

Considerations for the Child with Nonatopic Asthma

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Asthma guidelines provide clinicians with evidence-based management strategies for this chronic condition. The preferred therapy for patient with persistent asthma is inhaled corticosteroids. However, ~40% of the patients with persistent asthma continue to present with symptoms while treated according to the guidelines. Multiple factors are being explored to explain the variability in response to inhaled corticosteroids including asthma phenotype and genetic predisposition among others. The nonatopic asthma phenotype has been described in the literature. These patients tend to have milder symptoms of asthma and typically outgrow their asthma by adolescence. They present with chronic asthma symptoms in the absence of a positive allergy test, either skin prick test or specific immunoglobulin E blood test. Although patients with nonatopic asthma share many characteristics with patients with atopic asthma, there are several studies that suggest a different inflammatory pathway may be involved in their pathophysiology. Therefore, it is possible that children with nonatopic asthma could respond differently to inhaled corticosteroids compared with those with atopic asthma. Currently there is a variable definition of this phenotype. Furthermore, there is a paucity of therapeutic trial directed toward the patients with nonatopic asthma specifically. Future research should be guided toward identifying the inflammatory pathways in nonatopic asthma and potential phenotype-guided therapies.

Keywords: nonatopic asthma, skin allergy test, specific IgE, asthma phenotype

Introduction

ASTHMA IS ONE OF THE MOST common chronic diseases affecting the pediatric population. According to the Center for Disease Control (CDC), >25 million Americans have asthma. This accounts for ~7.7% of adults and 8.4% of children. Asthma prevalence has been increasing since the early 1980s in all ages, gender, and racial groups as reported from the CDC.* Although there are established guidelines for the management of asthma (National Asthma Education and Prevention Program and the Global Initiative for Asthma), 40% of the patients continue to present with symptoms when treated according to these guidelines.^{1,2} These guidelines recommend inhaled corticosteroids in all patients with persistent asthma of all ages and phenotypic characteristics. Multiple factors are being explored to explain the variability in response to inhaled corticosteroids, which include asthma phenotype, genetic predisposition, genetic and environmental interaction, pregnancy risk factors, allergy sensitization, race, gender, and socioeconomic status.

Recognizing the different asthma phenotypes could aid in determining the prognosis of asthma and guiding treatment strategies.³ Different researchers have defined phenotypes

on clusters based upon clinical features and patterns of asthma development. For example, in the 1980s, the Tucson Children's Respiratory Study described specific groups of children with asthma without evidence of atopic disease.^{4,5} It is possible that children with nonatopic asthma could respond poorly to inhaled corticosteroids compared with those with atopic asthma. Little research has been conducted to evaluate treatment response to inhaled corticosteroids in the child with nonatopic disease.

In this article, we review the different definitions or parameters used to describe and investigate the nonatopic asthma group. These include the clinical presentation, cellular components of airway inflammation, and pathologic findings. In addition, we detail some of the challenges that studying this group represents, which could, in part, explain the paucity of therapeutic studies to guide therapy in this phenotype. Lastly, we discuss some of the therapeutic alternatives that have been investigated in this phenotype.

Early description of children with different wheeze phenotypes

Tucson Children's Respiratory Study. This long-term longitudinal study evaluated how potential risk factors in the first 3 years of life could influence the development of chronic respiratory diseases, especially asthma in later childhood

*www.cdc.gov/asthma/most_recent_national_asthma_data.htm

and young adult life. They enrolled a large number ($N=1,246$) of infants at or soon after birth. They collected extensive data for 20 years including but not limited to (1) baseline prelower respiratory tract infection (LRI's) data, including lung function and assessment of various immunologic and allergic parameters; (2) data relating to a large number of risk factors (infectious, physiologic, genetic, familial, psychosocial, immunologic, allergic, and environmental); (3) microbiologic, virologic, and serologic data relating to the acute LRIs; and had a long follow-up period with excellent retention of enrolled subjects/families.^{4,5} Leveraging these data, they stratified patients into 4 groups according to their history of wheezing: (1) children who never had wheezing, (2) transient early wheeze (patients with at least 1 LRI with wheezes but no wheezes at 6 years of age), (3) late-onset wheeze (those who had no lower respiratory tract illness with wheezing during the first 3 years of life but who had wheezing at 6 years of age), and (4) persistent wheezes (patients with LRIs previous to 3 years of age and persistent wheezes at 6 year of age). The authors describe that after adjustment for skin test reactivity with multiple regression analysis, the children with persistent wheezing had significantly higher levels of immunoglobulin E (IgE) at the age of 6 years than the children with late-onset wheezing ($P=0.03$).⁵

This cohort by Martinez et al. stratified the different wheezes phenotypes.⁵ During this study, the authors identified a subset of patients who presented with persistent wheezes independent of allergic sensitization. This group was further described in the article by Stein and Martinez as the nonatopic wheezes.⁶ This cohort serves as the basis of recognition and further investigation guided toward this asthma phenotype.

Nonatopic wheezes. Utilizing data from several epidemiologic studies including the Tucson Children's Respiratory Study (TCRS), authors Stein and Martinez describe the nonatopic wheezing group.⁶ This cohort began with normal lung function, but by 11 years of age had slightly lower lung function and airway reactivity later.⁶ The authors concluded that a significant number of children who wheeze during the first decade of life do so in association with viral respiratory agents, especially respiratory syncytial virus, independently of allergic sensitization.⁶

Definition of nonatopic asthma patients

Variability exists in the clinical characteristics defining nonatopic disease (Table 1). Zimmerman et al. conducted a study in 123 children with asthma 6 years or older, in which they evaluated the association between the presence of allergy positive skin prick test (SPT) with severity of childhood asthma.⁷ The authors used a control cohort of 52 patients with cystic fibrosis and 29 healthy patients. They conducted SPT and defined 3 or more positive tests as significant atopy. Asthma severity was graded primarily on medication use. The authors concluded that patients with asthma had a higher percentage of positive SPT than the control cohort, and that there was a positive relationship between asthma severity and the number of positive SPTs.⁷ Although the primary outcome of this study was not to characterize atopic versus nonatopic disease, they found that 18% of the symptomatic asthma patients had negative SPT.⁷

Sinisgalli et al. described that approximately a third of their cohort of 321 pediatric asthma patients tested by SPT

TABLE 1. NONATOPIC ASTHMA PHENOTYPE DEFINITION BY RESEARCH GROUP

Stein and Martinez ⁶	Presence of chronic wheezes without associated increased risk for allergic sensitization or higher total serum IgE levels
Zimmerman et al. ⁷	Physician-diagnosed symptomatic asthma patients with negative skin prick allergy test
Sinisgalli et al. ⁸	Pulmonary physician-diagnosed asthma with negative skin prick allergy test
Turato et al. ¹²	Presence of multitrigger wheeze ^a and bronchodilator response reported by parents and pediatrician, and negative skin prick allergy test
Drewe et al. ¹⁴	Negative skin prick allergy test and positive answer to the following 2 questions in the ISAAC study ^b : (1) wheeze in the previous 12 months and (2) asthma ever
Khoshoo et al. ¹⁵	Positive methacholine challenge, negative skin tests, and normal values for total IgE in blood

^aRepeated episodes of wheezes, breathlessness, and cough that were present even apart from colds.

^bInternational Study of Asthma and Allergy in Childhood. IgE, immunoglobulin E; ISAAC, International Study of Asthma and Allergies in Childhood.

were negative to any aeroallergen.⁸ There was a higher presence of eczema in patients with positive SPT. The presence of eczema correctly predicted positive skin test findings in 75% of their asthmatic patients, and its absence correctly predicted the absence of positive skin test in only 37%. The authors conclude that there was no identifiable feature or group of features that could distinguish allergic from nonallergic asthma, as defined solely by a positive SPT. They go on to suggest that all children with asthma should undergo allergy testing to identify potential asthma triggers and to avoid the institution of unnecessary environmental control measure in patients with nonallergic asthma.⁸

There is certain variability in the definition of the nonatopic asthma cohort. There are groups that include the absence of atopic diseases such as allergic rhinitis, eczema, or food allergies, normal IgE levels, and normal eosinophil levels in the definition. The common denominator in terms of definition for this phenotype is physician-diagnosed asthma with negative SPT.

The Challenges of Studying This Phenotype

The main challenge studying this phenotype is the variability in the inclusion and exclusion criteria. As already suggested, the common denominator is the presence of asthma with negative SPT. As described in The International Study of Asthma and Allergies in Childhood with respect to atopy, there is a high level of concordance between the results of SPT reactivity and specific IgE (sIgE) to aeroallergens in studies done in Europe and the United States.⁹ However, in low- and middle-income countries, there is often a marked dissociation between the results of SPT and allergen sIgE, particularly in underprivileged populations.¹⁰ This effect has been observed especially in areas with a high prevalence of chronic parasitic infections. A study by van den Biggelaar et al. found that children with urinary schistosomiasis had a lower prevalence

of positive skin test reaction to house-dust mites than those free from this infection.¹¹ The authors suggest that the anti-inflammatory cytokine, interleukin (IL)-10, present in chronic schistosomiasis, appears central to suppressing atopy in African children.¹¹ Even with the limitations already described, there are several studies in the literature that have addressed the nonatopic asthma phenotype (Table 2).

Pathologic Findings in Patients with Nonatopic Asthma

A study by Turato et al. evaluated the pathologic findings in patients with nonatopic wheezes versus those with atopic wheezes.¹² The group defined the presence of atopy by an increase in total paper radioimmunosorbent test or specific radioallergosorbent test. The group designed the study to investigate whether, in children whose pattern of symptoms favors the diagnosis of asthma, airway pathology is influenced by atopic status.¹² They obtained bronchial biopsies from 55 children undergoing bronchoscopy for appropriate clinical indications, 18 patients with nonatopic multitrigger wheezes between 2 and 10 years of age, and 20 patients with atopic multitrigger wheezes between 2 and 15 years of age. They found that pathologic features such as increased epithelial loss ($P=0.03$ and $P=0.002$, respectively), thickened basement membranes (both $P<0.0001$), increased number of vessels ($P=0.003$ and $P=0.03$, respectively), eosinophils ($P<0.0001$ and $P=0.002$, respectively), and increased cytokines expression (IL-4) ($P=0.002$ and $P=0.0001$, respectively) were similar in both groups.¹²

Cellularity

Karakoc et al. investigated the association between persistent eosinophilia and asthma in children with and without atopy.¹³ These patients were part of the TCRS; chronic asthma was defined as physician-diagnosed asthma with the presence of symptoms in the previous year. Atopy was de-

fined as the presence of at least 1 positive SPT. Patients with persistently high eosinophil count were defined as $>5\%$ eosinophils measured in 3 out of 3 different occasions. They found a positive correlation of patient with chronic asthma and high eosinophils levels. However, these findings were independent of the presence of atopy.¹³

Drews et al. evaluated sputum cellularity in children of middle school age who were grouped as nonatopic asthma, atopic asthma, or control with neither asthma nor atopy.¹⁴ Atopy was defined as positive SPT. They performed sputum induction in 28 children with atopic asthma, 29 with nonatopic asthma, and 19 controls. They found that the sputum of patients with nonatopic asthma had a neutrophilia cell pattern. In contrast, patients with atopic asthma had a predominantly eosinophilic cell pattern. These findings suggest that different inflammatory pathways are present in the nonatopic versus atopic patient with asthma.¹⁴

Studies Involving Therapy for Patients with Nonatopic Asthma

Currently, children with persistent asthma are treated with inhaled corticosteroids as a first-line therapy irrespective of their atopic status and, thus, this anti-inflammatory treatment choice may not reflect optimal management of the underlying pathophysiology. There is a paucity of data addressing treatment strategies in the nonatopic asthma pediatric patient. Hereunder we discuss studies that evaluate alternative therapies in patients who share similar nonatopic characteristics.

Khoshoo et al. studied the effect of gastroesophageal reflux disease (GERD) therapy on bronchial hyperactivity in patients with nonatopic asthma and positive pH probes.¹⁵ The group identified 30 patients with nonatopic asthma who underwent extended esophageal pH monitoring. The patients included in the study had poorly controlled moderate persistent asthma and no history of atopy. Atopy was defined as a positive SPT. Nonatopic patients had negative skin tests and normal

TABLE 2. KEY POINTS FOR NONATOPIC ASTHMA

Stein and Martinez ⁶	General characteristics	Wheeze during the first decade of life in association with viral respiratory agents, especially RSV, independently of allergic sensitization. Less severe and less persistent wheezes than atopic phenotypes
Sinisgalli et al. ⁸	Clinical characteristics	No identifiable feature such as eczema, chronic rhinitis, asthma severity, or family history of atopy that could distinguish allergic from nonallergic asthma, as defined solely by a positive SPT
Turato et al. ¹²	Pathologic findings	Pathologic features such as increased epithelial loss, thickened basement membranes, increased number of vessels, eosinophils, and increased cytokines expression (IL-4) were similar in nonatopic and atopic asthma patients
Martinez et al. ⁵	Presence of eosinophilia	Positive correlation between chronic asthma and high eosinophils level; these findings were independent of the presence of atopy
Drews et al. ¹⁴	Sputum cellularity	Sputum of patient with nonatopic asthma had neutrophilia versus sputum of patients with nonatopic asthma with predominantly eosinophilia
Khoshoo et al. ¹⁵	Treatment for patient with Nonatopic asthma + GERD	After 2 years of treatment with esomeprazole and metoclopramide, most of the patients demonstrated improvement in the methacholine challenge test
Lazarus et al. ¹⁶	*Treatment for patients with low eosinophils levels	No significant difference in outcomes between patients treated with mometasone versus placebo compared with patients treated with tiotropium bromide versus placebo

*The subjects evaluated in this study do not exactly represent the Nonatopic asthma phenotype since this study include adult patients and is using the low eosinophils parameter rather than a negative skin prick test.

GERD, gastroesophageal reflux disease; IL, interleukin; RSV, respiratory syncytial virus; SPT, skin prick test.

values for total IgE in blood. Of the 30 patients, 21 had an abnormal pH study suggesting GERD, 15 out of these 21 subjects had a positive methacholine challenges test (MCT). These MCTs provide objective data that will confirm the presence of bronchial hyperresponsiveness. A negative MCT nearly rules out a diagnosis of asthma, thus improving the possible bias introduced by the subjective definition of physician-diagnosed asthma. The patients were treated with a proton pump inhibitor (esomeprazole 40 mg or lansoprazole 30 mg/day) along with a prokinetic (metoclopramide 0.1–0.15 mg/kg per dose given 3 times a day). After 2 years of treatment, of the 15 patients with abnormal pH study and positive MCT, only 4 still presented with an abnormal MCT.¹⁵

A recently published double-blind crossover trial specifically looked at treatment response in patients with mild well-controlled persistent asthma stratified by low versus high levels of sputum eosinophils.¹⁶ In this trial, 221 patients 12 years of age or older with low eosinophil (<2%) and 74 patients with high eosinophils were randomized to 12 weeks treatment with mometasone, tiotropium, or placebo. The primary outcome of this study was a composite of treatment failure, asthma control days, and forced expiratory volume in 1 second. Nearly 60% of the patients in the low-eosinophil stratum had a differential response to mometasone or tiotropium. Of those with a differential response, 57% had a better response to mometasone (versus 43% to placebo) and 60% had a better response to tiotropium (versus 40% to placebo). Importantly, in this population of patients low-sputum eosinophils, 80% had at least 1 positive allergen test by serum sIgE, so these results cannot be extrapolated to patients with nonatopic asthma. The authors suggest that their findings provide clinical equipoise for larger and longer study to compare inhaled corticosteroids with other treatments in patients with mild-to-moderate persistent asthma and low eosinophil levels.¹⁶ It would be important to assess the role of atopy in response to treatment in this population. In addition, the study did not include pediatric patients between 6 and 12 years of age, where the percentage of patients with nonatopic asthma is greater.

Conclusion

It is important to recognize different phenotypes of asthma as treatment responses may differ by phenotype. A significant portion of the pediatric asthma patients lack features of atopy and may have a less robust response to the first line of treatment with inhaled corticosteroids. Although identifying these phenotypes will help with prognosis and guidance of therapy, there are several challenges that need to be addressed to further investigate this group. Future research should be guided toward identifying the inflammatory pathways in nonatopic asthma and potential phenotype-guided therapies.

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