# Adherence to Inhaled Corticosteroid Treatment in Non-Atopic Children with Severe Recurrent Wheeze

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**Abstract:** *Background*: Recurrent wheeze is an important problem due to the probability of developing asthma. The treatment and adherence to therapy of recurrent wheezing in infants remains controversial.

*Objective*: The present study was designed to investigate the compliance to inhaled corticosteroids (ICSs) and the response to the therapy in non-atopic children with severe recurrent wheeze.

*Methods*: The non-atopic children with a severe recurrent wheeze who admitted to Behçet Uz Children Hospital were recruited to the study. The subjects practiced the skills to use ICSs and were followed-up for the adherence to ICSs following 6 months.

*Results*: One hundred and six children diagnosed as non-atopic severe recurrent wheezers participated to the study. The mean age of the children was 22.0±15.4 months. The compliance rate to the treatment was 33.9%. The expectations of parents about beneficial effects of the medication were not met in 59 patients (84.2%) in early treatment cessation group. There was a significant difference between the treatment compliant patients and the patients with early treatment cessation among the experience of benefit in reduction of exacerbation days and exacerbation frequency, number of cough and sleep deprivation (p=0.002, p=0.004, p=0.002, respectively). The most common reason for early treatment cessation was the parents' belief of the inefficiency of the medications on their 'non-asthmatic children'.

*Discussion*: Adherence to treatment with inhalers falls behind the expectations in severe recurrent wheezers. We suggest that, the physicians should participate to understand the barriers and concerns about regular treatment usage to increase compliance and prevent future development of asthma.

**Keywords:** Children, adherence, inhaled corticosteroids, asthma.

## INTRODUCTION

Wheezing is a frequent heterogenic condition for child health care professionals throughout the world. According to birth cohort studies, the estimated cumulative prevalence of wheezing in preschoolers is approximately 50% [1]. The estimated prevalence of any wheezing episode (wheezing ever) is about 40% and recurrent wheezing episodes (3 or more) is about 15% at 2 years of age [2]. Despite its high prevalence, underlying pathogenesis and the factors affecting the expression and the natural course of the disease remain poorly understood. The clinically proven evidence about this heterogeneous disorder at this age group help to better guide treatment decisions [3].

The diagnosis of asthma in children under 5 years of age is challenging due to high co-incidence of other wheezing disorders, and atopy is believed to be a crucial determinant in predicting the future development of persistent asthma in children with recurrent wheezing. Preschoolers with high risk of asthma who receive regular inhaled corticosteroid (ICS) treatment show better controlled persistent/ severe wheezing episodes and improvement in lung functions [4]. Although, the airway pathology that is typical of atopic asthma is also shown to be present in non-atopic preschool children with recurrent wheezing, the management of recurrent wheezing in preschool children remains controversial [5, 6]. Based on the present evidence, regular use of ICSs seems reasonable in non-atopic children with recurrent wheezing [7].

As it is similar in asthma, the maintenance treatment with ICS in recurrent wheezing seems to be effective if taken regularly. But it is generally known that, in many of the chronic diseases, compliance to the treatment decreases with prolonged treatment duration and increased number of daily dosages. Studies investigating ICS adherence in controller prescribed asthma patients have shown non-adherence rates up to 70% [8, 9]. Patients with chronic diseases or their caregivers encounter various difficulties in adhering to treatment. Forgetting, concerns about the side effects, fear of drug addiction, unbelief to the efficacy of the medication are some of those well-defined barriers for treatment adherence [10].

Studies which evaluate adherence to ICS treatment in non-atopic children with recurrent wheezing and the

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reasons for non-compliance to the treatment are extremely limited. Therefore, the present study is designed to investigate, at a period of 6 months, the adherence rates and the probable factors that affect compliance to treatment in non-atopic children with recurrent wheezing.

## MATERIAL AND METHOD

Non-atopic children with recurrent wheezing, who admitted to the Pediatric Department of Behçet Uz Children Hospital (İzmir, Turkey) between the dates of 01.01.2006 and 31.01.2006, were involved in the study. Subjects with an acute episode of recurrent wheezing were hospitalized, treated, educated about their disease and practiced the skills to use ICS medications. All of the patients' caregivers were informed about the disease, instructed about medication and its importance, educated for the practical skills how to use the medications and accessory devices by the pediatric allergist (94 children (88.7%)), by nurse (7 children (6.7%)) and by pharmacist (3 children (2.8%)). After discharge, they were followed-up for adherence to regular ICS treatment for the following 6 months. The diagnoses were confirmed and the children were followed-up by pediatricians and pediatric allergists.

Children under 3 years of age and who had experienced 3 or more wheezing episodes in the last year of life were involved in the study. Recurrent wheezing was defined by the, apart from colds, presence of 1) repeated episodes of wheezing responsive to bronchodilators, 2) shortness of breath and 3) cough lasting more than a week. Children who met the criteria of recurrent wheezing and did not meet the criteria for positivity in 'Asthma Predictive Index' and also who were negative for specific IgE for common aero-allergens and food allergens were defined as non-atopic recurrent wheezers. Asthma predictive index score was recorded according to the recommendations [11].

The demographical data of the patients regarding parent's education level, working status, living area, households and indoor air pollution were obtained from patient files and medical records of the hospital or completed by face-to-face interview with parents during hospitalization or out-patient visits. At the end of the 6 months period of follow-up, the parents of children were asked to visit the out-patient allergy clinic and the parents who were unable to come were contacted by phone to evaluate the adherence to ICS treatment.

Children with other significant diseases that might increase the recurrence risk of wheezing (e.g. congenital heart disease, pulmonary hypertension) and with other known chronic diseases were excluded from the study. Premature infants who had significant perinatal events (e.g. respiratory distress syndrome or hospitalization) during the neonatal period, whose parents could not confirm sufficient information about childs' health history and who refused to participate in the study were also excluded. All participants agreed to participate according to the principles expressed in the Declaration of Helsinki.

Serum samples were analyzed for specific IgE using a radioallergosorbent test (RAST). Patients whose specific IgE levels were below the lowest threshold for age among the food allergens were considered as non-atopic [12]. The lowest detection limit of the assay for common aeroallergens was 0.35kU/L [13]. The test was considered as negative even if the level was higher than the threshold but was incompatible with the patients' history [14].

### Statistical Analysis

SPSS 13 package program was used for the statistical analysis. Data were presented as mean ± standard deviation (SD) (minimum-maximum). Categorical values were analyzed by Chi-square. Continuous data were analyzed by T test. When the differences were statistically significant Fisher's exact test was performed for group comparisons. $P \leq 0.05$ was considered statistically significant.

## RESULTS

One thousand six hundred and ten children admitted to Pediatric Clinic of Behçet Uz Children Hospital between the dates of 01.01.2006 and 31.01.2006. One hundred thirty-seven children were diagnosed as non-atopic recurrent wheezers and 106 of them admitted to participate in the study. 35 (33%) of the participants were female and 71 (67%) was male. The mean age of the children was 22.0±15.4 months (range 3-60 months).

Maternal education status of participants was as; no formal education in 8 (7.5%), primary education in 76 (71.7%), secondary education in 21 (19.8%) and higher education in one (0.9%) mother. Paternal education of participants was as; no formal education in 3 (2.8%), primary education in 72 (68.0%), secondary education in 29 (27.4%) and higher education in 2 (1.9%) fathers. The working status of the mothers was as; 96

housewives (90.6%) and 10 working mothers (9.4%). The working status of the fathers was as; 5 non-regular workers (4.7%), 71 workers with a regular job (66.9%), 4 officers (3.8%), 21 trades men (19.8%) and 5 farmers (4.7%). Twelve (11.3%) of the children had no health-insurance.

Ninety-six (96.2%) children were living in urban and 4 (3.8%) were living in rural area. Forty-three (40.6%) children were living in flats, 52 (49.0%) in detached houses and 11 in squatter houses (10.4%). The heating system of the houses were wood or charcoal stoves in 76 (71.7%), climates in 13 (12.3%) and central heating in 2 (1.9%). Seventy-six of children (71.7%) exposed to smoking at home and 30 parents were non-smokers (28.3%). The current smoking rate among mothers was 24.5% (26 mothers) and the smoking rate during pregnancy was 16% (17 mothers). The current smoking rate of fathers was 67% (71 fathers).

Eleven patients (10.4%) were under treatment with leukotriene receptor antagonists and 12 patients (11.3%) with alternative treatment methods before hospitalization. ICS were applied by nebulizer in 48 children (45.3%) and by spacer in 58 children (54.7%).

At the end of the follow-up period, the adherence rate to the treatment was 33.9% (n=36) and 66% of participants (n=70) have ceased their treatment themselves. 87 children (82.1%) had experienced recurrence and 19 (17.9%) had no recurrence of wheezing symptoms in the follow-up period. The mean treatment duration for patients who ceased their treatment was 4.3±4.2 months and was 7.1±0.5 months for the compliant patients. There was a significant difference for treatment duration among compliant and incompliant groups (p=0.005). The frequency of exacerbations was 2.8±3.1 attacks for patients incompatible with treatment and was 3.7±3.3 attacks for treatment compliant patients. There was no significant difference for exacerbations among two groups (p=0.214). There was no significant relation between treatment adherence and the type of device used for drug application either nebulizer or spacer (p>0.05).

There was no statistical significant association between compliance to treatment and demographical characteristics of the patients including gender, age, living area, having health-insurance or not, home conditions, education level, and work status of the parents (p>0.05). Also, there was no significant relation between either recurrence of symptoms or compliance to the treatment and exposure to smoking, type of the device used for drug application, being under additional medical treatment, and treatment education providers (p>0.05).

The parents of patients who were compliant to treatment reported highly benefit from medications with a rate of 97.2% (35 children) and a child in this group was reported as having partial benefit from the treatment. In group who ceased treatment by their own decision, the expectations of parents about beneficial effects of the medication were not met in 59 patients (84.2%) and were met in 11 patients (15.8%).

The reasons reported by parents for early treatment cessation were, 1) parents belief of the inefficiency of medications on their 'non-asthmatic children' in 44 (62.8%), 2) difficulties in applying the drugs in 6 (8.5%), 3) forgetting regular drug application in 10 (14.2%), 4) parents' misunderstanding of regular medication use in 15 (21.4%), 5) recommendations of other practitioners to cease the treatment in 10 (14.2%), 6) parents observation of drug inefficiency in reducing wheezing symptoms in 4 (5.7%) and 6) parents' concerns about addiction to corticosteroids in 6 (8.5%).

The purpose of this study was to investigate the adherence to ICS treatment in non-atopic children with recurrent wheezing who are in general considered as non-asthmatics, and the comparison of the demographical data among the patients who were compliant and incompliant to treatment. Unexpectedly, we found that approximately only one third of the children were compliant to the treatment after 6 months of follow-up. Nearly all of the parents who were compliant to treatment reported their impression of the beneficial effects of medication on reducing both wheezing symptoms and frequency of wheezing episodes.

We found that more than half of the parents who ceased the treatment by self-decision ended treatment at about the $4^{th}$ month of follow-up period, and approximately 85% of these parents reported inefficiency of treatment on reducing wheezing symptoms and episodes. Approximately half of these parents who did not experience any improvement in symptoms reported that, they refused to administer asthma medications to their 'non-asthmatic children' either because of concerns about corticosteroid side effects or phobia of addiction to ICSs.

## DISCUSSION

Wheezing during early life remains a frequent heterogeneous disorder with various phenotypes and clinical expressions. The overlapping conditions that may cause lower airway obstruction complicate the explanation of pathogenesis and management of recurrent wheezing. Therefore, clarifying the natural course and the progress of wheezing in children, is a critical issue for managing the disorder and for estimating the possibility of consequent asthma development. Recent evidence indicates that clinical recovery and remission of symptoms are less frequent than it was previously believed, remodeling does not regress and may cause relapse of the symptoms in future life [15]. It is generally known that non-atopic children with recurrent wheezing have earlier onset of symptoms and have diminished lung functions persisting throughout their life [16]. These findings highlight the importance of persistent inflammation and re-modeling process which may provide an explanation for incomplete resolution of symptoms and possible decline in lung functions that occur over time as in asthma [17]. It has been shown that airway re-modeling is detected in early stages of symptoms even prior to the onset of symptoms and diagnosis. Interestingly, in a recent study it was shown that, even in non-atopic individuals, if the specific symptoms of multiple-trigger wheeze are present, the airway pathology is typical of the individuals with atopic asthma. Therefore, maintenance treatment with ICS is recommended for non-atopic recurrent wheezing with often small benefit when compared to asthmatics [18].

Although current asthma guidelines emphasize the importance of adherence to asthma treatment, the adherence in asthma patients falls behind the expectations. In asthmatic children, estimated adherence to ICSs vary widely between 46% and 58% in different studies, mostly has been reported to be less than 60% [9, 19]. To the best of our knowledge, except the present work, there is no study in the English-Language literature evaluating the adherence rate to treatment and demonstrating the barriers to compliance in non-atopic children with recurrent wheezing.

Family demographic characteristics were studied in relatively large amount of studies involving inconsistent asthmatic patients. In some studies, race was found to be related with non-adherence to treatment whereas not in others [20-22]. Besides, parental marital status and smoking at home were not found to be related to non-adherence to ICS treatment for asthmatic children [23, 24]. Similar to asthma studies, although we have found the parental smoking rate relatively high, we could not demonstrate any effect of smoking on adherence to treatment in children with recurrent wheezing.

It is generally accepted that, higher socioeconomic status including parental education, working status, income and access to healthcare is consistently associated with treatment adherence in asthma [23]. In a cross-sectional study, parental education beyond high school level was found beneficial for compliance to treatment asthma (OR, 0.6; 95% CI, 0.4-0.8). Other factors such as having a primary care physician (OR, 0.4; 95% CI, 0.2-0.8), having a follow-up visit (OR, 0.5; 95% CI, 0.4-0.8) and visiting an asthma specialist (OR, 0.5; 95% CI, 0.4-0.7) were associated with lower rates of incompliance [22]. Although, the parental educational level was low and non-adherence rate was high in the present study, we could not demonstrate any inverse relationship between parental education level and adherence to treatment in children with recurrent wheezing, which may be due to the small sample size of the study. Consistent with our results, a recent well-designed prospective clinical trial by Burgess *et al.* showed that the child's age, level of parental education and annual family income were found ineffective on adherence rate in asthmatic children aged 18 months to 7 years who used electronic monitoring device (Smart inhaler) adapted to ICS [25].

Barriers to ICS adherence are various and multifactorial. Parental psychological factors, behaviors and attitudes have been shown to contribute non-adherence to asthma medications. The most frequent set of parental factors associated with non-adherence involved parental non conviction expressed as ‘the medicine is not needed’ or ‘it will not work’, fear of adverse effects of ICSs, fear of addiction, and forgetting to take asthma medications [26, 27]. Despite relatively low risk of complication when compared with systemic steroids, ICSs may also have side effects as cataracts, osteoporosis, suppression of the hypothalamo-pituitary adrenal axis, growth retardation in children, thinning and bruising of the skin, adrenal insufficiency and Cushing syndrome. Factors related with treatment include frequent daily doses, complexity or inconvenience of inhaler device to the childs’ capacity or age, discomfort of drug administration (bad taste, long treatment duration vs.) [28, 29]. In a cross-sectional study Burgess *et al.* [25] assessed some of the reasons that resulted in missing the doses by parents. The most commonly reported reasons were

forgetting, being dissuaded by their childs' reaction to medication, trouble incorporating medication into daily routine, sleeping before evening dose, concerns about side-effects and the cost of the medication. However, the only statistically significant relationship was found between parental stress and reduced adherence to regular treatment [25]. Parental or caregivers' stress and maternal depressive symptoms were found effective on formation of beliefs and attitudes, which have a direct effect on non-adherence to treatment [30]. Besides, parental misunderstanding was found as another factor for reduced adherence rates to treatment [31]. Consistent with previous studies, the present study showed that forgetting drug application and misunderstanding of parents about using medications were the barriers to regular treatment in children with recurrent wheezing.

The other adherence barriers are the beliefs that controller medications are not necessarily needed and particularly reliever medications provides adequate control when needed. In a study, examining the patient perception about long term controller treatment usage, more than 60% of the participants tended to rely on relievers instead of controllers [32]. As well as, fear of adverse effects and addiction to ICSs are other factors for poor adherence. Thus the contents of medications are steroids, the parents have prejudice about their side effects. Parental perceptions of benefits and side effects of medications were evaluated in some studies and found as one of the major problem for adherence to treatment for asthma. Conn *et al.* [33] showed that approximately one third of the parents have strong concerns about asthma medications and in 17% of those, concern exceeded necessity. The study confirmed that there was a strong relationship between medication beliefs among parents of children with asthma and adherence [33]. In our study, concordant with detected high incompliance rate, the expectations of parents about beneficial effects of the medication were not met in approximately 85% in early treatment cessation group. The major reason for more than 60% of the participants who ceased the treatment early was defined as inefficiency of the medications on their 'non-asthmatic children'.

Improper use of inhalers is another important reason for non-adherence to treatment. It is known that the ability to effectively use an inhaler is an important issue. Pressured multi dose inhaler (MDI) devices are improperly used in pediatric age group under 12 years of age due to failure to shake the inhaler, poor hand-breath coordination, rapid inhalation and multiple actuations. If the patient has poor technique, the use of volume spacers or nebulizators is recommended to decrease some of those errors and increase lung deposition of drug. However, the use of spacers and nebulizers may add new problems to inhaler misuse by forming extra load of carrying, storage and cleaning for the caregivers [10]. In the present study, although the socio-economical and educational status were low, nearly half of the caregivers were using nebulizers, which is higher than the rates reported in the literature and only 8% of them mentioned difficulties of using those devices as a cause for non-adherence to the treatment. The high rates of prescription of nebulizers by pediatricians and family physicians can be explained by their ease of use and cost-effectiveness of applying medication at home by parents, instead of admission to hospital for mild and moderate exacerbations of wheezing.

The limitations of the study were; 1) the evaluation of treatment adherence was by parents self-reporting in which patients generally over report their degree of adherence when compared to objective methods

**Table 1: The Effect of Characteristics on Compliance to the Treatment with ICSs**

| Characteristics | Compliance to the treatment | | p value |
|---|---|---|---|
| | Patients with early treatment cessation (mean ± SD) | Patients adherent to the therapy (mean ± SD) | |
| Age of child (months) | 20.7±14,4 | 24.41±17,3 | 0.224 |
| Age of mother (year) | 27.1±4.7 | 27.2±4.5 | 0.886 |
| Age of father (year) | 31.1±5.2 | 31.1±4.8 | 0.981 |
| Treatment duration (months) | 4.3±4.2 | 7.1±5.0 | 0.005 |
| Frequency of exacerbations | 2.8±3.1 | 3.7±3.3 | 0.214 |
| Number of patients had no benefit from treatment | 11 | 1 | 0.007 |
| Number of patients had benefit from treatment | 24 | 21 | 0.226 |

including assessment of prescription refill records, using of biomarkers or counting dose on controller medications and 2) small sample size of the study to measure the correlations of the variables (Table **1**).

## CONCLUSIONS

The interventions for medication non-adherence are mainly dependent on patient education programs to improve communication between clinicians and patients. Shared decision-making about treatment regimen which is determined according to patients' goals and preferences seems to improve adherence rates when compared to merely clinicians' decision-making on controller treatment adherence [34]. We suggest that, the physicians who deal with wheezy children should participate to understand the major problems, barriers and concerns about regular treatment usage for both the caregivers and children to increase compliance and prevent future developing asthma. Prospective well-designed clinical studies are needed to understand the mechanisms of recurrent wheezing and the efficient treatment modalities to overcome the low adherence rates to treatment.

## CONFLICTS OF INTEREST AND SOURCE OF FUNDING

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