring mechanical ventilation and intubation[2; 33] • frequency of hospitalisation or emergency visits in the past year [2; 33]
Related to asthma control: • currently using or having recently stopped using oral corticosteroids[2] • not currently using ICS[2] • poor adherence to ICS-containing medications[2] • over-use of SABAs[2; 33] • poor adherence to a written asthma action plan[2] • lack of a written asthma action plan[2]
Related to co-morbidity e.g. pneumonia, diabetes and arrhythmias[2; 33]
Others: • Psychological, psychiatric and social conditions that cause difficult treatment adherence.[2; 33] • Confirmed food allergy or anaphylaxis[2]

The physical examination includes vital signs assessment, evaluation of severity and, consideration of complications (e.g. pneumothorax) and differential diagnoses (e.g. heart failure). Chest X-ray (CXR) is not routinely indicated in all patients with asthma exacerbation. It should be considered in patients with atypical symptoms, suspected complications or diagnostic uncertainty in asthma management.

Symptoms, signs and lung function measurements (PEF/FEV_1) are used to classify asthma exacerbations into categories of mild, moderate, severe and life-threatening (refer to **Table 9**).[33] While PEF or FEV_1 are useful and valid measures of airway calibre, it may not be applicable to be used in acute asthma exacerbation. Treatment should be initiated immediately based on the severity of asthma exacerbation.

Table 9: Classification of Severity of Asthma Exacerbation

Clinical Parameters	Mild	Moderate	Severe	Life-threatening
Level of consciousness	Alert	Alert	Alert/confused/ drowsy	Confused/ drowsy/coma
Speech	Normal	Speaks in phrases	Speaks in words	Unable to speak
Respiratory rate	Normal/	>20/min	>25/min	<12/min
Pulse rate	<100/min	100 – 120/min	>120/min	Bradycardia/ cardiac arrest
Blood pressure	Normal	Normal	Normal/ hypotension	Hypotension
Use of accessory muscles	Absent	Present	Very evident	Paradoxical chest movement/ absent
Breath sounds	Wheezing	Wheezing	Wheezing	Silent chest
Oxygen saturation (SpO_2)	≥95%	90 – 95%	<90%	<90%
PaO2	Normal	<80 mmHg	<60 mmHg	< 60 mmHg
PaCO2	Normal	<40 mmHg	<40 mmHg or normal	>45 mmHg

Note: Not all parameters need to be met to classify the severity. Classify using the most severe parameters.

Adapted: Plaza Moral V, Alobid I, Álvarez Rodríguez C, et al. GEMA 5.3. Spanish Guideline on the Management of Asthma. Open Respir Arch. 2023;5(4):100277.

Recommendation 8
- Rapid clinical assessment of severity* should be performed for all asthma exacerbation.
- Treatment should be initiated immediately based on severity of asthma exacerbation.

*Refer to **Table 9**.

7.2. Treatment

i. Oxygen therapy

Patients with asthma exacerbation are often hypoxaemic and may require oxygen therapy. Oxygen saturation of ≥94% should be maintained in all hypoxic asthma patients.[3]

An RCT on severe asthma exacerbation complicated by respiratory failure showed that high flow nasal cannula (HFNC) led to significantly higher pO_2 and, lower heart rate and respiratory rate at 24 and 48 hours after admission compared with conventional oxygen therapy (COT). However, overall clinical response was NS between the two groups.[53, level I]

Another RCT on severe asthma exacerbation with hypoxaemia in the ED setting found that HFNC gave higher comfort scale (MD=3, 95% CI 2 to 4) and reduction in dyspnoea (MD=4.7, 95% CI 1.5 to 7.8) than COT.[54, level I]

Non-invasive ventilation (NIV) involves the delivery of oxygen into the lungs via positive pressure without the need for endotracheal intubation. In a retrospective cohort study on patients admitted to ICU with asthma exacerbation, NIV reduced the risk of intubation (OR=0.36, 95% CI 0.32 to 0.40) and in-hospital mortality (OR=0.48, 95% CI 0.40 to 0.58) compared with no NIV.[55, level II-2]

A cohort study of adults with asthma exacerbation-related hospitalisation found that history of 1 - 2 asthmatic exacerbation in the past 12 months was a strong independent predictor for requirement of invasive mechanical ventilation with OR of 3.12 (95% CI 1.19 to 8.21).[56, level II-2]

- Patients who are having life-threatening asthma exacerbations with signs of respiratory distress, worsening hypoxaemia, hypercapnia, altered mental status, or failure to respond to maximal medical therapy should be considered for early intubation and referral to critical care.

Recommendation 9
- Oxygen saturation of ≥94% should be maintained in all hypoxic asthma patients.
- In asthma exacerbation in emergency department, high flow nasal cannula should be considered over conventional oxygen therapy.

ii. β_2-Agonists

Inhaled β_2-agonists is the first-line treatment in asthma exacerbation.[2; 3] In mild to moderate asthma exacerbations, pressurised metered dose inhaler via spacer is the preferred method of delivery. In severe and life-threatening exacerbations, continuous delivery of nebulised oxygen-driven β_2-agonists should be used.[3]

There is no new evidence on the effectiveness and safety of nebulised β_2-agonists in acute asthma.

- Oral SABA should not be used in asthma exacerbation due to their systemic side effects.[3]
- pMDI with spacer should not be used in life-threatening asthma.[3]
- There is no current evidence supporting the routine use of parenteral β_2-agonists in patients with asthma exacerbation. It should only be reserved for ventilated patients or those with life-threatening asthma in critical care settings who do not respond to other treatments.[2; 3; 26; 33]

Recommendation 10
- In asthma exacerbation, inhaled β_2-agonist is the first-line treatment.
- Oral short-acting β_2-agonist (SABA) should not be used in asthma exacerbation.

iii. Ipratropium bromide

A Cochrane systematic review demonstrated that combined inhaled therapy (ipratropium bromide + SABA) was more effective than SABA alone in adult patients with asthma exacerbation presenting to ED in terms of:[57, level I]
- lower risk of hospitalisation (RR=0.72, 95% CI 0.59 to 0.87)
- improved FEV_1 (MD=0.25 L, 95% CI 0.02 to 0.48)
- improved PEF (MD=36.58 L/min, 95% CI 23.07 to 50.09) and higher percent improvement in PEF (MD=24.88%, 95% CI 14.83 to 34.93)

iv. Systemic corticosteroids

Systemic corticosteroids reduce inflammation, hasten resolution of exacerbations and prevent subsequent relapses in asthma. The

medication should always be administered as early as possible. This is important especially in patients not responding to initial treatment with SABA, develop exacerbation while on OCS or has history of previous exacerbations requiring OCS.[2]

The suggested daily dose of prednisolone ranges from 0.5 to 1 mg/kg of the ideal body weight with a maximum of 50 mg daily or 200 mg of intravenous hydrocortisone in divided doses. This dosage should be maintained for 5 to 7 days and can be stopped without gradual reduction.[2; 33]

Administration of corticosteroids by oral, intramuscular (IM) or IV route provides similar biological results, but oral route is less invasive and cheaper.[2] A Cochrane systematic review on acute asthma patients showed similar effectiveness between a single dose of IM corticosteroids and OCS prior to discharge of from ED in proportion of relapse and risk of AEs.[58, level I]

v. Inhaled corticosteroids

Asthma patients should continue their maintenance inhaled corticosteroids (via pMDI or DPI) when prescribed with systemic corticosteroids.[3]

A cross-sectional study showed that additional budesonide inhalation suspension to a combination of LABA and IV systemic corticosteroids reduced length of hospital stay (OR=2.99, 95% CI 1.11 to 8.06) and shortened recovery time from symptoms (OR=6.58, 95% CI 2.03 to 21.3).[59, level III]

However, in a meta-analysis, there was NS difference between ICS vs systemic corticosteroids in admission to hospital among adults with asthma exacerbation. The included evidence comprised of both ICS delivered through pMDI and nebuliser.[60, level I] Data was drawn from studies beyond the scope of the CPG.

There is insufficient evidence to support the use of nebulised corticosteroids in asthma exacerbation in emergency department.

Recommendation 11

- Systemic corticosteroids should be given in all patients with asthma exacerbation.
  - These patients should continue their maintenance inhaled corticosteroids.

vi. Magnesium sulphate

A single dose of IV magnesium sulphate has been recommended for severe and life-threatening asthma.[2; 26] In acute exacerbation of asthma not responding to initial treatments and have persistent hypoxaemia, a single 2 g infusion of the medication over 20 minutes reduces hospital admissions in patients with FEV_1 <25 – 30% predicted at presentation.[2] A single dose of IV magnesium sulphate is safe and may improve lung function and reduce intubation rates in patients with acute severe asthma.[26]

There is no retrievable evidence of benefit from repeated dosing of magnesium sulphate in asthma exacerbation. Repeated doses could cause hypermagnesemia with muscle weakness and respiratory fatigue.[26]

Nebulised magnesium sulphate is not recommended for treatment in adults with acute asthma. Its addition to nebulised β2-agonist (with or without nebulised ipratropium) provides no benefit in terms of lung function or need for hospital admission.[26]

Recommendation 12

- A single dose of 2 g intravenous magnesium sulphate infusion over 20 minutes should be considered in acute severe and life-threatening asthma.

vii. Aminophylline

IV aminophylline has limited effectiveness apart from unfavourable AEs compared with standard therapy. Therefore, it should not be routinely used in asthma exacerbation. Consultation with a senior physician is advisable if its use is required.[3]

7.3. Monitoring and Evaluation

Monitoring and evaluation of severity of asthma exacerbation include mental status, vital signs and clinical examination. Restlessness is an early sign of hypoxia. It is essential to closely monitor patients and adjust their treatment as needed.

Oxygen saturation levels of <90% indicates the need for aggressive management. Saturation should be assessed before oxygen is commenced or five minutes after oxygen is removed or when saturation stabilises.[2]

Arterial blood gas (ABG) measurement is not routinely required. It should be considered for patients with PEFR <50% or those who do

not respond to initial treatment or are deteriorating. A PaO2<60 mmHg and a normal or increased $PaCO_2$ (especially >45 mmHg) indicates respiratory failure. Chest X-ray should be considered in patients who do not respond to treatment or if an alternative diagnosis or complication e.g. pneumothorax, pneumomediastinum or pneumonia is suspected.[2]

- The CPG DG opines that patients with severe or life-threatening asthma exacerbation should be monitored frequently to assess their response to treatment and ensure they do not deteriorate. Monitoring includes:
  - Vital signs - Monitor continuously or at least every 15 – 30 minutes, including SpO_2, respiratory rate, heart rate and blood pressure.
  - Mental status - Monitor for any signs of lethargy, restlessness or other changes indicating hypoxia or hypercapnia, or confusion.
  - Auscultation - Regularly check for changes in breath sounds, rhonchi or silent chest.
  - ABG - Monitor hypercapnia or hypoxaemia. A rising or normal PaCO2 may indicate impending respiratory arrest.

The specific frequency of monitoring might vary based on the severity of the exacerbation, response to treatment, and institutional protocols. Patients with severe exacerbations often require close, continuous observation until they stabilize.

Recommendation 13
- Monitoring and evaluation of severity of asthma exacerbation should include mental status, vital signs and respiratory assessment.
- In severe and life-threatening asthma arterial blood gases should be done

7.4. Criteria for Admission

All patients with progressive deterioration following initial treatment and those with severe or life-threatening asthma should be admitted.[2] Other factors that may be considered for admission are:
- older age[2]
- use of more than eight SABA puffs in previous 24 hours[2]
- past history of severe exacerbations (e.g. intubations, asthma admissions)[2]
- past history of unscheduled clinic and emergency department visits requiring use of OCS[2]
- living alone/socially isolated[3]
- psychological problems[3]
- physical disability[3]

Patients with asthma exacerbation who respond poorly to optimal treatment and are at-risk of respiratory failure should be considered for early referral to critical care team.[3]

7.5. Criteria for Discharge

There are no specific parameters that assure safe discharge of patients with exacerbation.[33] The decision is usually the result of the doctor's clinical observation of the patient's condition. Patients may be discharged from hospital if they can follow their prescribed treatment at home, have few symptoms or need less reliever medications.

Arrangements should be made for a follow-up appointment prior to discharge from the emergency department. Additionally, it is important to discuss strategies to improve asthma management, including medications adherence, proper inhaler techniques and an asthma action plan.[2] The follow-up plan should include a referral letter to a clinic for the patient to be seen within seven days.

Recommendation 14

- All patients with severe, life-threatening asthma should be admitted.
- Early referral to critical care team should be considered for patients with asthma exacerbation who respond poorly to optimal treatment.
- Patients with asthma may be discharged with asthma action plan if they:
  - have resolution of symptoms after treatment and
  - are able to follow their prescribed treatment at home
- Following asthma exacerbation, all patients should be given a follow-up plan upon discharge.

8. SPECIAL GROUPS

8.1. Severe Asthma

Severe asthma affects about 5 - 10% of asthma patients. These patients experience poor QoL, increased morbidity and mortality, and increased healthcare utilisation. Up to 40% of these patients rely on maintenance or frequent use of systemic corticosteroids which leads to serious AEs.

Asthma is heterogeneous, with various clinical phenotypes driven by complex biologic endotypes including type-2 (T2) high, T2 low and mixed endotypes. Patients with severe asthma should be evaluated by the respiratory physicians, discussed in MDTs and be considered for biologic therapy to improve outcomes.

In managing severe asthma, it is crucial to understand the definition of difficult-to-treat and severe asthma as follows:

Classification	Criteria
Uncontrolled asthma	Includes one or both of the following: • poor symptom control in the past four weeks (≥3 of the following) - daytime asthma symptoms more than twice/ week - reliever use more than twice/week - activity limitation due to asthma - night waking due to asthma • frequent exacerbations* - ≥2/year requiring OCS and/or - serious exacerbations (≥1/year) requiring hospitalisation
Difficult-to-treat asthma	Defined by any of the following: • uncontrolled asthma despite medium- or high-dose ICS with a second maintenance (usually LABA) or maintenance OCS • requires high-dose treatment to maintain good symptom control and reduce exacerbation risk The condition may be influenced by modifiable factors: • incorrect inhaler technique • poor adherence • smoking • co-morbidities It may be due to an incorrect diagnosis or asthma mimickers e.g. vocal cord dysfunction or COPD

Severe asthma	A subset type of difficult-to-treat asthma. It is characterised either by: • uncontrolled asthma despite adherence to maximal optimised high-dose ICS-LABA and management of contributory factors OR • worsening asthma control when high-dose treatment** is reduced Inhaler technique and other modifiable factors should be addressed before considering the diagnosis of severe asthma.

* also consider frequent nebuliser use in the local settings
**medium- or high-dose ICS with a second controller or maintenance OCS

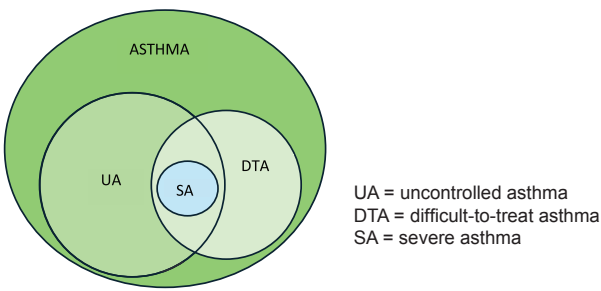


Figure 3: Relationship of asthma, uncontrolled asthma, difficult to treat asthma and severe asthma.

The above figure shows different asthma types with overlapping circles indicating shared features.

a. Risk Factors

Several risk factors can contribute to the development of severe asthma. A large cohort study on asthma patients found the following were significantly more prevalent in severe asthma than non-severe asthma:[61, level II-2]

- incompletely reversible airflow limitation
- being prone to exacerbation
- neutrophilic airway inflammation
- obesity
- vocal cord dysfunction
- obstructive sleep apnoea
- depression

- systemic inflammation
- gastrooesophageal reflux disease
- inhaler device polypharmacy
- Aspergillus sensitisation

Identifying and addressing these risk factors through early intervention, comprehensive asthma management strategies, patient education and multidisciplinary care can help reduce the risk of developing severe asthma and improve overall asthma outcomes.

T2 inflammation is present in 95% of patients with severe asthma and can be readily identified using biomarkers. It reflects the underlying pathobiology of asthma, which is directly involved in the causal pathway of asthma exacerbations. It also represents actionable targets for anti-inflammatory therapy, including ICS, OCS and biologics. An RCT demonstrated that the use of composite biomarkers of T2 inflammation is important and may support biomarker-adjusted steroid reduction.[62, level I]

b. Treatment

i. Systemic corticosteroids

Long-term treatment with OCS has been recognised as adjunct therapy in uncontrolled asthma. Systemic corticosteroids are considered the last therapeutic option and should be used at the lowest effective dose and for the shortest duration possible.[2; 33]

Exposure to both long-term and repeated acute courses of systemic corticosteroids (>4 courses of OCS in a lifetime) is associated with a high risk of serious AEs e.g. osteoporosis, fracture, pneumonia, heart failure, cardio-/cerebrovascular disease, type 2 diabetes mellitus, depression/ anxiety, cataract, renal impairment and weight gain, especially when prescribed onto a background of other corticosteroids.[63, level III; 64, level II-2]

ii. Biologics

Biologics are add-on treatments for severe asthma after optimising therapy. Phenotype assessment is mandatory prior to biologics selection. Currently, the approved biologics are anti-IgE (omalizumab), anti-IL5/5R (mepolizumab, reslizumab, benralizumab), anti-IL4Rα (dupilumab) and anti-Thymic Stromal Lymphopoietin (tezepelumab).

A recent local Health Technology Assessment showed mepolizumab, benralizumab, dupilumab and tezepelumab significantly reduced the exacerbations and hospitalisation/ED visit, improved lung function, asthma control and QoL, and reduced the use of oral corticosteroids especially among patients with high level of BEC (≥300 cells/μL) and unresponsive to the optimal therapy with acceptable safety profile.[65, level I]

A systematic review based on real-world evidence on omalizumab as an add-on therapy in patients with uncontrolled moderate-to-severe allergic asthma showed it:[66, level II-3]

- improved lung function: FEV_1 improved by 12.4% after one year of omalizumab therapy, by 23%, 29% and 48% after 3, 4 and 9 years respectively.
- reduced corticosteroids use
  - 70.8% of patients either stopped corticosteroids or were able to reduce the dose of OCS by 40% or more after one year
  - 34% reduction in mean total annual quantity of OCS prescribed between the 12 months pre- and post-omalizumab initiation
  - all patients stopped OCS after four and nine years

The primary papers used were of fairly good quality.

A Cochrane systematic review showed that dupilumab (anti-IL4Rα) compared with placebo in moderate to severe asthma improved the following:[67, level I]

- FEV_1 at 12 weeks (MD=0.14, 95% CI 0.11 to 0.16) and 24 weeks (MD=0.13, 95% CI 0.11 to 0.16)
- ACQ score at 12 weeks (MD= -0.74, 95% CI -1.20 to -0.28) and 24 weeks (MD= -0.43, 95% CI -0.67 to -0.19)
- FeNO at 12 weeks (MD= -17.58, 95% CI -21.87 to -13.29) and 24 weeks (MD= -19.50, 95% CI -24.74 to -14.25)
- immunoglobulin E level at 12 weeks (MD= -149.27, 95% CI -176.39 to -122.16) and 24 weeks (MD= -210.28, 95% CI -365.02 to -55.55)

However, it was associated with increased blood eosinophils at 12 and 24 weeks. There was NS difference in most adverse events. All primary papers were of low risk of bias.

Another Cochrane systematic review supported the use of anti-IL5/5R treatments as an adjunct to standard care in people with severe eosinophilic asthma and poor symptom as they reduced the rates of 'clinically significant' asthma exacerbation except for SC reslizumab:[68, level I]

- mepolizumab (anti-IL5) SC with RR=0.45 (95% CI 0.36 to 0.55
- mepolizumab IV with RR=0.53 (95% CI 0.44 to 0.64)
- reslizumab (anti-IL5) IV with RR=0.43 (95% CI 0.33 to 0.55)
- benralizumab (anti-IL5R) SC with RR=0.59 (95% CI 0.52 to 0.66)

There is limited evidence for improved health-related quality of life (HRQoL) scores and lung function, which may not meet clinically detectable levels. There were no excess serious adverse events with any anti-IL5/5R treatments. The majority of primary papers had low risk of bias.

A third Cochrane systematic review assessing the use anti-IL-13 or anti-IL-4 agents in patients with asthma showed:[69, level I]

- lower rate of exacerbations requiring hospitalisation or emergency department (ED) visit with tralokinumab vs placebo (RR=0.68, 95% CI 0.47 to 0.98)
- improved in adjusted asthma quality of life questionnaire score with anti-IL-13/-4 vs placebo (MD=0.18 units, 95% CI 0.12 to 0.24); however, it was not a clinically relevant improvement
- NS difference in all-cause serious AEs between interleukin-13/-4 agents and placebo

Factors to consider for biologics therapy include age, number of exacerbations in previous year, regular OCS use, asthma control, QoL, lung function, biomarkers (blood eosinophil count, FeNO and, serum total and allergen-specific IgE) and co-morbidities (e.g. nasal polyposis, atopic dermatitis) along with cost. A guide to targeted biologics selection is shown in **Appendix 10**.

iii. Macrolides

The addition of azithromycin in severe asthma patients, particularly those with eosinophilic phenotype, had been demonstrated to reduce exacerbations compared with placebo (overall: IRR=0.61, 95% CI 0.49 to 0.78; eosinophilic phenotype: IRR=0.63, 95% CI 0.44 to 0.92). However, its addition to the treatment regimen of severe asthma patients already receiving OCS showed no additional benefit.[70, level I]

A meta-analysis of five RCTs on uncontrolled asthma patients showed an improvement in FEV1 with the use of azithromycin compared with placebo (MD=0.06, 95% CI 0.01 to 0.12). However, no significant reduction in exacerbations was observed. This data was derived from three trials, which varied in dosage and duration from 12 weeks to 48 weeks.[71, level I] Primary papers of mixed quality were included.

For non-T2 asthma, treatment with azithromycin, bronchial thermoplasty or systemic glucocorticoids may be considered as treatment options.[33]

The CPG DG recommends the following:

- dosing of azithromycin for asthma is 500 mg per dose, 3 times per week or 250 mg daily
- up to one-year duration of azithromycin therapy

However, some patients may require a longer course of therapy based on specialist care. Prior to initiating the therapy, it is essential to investigate for potential non-tuberculous mycobacterial infection. In cases with long QTc medications or risk factors for hearing loss, an ECG and/or an audiogram should be considered.

Recommendation 15
- Biologics should be considered as add-on treatment for severe asthma after optimising therapy. Phenotype assessment should be conducted prior to this.
- Long-term oral corticosteroids should be reserved for severe asthma when no alternative treatments are available. They should be tapered off or to the lowest effective dose with side effects closely monitored.
- Azithromycin may be considered as an add-on treatment in asthma patients who remained uncontrolled on high-dose inhaled corticosteroids.

8.2. Pregnancy and Breastfeeding

During pregnancy, asthma may worsen, improve or remain unchanged. However, in patients with pre-existing severe asthma, the asthma control is more likely to worsen during pregnancy.[3]

a. Diagnosis

Diagnosis of asthma in pregnancy is made similar to non-pregnant woman.[3] However, bronchoprovocation tests are contraindicated.[2] In patients where clinical history is consistent with asthma and no alternative diagnosis is found, asthma treatment may be initiated and the confirmatory diagnostic investigations can be postponed until after delivery.[2]

b. Assessment and monitoring

A cross-sectional study on asthma in pregnancy showed that both GINA classification and ACT had significant association with spirometry values (FEV_1 and FVC) indicating that these tools can be effectively used to assess asthma control.[72, level III]

Two RCTs on pregnant asthma patients showed that FeNO was useful in guiding treatment and identifying the need of ICS (p=0.0002). FeNO-guided treatment demonstrated significantly better ACQ score and reduction in exacerbation rate compared with non-FeNO guided treatment.[73, level I; 74, level I] However, in a recent larger RCT found that FeNO-guided treatment in pregnant woman did not show any significant difference in perinatal outcomes or exacerbations compared with non-FeNO guided treatment.[75, level I]

During pregnancy, patients with asthma should be monitored every 4 to 6 weeks.[2; 3]

c. Treatment

Treatment of asthma during pregnancy provides more benefits than the potential risks associated with commonly used asthma medications.[2]

The treatment of asthma in pregnancy is the same as in non-pregnant patients as listed below.[2; 26; 3]

- ICS is safe and remains the preferred long-term maintenance and should be continued.
- Inhaled β_2-agonists and LTRA are safe and should be continued.
- Step-down treatment should be deferred until after delivery.
- Biologics for asthma should be considered only when benefits outweigh risks after consultation with a specialist.

Pregnant women are particularly susceptible to asthma exacerbation especially during the second trimester. Poor symptom control and exacerbations are associated with worse outcomes for both mother and foetus including an increased risk of pre-eclampsia, pre-term delivery, low birth weight and perinatal mortality.[2]

The treatment of asthma exacerbations is the same as in non-pregnant patients.[2; 26; 3]

- Prompt treatment with bronchodilators, oxygen and systemic corticosteroids is needed to avoid foetal hypoxia.
- Magnesium sulphate can be administered if indicated.
- Oxygen saturation should be maintained between 94 and 98%.
- Continuous foetal monitoring should be considered.
- Early referral to critical care is recommended for moderate to severe asthma exacerbations.

During labour, asthma treatment remains the same.[2; 26]

- The maintenance inhaler should be continued with reliever used as needed.
- For patients requiring anaesthesia, regional blockade is preferred.
- In patients who are on prednisolone exceeding 7.5 mg/day for more than 2 weeks prior to delivery, IV hydrocortisone 100 mg every 6 to 8 hours should be administered during labour to prevent adrenal insufficiency.
- Prostaglandin F2α should be used with caution due to the risk of bronchoconstriction.

Asthma patients should be encouraged to breastfeed and their asthma medications should be continued during lactation.[26]

Recommendation 16
- Pregnant asthma patients should be treated the same as non-pregnant patients, both during stable state and exacerbation.
- Inhaled corticosteroids-containing therapy should be initiated in pregnant asthma patients and continued if already being used.
- Stepping-down of asthma treatment in pregnancy should be delayed until after delivery.

8.3. Occupational Asthma

Occupational asthma (OA) is a form of work-related asthma caused by specific workplace exposures and triggered by immunologic or non-immunologic airborne stimuli present in the workplace.[76] Workplace exposures account for an estimated 5 – 20% of new cases of adult onset asthma.[2] Patients with pre-existing asthma or new adult-onset asthma whose symptoms worsen due to non-specific factors in the workplace are considered to have work-aggravated asthma and not OA.[76]

a. Risk factors

Over 400 causes of OA have been described. Individual susceptibility and level of workplace allergen exposure are key risk factors for developing OA.[76]

In a systematic review, a cross-sectional study showed that inhalable particulate dust was a risk factor for occupational asthma. A cohort study identified atopy to be a predictive risk of occupational asthma.[77, level III]

Common occupational groups and workplace agents identified to be at risk for OA are shown in **Table 10**.[76]

Table 10: Frequently Reported Causes of Occupational Asthma

Occupational Groups		
- Animal handlers	- Farm workers	- Plastics/rubber workers
- Bakers	- Food processors	- Storage workers
- Carpenters	- Forestry workers	- Textile workers
- Chemical workers	- Hairdressers	- Waiters
- Cleaners	- Laboratory technicians	- Welders
- Dental workers	- Metal workers	
- Electrical/electronic production workers	- Painters	

Workplace Agents		
- Animal's and insects' protein (animal dander, urine, saliva, serum proteins) - Chemicals and solvents (aldehydes, acids and alkalis)	- Colophony and fluxes - Drugs (antibiotics, others) - Dyes (used in textile) - Henna and persulphates - Isocyanates	- Metals (e.g. chromium, cobalt, nickel, zinc) - Plant protein (flour and grain dust, latex) - Wood dust

- Patients with OA exhibit typical asthma symptoms and are often employed in high-risk occupations. They experience a significant improvement in symptoms when away from work or on vacation.

b. Diagnosis and assessment

The diagnosis of OA is based on recognising characteristic symptoms and ruling out other possible explanations. A detailed occupational history should cover the nature of the patient's work, possible exposure to irritants, patterns of symptoms in relation to work and presence of improvement in symptoms on days off work.

- All working-age adults with new or worsening asthma symptoms, reappearance of childhood asthma or unexplained airflow obstruction should be asked about their occupation.

PEFR is an important tool in diagnosing and monitoring OA. An objective diagnosis of OA should be made using serial peak-flow measurements.[76]

- PEFR should be done as per **Appendix 3**.
- Minimum of four readings should be recorded per day, preferably before taking bronchodilator.
- The readings should be done two hours apart during waking hours.
- The duration of recording should be at least three weeks which ideally includes three series of workdays with three periods away from work.
- Work times, task exposures and medication should be recorded with timing specified.

A variability of ≥20% on workdays compared to off days is suggestive of work-related asthma.[3] Refer to **Appendix 11** on example of measurement.

Other diagnostic modalities for OA include specific IgE assays, skin prick tests for causative factors and specific inhalation challenge tests.[76]

c. Treatment

Early diagnosis and identification of occupational sensitisers, along with worker relocation or hazard substitution, are crucial aspects of OA management. Relocating away from exposure as soon as the diagnosis is confirmed, ideally within 12 months of experiencing the first work-related symptoms of asthma is recommended.[76]

A Cochrane systematic review on patients with OA showed that:[78, level II-1]

- removal from occupational exposure vs continued exposure resulted in –
  - increased likelihood of reporting absence of asthma symptoms (RR=4.80, 95% CI 1.67 to 13.86)
  - improved asthma symptoms (RR=2.47, 95% CI 1.26 to 4.84)
  - improvement in FEV_1 (MD=4.23, 95% CI 1.14 to 7.31)
  - improvement in non-specific bronchial hyperresponsiveness (SMD=0.43, 95% CI 0.03 to 0.82)
- reduced exposure vs continued exposure resulted in –
  - increased likelihood of reporting absence of symptoms (RR=2.65, 95% CI 1.24 to 5.68)
  - NS difference in FEV_1

- Patients with suspected OA should be referred to a specialist for further evaluation. Confirmed cases of OA should be notified using WEHU-L1 (JKKP7) form to the Department of Occupational Safety and Health.

Recommendation 17

- All working-age adults with new or worsening asthma symptoms, reappearance of childhood asthma or unexplained airflow obstruction should be asked about their occupation.
- Patients with suspected OA should be referred to a specialist for further evaluation and confirmed cases should be notified to the Department of Occupational Safety and Health.

8.4. Exercise-induced Bronchoconstriction

Exercise-induced bronchoconstriction (EIB) is defined as acute airway narrowing (which is transient and reversible) that occurs during or after exercise and can be observed in both patients who have and those who do not have chronic asthma.[79, level III]

Diagnosis of EIB in adults relies on typical clinical symptoms and demonstration of reversible airflow limitation, primarily through exercise or surrogate challenges.3 Diagnostic test involves measuring a post-exercise fall in FEV_1 of >10% measured 30 minutes after exercise cessation.[33] The recommended assessment for EIB is a decrease in FEV_1 post-challenge through exercise testing or indirect bronchoprovocation tests (e.g. mannitol challenge).[80]

Patients with well-controlled EIB can exercise safely with proper management. They are advised to perform gradual increase intensity of warm-up exercises before engaging in sports activities which can help reduce the severity of bronchoconstriction.[33] Patients can use SABA (in non-asthmatic EIB) or ICS-SABA or low-dose ICS-formoterol for reliever as needed, prior to exercise, with regular daily ICS regimen to help reduce EIB.[2] The recommendations on the use of LTRA in EIB are not consistent.[2; 26]

8.5. Asthma with Co-morbidities

Co-morbidity is a common problem in patients with asthma and associated with increased risk of AEs to treatment, poorer quality of life and increased healthcare utilisation compared with those without co-morbidities. Patients with multiple co-morbidities often have difficult-to-treat or severe asthma. Active management of co-morbidities is important to improve asthma control and asthma-related outcomes.

a. Obesity

Obesity is defined as BMI >27.5 kg/m^2.[81] Patients with asthma who are obese tend to have poor asthma control and do not respond well to standard asthma treatment. Thus, BMI should be recorded in all asthma patients.[2]

The treatment of obese asthma patients is no different from that of other asthma patients. ICS remains the mainstay of treatment. However, the response to ICS may be reduced due to activation of alternative pathways of inflammation (non-type-2 inflammation).[2]

Weight loss is important in managing these patients and should be advocated.[81] Weight reduction in obese adults with asthma improves symptoms, lung function, morbidity and health status.[26] A weight loss of at least 5% can lead to an improvement in FEV_1.[2; 81]

b. Obstructive sleep apnoea

The majority of obstructive sleep apnoea (OSA) patients are overweight but non-obese patients can also have OSA. For those who are obese, treatments are similar as outlined in the above section. Continuous positive airway pressure (CPAP) therapy is the recommended treatment

for OSA patients.[2; 82] CPAP therapy has been shown to reduce risk of asthma exacerbation.[2]

c. Allergic rhinitis

Most patients with asthma have allergic rhinitis while 10 – 40% of patients with allergic rhinitis have asthma.[3] Rhinitis is defined as irritation and inflammation of the mucous membranes of the nose and can be either allergic or non-allergic. Symptoms may vary with environmental and/or occupational exposure (e.g. furred pets, house dust mite, molds, pollens).[2] Intranasal corticosteroids is the most effective therapy for allergic rhinitis.26 LTRA as an add-on therapy can be beneficial in patients with concomitant seasonal allergic rhinitis and asthma.[3]

d. Chronic rhinosinusitis

Rhinosinusitis is defined as inflammation of the nose and paranasal sinuses and, characterised by more than two symptoms including nasal blockage/obstruction and/or nasal discharge (anterior/posterior nasal drip). Other symptoms may include facial pain/pressure and/or a reduction or loss of smell. Chronic rhinosinusitis (CRS) is defined when symptoms occur on most days for at least 12 weeks without complete resolution. It can be further classified into CRS with nasal polyps and without nasal polyps.[2]

CRS is associated with more severe asthma, especially in patients with nasal polyps. The treatment of CRS should follow the local guidelines.[83] The presence of nasal polyps may guide the selection of biologic treatment in severe asthma.[2]

e. Gastroesophageal reflux disease

GERD causes symptoms e.g. heartburn, epigastric or chest pain and dry cough. Patients with asthma are more likely to experience GERD compared with general population due to relaxation of lower sphincter caused by β_2-agonists. Treatment of GERD has no clear effect on symptoms, lung function or airway responsiveness. Proton-pump inhibitors has shown benefits in asthma patients with GERD who have symptomatic reflux and nocturnal respiratory symptoms.[2]

f. Anxiety and depression

Psychiatric co-morbidities e.g. anxiety and depression are linked to poor asthma control, reduced medication adherence and poor QoL. Patients with these co-morbidities have more frequent exacerbations and emergency department visits.[2] Referring to psychiatry services is important to aid proper assessment and effective management of these patients.

8.6. Asthma and COVID-19

Patients with asthma are not at increased risk of COVID-19. The risk of COVID-19-related death is only increased in patients with severe asthma or those on long-term OCS. During COVID-19 infection, patients with asthma should continue their ICS-containing medications.[2]

While nebulisers can transmit respiratory viral particles, most published literature was either inconclusive or did not substantiate a direct relationship between nebulised therapy and transmission of an infection. Therefore, if clinically indicated, nebuliser use should not be discouraged especially in life-threatening asthma and adherence to recommended safety measures should be emphasised.[84, level III]

The use of pMDI with spacer is an alternative to nebulisers. It should be either single patient use or autoclaved if manufacturer permits.[2] If a commercial spacer is not available or unaffordable, homemade or custom-made spacers e.g. plastic bottles may be used but should not be regarded as equivalent replacements due to their variable sizes, shapes and existing electrostatic charge on the devices' wall.[85]

A study evaluating the effectiveness of four accessory devices (homemade spacer, Dolphin spacer, DispozABLE paper spacer and AeroChamber Plus VHC) in delivering aerosolised drugs from a pMDI showed that homemade and Dolphin spacers had the lowest emitted dose fractions with large amounts of salbutamol remaining in these spacers ($p<0.05$) compared with the pMDI alone or the other accessory devices.[86, level III]

Asthma in patients with COVID-19 is treated similarly to those without COVID-19. During COVID-19 infection, patients with asthma should continue their ICS-containing medications. Potential interactions of COVID-19 and asthma medications should be assessed in particular ritonavir-boosted nirmatrelvir (paxlovid) with ICS-salmeterol or ICS-vilanterol which can cause increased cardiac toxicity of LABA.[2]

A cross-sectional study of patients who had recovered from COVID-19 (at least 7 days after COVID-19 infection) found that 1.5% of the patients were confirmed to have asthma. COVID-19 patients had higher odds of developing new-onset asthma (OR=4.55, 95% CI 1.29 to 17.89) with time between COVID-19 and asthma diagnosis ranged from 27 – 271 days. In the population who were confirmed asthma:[87, level III]

- most common clinical presentations were coughing (100%), sputum production (83.3%), wheezing (83.3%) and dyspnoea (50.0%)
- all patients had elevated blood eosinophils (291 – 1219 cells/μL) and four patients had increased FeNO (>20 ppb)

- all patients who were treated with medium or high-dose ICS and LABA with or without systemic corticosteroids had symptoms improvement

The Post-COVID-19 Management Protocol 2021 states that COVID-19 patients should be followed-up according to their COVID-19 category at 12 weeks after discharge. Symptomatic patients should have CXR and exertional test done. Patients with abnormalities should be referred for further management.[88]

9. REFERRAL

Asthma management can be challenging especially in cases where the condition is severe or complex. To ensure optimal patient care, timely referral to a respiratory physician or physicians experienced in asthma management is essential as they can offer advanced diagnostic and therapeutic strategies that go beyond standard care.

The indications for asthma referral include:

- difficulty in confirming the diagnosis of asthma
- severe or uncontrolled asthma
- severe or life-threatening asthma exacerbations
- asthma in pregnancy
- frequent unscheduled healthcare visits for exacerbations
- frequent bursts or ongoing use of OCS
- asthma with multiple co-morbidities
- asthma with concurrent food allergy or anaphylaxis
- suspected occupational asthma

10. IMPLEMENTING THE GUIDELINES

The management of asthma should be guided by an evidence-based approach, in order to provide quality care to the patients. Several factors may affect the implementation of recommendations in the CPG.

10.1. Facilitating and Limiting Factors

Existing facilitating factors for application of the recommendations in the CPG include:

- wide online dissemination of the CPG to healthcare providers nationwide
- regular respiratory scientific meetings/congress and trainings nationally where updates on asthma management are delivered
- Malaysian Thoracic Society Adults Severe Asthma Registry Steering Committee that oversees the programme on asthma and severe asthma registry
- Respiratory Pharmacy Protocol developed by the Clinical Pharmacy Working Committee (Respiratory Subspecialty) of MoH to optimise pharmacists' management of asthma in hospitals and clinics
- Asthma Malaysia website where reliable and credible information on asthma is provided to public
- World Asthma Day celebration and educational activities at various hospital level across country to raise awareness on asthma and its management
- Malaysian Thoracic Society Spirometry Certification Workshop, Inhaler Steering Committee

Existing barriers for application of the recommendations of the CPG are:

- insufficient knowledge on asthma diagnosis and its management among healthcare providers
- inadequate accessibility to asthma training at all levels of healthcare
- inadequate accessibility to diagnostic tools in asthma e.g. spirometry, etc.
- inadequate resources to manage asthma e.g. inhalers, biologics, sub-specialty clinic, etc.
- lack of proper subspecialty or post-basic training in respiratory medicine including asthma for allied healthcare
- lack of awareness, knowledge and understanding on asthma among patients and caregivers

10.2. Potential Resource Implications

The recommendations in this CPG require additional resources in terms of funds, healthcare infrastructures and human resources/expertise for their successful implementation as discussed below.

Training programmes for healthcare providers are needed to ensure they are equipped with the latest knowledge and skills in asthma management. These include ongoing education and certification programmes to keep healthcare providers updated on best practices and emerging treatments. Apart from that, educational resources in multiple languages and platforms should be made available and accessible to patients, caregivers and public. These will improve treatment adherence and asthma management which will prevent frequent and severe exacerbations.

In the diagnosis of asthma, spirometry is essential to confirm obstructive lung disease and reversibility. However, this vital tool is not readily available especially at primary care. On another note, inhalers are the primary method for delivering treatment for asthma. The issues related to the use of inhalers have been emphasised and addressed in length in this new edition of CPG. Numerous inhaler types are available in market to match different patients need. Unfortunately, these are not always accessible in healthcare facilities as well. These are dampened by commonly encounter incorrect inhaler techniques due to confusion and lack of training of the different devices in both patients and healthcare providers. It is important to emphasised that SABA inhalers are available without a prescription which allow patients to purchase them over-the-counter and this may lead to overreliance on SABA medications. Thus, healthcare providers should be educated on the harmful effects of SABA monotherapy which should be avoided in the clinical practice.

Biologics for treatment of severe asthma incurs a high cost and may not be accessible to many patients who may require them. This situation often leads to the need for long-term OCS and expose patients to risk to many AEs. There are also limited accessibility to specialised severe asthma clinics with trained personnel to manage these patients.

Several key performance indexes on asthma management being monitored by MOH is in line with the CPG recommendations. Thus, the following are proposed as clinical audit indicators for the CPG:

Percentage of newly diagnosed asthma patients who undergo spirometry for diagnosis = (Number of newly diagnosed asthma patients who undergo spirometry for diagnosis in a period / Number of newly diagnosed asthma patients in the same period) x100%

Target 80%

Percentage of adults with newly diagnosed asthma prescribed with inhaled ICS-containing therapy = (Number of adults with newly diagnosed asthma prescribed with inhaled ICS-containing therapy in a period / Number of adults with newly diagnosed asthma in the same period) x100%

Target 100%

Percentage of patients given a follow-up plan upon discharged following treatment for asthma exacerbations = (Number of patients given a follow-up plan upon discharged following treatment for asthma exacerbations in a period / Number of patients discharged following treatment for asthma exacerbations in the same period) x100%

Target 100%

Implementation strategies will be developed following the approval of the CPG by MoH which include Quick Reference and Training Module.

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Appendix 1

EXAMPLE OF SEARCH STRATEGY

Clinical Question: What are the effective and safe treatments for severe asthma?

Database: Ovid MEDLINE® ALL <1946 to February 28, 2023>
Search Strategy:

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1. ASTHMA/
2. asthma*.tw.
3. (asthma adj1 bronchial).tw.
4. 1 or 2 or 3
5. Uncontrol*.tw.
6. severe.tw.
7. difficult to treat.tw.
8. (poorly adj1 controlled).tw.
9. 5 or 6 or 7 or 8
10. 4 and 9
11. THERAPEUTICS/
12. therap*.tw.
13. treat*.tw.
14. 11 or 12 or 13
15. 10 and 14
16. limit 15 to (English language and humans and yr=”2017 -Current” and “all adult (19 plus years)”)
17. limit 16 to “systematic review”

Appendix 2

CLINICAL QUESTIONS

1. What are the risk factors of asthma in adults?
2. What are the diagnostic criteria of asthma in adults?
3. What are the treatment goals of asthma in adults?
4. What should be included in patient education for adults with asthma?
   - general information and modality of delivery
   - inhaler information and techniques
   - adherence improvement
   - self-management
   - self-monitoring
   - Asthma Action Plan
5. What is the accuracy of assessment tools in asthma in adults?
6. What are the criteria to step-up or step-down treatment for asthma in adults?
7. What are the effectiveness and safety of the following non-pharmacological interventions for asthma in adults:
   - smoking cessation
   - vaccination
   - allergen (indoor/outdoor) avoidance
   - lifestyle modification (exercise, diet, supplement)
   - complementary therapy
   - bronchothermoplasty
8. What are the effectiveness and safety of the following pharmacological interventions for asthma in adults:
   - short-acting bronchodilators (SABA)
   - inhaled corticosteroids (ICS)
   - combination of ICS/long-acting beta2-agonist (LABA)
   - maintenance and reliever therapy (MART)
   - long-acting muscarinic-antagonist (LAMA)
   - triple therapy of ICS/LABA/LAMA
   - leukotriene receptor antagonists
   - theophylline
   - macrolides
   - oral corticosteroids
   - biologic therapy
   - sublingual immunotherapy
   - combination ICS/SABA
   - emerging therapies
9. How should acute asthma be assessed?
10. How should severity of acute asthma in adults be graded?
    - mild, moderate, life-threatening, near fatal
    - life-threatening features
    - referral criteria to secondary care

11. What are the effectiveness and safety of the following interventions for acute asthma in adults:
    - oxygen
    - bronchodilators
    - corticosteroids
    - magnesium
    - ipratropium bromide
    - aminophylline
    - antibiotics/antiviral therapy
12. What are the parameters to monitor in acute asthma in adults?
    - clinical features (physical signs e.g. respiratory rate, cyanosis, PEFR)
    - investigations (SaO_2, arterial blood gases ABG)
13. When should mechanical ventilation be considered in acute asthma?
14. What are the discharge plans in acute asthma?
15. COVID-19 and asthma
    - What are the effective and safe therapies in COVID-19 with asthma?
    - What is the effectiveness and safety of homemade spacers in COVID-19 with asthma?
    - What is the effectiveness and safety of reusable spacers in COVID-19 with asthma?
    - What are the effective and safe treatment of post-COVID-19 persistent asthma-like symptoms?
16. Uncontrolled asthma, difficult to treat asthma and severe asthma
    - How should uncontrolled asthma, difficult to treat asthma and severe asthma be diagnosed and assessed?
    - What are the risk factors for severe asthma?
    - What are the effective and safe treatments for severe asthma?
17. Asthma in pregnancy
    - How should asthma in pregnancy be diagnosed and assessed?
    - What are the effective and safe pharmacological treatments of asthma in pregnancy?
    - What are the effective and safe pharmacological treatments of asthma in breastfeeding?
18. Occupational asthma (OA)
    - How should OA be diagnosed and assessed?
    - What are the risk factors for OA?
    - What are effective and safe treatments in OA?
19. Exercise-induced bronchoconstriction (EIB)
    - How should EIB be diagnosed and assessed?
    - What are effective and safe treatments in EIB?
20. What are effective and safe treatments of asthma with co-morbidity?
21. What are the referral criteria of patients with asthma to respiratory physicians?

Appendix 3

PEAK EXPIRATORY FLOW RATE VARIABILITY

Peak expiratory flow (PEF) rate variability is an alternative way to diagnose patients with asthma.

Firstly, patient need to be educated on the use the PEF meter at home. Preferably the correct technique and reading being done in the clinic before asking patient to do (record) it at home.

Patient is asked to use the same PEF meter (to reduce bias) to record his peak expiratory meter in the morning and evening preferably at the same time of the day. They need to be advised to do PEF reading three times and record the highest reading in a given table.

Diurnal PEF variability is calculated from twice daily readings as below:

$$\frac{\text{Day's highest} - \text{Day's lowest}}{\text{(Mean of day's highest and lowest)}} \times 100$$

Then the average of each day is calculated over 1 to 2 weeks.

Example:

Date	Morning PEFR	Evening PEFR	Mean of day's highest and lowest	Calculation	Diurnal PEF variability
8/4/2024	500	560	(500 + 560) ÷ 2 = 530	(560 - 500)/530 x 100%	11.3 %
9/4/2024	460	580	520	120/520 x 100%	23.0 %
10/4/2024	440	570	505	130/505 x 100%	25.7 %
11/4/2024	480	600	540	120/540 x 100%	22.2 %
12/4/2024	460	580	520	120/520 x 100%	23.0 %
13/4/2024	460	560	510	100/510 x 100%	19.6 %
14/4/2024	490	590	540	100/540 x 100%	18.5 %

Total diurnal PEF Variability = (11.3 + 23.0 + 25.7 + 22.2 + 23.0 + 19.6 + 18.5) = 143.3%

Mean Diurnal PEF Variability = 143.3 % ÷ 7 days
= 20.47 %

Diurnal PEF Variability is significant if the reading is >20% in adults

Appendix 4

PEAK EXPIRATORY FLOW NOMOGRAM

Mark the patient's height and age on the respective lines. Draw a straight line connecting the two points and extend this line to the corresponding gender line to get the expected PEF value.

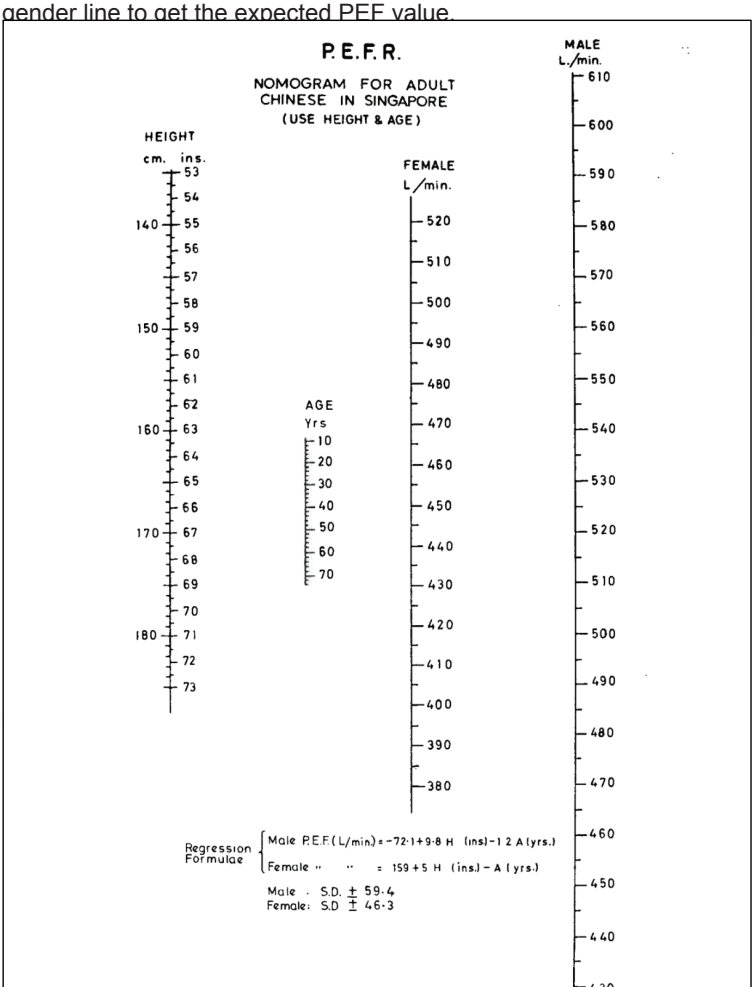


Fig. 1. Nomogram for prediction of PEFR from age and height in male and female Chinese adults.

Source: Da Costa JL, Goh BK. Peak expiratory flow rate in normal adult Chinese in Singapore. Singapore Med J. 1973;14(4):511-4

Appendix 5

A. SUGGESTED ASTHMA ACTION PLAN TEMPLATE

Name:	**Doctor:**
IC. No.:	**Hospital/Clinic:**
Best PEF:	**Date:**

This asthma action plan helps you to recognise and respond to worsening asthma

ASTHMA CONTROL	RELIEVER **Name:**	CONTROLLER **Name:**
WELL • No cough, wheeze, chest tightness or shortness of breath AND • Sleep well at night AND • Able to perform usual activities **OR** • PEFR: ____ to ____l/min (80% to 100% of personal best)	 Your reliever colour: _____	 Your controller colour: _____
	No need to use reliever except before exercise (if needed)	**Dose:** ___ inhalations ___ times a day
GETTING WORSE If you have **ANY** of these: • Cough, wheeze, chest tightness or shortness of breath • Waking up at night due to asthma symptoms • Able to perform some, but not all usual activities **OR** • PEFR: ____ to ____l/min (50% to 79% of personal best)	Take 2 to 4 inhalations every 20 minutes for a total 3 times and assess symptoms ⇩ ⇩ **If symptoms or PEFR improve** • lengthen interval to every 3 – 4 hours as needed • duration may be further lengthened based on continued good response **If symptoms worsen or persist** Proceed to **ALERT** management	**Dose:** ___ inhalations ___ times a day
ALERT If you have **ANY** of these: • Worsening cough, wheeze, chest tightness or shortness of breath • Difficulty walking or talking • Need to use reliever more frequently than every 4 hours **OR** • PEFR: Below ____l/min (less than 50% of personal best)	**Proceed to nearest hospital or clinic or dial 999 IMMEDIATELY AND DURING TRANSFER** ☐ With spacer – increase dose up to 10 inhalations every 20 minutes ☐ Without spacer – take 2 inhalations every 5 minutes	**Dose:** ___ inhalations ___ times a day

Note: The use of pMDI with spacer is encouraged

B. SUGGESTED ASTHMA ACTION PLAN TEMPLATE – MART (MAINTENANCE-AND-RELIEVER THERAPY)

Name:	**Doctor:**
IC. No.:	**Hospital/Clinic:**
Best PEF:	**Date:**

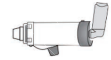
This asthma action plan helps you to recognise and respond to worsening asthma

ASTHMA CONTROL	RELIEVER Name:	CONTROLLER Name:
 **WELL** • No cough, wheeze, chest tightness or shortness of breath AND • Sleep well at night AND • Able to perform usual activities **OR** • PEFR: ____ to ____l/min (80% to 100% of personal best)	**No need to use reliever except before exercise (if needed)**	**Take _____ inhalations _____ times a day**
 **GETTING WORSE** If you have **ANY** of these: • Cough, wheeze, chest tightness or shortness of breath • Waking up at night due to asthma symptoms • Able to perform some, but not all usual activities **OR** • PEFR: ____ to ____l/min (50% to 79% of personal best)	**DON'T WAIT** Take **one** inhalation as needed (Maximum 12 inhalations a day including controller dose) ⇩ **If symptoms worsen or persist** Proceed to **ALERT** management	**Take _____ inhalations _____ times a day**
 **ALERT** If you have any of these: • Worsening symptoms (cough, wheeze, chest tightness or shortness of breath) OR • Difficulty walking or talking • Need to use reliever more than every 4 hours **OR** • PEFR: Below_____l/min (less than 50% of personal best)	**Proceed to the nearest hospital or clinic or dial 999 IMMEDIATELY** **AND** **Take one inhalation every 1 to 3 minutes up to 6 inhalations** (Maximum 12 inhalations a day including controller dose)	**Take _____ inhalations _____ times a day**

Note: The use of pMDI with spacer is encouraged

INHALER DEVICES AND TECHNIQUES

• Inhaler techniques must be checked and corrected, if necessary, at every single opportunity.
• Ensure no foreign object in the mouthpiece and the inhaler is not empty or expired.

	pMDI	pMDI AND SPACER (VHC)***	RESPIMAT®
		 Mouthpiece  Facemask	
PRIMING	Remove cap, shake inhaler well* and release several puffs** into air.	As per pMDI. Pre-wash is not necessary for antistatic spacer. However, non-antistatic spacer needs to be pre-washed (soak) with diluted mild detergent (do not rinse) and air-dried before first use to reduce electrostatic charge. Wipe mouthpiece before use.	Install cartridge. Hold inhaler upright with cap closed. Twist clear base in the direction of arrow until it "clicks". Open cap. Point mouthpiece towards ground. Press dose release button. Close cap and repeat above steps until a cloud is visible. Then repeat these steps three more times.
WHEN TO PRIME	• Before first-time use • When not used for 5 – 7 days	• Before first-time use • When not used for 5 – 7 days	• Before first-time use • When not used for 21 days • When not used for 7 days, release 1 puff
INHALATION TECHNIQUE	1. Remove cap and hold pMDI in an upright position. Shake pMDI well*.	1. Remove pMDI cap and spacer's mouthpiece cap (if any). Shake pMDI well*. Insert pMDI upright into back of spacer.	1. (Dose loading) Hold inhaler upright with cap closed. Twist clear base in the direction of arrow until it "clicks". Open cap.
	2. Sit upright or stand in an erect position.		
	3. Exhale slowly and fully (away from inhaler).		
	4. Slightly tilt chin up.		
	5. Place pMDI mouthpiece gently between teeth (without biting) to ensure a tight lip seal around mouthpiece.	**5a. Spacer with mouthpiece:** Place mouthpiece gently between teeth (without biting). Ensure a tight lip seal around mouthpiece. **5b. Spacer with facemask:** Apply mask to face and ensure an effective seal over mouth and nose.	5. Place mouthpiece gently between teeth (without biting) to ensure a tight lip seal around mouthpiece. **Do not cover air vent**.

	6. Inhale **slowly** through the mouth and press the canister down **ONCE** at start of inhalation. Continue to inhale **slowly and deeply.** Note: Do not actuate canister before starting inhalation.	**6a. Tidal Breathing Method (for VHC only)*****: Inhale **slowly and deeply** through mouth, pressing canister down **ONCE** at start of inhalation. **Inhale and exhale slowly 5 times** through mouth. Remove spacer from face/mouth. **6b. Single Breath Method:** Inhale **slowly and deeply** through mouth, pressing canister down **ONCE** at start of inhalation. Remove spacer from face/mouth and hold breath for 5 - 10 seconds or as long as comfortable. Exhale slowly (away from inhaler).	6. Inhale **slowly** through the mouth and press the dose release button **ONCE** at start of inhalation. Continue to inhale **slowly and deeply.** Note: Do not actuate dose before starting inhalation.
	7. Remove pMDI from mouth and hold breath for 5 - 10 seconds or as long as comfortable. Then exhale slowly (away from pMDI).		7. Remove Respimat from mouth and hold breath for 5 - 10 seconds or as long as comfortable. Then exhale slowly (away from Respimat).
	8. Repeat the steps (if needed) starting with shaking the pMDI. Wait 30 - 60 seconds before repeating. Replace cap after use.	7. Repeat the steps (if needed) starting with shaking pMDI. Wait 30 - 60 seconds before repeating. Remove pMDI from spacer. Replace cap(s) after use.	8. Repeat the steps starting with dose loading. Close cap after use.
CLEANING	Clean at least once a week; clean mouthpiece with a damp cloth.	Clean spacer once a week; cleaning instruction varies**.	Clean at least once a week. Clean mouthpiece including metal part inside mouthpiece with a damp cloth.
ADDITIONAL INFORMATION	After each inhalation of ICS, rinse mouth with water, gargle and spit out the water.		

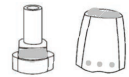
*Shaking pMDI well immediately before each actuation is important for delivering the correct dose. While only suspension formulations require shaking, to avoid confusion, it is recommended that all pMDI is to be shaken before use.

**Varies from product to product. Refer to manufacturer's recommendations.

***VHC are spacers that incorporate a one-way-valve. Tidal breathing can only be performed with VHCs.

DRY POWDER INHALERS (DPIs)

• DPIs are breath-actuated. Patients do not have to coordinate actuation with inhalation.
• Forceful and deep inhalation is needed to create turbulent energy within the device, which de-agglomerates the powder into fine particles. Sufficient inspiratory flow is needed for optimal drug delivery.

	ACCUHALER®	BREEZHALER®	ELLIPTA®	TURBUHALER®
				
PRIMING (before first use)	Not required.	Not required.	Not required.	Perform steps 1 and 2 (as below) two times for priming. The inhaler is now ready to use. To take a dose, continue following the instructions below (restart from Step 1).
INHALATION TECHNIQUE	1. Slide open the cover until a "click' sound is heard.	1.Remove the cap and tilt open the mouthpiece. With dry hands, remove one capsule from the pack and insert it into the device.	1. Hold the inhaler **upright** with the cover on the top.	1. Remove the cover. Hold the inhaler **upright** with the base grip at the bottom.
	2. (Dose loading) Hold the inhaler **horizontally**. Push lever until it "clicks".	2. (Dose loading) Close the mouthpiece and hold inhaler up-right. Press both side buttons together **ONCE** until it "clicks". Release the site buttons.	2. (Dose loading) Slide the cover down in upright position until a "click" sound is heard.	2. (Dose loading) While holding inhaler upright, turn the base grip as far as it will go in one direction and then turn backwards until "click" is heard (it does not matter which way it is turned first).
	Do not tip the inhaler upside down or shake the device after dose loading.			

<table>
<tr><td rowspan="8">INHALATION TECHNIQUE</td><td colspan="4">3. Sit upright or stand in an erect position.</td></tr>
<tr><td colspan="4">4. Exhale slowly and fully (away from the inhaler).</td></tr>
<tr><td colspan="4">5. Slightly tilt the chin up.</td></tr>
<tr><td colspan="4">6. Place the mouthpiece horizontally between teeth gently (without biting) to ensure a tight lip seal around the mouthpiece.
Do not cover airvents. Ensure the air vents are facing upwards for Ellipta®.</td></tr>
<tr><td colspan="4">7. Inhale forcefully and deeply through the mouth.
Note: A whirring sound should be heard during inhalation for Breezhaler®.</td></tr>
<tr><td colspan="4">8. Remove the inhaler from the mouth and continue to hold breath for 5 – 10 seconds or as long as comfortable. Then exhale slowly away from the inhaler.</td></tr>
<tr><td>9. Slide close the cover, a “click” sound is heard.</td><td>9. Inspect for any remaining powder left in the capsule. If there is so, close the mouthpiece and repeat the steps (Do not pierce the capsule again).
Once empty, dispose the capsule and close the cap.</td><td>9. Slide the cover upwards as far as it will go to cover the mouthpiece.</td><td>9. Repeat steps 1 to 8 if more than one dose is required. Replace the cover after use.</td></tr>
<tr><td>CLEANING</td><td colspan="4">The mouthpiece can be cleaned with a dry cloth/tissue. Never use water or liquid.
For Ellipta®, clean the mouthpiece immediately after inhalation, before sliding back the cover.</td></tr>
<tr><td>ADDITIONAL INFORMATION</td><td colspan="4">After each inhalation of ICS, rinse the mouth with water, gargle and spit out the water.</td></tr>
</table>

References:

1. Usmani OS. Choosing the right inhaler for your asthma or COPD patient. Therapeutics and clinical risk management. 2019 Mar 14:461-72.
2. Ohar JA, Ferguson GT, Mahler DA, Drummond MB, Dhand R, Pleasants RA, Anzueto A, Halpin DM, Price DB, Drescher GS, Hoy HM. Measuring peak inspiratory flow in patients with chronic obstructive pulmonary disease. International journal of chronic obstructive pulmonary disease. 2022 Jan 6:79-92.
3. The electronic Medicine Compendium (eMC) (Available at http://www.medicines.org.uk/emc/)
4. Usmani O, Capstick T, Saleem A et. Scullion J (Development Group). Choosing an appropriate inhaler device for the treatment of adults with asthma or COPD. MGP Guidelines. 2020 (Available at: https://www.guidelines.co.uk/respiratory/inhaler-choice-guideline/455503.article)
5. Asthma UK. How to use your inhaler (Available at https://www.asthmaandlung.org.uk/living-with/inhaler-videos)
6. National Asthma Council Australia. Inhaler technique for people with asthma or COPD (Available at: https://extranet.who.int/ncdccs/Data/AUS_D1_Inhaler_Technique_Infopaper-FULL- UPDATED-11-1.pdf)

Appendix 7

TEST OF ADHERENCE TO INHALERS (TAI)

SOALAN UJIAN PEMATUHAN ALAT SEDUT (TAI)

1. Berapa kalikah anda lupa mengambil alat sedut anda dalam tempoh 7 hari yang lalu?

Semua	1	Lebih daripada separuh	2	Lebih kurang separuh	3	Kurang daripada separuh	4	Tiada	5	**Jumlah**	

2. Anda lupa mengambil alat sedut anda:

Selalu	1	Hampir selalu	2	Kadang-kadang	3	Hampir tidak pernah	4	Tidak pernah	5	**Jumlah**	

3. Apabila berasa sihat, anda berhenti mengambil alat sedut anda:

Selalu	1	Hampir selalu	2	Kadang-kadang	3	Hampir tidak pernah	4	Tidak pernah	5	**Jumlah**	

4. Pada hujung minggu atau apabila pergi bercuti, anda berhenti mengambil alat sedut anda:

Selalu	1	Hampir selalu	2	Kadang-kadang	3	Hampir tidak pernah	4	Tidak pernah	5	**Jumlah**	

5. Apabila berasa resah atau sedih, anda berhenti mengambil alat sedut anda:

Selalu	1	Hampir selalu	2	Kadang-kadang	3	Hampir tidak pernah	4	Tidak pernah	5	**Jumlah**	

6. Anda berhenti mengambil alat sedut anda kerana bimbang akan kemungkinan kesan sampingan:

Selalu	1	Hampir selalu	2	Kadang-kadang	3	Hampir tidak pernah	4	Tidak pernah	5	**Jumlah**	

7. Anda berhenti mengambil alat sedut anda kerana percaya bahawa alat ini kurang membantu merawati penyakit anda:

Selalu	1	Hampir selalu	2	Kadang-kadang	3	Hampir tidak pernah	4	Tidak pernah	5	**Jumlah**	

8. Anda mengambil sedutan kurang daripada yang dipreskripsikan oleh 61ebuli:

Selalu	1	Hampir selalu	2	Kadang-kadang	3	Hampir tidak pernah	4	Tidak pernah	5	**Jumlah**	

9. Anda berhenti mengambil alat sedut anda kerana percaya bahawa pengambilannya mengganggu aktiviti harian atau kerja anda:

Selalu	1	Hampir selalu	2	Kadang-kadang	3	Hampir tidak pernah	4	Tidak pernah	5	**Jumlah**	

10. Anda berhenti mengambil alat sedut anda kerana tidak mampu membayarnya:

Selalu	1	Hampir selalu	2	Kadang-kadang	3	Hampir tidak pernah	4	Tidak pernah	5	**Jumlah**	

Source: Muneswarao J, Hassali MA, Ibrahim B, et al. Translation and validation of the Test of Adherence to Inhalers (TAI) questionnaire among adult patients with asthma in Malaysia. J Asthma. 2021;58(9):1229-36.

Appendix 8

ASTHMA CONTROL TEST™

Asthma Control Test provides a numerical score to determine the control of asthma symptoms.

1.	In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school or at home?					Score
	All of the time (1)	Most of the time (2)	Some of the time (3)	A little of the time (4)	None of the time (5)	
2.	During the past 4 weeks, how often have you had shortness ofbreath?					Score
	More than once a day (1)	Once aday (2)	3 to 6 times a week (3)	Once or twice a week (4)	Not at all (5)	
3.	During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness orpain) wake you up at night or earlier than usual in the morning?					Score
	4 or more nights a week(1)	2 to 3 nights a week (2)	Once a week (3)	Once or twice (4)	Not at all (5)	
4.	During the past 4 weeks, how often had you used your rescue inhaler or nebuliser?					Score
	3 or more times per day (1)	1 to 2 times per day (2)	2 or 3 times per week (3)	Once a week or less (4)	Not at all (5)	
5.	How would you rate your asthma control in the last 4 weeks?					Score
	Not controlled at all (1)	Poorly controlled(2)	Somewhat controlled(3)	Well controlled (4)	Completely controlled(5)	

Total score: _____

Modified: © Asthma Control Test™ (Available at: http://www.asthma.com/additional-resources/asthma-control-test.html?q=asthma+control+test)

COMMON MEDICATIONS IN ASTHMA

A. INHALED SHORT-ACTING β_2-AGONISTS (SABA)

DRUG	DOSAGE	COMMON ADVERSE DRUG REACTIONS	COMMENTS
Salbutamol 100 µg/dose inhaler, pMDI	• For relief of acute bronchospasm, 1 to 2 inhalations	• Tremor, headache, tachycardia	• Reliever therapy
Salbutamol 100 and 200 µg/dose inhaler, Easyhaler® (DPI)	• For relief of acute bronchospasm, 1 inhalation as a single starting dose; may be increased to 2 inhalations if necessary	• Tremor, palpitation, tachycardia	

B. INHALED CORTICOSTEROIDS (ICS)

DRUG	DOSAGE	COMMON ADVERSE DRUG REACTIONS	COMMENTS
Beclometasone dipropionate 50, 100 and 200 µg/dose inhaler, pMDI	Extra-fine formulation: • 50 - 200 µg twice/day; increase if necessary up to 400 µg twice/day (maximum daily dose: 800 µg)	• Oropharyngeal candidiasis, hoarseness of voice, pharyngitis, taste disturbance	• Maintenance therapy
Beclometasone dipropionate 200 µg/dose inhaler, Easyhaler® (DPI)	• 200 to 400 µg twice/day	• Oropharyngeal candidiasis, hoarseness of voice, cough, throat irritation,	• Maintenance therapy
Budesonide 100 and 200 µg/dose inhaler, pMDI	• 100 - 800 µg twice/day	• Oropharyngeal candidiasis, mild throat irritation, hoarseness of voice, cough,	• Maintenance therapy
Budesonide 100 and 200 µg/dose inhaler, Easyhaler® (DPI)	• 100 - 800 µg twice/day • Once/day dosing may be considered for mild to moderate asthma who are	• Oropharyngeal candidiasis, cough, throat irritation, difficulty in swallowing	• Maintenance therapy

	ICS-naïve (200 to 400 µg) or previously controlled on twice/day dose (up to 800 µg)		
Budesonide 100 and 200 µg/dose inhaler, Turbuhaler® (DPI)	• 100 - 800 µg twice/day • Once/day dosing may be considered for mild to moderate asthma who are ICS-naïve (200 to 400 µg) or previously controlled on twice/day dose (up to 800 µg)	• Oropharyngeal candidiasis, cough, hoarseness of voice, throat irritation	• Maintenance therapy
Ciclesonide 80 and 160 µg/dose inhaler, pMDI	• 160 µg once/day; in severe asthma, a higher dose of up to 640 µg/day (given as 320 µg twice/day) may be used	• Uncommon: dry mouth, dysphonia, headache, cough, bad taste, oropharyngeal candidiasis	• Maintenance therapy
Fluticasone propionate 50 and 125 µg/dose inhaler, pMDI	• 100 - 1000 µg twice/day Starting doses: • 100 µg twice/day (mild asthma) • 250 - 500 µg twice/day (moderate and moderate to severe asthma) • Up to 1000 µg twice/day may be used where additional clinical benefit is expected	• Oropharyngeal candidiasis, hoarseness of voice/dysphonia, bruises	• Maintenance therapy

C. INHALED CORTICOSTEROIDS/LONG-ACTING β_2-AGONISTS COMBINATION (ICS/LABA)

DRUG	DOSAGE	COMMON ADVERSE DRUG REACTIONS	COMMENTS
Beclometasone dipropionate 100 µg and formoterol 6 µg inhaler, pMDI	Maintenance therapy: • 1 to 2 inhalations twice/day (maximum: 4 inhalations/day)	• Oropharyngeal candidiasis, headache, dysphonia, pharyngitis	• Maintenance therapy (can be used as single inhaler for MART)

DRUG	DOSAGE	COMMON ADVERSE DRUG REACTIONS	COMMENTS
	Maintenance and reliever therapy (MART): • Maintenance dose: 1 inhalation twice/daywith additional 1 inhalation as needed in response to symptoms • If symptoms persist after a few minutes, anadditional inhalation should be taken • Maximum daily dose: 8 inhalations (allow up to 12 based on GINA)		
Beclometasone dipropionate 100 µg and formoterol 6 µg inhaler, Nexthaler®, DPI	Maintenance therapy: • 1 to 2 inhalations twice/day (maximum: 4 inhalations/day) MART: • Maintenance dose: 1 inhalation twice/daywith additional 1 inhalation as needed in response to symptoms • If symptoms persist after a few minutes, anadditional inhalation should be taken If patients • Maximum daily dose: 8 inhalations (allow up to 12 based on GINA)	• Oropharyngeal candidiasis, headache, dysphonia, pharyngitis	• Maintenance therapy (can be used as single inhaler for MART)
Budesonide 160 µg and formoterol 4.5 µg inhaler, Turbuhaler® (DPI)	Anti-inflammatory reliever therapy (Mild asthma): One inhalation as needed in response to symptoms. If symptoms persist after	• Oropharyngeal candidiasis, hoarseness of voice, headache, tremor, mild throat irritation, cough, palpitation	• Maintenance therapy (can be used as single inhaler for MART)

DRUG	DOSAGE	COMMON ADVERSE DRUG REACTIONS	COMMENTS
	should be taken. Not more than 6 inhalations should be taken on any single occasion. A total daily dose of >8 inhalations is not normally needed; however, a total daily dose of up to 12 inhalations could be used for a limited period. If patients find the treatment less effective or need more inhalations than usual, medical attention must be sought. Maintenance therapy: • 1 to 2 inhalations twice/day. Some patients may require up to a maximum of 4 inhalations twice/day Maintenance and reliever therapy: • 2 inhalations/day, given either as one inhalation in the morning and evening or as 2 inhalations in either the morning or evening • For some patients, a maintenance dose of 2 inhalations twice/day may be appropriate • Patient should take 1 additional inhalation as needed in response to symptoms. If symptoms persist after a few minutes, an additional inhalation should be taken. Not more than 6 inhalations should be taken on any single occasion • A total daily dose of >8 inhalations is not normally needed; however, a total daily dose of up to 12 inhalations could be used for a limited period. Patients using >8 inhalations/day are strongly recommended to seek medical advice.		

DRUG	DOSAGE	COMMON ADVERSE DRUG REACTIONS	COMMENTS
Budesonide 320 µg and formoterol 9 µg inhaler, Turbuhaler® (DPI)	• 1 inhalation twice/day • Some patients may require up to a maximum of 2 inhalations twice/day		• Maintenance therapy
Budesonide 80 µg and formoterol 4.5 µg inhaler, pMDI	• 2 inhalations once or twice/day (max: 4 inhalations twice/day)		• Maintenance therapy
Budesonide 160 µg and formoterol 4.5 µg inhaler, pMDI			• Maintenance therapy
Fluticasone furoate 100 µg and vilanterol 25 µg inhaler, Ellipta® (DPI)	• 1 inhalation once/day	• Headache, nasopharyngitis, oropharyngeal candidiasis, influenza, upper respiratory tract infection (URTI), dysphonia, cough	• Maintenance therapy
Fluticasone furoate 200 µg and vilanterol 25 µg inhaler, Ellipta® (DPI)			
Salmeterol 25 µg and fluticasone propionate 50 µg inhaler, pMDI	• 2 inhalations twice/day	• Headache, oropharyngeal candidiasis, throat irritation, hoarseness of voice/dysphonia, myalgia, muscle cramps	• Maintenance therapy
Salmeterol 25 µg and fluticasone propionate 125 µg inhaler, pMDI			
Salmeterol 25 µg and fluticasone propionate 250 µg inhaler, pMDI			
Salmeterol 50 µg and fluticasone propionate 100 µg inhaler, Accuhaler® (DPI)	• 1 inhalation twice/day	• Headache, oropharyngeal candidiasis, throat irritation, hoarseness of voice/dysphonia, myalgia, muscle cramps	• Maintenance therapy
Salmeterol 50 µg and fluticasone propionate 250 µg inhaler, Accuhaler® (DPI)			
Salmeterol 50 µg and fluticasone propionate 500 µg inhaler, Accuhaler® (DPI)			
Indacaterol acetate 150 µg, mometasone furoate 80 µg inhalation powder cap, Breezhaler (DPI)	• 1 cap once daily inhalation at same time each day	• Nasopharyngitis; asthma exacerbation. URTI, hypersensitivity, headache, oropharyngeal pain, dysphonia, musculoskeletal pain	• Maintenance therapy
Indacaterol acetate 150 µg, mometasone furoate 160 µg inhalation powder cap, Breezhaler (DPI)			
Indacaterol acetate 150 µg, mometasone furoate 320 µg inhalation powder cap, Breezhaler (DPI)			

D. LONG-ACTING MUSCARINIC ANTAGONISTS (LAMA)

DRUG	DOSAGE	COMMON ADVERSE DRUG REACTIONS	COMMENTS
Tiotropium 2.5 µg, solution for inhalation, Respimat® (Soft Mist Inhaler)	• 2 inhalations (5 µg) once/day, at same time of the day	• Dry mouth • Uncommon: headache, dizziness, insomnia, palpitations, pharyngitis, cough	• Maintenance therapy

E. ICS/LABA/LAMA

DRUG	DOSAGE	COMMON ADVERSE DRUG REACTIONS	COMMENTS
Indacaterol acetate 150 µg, glycopyrronium bromide 50 µg, mometasone furoate 160 µg inhalation powder cap, Breezhaler® (DPI)	• 1 cap once daily inhalation at same time each day	• Nasopharyngitis, asthma exacerbation, URTI, candidiasis, UTI, hypersensitivity, headache, tachycardia, oropharyngeal pain, cough, dysphonia, gastroenteritis, musculoskeletal pain, muscle spasms, pyrexia	• Maintenance therapy
Indacaterol acetate 150 µg, glycopyrronium bromide 50 µg, mometasone furoate 80 µg inhalation powder cap, Breezhaler® (DPI)			
Beclometasone dipropionate 100 µg, formoterol fumarate dihydrate 6 µg, glycopyrronium br 12.5 µg, pMDI	• 2 inhalations twice/day	• Dysphonia, oral candidiasis, muscle spasm, dry mouth	• Maintenance therapy

F. LEUKOTRIENE RECEPTOR ANTAGONISTS (LTRA)

DRUG	DOSAGE	COMMON ADVERSE DRUG REACTION	COMMENTS
Montelukast 10 mg tablet	• 10 mg once/day (in the evening)	• URTI, headache, abdominal pain, diarrhoea, pyrexia, elevated serum transaminases (alanine transaminase, aspartate transaminase) • Potential neuropsychiatric adverse effects including new-onset nightmares, behavioural changes, and, in some cases, suicidal ideation	• Maintenance therapy

G. METHYLXANTHINE

DRUG	DOSAGE	COMMON ADVERSE DRUG REACTION	COMMENTS
Doxofylline 400 mg tablet	• 1 tablet twice or thrice/day	• Nausea, vomiting, headache, irritability, insomnia, palpitations, tachycardia	-

H. NEBULISER

DRUG	DOSAGE	COMMON ADVERSE DRUG REACTIONS	COMMENTS
Ipratropium bromide 0.0125% nebulising solution (125 µg/ml) Ipratropium bromide 0.025% nebulising solution (250 µg/ml)	Asthma exacerbation: • 500 µg; repeated doses can be administered (4 to 6 hourly). The time interval between the doses may	• Headache, dizziness, throat irritation, cough, dry mouth, disturbance in gastrointestinal motility, nausea	Recommend to dilute the drug solution dose to a final volume of 4 – 5 ml in jet nebuliser

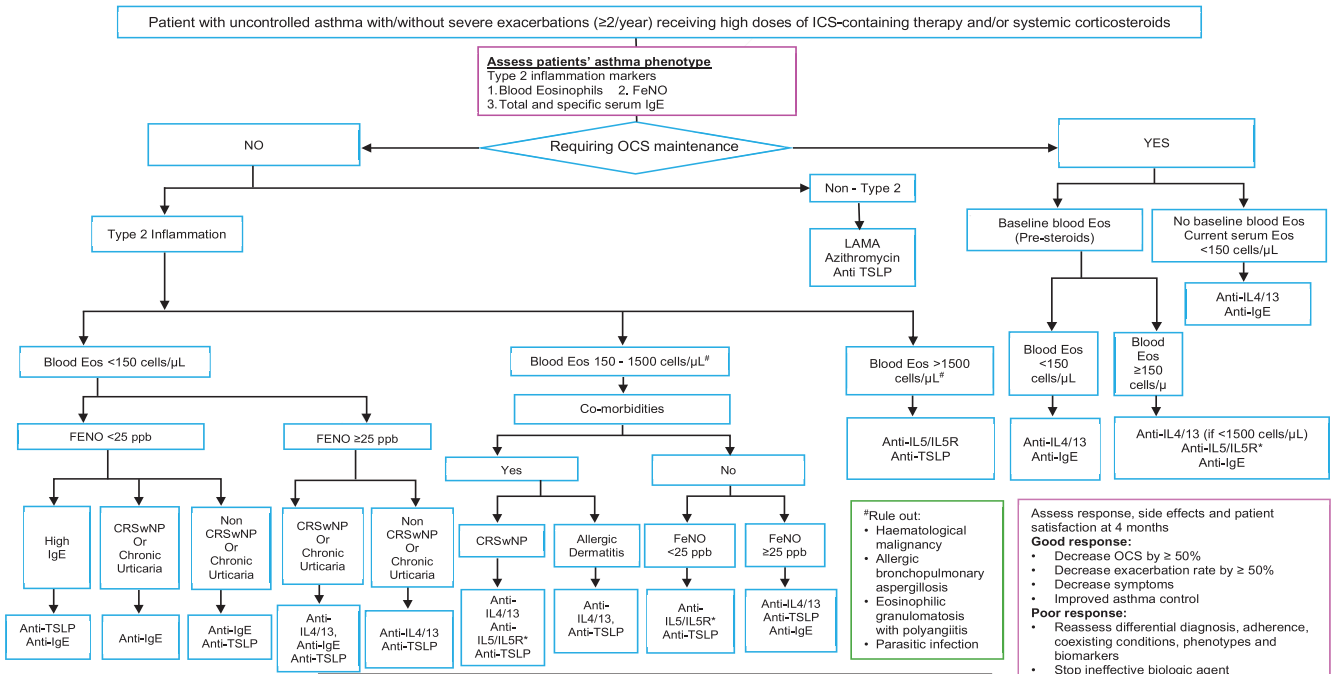
DRUG	DOSAGE	COMMON ADVERSE DRUG REACTIONS	COMMENTS
	be determined by the physician • It is advisable not to exceed the recommended daily dose • Daily doses exceeding 2 mg should only be given under medical supervision		unless the nebulizer is specifically designed for a small fill volume.
Salbutamol 0.5 % nebulising solution	Asthma exacerbation: • 2.5 to 5 mg every 20 minutes for the first hour (3 doses), then 2.5 to 10 mg every 1 to 4 hours as needed, or 10 to 15 mg/hour by continuous nebulisation	• Tremor, headache, tachycardia	
Ipratropium bromide 0.5 mg and salbutamol 2.5 mg/unit dose vial (UDV)	Asthma exacerbation: • 1 UDV every 4 to 6 hours	• Uncommon: Headache, throat irritation, cough, tachycardia, tremor, nervousness, dry mouth, dysphonia	

#Disclaimer: The information on common asthma medications in this section only serves as a general guide and is not all-inclusive. Doses may be different depending on formulation.

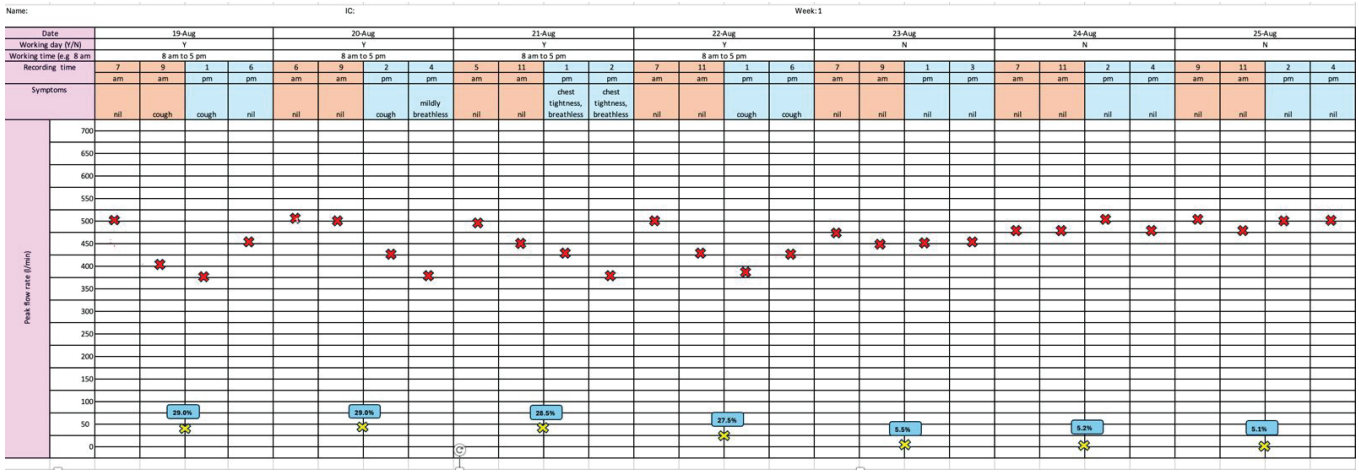
Source:

1. Drug Information Databases (Available at: http://www.wolterskluwercdi.com/lexicomp-online/databases/).
2. Formulari Ubat KKM (FUKKM) (Available at: https://www.pharmacy.gov.my/v2/ms/apps/fukkm).
3. Medication package insert
4. Micromedex® Solutions (Available at: http://www.micromedexsolutions.com/micromedex2/librarian).
5. The electronic Medicines Compendium (eMC) (Available at: https://www.medicines.org.uk/emc/).

ALGORITHM FOR BIOLOGIC THERAPY SELECTION IN SEVERE ASTHMA



EXAMPLE OF PEFR CALCULATION FOR OCCUPATIONAL ASTHMA



This is an example of the serial peak flow record of an employee (marked with a red cross) who works in a chemical lab.
The record shown is for week 1. (Due to space constraints, the charts for week 2 and week 3 are not included; however, the readings were taken in the same manner as in week 1)

Symptoms must be tracked for 3 weeks and must include three series of workdays along with three periods away from work. The daily variability is plotted by the physician (marked with a yellow cross) after calculation.

Calculating Variability in PEFR for Occupational Asthma

1. Record PEFR readings
2. Calculate daily variability:
   - For each day, find the highest and lowest PEFR readings
   - Calculate the daily variability using the formula

$$\text{Daily variability (\%)} = \frac{\text{(Highest PEFR – Lowest PEFR)}}{\text{Mean PEFR of the day}} \times 100\%$$

$$\text{e.g. Variability for Day 1 (\%)} = \frac{500 - 375}{431.25} \times 100\%$$

$$= \mathbf{29.0\%}$$

3. Calculate mean workday variability and mean non-workday variability:

$$\text{Mean workday variability (\%)} = \frac{\text{Sum of daily variability on workdays}}{\text{Number of workdays}}$$

$$= \frac{29.0 + 29.0 + 28.5 + 27.5 + 29.0 + 29.0 + 28.5 + 27.5 + 29.0 + 29.0 + 28.5 + 27.5}{12}$$

$$= \mathbf{28.5\ \%}$$

$$\text{Mean non-workday variability (\%)} = \frac{\text{Sum of daily variability on workdays}}{\text{Number of non-workdays}}$$

$$= \frac{5.5 + 5.2 + 5.1 + 5.5 + 5.2 + 5.1 + 5.5 + 5.2 + 5.1}{9}$$

$$= \mathbf{5.3\ \%}$$

4. Calculate work-related variability:

$$\text{Work related variability (\%)} = \text{Mean workday variability} - \text{Mean non-workday variability}$$
$$= 28.5\% - 5.3\%$$
$$\mathbf{23.2\%}$$

A variability of ≥20% on workdays compared to off days is suggestive of work-related asthma
The PEFR Monitoring Form for Occupational Asthma can be accessed from: Occupational Asthma PEFR Tracking Chart

LIST OF ABBREVIATIONS

AAP	asthma action plan
ABG	arterial blood gas
ACQ	Asthma Control Questionnaire
ACT	Asthma Control Test
AE(s)	adverse event(s)/effect(s)
AGREE II	Appraisal of Guidelines, Research and Evaluation II
AIR	anti-inflammatory reliever
AQLQ	Asthma Quality of Life Questionnaire
AUC	area under the curve
BCT	behaviour change techniques
BTS	British Thoracic Society
CI	confidence interval
COPD	chronic obstructive pulmonary disease
COT	conventional oxygen therapy
COX2	cyclooxygenase-2
CPAP	continuous positive airway pressure
CrI	credible interval
CRS	chronic rhinosinusitis
CXR	chest x-ray
DG	Development Group
DPI	dry powder inhaler
ECG	electrocardiogramme
ED	Emergency Department
e.g.	example
EIB	exercise-induced bronchoconstriction
FDA	(United States) Food and Drug Administration
FeNO	fractional exhaled nitric oxide
FVC	forced vital capacity
FEV1	forced expiratory volume in first one second
FMS	Family Medicine Specialist
GERD	gastroesophageal reflux disease
GINA	Global Initiative for Asthma
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HDM	house dust mite
HFA	hydrofluoroalkane
HFNC	high flow nasal cannula
HR	hazard ratio
HRQoL	health-related quality of life
ICS	inhaled corticosteroids
IgE	immunoglobulin E
IL	interleukin
IM	intramuscular
IRR	incident rate ratio
IV	intravenous
kU/L	kilo unit per litre
LABA	long-acting β2-agonists
LAMA	long-acting muscarinic antagonists
LLN	lower limit normal
LTRA	leukotriene receptor antagonists

MART	maintenance and reliever therapy
MCID	minimal clinically important difference
MD	mean difference
MDT	multidisciplinary team
µg	microgramme
mg	milligramme
ml	millilitre
mmHg	millimetres of mercury
MoH	Ministry of Health
NIV	non-invasive ventilation
NMA	network meta-analysis
NS	non-significant
OA	occupational asthma
OCS	oral corticosteroids
OR	odds ratio
OSA	obstructive sleep apnoea
p	p-value
PaO_2	partial pressure of arterial oxygen
$PaCO_2$	partial pressure of arterial carbon dioxide
PEF	peak expiratory flow
PEFR	peak expiratory flow rate
PIFR	peak inspiratory flow rate
pMDI	pressurised metered dose inhaler
ppb	parts per billion
PRN	as needed
PRO(s)	patient-reported outcome(s)
QoL	quality of life
RC	Review Committee
RCP	Royal College of Physicians
RCT	randomised controlled trial
RE	relative effect
RMTAC	Respiratory Medication Therapy Adherence Clinic
RoB	Risk of Bias
RR	relative risk
SABA	short-acting β2-agonists
SAE(s)	serious adverse event(s)/effect(s)
SD	standard deviation
SIGN	Scottish Intercollegiate Guidelines Network
SLIT	sublingual immunotherapy
SMD	standardised mean difference
SMI	soft-mist inhaler
SUCRA	surface under the cumulative ranking curve
T2	type-2
TAI	Test of the Adherence to Inhalers
TTG	teach-to-goal
VHC	valved holding chamber
WHO	World Health Organization
WMD	weighted mean difference

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