



Clinical characterization of children with resistant airflow obstruction, a multicenter study

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Author information:

TITLE: Clinical characterization of children with resistant airflow obstruction, a multicenter study

Authors: Sankaran Krishnan^a, MD, MPH, Allen J Dozor^a, MD, Leonard Bacharier^b, MD, Jason E Lang^c, MD, MPH, Charles G. Irvin^d, PhD, David Kaminsky^d, MD, Harold J Farber^e, MD, MPH, Lynn Gerald^f, PhD, MPH, Mark Brown^f, MD, Janet T Holbrook^g, PhD, MPH, Robert A Wise^h, MD, Julie Ryuⁱ, MD, Sonali Bose^h, MD, Yasin Razan^g, MSH, Jey Saams^g, RN, Robert J Henderson^g, MS, William G Teague^j, MD on behalf of the American Lung Association Airway Clinical Research Centers (ALA-ACRC) Network*

Affiliations:

1. Division of Pediatric Pulmonology, Allergy and Sleep Medicine, New York Medical College and Maria Fareri Children's Hospital at Westchester Medical Center
2. Division of Allergy, Immunology and Pulmonary Medicine, Washington University School of Medicine at St Louis
3. Division of Pulmonary and Sleep Medicine, Dept. Of Pediatrics, Duke Univ. School of medicine, Durham, NC
4. Department of Medicine, University of Vermont
5. Pediatric Pulmonology, Baylor College of Medicine and Texas Children's Hospital
6. College of Public Health, University of Arizona
7. Bloomberg School of Public Health, Johns Hopkins University
8. Pulmonary Medicine, Johns Hopkins University
9. Pulmonary Medicine, Rady Children's Hospital, University of California at San Diego.
10. Pediatric Pulmonology, University of Virginia

* A complete list of non-author contributors appears in Appendix 1 (Supplementary materials)

Address correspondence to:

Sankaran Krishnan, MD, MPH
New York Medical College
40 Sunshine Cottage Road - Skyline 1N-D29
Valhalla, NY 10595

Tel 914-493-7585

Fax 914-594-2350

Email: sankaran_krishnan@nymc.edu.

Short title: Children with Resistant Airflow Obstruction

Key words: pulmonary function tests, bronchodilator, allergic rhinitis

Abstract:

Objective: To characterize a cohort of children with airflow limitation resistant to bronchodilator (BD) therapy.

Methods: Pulmonary function tests performed in children 6-17 years of age at 15 centers in a clinical research consortium were screened for resistant airflow limitation, defined as a post-BD FEV_1 and/or an FEV_1/FVC less than the lower limits of normal. Demographic and clinical data were analyzed for associations with pulmonary function.

Results: 582 children were identified. Median age was 13 years (IQR: 11, 16), 60% were males; 62% were Caucasian, 28% were African-American; 19% were obese; 32% were born prematurely and 21% exposed to second hand smoke. Pulmonary diagnoses included asthma (93%), prior significant pneumonia (28%), and bronchiectasis (5%). 65% reported allergic rhinitis, and 11% chronic sinusitis. Subjects without a history of asthma had significantly lower post-BD $FEV_1\%$ predicted ($p=0.008$). Subjects without allergic rhinitis had lower post-BD $FEV_1\%$ predicted ($p=0.003$). Children with allergic rhinitis, male sex, obesity and Black race had better pulmonary function post-BD. There was lower pulmonary function in children after age 11 years without a history of allergic rhinitis, as compared to those with a history of allergic rhinitis.

Conclusions: The most prevalent diagnosis in children with BD-resistant airflow limitation is asthma. Allergic rhinitis and premature birth are common co-morbidities. Children without a history of asthma, as well as those with asthma but no allergic rhinitis, had lower pulmonary function. Children with BD-resistant airflow limitation may represent a sub-group of children with persistent obstruction and high risk for life-long airway disease.

Introduction:

Although typically not diagnosed until later in life, chronic obstructive pulmonary disease (COPD) is a disorder of molecular pathways and environmental exposures regulating lung growth and airway inflammation, and its development may start at conception.¹⁻¹⁴ Known factors associated with abnormal pulmonary function and risk for chronic obstructive pulmonary disease (COPD) during postnatal maturation include low birth weight,⁵ premature gestation,⁶ bronchopulmonary dysplasia (BPD),⁶ and asthma.⁷⁻¹⁴

It is not known how often children with respiratory symptoms, with or without a diagnosis of asthma, demonstrate airflow obstruction that does not completely reverse with an inhaled bronchodilator. This complication, often termed “fixed airflow obstruction”, is commonly seen by specialty physicians, but the phenotypic characteristics of children with fixed airflow obstruction are not well studied.¹⁰⁻¹⁷ Risk factors associated with bronchodilator (BD) - resistant airflow obstruction are poorly understood, though clinical experience suggests such children have often have a history of premature birth¹⁸⁻²³ or severe asthma.²⁴⁻²⁸ Studies have shown that children born prematurely, with or without a history of BPD have lower lung function in later life as compared to peers.^{20,21} In cohorts of severe asthma in children, using

cluster analysis, data from the NHLBI Severe Asthma Research Program (SARP)^{24,25} and others²⁶⁻²⁸ reveal specific clusters of children with poor lung function persisting post-BD. However, most studies of cohorts with poor lung function post-BD involved limited number of children.

The prognosis of children with BD-insensitive airflow obstruction is unknown. In one long-term cohort study, children with severe wheeze and airflow limitation early in life were more likely to acquire COPD as adults compared to their counterparts with wheeze and normal lung function.²⁹ More immediate questions exist about management of these children, such as whether any known therapy could prevent the attainment of COPD, or whether inhaled corticosteroids and/or long-acting beta adrenergic agonists are as effective in symptom control as in more typical children with asthma that demonstrate completely reversible airflow obstruction.¹⁶

The objective of this study was to identify and characterize school-age children with airflow obstruction refractory to complete reversal following inhaled beta agonist on pulmonary function testing with respect to demographics, history of respiratory infections, treatment history, allergen sensitization, environmental tobacco smoke exposure, and pulmonary function. These children may represent a unique sub-type of childhood asthma¹⁶ with possible implications for management and long-term outcome.

Patients and Methods:

A cohort of children with airflow obstruction both before and after inhaled beta agonist were identified from recent records at fifteen pediatric pulmonology clinical sites of the American Lung Association Airways Clinical Research Centers (ALA-ACRC) network. Criteria for inclusion in the analysis were:

- Age 6-17 years;
- Airflow obstruction pre-BD – defined by either an absolute ratio of FEV_1/FVC or FEV_1 expressed as % of predicted value less than lower limits of normal (LLN) according to the Global Lung Initiative (GLI) equations;³⁰
- Airflow obstruction post-BD - defined as by either the absolute FEV_1/FVC ratio or the FEV_1 (% predicted) that was less than LLN twenty minutes after a standard dose of bronchodilator (either 2.5 mg albuterol administered using a small-volume hand-held nebulizer or 4 inhalations of albuterol metered-dose inhaler, 90 mcg per inhalation, administered using a valved-holding chamber) as per ATS guidelines.^{31,32}
- Children with cystic fibrosis were excluded.

Spirometry³³ and plethysmographic lung volumes³⁴ were measured according to ATS-ERS guidelines at each institution. Latest data recorded in individual charts are reported. The study was approved by each center's institutional review board.

Analytic Methods:

Whereas the analysis was descriptive and done to generate novel hypotheses, there was no a priori sample size. The central dispersion of continuous variables was expressed as median (IQR), and categorical variables in column percent. Correlates of BD-resistant airflow obstruction were tested by univariate analysis. Multivariate regression was performed for spirometry variables after controlling for age, sex, race, obesity and birth status. Two-tailed p values of <0.05 were considered statistically significant. Data were analyzed using SAS for Windows, version 9.4 (SAS Institute, NC).

Results:

582 children with BD-resistant airflow limitation were identified at 15 centers. Demographic characteristics of the cohort are reported in Table 1. Median age was 13 years (IQR: 11, 16); 60% were males. 360 subjects (62%) were Caucasian and 164 (28%) were African-American. 109 (19%) were obese (BMI $> 95^{\text{th}}$ %). Birth history was available for 428 subjects, of which 137/428 (32%) reported a history of premature birth (<37 weeks gestational age at birth). 36 (6%) had been given a diagnosis of bronchopulmonary dysplasia as infants, while 10% had a history of supplemental oxygen use or mechanical ventilation in the newborn period. 120 (21%) reported a history of exposure to second-hand smoke (SHS). The most common pulmonary diagnoses reported were asthma (93%), prior significant pneumonia (28%), bronchiectasis (5%), and congenital disorders (3%). 65% of subjects reported a diagnosis of allergic rhinitis, 11% chronic sinusitis, and 9% had a history of hospitalization related to an RSV infection. Though information on severity of asthma in each subject (mild/moderate/severe persistent) is not available, all subjects were on asthma controllers at the time of study entry.

Since the majority of subjects (93%) had a clinical diagnosis of asthma, further analysis was conducted stratified by asthma status to evaluate subgroups of patients by their clinical phenotype. Table 2 describes the results of pulmonary function tests stratified by asthma status. Subjects without a history of asthma had significantly lower post-BD FEV₁% predicted as compared to those with history of asthma. In subjects with asthma, allergic rhinitis was a significant effect modifier.

Table 3 describes pulmonary function by rhinitis status in children with asthma. Subjects without rhinitis had lower post-BD FEV₁% predicted as compared to those with a history of allergic rhinitis. In children with allergic rhinitis, those of male sex, obesity and Black race had better pulmonary function post-BD as compared to those who were female, non-obese and Caucasians.

In children with asthma, multivariate analyses revealed significant differences in the effect of age > 11 (p-interaction = 0.017) and use of inhaled corticosteroids (ICS), alone or in combination with long-acting beta-agonists (LABA), (p-interaction = 0.009) on FEV₁ pre-BD % predicted, based upon rhinitis status. Similarly, there were significant differences in the effect of age (p-interaction = 0.002) and use of ICS or ICS + LABA (p-interaction = 0.003) on the post-BD FEV₁ % predicted, based upon rhinitis status. Age > 11 was chosen to assess for long-term effect of asthma on lung function, similar to analyses conducted in other similar cohorts.^{20,21,24,25} Based on these data, further stratified models examining the effect of allergic rhinitis on pre- and post-BD FEV₁% predicted are described in Table 4. In children without a history of allergic rhinitis, there was lower pulmonary function after age 11 as compared to younger children.

Additionally, in this group, those who reported ICS or ICS-LABA use had lower pulmonary function at baseline and post-BD.

Discussion:

Beta agonist-resistant airflow limitation or “fixed” obstruction in children has been previously described, but most studies have been limited to pre-selected populations. Several studies focused on severe asthma,²⁴⁻²⁸ and specifically excluded those with other diagnoses. However, children with diverse etiologies and persistent airflow limitation are often encountered in pediatric practice, and are usually treated as if they have asthma. The goal of this study was to characterize a diverse, heterogeneous group of school-age children with airflow obstruction that persists after inhaled beta agonist. These children may represent a unique phenotype,¹² with implications for management and long term outcome. For instance, there is growing interest in the use of anticholinergics, traditionally reserved for adults with COPD, for children with asthma.^{35,36} Better insight into this challenging group of patients could help optimize outcomes and suggest alternate therapies.

The majority (93%) of enrolled children in our large cohort carried a physician-diagnosis of asthma. Those with diagnoses other than asthma had lower lung function. Data on asthma severity was not available. Others have reported significant airflow limitation in specific cohorts of children with severe asthma. A cluster analysis of pediatric-age enrollees in the NIH/NHLBI Severe Asthma Research Program (SARP) identified a small cluster of children with severe asthma and significant airflow obstruction (18% of subjects). These children were mostly African-American, highly symptomatic, required frequent unscheduled health care visits for asthma care, and had high levels of exhaled nitric oxide (FeNO).²⁴ A subsequent analysis from France on a group of children with severe asthma also revealed a cluster with significant airflow

limitation.²⁵ Unlike the SARP analysis, this cluster of French children were older and had relatively less eosinophilic inflammation. Similarly, other cluster analyses²⁶⁻²⁸ of children with severe asthma, including the TENOR study²⁶ revealed clusters with significant airflow limitation. In all these studies, children born prematurely were excluded.

Almost a third of children in our cohort had a history of premature birth, with a significant proportion reporting a history of bronchopulmonary dysplasia, mechanical ventilation or supplemental oxygen use in the neonatal period, which is consistent with a growing literature documenting persistent decreased lung function in adolescents and adults following preterm birth.^{6, 22, 37-42}

In asthmatic children with persistent obstruction and allergic rhinitis (as a marker of atopic status), characteristics associated with a higher post-BD FEV₁ percent predicted included male sex, obesity (BMI > 95th percentile) and Black race. It is not clear why obese children in our cohort had a greater pre- and post-bronchodilator % predicted FEV₁. Mahut and coworkers in the GrowthOb study⁴⁴⁹ reported increased FVC and FEV₁ in a small cohort of overweight females 6-15 year olds, but not in males. Recently, Cibello et al⁴⁴ in a large, Italian, cross-sectional cohort, reported higher FEV₁ and FVC, but not FEV₁/FVC in obese Caucasian children, 10-17 years of age, as compared to controls with normal BMI. On the other hand, Peters et al from the South Texas Asthma Management Project study, with a predominant Hispanic population, reported no differences in FVC, FEV₁, or FEV₁/FVC in 132 obese children as compared to those with normal BMI.⁴⁵ It is also not understood why males in our study had lower FEV₁/FVC ratios pre-and post-BD after controlling for other confounders.

For children with a diagnosis of asthma with persistent obstruction and without allergic rhinitis, characteristics associated with a lower post-BD FEV₁ percent predicted included age; and older children who reported use of ICS or ICS-LABA had lower pulmonary function. It is speculative that non-atopic children with asthma and BD-resistant obstruction have either more severe asthma, were born with smaller airways, or possibly developed airway remodeling. This interesting sub-group may be at higher risk of persistent obstruction into adulthood. McGeachie et al have reported on a subgroup of subjects from the CAMP study with abnormal patterns of lung growth and decline at 23 years of age. Childhood impairment of lung function and male sex were the risk factors reported.⁴⁶ Similarly, Bui et al recently reported on a cohort of subjects longitudinally followed from age 7 to adulthood.⁴⁷ Being in the lowest quartile of lung function at age 7 was associated with increased risk of developing COPD or asthma-COPD overlap syndrome at age 45.

This is a cross-sectional, retrospective study with the limitations inherent to this study design. Data on disease severity at the time of spirometry, quality of life measures, and health care utilization data are not available. Spirometry data were extracted from medical records results collected as part of real world clinical care. Bronchodilator-resistant obstruction was defined based on response to a standard dose of inhaled beta-agonist, while responses to higher doses of beta-agonist, oral steroids or anticholinergics were not determined. Therefore it is not known how truly “fixed” their airflow obstruction truly is, and these data are not sufficient to draw mechanistic or pathophysiologic conclusions.

Conclusions:

Children with persistent obstruction post-bronchodilator most often carry the diagnoses of asthma and allergic rhinitis, and a significant proportion were born prematurely or have a history of mechanical ventilation or supplemental oxygen use in the neonatal period. Older children with a history of asthma without allergic rhinitis seem to have lower pulmonary function, despite being on controllers. The long-term clinical implications are unclear. Children with bronchodilator-insensitive airflow obstruction may represent a sub-type of asthma that could potentially progress in later life to COPD, and therefore merit longitudinal analyses as well as consideration of alternative therapeutic approaches.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Table1. Demographics

Baseline Characteristics	Total (N=582)
Age at last record, Median (Q1, Q3)	13 (11, 16)
Age at time of PFT, Median(Q1, Q3)	11 (8, 14)
Other demographic characteristics, N (%)	
Male	351 (60%)
Race or ethnic group	
Caucasian	360 (62%)
African American	164 (28%)
Mexican American	7 (1%)
Asian	12 (2%)
Other	39 (7%)
Health characteristics, N (%)	
Birth Term	
Full-term	291 (50%)
Pre-term	138 (24%)
Unknown term	153 (26%)
Mechanical ventilation as a newborn	47 (8%)
Supplemental oxygen as a newborn	56 (10%)
Reported ICS alone use at last visit, N(%)	182 (31%)

Reported ICS/LABA use at last visit, N(%)	295 (51%)
Reported ICS or ICS/LABA use at last visit	477 (82%)
Environmental Tobacco Exposure	
Yes	120 (21%)
No	312 (54%)
Unknown	150 (26%)
Respiratory diagnosis	
Asthma Status	
Yes	541 (93%)
No	22 (4%)
Unknown	19 (3%)
Croup	27 (5%)
Bronchopulmonary Dysplasia	36 (6%)
History of Pneumonia	162 (28%)
History of Aspiration	13 (2%)
Bronchiolitis Obliterans	19 (3%)
Congenital Respiratory Disorders	20 (3%)
Chronic Sinusitis	66 (11%)
Bronchiectasis	30 (5%)
Immunodeficiency	13 (2%)

Allergic Rhinitis Status	
Yes	378 (65%)
No	103 (18%)
Unknown	101 (17%)

Table 2. Pulmonary function tests stratified by asthma status

	Total (N=582)	Asthma (N=541)	No Asthma (N=22)	Unknown (N=19)	p*
Pre-BD spirometry, median (IQR)					
FEV1, % predicted	69.2 (58.5, 76.8)	70.0 (59.0, 76.9)	62.4 (40.6, 70.7)	63.5 (45.3, 73.6)	0.008
FVC, % predicted	87.9 (75.9, 100.2)	88.8 (77.3, 100.3)	65.9 (50.7, 79.2)	78.1 (63.8, 95.0)	<.001
FEV1/FVC, absolute ratio	0.69 (0.62, 0.75)	0.68 (0.62, 0.74)	0.77 (0.69, 0.85)	0.73 (0.63, 0.87)	0.004
FEF25-75, % predicted	39.5 (29.5, 50.3)	39.2 (29.6, 48.7)	47.9 (16.4, 57.2)	43.1 (26.6, 56.6)	0.43
Post-BD spirometry, median (IQR)					
FEV1, % predicted	75.8 (67.6, 83.9)	76.5 (68.4, 84.3)	64.2 (39.2, 73.1)	68.4 (54.4, 77.4)	<.001
FVC, % predicted	92.0 (78.5, 105.0)	93.0 (80.8, 105.4)	69.8 (56.1, 80.9)	79.7 (62.6, 98.3)	<.001
FEV1/FVC, absolute ratio	0.73 (0.67, 0.78)	0.73 (0.67, 0.77)	0.82 (0.67, 0.88)	0.74 (0.70, 0.88)	0.066
FEF25-75, % predicted	50.9 (38.9, 61.9)	50.8 (39.5, 61.3)	57.2 (40.2, 68.5)	56.7 (28.9, 71.4)	0.90

*p-values are based upon Chi-squared for categorical and Kruskal-Wallis tests for continuous characteristics

Table 3. Pulmonary function in children with asthma, stratified by rhinitis status

	Total (N=541)	Rhinitis (N=371)	No Rhinitis (N= 88)	Unknown (N=82)	p*
Pre-BD spirometry, median (IQR)					
FEV1, % predicted	70.0 (59.0, 76.9)	70.3 (59.3, 77.6)	69.0 (58.9, 76.0)	66.0 (57.7, 74.0)	0.13
FVC, % predicted	88.8 (77.3, 100.3)	89.7 (78.9, 100.7)	85.8 (72.9, 99.7)	86.0 (74.7, 96.3)	0.028
FEV/FVC, absolute ratio	0.68 (0.62, 0.74)	0.68 (0.61, 0.74)	0.69 (0.64, 0.75)	0.68 (0.62, 0.74)	0.50
FEF25-75, % predicted	39.2 (29.6, 48.7)	39.5 (29.6, 48.7)	40.4 (29.9, 50.6)	36.6 (29.9, 47.7)	0.75
Post-BD spirometry, median (IQR)					
FEV1, % predicted	76.5 (68.4, 84.3)	77.5 (70.0, 85.9)	74.0 (64.6, 83.1)	74.5 (67.4, 81.4)	0.003
FVC, % predicted	93.0 (80.8, 105.4)	94.5 (83.0, 106.5)	87.5 (76.3, 102.3)	91.4 (75.2, 101.8)	0.002
FEV/FVC, absolute ratio	0.73 (0.67, 0.77)	0.73 (0.68, 0.77)	0.73 (0.67, 0.79)	0.73 (0.67, 0.79)	0.87
FEF25-75, % predicted	50.8 (39.5, 61.3)	51.5 (41.0, 61.3)	49.1 (35.7, 60.2)	49.4 (38.7, 62.3)	0.31

*p-values are based upon Chi-squared for categorical and Kruskal-Wallis tests for continuous characteristics

Table 4. Multivariable Model for Percent Predicted FEV₁ in children with asthma by rhinitis status

		Pre-Bronchodilator		Post-Bronchodilator	
	N	%Predicted difference (95% CI)	P-Value*	%Predicted difference (95% CI)	P-Value*
Asthma with rhinitis (total)	371				
Age > 11	164 (44%)	1.32 (-1.59, 4.24)	0.37	1.49 (-1.34, 4.31)	0.30
Male (vs. female)	234 (63%)	2.84 (-0.13, 5.82)	0.061	3.13 (0.24, 6.02)	0.034
Obese (vs. non-obese)	74 (20%)	4.23 (0.59, 7.88)	0.023	4.22 (0.68, 7.76)	0.020
Black (vs. white)	130 (35%)	-1.64 (-4.75, 1.47)	0.30	3.91 (0.89, 6.94)	0.011
Other race (vs. white)	30 (8%)	3.23 (-2.19, 8.65)	0.24	3.72 (-1.54, 8.99)	0.17
Reported ICS use (vs. non-use)	112 (30%)	-1.46 (-6.03, 3.10)	0.53	-0.42 (-4.85, 4.01)	0.85
Reported ICS+LABA use (vs. non-use)	205 (55%)	-1.39 (-5.62, 2.85)	0.52	2.35 (-1.76, 6.46)	0.26
Asthma without Rhinitis (total)	88				
Age > 11	40 (45%)	-5.74 (-11.7, 0.21)	0.059	-7.33 (-13.16, -1.51)	0.014
Male (vs. female)	48 (55%)	0.35 (-5.6, 6.29)	0.91	1.17 (-4.64, 6.98)	0.69
Obese (vs. non-obese)	11 (13%)	4.94 (-4.11, 13.98)	0.28	5.31 (-3.53, 14.16)	0.24
Black (vs. white)	9 (10%)	8.75 (-1.17, 18.66)	0.084	12.14 (2.44, 21.84)	0.014

Other race (vs. white)	13 (15%)	3.31 (-5.24, 11.86)	0.45	3.09 (-5.27, 11.45)	0.47
Reported ICS use (vs. non-use)	25 (28%)	-11.73 (-19.94, -3.52)	0.005	-10.04 (-18.07, -2.01)	0.014
Reported ICS+LABA use (vs. non-use)	43 (49%)	-13.46 (-20.83, -6.09)	<.001	-11.57 (-18.77, -4.36)	0.002