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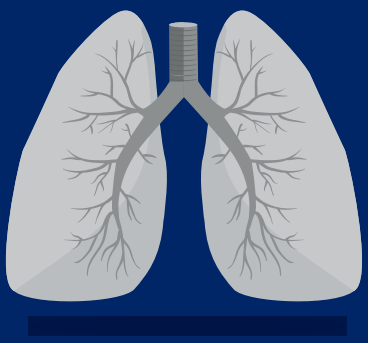
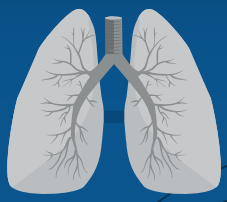


CLINICAL PRACTICE GUIDELINE
MANAGEMENT OF ASTHMA
MARCH 2020



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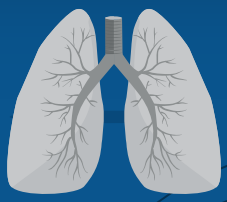
Clinical Practice Guideline Management of Asthma



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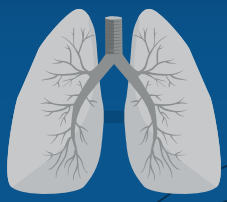
Clinical Practice Guidelines

Management of Asthma

March 2020



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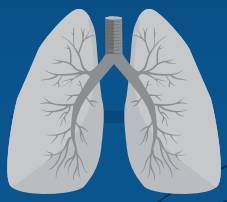


PAKISTAN CHEST SOCIETY
STRIVING FOR PULMONARY CARE

Message by the President Pakistan Chest Society (PCS)

I feel highly delighted on Pakistan Chest Society's endeavors for publishing this evidence-based guideline on diagnosis and management of asthma. Indeed, this has come true through consistent efforts and diligence of the working group for which I congratulate them.

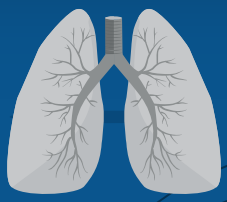
Asthma is a severe and growing threat affecting both children and adults in Pakistan. It affects quality of life, and acute exacerbation can be life-threatening.

About 7,500,000 Pakistani adults and 15 million children suffer from asthma due to increase in urban population, enlarging intercity industries, air pollution and other environmental factors.

Poor asthma control results in increased hospital admissions and urgent care visits. In addition, persistent symptoms cause considerable morbidity and absence from work. The disease significantly affects healthcare systems. It also affects the quality of life of the patients and their families.

This publication aims to update the outlook in precision medicine of asthma diagnosis and management, driven by underlying phenotypes. It is a superb managing tool and provides a benchmark for the standard care for people with asthma and a rich source of ideas for general practitioners, residents, physicians, pulmonologists and researchers.

PROF. DR. NISAR AHMED RAO
President,
Pakistan Chest Society



PAKISTAN CHEST SOCIETY
STRIVING FOR PULMONARY CARE

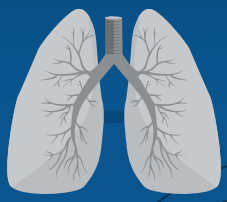
Message by the Chairman Guidelines Committee, Pakistan Chest Society (PCS)

It is a matter of great pleasure, pride and satisfaction that guideline for the **Management of Asthma** have been revised by the working group. Governing Council of PCS has mandated the Guideline committee to develop evidence based guidelines for important pulmonary diseases. Besides this document, guidelines on COPD, Sleep apnea, Noninvasive ventilation, Pre-operative pulmonary risk assessment and guideline on smoking Cessation have already been developed and will distributed during the 14th Biennial Chest Con 2020 in Karachi. It is very encouraging to note that PCS has been consistently working on developing and updating guidelines. These guidelines provide a highly valuable resource for the trainees and practicing physicians.

Asthma is a major global cause of chronic morbidity and mortality. This publication comprehensively covers all the aspects related to Asthma diagnosis and management. I hope this guideline will be useful for trainees, practicing physicians and health care workers with interest in Asthma.

Finally, I would like to acknowledge the hard work of Dr Shereen Khan and other members of the working group who revised this document and the members of PCS guideline committee for reviewing the document. PCS remain committed to always endeavor for the achievement of the best possible clinical practice.

Prof. Muhammad Irfan
Chairman Guidelines Committee, PCS



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Preface

It has been long since the last asthma guideline was published by Pakistan Chest Society. Meanwhile much research has been conducted in the field producing new concepts with evidences. There was a dire need to update the guidelines to incorporate the new concepts. Much care has been taken to match the guidelines with the national needs.

While this guideline is to manage the asthma in adult population, we feel there is a dire need for the paediatric asthma guidelines as well. I strongly suggest the PCS to collaborate with national pediatric associations/societies to produce these guidelines.

I am extremely grateful to all the contributors who worked hard to accomplish this task. Special mention must be made of Dr. Robina Aman and Dr. Maryam Khalid for valuable comments on the contents.

Hope, we will continue to update the guideline as new evidences in the field emerge.

Dr Shereen Khan
Chairman Asthma Working Group

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ASTHMA DEFINITION AND DIAGNOSIS

DEFINITION

"Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation".[1]

DIAGNOSIS

The diagnosis of asthma is not always straight forward because of different factors including failure to confirm reversible airflow obstruction, the relatively poor sensitivity of spirometry alone to absolutely confirm asthma (especially in children), the day to day variability of symptoms and the numerous phenotypes of disease.[2] That is why in clinical practice the asthma is both under and over diagnosed.

The initial diagnosis of asthma is based on the combination of presence of characteristic symptoms (cough, dyspnea, chest tightness and wheeze), demonstration of airflow limitation and variability as shown in the figure. Relying on a single characteristic for the diagnosis of asthma results in both over-diagnosis and under-diagnosis.[3,4,5]

Therefore every effort should be made to elicit detailed history of characteristic symptoms and demonstrate variable/reversible airflow obstruction in suspected patients of asthma.

DIFFERENTIAL DIAGNOSES OF ASTHMA

Certain diseases mimic asthma in their clinical presentation and need to be differentiated from asthma.

1. **COPD** : patients usually are more than 40 years of age with significant Cigarette smoking history (>10 pack years) or exposure to biomass fuels. Dyspnea is progressive rather than intermittent with little or no diurnal or day to day variability, and confirmed on spirometry by post Bronchodilator FEV/FVC < 0.7 and insignificant post Bronchodilator Reversibility i.e. improvement in FEV < 12% & 200ml.

2. **Cardiac Asthma**: patients usually having prior history of Ischemic Heart Disease. Dyspnea is sudden in onset, associated with orthopnea and paraoxysmal nocturnal dyspnea. Examination may reveal elevated JVP, wheezing, basal crackles, gallop rhythm. Chest X-Ray may show Cardiomegaly and features of acute pulmonary edema i.e. perihilar alveolar infiltrates, upward diversion of veins, interstitial shadowing in Bat Wing manner and Kerley B lines. Echocardiography and ProBNP levels may aid diagnosis.

3. **Upper Airway Cough Syndrome**: reflex bronchospasm induced by either nasal secretions trickling into the airways and induce inflammation as seen in Post Nasal Dripping in Sinusitis or regurgitation and aspiration of acidic food contents into upper airways in Gastro Esophageal Reflux Disease, resulting in chest tightness, wheezing, cough and mimic Cough Variant Asthma. These are also the common triggers of underlying Bronchial Asthma. Patient usually have history of seasonal or perennial rhinitis associated with nasal blockage, nasal polyps, frequent throat clearing, morning headaches, retrosternal burning, acid brash, chest pain, specially on lying down after taking meals.

4. **Vocal cord dysfunction (VCD):** In this condition, there is abnormal adduction of the vocal cords during inspiration. These patients present with dyspnea, cough and wheezing. Laryngeal auscultation may reveal harsh stridulous sounds during symptoms. Wheezing may be heard in the chest (transmitted from the upper airway). Flow-volume loop typically demonstrate inspiratory loop flattening. Direct laryngoscopy reveals paradoxical adduction of the true vocal cords during inspiration.

5. **Bronchiactasis:** There is abnormal and permanent distortion/dilatation of airways. In Pakistan, the common cause is tuberculosis. They present with long history of productive cough, dyspnoea, wheezing, fever, fatigue, and weight loss. The expectoration may be copious and posture related. Chest examination may reveal crepitations± rhonchi. Clubbingis seen in 2-3% patients. Chest x-ray sometime helpful in the diagnosis. The standard test is High-resolution computed tomography (HRCT) scan.

6. **Hyperventilation/Dysfunctional breathing:** It is relatively common condition usually seen in young girls. In this condition, minute ventilation exceeds metabolic demands, resulting in characteristic dysphoric symptoms like dizziness, paresthesia, sighing etc. Patient is otherwise normal. Chest x-ray is also normal. Reassurance and explanation of how hyperventilation produces the patient's symptoms are usually sufficient to terminate the episode of HVS. A number of drugs like benzodiazepines, selective serotonin reuptake inhibitors (SSRIs), beta blockers etc have been used to reduce the frequency and severity of episodes of hyperventilation. Stress reduction therapy and breathing retraining have all proved effective in reducing the intensity and the frequency of episodes of hyperventilation.

7. **Eosinophilic Bronchitis**: Eosinophilic bronchitis without asthma (EBWA) is characterized by cough for at least 2 months, a sputum eosinophil count greater than 3%, and no evidence of airway obstruction. Affected patients are usually middle-aged, are nonatopic, and have no history of smoking. Activation and eosinophilic infiltration of the superficial airway occurs, rather than of airway smooth muscle

8. **Upper respiratory Infections/bronchiolitis**: Dyspnea, wheezing usually associated with infective episode comprising of fever, malaise, bodyache, cough, rhinorrea, red eyes, watering of eyes. Usually caused by Viral infections and is self remitting, but may contribute in development of Asthma and also is a trigger factor for Asthma.

ASSESSMENT OF ASTHMA

Assessment of asthma control is an integral part of the management of patients with asthma. On each visit the level of the asthma control should be measured which includes assessment of both symptom control and future risk of adverse outcomes.[1, 2]

The assessment of symptom control can be subjective made by asking the patients view about their asthma control or it can better be measured objectively using a validated tool/ questionnaire like asthma control test, asthma control questionnaire, mini asthma quality of life questionnaire or consensus-based GINA symptom control tool. Of these the asthma control test [3, 4] and consensus-based GINA symptom control tool[1] are simple and more commonly used.

ASTHMA SYMPTOM CONTROL	**LEVEL OF ASTHMA SYMPTOMS CONTROL**		
IN THE PAST 4 WEEKS, HAS THE PATIENT HAD:	WELL - CONTROLLED	PARTLY - CONTROLLED	UNCONTROLLED
⌜ Daytime asthma symptoms more than twice /week? ⌜ Any daytime waking due to asthma? ⌜ Reliever needed for symptoms more than twice/week? ⌜ Any activity limitation due to asthma?	None of these	1-2 of these	3-4 of these

Adopted from GINA

Periodic follow-up and assessment of asthma control is necessary to tailor the treatment according to the individual patient's need depending upon the symptoms control thereby preventing both over-treatment and under- treatment and decreasing the risk of futures adverse outcome.

ASTHMA SEVERITY

The asthma severity is usually defined as the intrinsic intensity of the disease process. GINA recommends assessment of asthma severity retrospectively from the level of treatment required to control symptoms and exacerbations. The severity of asthma should be assessed when the asthma is well controlled on the minimum level of the controller medication for several months. On the basis of the severity asthma is categorized as:

1. MILD ASTHMA: well controlled with step 1 or step 2 treatment
2. MODERATE ASTHMA: well controlled on step 3 treatment
3. SEVERE ASTHMA: requiring treatment of step 4 or 5

In treatment naive asthmatics, the severity is assessed as follows:

CLASSIFICATION OF ASTHMA SEVERITY BY CLINICAL FEATURES BEFORE TREATMENT
Intermittent
Symptoms less than once a week Brief exacerbations Nocturnal symptoms not more than twice a month - FEV1 or PEF $\geq$ 80% predicted - FEV1 or PEF variability < 20%
Mild Persistent
Symptoms more than once a week but less than once a day Exacerbations may affect activity and sleep

Nocturnal symptoms more than twice a month □ FEV1 or PEF ≥ 80% predicted □ FEV1 or PEF variability 20-30%
Moderate Persistent
Symptoms daily Exacerbations may affect activity and sleep Nocturnal symptoms more than twice a week Daily use of inhaled short acting beta2 agonist □ FEV1 or PEF 60-80% predicted □ FEV1 or PEF variability >30%
Severe Persistent
Symptoms daily Frequent exacerbations Frequent nocturnal asthma symptoms Limitations of physical activities □ FEV1 or PEF < 60% predicted □ FEV1 or PEF variability >30%

Adopted from: Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. National Asthma Education and Prevention Program, Third Expert Panel on the Diagnosis and Management of Asthma. Bethesda (MD): National Heart, Lung, and Blood Institute (US); 2007 Aug

The severe asthma should always be differentiated from uncontrolled Asthma (discussed later).

The GINA guidelines recommend excluding the following factors before making the diagnosis of severe asthma

1. Poor inhaler technique
2. Poor medication adherence
3. Incorrect diagnosis of asthma symptoms due to alternative conditions such as inducible laryngeal obstruction cardiac failure or lack of fitness

4. Comorbidities and complicating conditions such as rhinosinusitis gastroesophageal reflux obesity and obstructive sleep apnea
5. Ongoing exposure to sensitizing or irritant agents in the home or work environment

ASSESSMENT OF FUTURE RISK OF ADVERSE OUTCOMES

GINA recommends assessing every patient for the future risk of exacerbation, persistent airflow limitation and side effects of medications.

FUTURE RISK OF EXACERBATION:

There are different factors or markers which can help physician predict the future risk of asthma exacerbation.

Measurement of the lung function is independent factor to assess the future risk of adverse outcome and should be measured at diagnosis and 3-6 after the initiation of treatment.[1, 2]

LEVEL OF INCREASED RISK	FACTORS
Greatly increased risk	History of previous asthma attacks
Moderately increased risk	Poor control, Inappropriate or excessive SABA use
Slightly increased risk	Old age Female Reduced lung function Obesity Smoking depression

Unclear	History of anaphylaxis Comorbid gastro-esophageal reflux COPD Raised FeNO at review Blood eosinophilia Poor adherence

Adopted from BTS/SIGN guideline

RISK OF PERSISTENT AIRFLOW LIMITATION

Different risk factors have been found to be associated with increased future risk of persistent airflow limitation [5]. These include:

1. Severe asthma
2. Smoking
3. Male patients
4. High FeNO
5. aspirin sensitivity

SIDE EFFECTS OF MEDICATIONS

Different drugs for asthma are associated with various side effects. Before starting the medications the risk benefit ratio should be assessed and the potential side effects should be explained to the patient. Where possible the drug with least side effect should be chosen.

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PHARMACOTHERAPY IN ASTHMA

Introduction

Asthma is a chronic and potentially serious chronic disease that imposes a substantial burden on patient, their families and the community. It causes respiratory symptoms, limitation of activity, and flare ups (attacks) that sometimes require urgent health care and may be fatal[1].

Fortunately asthma can be effectively treated and most patients can achieve good control of their asthma[1].

Asthma treatment should be customised to the individual patient, taking into account their level of symptom control, their risk factors for exacerbations, phenotypic characteristics and preferences as well as the effectiveness of available medications, their safety and their cost to the payer or patient.

Goals of pharmacological therapy in asthma are **reduce impairment** and **reduce risk**[1].

These will be;

- To minimize chronic symptoms that interfere with normal activity (including exercise)
- To prevent recurrent exacerbations
- To reduce or eliminate the need for emergency department visits, use of reliever medications or hospitalization
- To maintain normal or near normal pulmonary function.

These goals should be met with minimal possible dose of therapeutic agents to maximally prevent the adverse effects while satisfying patients' and families' expectations of asthma care.

Pharmacotherapy in asthma

Classification

Broadly asthma medications can be classified into two groups;

1. **Bronchodialators** which includes both short and long acting acting beta-2 agonists and muscarinic antagonists. It also includes theophylline (a methylxanthine).

2. **Anti inflammatory drugs** which includes inhaled corticosteroids (ICS), leukotriene modifiers especially leukotriene receptor antagonists, systemic steroids and monoclonal antibodies.

For better knowledge and to know about their role in asthma and to best manage asthma, the following classification is essential.

- **Reliever medications**
    1. Short-acting β2-agonists (SABA)
    2. Low dose inhaled corticosteroids-formoterol
    3. Short acting muscarinic antagonists (SAMA)
    4. Systemic steroids

- **Controller medications**
    1. Inhaled corticosteroids (ICS)
    2. Inhaled corticosteroids-long actingβ2 agonists (ICS-LABA)
    3. Leukotriene receptor antagonists
    4. Chromones

- **Add on controller medications**
    1. Long acting muscarinic antagonists (LAMA)
    2. Anti IgE
    3. Anti IL5, anti IL5R
    4. Anti IL4R
    5. Systemic steroids

Pharmacologic treatment is the mainstay of management in most patients with asthma. The stepwise approach to asthma management that forms the foundation of guideline-based asthma management has been shown to reduce symptoms and improve health-related quality of life. The stepwise approach to pharmacotherapy is based on increasing medications until asthma is controlled, and decreasing medications when possible to minimize side effects. Adjustment of the patient's management should be considered at every visit. *The first step in determining appropriate therapy for patients who are not already on a controller medication*

is classifying the severity of the patient's asthma. For patients already taking one or more controller medications, treatment options are guided by an assessment of asthma control rather than asthma severity[2].

Effective asthma management requires a preventative approach, with regularly scheduled visits during which symptoms are assessed, pulmonary function is monitored, medications are adjusted, and ongoing education is provided.

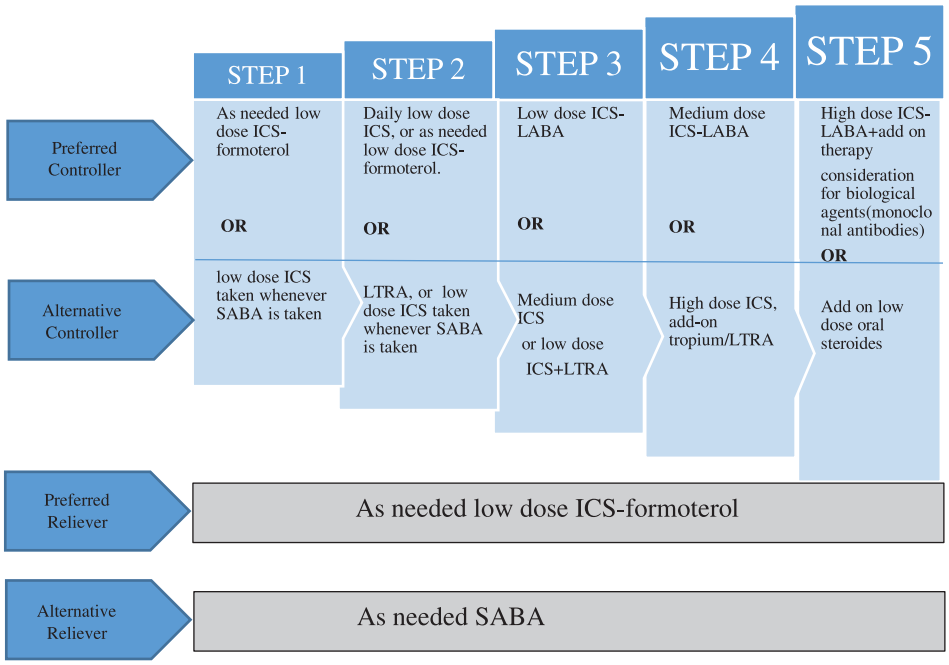
Patients should learn to monitor asthma control at home (eg, frequency and severity of dyspnoea, cough, chest tightness, and short-acting beta agonist [SABA] use). Patients with moderate to severe asthma and those with poor perception of increasing asthma symptoms may also benefit from assessment of their peak expiratory flow rate at home. A personalized asthma action plan should be provided with detailed instructions on how to adjust asthma medications based upon changes in symptoms and/or lung function**.**

Environmental triggers and co-existing conditions that interfere with asthma management should be identified and addressed for each patient.

A stepwise approach to therapy is recommended, in which the dose of medication, the number of medications, and/or the frequency of administration are increased as necessary and decreased when possible[2].

At each return visit, the patient's asthma control is evaluated. If the asthma is not well-controlled, therapy should be "**stepped-up**." If the asthma is well-controlled, therapy can be continued or possibly "**stepped-down**" to minimize medication side effects.

At each visit assess the control of asthma, check inhaler technique and compliance, adjust the dose (step up or down according to level of control).



Adopted and modified from GINA[1].

For a long time SABA had been the treatment of choice in step-1 but it was found to be associated with increased risk of asthma related deaths and hospitalization[3].

The evidence of the risk of SABA alone treatment in step 1 was further strengthened by the findings of UK national review of asthma deaths in 2014 where large number of deaths were associated with over use of SABA[4].

On the other hand evidences were emerging proving that ICS are more effective and safe in protecting against asthma related deaths, exacerbations and hospitalizations [5, 6, 7]. Recently the large Sigma 1 and 2 studies provided strong evidences which shifted the paradigm in favour ICS-LABA in the management of mild asthma [8, 9].

Currently many of the international guidelines prefer use of ICS LABA instead of as needed SABA, furthermore ICS is recommended to be taken whenever SABA is taken.

Initiating therapy in previously untreated patients

The initiation of asthma therapy in a stable patient who is not already receiving medications is based upon the severity of the individual's asthma [1, 2].

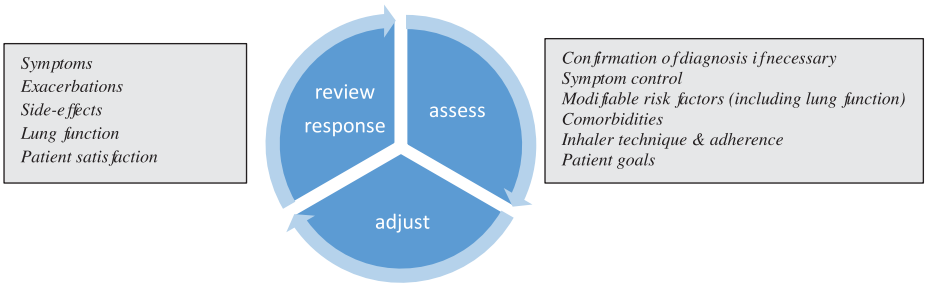
• LEVEL OF SEVERITY	• STEP OF MANAGEMNT
Intermittent	Step 1
Mild Persistent	Step 2
Moderate Persistent	Step 3 or 4
Severe Persistent	Step 5

Adjusting medication in patients already on controller therapy

In patients already taking controller asthma therapy, medication is adjusted according to asthma control. Control is assessed as discussed in the section of “Assessment of Asthma”.

In patients with well controlled asthma, medications can be continued unchanged or potentially reduced in step-wise fashion. In patients with poorly controlled asthma, treatment should be "stepped up". In patients with very poorly controlled asthma, it may be necessary to escalate therapy rapidly, then "step-down" again once good control is achieved.

Therapy should be reassessed at each visit, because asthma is an inherently variable condition, and the management of asthma is a dynamic process that changes in accordance with the patient's needs over time.



Adopted from GINA[1].

DOSAGES OF DIFFERENT INHALED CORTICOSTEROIDES:

Drugs	Daily dose (mcg)		
	Low	Medium	High
Beclomethasone dipropionate (CFC)	200-500	>500-1000	>1000
Beclomethasone dipropionate (HFA)	100-200	>200-400	>400
Budesonide (DPI)	200-400	>400-800	>800
Ciclesonide	80-160	160-320	>320
Fluticasone furoate	100	n.a	200
Fluticasone propionate (DPI)	100-250	>250-500	>500
Fluticasone propionate (HFA)	100-250	>250-500	>500
Mometasone furoate	110-220	>220-440	>440
Triamcinolone acetonide	400-1000	<1000-2000	>2000

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NON PHARMACOLOGICAL TREATMENT OF ASTHMA

Pharmacological treatment of asthma is the key for controlling symptoms and inflammation in airways. However, many patients have the perception that non pharmacological measures like dietary, environmental or life style changes, can help in control of asthma without or in addition to medicines.

Although the evidence to support efficacy of non pharmacological interventions is hard to obtain, yet the concerns and expectations of patients, relatives, and carers must be addressed properly. A few aspects of such interventions are discussed below.

- Aeroallergen Avoidance.
- Food Allergen Avoidance
- Nutritional supplements
- Tobacco smoke and other air pollutants
- Air pollution.
- Acupuncture
- Herbal medicines
- Homeopathy

Aeroallergen Avoidance

Exposure to house dust mites in early years of life has been shown to increase sensitization to house dust mites [1] and thus increased risk of asthma in later life [2]. However, interventions to reduce exposure to house dust mites and subsequent asthma are inconsistent [3].

Food Allergen Avoidance

Food allergy, specially eggs, frequently precedes onset of asthma. However, avoidance of such foods in pregnancy and during lactation, to prevent asthma in newborns, does not appear to be effective. Thus these measures cannot be recommended [4].

Nutritional Supplements

Recent changes in diet habits have decreased the in take of 3-polyunsaturated fatty acids (3-PUFAs) with an increase in 6 PUFAs. While 3-PUFAS are known to reduce inflammation and cytokines, yet their

supplementation in early life does not appear to have a beneficial and protective effect [5]. A Cochrane review of nine RCTs did not find sufficient evidence to recommend fish oil supplementation for the treatment of asthma [6].

Observational studies regarding supplementation with selenium, vitamin C, vitamin E or other antioxidants are inconclusive and need larger and controlled trials 7-9 .

No interventional studies have been reported about the beneficial effects of increased intake of fruits and vegetables on asthma.

Tobacco Smoke exposure and other air pollutants

Early life exposure to tobacco smoke and environmental smoke predisposes to persistent asthma in later life. Avoidance of tobacco smoke ensures better control of asthma.

Air Pollution

Studies strongly suggest that exposure to pollutants (including particulates, nitrogen dioxide, sulphur dioxide and ozone) [10], can increase the response to allergens, trigger an acute attack and can worsen chronic asthma 11.

Acupuncture

Few high level controlled trials have been conducted to establish role of acupuncture in asthma. A meta analysis of 11 trials did not find any effect of acupuncture in reducing symptoms [12].

Herbal Medicines.

No controlled trials have been conducted. The success stories of potions and herbal medicines (including Unani, Hakimi,and Ayurvedic) are at best anecdotal.

Homeopathy

A Cochrane review found some positive effect but no large scale high quality studies have been conducted [13].

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ACUTE ASTHMA EXACERBATIONS

DEFINITION:

An exacerbation is defined as an event characterized by change from the patient's previous status, including a progressive increase in relevant symptoms and a decrease in respiratory function[1]. The respiratory function is measured by peak expiratory flow (PEF), and forced expiratory volume in 1s (FEV1), and compared with the patient's previous or predicted values[2].

CAUSES / TRIGGERS:

Various factors are known to trigger an exacerbation and the most common causes of these are exposure to external agents, such as indoor and outdoor allergens, air pollutants, and respiratory tract infections (primarily viral). Exacerbations may also be triggered by exercise, weather changes, foods,
additives, drugs, and extreme emotional expressions, rhinitis or sinusitis, polyposis, gastroesophageal reflux, menstruation, or even pregnancy [3,4,5,6,7].
Some features are specifically associated with an increase in the risk of asthma-related death (table 1)

Table 1. Factors associated with asthma related deaths

• A history of near-fatal asthma requiring intubation and mechanical ventilation
• Hospitalization or emergency care visit for asthma in the past year
• Currently using or having recently stopped using oral corticosteroids (a marker of event severity)
• Not currently using inhaled corticosteroids
• Over-use of SABAs, especially use of more than one canister of salbutamol (or equivalent) monthly
• A history of psychiatric disease or psychosocial problems,
• Poor adherence with asthma medications and/or poor adherence with (or lack of) a written asthma action plan
• Food allergy in a patient with asthma

Adopted from GINA 2109.

ASSESSMENT:

It is very important to timely identify asthma exacerbations as they are known to be associated with worse outcomes. A brief history, review of patient's record and examination are necessary to determine: (fig-1)

1. Level of asthma control prior to the exacerbation
2. Triggers
3. Risk factors associated with fatal out come
4. Severity of exacerbation
5. Any other comorbid/condition which can mimic asthma exacerbation

Although less sensitive than the history of symptoms, serial PEF and FEV1 measurements are more objective and reliable indicators of severity and should be monitored[1].

Chest radiographs are only needed to exclude conditions like pneumonia or pneumothorax but not for all patients. Arterial blood gas (ABGs) analysis should be performed on critically ill patients or when patient has low oxygen saturations (less than 92%) despite treatment. ABGs will not only assess hypoxemia and the trend of PaCO2, but also acid base disturbances, such as respiratory acidosis and lactic acidosis[8.] Further investigations are warranted as per clinical indications.

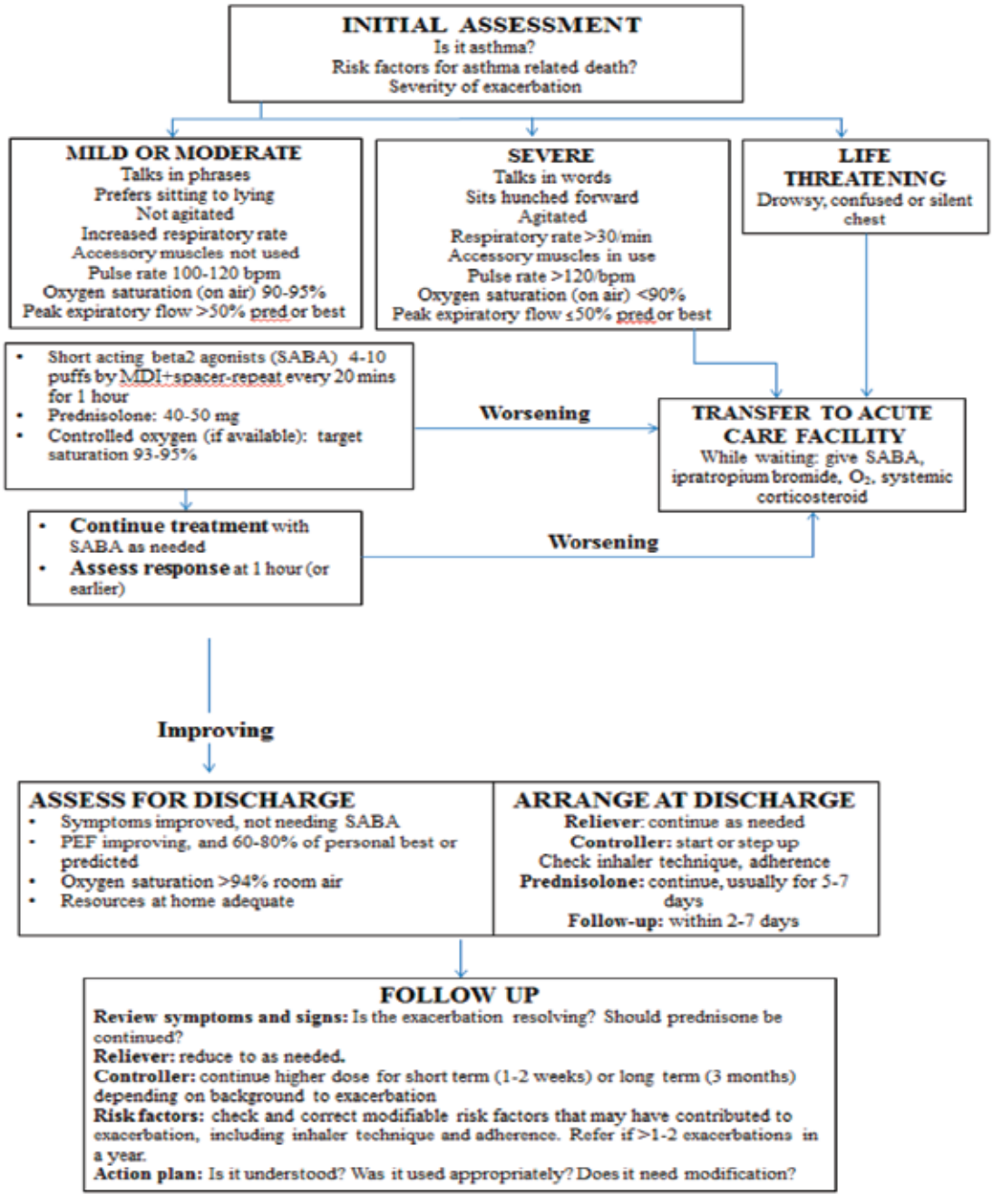

Figure 1 adopted from GINA 2019

MANAGEMENT:

Management of asthma exacerbations depends on its severity (fig-1).

Milder form of exacerbations, as depicted by change in symptoms interfering with normal activities, or PEF fallen by >20% for more than 2 days, can be treated as per written action plan given to the patients (it is important that the action plan should be according to patients literacy level.)[1,9]. The important considerations are:

- Patients already taking as needed ICS-formoterol should increase the dosing frequency up to a maximum of 12 puffs (72 mcg formoterol) beyond which a medical consultation should be taken.

This has been shown to reduce the risk of severe exacerbations as compared to only SABA rescue therapy which only eliminates the symptoms (GINA). In patients with fixed dose ICS-LABA, increasing the dose of steroids to four times can reduce the need for systemic steroids but more recent evidence is conflicting regarding their efficacy without the use of systemic corticosteroids [10].

- A short course of OCS is used (e.g. 40–50 mg/day usually for 5–7 days) in patients who:
  - Fail to respond to an increase in reliever and controller medication for 2–3 days
  - Deteriorate rapidly or who have a PEF or FEV1 <60% of their personal best or predicted value
  - Have a history of sudden severe exacerbations[1].

The management algorithm for more severe forms is shown in figure 1 and discussed below.

β2-Adrenergic Receptor Agonists

Bronchodilators are the mainstay of treatment of acute exacerbations especially short acting beta agonists (SABA).it can be administered both with spacers or nebulizers with equal efficacy [1,11].
It is recommended that in acute severe asthma SABAs are administered repetitively or continuously (there is some evidence in favour of continuous nebulization with SABA)[12]. The most commonly used SABA is salbutamol (albuterol).

Epinephrine

Its use is restricted for acute asthma related with anaphylaxis and angioedema [1,13].

Anticholinergics

Anticholinergic agents causes airway smooth muscle relaxation, enhance β2-agonist-induced bronchodilation via intracellular processes prolonging their bronchodilator effect and when combined with SABAs, it improve hospitalization rates, relapse rates and are associated with lung function improvement[1,14,15]. This combination therapy benefit is greater for the patients who present with acute severe asthma and are at a higher risk of hospitalization. Ipratropium bromide is the most common agent used. The adverse effects are of mild nature, such as mouth dryness and tremors.

Corticosteroids

In addition to its anti- inflammatory property, they also increase the number and sensitivity of β-adrenergic receptors. Oral administration is as effective as intravenous and Intramuscular administration [16,17]. The oral route is better tolerated and preferred, because it is quicker and less expensive. Intravenous route is considered in patients who may be unable to swallow or have gastro-enteral disturbances, such as vomiting [1]. The recommended daily dosage is 40-50 mg of prednisolone as a single dose, or 200 mg hydrocortisone in divided doses for 5-7 days[1].

Magnesium Sulfate

Hypermagnesemia causes relaxation of the smooth muscles and bronchodilation, possibly through inhibition of calcium influx into the muscles. It is recommended as a second line therapy at dose of 2 g infused over 20 minutes[1], it reduces the rate of hospitalization in acute severe asthma patients who show poor responsive to initial treatment, and have persistent hypoxemia[18]. It is contra-indicated for patients with renal insufficiency, hypermagnesemia and myasthenia Gravis. Nebulized magnesium has also been tried but failed to show promising results [9,19].

Methylxanthines

Because of their poor safety profile and inability to improved outcomes, such as improved pulmonary function or rate of hospitalization when given for severe acute asthma, this group has been excluded from many guidelines [1,9,20].

Leukotriene Modulators

Currently there is very little evidence in favor of this group and is generally not recommended for the management of asthma exacerbations [1].

Oxygen Supply

Patients with acute severe asthma may presents with low arterial PO_2 due to extensive *V/Q* mismatch. Oxygen should be administered via nasal cannula or mask, with a target of arterial oxygen saturation of 93–95%, or to those patients where saturation monitoring is not available[1]. Use of oxygen driven nebulization with SABAs further deteriorates the V/Q abnormalities, because of the pulmonary vasodilation of poorly ventilated areas[21].

Heliox

Heliox is a mixture of helium (70–80%) with oxygen (20–30%). Generally its efficacy has not been proven in routine care therefore it should only be considered for patients who do not respond to standard therapy[1].

Antibiotics

Use of antibiotic is associated with prolonged hospital stay and cost [22] .Current guidelines don't recommend routine use of antibiotics and should only be used when there is clear evidence of infection [1,9].

Table 2. Summary of drugs used in asthma exacerbations

S.NO	Drugs	Doses
1	Salbutamol (albuterol) solution for nebulization: single dose 2.5 mg/2.5 mL	Continuous nebulization for an hour and re-assess clinical response
2	Ipratropium bromide	Nebulization of 0.5 mg/2.5 mL/4–6 h in combination with salbutamol (same nebulizer)
3	Corticosteroids	Methylprednisolone iv infusion of 40 mg or hydrocortisone iv, 200 mg or oral prednisone 40 mg
4	Magnesium sulfate	Single iv infusion of 2 gram in 20 mins
5	Methylxanthines	Not recommended as first line; poor response and potential serious adverse events
6	Epinephrine (adrenaline)	0.3–0.4 mL subcutaneous of a 1:1000 (1 mg/mL) solution/20 min for 3 doses in case of no response
7	Heliox	Helium/oxygen mixture in a 80:20 or 70:30 ratio

Non-Invasive Mechanical Ventilation (NIV)

Unlike in acute exacerbation of chronic obstructive pulmonary disease and pulmonary edema, the role of NIV in asthma exacerbation remains controversial. Despite the lack of supporting evidence, NIV is commonly used in severe asthma exacerbation to prevent the need for intubation and mechanical ventilation.

The current guidelines recommend that NIV should only be used with close monitoring preferably in ICU[1,9].

A brief trial (for one or two hours) may be beneficial for those patients who are unresponsive to medical therapy. Prolonged trials of NIMV should be avoided. The criteria for a NIV trial include RR > 25 breaths per minute, heart rate > 110 beats per minute, hypoxemia with PaO_2/FiO_2 ratio greater than 200, hypercapnia with $PaCO_2$ < 60 mmHg, FEV_1 < 50% less than predicted and use of accessory respiratory muscles. Time should not be wasted in NIV if there is any absolute criterion for endotracheal intubation (respiratory arrest, hemodynamic instability or shock, GSC < 8), excessive respiratory secretions and risk of aspiration, severe agitation requiring sedation and poor patient collaboration. NIV can also be used in the asthmatic patients who are at risk for re-intubation, following extubation[23,24].

High Flow Nasal Cannula (HFNC)

HFNC has been getting very popular in the management of hypoxic respiratory failure of various etiologies including asthma particularly in paediatric group[25]. Studies have shown that its use reduces respiratory distress in moderate and severe asthma exacerbations and also reduces the need for intubation. Like NIV the trial of HFNC should also be given with close monitoring.

Invasive Mechanical Ventilation

Patients who don't improve with above discussed measures lead to the need for invasive mechanical ventilation. Major indications for initiation of invasive mechanical ventilation (IMV) are:

(1) Cardiac arrest;
(2) Respiratory arrest or bradypnea;
(3) Respiratory insufficiency with PaO_2 < 60 mmHg on 100% FiO_2 and $PaCO_2$ > 50 mmHg;
(4) Physical exhaustion; and
(5) Compromised level of consciousness.

Relative indications for IMV are:

(1) Hypercapnia $PaCO_2$ > 50 mmHg or $PaCO_2$ increased by 5 mmHg per hour;
(2) Worsening respiratory acidosis;,
(3) Inability to treat patient appropriately;
(4) Failure to improve with proper therapy; and
(5) Clinical signs of deterioration and respiratory fatigue such as tachypnoea of >40 breaths per minute, severe hypoxemic respiratory insufficiency, hemodynamic instability, paradoxical thoracic movement, and silent chest [26].

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DIFFICULT ASTHMA

Difficult asthma generally refers to a clinical situation where a prior diagnosis of asthma exists, and asthma-like symptoms and asthma attacks persist, despite prescription of high-dose asthma therapy[1]. In this document "difficult asthma" is used as an umbrella term which encompasses "Severe Asthma" and "Difficult to treat Asthma".

The terms "Severe Asthma" and "Difficult to Treat" Asthma have been used in literature in the past without a universally agreed definition. Consequently, data has been scarce on the management of these conditions[3]. Considerable progress in understanding and treating severe asthma has been made in the past 5 years. Advances include formulation of a standardized definition and evidence-based treatment guidelines, compilation of substantial evidence about phenotypic patterns and biomarkers, and the availability of novel targeted treatments.

Definitions:

In 2014, a consensus definition of severe asthma was published that drew a distinction between difficult-to-treat asthma and severe asthma.[3]

Difficult-to-treat asthma is asthma that remains uncontrolled despite treatment with high-dose inhaled glucocorticoids or other controllers, or that requires such treatment to
remain well controlled.[3]

Severe asthma is a subset of difficult-to-control asthma; the term is used to describe patients with asthma that remains uncontrolled despite treatment with high-dose inhaled glucocorticoids combined with a long acting β2-agonist (LABA), a leukotriene modifier, or theophylline for the previous year or treatment with systemic glucocorticoids for at least half the previous year.[3]
The term is also used to describe asthma that requires such treatment in order to remain well controlled; it excludes patients in whom asthma is vastly improved with optimization of adherence, inhaler technique, and treatment of coexisting conditions.

Who should manage Difficult Asthma?

Ideally, Difficult Asthma should be managed by a specialist preferably by a multi-disciplinary team in a severe Asthma clinic if possible.[2]

Stepwise Diagnosis and Management of Difficult Asthma

Step 1: Confirm the Diagnosis of Asthma

This includes revisting the diagnosis of asthma by confirming history of variable chest symptoms and variability of FEV1 in Lung Function Tests.[3,4]

Step 2: Check Inhaler Prescription, Technique and Adherence

Problems with inhaler techniques account for 50-80% cases of uncontrolled Asthma and thus must be reviewed and corrected on every visit. Optimizing inhaler prescription (High dose ICS + LABA combination) and use of spacer devices cannot be over emphasized. Newer devices with dose counters are now available which may help not only in improving adherence but can also aid in monitoring inhaler use.[2]

Step 3: Exclude and manage co morbidities and other factors

a. **Co-morbid conditions**

Important co morbidities such as

- Rhinosinusitis
- Gastro esophageal reflux disease
- Heart failure
- ABPA
- Obesity
- Asthma COPD Overlap (If patient has Asthma COPD overlap, they may have persistent symptoms and have higher morbidity than Asthma or COPD alone.)[4] should be sought and treated first.

b. **Psychosocial Comorbidities**: Anxiety, depression, financial and social problems are very common in these patients and should be addressed appropriately.[1] It has also been seen that severe asthma with psychosocial comorbidities have 5 times increased rate of emergency visits and healthcare utilization.[3,5]

c. **Problems with medications**: Overuse of SABA can increase airway hyper responsiveness and aggravate Asthma.[3] This should be carefully dissected and managed. The false sense of security resulting from immediate symptom relief from SABA use and low cost of these inhalers is a common cause of worsening disease and poor adherence to controller therapy.

d. **Other environmental exposures:** Environmental exposures, such as occupational exposures and tobacco smoke (associated with progression to severe asthma and reduced glucocorticoid sensitivity) are of particular concern and must be addressed.[2,3]

Step 4: Review and Step Up Management:

Implementation of the above critical steps results in the reclassification of disease in approximately 50% of patients who were thought to have severe asthma.[3]

After above factors are accounted for and addressed, step up of the current standard treatment should be done. This includes general measures, non-biologic add on therapy and biologic add on therapy.

a. **General Management:** Role of smoking cessation, exercise and mucus clearing strategies should not be undermined. Annual vaccinations should be done.

b. **Non Biologic Add On Therapy:**

Step up the patient to High Dose Inhaled Corticosteroids (800 mcg Budesonide or 500-1000 mcg fluticasone) and Inhaled LABA. Consider adding Tiotropium, a trial of it is warranted because of its much lower cost before considering expensive biologic therapy.[3] It increases lung function and time to first exacerbation. Other drugs recommended are Leukotriene modifiers (Montelukast), Theophylline and Oral Corticosteroids.[2] Daily administration of oral steroids over a long p[6]. These add ons must be added step wise, assessing for treatment response and adverse effects of medication. Ineffective treatment options should be withdrawn.[3]

c. Consider Add on Biologic/ Targeted Therapy in Refractory cases:

Targeted biologic therapy is now approved for the management of refractory disease and are available in the developed countries.

Targeted therapy means that treatment is tailored according to the diverse pathobiologic processes that can underlie clinical presentations.[3]

A recognition of "Asthma phenotypes" and their specific biomarkers is important before choosing one of these expensive agents.[6]

Asthma is known to be eosinophilic (IgE mediated, atopic) or non-allergic (neutophilic, late onset). There are other phenotypes but targeted biologic therapy is not approved/ available yet.[6]

Eosinophilic Asthma

Most advancement of Asthma management has been for this phenotype. Type 2 inflammation in the airway is characterized by the presence of cytokines (interleukin-4,interleukin-5, and interleukin-13) that were originally recognized as being produced by type 2 helper T (Th2) cells are also produced by innate lymphoid cells in response to infectious agents and pollutants and other "non-allergic" stimuli. Since interleukin-4 and interleukin-5 promote the production of IgE and eosinophils, respectively, this inflammation is frequently characterized by eosinophils and may be accompanied by atopy. In mild-to-moderate asthma, type 2 inflammation is common and generally promptly resolves after treatment with glucocorticoids. However, in the context of severe asthma, this phenotype is characterized by persistent evidence of active type 2 inflammation despite high-dose therapy with inhaled glucocorticoids.
Sputum eosinophilia, defined as 2% or more of leukocytes in a sample, is seen in more
than half of patients with severe asthma and has been labeled **glucocorticoid-resistant asthma.**

Biomarkers for Eosinophilic Inflammation:

- Blood eosinophil count≥300/µl
- FeNO ≥20 ppb
- sputum eosinophils≥2%

These advanced tests are currently not available in Pakistan but it is hoped that soon they will be.

Targeted Treatment options:

Of these, Omalizumab (Xolair) is available in Pakistan.

Anti IgE therapy:

Omalizumab is a monoclonal antibody that binds to free IgE, preventing activation of cells such as mast cells, basophils, and dendritic cells and down-regulating the high-affinity receptor for the Fc region of IgE (FcεRI).[3,4] Omalizumab has been available for clinical use in the developed countries since 2003. It has been tested almost exclusively in patients with allergic asthma, as defined by an IgE level of 30 IU per milliliter or more and at least one positive aeroallergen skin test or an elevated specific aeroallergen IgE level.[2,3]

When added to inhaled glucocorticoids (in most studies, without concomitant LABAs), omalizumab reduced severe exacerbations by 45% and hospitalizations by approximately 85% and allowed lower doses of inhaled glucocorticoids and a small decrease in the use of quick-relief therapy, with inconsistent effects on lung function. Baseline IgE levels are not predictive of response but are needed along with body weight to calculate the drug dose.[2,3]

How to administer targeted therapy?

Omalizumab (Xolair), subcutaneous injection every2 to 4 wk depending on dose (for dosing according to weight and IgE, see www .accessdata.fda.gov/drugsatfda_docs/ label/2007/103976s5102lbl.pdf)

Anti–Interleukin-5 Agents:

These include Mepolizumab, Reslizumab and Benralizumab. They are currently not available in Pakistan. For academic purposes dose and route of administration are described.

Mepolizumab (Nucala),100 mg given by monthly subcutaneous injection. Anti–interleukin-5; binds circulating interleukin-5[3]

Reslizumab (Cinqair), 3 mg/kg given by monthly intravenous infusion. Anti–interleukin-5; binds circulating interleukin-5[3]

Benralizumab: Given by subcutaneous injection. (Anti–interleukin-5; binds interleukin-5 receptor with resultant lysis of eosinophils.[3]

In Phase 3 trials:

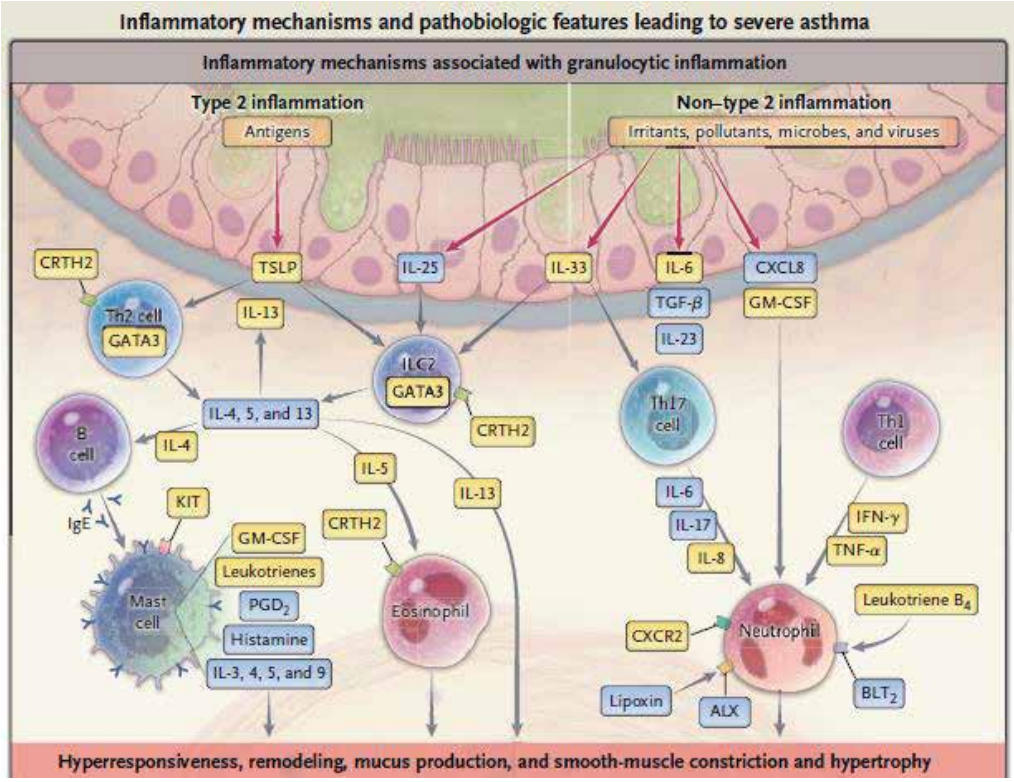
Dupilumab, given by subcutaneous injection. Anti–interleukin-4 and interleukin-13; binds common receptor subunit for interleukin-4 and interleukin-13 receptor.[3]

Fevipiprant, pill taken by mouth.Anti-CRTH2; blocks signaling at CRTH2(the PGD2 receptor).[3]

Neutrophilic Inflammation in Asthma:

Less well characterized are patients with severe asthma who have neutrophilic inflammation (variably defined as exceeding 40 to 60% neutrophils) in induced sputum samples; this type is typically not responsive to treatment with glucocorticoids.[2]

Some patients have coexisting infections in the sinuses or airways; others report exposure to occupational or environmental sensitizers, including tobacco smoke. Macrolide therapy has been proposed for moderate-to-severe asthma, but evidence is inadequate to direct treatment in patients who meet the criteria for severe asthma.[3]



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ALLERGEN IMMUNOTHERAPY

Asthma is one of the chronic diseases which has seen a number of therapeutic options over the last couple of decades. Since many cases of asthma are due to IgE mediated allergies, allergen immunotherapy (AIT) has been suggested as one of the options. AIT builds immune tolerance through the administration of specific allergens.

Ever since Leonard Noon and John Freeman published their work on immunotherapy in 1911 [1], it has been studied extensively under various names (e.g., allergen or allergy immunotherapy, specific or allergen-specific immunotherapy)[2]. AIT has proven to be effective in allergic asthma, allergic rhinitis, conjunctivitis, and stinging insect hypersensitivity. It is potentially disease modifying option the effects of which can be seen even many months after cessation of AIT.

Mechanism

After initial exposure to small therapeutic doses of specific allergen, decreased responsiveness of basophils and mast cells is observed over a matter of hours [2]. Successful immunotherapy induces a shift from T helper cell type-2 (Th2) immune responses, which are associated with the development of atopic conditions, to a better balance with more Th1 immune responses. It is also associated with the production of T regulatory cells that produce the anti-inflammatory cytokine, interleukin 10 (IL-10). IL-10 has been shown to reduce levels of allergen-specific immunoglobulin E (IgE) antibodies, increase levels of immunoglobulin G4 (IgG4) ("blocking") antibodies that play a role in secondary immune responses, and reduce the release of pro-inflammatory cytokines from mast cells, eosinophils and T cells [3].

Modes of Allergen Immunotherapy

There are two major modes of AIT; SCIT (SubCutaneous ImmunoTherapy) and SLIT (SubLingual ImmunoTherapy). In SCIT repeated small but gradually incremental doses of allergen are injected subcutaneously at regular intervals. In SLIT the small doses are given sublingually. Both modes have been proven to be effective. The dose of allergen has not been specified. To achieve a similar level of clinical efficacy, the cumulative amount of allergen in 1 year could be as much as 200-times greater with SLIT compared with SCIT [4].

Indications

AIT is indicated in patients with allergic rhinitis/conjunctivitis/asthma associate with IgE antibodies to specific allergen. Skin prick testing (SPT) is the preferred method of testing. AIT in indicated in

-patients with symptoms not well controlled with medications or avoidance of allergen

-patients with side effects of medications or

- patients who want to avoid long term use of medications.

Contraindications

AIT is not indicated in patients with severe and/or uncontrolled asthma. It is also contraindicated in patients with cardiovascular diseases like unstable angina, previous myocardial infarction, hypertension, or arrhythmias. Exposure to beta blockers may be associated with severe and treatment resistant anaphylactic reaction. Thus exposure to beta blockers is an absolute contraindication.

Special Situations

***Children*:** Although there is no age limit of AIT, yet special consideration should be given to children under the age of 6 years since so young children may not be cooperative in testing and repeated injections[5].

Elderly: Since the elderly frequently have co morbidities, and thus increased risk of anaphylaxis, the risk benefit ratio of AIT must be weighed before starting SPT and AIT.

Pregancy: AIT should not be started in pregnant women; however women who already are undergoing AIT and get pregnant may continue.

Sublingual Immunotherapy

SLIT is a novel way of immunotherapy. Small doses of allergen are given sublingually to be dissolved. Currently SLIT tablets are available for ragweed, grasses, and house dust mite-induced allergic rhinitis, but not in Pakistan. SLIT has the advantage that patients can take weekly tablets at home; avoid discomfort of injections, along with the favorable safety profile.

The most common side effects of sublingual immunotherapy are local reactions such as oral pruritus, throat irritation, and ear pruritus [6]. These adverse effects usually resolve after first few weeks of therapy.

Safety

SCIT and SLIT are generally considered safe procedure when used judiciously in well selected patients. However local and systemic reactions can occur. Thu SCIT must be started under strict medical supervision.

Ait in Polysensitised Individuals

During SPT many individuals are found to be sensitized to not one but multiple allergens. A substantial part of patients which could gain benefit from AIT, do not achieve it because of polysensitisation. Thus AIT is not suitable only in patients with multi-sensitization to various unrelated allergens, or in those with undetectable causal allergen [7].

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Asthma in special situations

1. Asthma in Pregnancy

The prevalence of asthma during pregnancy is approximately 4-8%.[1] Several physiological changes occur during pregnancy that could improve or worsen asthma. A meta-analysis of 14 studies concluded that among pregnant asthmatics about one third experience an improvement, one third have worsening and the remaining one third would show no change in disease severity.[2] However, the majority of women with asthma have normal pregnancies and the risk of complications is small in those with well-controlled asthma.[3]

It has been observed that pregnant women have a tendency to stop asthma medications due to the misconception that these would harm them and their babies.[4] On the contrary maintaining adequate asthma control during pregnancy is essential as uncontrolled asthma is associated with many maternal and fetal complications including hyperemesis, hypertension, pre-eclampsia, complicated labour, fetal growth retardation, preterm birth, increased perinatal mortality and neonatal hypoxia.[5-8]

Exacerbations requiring medical intervention occur in 20% and exacerbations requiring hospitalization occur in about 6% of pregnant asthmatics. Most of these exacerbations occur in late second trimester of pregnancy and are significantly associated with low birth weight babies.[9]

Management:

Pregnant women should be counselled regarding the importance and safety of continuing their asthma medications during pregnancy. Management of asthma in pregnancy is the same stepwise approach as in non-pregnant patients as the medicines used to treat asthma are safe in pregnancy.

1. **B_2 agonists:**

Both short and long acting B_2 agonists are safe in pregnancy with no increased risk of maternal complications or fetal malformations.[10-13]

2. **Inhaled corticosteroids:**

They should be used as usual during pregnancy as no significant association has been observed between major congenital malformations or adverse perinatal outcome and exposure to inhaled corticosteroids.[14,15]

3. **Theophyllines:**

No significant association has been observed between major congenital malformations or adverse perinatal outcome and exposure to theophyllines.[16] Since protein binding decreases during pregnancy resulting in increased free drug levels hence it is desired to measure and maintain a lower therapeutic theophylline level.[17]

4. **Oral corticosteroids:**

These should be used as usual whenever indicated during pregnancy.[16] There has been a slight concern of cleft palate with their use in first trimester of pregnancy but that association is not definite and even if it is real, their benefit in treating severe or life threatening asthma strongly outweighs the above risk.[7,18]

5. **Leukotriene Receptor Antagonists:**

Data regarding their safety in pregnancy is limited but the available data has not shown any increased risk of maternal complications or fetal malformations. Hence they should be used as indicated during pregnancy.[19]

6. **Sodium cromoglycate and nedocromil sodium:**

No significant association has been demonstrated between major congenital malformations or adverse perinatal outcome and exposure to sodium cromoglycate and nedocromil sodium.[16]

7. **Immunomodulation therapy:**

There are as yet no clinical data on the use of omalizumab for moderate-severe allergic asthma in pregnant asthmatics.

Management of Acute Exacerbation of Asthma in pregnancy:

Pregnant women are recommended to receive the same drug treatment for acute asthma as non-pregnant patients including nebulized β_2 agonist and systemic corticosteroids.[6,20] In severe cases intravenous β_2 agonist, aminophylline or magnesium sulphate can be used as indicated.[21] Oxygen should be delivered to maintain saturation 94-98% in order to prevent maternal and fetal hypoxia.[22]

Management during Labour:

Pregnant women should continue their usual asthma medications in labour. Asthmatic women can safely use all forms of usual labour analgesia.[5] In the absence of acute attack, Caesarean section should be reserved for usual obstetric indications.[20] If anaesthesia is required, regional blockade is preferable to general anaesthesia

due to potential risk of bronchospasm with certain inhaled anaesthetic agents. Women receiving oral steroids at dose exceeding prednisolone 7.5mg per day for more than two weeks prior to delivery should receive parenteral hydrocortisone 100mg 6-8 hourly during labour.[23] Prostaglandin F2α (carboprost/hemobate) used to treat postpartum haemorrhage due to uterine atony may cause bronchospasm.[17]

Management during breast-feeding:

Pregnant asthma patients should be encouraged to breast-feed after delivery and to continue their usual asthma medications during lactation.[24]

2. Occupational Asthma

It is defined as new onset asthma symptoms or definite worsening of previously quiescent asthma after employment, along with presence of history of exposure to known or suspected sensitizing agent.[25,26]

Workers reported to be at risk of developing asthma include bakers, food processors, forestry workers, chemical workers, plastic and rubber workers, metal workers, welders, textile workers, electrical and electronic production workers, storage workers, farm workers, painters, dental workers and laboratory technicians.[27,28]

The most frequently causative agents include isocyanates, flour and grain dust, colophony and fluxes, latex, animals, aldehydes and wood dust.[29-31]

Diagnosis:

A simple screening test to ask is whether their symptoms improve when they are away from work.[32] Those with positive answer should have further objective assessment. Serial measurement of peak expiratory flow (PEF) is the most commonly used investigation with high sensitivity and specificity in the diagnosis of occupational asthma. It requires:

1) At least three days of PEF recordings in each consecutive work period.
2) At least four evenly spaced readings per day.
3) At least three series of consecutive days at work with three periods away from work (usually three weeks).[33]

Management:

The main aim of management is to identify the cause, remove the worker from exposure and for the worker to have worthwhile employment.[34]

The duration of continued exposure following onset of symptoms and severity of asthma at diagnosis are important determinants of outcome. Early diagnosis and early avoidance of further exposure offer the best chance of complete recovery. Both removal of exposure and reduction of exposure improve symptoms of occupational asthma. Removal of exposure appears to be better than reduction of exposure but there is increased risk of unemployment associated with it.[34,35]

3. Aspirin Induced Asthma

Aspirin induced asthma (AIA) consists of clinical triad of asthma, chronic rhinosinusitis with nasal polyps and precipitation of asthma and rhinitis attacks in response to aspirin.[36] The prevalence of this syndrome in adult asthmatic population is 4 – 10%.[37] Majority of patients experience first symptoms during their third to fourth decade of life and once it develops, it persists for life.[38]

The diagnosis of AIA can be established by oral, nasal or bronchial challenge testing with aspirin in patients with suggestive history.[39] Typically, within minutes to 2 hours following ingestion of aspirin, an acute severe asthma attack develops and it is usually accompanied by rhinorrhea, nasal obstruction, conjunctival irritation and scarlet flush of head and neck. A normal sinus CT almost excludes AIA.[40]

Management:

Patients with AIA should avoid Aspirin or NSAIDs. When an NSAID is indicated, COX-2 inhibitors or alternative analgesics such as paracetamol are recommended.[41] Referral to allergy specialist for aspirin desensitization is recommended for selected subjects who need aspirin as antiplatelet therapy.[42]

4. Exercise Induced Asthma

Exercise induced asthma (EIA) is defined as fall in FEV1 of 10% or greater on an exercise challenge test (4-6 min of exercise at ear-maximum targets with total duration of exercise of 6-8 minutes).[43,44] Normally, bronchodilatation occurs during exercise and lasts for few minutes but in EIA the initial bronchodilatation is

followed by bronchoconstriction that generally peaks within 10-15 minutes after completing the exercise and resolves within 60 minutes.[38]

Management:

A warm-up period before exercise may reduce EIA symptoms. Pre-treatment with bronchodilator agents (SABA, SAMA or LAMA), a few minutes before exercise, is effective in attenuating the fall in FEV1 associated with EIA.[45] If above approach does not control the symptoms, then the patient is recommended to have maintenance therapy with ICS. Regular use of Leukotriene Receptor Antagonists may also help, especially in children.[46]

5. Gastro-esophageal Reflux Disease and Asthma

GERD is more prevalent in patients with asthma compared to the general population.[38] The presence of acid in the distal esophagus, mediated via vagal or other neural reflexes, can significantly increase airway resistance and airway reactivity. The treatment of asthma with agents such as theophylline may also lower esophageal sphincter tone and induce GERD symptoms.[47] All patients with asthma should be questioned about symptoms of GERD.[38]

Management:

A trial of anti-GERD measures including a proton pump inhibitor is recommended for 6-8 weeks. Benefit of proton pump inhibitors is limited to symptomatic GERD and night-time respiratory symptoms.[48]

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TYPES OF INHALERS

Asthma being chronic airway inflammatory disease, with episodic airflow limitation requiring inhaled therapy as a cornerstone of treatment. Quick and direct delivery to the site of pathology that is airways can be ensured with inhaled therapy with minimum side effects, Inhaled therapy can be given via number of devices like nebulizers, pressurized Metered dose inhlers (p MDI), Dry powder inhalers (DPI), BA- MDI (Breath actuated MDI), Soft mist inhalers (SMI) etc.

Asthma control cannot be achieved with poor inhaler technique and leads to non adherence of inhaler therapy. A variety of factors including age, patient preference, dexterity, cognitive ability, inspiratory capacity and health literacy can impact patient ability and intention to use inhaler properly.

Lot of innovations being made in design, particle size and formulations of drug used in inhalers to improve its efficiency. Available DPI `s are either single capsule or multi dose with dose counter (Diskus or nexthaler) DPI. Newer MDI are CFC free (ozone friendly) and has dose counter to help facilitate and realize when it gets empty.

Inhalers	Advantages	Disadvantages
pMDI	1. Compact and Portable 2. Multidose device 3. Metered dose 4. Familiar/ Established 5. Available for most inhaled medications 6. Quick & easy to use 7. Suitable for emergencies	1. Needs coordination 2. High deposition in mouth and oropharynx 3. “Cold Freon” Effect 4. Contain propellant 5. Some may not have dose counter.
pMDI with spacer	1. Easier to coordinate 2. Can be used easily with low inspiratory effort 3. Low mouth and oropharyngeal deposition 4. Higher lung deposition than pMDI	1. Less portable than pMDI 2. Cost increases 3. Needs more regular maintenance 4. Some spacers may acquire electronic charge.
3. DPI	1. Compact & portable 2. Breath actuated	1. Requires inspiratory effort 2. May not be suitable for emergency

	3. Does not contain propellant 4. Multidose devices available	3. Multiple designs (may be confusing) 4. May be complicated to load. 5. Partly sensitive to humidity. 6. May not be suitable for young children.
4. Nebulizer	1. Can be used at any age or critically ill, even semi- conscious patient. 2. No specific inhalation technique required.	1. Most lack portability 2. May need electric supply 3. Costly 4. Device cleanliness & maintenance required 5. Can result longer treatment time.

Other inhalers like BA- MDI (breath actuated Metered dose inhaler) & SMI (soft mist inhaler) are available in USA and Europe. These type of inhalers , not yet available in Pakistan but much easy to use and don`t need breath coordination by the patient.

Selection of Inhaler Type

To improve patient compliance and get maximum benefit of inhaler, it is important to select right device for right patient. Selection of inhaler type for any individual patient must be done in consultation with patient , keeping in view affordability, age, general condition, dexterity, cognition and most importantly it`s inspiratory effort.

Ask the patient to try both of the following inhalation maneuvers

1. Quick & Deep: Can a patient take quick and deep breath in (within 2- 3 sec),
2. Slow & steady: Can a patient take slow & steady breath in (over 4-5 sec).

Prescribe DPI if patient can perform maneuver 1 only that is take deep & quick breath in & can`t perform 2. Prescribe pMDI if can perform maneuver 2 only, i.e, slow & steady inspiration over 4-5 seconds. If can perform both inhalation maneuvers, then consider patient preference.

There are many different devices in market to check for inspiratory effort like AIM machine, In check DIAL Inspiratory flow meter, Flo tone trainer, etc.

Select appropriate drug formulation once inhaler device type has been chosen, in line with local formulary.

Patient engagement & training for Inhaler technique are of paramount importance.

Steps for using pMDI & pMDI with spacer are given below

Steps for using a pressurized metered dose inhaler device

- Remove the mouthpiece cap from the inhaler
- Shake the inhaler well and hold it upright (prime the inhaler before first use and if the inhaler has not been used for more than a week. This is done by releasing four sprays in the air away from the face and eyes)
- Breathe out gently and completely
- Put mouthpiece between teeth without biting and close lips to form a good seal
- Start to breathe in slowly through mouth and at the same time actuate the device by pressing down firmly on canister
- Continue to breathe in slowly and deeply to full capacity
- Hold breath for about 10 seconds or for as long as comfortable
- While holding breath, remove inhaler from mouth
- Breathe out gently
- Replace the mouthpiece cap
- If an extra dose is needed, wait for 1 min and then repeat above steps

Steps for using a pressurized metered dose inhaler device with spacer

- Assemble spacer
- Remove the mouthpiece cap from the inhaler
- Hold the inhaler upright and shake well (prime the inhaler before first use and if the inhaler has not been used for more than a week. This is done by releasing four sprays in the air away from the face and eyes)
- Insert the inhaler firmly in an upright position into the spacer
- Holding the spacer level, press down firmly on the canister once
- Breathe out gently and completely
- Remove the mouthpiece cap from the spacer and put mouthpiece between teeth without biting and close lips to form a good seal
- Start to breathe in slowly through mouth
- Breathe in slowly and deeply to full capacity, remove spacer from mouth and hold breath for about 10 seconds or for as long as comfortable then breathe out gently OR breathe in and out normally for 4 breaths
- Replace the mouthpiece cap
- If an extra dose is needed, wait for 1 min and then repeat above steps

Care of the spacer

- Disassemble the spacer
- Clean your spacer before first use and then nearly once a month
- Dismantle your spacer and wash all parts in clean warm water with a mild detergent
- Allow the parts to air dry without wiping- DO NOT dry with a cloth or paper towel

The general steps for using a dry powder inhaler for as follows:

1. Remove the cap from the dry powder inhaler.
2. Load a dose of medicine (how you do this depends on the type of inhaler you have).
3. Turn your head and breathe out as much air as you can -- try and empty your lungs.
4. Put the dry powder inhaler up to your mouth.
5. Place the mouth-piece in your mouth and seal your lips firmly around the opening so no air or medicine can escape out the sides.
6. Using just your mouth, breathe in once -- very deep and fast -- filling your lungs as deeply as you can. Dry powder inhalers are breathe-activated, so it's the breathing in deep and fast that gives you the right dose of medicine. Never breathe *into* the inhaler.
7. Take your mouth off the inhaler and hold your breath for at least 10 seconds. Then slowly breathe out.
8. If your doctor prescribed more than one dose of medication, wait about 1 minute before taking the next dose.
9. Replace the cap on the dry powder inhaler. Gargle and rinse your mouth with water or mouthwash (usually advised only for steroid-type inhalers).

pMDI & DPI proper technique can be seen at https://www.ers-education.org/umbraco/sdi/media/showMedia.aspx

Strategies to ensure effective use of inhaler device.

Remember 4 C`s

Choose

(i) Choose the most appropriate inhaler device for the patient before prescribing. Consider the medication options, the available devices, patient skills, and cost

(ii) If different options are available, encourage the patient to participate in the choice

(iii) For pMDIs, use of a spacer improves delivery and (with ICS) reduces the potential for side effects

(iv) Ensure that there are no physical barriers, for example, arthritis, that limit the use of the inhaler

(v) Avoid use of multiple different inhaler types where possible, to avoid confusion

Check

(vi) Check inhaler technique at every opportunity

(vii) Ask the patient to show you how they use their inhaler (do not just ask if they know how to use it)

(viii) Identify any errors using a device-specific checklist

Correct

(ix) Show the patient how to use the device correctly with a physical demonstration, for example, using a placebo inhaler

(x) Check technique again, paying attention to problematic steps. You may need to repeat this process 2-3 times

(xi) Only consider an alternative device if the patient cannot use the inhaler correctly after several repeats of training

(xii) Recheck inhaler technique frequently. After initial training, errors often recur within 4–6 weeks

Confirm

(xiii) Clinicians should be able to demonstrate correct technique for each of the inhalers they prescribe

(xiv) Pharmacists and nurses can provide highly effective inhaler skills training

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ASTHMA-COPD OVERLAP SYNDROME (ACOS)

Asthma and chronic obstructive pulmonary disease (COPD) are two of the most commonly encountered chronic lung diseases. However differentiating between the two may be difficult at times. Asthma is characterized clinically by cough, shortness of breath, wheeze, and tightness of chest, and spirometrically with reversible airway obstruction, usually associated with atopy. In contrast COPD is progressively worsening shortness of breath associated with minimally reversible airway obstruction usually after exposure to smoke. However physicians identified patients who had features of both and these patients were assigned to an entity of overlap of both asthma and COPD.

In 1961, a "Dutch hypothesis," presented by Orie and colleagues[1] acknowledged the frequent problems in differentiating between asthma and COPD, especially in older adults who currently smoke or have a significant history of cigarette smoking. "Dutch hypothesis" tried to answer the question, hypothesizing that asthma and Bronchial Hyper Responsiveness (BHR) predispose to COPD later in life and that asthma, COPD, chronic bronchitis, and emphysema are different expressions of a single airway disease.

Several terms have been identified within the literature that described the overlap phenotype of asthma and COPD: 'Asthmatic bronchitis', 'COPD with a prominent asthmatic component', 'asthma that complicates COPD' and 'mixed COPD-asthma' [2]. The consensus document selected to call this differential entity as "mixed COPD–asthma phenotype" [7]. However the term Asthma-COPD Overlap Syndrome (ACOS) has been more frequently used lately.

The prevalence of ACOS varies considerably because it has been diagnosed using different criteria, which depend on the study design and the population. Within the published literature, ACOS prevalence varied between asthmatic patient populations and COPD patient populations. This may be attributable to differences in age or smoking status, which are both risk factors for COPD and ACOS [3]. In patients with a pre-existing diagnosis of asthma, the prevalence of ACOS was 29% when they had chronic bronchitis and/or impairment in the diffusing capacity of the lung for carbon monoxide (DLCO). In patients with a pre-existing diagnosis of COPD, the prevalence of ACOS was 13% when the patients had self-reported, physician-diagnosed asthma before the age of 40 years and increased up to 55% when the patients met any criteria for asthma[2].

DEFINITION

ACOS has not yet been defined definitively. Just as asthma and COPD are heterogenous disorders, each having its own broad range of underlying mechanisms and pathophysiology, so is the ACOS. ACOS does not appear to be a single disease and represents a spectrum of disease process ranging from asthma at one end and COPD at the other. ACOS is still poorly characterized, both in terms of general risk factors and pathophysiology, and in terms of clinical symptoms, treatment response and prognosis.

A joint document issued by Global Initiative against Asthma (GINA) and Global Initiative

for Chronic Obstructive Lung Disease (GOLD) document[4] defines that ACOS is "characterized by chronic airflow limitations with several features associated with asthma and several features associated with COPD" but this definition is vague. Many attempts have been made to define this collection of symptoms [6]. A round table discussion tried to reach a consensus on defining ACOS [7]. Three key features were identified to be included in the operational definition:

1) Persistent airflow limitation on spirometry despite adequate administration of a short-acting bronchodilator in subjects 40 years of age or older;

2) A "significant" history of cigarette smoking or an equivalent lifetime exposure to biomass; and

3) A physician diagnosis of asthma before 40 years of age.

Another consensus document [8] agreed on the same components or traits of ACOS.

DIFFERENTIATING ASTHMA, COPD, AND ACOS

The joint GINA/GOLD guideline proposes that clinicians should assemble the features for asthma and for COPD that best describe the patient and compare the number of features in favor of each diagnosis. In practice, if three or more features of either asthma or COPD are present, that diagnosis is suggested; if there are similar numbers of features of asthma and COPD, the diagnosis of ACOS should be considered. The relevant variables are age at onset, pattern and time course of symptoms, personal history or family history, variable or persistent airflow limitation, lung function between symptoms, and severe hyperinflation.

Table 1 highlights features differentiating asthma, COPD, and ACOS.

Table 1: Usual features of Asthma, COPD and ACOS

Feature	Asthma	COPD	ACOS
Age of onset	Usually childhood but can commence at any age	Usually >40 years of age	Usually >40 years of age but may have symptoms in childhood or early adulthood
Pattern of Symptoms	Variable, with triggers	Chronic, usually continuous	Persistent with prominent variability
Lung Function	Variable with reversibility e.g., BDR,	Persistent post BD $FEV_1/FVC < 0.7$	Airflow limitation variable but not fully reversible
Lung function between symptoms	May be normal	Persistent airflow limitation	Persistent airflow limitation
Past or family history	Allergies or childhood asthma or family history of asthma	History of exposure to noxious gases and particles	History of doctor diagnosed asthma, or allergies, and a family history of asthma, and/or history of exposure to noxious agents
Time Course	Often improves spontaneously or with treatment	Slowly progressive over years despite treatment	Symptoms partly but significantly reduced with treatment. Progress is usual and treatment needs high.
Chest X-ray	Usually normal	Severe hyperinflation or other changes of COPD	Similar to COPD

Exacerbations	Occur but risk reduced by treatment	Can be reduced by treatment, if present, co morbidities contribute to impairment	More common than in COPD but reduced by treatment. co morbidities contribute to impairment
Airway Inflammation	Eosinophils and/or neutrophils	Neutrophils eosinophils in sputum, lymphocytes in airways. May have systemic inflammation	Eosinophils and/or neutrophils in sputum
Normal FEV_1/FVC pre- or post BD	Compatible with diagnosis	Not compatible with diagnosis	Not compatible unless other evidence of airflow limitation
Post BD FEV_1/FVC<,0.70	May improve spontaneously or with treatment	Required for diagnosis	Usually present
Post BD increase in FEV1□12% and 200 ml from baseline (reversible airflow limitation)	Usual at some time in course of asthma	Common and more likely when FEV_1 is low	Common and more likely when FEV_1 is low
Post BD increase in FEV1□12% and 400 ml from baseline (marked reversibility)	High probability of asthma	Unusual in COPD.	Compatible with diagnosis

Adapted from Diagnosis of diseases of Chronic Airflow Limitation: Asthma, COPD, And Asthma-COPD Overlap Syndrome [4].

POTENTIAL BIOMARKERS

Two biomarkers may be of utility in identifying ACOS. Serum periostin, a matricellular protein highly expressed in allergic diseases, and YKL-40, a glycoprotein that is secreted by inflammatory and airway epithelial cells, and is upregulated in COPD (Table 2). [5]

Table 2: Potential ACOS Biomarkers

	Periostin	*YKL-40*
Asthma	High	Low
ACOS	High	High
COPD	Low	High

DIAGNOSIS

Although there is no agreed, established and validated definition for ACOS, this entity is widely recognized in clinical practice as an individualized phenotype demarcated from the spectrum of COPD, or a subset of COPD. Thus it was imperative that consensus be reached to standardize the diagnosis. Certain diagnostic criteria have been proposed and agreed upon by national guidelines [7,8] and studies [8,11] (table 3).

TABLE 3: Diagnostic Criteria for ACOS

Major	Minor
1. Persistent airflow limitation (post-bronchodilator $FEV_1/FVC < 0.70$ or LLN) in individuals 40 years of age or older; LLN is preferred **2.** At least 10 pack-years of tobacco smoking **OR** equivalent indoor or outdoor air pollution exposure (e.g. biomass) **3.** Documented history of asthma before 40 years of age **OR** BDR of >400 mL in FEV_1	**1.** Documented history of atopy or allergic rhinitis **2.** BDR of FEV_1 >200 mL and 12% from baseline values on 2 or more visits **3.** Peripheral blood eosinophil count of >300 cells·uL−1

FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; BDR: post-bronchodilator reversibility using 400 ug of albuterol/salbutamol (or equivalent); LLN: lower limit of normal

Presence of all three major criteria and at least one minor criterion has been proposed for diagnosis of asthma-chronic obstructive pulmonary disease overlap syndrome. [7]

MANAGEMENT

In principle, ACOS has similar goals of treatment as asthma and COPD: a) control and relief of symptoms, b) a reduction in the frequency of exacerbations, c) a reduction in the rate of decline in lung function and d) limiting adverse effects from therapeutic treatments. [2]

The clinical evidence of pharmacological therapy is lacking as very few studies have been conducted on defined patients of ACOS and such patients with overlapping symptoms have been excluded from trials. However following suggestions have been strongly recommended by consensus. [2, 12]

Majority of patients have been reported to have benefitted from a combination of inhaled corticosteroids (ICS) and long acting bronchodilators (LABA). A valid concern has been raised about use of LABA alone in patients with most features of asthma. However ICS/LABA combination has been favored by most consensus guidelines. [2, 12].

Patients responding poorly to ICS/LABA or with severe disease should be offered triple therapy with ICS/LABA and LAMA (long acting anti muscarinic agents). This practice appears to benefit COPD patients with concomitant asthma. [13]

Other components of treatment may comprise the following: a) patient education, b) smoking cessation, c) allergen avoidance, d) flu vaccination, e) pulmonary rehabilitation and f) management of any comorbidity.

PROGNOSIS

Patients with ACOS experience more rapid decline in lung function [14], frequent exacerbations [15], have poorer health-related quality-of-life (HRQoL) outcomes [16], and require a large amount of medical resources compared to patients with asthma or COPD alone [17].

CONCLUSION

ACOS can be termed as interim term as many lacunae exist on definitive definition, pathophysiology, molecular basis of disease, clinical features, diagnostic biomarkers, and management principles. More studies need to be conducted to enlighten this entity.

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COVID-19 AND ASTHMA

COVID-19 started in December, 2019 in China, within almost three months it became a pandemic. People with preexisting pulmonary disease are at higher risk of severe disease and mortality[1] but not much is known about the association between asthma and COVID-19. While for most it remains unclear if asthma is a risk factor for COVID-19, a study in United Kingdom found that 14 % of patients admitted in hospitals had asthma[2].

Viral infection is a known trigger for asthma exacerbation but no data is available to know that how much severe exacerbation COVID-19 can cause in patients with asthma. Not only asthma itself but also the treatment, most importantly biologic agents, can possibly place the patients at higher risk of severe disease[3].

COVID-19 and Asthma diagnosis

Spirometry is an aerosol generating procedure, so it can cause infection transmission. If necessary for diagnosis it can be performed with recommended precautions[4]. Otherwise diagnosis can be made on the basis of history.

Infection Prevention with Asthma

People with asthma should practice some extra measures for infection prevention in addition to usual measures, these are[5]:

- Avoidance of disinfectant that can cause asthma attack.
- Pour the disinfectant product on a cleaning towel, instead of spraying.
- Rooms should be aerated in a way that air blows out.

COVID-19 and Asthma treatment[3,4,5]

- Patients should continue the usual treatment prescribed by their physician.
- In case of exacerbation change in treatment can be made according to patient's Asthma Action Plan.
- Patients who need long term oral corticosteroids or biologic agents may continue with same.
- Asthma exacerbation can be treated the same way as non-COVID patients, these patients can be treated with metered dose inhalers but nebulized bronchodilators can be used if necessary.[6]

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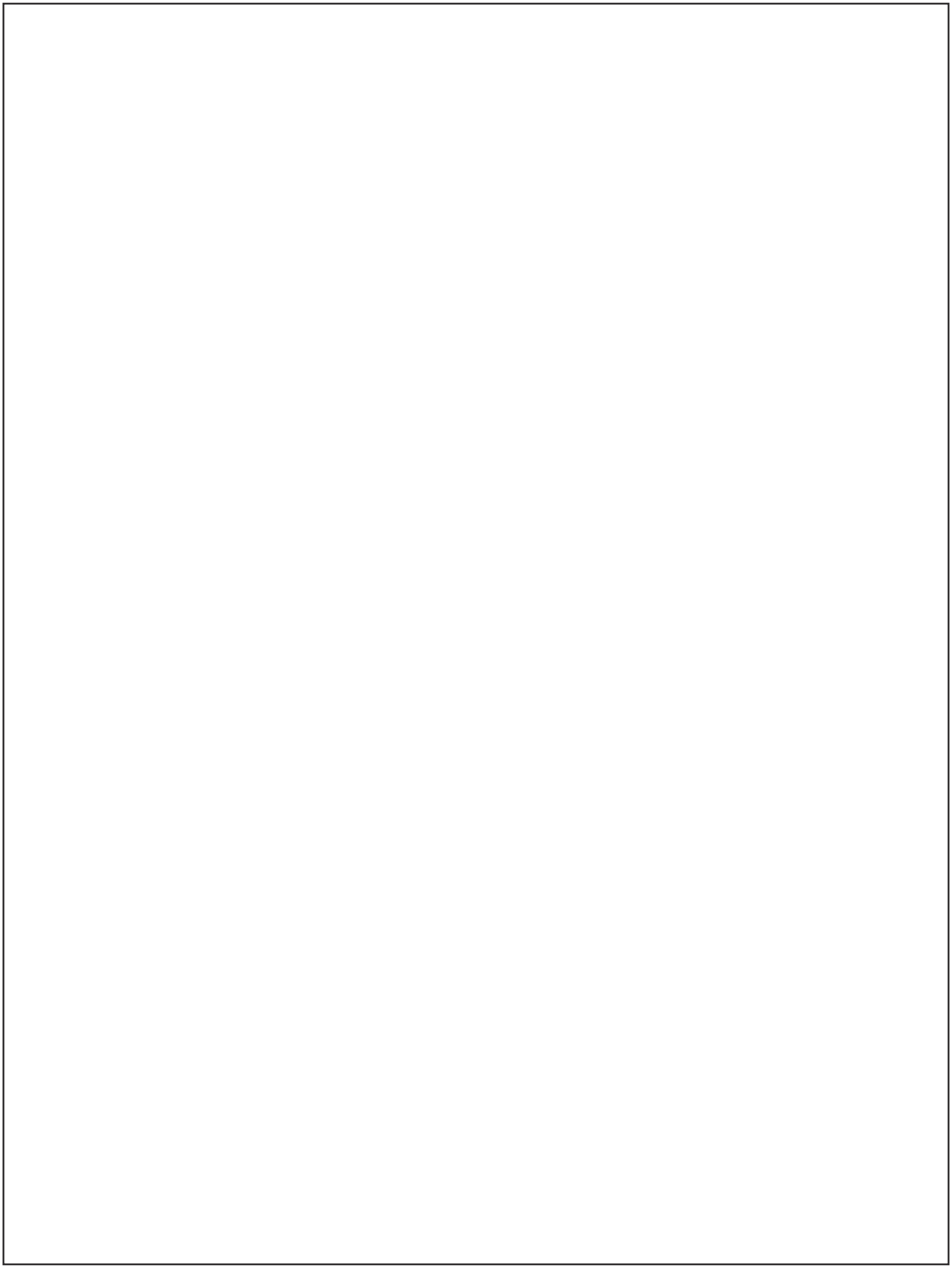

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