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.

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

### Table 1: High Daily Dose ICS – Definition

<table>
<thead>
<tr>
<th>Inhaled corticosteroid</th>
<th>Threshold daily dose in mg considered as high</th>
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<tbody>
<tr>
<td></td>
<td>Age 6–12 years</td>
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<tr>
<td>Beclomethasone dipropionate</td>
<td>≥800 (DPI or CFC MDI) ≥320 (HFA MDI)</td>
</tr>
<tr>
<td>Budesonide</td>
<td>≥800 (MDI or DPI)</td>
</tr>
<tr>
<td>Ciclesonide</td>
<td>≥160 (HFA MDI)</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>≥500 (HFA MDI or DPI)</td>
</tr>
<tr>
<td>Mometasone furoate</td>
<td>≥500 (DPI)</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>≥1200</td>
</tr>
</tbody>
</table>
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, benralizumab; antiIL13 antibody, lebrikizumab 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