Review Article

Pediatrics

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# Is it Difficult to Treat Asthma in Children?

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## Abstract

**Introduction:** Asthma, the commonest chronic lung disease in childhood, is managed effectively with inhaled medications in most of the cases. But a subset of pediatric asthma patients continues to experience substantial morbidity even after higher doses of medications; they are referred to as problematic severe asthma. In many such cases, the apparent resistance to therapy is actually due to a number of remediable factors. These cases are called 'difficult to treat asthma'. The physician dealing with a child with problematic severe asthma needs to follow a systematic step- wise approach to find any possible underlying causes of poor response to therapy. The evaluation starts with revisiting the diagnosis of asthma and goes through a checking the prescription, patient compliance, assessment for co-morbidities, environmental triggers and psychological factors. Only in a very small number of cases where no such remediable factors are identified, a diagnosis of severe therapy-resistant asthma is made and the child should be referred to a pediatric pulmonologist for further evaluation and therapy.

**Keywords: Severe therapy-resistant asthma, Problematic severe asthma, Metered dose inhaler, Allergic rhinitis.**

## Introduction

Childhood asthma is the most common chronic lung disease of childhood and is one of the greatest burdens on healthcare resources [1]. Though the disease can be controlled adequately with inhaled corticosteroids and ß2 agonists in most cases, a subset of patients (about 0.5-5%) continues to experience significant morbidity despite therapy [2]. Difficult to treat asthma (DTA) is significant ongoing symptoms due to underlying modifiable factors, which when addressed leads to better control, and not due to resistance to medications [3]. It comprises of only 5–10% of all asthmatics but accounts for approximately 50% of total cost of asthma therapy [4]. Up to 40 % of children referred for investigation of 'severe asthma' fall in this group [5].

## Nomenclature

A variety of terminologies has been used to describe children with severe asthma [6] such as refractory asthma, difficult to control asthma, brittle asthma, chronic severe asthma, therapy-resistant asthma, steroid-dependent asthma. Although these may sound confusing, actually each one of these names points to a different aspect of the condition. According to the currently accepted nomenclature, problematic severe asthma is defined as asthma that is poorly controlled despite high doses of prescribed medicines. Problematic severe asthma can be either difficult to treat asthma (DTA) or severe therapy-resistant asthma [7]. Severe therapy-resistant asthma, as the name implies is poorly controlled asthma despite adequate therapy; when factors making asthma difficult cannot be identified. But difficult-to-treat asthma is when there are additional identifiable and potentially remedial issues in a case of asthma; so, it can also be conceptualized as 'asthma plus' [8]. A Swedish study found that 39% of children with

'problematic severe asthma' on the investigation had difficult to treat asthma [9].

## Definitions

Problematic severe asthma is defined in different age groups as follows [10, 11]:

### *School age children*

Persistent asthma symptoms despite 800 mcg/day of inhaled corticosteroids (ICS) (budesonide or equivalent) and who have also undergone trials of at least two of three controllers (long-acting β2-agonist, LTRA & oral theophylline)

### *Pre-school children*

Any child falling into one or more of the following categories despite trials of maximal guideline-recommended treatment:

- Persistent (most days for >3 months) chronic symptoms of airways obstruction with poor QOL
- Acute exacerbations with any/all of-1) at least one ICU admission 2) at least two hospital admissions requiring IV medications 3) at least two courses of oral steroids during the previous year
- Persistent airflow obstruction following steroid trial with post-bronchodilator Z score of <-1.96
- Need for alternate-day or daily oral steroids to achieve control

Once a child with asthma fits into the above definition, the next responsibility of the physician is to follow a systematic approach to find a remediable cause of the presumed 'non-response' in the child. If such a factor is found then the child is labeled as 'difficult to treat asthma' and those factors are addressed but in the case of inability to find any such factors, a diagnosis of 'severe therapy-resistant asthma' is made.

## Approach to "Difficult to Treat Asthma (DTA)"

### *Step 1: Ascertain the diagnosis*

It has been aptly said that "all that wheezes is not asthma!" It was found that 50% of children investigated for problematic severe asthma found to have the incorrect diagnosis or to have an associated diagnosis [12]. Therefore, the first step is to ensure the child has asthma and not another wheezing disorder or disorder with noisy breathing.

Disorders that may be wrongly diagnosed as asthma are as follows [6, 13]:

- Proximal airway obstruction (e.g. inhaled foreign body, tracheal or bronchial stenosis, lymph node or tumor compression)
- Airway malacia
- Recurrent aspiration (e.g. Gastroesophageal reflux disease, laryngeal cleft, tracheo-esophageal fistula)
- Congestive heart failure (e.g. congenital heart disease with increased pulmonary blood flow)
- Cystic fibrosis
- Obliterative bronchiolitis
- Primary ciliary dyskinesia
- Interstitial lung disease
- Endobronchial lesions (e.g. tumors)
- Bronchiectasis
- Hyperventilation
- Eosinophilic lung disease
- Vocal cord dysfunction

The correct diagnosis of asthma can be established in the following ways:

**History:** As with any other clinical condition, the diagnosis of asthma should start with a detailed yet focused history. The symptoms which are more supportive of a diagnosis of asthma and those which point more towards an alternative diagnosis are summarized in **table 1 [14]**.

**Table 1. Symptoms to be specifically assessed while evaluating a case of asthma** [ 14 ]

| Symptoms more supportive of asthma | Symptoms less supportive of Asthma |
|---|---|
| >1 type of symptom (wheeze, shortness of breath, cough, chest tightness) | Isolated cough with no other respiratory symptoms |
| Symptoms worse at night or in early morning | Chronic production of sputum or chest pain |
| Symptoms vary over time and in intensity | Shortness of breath associated with dizziness, light-headedness or peripheral tingling |
| Symptoms are triggered by viral infections, exercise, allergen exposure, changes in weather, laughter, irritants, e.g. car exhaust fumes, smoke, or strong smells | Exercise-induced dyspnea with noisy inspiration (stridor) |

Symptoms such as productive cough points towards an alternate diagnosis of suppurative lung disease, while exercise-induced dyspnea along with stridor especially in an adolescent is strongly suggestive of vocal cord dysfunction.

There is no clinical examination finding which is confirmatory of asthma. A child having an acute exacerbation will be having a variable degree of respiratory distress with/ without hypoxemia and polyphonic wheeze.

A child with inadequate control on medications may or may not demonstrate wheeze at the time of examination but will develop symptoms on exertion. There are definitely certain 'red flags' which when present should make the physician think about a diagnosis other than asthma and also dictate appropriate investigations **(Table 2) [14]**.

**Bronchodilator responsiveness:** In a school-aged child, the diagnosis of asthma can be aided by spirometry **[15]**. Evidence of reversible airflow obstruction with significant bronchodilator response (>12 % increase in FEV1) is a robust indicator of asthma.

**Table 2. Red flags while assessing a child with suspected asthma**

| Signs and Symptoms | |
|---|---|
| Neonatal onset of disease | Cardiovascular abnormality |
| Coughing or choking during feeds | Biphasic, monophonic wheezing, stridor |
| Difficult feeding | Clubbing |
| Persistent localized findings in chest | Multifocal recurrent infections |

**Demonstration of atopy:** Assessment of atopic status using skin prick testing or serum total IgE and specific radioallergosorbent tests (RASTs) is important to help support the clinical diagnosis of asthma **[3]**.

**Bronchial hypersensitivity:** a methacholine or histamine challenge showing airway hyper-reactivity to confirm the diagnosis is an option which should only be undertaken in a research setting and currently not recommended for the diagnosis of asthma.

### *Step 2: Check prescription*

After a correct diagnosis of asthma is made, it is equally important to select the most appropriate plan of therapy for the patient. The choice of inhalation devices, the most commonly used medication delivery method in children with asthma, varies with the age and developmental abilities of the child **(Table 3)**.

Failure to take prescribed treatment is the commonest reason for continuing symptoms in patients with problematic severe asthma [16].

**Table 3. The different inhalation devices suited for children of different age groups [ 14 ].**

| Age group | Preferred device | Alternate device |
|---|---|---|
| 0-3 years | MDI with spacer and face mask | Nebulizer with face mask |
| 4-5 years | MDI with spacer and mouth piece | MDI with spacer and face mask/ nebulizer with mouth piece or face mask |
| ≥ 6 years | MDI with spacer | DPI |

* **MDI:** Meter dose inhaler; **DPI:** Dry powder inhaler.

*Step 3: Check adherence to prescription*

Interestingly, asthmatics who are more ill are actually less likely to take their medicines properly [17]. In children with problematic asthma, nurse visit revealed 40% had poor inhaler technique, 15% used an inappropriate device and 50% had poor prescription uptake [5]. The adolescent population is the most notorious for noncompliance; some of the reasons being forgetfulness, denial, embarrassment, inconvenience, fear of side effects, a lack of efficacy of medicines, and laziness [18]. Again, the adherence seems to depend on the type of medication as well as the non-adherence to MDI was more common than montelukast [19]. Many times there are multiple reasons for a poor prescription uptake such as poor understanding, no supervision by parents and continued use of empty canister [20]. Among the low-income African-American children, 11-15% demonstrated metered dose inhaler and spacer technique suggesting no drug delivery [19]. Therefore, demonstration and checking of inhalation technique with patient's own medication and device is advisable in the beginning as well as on each follow-up visit.

*Step 4: Search for co-morbid conditions*

Certain disorders that accompany and exacerbate asthma should be looked for in children with problematic severe asthma.

**Allergic rhino-sinusitis:** Prevalence of rhinitis in asthmatic children is 60-80% [21]. Not only that the presence of allergic rhinitis makes asthma more difficult to treat [22], treatment of AR reduced risk of emergency visits and hospitalizations due to asthma [23].

**Gastro-esophageal reflux disease (GERD):** The association between asthma and GERD is complex. Depending on the criteria used for diagnosis, 25-80% children with chronic respiratory diseases have GERD [24]. But the relation between the two is not established. Treatment of GERD in asthmatic adults and children did not improve asthma control [25, 26]. But, an empirical trial of anti reflux therapy may be considered in younger children in whom the symptoms of GERD are difficult to assess, especially in the absence of 24-hour PH monitoring facilities.

**Obesity:** Obesity might lead to dyspnea due to deconditioning, a pauci-inflammatory form of asthma [27] and corticosteroid resistance [28]. The cause underlying obesity's impact on asthma risk is unknown. Commonly cited potential etiologies include airway smooth muscle dysfunction from thoracic restriction, obesity-related circulating inflammation priming the lung, and obesity-related comorbidities mediating asthma symptom development [29]. In the Childhood Asthma Management Program (CAMP)

study, no significant association was found between body mass index (BMI) and many markers of asthma control; however, there was a decrement in the FEV1/FVC ratio with increasing BMI [30]. It has also been reported that overweight children with asthma are more likely to be admitted to hospital when presenting at the emergency department with exacerbations [31].

Other co-morbid conditions include Allergic bronchopulmonary aspergillosis (ABPA), Churg-Strauss syndrome, dysfunctional breathing including sleep disordered breathing.

### *Step 5: Check for adverse environment*

Persistent allergen exposure in the sensitized patient causes eosinophilic airway inflammation, bronchial hyperresponsiveness, and secondary steroid resistance. The level of allergen exposure correlates with more severe disease, including hospital admissions, acute visits, and school days missed. Passive smoking, house dust, pet allergen exposure, damp and mold in the home, fireplaces, wood-stoves, kerosene heaters and gas for cooking have been associated with increased asthma morbidity [32]. Installation of more effective nonpolluting heating in the homes of children with asthma may significantly reduce symptoms [33]. Table4 summarizes the potential contributing socioeconomic and psychological factors of difficult to treat asthma in children [34].

Stressful life events can cause exacerbation of asthma symptoms [35]; asthma in itself, like any chronic illness, can be a cause of psychological morbidity. The adolescents with asthma having anxiety or depressive disorders had significantly more days of asthma symptoms than those with no depression or anxiety and the number of asthma symptoms was significantly related to anxiety and depressive symptoms [36]. Quite expectedly, life events with a definite positive effect can counteract the increased risk of an asthma exacerbation precipitated by a severely negative life event [37]. A Cochrane review though assessing psychological interventions for children with asthma concluded that the data were inadequate to draw any firm conclusions on the role of psychological interventions [38]. Another Cochrane review [39] by the same author looking at family therapy found only two studies suitable for inclusion. Though the results indicated that family therapy may be a useful adjunct in the management of children with asthma, the conclusions were limited by the small study sizes and lack of standardization of outcomes.

**Table 4. Potential Contributing Socioeconomic and Psychological Factors of difficult to treat asthma [ 34]**

| **Socioeconomic risk factors** | **Psychological factors** |
|---|---|
| Poverty | Negative emotions |
| Race | Functional symptoms |
| Access to medical care | Anxiety/panic disorders |
| Adherence | Depression |
| **Environment** | **Psychosocial issues** |
| Indoor and outdoor allergens and irritants | Crime, violence and Un-employment |

## Conclusion

Difficult to treat asthma is actually not 'difficult' if the modifiable risk factors are identified and managed appropriately. Adherence to therapy and environmental modifications are crucial in our setting. Referral to a Pediatric Pulmonologist is needed in a few therapy-resistant cases only.

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### Publication History

- Article Received: June 18, 2017
- Revision Received: July 03, 2017
- Article Accepted: July 10, 2017
- Article Published: July 10, 2017

### Managing Editor

Dr. Varshil Mehta and Dr. Sojib Bin Zaman



### Cite this article as

Mandal A, Sahi P. Is it Difficult to Treat Asthma in Children?. Journal of Medical Research and Innovation. 2017;1(3):23-30. doi:10.5281/zenodo.825267