

DIFFICULT TO TREAT ASTHMA-IS IT ACTUALLY DIFFICULT?**Harender Kumar¹, Amol Chandra^{2*}**¹Medical Specialist, Department of Medicine, Dr. Baba Saheb Ambedkar Hospital, Delhi (INDIA).²Assistant Professor, Department of Pulmonary Medicine, Rajshree Medical Research Institute, Bareilly, Uttar Pradesh (INDIA).**ABSTRACT**

Asthma is a chronic inflammatory disorder characterised by bronchial hyper-responsiveness manifesting as variable airway obstruction leading to classical symptoms like difficulty in breathing, chest tightness, wheezing, and/or cough. Majority of asthma patients are amenable to treatment with conventional inhalational therapy including inhaled cortico-steroids, beta 2 agonists. However, in a subset of patients (approx 10%) it is difficult to control the symptoms with the conventional treatment regimens, and these patients are labelled as “difficult to treat asthma” patients. Exclusion of alternative diagnoses and co-morbidities is one of the most important aspects. Adherence to the prescribed treatment regimen is of paramount significance in the management of difficult to treat asthma so that inadvertent escalation of doses and addition of other drugs should be discouraged. Managing asthma that is refractory to usual treatment requires a systematic approach to ensure a correct diagnosis, identify coexisting disorders, tailor treatment, and evaluate adherence.

KEY WORDS: Bronchial asthma, Refractory Asthma, obstructive airways disorders.**INTRODUCTION**

According to an estimate approximately 300 million people are affected globally from asthma which is a major preventable cause of morbidity and mortality.^{1,2} Many researchers have defined asthma in a number of ways, which is why, still there is no universally accepted definition of bronchial asthma. Global initiative for asthma (GINA) committee 2014 has defined asthma as a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by 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.

Majority of patients with bronchial asthma are easily diagnosed and responds to the standard treatment with a short-acting inhaled β_2 -agonists for symptomatic control, and to long term therapy with inhaled glucocorticosteroids to control airway inflammation & hyper-responsiveness. However a subgroup of asthmatics it is difficult to achieve good asthma control despite of using high medication dosages along with recommended add-on therapies. A term to describe this subgroup of asthmatic patients is “Refractory Asthma” or “difficult to treat asthma”. Other terminologies have also been proposed for difficult to treat asthma including “chronic persistent asthma”, “life threatening asthma”, “brittle asthma” and “steroid resistant asthma”.³ Approximately 5%–10% of asthmatic patients suffer from “difficult to treat asthma”.^A By definition it is persistence of symptoms and/or frequent exacerbations despite prescription for maximal recommended inhaled corticosteroid (ICS) treatment apart from other maintenance

therapies that are being used simultaneously (i.e., prescribed treatment at Global Initiative For Asthma Step 4/5).^{3,4}

In 2000, certain criteria have been laid down by the ATS for diagnosing refractory asthma.⁵ At least one major and two minor criteria are required for making the diagnosis of refractory asthma. (Table -1)

Very obvious question arise that why in a subset of patients the asthma is difficult to treat or is it actually refractory? In our further discussion three issues are necessary to be addressed. First is the patient actually suffering from asthma? Second, is the typical symptomatology of asthma worsened by some environmental factors or co-morbidities? Lastly, is the patient adherent to the prescribed therapy along with proper technique? (Majority of times the most neglected issue).

Is it actually asthma?

Prior to the formulation of any treatment regimen in such patient due consideration must be given to reensure that the care-giver is dealing with the case of bronchial asthma. Reconsideration to the diagnosis of asthma is to be given because approximately 10% of the cases are misdiagnosed.⁶ Other factors that require attention include persistence of exposure to factors that may contribute to a poor response to conventional therapy, non-adherence with oral steroids, in certain cases psychological factors are important i.e., patients perception of their symptoms or their disease.^{7,8,9} Emphasis should be laid down to differentiate asthma for other obstructive airways disorders, particularly chronic obstructive pulmonary disease (COPD) and vocal cord dysfunction.

Asthma is characterised by reversible airway obstruction which is defined by 12% and 200mL improvement in forced expiratory volume in one second (FEV1) in response to inhaled bronchodilators.¹⁰ COPD can be distinguished from asthma as the airflow limitation in COPD is usually irreversible, associated with the history of cigarette smoking or biomass fuel gas exposure with the usual age of presentation >40years. Thus, the diagnosis of asthma needs to be confirmed by the presence of typical symptoms along with the evidence of variable airflow limitation or bronchial hyper-responsiveness. Needless to say, alternative diagnoses are to be considered and should be excluded before considering the diagnosis of difficult to treat asthma. (Table -2) Careful history taking along with the use of relevant investigation modalities will help to reach to the correct diagnosis.

Are the asthma symptoms worsened by any environmental factors or co-morbid conditions?

Once the diagnosis of asthma is confirmed focus should be on those factors that may lead to continuing asthma symptoms despite of adequate treatment. One of the most important factors is the continuous exposure to the allergen either at the workplace or at home contributing to the persistence of symptoms or increasing its severity. Smoking is another factor that contributes to the severity of asthma. In addition, smokers have decreased response to the inhaled corticosteroids and increased decline in the pulmonary functions, as compared to non-smokers. Therefore, strategies targeting smoking cessation are pivotal in managing difficult to treat asthma in smokers.

Several studies have suggested that in a number of patients with difficult to treat asthma there is high incidence of previously undiagnosed co-morbid conditions/ risk factors that contribute to the persistence of symptoms or increase in severity of the disease.(Table-3)

Adherence to prescribed therapy and correct use of inhalation technique?

Amongst one of the most neglected issue that is required to be addressed is the adherence to the therapy and, still more important, how to use it correctly. Adherence to treatment in asthma

patients is very often suboptimal. Moreover, majority of patients on inhalational medications are unaware of proper inhalational technique, thus making it still more important to check the method by which the patients take the inhalational medications. Demonstration of correct inhalational technique at regular intervals definitely improves the outcome.

CLINICAL SUBTYPES OF DIFFICULT TO TREAT ASTHMA

There is considerable variability amongst the patients with asthma depending upon the clinical characteristics, triggering factors and the type of airway inflammation.¹¹ Over a past few decades researchers have tried to sub-divide the patients with asthma into distinct phenotypes, but they have failed to reach a definitive classification. The various asthma phenotypes were defined with respect to clinical or physiological characteristics or by environmental triggers or by underlying pathobiology. Although there is a considerable overlap among asthma phenotypes none of the studies to date have linked the clinical, immunological and pathological characteristics. For patients with difficult to treat asthma three clinical phenotypes are proposed from the management point of view. They include patients with frequent severe exacerbations, patients with chronic persistent airflow limitation and lastly patient dependent on oral corticosteroids to keep their asthma under control.

1. Asthma patients with frequent severe exacerbation

Certain studies have focussed to identify the factors leading to recurrence of asthma exacerbations, hospitalizations and emergency department visits. Apart from psychosocial factors such as low socio-economic status, inaccessibility of medical care, or co-existing psychiatric illness, certain patient related characteristics such as female sex, smoking, increasing age non-compliance to treatment, are ascribed to frequent severe exacerbations. Along with the above mentioned factors several endogenous and exogenous factors can lead to difficult-to-treat asthma.

A) Physiologic factors

Various studies have shown that it is the reduced perception of airway obstruction that culminates into frequent exacerbation. Some patients detect the worsening of their disease in late stages as compared to others thereby exacerbating more easily and frequently. Approach to these patients is directed towards self assessment along with objective measurements of airflow limitation (domiciliary PEFr measurements). Some frequent exacerbators suffer from excessive airway narrowing with subsequent closure during an asthma attack. Patients with frequent exacerbations incur more airway closure under stable circumstances than severe asthmatic without exacerbations.

B) Co-morbidities

Certain clinical and environmental factors are associated with difficult-to-treat asthma. A study showed that frequent exacerbations are associated with one or more factors other than asthma itself. Along with factors like younger age and shorter asthma duration frequent exacerbations are strongly associated with psychological dysfunctioning, recurrent respiratory tract infections, gastro-esophageal reflux, severe nasal sinus disease and obstructive sleep apnoea.¹² According to study conducted by ten Birke and colleagues patients with frequent exacerbations exhibit at least one of the above factors.¹² The study also emphasized that there is high prevalence of unidentified contributing factors in difficult-to-treat asthma associated with frequent exacerbations. These factors need to be identified and addressed.

2. Asthmatic patients with persistent airflow limitation

According to an estimate approximately 50% of non-smoking adult patients with difficult to treat asthma have persistent or fixed airflow limitation. Persistent airflow limitation has been defined as FEV₁ less than 75% of the predicted value despite maximum bronchodilatation. A number of factors have been proposed to contribute to fixed airflow limitation in bronchial asthma.

A) Genetic and environmental factors

Injury to the bronchial epithelium followed by abnormal repair may be inherited or acquired, leads to structural and functional changes in the airways thereby manifesting as persistent airflow limitation.¹³ Genetic and environmental factors interact to modify airway inflammation contributing to the progressive loss of lung function. Certain studies have shown increased decline in lung function in patients previously infected with *Chlamydia pneumoniae* thereby suggesting that pathogens like *Chlamydia pneumoniae* may promote development of persistent airflow limitation. Use of macrolide antibiotics in such patients may show improvement in lung function.

B) Structural changes of large airways

Repeated airway inflammation leads to airway remodelling. Recurrent injury to the bronchial mucosa leads to sub-epithelial fibrosis, increased vascularity of mucosa along with smooth muscle hyperplasia and hypertrophy. Mass of the smooth muscle that has undergone hypertrophy is a key determinant as to how much degree of airflow limitation will be there.

Data from certain studies suggests that airway inflammation in bronchial asthma not only involves the central airways but also distal lung and lung parenchyma. Structural changes described in larger airways may also extend to the peripheral airways (calibre <2 mm). The clinical significance of the distal airway involvement is yet to be deciphered but it has been shown that patients with distal airway involvement tend to have severe asthma, in particular, with persistent airflow limitation. Persistent airflow limitation may be due to the deposition of thick tenacious mucus in the airways. Epithelial abnormalities in such patients include goblet cell hyperplasia and mucus hyper-secretion.

Although the pathogenesis of persistent airflow limitation is still unclear, increased smooth muscle mass, loss of airway elasticity, peripheral airway involvement, occlusion of airways by mucus plugs are some of the possible mechanisms that can contribute to the persistent airflow limitation leading to difficult-to-treat asthma.

3. Patients dependent on oral corticosteroids to asthma under control

According to the definition difficult-to-treat asthma is characterised by inadequate response to inhaled steroids treatment. Although the true steroid dependent patients are very less after excluding those that are misdiagnosed, non-adherent to treatment, poor inhalational techniques, with irreversible airflow limitation and simultaneous co-morbidities. Several reasons have been ascribed as to why these patients are resistant to inhaled steroids. Firstly, and most commonly the airways are too inflamed to be treated by the conventional doses of inhaled steroids, and increasing the doses of inhalational steroids is sufficient to get rid of their symptoms. Secondly, asthma has now been recognised as “one airway one disease”, i.e., upper airways are equally or at least to some extent are involved, and thus to keep the disease under control systemic approach should be there. Thus in clinical practice when the patients are responding poorly to increase doses of inhaled steroids then it is better to add low dose oral steroids with moderate doses of inhaled steroids. Thirdly, steroid dependent patients have predominantly neutrophilic

inflammatory infiltrate in their airways that may be one of the reasons for inadequate response to inhaled steroids.

Lastly, regular use of steroids may lead to receptor down-regulation, so as to make them less effective. Various mechanisms that can be attributed to the decreased anti-inflammatory cortico-steroid effect include reduced cortico-steroid affinity of glucocorticoid receptor or decreased GR translocation into the nucleus. Persistent viral infections may also contribute to the reduced anti-inflammatory effect of cortico-steroids or activation of pro-inflammatory transcription factors that may hinder the corticosteroid effect. Viruses like *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* are associated with those patients in whom there is poor asthma control or steroid dependence.

MANAGEMENT

Management of the patients with difficult-to-treat asthma is also very difficult and cumbersome. Such patients should be managed at specialized centres with access to the tests that are not routinely available (nitric oxide in exhaled air, analysis of induced sputum and bronchial biopsy), along with medical professional that have expertise in evaluating and treating such patients.^{14,15}

Patient education

Educating the patients to improve the level of self-care is the most important yet the most neglected aspect of integrated management of difficult-to-treat asthma. The care-givers should address each and every query and difficulty in understanding the way to take inhalational medications, as in majority of times it is the communication gap between the care-giver and the patient which leads to poor asthma control. Comprehensive patient education regarding the disease, its course, aggravating or relieving factors, along with the proper use or rescue and routine medications, may avert from asthma becoming difficult to treat.

Pulmonary rehabilitation

Rehabilitation programs have got a definite role to play in patients with difficult to treat asthma. Majority of these patients are crippled by sedentary lifestyle or inactivity or may suffer from systemic side effects of corticosteroids. Pulmonary rehabilitation programs improve the health related quality of life, increase exercise endurance and provides a sense of well being.

Pharmacotherapy

Conventional treatment in such cases include use of high dose inhalational corticosteroids (>1600µg/day beclomethasone dipropionate or equivalent) along with long acting β_2 agonists).¹⁶ Using higher doses is helpful in only small subset of patients because steroids possess a dose-effect relationship but the dose response curves may vary amongst patients. Change of the inhalation device may be of help in some cases, for example, switching the inhalational device from dry powdered inhaler to nebulisation. As a clinician one must focus on the fact that it is the amount of drug that is delivered to the target site which is most important rather than the device. Every effort should be made to identify any endogenous and exogenous aggravating factor, which if timely and accurately addressed, is of immense value.

Additional treatments including extra-fine aerosol corticosteroids may be beneficial in patients with peripheral airway inflammation; nasal corticosteroids may be used in patients with

rhino-sinusitis; leukotriene modifiers can be tried in those with aspirin sensitivity; anti-IgE therapy, Omalizumab, may be used to its effect in those with allergic symptoms with frequent exacerbations.^{17,18} Various steroid-sparing medications have been investigated in the quest to reduce the dose of oral corticosteroids. Initial reports on treatment with oral gold, methotrexate and cyclosporine were promising but studies over past few decades shows that their role needs to be re-evaluated. In most of the studies their minimal steroid sparing efficacy needs to be re-considered taking into account their serious side effects.

One of the latest subclass of drugs included in the treatment of asthma is humanized monoclonal antibodies against TNF α .¹⁹ These drugs have shown promising response in diseases like rheumatoid arthritis and Crohn's disease. Eterncept and infliximab have also shown some role to play in refractory asthma. These drugs may produce improvement in lung function, airway hyper-responsiveness and reduction in number of asthma exacerbations.

Bronchial thermoplasty

One of the important contributing factors in severe or refractory asthma is the increase in the airway smooth muscle mass. Bronchial thermoplasty is a procedure where thermal energy is delivered in a controlled manner to the hypertrophied airway wall under various bronchoscopic procedures in order to produce reduction in the airway smooth muscle mass. Bronchial thermoplasty is one of the recent management approaches in the management of refractory or difficult-to-treat asthma. The procedure has been shown to improve the quality of life, produce symptomatic alleviation, reduced use of reliever medications, reduced number of exacerbations and improved lung functions.²⁰ Further studies are required to assess the long-term results of this recent technique.

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TABLE -1 : CRITERIA FOR DIAGNOSIS OF REFRACTORY ASTHMA

MAJOR CRITERIA

1. Use of oral corticosteroids $\geq 50\%$ of the time
2. Continuous use of high doses of inhaled corticosteroids ($\geq 1200\mu\text{g/day}$ beclomethasone or equivalent).

MINOR CRITERIA

1. Requirement for daily treatment with long acting beta 2 agonists, theophylline or leukotriene antagonists.
2. Daily asthma symptoms requiring rescue medications.
3. Persistent airway obstruction ($\text{FEV}_1 < 80\%$ predicted); diurnal PEF variability $>20\%$.
4. 1 or more urgent care visits for asthma in last year.
5. 3 or more courses of oral steroids bursts in the last year.
6. Prompt deterioration with $\leq 25\%$ reduction in oral or inhaled corticosteroids dose
7. Near fatal asthma event in past

**TABLE-2 : ALTERNATIVE DIAGNOSIS: DIFFICULT TOTREAT
ASTHMA IN ADULTS**

1. Chronic Obstructive Pulmonary Disease (COPD)
2. Vocal cord dysfunction
3. Bronchiectasis/ cystic fibrosis
4. Congestive heart failure
5. Central airway obstruction:
 - a. Foreign body
 - b. Tumour / malignancy
6. Recurrent aspiration
7. Recurrent pulmonary embolism
8. Allergic bronchopulmonary aspergillosis (ABPA)
9. Churg strauss syndrome
10. Hyperventilation/ panic disorder

TABLE-3 : CO-MORBIDITIES/ RISK FACTORS FOR POOR ASTHMA CONTROL

1. Systemic disorders
 - a. Thyrotoxicosis
 - b. Carcinoid syndrome
 - c. Churg strauss syndrome/ other forms of vasculitis
2. Chronic infections
 - a. Mycoplasma
 - b. Chlamydia
3. Drugs
 - a. Beta blockers
 - b. Non-steroidal anti-inflammatory drugs
4. Unidentified exacerbating factors
 - a. Unidentified allergen exposure
 - b. Gastro-esophageal reflux disease (GERD)
5. Psychological factors

Corresponding Author:

Dr. Amol Chandra, Assistant Professor, Department of Pulmonary Medicine, Rajshree Medical Research Institute, Bareilly, Uttar Pradesh (INDIA)

Phone no. +91- 8192848307. **Email Id:**dr_amol2000@yahoo.co.in

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