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Electronic adherence monitoring identifies severe preschool wheezers who are steroid responsive

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Abstract

Little is known about adherence to inhaled corticosteroids (ICS) in preschool children with troublesome wheeze. Children with aeroallergen senitization, or those reporting multiple trigger wheeze (MTW), are more likely to respond to ICS. We hypothesized that adherence to ICS and symptom control are only positively related in atopic children, or those reporting MTW. Patients aged 1 to 5 years with recurrent wheeze prescribed ICS were recruited from a tertiary respiratory clinic. Clinical phenotype and aeroallergen senitization were determined, and adherence assessed using an electronic monitoring device (Smartinhaler). Symptom control (test for respiratory and asthma control in kids [TRACK]), quality of life (PACQLQ), airway inflammation (offline exhaled nitric oxide) were assessed at baseline and follow-up. Forty-eight children (mean age 3.7 years; SD, 1.2) were monitored for a median of 112 (interquartile range [IQR], 91-126) days. At baseline n = 29 reported episodic viral wheeze and n = 19 reported MTW. Twenty-four out of 48 (50%) wheezers had suboptimal ICS adherence (<80%). Median adherence was 64% (IQR, 38-84). There was a significant increase in TRACK and PACQLQ in the group as a whole, unrelated to adherence. In subgroup analysis only atopic wheezers with moderate or good adherence ≥ 60% had a significant increase in TRACK. There was no relationship between clinical phenotype, and adherence or TRACK. In this pilot study, overall adherence to ICS was suboptimal and was positively related to symptom control in atopic wheezers only. Assessments of adherence are important in preschool troublesome wheezers before therapy escalation to help identify those with an ICS responsive phenotype.

KEYWORDS

adherence, atopy, inhaled corticosteroids, monitoring, preschool wheeze

1 | INTRODUCTION

Wheezing in preschool children results in significant morbidity and healthcare costs worldwide.[1-3] Prevention of acute symptoms and hospitalization is challenging because it is a heterogeneous disease, and little is known about the pathophysiological mechanisms underlying different phenotypes. However, there is good evidence that preschool wheezers with a phenotype that fits with "persistent asthma", characterized by recurrent and persistent wheezing respond to maintenance inhaled corticosteroids (ICS) with a reduction in exacerbations and improved symptom control.[4] Children whose parents report they have multiple trigger wheeze (wheeze during and between episodes) may be more steroid responsive than those with only episodic viral wheeze.[5] In addition, preschool wheezers with either or both of aeroallergen senitization and elevated blood eosinophils are the group most likely to respond to ICS.[6] Although the efficacy of maintenance ICS has been assessed in the context of clinical trials, little is known about the relationship between adherence to prescribed ICS and efficacy in the sub-group of preschool children with severe, troublesome wheeze in the clinic.

Adherence to maintenance ICS in school age children ranged from 20%[7] up to 74%,[8] and higher adherence was associated with better asthma control. In younger children aged (2-6 years) with wheeze/asthma, objectively monitored adherence for 12 months was reported as a median of 87% and >80% adherence was associated with better symptom control assessed using the asthma control questionnaire.[9] In another study that included young children (18 months-7 years), median adherence rate during 1 month of monitoring was 71% with a range of 21% to 100%.[10] Both studies that included young children used electronic monitoring devices (Smartinhalers) to assess adherence. However, neither reported the impact of adherence on symptom control in children with a phenotype that is likely responsive to ICS.

Much of the data that has shown relationships between objective monitoring of adherence and asthma control in school age children has been in difficult asthma, the majority of such patients having allergic, eosinophilic disease which is steroid responsive. However, preschool wheezers may not all have an ICS responsive phenotype. Monitoring adherence to prescribed ICS may be beneficial in wheezers to help identify those with a steroid responsive phenotype. The impact of adherence to prescribed ICS in a population of preschool children with severe recurrent wheeze has not previously been reported. We hypothesized that firstly, adherence to prescribed ICS would be higher in children with severe preschool wheeze attending a specialist pediatric respiratory clinic compared with published data in school age children with difficult asthma and secondly, that a period of adherence monitoring would result in improved symptom control only in those with ICS responsive features (above). We investigated adherence to ICS using electronic monitoring devices for 4 months and related this to symptoms, offline exhaled nitric oxide (FeNO), quality of life and unscheduled healthcare visits (UHCV) in children aged 1 to 5 years with recurrent, troublesome preschool wheeze.

2 | METHODS

2.1 | Design and setting

A pilot, prospective observational cohort study, with up to 4 months monitoring of children aged 1 to 5 years with recurrent, troublesome wheeze, who were seen regularly in the respiratory outpatient clinic at the Royal Brompton Hospital, London between March 2017 and November 2019. Children had been referred to our specialist respiratory clinic for further assessment or management of persistent and severe symptoms.

2.2 | Ethical considerations

The study was approved by the Regional Ethical Committee (NRES Committee London-Westminster). All parents/legal guardians gave written informed consent.

2.3 | Inclusion criteria and collection of baseline data

All eligible children had a documented diagnosis of preschool wheeze by a healthcare professional and were prescribed maintenance ICS by their clinician. Children with other significant primary pulmonary disorders were excluded. All children were classified into one of two groups at inclusion, based on reported pattern of symptoms. (a) Episodic viral wheeze (EVW): wheezing during discrete time periods, with absence of wheeze between episodes. (b) Multiple-trigger wheeze (MTW): wheezing in discrete exacerbations, but also symptoms between episodes.[5]

Assessments were made at a baseline visit at the start of the monitoring period and at follow-up between 8 to 16 weeks later at the end of the monitoring period. All visits were undertaken as part of routine clinic visits, hence the variability in follow-up duration.

2.4 | Symptom control

Symptom control was assessed using test for respiratory and asthma control in kids (TRACK) questionnaire. This is a standardized tool validated to identify symptom control over the preceding 4 weeks in children with preschool wheeze.[11] It is a five-item, 100-point caregiver-completed questionnaire, with poor asthma control defined as a score of <80/100 (see Figure 1 online supplement). A change in score of >10 is the minimum clinically meaningful change.[12]

2.5 | Quality of life

All parents completed a parental and child quality of life questionnaire (PACQLQ).[13]

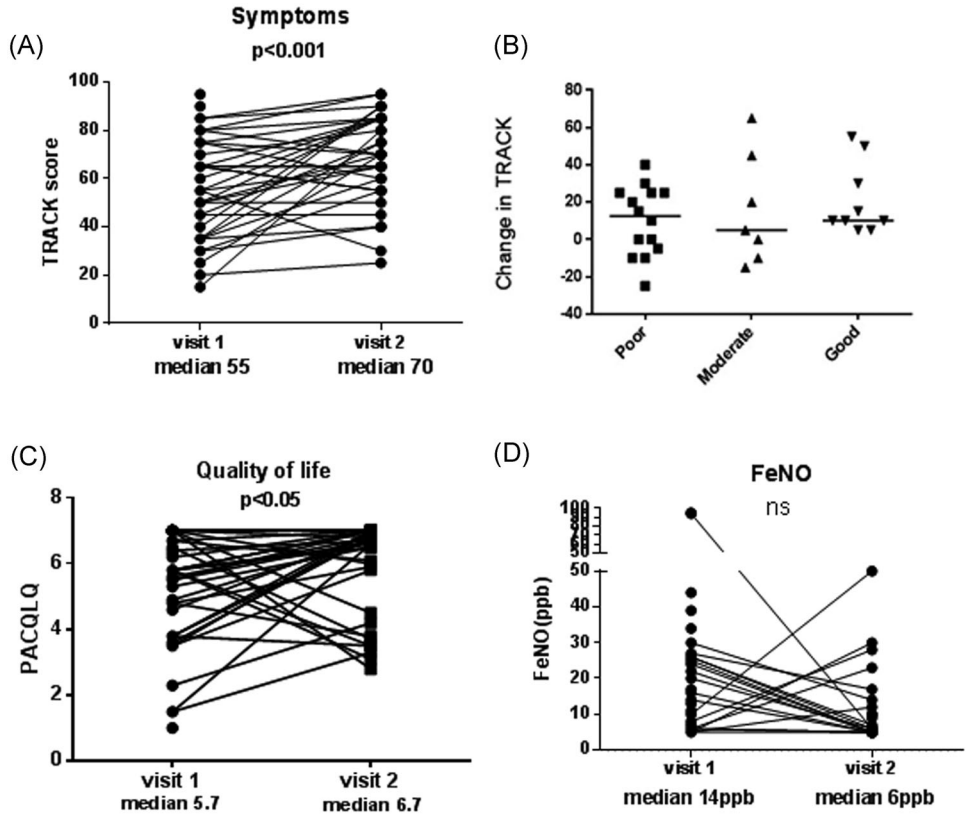

FIGURE 1 Change in symptom score, quality of life and exhaled nitric oxide between baseline and follow up visits. (A) Symptom score (test for respiratory and asthma control in kids [TRACK]) at baseline (visit 1) and follow-up (visit 2). B, Change in TRACK according to level of monitored adherence. C, Parental and child quality of life questionnaire (PACQLQ), and (D) exhaled nitric oxide (FeNO) at baseline and follow up

2.6 | Exhaled nitric oxide

Exhaled FeNO was assessed using the offline technique using an electrochemical analyzer (NIOX Vero; Aerocrine, Solna, Sweden) as previously described.[14] Published reference values for preschool healthy children were used to define the cut-off for normal (≥11.5 ppb).[15]

2.7 | Atopic status

Atopy was defined as at least one positive skin prick test (≥3 mm wheal) to one of a range of aero-allergens (house dust mite, grass, tree pollen, cat, dog).

2.8 | Assessment of inhaler technique and adherence to ICS

All carers were shown how to use their child's inhaler with a spacer correctly, and a Specialist Respiratory Nurse checked, and where necessary, corrected their technique regularly. Carers were all given a written personalized wheeze plan with clear instructions about when the treatment should be administered. All families were issued with an electronic monitoring device at the baseline visit (Smartinhaler; Nexus6 Ltd, Auckland, New Zealand). Smartinhalers were available for beclomethasone diproprionate, fluticasone proprionate and Seretide (fluticasone proprionate plus salmeterol combination inhaler) metered dose inhalers. The devices contain a microchip that records the date and time the inhaler is actuated. Participants and their guardians were informed that the Smartinhaler would record the total number of actuations of ICS per day. Adherence was defined as the percentage of controller medication doses taken relative to the number of doses prescribed. Adherence was defined a priori as a ratio of doses taken; good adherence ≥80%, moderate adherence between 60% and 79% and poor adherence <60%.[9] Daily adherence was calculated with a maximum of 100%, to avoid falsely increased values due to dose dumping.

2.9 | Follow-up

A minimum of 8 weeks and up to 16 weeks of adherence monitoring was undertaken. At follow up, symptom control using TRACK, PACQLQ, and offline FeNO were assessed. In addition, UHCVs for acute attacks were recorded.

2.10 | Analysis

The associations between adherence and changes in PACQLQ, FeNO and symptom control from baseline to the end of the monitoring period were assessed using the non-parametric the Wilcoxon Signed Rank Test, differences between unpaired data were assessed using the Mann Whitney test for two groups, or the Kruskal Wallis test for >2 groups. Data were analyzed using GraphPad Prism v6 software and $P < .05$ was considered statistically significant.

3 | RESULTS

Forty-eight children mean age 3.7 (SD, 1.2) years were included. Table 1 provides a summary of the baseline characteristics and prescribed treatments at inclusion. The median number of hospital admissions ever per patient was 3 (range, 0-20) and median daily dose of prescribed ICS was 400 (range, 100-1000) mcg.

TABLE 1 Baseline demographics of children included

N = 48	
Age (y); mean (SD)	3.7 (1.2)
Male sex, n (%)	26 (54%)
Atopy[a], n (%)	25 (52%)
TRACK score; median (range)	55 (15-95)
PACQLQ score; median (range)	5.5 (1.0-7.0)
Admissions for wheeze ever; median (range)	3 (0-20)
Offline FeNO (ppb); median (range)	14 (5-95)
ICS dose/day (BDP); median mcg (range)	400 (100-1000)
Clinical phenotype: EVW; n	29/48 (60%)

Abbreviations: BDP, beclomethasone diproprionate; EVW, episodic viral wheeze; FeNO, exhaled nitric oxide; ICS, inhaled corticosteroids; IgE, immunoglobulin E; PACQLQ, parental asthma child quality of life questionnaire; TRACK, test for respiratory and asthma control in kids.
[a]Atopy defined as ≥1 positive skin prick test, or ≥1 positive specific IgE to aero-allergen (≥3 mm wheal diameter).

3.1 | Adherence to ICS and control of preschool wheeze symptoms

Although 48 electronic monitoring devices were given to patients recruited, only 36 out of 48 (75%) were returned. This was despite repeated reminder phone calls from the nurse and despite waiting for up to 6 months for the device to be returned. There was no difference in the demographic characteristics at baseline between children whose monitors were and were not returned. Children were brought to the clinic for appointments, but families failed to return the monitoring device. The reported reasons for devices not being returned were loss of device or forgetting to return the device.

Median period of monitoring for the 36 children who did return the monitoring device was 112 (range, 91-126) days. Median adherence during this period was 64% (range, 0%-94%). Twelve out of 36 (33%) had >80% adherence (good), 8 out of 36 (22%) had adherence between 60% and 79% (moderate) and 16/30 (44%) had <60% adherence (poor). There were no differences in baseline TRACK score, PACQLQ, FeNO, or attacks in the preceding 3 months in those with good or suboptimal adherence (<80%) (Table 2).

There was a significant increase in TRACK score between baseline and follow-up visit for the children as a group, median TRACK at baseline 55 (range, 15-95), increasing to median TRACK at follow-up 70 (range, 25-95), $P < .01$ (Figure 1A). However, there was no relationship between level of adherence and change in TRACK (Figure 1B). There was a significant improvement in PACQLQ between baseline and follow up visit for the group as a whole (Figure 1C), but no difference in offline FeNO measurements (Figure 1D) from baseline to follow-up.

The assessments were compared in children who had not returned the monitoring devices with those who returned the device and had suboptimal (<80%) or good (≥80%) recorded adherence (Table 2). There was no improvement in TRACK, PACQLQ, FeNO, or UHCVs in the group who did not return the device. Those who returned the device but had suboptimal adherence did have a significant improvement in TRACK score, but no change in PACQLQ, FeNO, or UHCVs (Table 2). However, only children who returned the device and had good recorded adherence had a normal TRACK score (>80), improvement in PACQLQ and a lower number of UHCVs at follow-up (Table 2).

TABLE 2 Change in symptoms, quality of life, exhaled nitric oxide, and unscheduled healthcare visits according to level of adherence

	Level of adherence		
N = 48	Device not returned n = 12	Suboptimal n = 24 (<80%)	Good n = 12 (≥80%)
TRACK score			
Baseline	52 (40-90)	55 (15-85)	45 (30-85)
Follow up	75 (50-85)	65 (25-95)	85 (40-95)
P	ns	.025	<.01
PACQLQ			
Baseline	4.35 (1.0-6.4)	6.2 (1.0-7.0)	5.6 (3.8-7.0)
Follow up	5.05 (3.5-6.6)	6.8 (2.8-7.0)	6.8 (3.8-7.0)
P	ns	ns	<.05
FeNO			
Baseline	13.5 (5.0-44)	24 (5-94)	8.5 (5-95)
Follow up	5.0 (5-28)	7.5 (5-23)	7.0 (5.0-50.0)
P	ns	ns	ns
UHCV	1 (0-1)	1 (0-4)	0 (0-1)

Abbreviations: FeNO, exhaled nitric oxide; ns, not significant; PACQLQ, parental asthma child quality of life questionnaire; TRACK, test for respiratory and asthma control in kids; UHCV, unscheduled healthcare visits.

3.2 | Relationship between adherence and wheeze phenotype

As episodic symptoms might have influenced whether parents gave maintenance treatment, we investigated the relationship between clinical phenotype reported at baseline visit and adherence. The parents of 60% of children reported episodic viral wheeze. Median adherence was similar in both groups, EVW (63% [0%-91%]) versus MTW (75% [0%-94%]), P = ns.

3.3 | Relationship between adherence, atopic status and symptom control

To determine whether change in symptom control with ICS treatment was related to objective biomarkers that determine steroid responsiveness, we assessed adherence and TRACK score at baseline and follow-up in atopic and non-atopic wheezers separately. Overall adherence was similar in atopic (n = 17) and non-atopic (n = 18) children; median adherence atopic 52.5 (range, 0-91)% versus non-atopic 76 (range, 0-94)%, P = ns. There was a significant and clinically meaningful increase (TRACK increase of >10) in symptom score only in atopic wheezers from baseline to follow-up (Figure 2A), while TRACK remained similar in non-atopic wheezers (Figure 2B). When all wheezers were divided according to atopic status and adherence, only atopic wheezers with adherence ≥60% had a significant increase in TRACK score from baseline to follow-up (Figure 3A). In contrast, atopic wheezers with adherence <60% and non-atopic wheezers with adherence ≥60% or <60% had no significant improvement in TRACK score (Figure 3B-D).

4 | DISCUSSION

We investigated adherence to ICS in children aged 1 to 5 years with moderate to severe wheezing attending a tertiary respiratory center. One-quarter of families did not return the electronic monitor, which meant an objective assessment of adherence could not be made, but suggests adherence was likely suboptimal in that group. Of those who did return the monitor, adherence was suboptimal (<80%) in two-thirds.

Preschool children aged 2 to 6 years from a Dutch cohort with milder wheezing monitored for 12 months had median adherence of 87%.[9] Only 33% of children in our study had good adherence (>80% of prescribed doses), compared with 63% reported in the Dutch study. However, poor adherence to treatment may be rational, especially if the therapy prescribed is identified as ineffective by parents.[16] Hence parents of children reporting episodic viral wheeze, a group which may be less likely to be steroid responsive, may be right not to give the treatment. We therefore investigated the relationship between clinical phenotype, adherence, and symptom control. However, there was no relationship between adherence to ICS and whether episodic viral or MTW was reported. We accept that allocating a child to one or other of these categories relies on the accuracy of parental reporting, and symptom patterns may change over time and with treatment. In a randomised controlled trial (INFANT trial), children with aeroallergen senitization and an elevated peripheral blood eosinophil count responded best to ICS.[6] We did not have contemporaneous blood eosinophil counts in this study, but we were able to investigate whether atopic status influenced the relationship between adherence and response to ICS. Overall adherence was similar in atopic and non-atopic children, however, atopic wheezers had an improvement in TRACK score from baseline to follow-up but non atopic wheezers did not. Importantly, only those atopic wheezers with moderate or good (≥60%) adherence to ICS during the monitoring period had a significant and clinically meaningful improvement in symptom score, but this was not seen in atopic wheezers with poor adherence, or in non-atopic wheezers. This suggests that this is a steroid responsive group. In summary, even in those with troublesome wheezing, an improvement in symptom control was only apparent in atopic wheezers with moderate-good adherence to ICS.

There are other potential reasons for poor adherence, which we tried to exclude. We ensured the recruiting nurse provided education

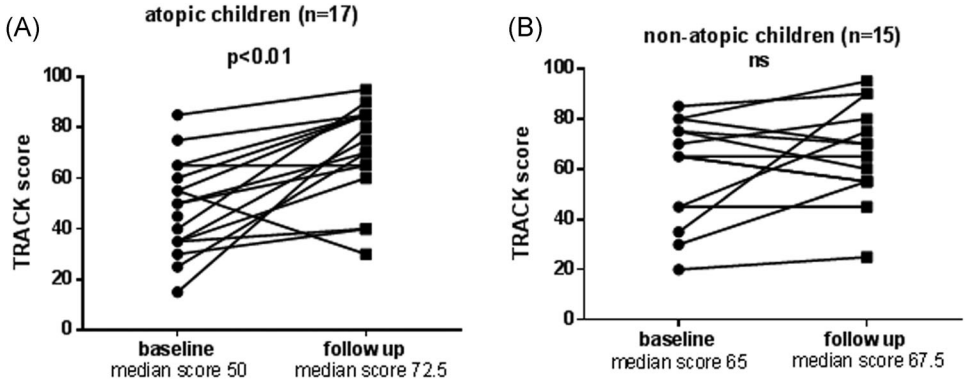

FIGURE 2 Change in symptom score in atopic and non-atopic symptom between baseline and follow up visit. A, Symptom score at baseline and follow-up in atopic children. B, Non-atopic children. TRACK, test for respiratory and asthma control in kids

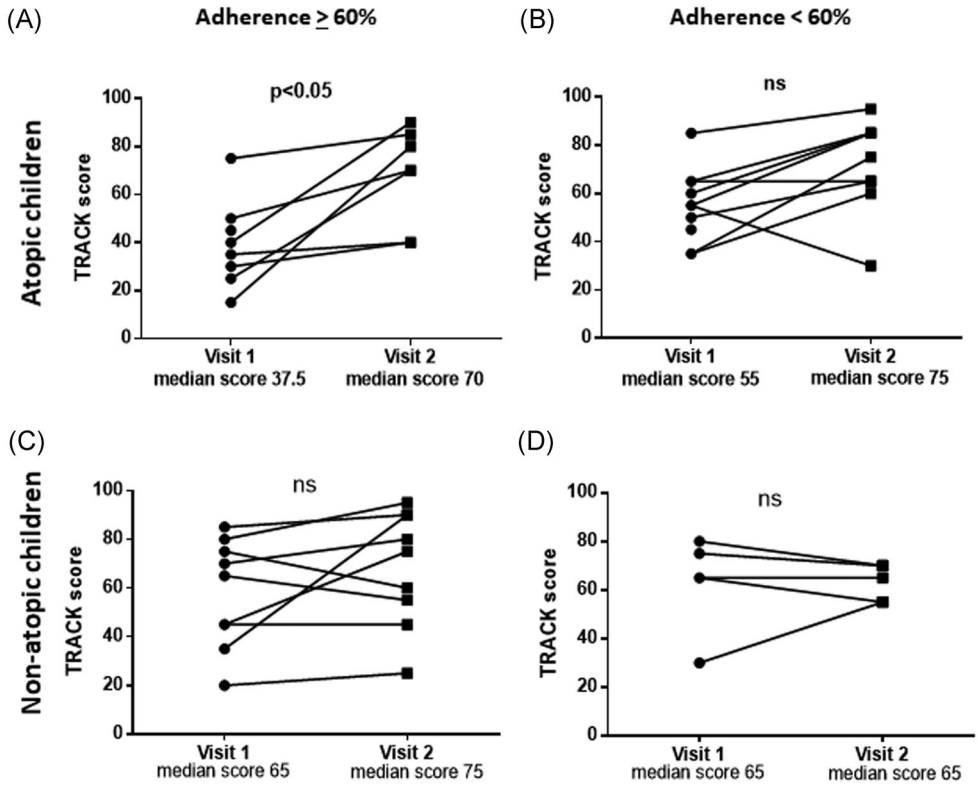

FIGURE 3 Change in symptom score in atopic and non-atopic children according to level of adherence. Relationship between adherence and change in symptom score from baseline (visit 1) to follow up (visit 2) in atopic children with (A) ≥60% adherence to inhaled corticosteroids and (B) <60% adherence to inhaled corticosteroids. Change in symptom score in non-atopic children with (C) ≥60% adherence to inhaled corticosteroids and (D) <60% adherence to inhaled corticosteroids. TRACK, test for respiratory and asthma control in kids

about the inhaler technique, and checked correct technique, provided education about the need for the inhaler and a clear personalized wheeze plan. We had considered parental commitment to administering medication would be high in this group since most children had suffered frequent attacks requiring hospitalization and the median dose of prescribed ICS was high.[17] A previous study in preschool children investigated reasons for poor adherence and found the most common reasons were parental forgetfulness and their child's reaction when the medication was given.[10] Administering inhaled therapy to children in this age-group is a challenge and lack of cooperation from the child may also be a reason for missed doses. Another contributory factor in this age group may be parental anxiety about the adverse effects of steroids.[18]

Limitations of the study include the relatively small number of patients recruited, and several families did not return the monitoring device, but this was a pragmatic study undertaken in the clinic and this rate of failure to return the device reflects our experience in school age children,[8] and highlights the potential costs incurred of lost devices (£150 per device), especially if they are given indiscriminately to children unlikely to improve with ICS therapy. Importantly, the findings relating to benefit in atopic children were only assessed in the sub-group for whom adherence data was available. We also could not assess change in TRACK score, or FeNO in children according to blood eosinophils as this had not been measured in the clinic. We accept that the subgroups contain relatively small numbers, but there is no large study published. These pilot data therefore require future validation. A further limitation is that these data were obtained in children with severe, troublesome wheeze in a tertiary setting, benefits of adherence monitoring in children with milder wheezing cannot be assumed from this study.

The ERS Task Force has stated that children with frequent and severe attacks may respond to ICS and so should be given a trial.[19] Our study suggests if a trial of ICS is started, especially in a group with severe, recurrent wheeze, then adherence needs to be monitored objectively. If ICS have been administered to the child, and there is no benefit after a period of monitoring with evidence of good adherence, rather than escalating the dose, they should be discontinued. Use of adherence monitoring may be a way of identifying the sub-group of preschool wheezers who are ICS responders. Conversely, if adherence has been poor, the reasons should be explored. Our data, in line with the previously published INFANT study,[6] also suggest that maintenance ICS therapy may be of most benefit in atopic preschool wheezers. However, to date, we are not able to determine airway medication deposition, only that the inhaler was activated.

We had hypothesized that adherence to ICS in this age group would be higher than in school-age children as parents would be committed to give the medication, especially as we have only included children attending a tertiary respiratory clinic. However, adherence to

ICS was suboptimal in approximately half of children despite recurrent troublesome wheeze. Good adherence must not be assumed in this age group, and just as for older children with difficult asthma, if a preschool wheezer is not improving on high-dose ICS, then it is essential to ensure adequate adherence using objective monitoring before continued escalation of therapy. Getting the basics of management right is as important for preschool wheezers as for older children with asthma, especially as biologics may soon be considered for young children.

AUTHOR CONTRIBUTIONS

YB, NS, JC, PH, AJ, and RM-C undertook recruitment and assessments of patients. AB oversaw and edited the manuscript. LF developed the study protocol, helped with data analysis, study supervision, and manuscript writing. SS conceived and supervised the study, undertook data interpretation, manuscript writing, and editing.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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