

Management of Difficult to Treat Asthma

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Difficult to treat asthma

- No clearcut definition
- Used synonymously with many terms under various guidelines like “Refractory asthma”, “severe asthma,” “steroid-dependent and/or resistant asthma,” “difficult to control asthma,” “poorly controlled asthma,” “brittle asthma,” or “irreversible asthma.
- No definite prevalence , though most estimates keep it around 5% of all asthmatics
- Accounts for considerable cost in overall asthma management
- Mostly manageable with proper confirmation of diagnosis, evaluation and optimisation of treatment

Definition

- 1999, an ERS Task Force-
‘difficult/therapy-resistant asthma’ defined as poorly controlled asthma with a continued requirement for shortacting β 2 agonists despite delivery of a reasonable dose of inhaled corticosteroids (ICS) and follow-up by a respiratory specialist for a period of >6 months.
- 2000 an ATS Workshop-
‘refractory asthma’, adopted ,term definition included one of two major criteria (continuous high-dose ICS or oral corticosteroids for >50% of the time during the previous year), with two out of seven additional minor criteria.

- 2003, The European Network for Understanding Mechanisms of Severe Asthma defined 'severe asthma' as confirmed asthma (typical asthma symptoms, reversibility in FEV1 or airway hyper-responsiveness) plus the occurrence of one or more exacerbations in the previous year despite oral corticosteroids or high-dose ICS
- 2007, an international workshop was organised in Paris (NAEPP/EPR3)- 'severe asthma' reserved for those patients who have refractory asthma after an extensive re-evaluation of the correct diagnosis, aggravating comorbidities and environmental factors and an appropriate observation period of at least 6 months.

- 2008, later in 2011, the British Thoracic Society (BTS) and Scottish Intercollegiate Guideline Network (SIGN) guidelines defined difficult asthma as “persistent symptoms and/or frequent exacerbations in patients with a prior diagnosis of asthma despite treatment at step 4 or step 5.”
- 2009, the WHO Consultation on Severe Asthma-
 - Severe asthma was defined as ‘uncontrolled asthma which can result in risk of frequent severe exacerbations (or death) and/or adverse reactions to medications and/or chronic morbidity (including impaired lung function or reduced lung growth in children)’.
 - Adopted the definitions of ‘severe’ and ‘difficult’ asthma from the Paris Workshop in 2007 and extended it with a third group of patients with ‘untreated’ severe asthma.

ATS 2000 Difficult to treat asthma

Major characteristics

To achieve control to a level of mild-moderate persistent asthma

1. Treatment with continuous or near continuous ($\geq 50\%$ of year) oral corticosteroids
2. Requirement for treatment with high-dose inhaled corticosteroids (Beclomethasone dipropionate $> 1260 \mu\text{g/d}$)

Minor characteristics

1. Requirement for daily treatment with a controller medication in addition to inhaled corticosteroids, eg, long-acting β -agonist, theophylline, or leukotriene antagonist
2. Asthma symptoms requiring daily short-acting β agonists
3. Persistent airway obstruction (FEV1 $< 80\%$ predicted; diurnal PEF variability $> 20\%$)
4. One or more urgent care visits for asthma per year
5. Three or more oral steroid “bursts” per year
6. Prompt deterioration with $\leq 25\%$ reduction in oral or inhaled corticosteroid dose
7. Near fatal asthma event in the past

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS IN PATIENTS WITH DIFFICULT CONTROL ASTHMA

1. The Epidemiology and Natural History of Asthma and Treatment Regimens (TENOR)

- It is a prospective and multicentric study of three years follow up in North American patients with severe or difficult to treat asthma
- Study included children
- These data show that the main reason for a physician to classify difficult asthma is the need of multiple prescribed medication

DEMOGRAPHIC AND CLINICAL...

2. *Severe Asthma Research Program (SARP)*

- It was the result of a workshop on severe asthma held in the US by the *National Heart, Lung and Blood Institute*(NHLBI) in 2000
- The *American Thoracic Society's (ATS) definition* on resistant asthma was used
- Severe asthma was distinguished by persistent symptoms, abnormal pulmonary function responding to bronchodilators, high consumption of drugs and significant comorbidities

DEMOGRAPHIC AND CLINICAL...

3. European Network for Understanding Mechanisms of Severe Asthma (ENFUMOSA)

- Main conclusions in this study were associated to-
persistent symptoms,
abnormal pulmonary function(in spite of high doses of control medication) ,
concomitant symptoms with an irreversible component in airway obstruction,
neutrophilic inflammation,
active liberation of mediators and reduced atopy association

- From the results in these studies, risk factors for severe asthma are:
female gender,
high BMI,
sensitivity to aspirin,
gastro esophageal reflux,
sinusitis,
pneumonia history,

beginning of asthma symptoms in adult late age.

CLINICAL PHENOTYPES OF SEVERE ASTHMA

- From a clinical point of view, three categories of patients with severe asthma seem to be of particular importance:
 - (1) those suffering from frequent severe exacerbations with relatively stable episodes between exacerbations (exacerbation prone asthma);
 - (2) those who develop irreversible airflow obstruction (asthma with fixed airflow obstruction); and
 - (3) those who depend on systemic corticosteroids for daily control of their asthma (steroid-dependent asthma)

INFLAMMATORY PHENOTYPES OF SEVERE ASTHMA

Two phenotypes--persistent eosinophilic and non-eosinophilic forms

- Severe asthma with persistent eosinophilia
 - mixed eosinophilia and neutrophilia in bronchial biopsies and induced sputum despite the use of high-intensity ICS or OCS treatment.
 - severe exacerbations, sinus disease, involvement of the peripheral airways, airway remodelling and fixed airflow obstruction, and responds favourably to treatment with anti-interleukin 5 monoclonal Ab
- Non-eosinophilic subtype
 - airway eosinophils are either absent or suppressed by treatment in the presence of a high level of asthma symptoms
 - increased percentage of neutrophils
 - responds poorly to currently available anti-inflammatory therapy.

Am. J. Respir. Crit. Care Med. January 20, 2012

Table 1 Tests to distinguish severe asthma from alternative diagnosis that may mimic asthma

Routine screening test in adults

Exclusion (if test is normal)

Air trapping measured by body plethysmography

Bronchiolitis obliterans

Carbon monoxide diffusion capacity

Emphysema or parenchymal lung disease

- Chest HRCT scan

Parenchymal lung disease

Bronchiolitis obliterans

Bronchiectasis

Congestive heart failure

<u>Suspected alternative or additional diagnoses in adults</u>	<u>Diagnostic test</u>
Intrabronchial obstruction	Bronchoscopy
Vocal cord dysfunction	Laryngoscopy during attack
Dysfunctional breathing/panic attacks	Blood gases during attack Hyperventilation provocation test
Recurrent micro aspiration	Proximal oesophageal pH measurement Bile salts in bronchoalveolar lavage fluid
Cystic fibrosis (CF)	Sweat test
Allergic bronchopulmonary aspergillosis	Aspergillus IgE/precipitins/sputum c/s
Emphysema	High resolution CT scan
Hypersensitivity pneumonitis	
Bronchiectasis (including ABPA, CF)	
Recurrent pulmonary embolism	CT pulmonary angiography
Pulmonary arterial hypertension	
Bronchiolitis	Transbronchial or thoracoscopic lung biopsy
Sarcoidosis	
Systemic	
Churg- Strauss syndrome	Biopsy of affected organ(s) Antineutrophilic cytoplasmic anti bodies

Asthma is confirmed by a history of wheeze either spontaneously or on exertion, as well as variable airflow limitation (in school age and above) by:

- Variability of peak expiratory flow (amplitude %mean of twice daily measurements > 8%)
- Reversibility in FEV1 to 400 mcg inhaled salbutamol (>12% predicted and >200 ml)
- Airway hyperresponsiveness to methacholine (PC20 <8 mg/ml)
- Fall in FEV1 >12% plus >200 ml when tapering treatment (any one or more of inhaled corticosteroids, oral corticosteroids, long- and short acting beta-2 agonists) as long as the patient can tolerate this.

- The term 'difficult asthma' is reserved for asthma that remains uncontrolled despite the prescription of high-intensity asthma treatment due to:
 - <persistently poor compliance;
 - <psychosocial factors, dysfunctional breathing, vocal cord dysfunction;
 - <persistent environmental exposure to allergens or toxic substances;
 - <untreated or undertreated comorbidities such as chronic rhinosinusitis, reflux disease or obstructive sleep apnoea syndrome.

Factors Which May Contribute to Difficult-to-Treat Asthma

Factor	Examples
Incorrect diagnosis	Chronic obstructive pulmonary disease (COPD) Obliterative bronchiolitis (OB) Pulmonary eosinophilic syndromes Allergic bronchopulmonary aspergillosis (ABPA) Vocal cord dysfunction (VCD) Fibrotic lung disease Bronchiectasis Churg–Strauss syndrome
Unrecognized systemic disease	Pulmonary hypertension, congestive cardiac failure
Unrecognized trigger factors	Pets, Drugs, Occupational exposures, gastroesophageal reflux
Dysfunctional Breathing	
Poor compliance with treatment	
Psychosocial	Anxiety, depression
Rare cause	<i>Mycoplasma pneumoniae</i> , NTM

Factors Which May Contribute to Difficult-to-Treat Asthma

A. Incorrect diagnosis

B. Existence of another illness with similar symptoms

- Superior airway obstructive disease (vocal chord dysfunction, tracheal stenosis)
- Hyperventilation-anxiety syndrome
- Hyperthyroidism
- Rhinosinusopathy
- Gastric-esophageal reflux
- Bronchiectasis

C. Non controlled worsening factors

- Exposition to allergens (pets)
- Occupational asthma
- Pharmaceuticals (beta blockers, NSAIDS)

D. Not complying to therapy

E. Rare causes: Chlamydia, NTM

The most common differential diagnosis of difficult asthma

- a: psychiatric disease (20.7%);
- b: asthma (15.9%);
- c: cystic fibrosis (7.6%);
- d: upper airways obstruction (7.3%);
- e: bronchiectasis (7.0%);
- f: bronchopulmonary aspergillosis (5.4%);
- g: *a1-antitrypsin deficiency* (5.4%);
- h: *chronic obstructive pulmonary disease* (4.3%);
- i: bronchopulmonary thromboembolic disease (3.3%);
- j: cardiac (3.2%);
- k: muscle weakness (3.0%);
- l: diffuse parenchymal lung disease (2.9%);
- m: Churg–Strauss syndrome (2.9%);
- n: bronchiolitis (2.7%);
- o: poor compliance (1.9%);

ENVIRONMENTAL FACTORS THAT COULD PLAY A ROLE IN REFRACTORY ASTHMA

1. Tobacco smoke
 - a. *In utero*
 - b. Environmental
 2. Allergen sensitization
 3. Viral infections
 4. Occupational agents
 5. Air pollutants
 6. Stress
-

EVALUATION OF PATIENTS WITH REFRACTORY ASTHMA

1. Confirm reversible airflow limitation and quantify severity:
 - a. FEV₁, peak flow, and flow–volume loop before and after bronchodilator treatment*
 - b. Total lung capacity and residual volume[†]
 - c. Diffusion capacity (in adults—usually not indicated in children)[‡]
2. Consider other diagnoses in differential diagnosis of cough, dyspnea, and wheeze:
 - a. Chronic obstructive pulmonary disease
 - b. Cystic fibrosis
 - c. Vocal cord dysfunction, or other mechanical upper airway obstruction
 - d. Obstructive sleep apnea
 - e. Churg–Strauss syndrome
 - f. Cardiac dysfunction
 - g. Allergic bronchopulmonary aspergillosis (ABPA)
3. Investigate for the presence or absence of concomitant disorders that can exacerbate asthma:
 - a. Allergen skin tests (atopy and allergic rhinitis)
 - b. CT scan of the sinuses (sinus disease)
 - c. Twenty-four-hour esophageal pH monitoring (gastroesophageal reflux disease)
 - d. Chest radiograph (pulmonary infiltrates, interstitial lung disease, bullous lung disease)
 - e. Blood for eosinophil count, immediate hypersensitivity skin testing to aspergillus, IgE level (Churg–Strauss or allergic bronchopulmonary aspergillosis)

Diagnostic Approach to Difficult-to-control Asthma

- -Is the diagnosis correct or is there an alternative diagnosis?
- -Is the patient compliant with treatment and is the technique correct ?
- -Are there inciting agents ? e.g. Inhaled allergens.
- -Are there aggravating factors? e.g. Rhinosinusitis, GERD etc.

Diagnostic Approach....

Exhaustive history and clinical examination critical in making an **accurate diagnosis**

Pre-and post-bronchodilator spirometry essential for **diagnosing reversible airway obstruction.**

Flow-volume loops helpful to rule out **upper airway obstruction**

Diagnostic approach ..

Methacholine challenge test(or mannitol) to **evaluate bronchial hyperresponsiveness which is a cardinal feature of asthma**

Skin Prick test, phadiatop, or FX5

Laryngoscopy/320 slice CT to evaluate **upper airway dysfunction**

CXR and HRCT chest **when indicated**

Investigate appropriately for other diseases **as required**

Assessment

- Diagnosis: is it really asthma ?
- Risk profile: will the patient die from his disease?
- Triggers :allergens etc
- Complications:Osteoporosis,Steroid
myopathy,Depression,Obesity,VCD,Diabetes mellitus
- Asthma management skills:education,proper inhalation
technique,dose,adherance

Diagnosis and treatment of recognised comorbidities in severe asthma

Comorbid condition	Test	Treatment
Gastro-oesophageal reflux	3 months empirical therapy trial with proton pump inhibitors or oesophageal pH testing	Lifestyle modifications Proton pump inhibitors Surgery
Obesity with or without obstructive sleep apnoea syndrome	Polysomnography	Weight control Positive airway pressure Oral appliances Surgery
Sinus disease	CT scan Nasendoscopy	Nasal irrigation with saline Corticosteroid spray Corticosteroid drops Surgery
Depression/anxiety	Evaluation by mental health professional	Medical treatment or psychotherapy by mental health professional

Treatment of difficult asthma

- Guidelines recommend **treatment scale according to severity for control of the disease at all times**
- No clear internationally accepted regimens for difficult to treat asthma despite **treatment at the highest point on the scale (step 5 GINA 2008, step 6 NAEPP/EPR3)**
- This is due to **paucity of studies and different definition used in the available studies**
- Treatment should be aimed to **obtain the best possible results when there is failure of optimal control**
- Also aim to have the **fewest undesirable effects**
- Have a good **treatment plan**

The 2008 GINA guidelines, in the last step in achieving control,

- high doses of inhaled corticosteroids,
- long acting β -2-agonist,
- Extended release theophylline,
- anti-leukotrienes,
- the smallest possible dose of oral corticosteroids to maintain control
- in patients with allergic asthma, addition of omalizumab.

High intensity asthma treatment is defined as:

- 1000 mcg/day fluticasone equivalent combined with long acting beta-2-agonists or other controllers (adults)
- 500 mcg/day fluticasone equivalent (school-aged children)
- 400 mcg/day budesonide equivalent and oral leukotriene receptor antagonists (pre-school children)

The treatment regiment suggested by the Spanish guidelines

1. Act on those influencing in a lack of control (treat comorbidity, avoid reactants and improve compliance).
2. Intensive initial treatment beginning with drugs recommended for severe asthma and a short cycle of oral steroids +/-other drugs
3. Failure to oral steroids ,the possible causes investigated: incomplete absorption, conversion failure, quick elimination or resistance.
4. 'alternative' treatments (gold dust, ciclosporine, metotrexate or others) only in exceptional circumstances.
5. Organize a follow up plan designed for each individual patient, with the action plan written on paper.

- Omalizumab has shown a reduction of 50% of steroids dose in atopic asthma with high IGE levels
- [?] Safety profile requires long term evaluations
- [?] Administered every 2 or 4 weeks at a dose of 150-375m

Recommendation of steroid sparing and other drugs

- Colchicine, chloroquine, dapsons: not recommended (evidence level C).
- Azathioprine: little evidence as steroid sparing agent (evidence level B).
- IV gamma globulin: contradictory steroid sparing reports, expensive and high rate of adverse events (fever, aseptic meningitis, urticaria).
- Macrolides (Troleandomycin): not enough evidence (evidence level B).
- Gold dust: not recommended as steroid sparing agent (evidence level B).

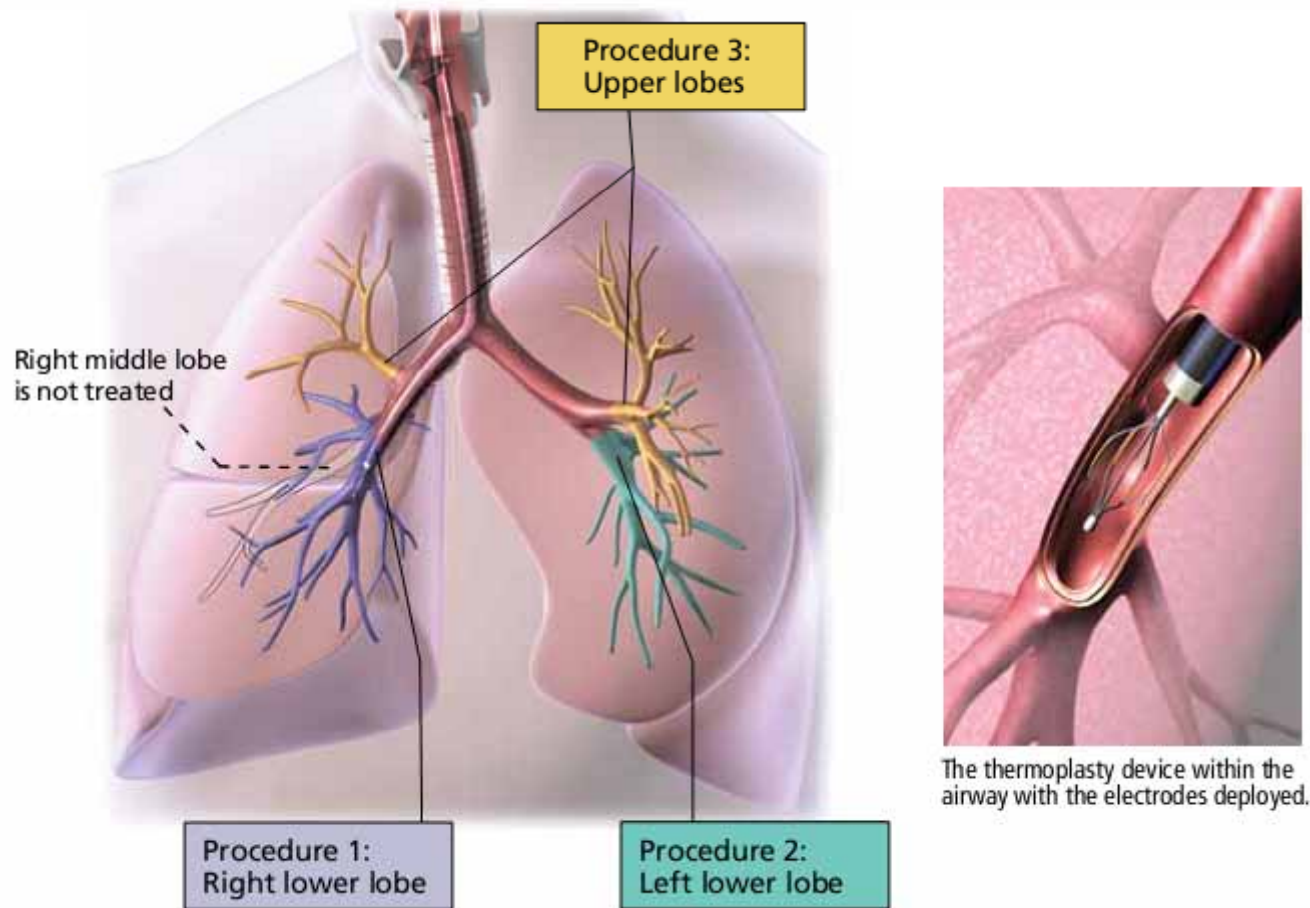
Recommendation..

- Ciclosporin: no support for oral corticosteroids-dependent asthma treatment (evidence level B).
- Methotrexate: modest benefit , significant side effects and toxicity risk;to use with laboratory guidance (evidence level B).
- Omalizumab: costly humanized anti-IgE monoclonal antibody approved for severe allergic asthma treatment (evidence level B).
Administered every 2 or 4 weeks at a dose of 150-375m SC
- Anti-TNF- α : Marked heterogeneity in response to the treatment, may be useful in small subgroup

Newer treatments...

- Dissociated steroid(Transrepresses with little transactivation)
(eg, AL-438, ZK 216348)
- inhaled p38, MAPK and JAK inhibitors
- Bariatric surgery decreases the intensity of medication required to control patients' asthma symptoms, justifying it in patients with a BMI \geq 35
- Bronchial thermoplasty for severe refractory asthma:
-it involves delivery of radiofrequency energy to the airway wall, which ablates the smooth muscle layer, lessening bronchoconstriction and improving symptoms.

Lancet 2008; 372: 1073–87
OBES SURG (2011) 21:200–206



Education and removal of factors that can interfere with control

- Educate about adherence and proper technique
- Cochrane review showed that education about self-management significantly improved health outcomes
- Educational material used should be at appropriate health literacy level
- Implement strict environmental control
- Advise about the negative effects of smoking and obesity on asthma control
- Smoking cessation to be emphasised as smoking reduces the effects of ICS

Education and removal...

- Treat comorbid conditions such as rhinosinusitis and gastroesophageal reflux
- No evidence for any benefit from empiric treatment of gastroesophageal reflux
- 1 study has shown a reduction in asthma exacerbations in patients with symptoms of reflux given lansoprazole 30mg BD compared to placebo

J Allergy Clin Immunol 2010; 125: 307-311.

Follow-up and written action plan

- Close monitoring essential
- 2 to 3 visits per month in the first 2 months until best results are achieved
- Then monitor 3 monthly
- Self treatment plan needed to avoid life-threatening attacks

Conclusion

- Management of difficult to treat asthma depends heavily upon the detection of misdiagnosis, enforcement of treatment and removal of comorbidities/triggers
- Treatment is basically same as that of other severe asthma once other factors are tackled