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Blood eosinophils in managing preschool wheeze: Lessons learnt from a proof-of-concept trial

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Abstract

Background: Management of preschool wheeze is based predominantly on symptom patterns.

Objective: To determine whether personalizing therapy using blood eosinophils or airway bacterial infection results in fewer attacks compared with standard care.

Methods: A proof-of-concept, randomized trial to investigate whether the prescription of inhaled corticosteroids (ICS) guided by blood eosinophils, or targeted antibiotics for airway bacterial infection, results in fewer unscheduled healthcare visits (UHCVs) compared with standard care. Children aged 1–5 years with ≥2 wheeze attacks in the previous year were categorized as episodic viral wheeze (EVW) or multiple trigger wheeze (MTW). The intervention group was prescribed ICS if blood eosinophils ≥3%, or targeted antibiotics if there is positive culture on induced sputum/cough swab. The control group received standard care. The primary outcome was UHCV at 4 months.

Results: 60 children, with a median age of 36.5 (range 14–61) months, were randomized. Median blood eosinophils were 5.2 (range 0–21)%, 27 of 60 (45%) children were atopic, and 8 of 60 (13%) had airway bacterial infection. There was no relationship between EVW, MTW and either blood eosinophils, atopic status or infection. 67% in each group were prescribed ICS. 15 of 30 control subjects and 16 of 30 patients in the intervention group had UHCV over 4 months ($p = .8$). The time to first UHCV was similar. 50% returned adherence monitors; in those, median ICS adherence was 67%. There were no differences in any parameter between those who did and did not have an UHCV.

Conclusion: Clinical phenotype was unrelated to allergen sensitization or blood eosinophils. ICS treatment determined by blood eosinophils did not impact UHCV, but ICS adherence was poor.

KEYWORDS
asthma, attacks, eosinophils, inhaled corticosteroids, management, phenotype, preschool wheeze

This trial was registered on ClinicalTrials.gov: NCT02517099.

1 | INTRODUCTION

At least one third of all children younger than 5 years suffer from recurrent wheezing and breathlessness, but despite the high incidence,[1] there are few effective therapies.[2] Current guidelines recommend the management of preschool wheezing should be determined by clinical phenotype.[3] However, this is based predominantly on expert consensus. The two clinical phenotypes are episodic viral wheeze (EVW), in which wheeze occurs during discrete episodes, usually in association with an upper respiratory tract infection, with no interval symptoms; and multiple trigger wheeze (MTW), with discrete episodes and also interval symptoms.[3] This approach has several limitations: i) it relies on accurate parental reporting of symptom patterns, which may not always be clearly distinguishable as episodic or multiple trigger[4]; ii) clinical phenotypes may switch within patients in a period as short as 3 months[5]; iii) the underlying endotype is not considered; and iv) the current guidelines have not been compared with other strategies. It is essential that the correct approach is adopted since therapeutic options include inhaled corticosteroids (ICS), which may result in adverse effects.[6]

The pathology of allergic asthma in school-aged children is characterized by airway eosinophilia,[7] which is usually steroid-sensitive, and the mainstay of therapy includes regular ICS. It is assumed that MTW resembles allergic asthma and is responsive to steroid therapy, while EVW is distinct and steroid-unresponsive. Preschool wheezers have been shown to have airway eosinophilia.[8,9] Levels of exhaled nitric oxide are more likely to be elevated in MTW.[10] Lung function assessments also suggest MTW is associated with increased airway resistance and is distinct from EVW.[10] In addition, the Individualized Therapy for Asthma In Toddlers (INFANT) study has shown preschool wheezers who were most likely to have reduced exacerbations with regular ICS had aeroallergen sensitization and, in a *post hoc* analysis, high blood eosinophils.[11] The lower airway is not sterile, and its microbiome is altered in children with asthma.[12] A significant proportion of recurrent severe preschool wheezers also have airway bacterial infection identified using traditional culture techniques.[4] An important unanswered question is the relevance of the microbial flora in determining recurrent wheezing in preschool children.

Since preschool wheezing is predominantly characterized by frequent exacerbations and a subgroup of wheezers have evidence of eosinophilia, while others may have evidence of airway bacterial infection, we hypothesized that management using objective evidence of inflammatory and infective phenotype, rather than symptom patterns and clinical phenotype alone, would lead to improved outcomes. We undertook a proof-of-concept trial to determine whether targeted treatment of preschool wheeze determined by eosinophilic inflammation and infection would result in fewer unscheduled healthcare visits (UHCVs) compared with standard clinical care.

Key Messages

Preschool wheeze comprises varying clinical and pathological phenotypes. Although aeroallergen sensitization identifies preschool wheezers who are more likely to respond to inhaled corticosteroids, blood eosinophils may be a useful biomarker; this has not been tested prospectively.

We have shown there is no relationship between clinical phenotypes and aeroallergen sensitization or blood eosinophils in preschool wheeze. Inhaled corticosteroids prescribed according to blood eosinophils did not reduce unscheduled healthcare visits compared with standard clinical care; however, adherence to inhaled corticosteroids was poor.

Objective assessments of inhaled corticosteroid adherence are essential in preschool wheeze prior to therapy escalation. Future trials of biomarker-directed treatment must include assessments of parental acceptability of inhaled corticosteroids.

2 | METHODS

2.1 | Trial design and participants

This study was a single-centre, randomized, single-blind trial comparing management of preschool wheeze determined by blood eosinophils or airway infection (intervention) with routine clinical care (control). The primary outcome was UHCV at 4 months.

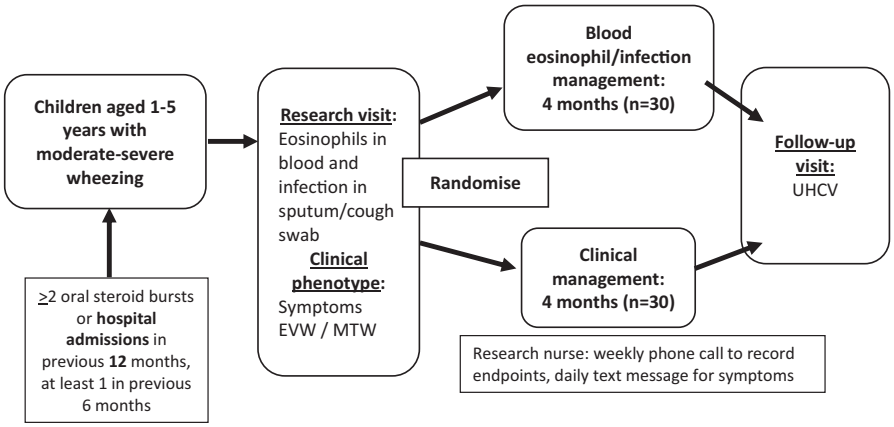
Inclusion criteria were as follows:

- Age 1–5 years
- Doctor diagnosed wheeze and confirmed using a validated video questionnaire.[13]
- Moderate-to-severe wheeze—defined as requiring at least two admissions and/or two short courses of oral steroids for an acute wheeze attack in the last 12 months with at least one admission and/or course of oral steroids in the last 6 months (Figure 1).

Exclusion criteria are detailed in the Appendix S1.

Wheezers were categorized according to European Respiratory Society criteria as having MTW or EVW[3] at recruitment from parental symptom reports. Patients were recruited and randomized at the Royal Brompton Hospital, London, and additional subjects were identified from four other paediatric clinics within the region, used as patient identification sites. Ethics approval was obtained from London-Hampstead National Research Ethics Committee (15/LO/0050). All patients' legal guardians gave written informed consent to participate.

FIGURE 1 Trial design



Overview of trial design including recruitment criteria, randomisation and primary outcome. EVW: episodic viral wheeze; MTW: multiple trigger wheeze; UHCV: unscheduled healthcare visit

2.2 | Baseline research visit (see Appendix S1 for details)

A research visit was undertaken prior to randomization at least 2 weeks after the most recent wheeze attack. The following were assessed:

Symptoms—using a clinical questionnaire with details about symptom patterns, the Test for Respiratory and Asthma Control in Kids (TRACK)[14] and the quality of life using the Pediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ).[15]

Total IgE and specific IgE to common aeroallergens were measured. Atopy was defined as ≥1 positive specific IgE (≥0.35 kU/L) to any allergen tested.

An oropharyngeal swab and sputum induction was measured using 3.5% hypertonic saline as previously described[16] for bacterial culture and viral PCR to assess airway infection.

Exhaled nitric oxide (FeNO) was measured using the offline technique with a chemiluminescence analyser (NIOX MINO, Aerocrine AB).[17] Cigarette and e-cigarette exposure was assessed using urine cotinine levels.

2.3 | Randomization and intervention (see Appendix S1 and Table 1)

Children underwent seasonal randomization between September and April each year for three consecutive seasons: 2015–2018. In the intervention group, treatment was determined by blood eosinophils or bacterial infection from oropharyngeal swab/induced sputum (Figure 1 and Table 1). Based on previous data,[16] prescription of ICS was based on blood eosinophils ≥3%. Beclomethasone dipropionate 200 mcg twice daily via a metered-dose inhaler and spacer was prescribed for 4 months. As-required bronchodilators and prescribed leukotriene receptor antagonists continued in both study arms. In the control arm, children were treated as directed by their named paediatrician when assessed at the baseline visit.

Parents/carers were not aware of their treatment group and were contacted 3–5 days after the research visit with treatment instructions. Throughout the 4-month follow-up, adherence to ICS was monitored by Smartinhaler® (Adherium Ltd), a validated electronic device logging the date and time of each ICS actuation.

2.4 | Monitoring and follow-up

All children were followed up with one telephone contact every week to ask about any UHCV and to remind them to take the treatment. All parents/carers were sent an automated text message once daily asking whether their child had symptoms in the last 24 h, to which they responded yes/no. A follow-up visit was undertaken at the end of 4 months when TRACK and PACQLQ questionnaires were repeated.

2.5 | Sample size calculation and analysis plan (see Appendix S1)

A proof-of-concept study was undertaken to help define sample size and guide design for a future larger trial. Based on available published data, approximately five healthcare attendances occurred per child per year.[18] We aimed to reduce the proportion of healthcare contacts by at least one third per year. To achieve this with 80% power, and accepting statistical significance at the 5% level, we required a minimum of 36 patients with moderate wheeze per group.

Results are given as median (range) for scalable variables and proportions for the rest. Analysis used SPSS V27 (IBM Ltd). Comparisons between groups or unmatched comparisons within groups used the Mann-Whitney U test or chi-squared tests. Matched comparisons used the Wilcoxon test. Analysis of time to an unscheduled healthcare visit used Cox regression forward conditional testing.

3 | RESULTS

3.1 | Patient demographics

The number of children/carers approached and eligible and those who agreed to take part are shown in Figure 2. The total number randomized over three seasons was 60, 30 in each group. Demographic characteristics are summarized in Table 2.

3.2 | Blood eosinophils, atopy and clinical wheeze phenotype at baseline (Table 2)

Atopic children had significantly higher blood eosinophils than non-atopic children (non-atopic 0.3 [0–1.1] $\times$ 10^9/L vs atopic 0.7 [0.91–2.3] $\times$ 10^9/L, p = .005). Blood eosinophils were similar in EVW (median 0.5 [range 0–2.3] $\times$ 10^9/L or 6% [0%–21%]) and in MTW (median 0.4 [range 0.1–1.7] $\times$ 10^9/L or 5% [1%–13%], p = .8). 19 of 39 (49%) children with EVW and 8 of 21 (38%) children with MTW were atopic.

3.3 | Blood eosinophils, clinical wheeze phenotype and prescription of ICS in control vs intervention groups

21 of 30 (70%) children in the control group and 20 of 30 (67%) in the intervention group were prescribed ICS. 10 of 18 (56%) children with EVW, and 11 of 12 (92%) with MTW were prescribed ICS in the control group. Blood eosinophils were similar in the children who were or were not prescribed ICS in the control group (prescribed ICS 0.55 [range 0.2–1.7] $\times$ 10^9/L vs not prescribed ICS 0.30 [range 0.20–0.90] $\times$ 10^9/L, p = .07). In the intervention group, 17 of 21 (81%) with EVW and 3 of 9 (33%) with MTW were prescribed ICS.

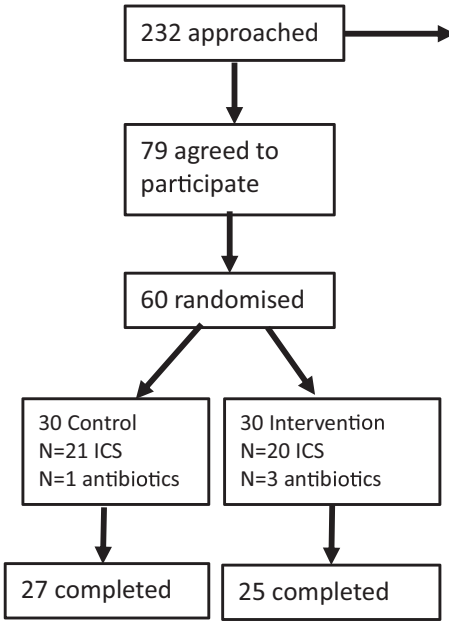
3.4 | Infection in sputum or oropharyngeal swab

All children had an oropharyngeal swab at baseline; 8 of 60 had positive bacterial culture. Induction of sputum was performed in 17 of 60 children; a sample was obtained from 13 of 17 children. The main reason sputum induction was not performed was parental refusal.

TABLE 1 Protocol for treatment prescription in intervention and control groups

Group	Intervention (n = 30)	Control (n = 30)
Blood eosinophils ≥3%; no bacterial culture positive	ICS (n = 18)	All treatment determined by child's named paediatrician ICS prescribed: n = 21/30 As-required bronchodilators (n = 9)
Blood eosinophils <3%; no bacterial culture positive	Only as-required bronchodilators; stop ICS if prescribed (n = 7)	
Blood eosinophils ≥3%; bacterial culture positive	ICS (n = 2)	
Blood eosinophils <3%; bacterial culture positive	Targeted antibiotics for 4 weeks (n = 3)	

Abbreviation: ICS, inhaled corticosteroids.



Reason for declining (n=123)	n
Could not contact after first approach	64
Currently well	2
Blood test	8
Don`t want to change treatment	5
Lack of time	22
Currently unwell	5
Fear of hospitals	1
No reason given	7
Don`t want more tests	9

FIGURE 2 Consort diagram of recruitment

TABLE 2 Demographics at baseline assessment

Variable	Control group ($n = 30$)	Intervention group ($n = 30$)	All subjects ($n = 60$)
Age, months: mean (SD)[a]	36.5 (14–60)	36.5 (15–61)	36.5 (14–61)
Gender (male): *n* (%)	21 (70.0)	21 (70.0)	42 (70.0)
Ethnicity			
Asian	6/29 (20.69)	7 (23.33)	13/59 (22.03)
Black	2/29 (6.90)	4 (13.33)	6/59 (10.17)
Mixed race	0	3 (10.00)	3/59 (5.08)
Other	5/29 (17.24)	1 (3.33)	5/59 (8.47)
White	17/29 (58.62)	15 (50.00)	32/59 (54.24)
Height (cm)[a]	95.9 (10.3)	94.7 (11.6)	95.3 (10.9)
Weight (kg)[a]	15.6 (3.2)	15.2 (3.6)	15.4 (3.4)
Smoking: yes	11/30 (36.67)	9/30 (30.00)	20/60 (33.3)
Urine cotinine			
Test performed	23 (76.7)	24 (80.0)	47 (78.3)
Test positive (%)	4/23 (17.4)	2/24 (8.3)	6/47 (12.8)
Clinical wheeze phenotype			
EVW	18/30 (60%)	21/29 (72%)	38/59 (64%)
MTW	12/30	9/29	21/59
Blood granulocytes			
Neutrophils (10^9/L)[b]	3.9 (2.0–11.0)	3.8 (1.0–24.0)	3.9 (1.0–24.0)
Eosinophils (10^9/L)[b]	0.45 (0.20–1.7)	0.60 (0.0–2.3)	0.50 (0.20–2.3)
Eosinophils (%)[b]	5.2 (2–21)	5.2 (0–16)	5.2 (0–21)
Total IgE (IU/ml)[b]	40 (12–6100)	43 (0.2–1070)	43 (0.2–6100)
Atopic (%)	15 (50)	12 (40)	25 (45)
Vitamin D (nmol/L)[b]	55 (18–99)	60 (15–119)	56 (15–119)
QoL			
PACQLQ[b]	5.8 (2.4–7.0)	6.7 (1.5–7.0)	6.4 (1.5–7.0)
TRACK	60 (15–85)	60 (20–90)	60 (15–90)
Admissions ever for wheeze[b]	5 (0–30)	5 (0–20)	5 (0–30)
LTRA prescribed (*n*)	17/30	11/30	28/60
ICS prescribed (*n*) before randomization	27/30 (90%)	24/30 (80%)	51/60 (85%)
ICS dose[c] (mcg/day); median (range)[b]	100 (50,200)	100 (50,400)	100 (50,400)
ICS prescribed (*n*) after randomization[b]	21/30 (70%)	20/30 (66.7%)	48/60 (80%)
Infection			
Positive bacterial culture on cough swab/ sputum (*n*)	8/30	6/30	14/60

Note: No significant differences in any parameter between control and intervention groups.

Abbreviations: EVW, episodic viral wheeze; ICS, inhaled corticosteroids; IgE, immunoglobulin E; LTRA, leukotriene receptor antagonist; MTW, multiple trigger wheeze; PACQLQ, Pediatric Asthma Caregiver's Quality of Life Questionnaire; QoL, quality of life; TRACK, Test for Respiratory and Asthma Control in Kids.

[a]Mean (SD).

[b]Median (range).

[c]Equivalent dose of beclomethasone.

6 of 13 had a positive sputum culture, and all those had negative oropharyngeal swabs. The pathogens cultured from the 14 positive samples are listed in Table S1. Four children with positive sputum were in the intervention group. 1 patient with high blood eosinophils (7%) and a positive sputum was prescribed ICS.

3.5 | Primary outcome: unscheduled healthcare visits

A similar number of children in the control group (15/30) and in the intervention group (16/30) had UHCV ($p = .8$), 31 subjects in total. 12 of 31 had a single UHCV, 13 had 2, 4 had 3 visits, and 2 had 4. Of children who had an UHCV, 19 of 31 (61%) were atopic, 22 of 29 (76%) had a raised eosinophil count, 19 of 31 (61%) were prescribed ICS, and 18 of 31 (58%) were EVW. None of the above were significantly different from those without a UHCV. At the UHCVs, 14 courses of oral steroids were prescribed in nine subjects in the control group and 13 courses in 10 subjects in the intervention group ($p = .7$). The severity of UHCV (admission>emergency room visit>primary care visit) showed no differences. For those 31 destined to have an UHCV, the time to first UHCV was 47 (range 0–103) days in the control group and 38 (range 1–109) days in the intervention group ($p = .6$) with no effect of atopy status, ICS use, whether EVW or MTW, or eosinophil count. UHCV was compared between children who met INFANT trial[11] criteria (atopic and blood eosinophils ≥0.3 × 10^9/L) and who were prescribed ICS vs the rest of the children. The number of UHCV was similar in atopic children with elevated blood eosinophils prescribed ICS and the remainder of the children prescribed ICS (Tables S2 and S3). Table 3 shows the relationships between clinical phenotype, blood eosinophils, atopic status, prescription of ICS and UHCV, regardless of the randomization group. There were no differences in UHCV or prospectively recorded symptoms by text message when assessed by any of these biomarkers.

3.6 | Secondary outcomes

Secondary outcomes, including symptom score (TRACK), PACQLQ and FeNO, were similar in control and intervention groups at 4 months (Table 4). The number of parents/carers who responded to daily text messages asking about symptoms was 29/30 (97%) in the control group and 28/30 (93%) in the intervention group. An electronic monitoring device (EMD) to assess ICS adherence was given to all children. Only 20 of 60 children returned the EMD at 4 months. Median ICS adherence was similar in both groups, control: 67% (range 0%–87%); and intervention: 65% (range 0%–91%; Table 4).

4 | DISCUSSION

In this proof-of-concept trial to compare efficacy of ICS determined by blood eosinophils with clinician-directed treatment in reducing UHCVs in children with recurrent moderate-to-severe wheeze, we found no difference in UHCV between the groups, either total visits, visit type (emergency department, primary care, hospitalization) or when the number of visits per subject was considered. Courses of oral corticosteroids were similar, and the time to first UHCV was also

TABLE 3 Relationship between clinical wheeze phenotype, blood eosinophils, atopic status, ICS prescription and unscheduled healthcare visits and symptom days

UHCV	EVW/ICS+	EVW/ICS-	MTW/ICS+	MTW/ICS-	Total
No	16	5	6	2	29
Yes	11	7	8	5	31
Total	27	12	14	7	60
UHCV	**Eos^{hi}/ICS+**	**Eos^{hi}/ICS-**	**Eos^{lo}/ICS+**	**Eos^{lo}/ICS-**	
No	20	4	2	3	29
Yes	17	5	1	6	29
Total	37	9	3	9	58
Symptoms					
Median (%) symptom yes days	7	12	19	16	NS
UHCV	**$Atopy^+$/ICS+**	**$Atopy^+$/ICS-**	**$Atopy^-$/ICS+**	**$Atopy^-$/ICS-**	
No	12	3	10	4	29
Yes	10	2	9	10	31
Total	22	5	19	14	60
Symptoms					
Median (%) symptom yes days	8	8	10	15	NS

Abbreviations: $Atopy^-$, negative specific IgE to tested aeroallergens; $Atopy^+$, >1 specific IgE to tested aeroallergens; Eos^{hi}, high blood eosinophils; Eos^{lo}, low blood eosinophils; EVW, episodic viral wheeze; ICS, inhaled corticosteroids; MTW, multiple trigger wheeze; UHCV, unscheduled healthcare visit.

TABLE 4 Secondary outcomes for control and intervention groups at 4 months

	Control	Intervention	*p*
Days to first UHCV, median (range; censored at 120 days)	111 (0, 120)	108 (1, 120)	.7
UHCV steroid courses	14 courses in 9 subjects	13 courses in 10 subjects	.7
Median (range), UHCV total score of all subjects; those with UHCV	0.5 (0, 11); 3 (1, 11)	0.5 (0, 7); 2 (1, 7)	.9; .9
Change in PACQLQ score baseline to 4 m, median (range). 26 of 30 subjects each. Minus = 'improvement'	−0.08 (−4.3 - +3.2)	0 (−2.9 - +3.2)	.8
Change in TRACK score at 4 months, median (range). 25 of 30 subjects each. + = 'improvement'	0 (−40, +75)	+15 (−30, +55)	.08
% of days texted symptoms present, median (range)	12 (0–49)	9 (0–45)	.4
% of adherence, median (range; *n* = 10/group)	67 (0–87)%	65 (0–91)%	.8

Note: Comparisons by chi-squared or Mann-Whitney tests.

Abbreviations: PACQLQ, Pediatric Asthma Caregiver's Quality of Life Questionnaire; TRACK, Test for Respiratory and Asthma Control in Kids; UHCV, unscheduled healthcare visit.

similar in both groups. Symptom score, quality of life and symptom-free days were also not different between the groups.

A significant strength and novelty of this trial design was to prospectively compare objective biomarker-based management with current clinical care. Although the INFANT trial showed benefit of aeroallergen sensitization in identifying differential responders to ICS, utility of blood eosinophils was ascertained from the *post hoc* analysis.[11] We aimed to investigate the role of blood eosinophils alone, without atopic status, in prevention of attacks because evidence of sensitization may not become apparent until later in preschool age,[19] and we had shown a correlation between lower airway and blood eosinophils in this age group.[16] The cut-off for blood eosinophils used was determined by our data in severe preschool wheezers. However, we observed no difference in UHCV even when eosinophil counts of 0.7×10^9/L, 0.5×10^9/L or 0.3×10^9/L were used. Previous exacerbation history was not a marker of differential response in the INFANT trial, while our inclusion criteria were based on number of exacerbations in the last 12 months. UHCVs was a secondary outcome in the INFANT trial, but we chose UHCVs as the primary outcome because data from trials of anti-eosinophilic biologics using blood eosinophils as a biomarker have shown a reduction in asthma attacks.[20] The use of text messaging to prospectively record the presence or absence of symptoms in the previous 24 h was a novel approach that proved successful, with approximately 95% response rate. This may be a better approach than symptom diaries for future trials.

This was a proof-of-concept study as it was difficult to undertake power calculations to understand the sample size required in a design that compared current clinical care with biomarker-based care since all previous clinical trials of preschool wheeze have compared intervention with placebo. It is likely that an inadequate sample size is an explanation for the findings. Our preliminary power calculation was based on five UHCV per year, but half of the children recruited had no further visits. Previous trials in preschool wheeze have shown a similar 'dropout' because of improvement reflecting the natural history of the disease.[11] We chose to only randomize during the autumn/winter to avoid seasonal variations and minimize the intervention period. However, as these were children with at least one attack in the previous 6 months, there was reluctance from families to participate if treatment might be changed at a time when their child was likely to be more unwell. Therefore, of the patients who were approached and eligible, 61% declined participation and a further 20% changed their mind.

An additional limitation in the interpretation of the findings was the disappointing level of adherence to ICS when monitored using an EMD. To our knowledge, this is the first trial in preschool children incorporating electronic monitoring. Fifty per cent (20/40) of families whose children were prescribed ICS did not return the EMD (approx. £120 per device), suggesting adherence in those children was likely to be negligible, and of those who did return the monitor, average adherence was only 67%. This was despite weekly phone calls to remind families about taking prescribed therapy. An explanation may be that parents did not think ICS was beneficial or were concerned that ICS had unacceptable side effects. It is difficult to disentangle whether inadequate power, unexpectedly high prescription rate of ICS in the control group, or inadequate adherence to ICS were the main factors that have influenced the results.

We aimed to investigate the efficacy of managing preschool wheeze using objective biomarkers including blood eosinophils and infection. An induced sputum sample was obtained from very few children (17/60) as most parents declined this procedure because of time constraints; the majority therefore only had results from an oropharyngeal swab. With such small numbers, conclusions about the role of infection cannot be drawn.

Several limitations in the trial design have been highlighted and must be considered for future trials: 1. there was no relationship between EVW and MTW and allergen sensitization or blood eosinophils; 2. median blood eosinophil count among all wheezers was 0.5×10^9/L (5%), suggesting the majority warrant ICS according to our cut-off of 3%. A composite biomarker of aeroallergen sensitization and blood eosinophils may be more discriminatory; 3. half of children did not have a further UHCV, so sample size for future trials needs to increase to account for this; 4. our intervention period was only 4 months, but to see an impact on UHCV, a longer period may be needed; 5. parental behaviours, even for this young age group, are not always in line with clinicians' advice since ICS adherence was poor;

6. two thirds of parents approached were reluctant to participate as they did not want a change in their child's treatment plan, which is akin to a recent biomarker-directed trial in adult severe asthma.[21]

To address these limitations and understand the role of biomarker-directed treatment for preschool wheeze, future trials should be multicentre, not include clinical phenotype alone in decision-making and include a control arm that incorporates a fixed management algorithm to decide prescription of ICS.

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AUTHOR CONTRIBUTIONS

Sejal Saglani: Conceptualization (lead); Data curation (lead); Funding acquisition (lead); Investigation (lead); Methodology (lead); Project administration (lead); Supervision (lead); Writing – original draft (lead); Writing – review & editing (lead). **Yvonne Bingham:** Data curation (lead); Investigation (lead); Project administration (lead); Writing – review & editing (supporting). **Ian Balfour-Lynn:** Data curation (supporting); Investigation (supporting); Writing – review & editing (supporting). **Stephen Goldring:** Data curation (supporting); Investigation (supporting); Writing – review & editing (supporting). **Atul Gupta:** Investigation (supporting); Writing – review & editing (supporting). **Winston Banya:** Formal analysis (supporting). **John Moreiras:** Data curation (supporting); Investigation (supporting); Writing – review & editing (supporting). **Louise Fleming:** Methodology (supporting); Project administration (supporting); Writing – review & editing (supporting). **Andrew Bush:** Conceptualization (supporting); Funding acquisition (supporting); Supervision (supporting); Writing – review & editing (equal). **Mark Rosenthal:** Data curation (lead); Formal analysis (lead); Methodology (supporting); Validation (lead); Writing – review & editing (equal).

PEER REVIEW

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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