# **Difficult Asthma in Children**

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Difficult asthma is asthma that is uncontrolled despite GINA step 4 and 5 (medium or high dose ICS with a second controller; maintenance of oral corticosteroids), or that requires such treatment to maintain good symptoms control and reduce the risk of exacerbations.

Keywords: asthma ; difficult asthma ; children

# 1. Introduction

Once a diagnosis of difficult asthma has been confirmed, all possible risk factors or comorbidities need to be considered in patients with persistent symptoms despite standard treatment<sup>[1][2]</sup>. Periodical and careful assessments carried out by the specialist and by the family pediatrician can help identify potentially modifiable factors responsible for poorly controlled asthma. Indeed, poor symptom control is a consequence of modifiable factors that need to be carefully assessed, such as (1) nonadherence to medication or inadequate inhalation technique, (2) persistent environmental exposures, (3) comorbidities, and (4) psychosocial factors.

### 2. Adherence to Medication

Good adherence is most commonly defined as taking between 70–80% of prescribed treatment<sup>[3]</sup>. Suboptimal adherence to ICS leads to poor asthma control, severe asthma attacks, and frequent use of healthcare resources<sup>[4]</sup>. Although it is known that half of difficult-to-treat patients have poor adherence to prescribed medication or improperly use the suggested devices<sup>[5][6]</sup>, clinicians are not used to always check adherence and inhaler technique at the time of patient's evaluation<sup>[Z]</sup>. Explaining and showing the spacer's correct use is the most effective model to improve the inhaler technique and asthma control<sup>[8][9]</sup>.

Several measurement tools, both subjective and objective, have been developed to assess adherence in adults and children with asthma<sup>[10]</sup> (Table 1). Unfortunately, each of these measures has limitations, such as the unavailability of self-report adherence questionnaires validated for the pediatric population, the often poor availability of electronic monitoring devices (EMD), the high production costs, the ability of patient/parent to manipulate the data, and the ability of EMD to measure inhalation and inhaler technique<sup>[10]</sup>.

Table 1. Tools for monitoring the adherence to prescribed treatment.

| Measurement Tools of Treatment Adherence |                            |                                   |  |  |  |  |
|--|----------------------------|-----------------------------------|--|--|--|--|
| Subjective                               | Physician as               | sessment of adherence             |  |  |  |  |
|  | Self-report questionnaires |                                   |  |  |  |  |
|  |                            | Morisky scale                     |  |  |  |  |
|  |                            | Medication adherence report scale |  |  |  |  |

|           | Drug levels                      |  |  |  |  |
|-----------|----------------------------------|--|--|--|--|
| Objective | Exhaled nitric oxide             |  |  |  |  |
|           | Prescription data                |  |  |  |  |
|           | Weighing inhaler canisters       |  |  |  |  |
|           | Dose counters                    |  |  |  |  |
|           | Directly observed therapy        |  |  |  |  |
|           | Nurse home visits                |  |  |  |  |
|           | Electronic monitoring devices    |  |  |  |  |
|           | Integrating digital technologies |  |  |  |  |
|           |                                  |  |  |  |  |

## 3. Environmental Exposures

#### 3.1. Tobacco Smoke

It is known that exposure to environmental tobacco smoke increases pediatric asthma severity<sup>[11]</sup> and, in particular, increases resistance to steroids<sup>[12]</sup>. Therefore, the assessment of passive and/or active smoke exposure is mandatory for all children with difficult asthma. As parents and patients (especially if teenagers) can deny the exposure to tobacco smoke, levels of salivary or urinary cotinine can be used to determine actual exposure<sup>[13]</sup>.

### 3.2. Air Pollution

There is increasing evidence of the association between air pollution and asthma exacerbations as well as new onset of asthma in children. Air pollution is a mixture of particles and gases emitted from several sources or generated in the atmosphere through chemical reactions (fine particles < 2.5  $\mu$ m in diameter, nitrogen dioxide, and ozone). All these elements can cause oxidative stress into the airways, leading to inflammation and remodeling, especially in asthmatic children<sup>[14]</sup>.

#### 3.3. Allergen Exposure

Children with poor asthma control despite proper treatment should be investigated for allergy sensitization<sup>[15]</sup>. Several studies reported the increased risk of asthma in children with a family history of atopy, early-onset atopic dermatitis, sensitization to egg or milk in the first years of life<sup>[16]</sup>. In addition, the poor control of asthma symptoms is directly correlated with both specific IgE levels and the number of sensitizations<sup>[15]</sup>. Consequently, it is essential that allergen exposure is minimized in all patients with difficult asthma before any drug escalation.

# 4. Comorbidities

Co-morbidities are important in the management of difficult asthma<sup>[17]</sup>, as they may contribute to poor disease control, as well as mimicking asthma symptoms (Table 2). Researching and optimizing the management of these conditions also through a multidisciplinary team is mandatory in all asthmatic patients with poor symptom control <sup>[18]</sup>.

| Comorbidity                    | Diagnosis      | Treatment |
|--------------------------------|----------------|-----------|
| Dhinasinusitis/nasal polynasis | ENT evaluation | Topic CS  |
| rtimosinusius/nasai polyposis  | Sinus CT       | Surgery   |

#### Table 2. Asthma comorbidities.

| Allergic rhinoconjuctivitis       | Anamnestic data<br>SPT test<br>Specific IgEs   | Allergen avoidance<br>Topic CS<br>Antihistamines<br>Antileukotriene |
|-----------------------------------|--|---|
| Dysfunctional breathing           | Anamnestic data<br>Nijmegen questionnaire  | Breathing<br>rehabilitation   |
| Vocal cord dysfunction            | ENT evaluation<br>Laryngoscopy   | Speech retraining   |
| Obesity                           | BMI  | Diet  |
| Obstructive sleep apnea           | Anamnestic data<br>Polisomnography   | Weight loss<br>Nocturnal CPAP                                       |
| Gastroesophageal reflux           | PPI trial<br>pH-impedance  | PPI<br>Lifestyle changes  |
| Bronchiectasis                    | Chest CT scan  | Hypertonic solutions<br>Physiotherapy<br>Macrolide                  |
| Bronchopulmonary<br>aspergillosis | Total IgE<br>IgE for Aspergillus Fumigatus IgG for Aspergillus<br>Fumigatus<br>Chest CT scan | Prednisone<br>Voriconazole  |

## 5. Psychosocial Factors

Although the literature on psychiatric and behavioral disorders among children with asthma is conflicting, most research reported that children with asthma display more emotional and behavioral problems than their healthy peers<sup>[19]</sup>.

Anxiety, depression, and symptoms of inattention, hyperactivity, and oppositional behaviors are often reported by patients and their parents. Children with asthma and internalizing disorders are at risk of having worse asthma control, increased use of rescue medications, more access to healthcare facilities for attacks, poorer pulmonary outcomes, and more missed school days<sup>[20][21][22]</sup>. Moreover, the caregivers of children with asthma can suffer too from chronicity, developing emotional difficulties that can interfere with the management of the young patient.

Questionnaires assessing the quality of life for both the child and family (Pediatric asthma quality of life questionnaire; PAQLQ)<sup>[23]</sup> as well as symptom control (Asthma control test; ACT)<sup>[24]</sup> are useful tools to estimate the severity and the impact of the disease on patient's life. Consequently, psychosocial interventions, including educational programs, behavioral support, cognitive-behavioral therapy, and family interventions can be considered to reduce the psychological impact of the disease and to better control asthma symptoms.

### 6. Socioeconomic Factors

In addition, we must not forget that low socioeconomic status (low income, educational level, parents' occupation) is often associated with poor asthma control (need for rescue therapy for asthma exacerbation, need for emergency health service visits, need for hospitalization for asthma exacerbation and fatal outcome)<sup>[25]</sup>. In these cases, the role of the family pediatrician becomes fundamental in identifying children vulnerable to asthma with a worse prognosis.

### 7. Conclusion

Poor controlled asthma represents a challenge for physicians; therefore, a multidisciplinary systematic assessment is warranted. Early identification of modifiable factors for children with difficult-to-treat asthma allows establishing better control of asthma without the need for further invasive investigations and treatment escalation.

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