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Getting the basics right resolves most cases of uncontrolled and problematic asthma

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Abbreviations:

ICS Inhaled corticosteroids

GP General practitioner

BMI Body mass index

Abstract:

Aim

The prevalence of true therapy-resistant asthma among children whose asthma remains uncontrolled, despite daily controller therapy, is unknown. The aim of this study was to investigate underlying causes in children with uncontrolled asthma.

Methods

This was a retrospective chart review of 142 children aged from five to 17-years-old over a five-year period. The patients had uncontrolled asthma and were referred by general practitioners to a hospital-based paediatric asthma clinic.

Results

An underlying cause for uncontrolled asthma was found in 138 children (97.2%). The causes were poor adherence (n=53, 37.3%), on-going exposure to environmental triggers (n=40, 28.2%), comorbidities (n=28, 19.7%), incorrect inhaler technique (n=11, 7.7%) and incorrect diagnosis (n=6, 4.2%). After properly addressing these basics in asthma management, the asthma was well controlled in all 138 patients and lung function was normal. Only four children (2.8%) fulfilled the criteria for true therapy-resistant asthma.

Conclusion

A remedial cause in the basics of asthma management could be found in 97% of children with uncontrolled asthma referred to a hospital-based asthma clinic. True therapy-resistant asthma was found to be very rare in children.

Key Notes

- The prevalence of true therapy-resistant asthma among children whose asthma remains uncontrolled despite treatment with inhaled corticosteroids is unknown.
- This study found that the remedial cause could be identified in the basics of asthma management in 138 out of 142 children (97.2%) with uncontrolled asthma and true therapy-resistant asthma was very rare (2.8%).
- Getting the basics of asthma management right resolved uncontrolled asthma in 97% of cases.

INTRODUCTION

Asthma is the most common chronic illness of childhood and has a major impact on the daily life of affected children and their families. In clinical trials, childhood asthma has usually been well controlled by treatment with inhaled corticosteroids (ICS) (1). In real life, however, many children with asthma remain symptomatic despite ICS (2). Different terms are used to describe this issue, such as uncontrolled asthma, problematic asthma or difficult to treat asthma (3). In this paper we will use the term uncontrolled asthma to describe these patients. The term problematic severe asthma has been used to describe children who have uncontrolled asthma despite being prescribed multiple controller therapies, including ICS, long-acting beta agonists and leukotriene receptor antagonists (3,4). There is widespread agreement that the term true therapy-resistant asthma should be reserved for children with uncontrolled or problematic severe asthma whose asthma remains uncontrolled despite treatment with multiple controller drugs after addressing the basics of asthma management (3,4). These include re-confirming the diagnosis of asthma and excluding other causes of their respiratory symptoms (5), teaching and maintaining proper inhalation techniques (6), adherence to daily controller therapy (7), controlling exposure to environmental triggers, such as

tobacco smoke and relevant inhalant allergens (8), and identifying and treating comorbidities such as allergic rhinitis and dysfunctional breathing (9,10).

Only a minority of children with uncontrolled or problematic severe asthma have true therapy-resistant asthma (3,4). There is a consensus among experts that getting the basics right in managing childhood asthma may help to control the disease in many children with uncontrolled or problematic severe asthma (3,11). To our knowledge, however, the exact percentage of children with uncontrolled asthma or problematic severe asthma who have true therapy-resistant asthma has never been investigated. As a result, there is still controversy about the prevalence of true therapy-resistant asthma (12). It is important to resolve this controversy, because true therapy-resistant asthma places a major burden on healthcare costs, due to the frequent use of hospital facilities and staff for repeated exacerbations and the high cost of step four management options, such as omalizumab.

The aim of our study was to investigate the underlying causes of uncontrolled asthma in children who had been referred to a hospital-based paediatric asthma clinic by primary care practitioners. We also assessed the prevalence of true therapy-resistant asthma among the children.

METHODS

Patients

This study comprised a retrospective cohort study carried out between 1 January 2005 and 31 December 2009. We reviewed the medical records of all children from five to 17-years-of-age who had been referred to a hospital-based paediatric asthma clinic at the Princess Amalia Children's Centre in Zwolle, the Netherlands, by primary care practitioners because of uncontrolled asthma. Uncontrolled asthma was defined as asthma that was insufficiently controlled despite the fact that these children had been prescribed daily ICS treatment. In the Netherlands, all children with a medical problem are seen by their general practitioner (GP) in the first instance and can only be seen by paediatricians, who are all hospital based in the Netherlands, after a GP referral. According to the

national Dutch guidelines on the management of childhood asthma, GPs are recommended to refer children with problematic severe asthma or uncontrolled asthma to a paediatrician for evaluation and management (13) The Princess Amalia Children's Centre is the paediatric department of the Isala hospital, a large 950-bed general teaching hospital serving a population of approximately 400,000 inhabitants. All children in the hospital's catchment area visit the Princess Amalia Children's Centre if they have been referred by their GP. Children referred for problematic severe asthma or uncontrolled asthma are always seen by one of the two paediatric respiratory physicians (EdG, PB). Details of our paediatric asthma management programme have previously been published (14). In short, after the diagnosis of asthma has been confirmed following the international guidelines (15), children are prescribed daily, low to moderate dose ICS treatment according to the national Dutch guidelines for the management of childhood asthma (16). The children and their parents receive comprehensive instructions on how to use the inhalers and self-management education from dedicated paediatric asthma nurse specialists (14). Sensitisation to aeroallergens is recorded and allergen exposure reduction measures are implemented if required after home visits by the paediatric asthma nurse specialists (17). Patients are screened for potential comorbidities, such as allergic rhinitis, dysfunctional breathing, obesity, anxiety and depression. Detailed notes are taken about the patient's history, they undergo a physical examination and appropriate follow-up testing is carried out if required (18).

Identified comorbidities include allergic rhinitis, which is treated with nasal corticosteroids, and dysfunctional breathing, which is treated with breathing exercises under the supervision of a paediatric physiotherapist. Patients are followed up until their asthma has been satisfactorily controlled for at least six months. If their asthma remains inadequately controlled after addressing the basics of asthma management outlined above, a long-acting bronchodilator and, or, montelukast is added to their daily ICS maintenance treatment, in line with the national Dutch asthma guidelines (16).

For the purpose of this study, we included all patients who had been using ICS for at least three months before they were referred by their GP and who were able to undergo pulmonary function testing. We excluded patients with bronchopulmonary dysplasia, cystic fibrosis and bronchiectasis and those with major neuromuscular or cardiovascular comorbidities.

The study was approved by the hospital's ethical review board.

Methods

The following data were extracted from the patients' electronic files: date of birth and age, gender, body mass index (BMI) at referral and during the follow-up period, type and dosage of daily controller treatment for asthma at each visit, sensitisation to aeroallergens, history of tobacco smoke exposure at home and home visit reports on home dampness and ventilation, tobacco smoke and aeroallergen exposure. We also detailed any relevant comorbidities and their treatment as well as the frequency of asthma exacerbations during follow-up and the assessment of asthma control by a paediatric respiratory physician following national Dutch asthma guidelines (16). Asthma exacerbation was defined as seeking urgent medical consultation if an increase in asthma symptoms could not be controlled at home by the patient's reliever medication, a short-acting bronchodilator. Asthma control was assessed at least once a year using the childhood Asthma Control Questionnaire (ACQ) and the last recorded questionnaire was used in the data analysis. An aggregate questionnaire score of less than one was considered to indicate well-controlled asthma (19).

Reasons for uncontrolled asthma.

After reviewing the patient's file, an independent investigator not involved in patient care (WK) recorded whether the patient's asthma was adequately controlled after addressing the basics of asthma management - while receiving ICS, with or without a long-acting beta agonist or montelukast - or whether the patient fulfilled the criteria for true therapy-resistant asthma.

The independent investigator identified the most important cause of uncontrolled asthma in patients whose asthma became adequately controlled after addressing the basics of asthma management, as outlined below.

Inhaler technique

Inhaler technique was evaluated and recorded at every follow-up visit. Poor inhaler technique was considered to be the cause of uncontrolled asthma if patients showed poor inhaler technique at referral and their asthma control improved after they were shown and demonstrated the correct use of an inhaler (6,20).

Adherence

Adherence to daily controller therapy was assessed using a structured interview at every follow-up visit. After expressing sympathy for the fact that many patients found it difficult to take their controller medication on a daily basis, patients and parents were asked about their experiences and how often they were likely to miss a dose during a typical week. Patients were considered to be adherent if they, or their parents, reported that they never missed a dose (21) and patients were considered to be non adherent if they, or their parents, reported missing doses at least once a week and were interviewed about their reasons for non adherence. Non-adherence was considered to be the cause of the uncontrolled asthma if asthma control improved when non-adherence had been addressed by tailored self-management education and was no longer apparent from the structured interview at follow up.

On-going exposure to environmental triggers.

Reports of home visits performed by paediatric asthma nurses were used to assess on-going exposure to relevant aeroallergens that the patient was sensitised to, such as house dust mites and cats and dogs. They also assessed tobacco smoke at home. If there was on-going exposure to

environmental triggers, parents received comprehensive counselling on reducing exposure to relevant aeroallergens and were asked to avoid smoking in the house (22). On-going exposure to environmental triggers was considered to be the cause of uncontrolled asthma if asthma control improved after reducing environmental triggers in the home, as assessed by a parental report to the asthma nurse.

Comorbidity.

Patient records were checked for evidence of allergic rhinitis, dysfunctional breathing, recurrent lower respiratory tract infections and obesity, defined as a body mass index (BMI) of > 2.5 standard deviation scores above the mean weight for the child's age. Any diagnosis of allergic rhinitis was made by the paediatric respiratory physician or the ear, nose and throat surgeon (23). If allergic rhinitis was diagnosed, treatment with nasal corticosteroids was instituted, together with an oral non-sedating antihistaminic agent if needed (23). Dysfunctional breathing was defined as a chronic or recurrent change in breathing pattern, causing respiratory and non-respiratory complaints such as dizziness, chest pain, excessive yawning and anxiety (10). This was confirmed after a paediatric physiotherapist examined breathing patterns during a treadmill test (24). If dysfunctional breathing was diagnosed, the patient was referred to a paediatric physiotherapist for breathing and relaxation exercises. Obese children were referred to a paediatric dietician for nutritional advice and were encouraged to exercise more. If BMI decreased by at least one standard deviation score, the obesity treatment was considered to be successful. Patients with symptoms of anxiety or depression were referred to a paediatric psychologist for evaluation and targeted treatment. If asthma control improved after successful therapy for allergic rhinitis, dysfunctional breathing, obesity or psychological problems, then that comorbidity was considered to be the cause of uncontrolled asthma.

True therapy-resistant asthma.

Patients were considered to have true therapy-resistant asthma if their asthma remained incompletely controlled despite step three treatment - daily ICS plus long-acting bronchodilator, montelukast or both - and despite addressing the basics of asthma management, such as inhaler technique, adherence, on-going exposure to triggers and treating relevant comorbidities.

Statistical analysis.

Data were analysed using SPSS version 17.0. Normally distributed data were analysed by parametric methods and non-normally distributed data by non-parametric techniques.

RESULTS

During the five-year study period, 142 children referred to our clinic for uncontrolled asthma fulfilled the inclusion criteria and were included in this study. Their clinical characteristics are presented in Table 1. The causes of uncontrolled asthma in the 142 children are shown in Figure 1. Only four patients (2.8%) met the criteria for true therapy-resistant asthma. In the other 138 patients (97.2%), uncontrolled asthma was due to shortcomings in basic asthma management (Figure 1). The diagnosis of asthma was rejected in six children: four with dysfunctional breathing, one with allergic rhinitis and one with a chronic cough associated with tobacco smoke exposure at home. In all six of these patients, symptoms improved after appropriate therapy for the real underlying cause of their symptoms. Asthma medication could be withdrawn in all these six patients without any increase or re-occurrence of symptoms. Comorbidity was identified as the major cause of problematic asthma in 28 children (19.7%). Allergic rhinitis was diagnosed in 18 (64%) children, dysfunctional breathing in four (14%) and a combination of allergic rhinitis and dysfunctional breathing in six (21%). None of the children in this cohort had uncontrolled asthma because of obesity, anxiety or depression.

On-going exposure to environmental triggers was identified as the cause of uncontrolled asthma in 40 children (28.2%), relevant aeroallergen exposure in 28 (70%) and a combination of on-going allergen and cigarette smoke exposure in the remaining 12 (30%).

Poor inhaler technique was identified as the main reason for uncontrolled asthma in 11 patients (7.8%). The most common reason for uncontrolled asthma, however, was non-adherence, which occurred in 53 children (37.3%) (Figure 1).

Partly or completely controlled asthma was achieved in 138 patients (97.2%) after addressing the basics of asthma management. One of the patients in the true therapy-resistant asthma group moved out of the region before good asthma control was achieved and the remaining three patients (2.1%) remained uncontrolled throughout the follow-up period. One patient, who had on-going exposure to smoking at home, was uncontrolled at every follow-up visit and the other two were only uncontrolled during periods when they did not adhere to the therapy. Their asthma was well controlled during periods of good adherence.

The relationship between daily controller therapy before and after referral and to our centre is presented in Table 2. Although the proportion of children on combination therapy was slightly higher after attending our centre, than at referral, the daily ICS dose was lower. Daily controller therapy could be withdrawn altogether from patients if asthma was ruled out. During the first two years of follow up after referral, 23 patients (16%) had an asthma exacerbation requiring oral prednisolone and eight of these children - 6% of total study population - were hospitalised.

DISCUSSION

This study showed that when most children were referred to paediatric respiratory specialist care with uncontrolled asthma – that is asthma insufficiently controlled despite prescription of daily ICS treatment - the cause could be found in one of the basics of asthma management (Figure 1). True therapy-resistant asthma was very rare in children with on-going symptoms despite ICS therapy. The children's asthma could be well controlled by enrolling in a comprehensive programme of careful

guideline-based diagnosis and management, performed by paediatric respiratory physicians and paediatric asthma nurses (14), and by addressing and resolving the issues of non adherence, poor inhalation technique, on-going exposure to environmental triggers and by treating comorbidities such as allergic rhinitis and dysfunctional breathing (11,25). Our results, therefore, support the recommendation that basic asthma management should be reviewed and addressed in children with problematic severe asthma and uncontrolled asthma before increasing their maintenance medication (3,4,12). We believe that this key issue should be given more emphasis in future paediatric asthma guidelines.

Although the basics of asthma management addressed in this study are well known, it is striking that they remained inadequately addressed in many children with asthma, not just in our cohort but in other studies (26). For example, in a sample of children referred to a national UK centre for problematic asthma, home visits identified potentially modifiable factors in the basics in asthma management in almost 80% of cases (17). This was similar to our study, which found that non-adherence and on-going environmental exposures were the most common causes of problematic severe asthma. Similarly, although allergic rhinitis has been identified as a relevant comorbidity in children with asthma for many years (27), it remains unrecognised and untreated in many asthmatic children (28). We have previously shown that treating allergic rhinitis with nasal corticosteroids may help to improve asthma control (9). Although dysfunctional breathing is less well known as a comorbidity in children with asthma, perhaps because there are no agreed diagnostic criteria for this condition in children (29), it may have deleterious effects on asthma control (10). Although further studies are needed to examine treatment options for dysfunctional breathing, in this study the patients with dysfunctional breathing appeared to improve after breathing and relaxation exercises under the supervision of a paediatric physiotherapist, confirming earlier observations in adults (30). The main strength of this study was that it quantified the proportions of children who had uncontrolled asthma because of problems with basic asthma management. This was based on a

careful review of their medical records and follow up after the identified causes for uncontrolled asthma had been addressed and resolved. To our knowledge, the only earlier study that examined the prevalence of problems in basic asthma management was based solely on nurse-led assessments, carried out during home visits to patients with problematic severe asthma, and it did not report any follow-up data after these problems had been addressed (17). The main limitation of this study was the retrospective study design, which was subject to information and confirmation bias. In addition, as it was not a controlled study we cannot state with certainty that asthma control improved in these children because of the interventions we carried out. We did not quantify allergen or tobacco smoke exposure at home and relied on parental reports rather than measuring adherence objectively. Although this weakens the robustness of our findings, it reflects normal clinical practice.

CONCLUSION

True therapy-resistant asthma was very rare in our cohort of children with uncontrolled asthma, who were referred to paediatric respiratory specialist care by their GPs. Carefully addressing the basics of asthma management, including adherence, on-going exposure to environmental triggers, comorbidities such as allergic rhinitis and dysfunctional breathing and ensuring proper inhaler technique led to well-controlled asthma in the large majority of children with uncontrolled asthma. The basics of asthma management should be covered before stepping up treatment in children with uncontrolled asthma. We believe that more emphasis on this key issue is required in future paediatric asthma guidelines.

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Table 1. Patient characteristics

Patients (n)	142
Male, number (%)	95 (66.9%)
Age, median (min-max)	8 years (5-17)
BMI, median (min-max)	16.6 kg/m ² (12.3-24.6)
Total IgE, median (IQR)	317 kU/L (72-842)
Sensitisation to aeroallergens, number (%)	
None	25 (17.6%)
Only house dust mite (HDM)	21 (14.8%)
Only dog/cat	1 (0.7%)
Only pollen	7 (4.9%)
Combination(HDM and/or dog/cat and/or pollen)	88 (62.0%)
Home exposure only to aeroallergens#, number (%)	92 (64.8%)
Home exposure only to cigarette smoke*, number (%)	1 (0.7%)
Home exposure aeroallergens and cigarette smoke, number (%)	38 (26.8%)
FVC pre-bronchodilator, mean (SD)	99.2 % (12.3)
FEV1 pre-bronchodilator, mean (SD)	98.1 % (15.4)

FeNO median (min-max)	23 ppb (5-168)
Maintenance treatment at referral:	
- Fluticasone ≤250 ug/day	90 (63%)
- Fluticasone 251-500 ug/day	23 (16%)
- Fluticasone + long acting beta agonist	29 (20%)

#Defined as sensitised to aeroallergens and reports of home visits on these aeroallergens, performed by paediatric asthma nurses.

*Defined as smoking reported by paediatric asthma nurses during home visits.

BMI: body mass index; HDM: house dust mite; FeNO: fraction of nitric oxide in exhaled air; IgE: immunoglobulin E; IQR: interquartile range; FVC: forced vital capacity; FEV1: forced expiratory volume in one second

Table 2. Daily controller therapy in 142 children referred with uncontrolled asthma, before referral and after workup in the paediatric asthma clinic

	After workup at specialist centre				Total before referral:
	fluticasone < 250 ug/day	fluticasone 251-500 ug/day	combination therapy	medication stopped (no asthma)	
Before referral:					
Fluticasone < 250 ug/day	76	1	12	1	90
Fluticasone 251-500 ug/day	11	2	6	4	23
Combination therapy	8	2	17	2	29

Total after referral	95	5	35	7	142
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Figure 1. Causes of problematic asthma

