Difficult-to-control asthma in children – an overview

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ABSTRACT

Difficult-to-control asthma is asthma which is inadequately controlled despite appropriate therapy, adjusted for clinical severity of the asthma. There are many terminologies used, interchangeably, to describe this condition. Difficult-to-control asthma may be divided into 'false' difficult-to-control and 'true' difficult-to-control asthma; the latter has major and minor criteria that must be met to diagnose it appropriately. To diagnose true difficult-to-control asthma, the clinician must rule out conditions that mimic asthma as well as co-morbid conditions.

To make a diagnosis, it is necessary to take a good clinical history, perform a careful examination of the patient and investigate the patient appropriately. These steps will help to rule out conditions that are often wrongly diagnosed and treated as asthma.

Management consists of environmental control, psychosocial therapy and treating comorbid conditions.

Pharmacological therapy is challenging. It may require manipulation of dosages of inhaled corticosteroids, oral (or occasionally intramuscular) corticosteroids, long-acting β_2-agonists, leukotriene antagonists, omalizumab and, as a last resort, immunosuppressant therapy.

INTRODUCTION

Difficult-to-control asthma presents a diagnostic and management challenge to practising medical practitioners. This challenge is even more obvious in rural areas, where there is a scarcity of human and diagnostic resources. This asthma, also referred to as problematic asthma, occurs in a heterogeneous group of children and has a significant impact on morbidity.[1]

Difficult-to-control asthma is defined as asthma which is inadequately or poorly controlled despite an appropriate therapeutic strategy that is adjusted to clinical severity of the asthma. Other terminologies have been used and include: severe asthma, persistent asthma, steroid-resistant asthma, steroid-insensitive asthma, refractory asthma, persistent asthma, difficult-to-treat asthma and difficult asthma. These terms have been used interchangeably.[2] Asthma in this condition may be mild, moderate or severe and may coexist with another condition.[2] However, the defining phenomenon is asthma that is unresponsive to conventional therapy.[2]

SUBGROUPS OF DIFFICULT-TO-CONTROL ASTHMA

Difficult-to-control asthma can be divided into two subgroups for ease of investigation and management. The subgroups are as follows:

- **True difficult-to-control asthma:** This is genuinely difficult-to-control asthma which needs a thorough diagnostic work-up and appropriate treatment by an experienced specialist.
- **False difficult-to-control asthma:** This is asthma which is affected by factors commonly unrelated to asthma, which in themselves, lead to a limited treatment response. This is a form of asthma which is only 'apparently' difficult-to-control. In this condition other co-morbid conditions (such as allergic rhinitis) may make asthma worse.

DIAGNOSTIC CRITERIA

According to the American Thoracic Society workshop consensus for definition of severe/refractory asthma the following criteria are used for diagnosis: [3]

Major characteristics

- Treatment with continuous or near continuous (> 50% of year) oral corticosteroids
- Need for treatment with high-dose inhaled corticosteroids (ICS)

Minor characteristics

- One or more asthma exacerbations per year
- Use of daily short-acting β_2-agonist because of asthma symptoms
- Airway obstruction (forced expiratory volume in 1 second (FEV_1) <80% of predicted, diurnal peak expiratory flow variability of >20%)
- Needing three or more oral corticosteroid courses per annum
- A near-fatal asthma event in the past
- Deterioration with reduction in oral or intravenous steroid dose
- Needs additional daily treatment with a controller medication such as long-acting β-agonist (LABA), leukotriene antagonist, or theophylline

A diagnosis of difficult-to-control asthma requires that two major criteria, or one major criterion and two minor criteria are met.[4] In addition false difficult-to-control asthma must have been ruled out.

Patients with difficult-to-control asthma have a poor quality of life as a result of asthma exacerbations which are often unpredictable. Quality of life is also impaired by adverse effects of medications, especially corticosteroids. These patients also have a high frequency of comorbid conditions.[5]

Differential diagnosis of false difficult-to-control asthma

Younger children may present a diagnostic challenge because of the fact that there are many causes of wheezing, other than asthma, in this age group. The younger the child, the greater is the possibility of finding other causes for wheezing.[5]

When assessing a patient with difficult-to-control asthma it is imperative to confirm that the diagnosis

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is correct, as a great percentage of these patients will actually have been wrongly diagnosed as asthmatics. It is necessary to rule out conditions that may mimic asthma if asthma symptoms do not respond to treatment as expected. There are other conditions sharing common features with asthma, and other confounders like allergic rhinitis that may make symptoms worse.[6]

True difficult-to-control asthma

This occurs in children with true therapy-resistant asthma and constitutes less than 50% of patients who are investigated for problematic asthma.[1] Phenotypes of difficult asthma are listed in Table II.

Table I. Factors that can be classified under false difficult-to-control asthma

1. **Incorrect diagnosis of asthma**

   Other alternative diagnoses to consider in difficult-to-control asthmatic patients:

   a) Conditions to be considered as a cause of wheezing in infants.[4]

   Upper airways
   - Congenital anomalies such as laryngomalacia, laryngeal angiomatosis, vocal cord paralysis

   Large airway obstruction
   - Tracheomalacia, bronchomalacia, tracheal stenosis
   - Laryngeal webs and vascular rings
   - Tracheal or bronchial foreign body

   Small airway obstruction
   - Bronchiolitis, including bronchiolitis obliterans
   - Cystic fibrosis
   - Bronchopulmonary dysplasia
   - Primary ciliary dyskinesia
   - Cardiac disease

   Others
   - Gastro-oesophageal reflux

   b) Conditions to be considered in older children and adolescents
   - Hyperventilation syndrome
   - Upper airway obstruction, e.g. vocal cord dysfunction, tracheal stenosis, laryngeal tumours
   - Gastro-oesophageal reflux disease
   - Bronchiectasis
   - Cystic fibrosis
   - Chronic obstructive lung disease
   - Restrictive lung disease
   - Endobronchial lesions
   - Cardiac asthma/congestive heart failure
   - Hyperthyroidism

2. **Asthma and comorbid conditions**
   - Allergic rhinitis and all of the above
3. **Continued exposure to aggravating factors**
   - Exposure to allergens such as pets and grass pollen
   - Use of drugs such as nonsteroidal anti-inflammatories and betablockers
   - Occupational exposure such as in baker's asthma
4. **Non-adherence to treatment**
5. **Incorrect choice of inhalers and poor inhaler technique**

Table II. Phenotypes of difficult-to-control asthma

- Very severe asthma
- Unstable asthma
- Life-threatening asthma
- Corticosteroid-dependant asthma
- Corticosteroid-resistant asthma

The above-mentioned phenotypes constitute severe persistent asthma and represent about 10% of asthmatics. These patients have a high morbidity and mortality and account for approximately 30% of health costs.[7] It should however be noted that Bousquet *et al.* introduced a new terminology to categorise patients with difficult-to-control asthma, at a World Health Organization meeting convened in April 2009:[8]

a) Untreated severe asthma which may be controlled with adequate adherence and technique.

b) Difficult-to-treat asthma with a partial or poor response to treatment due to factors other than asthma alone, e.g. poor adherence and access to treatment.

c) Treatment-resistant severe asthma. This asthma has two categories of responsiveness to medications: (i) the first group consists of those patients who are not optimally controlled despite high-dose ICS or high-dose ICS/LABA combination and chronic use of systemic steroids; and (ii) the second group consists of patients with well-controlled asthma requiring the highest level of recommended treatment for control to be maintained.

PATHOGENESIS

Severe asthma is a heterogeneous disease. In some cases extensive inflammation involves all airways up to the most peripheral, whereas in others there is an increase in smooth muscles, extensive remodelling and little inflammation.[7] Inflammation may involve neutrophils alone or in combination with eosinophils.

Bronchoalveolar lavage and bronchial biopsy have identified two pathological patterns in patients with severe asthma not controlled with high doses of corticosteroids. These are those with eosinophilia and those without eosinophilia.[4] Pathological studies by Wenzel *et al.* cited by Moore and Peter,[9] made it possible for these two subgroups to be described as either eosinophil-positive or -negative on the basis of the presence or absence of eosinophils.

CORTICOSTEROID-RESISTANT ASTHMA

Steroid resistance is rare, only affecting 1 in 1 000 to 1 in 10 000 asthma patients.[4] These patients fail to respond clinically after a 2-week course of oral prednisone or prednisolone. There is failure to increase FEV_1 by >15%. It has been shown that the precorticosteroid FEV_1 measurement and the duration of asthma, of both corticosteroid-sensitive and corticosteroid-insensitive asthma is not different.[9]

Steroid-resistant asthma can be eosinophilic, dominated by eosinophils on bronchial biopsy or bronchoalveolar lavage specimens, or non-eosinophilic and dominated by neutrophils.[10] Studies have demonstrated that about 75% of these patients are atopic and have a positive skin test to major allergens.[11] It is worth noting that the existence of eosinophil-positive or -negative phenotypes was challenged by Ten Brinke, cited by Moore and Peter,[9] on the basis that treatment

of patients with high-dose parenteral corticosteroids eliminated eosinophils.[9]

This may be explained on the basis that the patients with eosinophilia may have been inadequately treated.

Causes of steroid resistance

The cause of steroid resistance is controversial.[10] Rarely patients may have congenital decreased numbers of steroid receptors despite normal binding capacity. More commonly patients may have normal or increased numbers of receptors, but reduced affinity for glucocorticoids.

Some patients may have pharmacokinetic abnormalities with poor absorption of steroids, rapid steroid elimination, or failure to convert prednisone to prednisolone.

There are two types of glucocorticoid receptors (GRs), GR-alpha and GR-beta. GR-beta inhibits the activity of GR-alpha by not binding glucocorticoids and antagonising the activity of GR-alpha. The up-regulation of a functionally inactive GR-beta thus inhibits the glucocorticoid-glucocorticoid receptor complex from modulating transcription of proinflammatory molecules. This results in reducing the efficiency of the active GR-alpha.

APPROACH TO EVALUATION AND DIAGNOSIS OF A SUSPECTED DIFFICULT-TO-TREAT ASTHMATIC

The initial evaluation of patients referred for difficult asthma is to confirm that the patients indeed have asthma. Taking a new and comprehensive history is very important even if the patient is 'previously known' to be asthmatic. These patients will have a history of significant and frequent asthma exacerbations despite asthma controller therapy which is consistent with severe persistent asthma.[5] Clinicians should elicit if there is a history of exacerbations of symptoms at night, with exercise or on exposure to allergens. Comorbid conditions such as rhinitis and gastro-oesophageal reflux should also be excluded.

A thorough medical examination is necessary, looking for signs of allergy such as allergic shiners, nasal crease, allergic salute and rhinitis with polyps. The chest should be checked for wheezes. Diseases other than asthma should also be excluded, e.g. vocal cord dysfunction, congenital causes of upper airway obstruction, bronchiectasis and other chronic airway diseases.

Initial testing will depend on the history and should include skin-prick test for food and aeroallergens, and spirometry before and after administration of bronchodilator so as to determine the level of lung function and degree of reversibility.

If there is decreased pulmonary function and bronchodilator reversibility, response to oral corticosteroids should be assessed.

Chest X-ray should be performed and if indicated a high-resolution computed tomography (CT) scan of the chest may be considered. Methacholine challenge test to evaluate bronchial hyperresponsiveness, which is a cardinal feature of asthma, may be performed if the diagnosis of asthma is doubtful from the history and physical examination. Bronchoscopy with bronchoalveolar lavage and bronchial biopsy are also recommended where expertise is available. It is worth noting that measurement of exhaled nitric oxide may be used as a non-invasive test to assess the presence of eosinophil inflammation.

For patients who have been on high doses of inhaled or oral corticosteroids evaluation for adverse steroids effect should be performed. Growth monitoring for children is mandatory; bone densitometry, evaluation for cataracts and testing intraocular pressure may also be necessary.

If there is no evidence of steroid side-effects despite administration of high dosages, adherence and inhaler techniques should also be checked.

TREATMENT OF DIFFICULT-TO-CONTROL ASTHMA

For ease of discussion, treatment will be divided into non-pharmacological and pharmacological.

Non-pharmacological treatment

Inhaler technique and adherence to treatment

It is necessary to make sure that medications that are prescribed are actually being taken correctly. There is generally a fear of using inhalers among most parents because of a belief that the child becomes addicted to inhalers and also because of steroid phobia. Parents must be asked to bring medications that their children are using, for monitoring of drug use and to demonstrate the functionality of the device and their ability to use it appropriately. Issues such as inappropriate use of drug delivery devices, expired medications and nonadherence to therapy regimens have been shown to contribute to poor control in almost half of patients.[1] Poor adherence is more common with metered dose inhalers than with oral medications. Adolescent asthmatics are at higher risk of nonadherence for reasons such as denial, embarrassment, laziness, forgetfulness, fear of side-effects and inconvenience.

Environmental control

High allergen exposure can lead to exacerbations, increased inflammation and bronchial hyperresponsiveness. Some allergens such as cat dander can actually be inhaled from clothes of classmates at school. Environmental control interventions are likely to succeed where aeroallergens such as house-dust mites, cockroaches, moulds and pets are removed from proven allergic patients.[1] No evidence is available to support allergen avoidance in the primary prevention of asthma.[12]

Environmental tobacco smoking, both active and passive, is common in asthmatic children, although the frequency is not known. It has been shown to cause steroid resistance in adults.[1] It probably does the same in children.

Psychosocial factors

Stress and depression can trigger an asthma exacerbation because of amplification of the airway eosinophillic response to allergens.[1] It is important to have a multidisciplinary team consisting of psychologists and social workers, among others, to help in the management of these children. They can be of great help in comanaging conditions such as vocal cord dysfunction and hyperventilation syndrome.

Social factors, such as poverty, can affect asthma control as they influence access to medical care.

Pharmacological treatment

Treatment of comorbid conditions

The main comorbid conditions that need to be treated are allergic rhinitis and gastro-oesophageal reflux.

- *Allergic rhinitis:* There is an association between allergic rhinitis and asthma with a reported prevalence of 80-100%.[12,13] Diagnosis of allergic rhinitis often precedes that of asthma and is an independent risk factor for both allergic and non-allergic asthma.[13]

Almost all patients with severe, corticosteroid-dependent asthma have sinonasal involvement.[13] Observational data have shown that treatment of allergic rhinitis improves control of asthma.[13] Intranasal steroids such as budesonide and fluticasone, oral second-generation H_1-receptor antagonists and leukotriene receptor antagonists may be used with good effect.

- *Gastro-oesophageal reflux disease:* There are differing opinions of evidence that reflux causes asthma. Some authors estimate its prevalence in patients with asthma to be 34-80%, while other reports describe this evidence as being of poor quality.[1,14] Proton pump inhibitors such as omeprazole and lansoprazole given twice a day orally have shown some therapeutic benefit, even though it may take some time before there is symptomatic improvement.[14]

Treatment of severe, therapy-resistant asthma

According to guidelines for management of chronic asthma, the treatment of asthma should follow a stepwise approach according to asthma severity, the aim being to achieve control of the disease at all times. There are however no internationally accepted guidelines, or regimens, for management of therapy-resistant asthma, save for reliance on individual trials on single patients.[1,4] Treatment should aim to achieve optimal or near optimal control through an intensive initial phase, until the best possible results are achieved.

High-dose ICS such as budesonide 800 μg/day or fluticasone 500 μg/day in combination with LABA and oral prednisolone 1-2 mg/kg/day with a maximum dose of 40 mg/day should be tried. The prednisolone should be given for a period of 7-14 days. If there is no control achieved the lowest possible daily oral corticosteroid dose should be used, with careful monitoring for side-effects.

An alternate approach may be to use an ICS/LABA combination, together with a short course of oral corticosteroids. When control is achieved, dosages should be reduced to the lowest possible that maintains control.

The use of LABA or combination therapy with ICS in children under 5 years of age is not recommended because of lack of published double-blind randomised placebo-controlled trials on the addition of LABAs to ICS in this age group.

In case of clinical deterioration on withdrawal of oral corticosteroids, other drugs such as antileukotrienes, e.g. montelukast, should be added to the continuation of low-dose oral corticosteroids. It should be emphasised that there are no studies to define the most effective combination of asthma drugs.[4] Omalizumab, although not as yet commercially available in South Africa, may also be used in children 12 years and older. It is a monoclonal antibody against IgE which is effective in reducing corticosteroid dose required in atopic asthma with high levels of IgE by 50%.[4] It is administered subcutaneously every 2-4 weeks. In children not responding to oral corticosteroids, it has been demonstrated that they respond to intramuscular triamcinolone. It is unclear whether the response is due to improved compliance or better antiinflammatory properties of triamcinolone.[4] Immunosuppressant drugs like methotrexate and cyclosporine should not be used except in exceptional cases and only by somebody with experience in this form of therapy.

CONCLUSION

Difficult-to-control asthma can be both challenging and exciting to manage. It needs careful history taking, examination and the performance of appropriate special investigation to make the correct diagnosis and provide appropriate treatment.

Declaration of conflict of interest

The author is in the speakers' bureaux of MSD, GlaxoSmithKline, the South African Medical Association, and Nestlé, and has been sponsored by MSD and GlaxoSmithKline to attend international congresses overseas. The author is an executive committee member of the Allergy Society of South Africa. The subject matter of this article has not been influenced by the author's association with the above-mentioned companies.

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