

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 $\geq 3\%$, 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.

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.

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 trigger⁴; ii) clinical phenotypes may switch within patients in a period as short as 3 months⁵; 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.

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).

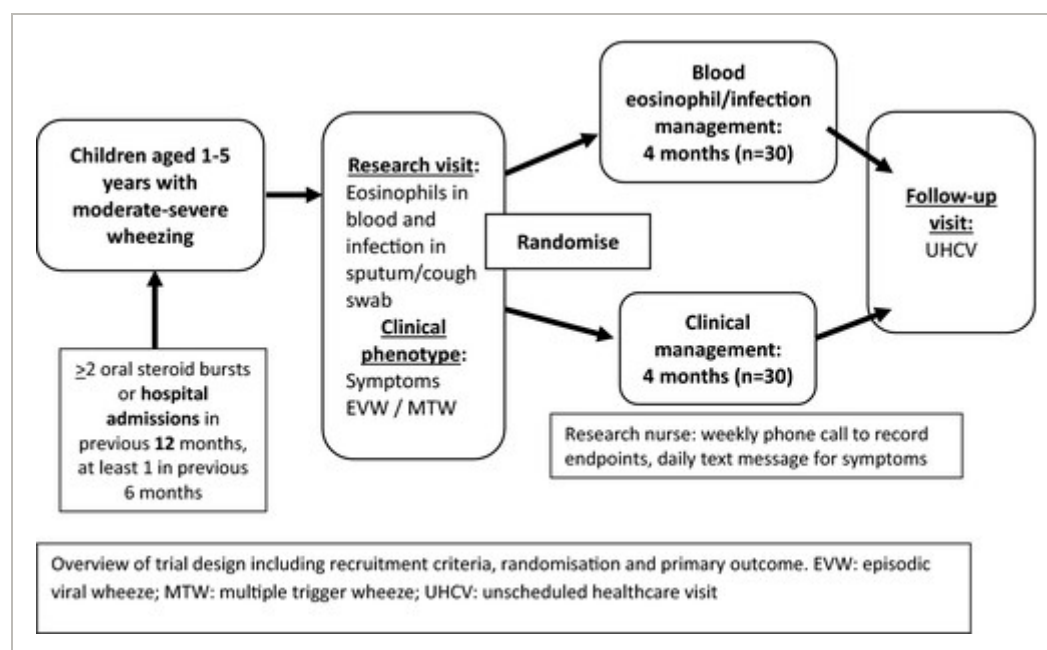


FIGURE 1

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Trial design

Exclusion criteria are detailed in the Appendix [S1](#).

Wheezers were categorized according to European Respiratory Society criteria as having MTW or EVW³ 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.

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 described¹⁶ 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 $\geq 3\%$. 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.

TABLE 1. Protocol for treatment prescription in intervention and control groups

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

Abbreviation: ICS, inhaled corticosteroids.

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)

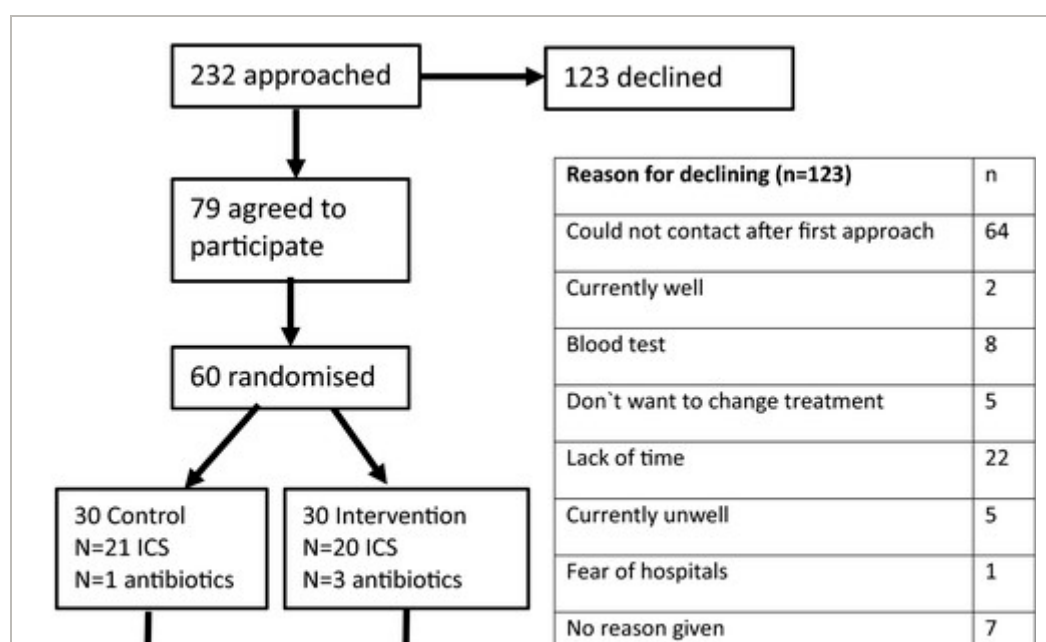
A proof-of-concept study was undertaken to help define sample size and guide design for a future larger trial. Based on available published data, approximately five healthcare attendances occurred per child per year.¹⁸ We aimed to reduce the proportion of healthcare contacts by at least one third per 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.

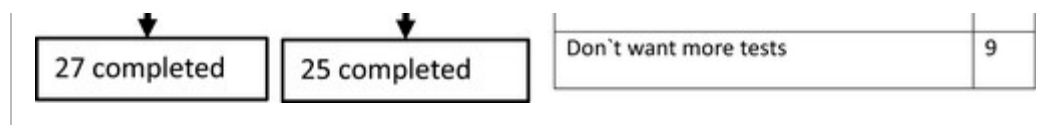
Results are given as median (range) for scalable variables and proportions for the rest. Analysis used SPSS V27 (IBM Ltd). Comparisons between groups or unmatched comparisons within groups used the Mann-Whitney U test or chi-squared tests. Matched comparisons used the Wilcoxon test. Analysis of time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



**FIGURE 2**
[Open in figure viewer](#)
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Consort diagram of recruitment

TABLE 2. Demographics at baseline assessment

Variable	Control group (<i>n</i> = 30)	Intervention group (<i>n</i> = 30)	All subjects (<i>n</i> = 60)
Age, months: mean (SD) ^a	36.5 (14–60)	36.5 (15–61)	36.5 (14–61)
Gender (male): <i>n</i> (%)	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			

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.

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. 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 trial¹¹ criteria (atopic and blood eosinophils $\geq 0.3 \times 10^9/L$) 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.

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.

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).

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

	Control	Intervention	<i>p</i>
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; <i>n</i> = 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.

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 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 $0.7 \times 10^9/L$, $0.5 \times 10^9/L$ or $0.3 \times 10^9/L$ 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 $0.5 \times 10^9/L$ (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).

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REFERENCES



1 Granell R, Sterne JA, Henderson J. Associations of different phenotypes of wheezing illness in early childhood with environmental variables implicated in the aetiology of asthma. *PLoS One*. 2012; **7**(10):e48359.

[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

2 Bacharier LB, Guilbert TW. Diagnosis and management of early asthma in preschool-aged children. *J Allergy Clin Immunol*. 2012; **130**(2): 287- 296.

[Crossref](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

3 Brand PL, Baraldi E, Bisgaard H, et al. Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. *Eur Respir J*. 2008; **32**(4): 1096- 1110.

[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

4 Robinson PFM, Fontanella S, Ananth S, et al. Recurrent severe preschool wheeze: from prespecified diagnostic labels to underlying endotypes. *Am J Respir Crit Care Med*. 2021; **204**(5): 523- 535.

[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

5 Schultz A, Devadason SG, Savenije OE, Sly PD, Le Souef PN, Brand PL. The transient value of classifying preschool wheeze into episodic viral wheeze and multiple trigger wheeze. *Acta Paediatr*. 2010; **99**(1): 56- 60.

[Wiley Online Library](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

6 Kelly HW, Sternberg AL, Lescher R, et al. Effect of inhaled glucocorticoids in childhood on adult height. *N Engl J Med*. 2012; **367**(10): 904- 912.

[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

7 Saglani S, Lloyd CM. Novel concepts in airway inflammation and remodelling in asthma. *Eur Respir J*. 2015; **46**(6): 1796- 1804.

[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

8 Saglani S, Payne DN, Zhu J, et al. Early detection of airway wall remodeling and eosinophilic inflammation in preschool wheezers. *Am J Respir Crit Care Med*. 2007; **176**(9): 858- 864.

[Crossref](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

9 Turato G, Barbato A, Baraldo S, et al. Nonatopic children with multitrigger wheezing have airway pathology comparable to atopic asthma. *Am J Respir Crit Care Med*. 2008; **178**(5): 476- 482.

[Crossref](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

10 Sonnappa S, Bastardo CM, Wade A, et al. Symptom-pattern phenotype and pulmonary function in preschool wheezers. *J Allergy Clin Immunol*. 2010; **126**(3): 519- 526.

[Crossref](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

11 Fitzpatrick AM, Jackson DJ, Mauger DT, et al. Individualized therapy for persistent asthma in young children. *J Allergy Clin Immunol*. 2016; **138**(6): 1608- 1618.e12.

[Crossref](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

12 Hilty M, Burke C, Pedro H, et al. Disordered microbial communities in asthmatic airways. *PLoS One*. 2010; **5**(1):e8578.

[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

13 Cane RS, McKenzie SA. Parents' interpretations of children's respiratory symptoms on video. *Arch Dis Child*. 2001; **84**(1): 31- 34.

[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

14 Murphy KR, Zeiger RS, Kosinski M, et al. Test for respiratory and asthma control in kids (TRACK): a caregiver-completed questionnaire for preschool-aged children. *J Allergy Clin Immunol*. 2009; **123**(4): 833- 839.e9.

[Crossref](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

15 Juniper EF, Guyatt GH, Feeny DH, Ferrie PJ, Griffith LE, Townsend M. Measuring quality of life in the parents of children with asthma. *Qual Life Res*. 1996; **5**(1): 27- 34.

[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

16 Jochmann A, Artusio L, Robson K, et al. Infection and inflammation in induced sputum from preschool children with chronic airways diseases. *Pediatr Pulmonol*. 2016; **51**(8): 778- 786.

[Wiley Online Library](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

17 Daniel PF, Klug B, Valerius NH. Measurement of exhaled nitric oxide in young children during tidal breathing through a facemask. *Pediatr Allergy Immunol*. 2005; **16**(3): 248- 253.

[Wiley Online Library](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

18 Stevens CA, Turner D, Kuehni CE, Couriel JM, Silverman M. The economic impact of preschool asthma and wheeze. *Eur Respir J*. 2003; **21**(6): 1000- 1006.

[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

19 Lau S, Matricardi PM, Wahn U, Lee YA, Keil T. Allergy and atopy from infancy to adulthood: messages from the German birth cohort MAS. *Ann Allergy Asthma Immunol*. 2019; **122**(1): 25- 32.

[Crossref](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

20 Pavord ID, Menzies-Gow A, Buhl R, et al. Clinical development of mepolizumab for the treatment of severe eosinophilic asthma: on the path to personalized medicine. *J Allergy Clin Immunol Pract*. 2021; **9**(3): 1121- 1132.e7.

[Crossref](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

21 Heaney LG, Busby J, Hanratty CE, et al. Composite type-2 biomarker strategy versus a symptom-risk-based algorithm to adjust corticosteroid dose in patients with severe asthma: a multicentre, single-blind, parallel group, randomised controlled trial. *Lancet Respir Med*. 2021; **9**(1):

57- 68.

[Crossref](#) | [CAS](#) | [PubMed](#) | [Web of Science®](#) | [Google Scholar](#)

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Appendix S1

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

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METHODS:

Trial Design and Participants

A single centre, randomised, single-blind controlled trial comparing management of preschool wheeze determined by blood eosinophils or airway infection (intervention) to routine clinical care (control). Aeroallergen sensitisation was not included as a biomarker to determine management since the focus was to determine the role of blood eosinophils as a biomarker in this age group. The primary outcome was UHCV at 4 months. Randomisation was seasonal, between September and April each year for 3 consecutive seasons from 2015-2018.

Inclusion criteria:

- Age 1-5 years
- Doctor diagnosed wheeze and confirmed using a validated video questionnaire¹³.
- Moderate to severe wheeze - defined as requiring at least 2 admissions **and/or** 2 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 (Fig 1).

Exclusion criteria:

- Known cardiac disease
- Other chronic respiratory condition (physician diagnosed)
- Unsafe swallow
- Prematurity <34 weeks
- Positive pressure ventilation in the newborn period
- Family not contactable by telephone (weekly telephone follow-up was part of the protocol).

Wheezers were categorised according to European Respiratory Society criteria as having MTW or EVW³ at recruitment from parental symptom reports. Patients were recruited and randomised at The Royal Brompton Hospital, London, additional subjects were identified from 4 other paediatric clinics within the region, used as patient identification sites. Ethical approval was obtained from London-Hampstead National Research Ethics Committee (15/LO/0050). All patients' legal guardians gave written informed consent to participate.

Baseline research visit

A baseline research visit was undertaken prior to randomisation at least 2 weeks after the most recent wheeze attack (needing admission or oral steroids).

i) Symptom questionnaires and clinical assessment

Carers completed a clinical questionnaire which included details about symptom pattern to define clinical phenotype, EVW or MTW. Symptom control was assessed using the Test for Respiratory and Asthma Control in Kids (TRACK)¹⁴ and quality of life assessed using the Pediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ)¹⁵. Details about pregnancy, gestation, delivery, family demographics, past medical history including co-morbidities and atopy, and current and previous medication use were collected (see online supplement for full questionnaire). An independent clinician assessed the child on the day of the visit and made a clinical management plan based on the history and examination. Only the research nurse was told the plan, which would be used if the children were randomised to the control arm.

ii) Assessment of atopy

Blood was collected for total IgE and specific IgE to aeroallergens (house dust mite, grass pollen, tree pollen, cat, dog, *Aspergillus fumigatus*) and food allergens (milk, egg, peanut). Atopy was defined as ≥ 1 positive specific IgE (≥ 0.35 kU/L) to any allergen tested.

iii) Airway infection

An oropharyngeal swab was taken and sent for bacterial culture. Sputum induction was performed using 3.5% hypertonic saline as previously described¹⁶ and processed for bacterial culture and viral PCR (FTD Respiratory pathogens 21 multiplex kit; Fast Track Diagnostics Ltd, Malta).

iv) Exhaled nitric oxide (FeNO)

Exhaled nitric oxide was measured using the offline technique with a chemiluminescence analyser (Niox Mino, Aerocrine AB, Sweden)¹⁷.

v) Cigarette and e-cigarette exposure

Urine was analysed for cotinine levels to assess exposure to nicotine.

Randomisation and Intervention

Children underwent seasonal randomisation between September and April each year. For those in the intervention group, treatment was determined by blood eosinophils, or bacterial infection from oropharyngeal swab/induced sputum (Fig 1). Based on our previous data comparing blood and broncho-alveolar lavage eosinophils¹⁶, children with blood eosinophils $\geq 3\%$ were prescribed beclomethasone dipropionate 200mcg twice daily to be taken via a metered dose inhaler and spacer for 4 months. Children with blood eosinophils $< 3\%$ who were already prescribed regular ICS were asked to stop them for 4

months. Children with a positive bacterial culture result from oropharyngeal swab or sputum, but no blood eosinophilia, were treated with a 4 week course of antibiotics targeted to the organism identified. If these children were prescribed regular ICS, they were also stopped for 4 months. Children with both eosinophilia and bacterial infection were prescribed ICS for 4 months, and no antibiotics. The use of bronchodilators for acute symptoms, and previously prescribed leukotriene receptor antagonists continued during the intervention period in both study arms. All children were asked to stop prescribed ICS for 2 weeks prior to attending for the baseline visit when bloods and sputum samples were taken (Fig 1). In the control arm, children were treated as directed by their named paediatrician when they were assessed at the baseline visit.

Parents/carers were not aware of their treatment group. All patients underwent similar investigations 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, Auckland, New Zealand), a validated electronic device logging the date and time of each ICS actuation, in all children.

Monitoring and Follow up

All children were followed during the 4 month study period with one telephone contact every week to ask about attacks, any UHCV, the nature of these visits and to remind them to take the treatment. All parents/carers were sent an automated text message once daily asking if their child had symptoms in the last 24 hours, 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.

Sample size calculation and analysis plan

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, it was apparent that approximately five healthcare attendances occurred per child per year¹⁸. In the current study, 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 evaluable patients with moderate wheeze per group. Evaluable patients were those from whom at least a blood sample to assess inflammation and an oropharyngeal swab to determine infection could be obtained prior to randomisation.

Results are given as median (range) for scalable variables and proportions for the rest. Analysis used SPSS V27 (IBM Ltd. UK). Comparisons between groups or unmatched

comparisons within groups used the Mann Whitney U test or Chi squared tests. Matched comparisons used the Wilcoxon test. Detailed analysis of time to an unscheduled healthcare visit used Cox regression forward conditional testing (see online supplement).

Questionnaire administered for each participant

Pre school respiratory disease: LCI and FE_{NO}

Background

Name _____ Hospital number _____

Referring Consultant (circle): AB / CH / HLT / IBL / JD / LF / MRO / SC / SS / other

DOB

Date of assessment

Age (decimal years)

Sex (circle) male / female

Ethnicity (circle) Caucasian / Asian / Black / Chinese / Mixed Caucasian and Asian / Mixed Caucasian and Black / Other

Diagnosis (tick all that apply)

Pre school wheeze..... ☐
Recurrent chest infections..... ☐
Persistent cough..... ☐

Upper airway problem / noisy breathing..... ☐
Bronchiectasis..... ☐
Other _____

Symptoms

What is your child's main symptom? (circle) wheeze / cough / other (specify) _____

Which of the video clips, if any, represents your child's symptoms? 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐

Wheeze

Has your child ever wheezed? yes ☐ no ☐ If no go to next section

How many episodes of wheeze has he / she ever had? 1 ☐ 2 ☐ 3 ☐ >3 ☐

How many episodes in the past 6 months? 1 ☐ 2 ☐ 3 ☐ >3 ☐

Has he / she ever been completely wheeze free? yes ☐ no ☐

Does he / she only wheeze with colds? yes ☐ no ☐

Does he /she wheeze apart from colds? yes ☐ no ☐

If yes:

Does the wheeze increase with a cold? yes ☐ no ☐

Does he / she wheeze most days? yes ☐ no ☐

Has he / she ever been completely wheeze free? yes ☐ no ☐

Has he / she ever been admitted to hospital with wheeze? yes ☐ no ☐ number of admissions

Allergies

Does your child have eczema (Dr diagnosed)? yes ☐ no ☐

Does he / she have any treatment for this? yes ☐ no ☐ N/A ☐

If yes: what treatment? (circle) moisturiser / steroid cream / both

Is your child atopic? yes ☐ no ☐
yes ☐ no ☐

Medications

Medication	Name (circle)	Ever prescribed	Currently prescribed	Current dose and frequency	Age when started	
Reliever medication	Salbutamol / terbutaline	Yes / No	Yes / No			
Inhaled steroid 1	Budesonide / fluticasone / beclomethasone	Yes / No	Yes / No			
Inhaled steroid 2	Budesonide / fluticasone / beclomethasone	Yes / No	Yes / No			
Long-acting beta agonist	Salmeterol	Yes / No	Yes / No			
Leukotriene receptor antagonist	Montelukast	Yes / No	Yes / No			
Combination inhaler	Seretide	Yes / No	Yes / No			
Oral steroids	Prednisolone	Yes/ No	Number of courses	Date of last course		
Antibiotics	Name	Number of courses				

Does he / she respond to the reliever inhaler? yes ☐ no ☐ N / A ☐

Does he / she respond to the steroid inhaler? yes ☐ no ☐ N / A ☐

Does he / she respond to oral steroids? yes ☐ no ☐ N/A ☐

Inhaler technique (circle): satisfactory / unsatisfactory

Details:

Other medication

Name	Dose and frequency	Age when started

Birth and Early Life History

Gestational age:

weeks

Smoking status (mother):

never smoked / ex-smoker / current smoker / smoked during pregnancy

Smoking status (father):

never smoked / ex-smoker / current smoker / smoked during pregnancy

Current household smoking (circle all that apply): mother / father / both / other household member / none

Urinary cotinine:

Other relevant past medical history:

Assessments

Height		Centile	Weight		Centile

Viral infection in past 2 weeks: yes / no / possibly

High dose systemic CS in past 2 weeks: yes / no

Visit to GP because of respiratory symptoms in past 2 weeks: yes / no

Hospital attendance / admission because of respiratory symptoms in past 2 weeks: yes / no

Fever in the past 2 weeks: yes / no

High dose systemic CS in past 2 months: yes / no

Visit to GP because of respiratory symptoms in past 2 months: yes / no

Hospital attendance / admission because of respiratory symptoms in past 2 months: yes / no

Exhaled Nitric Oxide

FE_{NO} measured: yes / unable to do / not attempted

FE _{NO} , ppb	1	2	3	Mean

Paediatric Asthma Caregivers Quality of Life Questionnaire: PACQLQ (© E Juniper)

This questionnaire is designed to find out how you have been during the last week. We want to know the ways in which your child's asthma has interfered with your normal activities and how this has made you feel. Please answer each question by placing a tick in the appropriate box.

		1	2	3	4	5	6	7
During the past week, how often:		All of the time	Most of the time	Quite often	Some of the time	Once in a while	Hardly any of the time	None of the time
1	Did you feel helpless or frightened when your child experienced cough, wheeze or breathlessness?							
2	Did your family need to change plans because of your child's asthma?							
3	Did you feel frustrated or stressed because your child was irritable due to asthma?							
4	Did your child's asthma interfere with your job or work around the house?							
5	Did you feel upset because of your child's cough, wheeze or breathlessness?							
6	Did you have sleepless nights because of your child's asthma?							
7	Were you bothered because your child's asthma interfered with family relationships?							
8	Were you awakened during the night because of your child's asthma?							
9	Did you feel sad that your child has asthma?							
During the past week how worried or concerned were you:		Extremely worried / concerned	Very worried / concerned	Fairly worried / concerned	Somewhat worried / concerned	A little worried / concerned	Hardly worried / concerned	Not worried / concerned
10	About your child's performance of normal daily activities?							
11	About your child's asthma medications and side effects?							
12	About being over-protective of your child?							
13	About your child being able to lead a normal life?							

PACQLQ:

☐

Emotional function: $(1+3+5+7+9+10+11+12+13)/9$

Activity limitation: $(2+4+6+8)/4$

☐

Total score: $(\text{total emotional} + \text{total activity})/13$

☐

1 **TRACK Test for Respiratory and Asthma Control in Kids**

2 **For kids under 5 years of age**

3 **How to take TRACK**

4 Step 1: Make a check mark in the box below each of your selected answers.

5 Step 2: Write the number of your answer in the score box provided to the right of each question.

6 Step 3: Add up the numbers in the individual score boxes to obtain your child's total score.

7 Step 4: Take the test to your child's healthcare provider to talk about your child's total TRACK score.

8

9 1 During **the past 4 weeks**, how often was your child bothered by breathing problems, such as wheezing,
10 coughing, or shortness of breath?

11 Not at all Once or twice Once every week 2 or 3 times a week 4 or more times a week

12 ☐ ☐ ☐ ☐ ☐

13 20 15 10 5 0

14 2 During **the past 4 weeks**, how often did your child's breathing problems (wheezing, coughing, shortness
15 of breath) wake him or her up at night?

16 Not at all Once or twice Once every week 2 or 3 times a week 4 or more times a week

17 ☐ ☐ ☐ ☐ ☐

18 20 15 10 5 0

19 3 During **the past 4 weeks**, to what extent did your child's breathing problems, such as wheezing, coughing,
20 or shortness of breath, interfere with his or her ability to play, go to school, or engage in usual activities
21 that a child should be doing at his or her age?

22 Not at all Slightly Moderately Quite a lot Extremely

23 ☐ ☐ ☐ ☐ ☐

24 20 15 10 5 0

25 4 During **the past 3 months**, how often did you need to treat your child's breathing problems (wheezing,
26 coughing, shortness of breath) with quick relief medications (salbutamol, Ventolin)?

27 Not at all Once or twice Once every week 2 or 3 times a week 4 or more times a week

28 ☐ ☐ ☐ ☐ ☐

29 20 15 10 5 0

30 5 **During the past 12 months**, how often did your child need to take oral corticosteroids (prednisone,
31 prednisolone) for breathing problems not controlled by other medications?

32	Never	Once	Twice	3 times	4 or more times
33					
34	20	15	10	5	0

35 **Total**

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RESULTS:

Patient Demographics

The number of children approached and eligible and those that agreed to take part are shown in Figure 2. The total number of children randomised over 3 seasons was 60, 30 children in each group. Demographic characteristics are summarised in Table 1. The median number of acute admissions ever per child at baseline was 5 (range 0-30). Not all children had previously been hospitalised since inclusion criteria were admissions and/or courses of oral corticosteroids. 36/60 (60%) children had >3 wheeze attacks in the previous 6 months. 51/60 (85%), had been prescribed maintenance ICS at baseline, while only 21/60 (35%) had a clinical wheeze phenotype of MTW.

Blood eosinophils, atopy and clinical wheeze phenotype at baseline (Table 1)

At baseline median blood eosinophils for all children was 0.5 (range $0-2.3$) $\times 10^9/L$ and 27/60 (45%) children were atopic. Atopic children had significantly higher blood eosinophils than non-atopic children (Non-atopic 0.3 (0 to 1.1) $\times 10^9/L$ vs Atopic 0.7 (0.91 to 2.3) $\times 10^9/L$, $p=0.005$). Total IgE in atopic children vs non-atopic children was median 235 (18 to 6160)IU/ml vs 16 (0.2 to 511)IU/ml, $p<0.001$. Blood eosinophils were similar in EVW (median 0.5 [range 0 to 2.3] $\times 10^9/L$, or 6% [0 to 21%]), and in MTW (median 0.4 [range 0.1 to 1.7] $\times 10^9/L$ or 5% [1 to 13%], $p=0.8$). 19/39 (49%) children with EVW and 8/21 (38%) children with MTW were atopic.

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

21/30 (70%) children in control group and 20/30 (67%) in the intervention group were prescribed ICS. 10/18 (56%) children with EVW, and 11/12 (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 to 1.7) $\times 10^9/L$ vs not prescribed ICS 0.30 (range 0.20 to 0.90) $\times 10^9/L$, $p=0.07$). In the intervention group, 17/21 (81%) with EVW and 3/9 (33%) with MTW were prescribed ICS. We did not use atopy to decide management, but the number of atopic children in the intervention group that were prescribed ICS was 12/30 (40%) and the number of atopic children prescribed ICS in the control group was 10/30 (33%), $p=0.8$.

Infection in sputum or oropharyngeal swab at baseline

All children had an oropharyngeal swab at baseline, 8/60 had a positive bacterial culture. Induced sputum was performed in 17/60 children, a sample was obtained from 13/17. The main reason sputum was not performed was parental refusal. 6/13 had a positive sputum culture, and all those had negative oropharyngeal swabs. The bacteria cultured from positive sputum and oropharyngeal swabs from 14 children are listed in Supp Table 1. Four children with a positive sputum were in the intervention group. 1 patient with high blood eosinophils (7%) and a positive sputum was prescribed ICS.

Primary outcome – impact on unscheduled healthcare visits

A similar number of children in the control group (15/30) and in the intervention group (16/30) had an UHCV ($p=0.8$), 31 subjects in total. 12/31 had a single UHCV, 13 had 2, 4 had 3 visits and 2 had 4. Of children that had an UHCV, 19/31 (61%) were atopic, 22/29 (76%) had a raised eosinophil count, 19/31 (61%) were prescribed ICS and 18/31 (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 9 subjects in the control group and 13 courses in 10 subjects in the intervention group ($p=0.7$). Scoring for 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 to 103) days in the control group and 38 (range 1 to 109) days in the intervention group ($p=0.6$) with no effect of atopy status, ICS use, whether EVW or MTW or eosinophil count. UHCV were compared in children that met INFANT trial¹¹ criteria (atopic AND blood eosinophils $\geq 0.3 \times 10^9/L$) and were prescribed ICS vs the rest of the children. Number of UHCV was similar in atopic children with elevated blood eosinophils prescribed ICS and the remainder of the children prescribed ICS (Supp Tables 2&3). Table 2 shows the relationships between clinical phenotype, blood eosinophils, atopic status, prescription of ICS and UHVC, regardless of randomisation group. There were no differences in UHCV or prospectively recorded symptoms by text message when assessed by any of these biomarkers.

Secondary outcomes

Secondary outcomes, including symptom score (TRACK), PACQLQ, FeNO were similar in control and intervention groups at 4 months (Table 3). The number of parents/carers that responded to daily text messages asking about symptoms was 29/30 (97%) in the control group and 28/30 (93%) in the intervention group. Of those that responded, the median number of days with symptoms was 13 (range 0 to 65) in the control group and 12 (range

127 0 to 56) in the intervention group. An electronic monitoring device (EMD) to assess
128 adherence to prescribed ICS was given to all children regardless of experimental group.
129 Only 20/60 children returned the EMD at 4 months, 10 in each group. Median adherence
130 to ICS over the 4 months was similar in both control and intervention groups, control: 67%
131 (range 0 to 87%), intervention: 65% (range 0 to 91%) (Table 3).

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153 **Supp Table 1. Bacterial organisms cultured from induced sputum and oropharyngeal swabs from**
 154 **14/60 children**

Subject number	Organisms cultured
1	Moraxella catarrhalis
2	Staphylococcus aureus
3	Beta-haemolytic strep, Staphylococcus aureus
4	Pseudomonas aeruginosa
5	Staphylococcus aureus
6	Pseudomonas aeruginosa
7	Staphylococcus aureus
8	Staphylococcus aureus
9	Pseudomonas aeruginosa
10	Staphylococcus aureus
11	Staph aureus, Haemophilus influenzae
12	Moraxella catarrhalis
13	Haemophilus influenzae
14	Haemophilus influenzae

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159 **Supp Table 2. Relationship between blood eosinophils, atopic status, and UHCV in all children**

UHCV	Non-atopic and blood eosinophils $<0.3 \times 10^9/\text{ml}$	Atopic and blood eosinophils $\geq 0.3 \times 10^9/\text{ml}$	Total
No	15	14	29
Yes	21	10	31
Total	36	24	60

160 No significant difference in number of UHCV in atopic children with high blood eosinophils compared to
 161 non-atopic with normal blood eosinophils. UHCV: unscheduled healthcare visit.

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164 **Supp Table 3. Relationship between blood eosinophils, atopic status, and UHCV ONLY in children**
165 **prescribed ICS**

UHCV	Non-atopic and blood eosinophils <0.3x10 ⁹ /ml	Atopic and blood eosinophils ≥0.3x10 ⁹ /ml	Total
No	11	10	21
Yes	11	9	20
Total	22	19	41