CHAPTER

49

Approach to Difficult Asthma

Amita Nene

INTRODUCTION

There are 300 million asthmatics worldwide. The correct diagnosis of asthma is usually easily made and most patients with asthma respond to therapy. Approximately 5% of patients with asthma, however, have disease that is difficult to control despite taking maximal doses of inhaled medications.

DEFINITION

Previously, difficult asthma has been defined as a disease that causes severe, life-threatening attacks or frequent hospitalization. More recently, the definition of difficult asthma has been expanded to include patients with asthma who require very high doses of inhaled corticosteroids (ICS) along with other controller agents (Table 1), or require near continuous oral steroid treatment to maintain asthma control

Other Names for difficult asthma

- Severe asthma
- Refractory asthma
- Difficult to control asthma
- Therapy-resistant asthma
- Steroid-dependent asthma

APPROACH TO A PATIENT WITH DIFFICULT ASTHMA

A high percentage of patients who are labelled with severe or difficult asthma actually do not have severe refractory asthma. Distinguishing severe refractory asthma from difficult-to-control asthma is critically important because it identifies the patients who may benefit from novel and, sometimes, expensive treatments.

Table 1: High Daily Dose ICS – Definition

Inhaled corticosteroid	Threshold daily dose in mg considered as high	
	Age 6–12 years	Age >12 years
Beclomethasone dipropionate	≥800 (DPI or CFC MDI) ≥320 (HFA MDI)	≥2000 (DPI or CFC MDI) ≥1000 (HFA MDI)
Budesonide	≥800 (MDI or DPI)	≥1600 (MDI or DPI)
Ciclesonide	≥160 (HFA MDI)	≥320 (HFA MDI)
Fluticasone propionate	≥500 (HFA MDI or DPI)	≥1000 (HFA MDI or DPI)
Mometasone furoate	≥500 (DPI)	≥800 (DPI)
Triamcinolone acetonide	≥1200	≥2000

A systematic evaluation of patients with difficult asthma should include:

1. Confirming that patient with ''difficult asthma'' actually has asthma
2. Evaluation of risk factors and triggers
3. Management of Comorbid conditions
4. The initial determination of phenotypes which may be useful in optimising therapy
5. Ensuring compliance to treatment
6. Controlling other factors that prohibit asthma control

Reassessing the Diagnosis of Asthma

When there is a lack of response to standard therapy, the diagnosis of asthma should be questioned and revisited. Obtaining pulmonary function testing with flow/volume curves and documenting reversible airway obstruction become essential. A flattened inspiratory curve, for example, is indicative of upper airway obstruction which can mimic asthma.

In patients with a history of asthma but normal lung function, methacholine challenge testing can help confirm airway hyper-responsiveness and thus confirm or rule out the diagnosis of asthma. Normal test results will point away from asthma and lead to a search for other causes of respiratory difficulty

Alternate Diagnoses to Consider in patients with Difficult Asthma

- Hyperventilation
- Vocal cord dysfunction
- Congestive heart failure
- Chronic obstructive pulmonary disease
- Gastro-esophageal reflux disease
- Restrictive lung disease
- Obstructive Sleep apnea
- Central airway obstruction / Endobronchial lesions
- Recurrent aspiration

- Drug side effects (e.g. ACE inhibitor-induced cough)
- Pulmonary embolism

Concomitant Disorders that worsen Asthma

Sometimes patients have asthma that is difficult to control because it is associated with another undiagnosed or untreated illness that worsens asthma, such as

- Gastroesophageal reflux disease
- Allergic rhinitis
- Chronic rhinosinusitis
- Endocrinopathies (eg, hyperthyroidism, carcinoid syndrome)
- Allergic bronchopulmonary aspergillosis
- Aspirin-exacerbated respiratory disease
- Churg-Strauss syndrome/other vasculitides

The minimum evaluation of the patient with difficult asthma includes the following: Complete blood count with eosinophil count, serum total IgE level, chest radiograph, pulmonary function tests with both careful inspection of the inspiratory and expiratory flow–volume loop and reversibility testing, and home PEF monitoring.

If clinically indicated, a methacholine challenge test, chest CT scan, fiberoptic bronchoscopy, echocardiogram, sleep study, plasma brain natriuretic peptide, sputum for eosinophil count and culture, serum IgE for aspergillus, antineutrophil cytoplasmic antibodies and thyroid function tests should be performed.

Aggravating Factors and Triggers

Identifying and eliminating triggers will help with asthma management. These include

- Cigarette smoking
- Allergens such as dust mites or cockroaches,
- Pets like cats and dogs
- Medications such as aspirin, NSAIDs and beta-blockers
- Monosodium gluatamate (Ajinomoto)
- Wine
- Occupational Allergens

Compliance and Correct Inhaler Technique

It is important to ensure adherence to the medication regimen. Poor adherence is common and even more so with inhalers compared with oral medications

Even when patients are compliant, use of improper inhaler techniques may prevent appropriate delivery of the drug. Therefore, a patient demonstration of proper techniques should be part of every physician visit.

Sub-phenotypes of severe refractory asthma

Severe refractory asthma is a heterogeneous condition, and over the past few years several clinical phenotypes have been identified. These phenotypes are characterised by different clinical and physiological features, probably reflecting separate immuno-pathologies. Thus, characterisation of sub-phenotypes of severe asthma may be very helpful in understanding the underlying pathophysiology and may be used to target treatment.

Identified phenotypes of severe refractory asthma

- Early onset severe allergic asthma
- Late onset non-atopic, inflammation predominant asthma with fixed airflow limitation
- Late onset obese female preponderant asthma

Socioeconomic Factors and Psychological Factors

When there is no obvious medical reason for difficult asthma, socioeconomic factors must be taken into account. These include issues like poverty, access to medical care and environmental risk factors.

Negative emotions can influence the symptoms and management of asthma and should be addressed. Asthmatics with comorbid depression are especially difficult to treat and depression should be treated at the earliest.

When patients present with atypical symptoms or do not respond properly to medications, functional symptoms should be suspected.

TREATMENT OF DIFFICULT ASTHMA

Corticosteroids

Corticosteroids have numerous beneficial effects in asthma on both inflammatory and structural cells.

- They address most of the causes of airflow obstruction in asthma, including :
- Airway smooth muscle contraction
- Mucosal edema
- Airway inflammation
- Increased mucus secretion, and
- Perhaps airway remodeling.
- Corticosteroids decrease the number of eosinophils, mast cells, and dendritic cells in the airway.
- They decrease cytokine production from T lymphocytes and macrophages

Resistant Inflammation In Difficult Asthma

There is considerable evidence to suggest that many patients with difficult asthma have "resistant" inflammation with a persistent inflammatory state in the airway. Patients with difficult asthma should receive maximal doses of inhaled corticosteroids. There is evidence that regular use of inhaled corticosteroids in general is associated with decreased risk of death from asthma

Long acting β2 Agonists (LABA)

Regular long-acting and as-needed short-acting β2-

agonist use is recommended for patients with difficult asthma. β2-Agonists act mainly to cause bronchodilation but may also decrease :

- Mast cell mediator release
- Plasma exudation
- Cholinergic transmission and
- Improve mucociliary clearance.

Numerous studies have documented that the addition of salmeterol or formoterol to inhaled corticosteroid therapy improves asthma control more than increasing or doubling the dose of corticosteroids.

Leukotriene modifiers

The leukotriene modifier montelukast decreases airway eosinophilic inflammation and improves asthma control in adult patients with persistent asthma.

Leukotriene modifiers may be particularly beneficial in patients with aspirin sensitivity where leukotriene production is typically increased.

Anti-cholinergic agents

Anti-cholinergic agents can be used in addition to β2-agonists in the treatment of patients with difficult asthma. The long-acting anticholinergic agent, tiotropium bromide improved lung function and symptoms in moderate to severe asthma patients not controlled on moderate to high dose ICS with or without LABAs. In patients taking high doses of ICSs and LABAs, the addition of tiotropium bromide provided improvements in FEV1, reduced as needed use of short acting β2-agonists and modestly reduced the risk of a severe exacerbation

Slow release Theophylline

These are poor bronchodilators as compared to β2-agonists and therefore the latter are preferred. However when patient has severe asthma, these are also used.

Anti IgE Therapy

In patients with allergic asthma and an elevated IgE level, administration of the monoclonal antibody against IgE, omalizumab, can result in

- Decreased airway inflammation
- Improved asthma control and
- May allow tapering of corticosteroid medications.

The dose and frequency of injections are determined by serum IgE level and weight. This medication is given subcutaneously every 2 or 4 weeks. Treatment for a minimum of 12 week is recommended before assessing the response.

Macrolides

The role of microorganisms such as Chlamydia and Mycoplasma remains a subject of debate, both in exacerbations and in the chronicity of bronchial asthma. Clarithromycin seems to play a beneficial role as an anti-inflammatory agent in infectious and predominantly neutrophilic asthma.

Novel Therapies

Novel targeted therapies that may be of benefit for patients with severe asthma include antiTh2 targets such as antiIL5 antibody, mepolizumab; antiIL5Rα antibody, benrazilumab; antiIL13 antibody, lebrikuzimab and antiIL4Rα antibody, dupilumab. These treatments will likely be targeted towards patients with an eosinophilia, and in some cases towards patients who express high levels of Th2 biomarkers, such as serum periostin.

Bronchial thermoplasty

Preliminary investigations with radiofrequency ablation of airway smooth muscle have offered a novel promising treatment option in severe refractory asthma. Several studies showed improved pulmonary function testing, airway hyper-responsiveness, asthma-related quality of life and symptom scores. No clinical complications were observed in the long run, and pulmonary function remained stable over a period of 5 years. Therefore, this approach might be a reasonable option for patients with difficult asthma not responding to current treatment.

REFERENCES

1. Chung KF, Wenzel SE, Brozek Jl *et al.* International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014; 43:343-73.
2. Wener RR, Bel EH. Severe refractory asthma: an update. *Eur Respir Rev* 2013; 22:227-35.
3. Kerstjens HA, Disse B, Schro der-Babo W, et al. Tiotropium improves lung function in patients with severe uncontrolled asthma: a randomized controlled trial. *J Allergy Clin Immunol* 2011; 128:308–314.
4. Kerstjens HA, Engel M, Dahl R, et al. Tiotropium in asthma poorly controlled with standard combination therapy. *N Engl J Med* 2012; 367:1198–1207.
5. Flood-Page P, Swenson C, Faiferman I, et al. A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma. *Am J Respir Crit Care Med* 2007; 176:1062–1071.
6. Corren J, Lemanske RF, Hanania NA, et al. Lebrikizumab treatment in adults with asthma. *N Engl J Med* 2011; 365:1088–1098.
7. Castro M, Mathur S, Hargreave F, et al. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. *Am J Respir Crit Care Med* 2011; 184:1125–1132.
8. Castro M, Rubin AS, Laviolette M, et al. Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma: a multicenter, randomized, double-blind, sham-controlled clinical trial. *Am J Respir Crit Care Med* 2010; 181:116–124.
9. Thomson NC, Rubin AS, Niven RM, et al. Long-term (5 year) safety of bronchial thermoplasty: Asthma Intervention Research (AIR) trial. *BMC Pulm Med* 2011; 11:8.
10. Le AV, Simon RA. The Difficult-to-Control Asthmatic: A Systematic Approach. *Allergy Asthma Clin Immunol* 2006; 2:109-16.