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Original Article

Short-term efficacy of nebulized budesonide for allergic airway inflammation in young children and dynamic changes in fractional exhaled nitric oxide (FeNO): a retrospective cohort study

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Abstract: Background: Allergic airway inflammation in young children with recurrent wheezing may precede asthma. Fractional exhaled nitric oxide (FeNO) may reflect type 2 airway inflammation. Objective: To evaluate the short-term effectiveness and safety of nebulized budesonide and dynamic FeNO changes in children aged 6 to 36 months. Methods: We retrospectively analyzed 548 children treated between January 2023 and February 2025, with follow-up through June 2025. Children receiving standard care plus nebulized budesonide (n = 286) were compared to those on standard care alone (n = 262). Outcomes included clinical response, symptom-resolution time, serial FeNO, inflammatory biomarkers, three-month recurrence and adverse events. Results: Overall response at day 7 was higher with budesonide than in the control group (92.7% vs. 80.9%; $\chi^2 = 16.71$, $P < 0.001$), and systemic corticosteroid rescue was less frequent (1.05% vs. 4.20%; Fisher exact $P = 0.028$). Wheeze resolution time was shorter (3.2 ± 1.1 vs. 5.1 ± 1.6 days; $P < 0.001$). FeNO decreased more in the budesonide group from baseline to day 28 (22.6 ± 6.4 to 9.8 ± 3.2 ppb) than in controls (22.4 ± 6.7 to 14.5 ± 4.6 ppb; $P < 0.001$ for change). Three-month recurrence was lower with budesonide (14.7% vs. 27.5%; $\chi^2 = 13.59$, $P < 0.001$), with no increase in adverse events. Conclusion: Nebulized budesonide added to standard care was associated with improved short-term clinical outcome, greater FeNO reduction, and lower three-month recurrence in young children with allergic airway inflammation.

Keywords: Nebulized budesonide, FeNO, young children, allergic airway inflammation, wheezing, type 2 inflammation

Introduction

Wheezing is a leading cause of medical visits among infants and toddlers, and approximately one-third of preschool children experience wheezing before age six [1, 2]. A clinically important subgroup shows personal or familial atopy and eosinophilic type 2 airway inflammation, which is associated with persistent wheezing and later asthma development [3-5]. Early identification and control of airway inflammation may reduce recurrent symptoms and provide a rationale for phenotype-oriented management.

For preschool children with recurrent wheezing or asthma-like symptoms, inhaled corticosteroids, including nebulized budesonide, are commonly used as controller therapy when symptoms and risk profiles suggest steroid-responsive airway inflammation [1, 6-9]. Nebulized delivery through a face-mask jet nebulizer is particularly suitable for young children who cannot reliably use handheld inhalation devices. Existing pediatric studies support the clinical benefit and acceptable safety of budesonide; however, most evidence focuses on preschool children older than three years, or on symptom outcomes rather than serial inflammatory biomarker responses [7-12].

Fractional exhaled nitric oxide (FeNO) is a non-invasive biomarker reflecting airway epithelial inducible nitric oxide synthase activity and IL-13-mediated eosinophilic airway inflammation [10, 11]. Standardized single-breath FeNO is

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mainly validated in cooperative older children, but offline tidal-breathing sampling and controlled tidal-breathing techniques allow FeNO assessment in selected younger children in specialized settings [2, 12]. Pediatric studies have shown that elevated FeNO is associated with an allergic wheeze, that FeNO may decrease after anti-inflammatory therapy, and that FeNO may help identify children more likely to benefit from inhaled corticosteroids [10-15]. Nevertheless, data comparing serial FeNO changes in children younger than three years treated with or without nebulized budesonide remain insufficient.

Alongside FeNO, peripheral blood eosinophils, total serum IgE, and type 2 cytokines such as IL-4, IL-5 and IL-13 provide complementary information on systemic allergic inflammation and anti-inflammatory treatment response [5, 16-18]. Combining FeNO with peripheral biomarkers may therefore characterize inflammatory control more comprehensively than any single marker [13-15].

In this context, this single-center retrospective cohort study evaluated children aged 6 to 36 months with allergic airway inflammation. The study aimed to determine whether routine use of nebulized budesonide in addition to standard care was associated with improved short-term clinical outcomes and safety, to describe FeNO changes over 28 days, and to explore whether FeNO and other type 2 inflammatory markers were associated with treatment response and three-month recurrence.

Materials and methods

Study design and setting

This was a single-center retrospective cohort study conducted in the Department of Pediatrics of a tertiary teaching hospital. Electronic medical records were reviewed for children aged 6 to 36 months diagnosed with allergic airway inflammation, defined clinically as recurrent wheezing with cough or dyspnea. Index treatment episodes dated from January 1, 2021 through February 28, 2025 were included, and follow-up records were extracted through June 30, 2025 to ensure completion of the 28-day treatment assessment and three-month recurrence evaluation for every analyzed record. The study protocol was reviewed and approved by the Research Ethics Committee of the Affiliated Hospital of Chengdu University. Because only de-identified retrospective clinical data were analyzed, the requirement for individual written informed consent was waived. All procedures conformed to the Declaration of Helsinki.

Study population

Inclusion criteria: Records were eligible if all of the following conditions were documented: age between 6 and 36 months; clinical diagnosis of allergic airway inflammation with recurrent wheezing, defined as at least two wheezing episodes in the preceding year, or persistent cough lasting more than one month; evidence supporting an allergic or type 2 inflammatory phenotype, including personal history of atopic dermatitis, food allergy or allergic rhinitis, parental history of asthma or atopy, peripheral blood eosinophils of at least 4%, absolute eosinophil count of at least 0.30×10^9/L or age-adjusted elevation of total serum IgE; complete FeNO measurements at baseline, day 7, day 14 and day 28; and available clinical follow-up for at least three months after the index treatment episode.

Exclusion criteria: Records were excluded when any of the following conditions were present: congenital airway or cardiac malformation; chronic lung disease such as cystic fibrosis, primary ciliary dyskinesia or bronchopulmonary dysplasia; congenital or acquired immunodeficiency; systemic immunotherapy within the preceding month; acute bacterial pneumonia requiring systemic antibiotic treatment directed at lower respiratory infection; systemic corticosteroid exposure within four weeks before the index evaluation; gestational age younger than 35 weeks or birth weight lower than 2000 g; or incomplete documentation of key clinical, laboratory, or follow-up outcomes. After eligibility criteria were applied, 548 children were included in the analysis. Group classification was based on routine medication administration records and outpatient prescription records rather than random assignment.

Children were classified into the budesonide group when scheduled nebulized budesonide was recorded within the index treatment episode and continued according to the treating physician's pathway. Children were classi-

fied into the control group when standard care was recorded without scheduled inhaled corticosteroid therapy during the index episode. Treatment selection reflected clinical judgment, symptom pattern, caregiver preference, and clinician assessment of allergic versus infection-related wheezing; therefore, non-random treatment allocation and confounding by indication were addressed analytically by baseline comparability assessment and multivariable adjustment for clinically relevant covariates.

Recorded treatment pathways

Budesonide group: For the budesonide group (n = 286), clinical records indicated use of nebulized budesonide suspension (Pulmicort Respules, 0.5 mg/2 mL) in addition to standard care. The usual recorded regimen consisted of 0.5 mg twice daily during the first 7 days, followed by 0.5 mg once daily through day 28 when symptoms were controlled and the treating physician maintained inhaled corticosteroid therapy. Standard care included age-appropriate hydration, nebulized salbutamol 2.5 mg and ipratropium bromide 0.25 mg by jet nebulizer four to six times per day for three to five days as clinically required, montelukast 4 mg orally at bedtime when prescribed, and oxygen supplementation when transcutaneous oxygen saturation was 92% or lower on room air. Nebulization was delivered through a silicone face mask connected to a jet nebulizer with driving oxygen flow of 6 to 8 L/min for approximately 10 minutes. Inpatient adherence was derived from nursing medication records, and outpatient adherence was derived from caregiver treatment diaries reviewed at follow-up visits.

Control group: Control group children (n = 262) received the same standard care pathway without scheduled nebulized budesonide or other scheduled inhaled corticosteroid therapy during the index treatment episode. The absence of scheduled inhaled corticosteroid therapy reflected documented clinical considerations, including milder or infection-predominant symptoms, caregiver concern about corticosteroid use, or clinician judgment that immediate inhaled corticosteroid maintenance was not required. Rescue inhaled or systemic corticosteroid use during clinical deterioration was retained as an outcome and did not change the original group classification.

Outcome definitions and measurements

FeNO measurement: FeNO values were extracted from routine measurements performed with a portable nitric oxide analyzer (Sunvou-CA2122, Wuxi, China) calibrated for tidal-breathing offline sampling in young children. Measurements followed the principles of American Thoracic Society/European Respiratory Society FeNO guidance for pediatric testing whenever feasible. FeNO was recorded at baseline, day 7 ± 1, day 14 ± 2 and day 28 ± 3. Children rested in a quiet room for at least 10 minutes before testing. Measurements were avoided within one hour after food intake and were postponed for 24 hours after acute upper respiratory infection symptoms when possible. Exhaled breath was collected with a tight-fitting mask and one-way valve into a Mylar bag and analyzed within 10 minutes. Each visit included duplicate measurements, and the mean was recorded when the two values differed by no more than 10%. The intraclass correlation coefficient for repeated measurements at the same visit was 0.93.

Clinical assessment: Clinical severity was assessed using the modified Pulmonary Index Score (mPIS), which incorporates wheezing, accessory muscle use, respiratory rate, oxygen saturation, and inspiratory/expiratory ratio. Time to symptom resolution was defined as the number of days from initiation of index treatment to disappearance of audible wheezing, resolution of dyspnea (defined as respiratory rate below the age-specific 95th percentile without accessory muscle use), and resolution of paroxysmal cough. Clinical efficacy was assessed within 14 days after treatment initiation, with primary evaluation based on symptom resolution, pulmonary wheezing, and change in mPIS from baseline. Markedly effective was defined as complete disappearance of wheezing and cough, disappearance of pulmonary wheezes, and mPIS ≤ 1 within 7 days. Effective was defined as obvious improvement in symptoms and signs, with a decrease in mPIS by ≥ 3 points from baseline within 14 days but without complete symptom resolution. Ineffective response was defined as no obvious improvement or worsening of symptoms/signs within 14 days, a decrease in mPIS by < 3 points, occurrence of acute exacerbation, or need for systemic corticosteroid rescue. Overall response was defined as the sum

of markedly effective and effective cases. Children who required systemic corticosteroid rescue were classified as ineffective for clinical efficacy analysis.

Laboratory values: Venous blood samples were obtained during routine care at baseline and day 28 ± 3. Complete blood count with differential was performed using a Sysmex XN-9000 hematology analyzer to obtain absolute eosinophil count and eosinophil percentage. Total serum IgE was measured using a Siemens Immulite 2000 chemiluminescent immunoassay, and serum IL-4, IL-5, and IL-13 were measured using enzyme-linked immunosorbent assay kits (Quantikine ELISA, R&D Systems). Three-month recurrence was defined as a new wheezing episode or persistent cough requiring medical evaluation within three months after the index treatment episode. Adverse events, including oral candidiasis, hoarseness or throat irritation, caregiver-reported growth concern, or any serious treatment-related event, were extracted chronologically from inpatient records, outpatient notes and follow-up documentation.

Statistical analysis

Statistical analyses were performed using SPSS version 26.0 (IBM Corp.) and GraphPad Prism version 9.0. Continuous variables were examined for normality by the Shapiro-Wilk test. Normally distributed data were presented as mean ± SD and were compared using Student's t-test, whereas non-normally distributed data were presented as median and interquartile range and were compared using the Mann-Whitney U test. Categorical variables are presented as number and percentage and were compared using the chi-square test or Fisher's exact test when expected cell counts were small. FeNO across baseline, day 7, day 14 and day 28 was analyzed using repeated-measures analysis of variance with time as the within-subject factor and treatment group as the between-subject factor. Mauchly's test was used to assess sphericity, and Greenhouse-Geisser correction was applied when sphericity was violated. Pairwise within-group comparisons across time points and between-group comparisons of change from baseline were adjusted using the Bonferroni method. Pearson or Spearman correlation was used according to data distribution to examine associations between day-28 FeNO and inflammatory markers. Multivariable logistic regression evaluated factors associated with day-7 overall response and three-month recurrence, with covariates selected before analysis on clinical grounds, including age, sex, baseline mPIS, baseline FeNO, atopy status, tobacco smoke exposure, and prior wheezing burden. The target sample consisted of all eligible records within the prespecified index-treatment window; the final sample of 548 records provided more than 90% power to detect an absolute between-group difference of 10% in overall response at a two-sided alpha level of 0.05. Complete-case analysis was used for key clinical and FeNO outcomes, and no last-observation-carried-forward imputation was performed. A two-tailed P value < 0.05 was considered significant.

Results

Patient enrollment and baseline characteristics

Among children aged 6 to 36 months with allergic airway inflammation screened during the index-treatment window, 612 records were assessed and 548 met the eligibility criteria for analysis: 286 in the nebulized budesonide group and 262 in the control group. Sixty-four records were excluded because exclusion criteria were present or key clinical, FeNO, or follow-up data were incomplete. The mean age was 18.4 ± 7.6 months, and 58.4% of children were male. Baseline characteristics were balanced between groups, including age, sex, body weight, gestational age, history of atopy, breastfeeding, tobacco smoke exposure, prior wheezing episodes, baseline mPIS, baseline FeNO, eosinophil count, and total IgE (all P > 0.05; **Table 1**).

Overall clinical efficacy

At day 7, the budesonide group had a higher overall response rate than the control group (92.7% vs. 80.9%; $\chi^2 = 16.71$, df = 1, P < 0.001). The absolute risk difference was 11.7% (95% CI, 6.1% to 17.4%), and the relative response ratio was 1.15 (95% CI, 1.07 to 1.22). Pearson's χ^2 test of the three-category clinical efficacy distribution showed a significant between-group difference ($\chi^2 = 30.77$, df = 2, P < 0.001;

Table 1. Baseline demographic and clinical characteristics of the study population

Variable	Budesonide group (n = 286)	Control group (n = 262)	Statistic	*P* value
Age (months), mean ± SD	18.6 ± 7.5	18.2 ± 7.7	t = 0.61	0.541
Male, n (%)	168 (58.7)	152 (58.0)	χ^2 = 0.03	0.864
Body weight (kg), mean ± SD	11.2 ± 2.4	11.0 ± 2.3	t = 0.99	0.323
Gestational age (weeks)	39.1 ± 1.3	39.0 ± 1.4	t = 0.86	0.392
Family history of atopy, n (%)	121 (42.3)	108 (41.2)	χ^2 = 0.07	0.793
Personal eczema history, n (%)	104 (36.4)	92 (35.1)	χ^2 = 0.10	0.755
Breastfed ≥ 6 months, n (%)	188 (65.7)	176 (67.2)	χ^2 = 0.13	0.715
Tobacco smoke exposure, n (%)	78 (27.3)	69 (26.3)	χ^2 = 0.06	0.802
Prior wheezing episodes, median (IQR)	3 (2-4)	3 (2-4)	Z = -0.42	0.677
Baseline mPIS, mean ± SD	8.2 ± 1.6	8.1 ± 1.7	t = 0.71	0.479
Baseline FeNO (ppb), mean ± SD	22.6 ± 6.4	22.4 ± 6.7	t = 0.36	0.722
Eosinophils ($\times 10^9$/L)	0.42 ± 0.18	0.41 ± 0.19	t = 0.63	0.527
Total IgE (IU/mL), median (IQR)	112 (62-198)	108 (60-192)	Z = -0.28	0.781

mPIS, modified Pulmonary Index Score; FeNO, fractional exhaled nitric oxide; IQR, interquartile range.

Table 2. Clinical response at day 7

Outcome	Budesonide group (n = 286)	Control group (n = 262)	Statistical test	*P* value
Clinical efficacy distribution	-	-	Pearson χ^2 = 30.77, df = 2	< 0.001
Markedly effective, n (%)	156 (54.5)	88 (33.6)	-	-
Effective, n (%)	109 (38.1)	124 (47.3)	-	-
Ineffective, n (%)	21 (7.3)	50 (19.1)	-	-
Overall response, n (%)	265 (92.7)	212 (80.9)	Pearson χ^2 = 16.71, df = 1	< 0.001
Required systemic CS rescue, n (%)	3 (1.0)	11 (4.2)	Fisher exact test	0.028

CS = Corticosteroids.

Table 2). Markedly effective response was more frequent in the budesonide group, whereas ineffective response was less frequent. No child required mechanical ventilation during the index episode. Rescue systemic corticosteroid use was less common in the budesonide group than in the control group (3/286, 1.0% vs. 11/262, 4.2%; Fisher exact test, P = 0.028).

Time to symptom resolution

The budesonide group had shorter mean time to wheeze resolution than the control group (3.2 ± 1.1 vs. 5.1 ± 1.6 days, P < 0.001; **Table 3**). Time to cough resolution, time to dyspnea resolution, duration of supplemental oxygen, and length of hospital stay among inpatients were also shorter in the budesonide group. The reduction in mPIS at day 7 was greater in the budesonide group than in the control group (-6.4 ± 1.5 vs. -4.5 ± 1.7 points, P < 0.001).

Dynamic changes in FeNO

Table 4 presents FeNO values at baseline, day 7, day 14, and day 28. Baseline FeNO did not differ between groups (22.6 ± 6.4 vs. 22.4 ± 6.7 ppb, P = 0.722). FeNO decreased over time in both groups, but the decline was significantly greater in the budesonide group. By day 7, FeNO decreased by 28.3% in the budesonide group and 11.6% in the control group. By day 14, the reductions were 43.4% and 23.7%, respectively, and by day 28 they were 56.6% and 35.3%, respectively. Mauchly's test indicated violation of sphericity for the time effect (W = 0.74, P < 0.001). Therefore, Greenhouse-Geisser correction was applied (epsilon = 0.78). The corrected repeated-measures model showed significant effects of time (F = 514.3, P < 0.001), group (F = 86.9, P < 0.001), and group-by-time interaction (F = 142.6, P < 0.001). Bonferroni-adjusted pairwise comparisons showed significant reduc-

Table 3. Time to symptom resolution and clinical improvement

Item (days, mean ± SD)	Budesonide group	Control group	t value	*P* value
Time to wheeze resolution	3.2 ± 1.1	5.1 ± 1.6	16.21	< 0.001
Time to cough resolution	5.6 ± 1.8	8.4 ± 2.3	15.91	< 0.001
Time to dyspnea resolution	2.4 ± 0.9	3.8 ± 1.2	15.49	< 0.001
Duration of supplemental O_2	1.6 ± 0.7	2.5 ± 1.0	12.32	< 0.001
Length of hospital stay (inpatients)	5.8 ± 1.7	7.6 ± 2.1	11.07	< 0.001
mPIS reduction at day 7 (points)	-6.4 ± 1.5	-4.5 ± 1.7	13.88	< 0.001

Table 4. Dynamic changes in FeNO during the 28-day observation period

Time point	Budesonide group (n = 286)	Change from baseline	Control group (n = 262)	Change from baseline	*P* value for Δ
Baseline	22.6 ± 6.4	-	22.4 ± 6.7	-	0.722
Day 7	16.2 ± 5.2	-6.4 ± 3.8 (-28.3%)	19.8 ± 6.1	-2.6 ± 3.5 (-11.6%)	< 0.001
Day 14	12.8 ± 4.1	-9.8 ± 4.2 (-43.4%)	17.1 ± 5.5	-5.3 ± 3.9 (-23.7%)	< 0.001
Day 28	9.8 ± 3.2	-12.8 ± 4.4 (-56.6%)	14.5 ± 4.6	-7.9 ± 4.1 (-35.3%)	< 0.001

Values are presented as mean ± SD. FeNO, fractional exhaled nitric oxide; BUD, budesonide. *P* values compare FeNO change from baseline between groups at each time point. Repeated-measures ANOVA used Greenhouse-Geisser correction because sphericity was violated (Mauchly W = 0.74, P < 0.001; epsilon = 0.78); treatment-by-time interaction, F = 142.6, P < 0.001.

Table 5. Changes from baseline in peripheral inflammatory biomarkers as of day 28

Marker	BUD baseline	BUD day 28	Control baseline	Control day 28	P (Δ)
Eosinophils ($\times 10^9$/L)	0.42 ± 0.18	0.21 ± 0.10	0.41 ± 0.19	0.32 ± 0.14	< 0.001
Eosinophil percentage (%)	5.6 ± 2.1	2.8 ± 1.2	5.5 ± 2.2	4.1 ± 1.6	< 0.001
Total IgE (IU/mL)	112 (62-198)	78 (44-142)	108 (60-192)	98 (54-172)	< 0.001
IL-4 (pg/mL)	9.4 ± 2.8	5.1 ± 1.7	9.3 ± 2.7	7.3 ± 2.2	< 0.001
IL-5 (pg/mL)	11.2 ± 3.6	5.8 ± 2.0	11.0 ± 3.4	8.4 ± 2.7	< 0.001
IL-13 (pg/mL)	13.5 ± 4.1	6.6 ± 2.3	13.2 ± 4.2	9.8 ± 3.1	< 0.001

Total IgE is presented in median (IQR), and all other items as mean ± SD. P (Δ) indicates the comparison of changes from baseline between groups.

tions from baseline at day 7, day 14, and day 28 within each group, with larger changes in the budesonide group at every follow-up time point (all adjusted P < 0.001).

Changes of inflammatory biomarkers in peripheral blood

Both groups showed decreases in peripheral inflammatory biomarkers from baseline to day 28, but the reductions were greater in the budesonide group. Eosinophil percentage decreased from 5.6% to 2.8% in the budesonide group and from 5.5% to 4.1% in the control group. Total IgE, IL-4, IL-5, and IL-13 followed the same pattern (**Table 5**). Day-28 FeNO correlated moderately with eosinophil count (r = 0.61, P < 0.001), IL-5 (r = 0.58, P < 0.001) and IL-13 (r = 0.54, P < 0.001), suggesting that FeNO reflected type 2 inflammatory activity in this cohort.

Subgroup analysis by atopy status and age

Table 6 presents subgroup analyses by atopy status, age group, and sex. The FeNO reduction associated with budesonide was greatest among atopy-positive children (P for interaction = 0.018). Atopy-positive children also had the lowest recurrence proportion in the budesonide group. FeNO reductions were directionally consistent across age strata and sex strata, and no significant interaction was observed for age group or sex (P for interaction = 0.842 and 0.904, respectively).

Table 6. Subgroup analysis of FeNO reduction (ppb) at day 28 and 3-month recurrence

Subgroup	n (BUD/Ctrl)	Δ FeNO BUD	Δ FeNO Control	Recurrence BUD (%)	Recurrence Ctrl (%)
Atopy-positive	164/142	-14.6 ± 4.4	-9.1 ± 3.7	11.0	30.3
Atopy-negative	122/120	-10.2 ± 4.0	-6.5 ± 3.6	19.7	24.2
Age 6-12 months	92/86	-12.2 ± 4.5	-7.6 ± 3.9	16.3	30.2
Age 13-24 months	118/105	-13.1 ± 4.1	-8.0 ± 4.1	13.6	26.7
Age 25-36 months	76/71	-13.0 ± 4.0	-8.1 ± 3.8	14.5	25.4
Boys	168/152	-12.7 ± 4.2	-7.8 ± 3.9	14.9	28.3
Girls	118/110	-13.0 ± 4.3	-8.1 ± 4.1	14.4	26.4

BUD, budesonide; Ctrl, control. P for interaction was 0.018 for atopy status, 0.842 for age group and 0.904 for sex.

Table 7. Three-month recurrence and adverse events

Outcome, n (%)	Budesonide group	Control group	Statistical test	*P* value
3-month recurrence	42 (14.7)	72 (27.5)	$\chi^2 = 13.59$	< 0.001
Unscheduled ED visit	31 (10.8)	58 (22.1)	$\chi^2 = 12.83$	< 0.001
Need for repeat ICS course or systemic corticosteroids	38 (13.3)	66 (25.2)	$\chi^2 = 12.60$	< 0.001
Oral candidiasis	7 (2.4)	1 (0.4)	Fisher exact	0.070
Hoarseness/throat irritation	5 (1.7)	2 (0.8)	Fisher exact	0.453
Caregiver-reported growth concern	0 (0.0)	0 (0.0)	-	1.000
Serious adverse event	0 (0.0)	0 (0.0)	-	1.000

ED, emergency department; ICS, inhaled corticosteroid.

Recurrence within three months and adverse events

Three-month recurrence requiring medical attention occurred in 42 children in the budesonide group and 72 children in the control group (14.7% vs. 27.5%; $\chi^2 = 13.59$, P < 0.001). This corresponded to a relative risk of 0.53 (95% CI, 0.38 to 0.75) and a relative reduction of 46.6% in the budesonide group. Compared to the control group, the budesonide group also had fewer unscheduled emergency department visits and fewer repeat inhaled corticosteroid courses or systemic corticosteroid treatments. Oral candidiasis occurred in 7 children (2.4%) in the budesonide group and 1 child (0.4%) in the control group (Fisher's exact P = 0.070). Hoarseness or throat irritation was uncommon and did not differ significantly between groups. No caregiver-reported growth concern, adrenal suppression, or serious treatment-related adverse event was recorded during the 28-day treatment period or three-month follow-up (**Table 7**).

Predictors of treatment response and recurrence

Multivariable logistic regression evaluated variables associated with clinical response and three-month recurrence (**Table 8**). Higher baseline FeNO (OR 1.36, 95% CI 1.18-1.57, P < 0.001, per 5-ppb increase), atopy-positive status (OR 1.78, 95% CI 1.21-2.62, P = 0.003), and budesonide treatment (OR 3.02, 95% CI 1.94-4.71, P < 0.001) were associated with day-7 clinical response. Higher residual FeNO at day 28 (OR 1.74, 95% CI 1.45-2.10, P < 0.001, per 5-ppb increase), passive smoke exposure (OR 1.96, 95% CI 1.27-3.03, P = 0.002), and at least three previous wheezing episodes (OR 1.83, 95% CI 1.20-2.79, P = 0.005) were associated with three-month recurrence. Receiver operating characteristic analysis showed that a residual day-28 FeNO threshold of 12 ppb was associated with three-month recurrence with a 71.9% sensitivity and 76.4% specificity (AUC 0.81, 95% CI 0.77-0.85).

Discussion

In this retrospective cohort of 548 children aged 6 to 36 months with allergic airway inflammation, routine use of nebulized budesonide in addition to standard care was associated with a higher overall response rate, faster resolution of wheezing, cough and dyspnea, greater reductions in FeNO and peripheral type 2 inflammatory biomarkers, and lower three-

Table 8. Multivariable logistic regression for clinical response and three-month recurrence

Variable	Outcome	OR (95% CI)	Wald χ^2	*P* value
Baseline FeNO (per 5-ppb ↑)	Response	1.36 (1.18-1.57)	17.62	< 0.001
Atopy-positive	Response	1.78 (1.21-2.62)	8.63	0.003
Budesonide treatment	Response	3.02 (1.94-4.71)	23.57	< 0.001
Day-28 FeNO (per 5-ppb ↑)	Recurrence	1.74 (1.45-2.10)	35.41	< 0.001
Tobacco-smoke exposure	Recurrence	1.96 (1.27-3.03)	9.18	0.002
≥ 3 prior wheezing episodes	Recurrence	1.83 (1.20-2.79)	7.86	0.005
Budesonide treatment	Recurrence	0.45 (0.30-0.69)	13.65	< 0.001

OR, odds ratio; CI, confidence interval; FeNO, fractional exhaled nitric oxide. Models were adjusted for age, sex, baseline mPIS, baseline FeNO, atopy status, tobacco smoke exposure and prior wheezing burden as appropriate for the analyzed outcome.

month recurrence. This association was observed across age strata and appeared strongest in atopy-positive children. These findings suggest that serial FeNO may serve as a useful pharmacodynamic readout of anti-inflammatory response in carefully selected young children when tidal-breathing measurement is technically feasible.

Nebulized budesonide has been evaluated in pediatric wheezing and asthma populations and is supported by clinical experience and by guideline-based practice for steroid-responsive wheezing phenotypes [1, 6, 7]. Li and colleagues reported that different budesonide nebulization strategies improved Test for Respiratory and Asthma Control in Kids scores in Chinese preschool children with recurrent wheezing [7]. Other pediatric studies have also linked budesonide-containing regimens with shorter symptom duration and improved inflammatory profiles [8, 9]. The present cohort extends these observations to younger children by integrating clinical outcomes with serial FeNO and peripheral type 2 biomarker changes.

The serial FeNO pattern deserves attention. Although standardized single-breath FeNO is usually more reliable in cooperative older children, controlled tidal-breathing and offline sampling can yield clinically interpretable values in specialized pediatric settings [2, 10-12]. In this study, FeNO decreased progressively from day 7 to day 28, and the decline was greater in the budesonide group than in the control group. This pattern supports the interpretation that FeNO can reflect anti-inflammatory response over a short treatment interval, but it should be used as an adjunct to clinical assessment rather than as a stand-alone decision tool in infants and toddlers.

The correlations between day-28 FeNO and eosinophils, IL-5, and IL-13 support the biological plausibility that FeNO reflected type 2 airway inflammation rather than nonspecific airway irritation. This is consistent with evidence that type 2-high childhood asthma is associated with a more persistent and severe phenotype [5], and with reviews emphasizing early endotype assessment in recurrent preschool wheeze [16]. Early-life immune environment may also influence later asthma development, as shown by longitudinal data linking mucosal cytokine profiles during viral infections to asthma outcomes [18]. Therefore, a decline in FeNO and type 2 cytokines after budesonide use may indicate suppression of an inflammatory pathway relevant to recurrent wheezing.

The subgroup analysis suggested that children with atopy-positive status had a larger FeNO reduction and lower recurrence after budesonide-containing care than atopy-negative children. This observation is consistent with phenotype-oriented management, in which atopic or multiple-trigger wheezing phenotypes were more likely to benefit from inhaled corticosteroids than transient viral wheeze [1, 3, 4, 17, 19]. Serial FeNO combined with clinical risk indices such as the modified Asthma Predictive Index may help identify children most likely to benefit from anti-inflammatory therapy, although prospective validation is required.

The lower three-month recurrence in the budesonide group may reflect better short-term suppression of residual eosinophilic airway inflammation after symptom improvement. Residual FeNO at day 28 was associated with

recurrence, and a threshold of 12 ppb showed moderate discrimination in this cohort. These findings support a translational monitoring pathway in which children with persistent symptoms or day-28 FeNO of at least 12 ppb may receive closer follow-up, adherence review, environmental risk assessment, and reassessment of anti-inflammatory treatment, whereas children with symptom resolution and low residual FeNO may receive routine follow-up. This FeNO-informed pathway should be interpreted as a risk-stratification framework rather than a validated discontinuation rule.

Guidelines and pediatric studies generally support an acceptable safety profile for nebulized budesonide at clinically used doses [1, 6-9]. In the present cohort, oral candidiasis and hoarseness were uncommon, and no serious treatment-related adverse event, adrenal suppression, or caregiver-reported growth concern was recorded during the observation period. The retrospective design and short follow-up limit definitive safety conclusions, but the available data are consistent with favorable short-term tolerability when inhalation technique and oral care are appropriately managed.

Several limitations should be considered. First, the study was retrospective and single center, and treatment allocation reflected clinical decisions rather than randomization; therefore, residual confounding, selection bias and confounding by indication cannot be excluded despite baseline comparisons and multivariable adjustment. Second, FeNO was measured using tidal-breathing offline sampling rather than standardized single-breath testing, so environmental nitric oxide, mask seal, and breathing-pattern variability may have influenced values; duplicate measurements and standardized testing conditions were used to reduce this variability. Third, follow-up lasted three months, which did not determine school-age asthma incidence or long-term lung-function trajectories. Fourth, viral etiology was not systematically documented, and virus-specific wheezing phenotypes may differ in corticosteroid responsiveness [20]. Multicenter prospective studies with longer follow-up, standardized viral testing and lung-function measures are needed to validate the role of FeNO-guided budesonide management in early life.

Conclusion

Nebulized budesonide in addition to standard care was associated with faster symptom resolution, higher clinical response, greater reduction of FeNO and peripheral type 2 inflammatory biomarkers, lower three-month recurrence, and acceptable short-term safety in children aged 6 to 36 months with allergic airway inflammation. Residual day-28 FeNO was associated with recurrence, and a 12-ppb threshold may help identify children requiring closer follow-up in this cohort. These findings support further evaluation of FeNO-assisted individualized monitoring for young children with allergic airway inflammation, although prospective validation is needed before FeNO thresholds can be used as definitive treatment discontinuation rules.

Disclosure of conflict of interest

None.

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