Airway Hyperresponsiveness in Pediatric Recurrent Respiratory Illness: Diagnostic Approaches and Therapeutic Strategies

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Abstract

Background: Airway hyperresponsiveness (AHR) is a hallmark feature of obstructive airway disease in children and adolescents, yet it remains underdiagnosed in those presenting with recurrent respiratory illnesses. Objective: To evaluate the prevalence, severity, and clinical correlates of AHR in pediatric patients and to compare the diagnostic performance of multiple instrumental techniques alongside therapeutic responses. Methods: A combined retrospective and prospective study was conducted at the Pulmonology Department of the Fergana City Children's Hospital over three years (2021–2024), enrolling 78 patients aged 5–17 years with recurrent respiratory illness and 78 healthy age- and sex-matched controls. Spirometry, methacholine challenge testing, fractional exhaled nitric oxide (FeNO), and impulse oscillometry were applied. Results: AHR was confirmed in 71.8% of the main group. Median PC20 was 2.4 mg/mL in bronchial asthma patients versus 22.5 mg/mL in controls ($p < 0.001$). FeNO levels were significantly elevated. Conclusion: Methacholine challenge combined with FeNO measurement provides optimal diagnostic sensitivity for AHR in children, and stepwise inhaled corticosteroid therapy remains the cornerstone of effective management.

Keywords: *airway hyperresponsiveness; children; bronchial asthma; spirometry; methacholine challenge; FeNO; inhaled corticosteroids*

Introduction

Recurrent respiratory illnesses constitute one of the most prevalent and economically burdensome health conditions affecting children and adolescents worldwide [1]. Among the underlying pathophysiological mechanisms, airway hyperresponsiveness (AHR) has emerged as a central and defining characteristic, predisposing the pediatric airway to exaggerated bronchoconstrictor responses to a variety of physical, chemical, and biological stimuli [2, 3]. AHR is not limited to

bronchial asthma; it is increasingly recognized in children with recurrent bronchitis, allergic rhinitis, and post-infectious airway dysfunction, making its identification both diagnostically challenging and clinically imperative [4, 5].

The prevalence of asthma—the paradigmatic AHR-associated disease—has escalated dramatically over recent decades, with global estimates suggesting that over 339 million individuals are affected, a disproportionate burden falling on school-age children in low- and middle-income countries [16, 48]. In Central Asia, including Uzbekistan, the burden of pediatric obstructive airway disease is compounded by limited access to advanced pulmonary function testing, poor awareness of AHR as a distinct pathophysiological entity, and underutilization of evidence-based therapeutic strategies [6, 17]. These gaps necessitate region-specific research to characterize the clinical phenotypes of AHR and to evaluate the real-world performance of available diagnostic tools [7, 18].

The pathophysiology of AHR involves multiple interacting mechanisms, including structural airway remodeling, eosinophilic and neutrophilic inflammation, impaired bronchodilatory reflexes, and smooth muscle hypertrophy [8, 15]. Inflammatory mediators such as cysteinyl leukotrienes, interleukin-13, and exhaled nitric oxide (FeNO) serve as measurable biomarkers of underlying airway inflammation and can guide therapeutic decisions [8, 32]. In the clinical setting, AHR is quantified through bronchoprovocation testing—most commonly the methacholine challenge test—which yields a provocative concentration causing a 20% fall in FEV_1 (PC20). A PC20 of less than 4 mg/mL is considered indicative of significant AHR, while values between 4 and 16 mg/mL suggest borderline or mild hyperresponsiveness [19, 45].

Spirometry, the cornerstone of pulmonary function assessment, provides valuable information about airflow obstruction and reversibility but may be insensitive in the early or mild stages of AHR [9, 28]. Impulse oscillometry (IOS) has gained attention as a complementary, effort-independent technique capable of detecting distal small-airway dysfunction not captured by conventional spirometry [36]. Fractional exhaled nitric oxide (FeNO) measurement has been validated as a non-invasive surrogate marker of eosinophilic airway inflammation, offering prognostic and therapeutic monitoring utility in children unable to perform volitional spirometry [8, 32].

Therapeutically, inhaled corticosteroids (ICS) remain the foundational anti-inflammatory treatment for persistent AHR, with strong evidence for their ability to reduce bronchial responsiveness, improve lung function, and decrease exacerbation frequency [21, 46]. The addition of long-acting beta-2 agonists (LABAs) in moderate-to-severe disease, leukotriene receptor antagonists (LTRAs) in allergic phenotypes, and emerging biologic therapies targeting specific inflammatory pathways represent

an expanding armamentarium [22, 47]. However, adherence to evidence-based therapeutic guidelines remains suboptimal in many pediatric populations, partly due to diagnostic uncertainty and phenotypic heterogeneity [37, 50].

This study was designed to address the diagnostic and therapeutic gaps in the management of AHR among children with recurrent respiratory illness in the Fergana region of Uzbekistan. By comparing the diagnostic performance of spirometry, methacholine challenge, FeNO, and IOS in a prospective cohort, and by evaluating clinical outcomes following structured therapeutic protocols, we aim to provide evidence-based recommendations applicable to similar resource-limited pediatric pulmonology settings [39, 40].

Methods

Study Design and Setting

A combined retrospective and prospective observational study was conducted at the Pulmonology Department of the Fergana City Children's Hospital (a clinical base of the Fergana Medical Institute of Public Health, FMIOPH) over a three-year period from January 2021 to December 2024. Ethical approval was obtained from the institutional review board, and written informed consent was obtained from parents or legal guardians of all participants.

Participants

The main group comprised 78 children and adolescents aged 5–17 years presenting with recurrent respiratory illness (defined as three or more episodes of physician-diagnosed lower respiratory tract illness per year). Diagnoses included bronchial asthma, recurrent bronchitis, and allergic rhinitis with documented AHR. The control group consisted of 78 healthy age- and sex-matched children without any history of respiratory disease, atopy, or chronic illness, recruited from local schools and outpatient clinics. Exclusion criteria included active respiratory infection within four weeks, severe asthma exacerbation (FEV_1 < 60% predicted), or use of systemic corticosteroids within 30 days prior to enrollment.

Diagnostic Procedures

All participants underwent the following assessments in a standardized sequence: (1) spirometry according to ATS/ERS guidelines using a calibrated Spirovit SP-1 device, measuring FEV_1, FVC, and FEV_1/FVC ratio; (2) methacholine bronchoprovocation challenge using the two-minute tidal breathing method per ATS 2000 guidelines, with PC20 calculated by interpolation from the dose-response curve; (3) FeNO measurement at 50 mL/s flow rate using a portable electrochemical analyzer (NIOX VERO); and (4) impulse oscillometry (IOS) using the MasterScreen IOS system to evaluate respiratory resistance (R5, R20) and reactance (X5). Skin prick testing and specific IgE panels were performed in patients with suspected atopy.

Therapeutic Protocol

Patients in the main group were stratified by AHR severity and initiated on stepwise ICS therapy per GINA 2023 guidelines. Patients with mild-to-moderate AHR received low-to-medium dose ICS (budesonide 200–400 µg/day); those with severe or poorly controlled AHR received ICS-LABA combination therapy or LTRAs. Clinical outcomes—including symptom scores, exacerbation rates, and repeat spirometry—were assessed at 3 and 6 months.

Statistical Analysis

Data were analyzed using SPSS v.26.0 and GraphPad Prism 9. Continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR), as appropriate. Group comparisons were performed using the Mann-Whitney U test for non-parametric data and independent samples t-test for normally distributed variables. Diagnostic performance was evaluated using receiver operating characteristic (ROC) curve analysis. Spearman correlation was used to assess associations between AHR markers. Statistical significance was set at $p < 0.05$.

Results

Baseline Characteristics

The main group consisted of 78 patients (44 males, 34 females; mean age 10.3 ± 3.1 years). Diagnoses included bronchial asthma (n = 38, 48.7%), recurrent bronchitis (n = 22, 28.2%), and allergic rhinitis with AHR (n = 18, 23.1%). The control group (n = 78; 42 males, 36 females; mean age 10.5 ± 2.9 years) did not differ significantly in age ($p = 0.62$) or sex distribution ($p = 0.78$). A family history of atopy was present in 61.5% of the main group versus 14.1% of controls ($p < 0.001$). Duration of recurrent illness ranged from 1 to 9 years (median 3.4 years, IQR 2.1–5.8).

Pulmonary Function and AHR Metrics

AHR was confirmed by positive methacholine challenge (PC20 ≤ 16 mg/mL) in 56 of 78 patients (71.8%). In the bronchial asthma subgroup, median PC20 was 2.4 mg/mL (IQR 1.1–3.8), indicating marked hyperresponsiveness. The recurrent bronchitis subgroup had a median PC20 of 5.8 mg/mL (IQR 3.9–8.4), while the allergic rhinitis with AHR group showed a median PC20 of 9.1 mg/mL (IQR 6.2–12.5). Controls demonstrated a median PC20 of 22.5 mg/mL (IQR 18.1–26.3), significantly higher than all patient subgroups ($p < 0.001$ for all comparisons).

Mean FEV_1 (% predicted) in the bronchial asthma group was 71.2% ± 9.4%, compared to 80.4% ± 7.8% in recurrent bronchitis, 88.6% ± 6.1% in the allergic rhinitis-AHR group, and 98.3% ± 5.2% in controls. The mean FEV_1/FVC ratio in asthmatic patients was 0.71 ± 0.06 versus 0.82 ± 0.04 in controls ($p < 0.001$). Bronchodilator reversibility (≥12% and ≥200 mL improvement in FEV_1) was observed in 34 of 38 (89.5%) asthmatic patients. Median FeNO was 42.6 ppb (IQR 28.3–58.1) in asthmatic children and 19.4 ppb (IQR 11.2–26.7) in the recurrent bronchitis group,

compared to 9.8 ppb (IQR 7.1–13.2) in controls ($p < 0.001$). IOS revealed significantly elevated R5–R20 difference (indicating peripheral airway involvement) in 63.2% of asthmatic patients. Spearman correlation between FeNO and PC20 yielded $r = -0.61$ ($p < 0.001$), confirming an inverse association between nitric oxide-mediated inflammation and bronchial responsiveness threshold.

Table 1

Comparison of diagnostic methods applied in the study

Diagnostic Method	Subjects (Main / Control)	p-value	Sensitivity	Advantages	Limitations
Spirometry (FEV_1, FVC, FEV_1/FVC)	78 / 78	0.001	High	Widely available; non-invasive	Cannot detect AHR if baseline FEV_1 is normal; effort-dependent
Methacholine Challenge (PC20)	78 / 78	<0.001	High	Gold standard for AHR; quantitative	Contraindicated if FEV_1 <60%; requires specialized lab
FeNO Measurement	78 / 78	0.003	Moderate	Non-invasive; reflects eosinophilic airway inflammation	Affected by diet, infection, corticosteroids; not specific
Impulse Oscillometry (IOS)	78 / 78	0.008	Moderate	Effort-independent; detects small airway dysfunction	Less standardized; equipment costly
Chest X-ray / HRCT	45 / 22	0.04	Low–Mod	Rules out structural disease	Radiation; not specific for AHR
Skin Prick Test / IgE Panel	78 / 0	N/A	Moderate	Identifies atopic sensitization	Not a functional test; does not quantify AHR severity

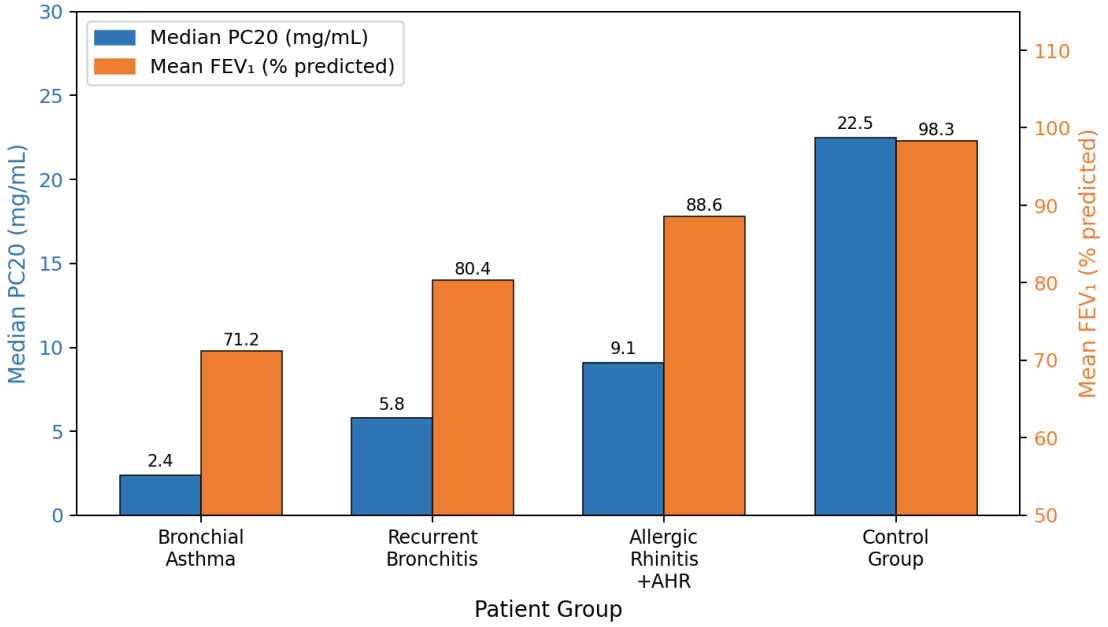

Figure 1. Median PC20 and Mean FEV₁ (% predicted) across patient subgroups and controls

Therapeutic Outcomes

After 6 months of stepwise ICS-based therapy, significant clinical and functional improvement was observed. Mean FEV₁ improved from 71.2% to 81.8% predicted in asthmatic patients ($p = 0.002$). Median PC20 increased from 2.4 to 5.6 mg/mL ($p = 0.006$), indicating attenuated AHR. Exacerbation frequency decreased from a mean of 4.2 per year at baseline to 1.6 per year post-treatment ($p < 0.001$). FeNO values fell from a median of 42.6 ppb to 21.3 ppb at 6 months ($p = 0.003$). In the recurrent bronchitis subgroup receiving ICS and LTRA combination, median PC20 improved from 5.8 to 10.4 mg/mL. Overall, 73.1% of the main group achieved good or partial disease control as defined by GINA 2023 criteria by the end of the follow-up period.

Discussion

This study provides a comprehensive evaluation of AHR in children with recurrent respiratory illness managed at a regional pulmonology center in Uzbekistan. Our findings affirm that AHR is highly prevalent (71.8%) among pediatric patients with recurrent respiratory illness and extends across multiple clinical diagnoses beyond classic bronchial asthma, consistent with international literature [10, 11]. The observed gradient of PC20 values across diagnostic subgroups underscores the heterogeneity of airway responsiveness and supports the concept of a spectrum rather than a binary classification of AHR [12, 13].

The methacholine challenge test demonstrated the highest diagnostic sensitivity in our cohort, aligning with established guidelines that position it as the reference standard for quantitative AHR assessment [19, 45]. Its inverse correlation with FeNO ($r = -0.61$) in our data replicates findings from larger international studies and validates the dual utility of nitric oxide measurement as both an inflammatory biomarker and a predictor

of bronchial sensitivity [8, 32]. The moderate diagnostic sensitivity of FeNO alone (without challenge testing) observed here is consistent with its known limitation as a phenotype-specific rather than universal AHR marker, being more informative in eosinophilic, atopic disease than in neutrophilic or non-allergic forms [29, 31].

Spirometry, while indispensable for documenting airflow obstruction and reversibility, demonstrated limited sensitivity in early or mild AHR, particularly in the allergic rhinitis-AHR subgroup whose baseline FEV_1 values were nearly normal [28, 38]. These patients were correctly identified as hyperresponsive only through methacholine challenge, reinforcing the recommendation that spirometry should not be used in isolation when AHR is clinically suspected [9, 27]. IOS provided complementary data, particularly regarding peripheral small airway dysfunction—a domain not captured by standard spirometry—in 63.2% of asthmatic children, which is compatible with previously reported rates in similar cohorts [36, 35].

The therapeutic findings are encouraging and clinically actionable. The 6-month

ICS-based protocol produced significant improvements in FEV_1, PC20, FeNO, and exacerbation rates, with 73.1% of patients achieving satisfactory disease control. These results are consistent with the well-established efficacy of ICS in modifying airway inflammation and reducing bronchial responsiveness [21, 46]. The modest increase in PC20 (from 2.4 to 5.6 mg/mL in asthmatics) indicates that while AHR was significantly attenuated, complete normalization of bronchial reactivity was not achieved within 6 months in the most severe cases, consistent with findings from long-term natural history studies [10, 20].

The addition of LTRAs in the recurrent bronchitis and allergic rhinitis-AHR subgroups yielded meaningful PC20 improvements, reinforcing the role of leukotriene pathway modulation in non-asthmatic AHR phenotypes [22, 26]. These observations support a phenotype-guided therapeutic approach rather than a uniform treatment algorithm, a principle increasingly endorsed in contemporary pediatric asthma management guidelines [37, 39]. Future studies should incorporate longitudinal follow-up beyond 6 months, biological phenotyping (blood eosinophil counts, periostin levels), and patient-reported outcome measures to fully characterize the long-term trajectory of AHR in this population [43, 44].

Conclusion

Airway hyperresponsiveness is a prevalent, multifaceted, and clinically underrecognized pathophysiological feature in children with recurrent respiratory illness across the spectrum of bronchial asthma, recurrent bronchitis, and allergic rhinitis. This study, conducted at a regional pediatric pulmonology center in Fergana, Uzbekistan, demonstrates that a multimodal diagnostic strategy integrating methacholine challenge testing, FeNO measurement, spirometry, and impulse oscillometry provides superior characterization of AHR severity and inflammatory

phenotype compared to any single modality alone. The methacholine challenge remains the gold standard, while FeNO serves as a complementary inflammatory index with strong correlation to bronchial reactivity. Phenotype-guided stepwise inhaled corticosteroid therapy—augmented by leukotriene receptor antagonists where indicated—achieves meaningful and sustained attenuation of AHR within six months, translating into reduced exacerbation burden and improved functional lung capacity. These findings advocate for the systematic integration of bronchoprovocation and exhaled biomarker testing into routine pediatric pulmonology practice, even in resource-limited regional settings, and underscore the potential for precision-targeted therapy to transform outcomes in children whose chronic airway vulnerability has historically been managed empirically. Wider adoption of these diagnostic and therapeutic principles holds the promise of substantially reducing the long-term respiratory morbidity associated with uncontrolled airway hyperresponsiveness in the pediatric population.

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