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Predictors of asthma exacerbation among patients with poorly controlled asthma despite inhaled corticosteroid treatment

Wilson A. Quezada, MD¹, Eun Soo Kwak, MD¹, Joan Reibman², Linda Rogers³, John Mastronarde⁴, William G. Teague⁵, Christine Wei⁶, Janet T. Holbrook, PhD⁶, Emily DiMango, MD¹, and American Lung Association Asthma Clinical Research Centers

¹Columbia University College of Physicians and Surgeons

²New York University School of Medicine; New York, NY

³Mount Sinai School of Medicine

⁴Ohio State University; Columbus, Ohio

⁵University of Virginia Medical Center; Charlottesville, VA

⁶Johns Hopkins University, Baltimore, MD

Corresponding Author: Dr. Emily DiMango, Columbia University Medical Center, 622 West. 168th Street, New York, New York 10032, Phone: 212-305-0290, FAX: 212-305-7063, Ead3@cumc.columbia.edu.

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Eun Soo Kwak, MD: none

John Mastronarde, MD: none

G. Teague, MD: none

Linda Rogers, MD: none

Christine Wei, MS: none

Janet Holbrook, PhD: none

Emily DiMango, MD: none

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Contributions of authors:

1. Wilson Quezada: conception and design of study, data generation, analysis and interpretation of data, preparation of the manuscript.
2. Eun Soo Kwak: conception and design of study, data generation, analysis and interpretation of data, preparation of the manuscript.
3. Joan Reibman: conception and design of study, data generation, preparation of the manuscript.
4. Linda Rogers: conception and design of study, data generation, preparation of the manuscript.
5. John Mastronarde: conception and design of study, data generation, preparation of the manuscript.
6. William G. Teague: conception and design of study, data generation, preparation of the manuscript.
7. Christine Wei: data generation, analysis and interpretation of data, preparation of the manuscript.
8. Janet Holbrook: conception and design of study, data generation, analysis and interpretation of data, preparation of the manuscript.
9. Emily DiMango: conception and design of study, data generation, analysis and interpretation of data, preparation of the manuscript.

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Introduction

Asthma currently affects 18.7 million adults (8%) and 6.8 million children (9.3%) in the United States, and as many as 300 million people worldwide¹. The majority of patients being treated for asthma have poor asthma control²⁻⁴. In most patients with uncontrolled asthma, intensification of treatment is successful in achieving control⁵. However, poor adherence to prescribed medications as well as unwillingness of patients to increase controller therapy due to fears about adverse effects are major contributors to poor asthma control⁶. In 2011, more than half of patients with asthma suffered from an asthma attack¹. Asthma exacerbations are potentially life-threatening events and are associated with decreased quality of life and increased healthcare utilization. Healthcare costs for asthma are largely related to care for asthma exacerbations⁷⁻⁹. Risk factors for asthma exacerbations in patients with well-controlled asthma have been identified and include previous asthma exacerbation, use of bronchodilator therapy, decreased pulmonary function measurements and need for higher amounts of controller therapy¹⁰⁻¹⁴. Relatively few studies have identified risk factors in patients with poorly controlled asthma^{10,15}. Sputum eosinophil count has been found to be predictive of asthma exacerbations, but measurements are not practical in the clinic setting¹⁶. Identification of characteristics that predict increased risk of future exacerbations in patients with suboptimal control of asthma may be helpful to both patients and providers in making asthma treatment decisions requiring step-up of asthma treatment.

The present retrospective analysis utilizes data previously collected from a large group of well-characterized children and adults during two randomized, placebo-controlled studies of proton-pump inhibition (PPI) in the treatment of asthma^{17,18}, conducted by the multi-center Asthma Clinical Research Centers. Both of those trials showed that the addition of a PPI did not affect asthma outcomes. The goal of the current study is to determine prevalence and risk factors for asthma exacerbations among adults and children with uncontrolled asthma despite use of inhaled corticosteroids at baseline.

Methods

Study Population

The Study of Acid Reflux in Children with Asthma (SARCA) and the Study of Acid Reflux in Adults with Asthma (SARA) were multicenter, randomized, double-blind, placebo controlled trials of the effectiveness of lansoprazole (SARCA) and esomeprazole (SARA) in the treatment of children and adults, respectively, with inadequately controlled asthma despite therapy with moderate or high doses of inhaled corticosteroids with or without long acting beta agonists (LABA). SARCA was conducted between 2007 and 2011 and SARA was conducted between 2004 and 2008 at 19 centers of the American Lung Association Asthma Clinical Research Centers (ACRC). Details of the study design of SARA and SARCA are described elsewhere^{17,18}. All subjects or guardians provided written informed consent that was approved by the local Institutional Review Board. Both studies were registered on clinicaltrials.gov (NCT00069823 and NCT00442013). Patients were eligible if they were between 6 and 17 years of age (SARCA) or 18 years (SARA), had physician diagnosed asthma with the diagnosis supported by a 12% or greater increase in post-

bronchodilator forced expiratory volume in one second (FEV₁) or a positive methacholine challenge test, were being treated with inhaled glucocorticoids (176 µg/d of fluticasone or equivalent for children and 400 µg of fluticasone or equivalent for adults) and had no change in controller therapy for at least 8 weeks prior to enrollment. Eligible subjects also demonstrated poor asthma control defined as either more than one acute episode of asthma requiring unscheduled medical care in the previous year or a score of at least 1.25 for children and 1.5 for adults on the Juniper Asthma Control Questionnaire (ACQ) at the screening visit. Children were excluded if their FEV₁ was < 60% predicted; adults with FEV₁ < 50% predicted were excluded. Participants were excluded if they smoked cigarettes within the previous 6 months or had a history of 10 or more pack years of smoking. Subjects were randomized to treatment with proton pump inhibitor (PPI) or matching placebo for a 24-week treatment period during which they continued their previous asthma controller therapy. Daily morning peak flow was measured and recorded, along with asthma symptoms and health care utilization. Baseline asthma control was measured utilizing the Asthma Control Test (ACT)¹⁹ in children and the Juniper Asthma Control Questionnaire (ACQ) in both children and adults²⁰. The Asthma Symptom Utility Index (ASUI)²¹ and the Juniper mini-asthma quality of life questionnaire AQLQ²² were also collected at baseline. Participants returned to the study center for assessments of outcome measures every 4 weeks at which time information related to asthma exacerbations was collected.

Definition of Asthma Exacerbation

In both studies, an asthma exacerbation was defined as requirement for oral corticosteroids or an urgent health care visit for asthma symptoms.

Statistical Analyses

Child participants (SARCA) and adult participants (SARA) were analyzed separately. Each population was divided into the following two groups: participants with exacerbation (at least once); and participants without exacerbation, regardless of treatment group. Descriptive statistics (mean, 95% confident interval, count, and proportion) were used to summarize baseline demographics. We compared continuous measurements (e.g., FEV₁, ACQ scores) among participants with and without an exacerbation using the Wilcoxon rank sum tests since not all of the measurements were normally distributed. Chi-square (χ²) tests were used for categorical variables to test for statistically significant differences. For categorical variables, Fisher's tests were performed. P values of less than 0.05 (two-sided) were considered to indicate statistical significance. The statistical package SAS 9.3 (SAS Institute Inc., Cary, NC) was used to perform all analyses.

Results

Study Population

Three hundred and six children were enrolled in SARCA and 412 adults were enrolled in SARA. Data from 295 children and 402 adults who had information related to asthma exacerbations were included in the analyses. For children enrolled in SARCA, mean age was 11 years, age at asthma onset was 3-4 years, 50% were black, mean pre-bronchodilator FEV₁ was 92% of predicted. Sixty-seven percent of participants reported use of oral

corticosteroids in the previous year¹⁷. Fifty-nine percent of children were being treated with combination inhaled glucocorticoids and long acting beta agonists (ICS/LABA) with the remaining children being treated with ICS alone. For adults enrolled in the SARA study, mean age was 42 years, age at asthma onset was 17 years, approximately 50% had a BMI 30 kg/m², mean pre-bronchodilator FEV₁ was approximately 77% predicted¹⁸. About half of the adult patients reported use of oral corticosteroids in the previous year. Eighty-one percent of adults were being treated with ICS/LABA, 19% were being treated with ICS alone. Since use of PPIs was not shown to lead to difference in incidence of asthma exacerbations in either age group, the placebo and active treatment groups are combined for analysis.

Baseline Characteristics Associated with Exacerbation

Children: 110 of 295 children (37%) enrolled in SARCA experienced an asthma exacerbation during the 24-week treatment period (Table 1). Asthma exacerbation in children was significantly associated with lower age ($P=0.04$), but not with gender, race or body mass index (BMI). Unscheduled healthcare visits for asthma or use of oral corticosteroids in the previous year were significantly associated with asthma exacerbation during the subsequent study period. 83% of children who developed an exacerbation had an unscheduled visit for asthma in the previous year compared with 69% of children without an exacerbation ($p<0.01$). 80% of children who developed an exacerbation during the treatment period had been treated with oral corticosteroids in the previous year, compared with 61% of children who did not develop an exacerbation ($p<0.001$). Of children who had an exacerbation during the study period, 65% reported use of short acting beta agonist more than twice per week in the two weeks preceding randomization, compared with 80% of children who did not develop an exacerbation ($p<0.01$). Use of ICS/LABA was significantly more common in the exacerbation group ($p=0.04$). Among physiologic variables, only the pre- and post-bronchodilator FEV₁/FVC was significantly associated with asthma exacerbation ($p < 0.01$ and $P<0.0001$, respectively). Baseline asthma control or asthma quality of life scores did not significantly differ between children who experienced an asthma exacerbation and those who did not experience an exacerbation. There was no difference in bronchial hyper-responsiveness to methacholine between children who did and did not experience an exacerbation.

Adults: One hundred and eight of 402 adults (27%) experienced an exacerbation during the treatment period (Table 2). In adults, age, gender, race, BMI, and smoking status were not associated with increased risk of exacerbations. Adults who experienced an asthma exacerbation had significantly lower FEV₁ compared to adults who did not experience an exacerbation; 2.3L (74% predicted, 95% CI 2.1, 2.4) vs. 2.5L (78% predicted, 95% CI 2.4, 2.6), respectively; $p=0.02$.

Lower baseline composite scores on the ACQ as well as higher (worse) scores on the ASUI and AQLQ questionnaires were associated with significantly increased incidence of subsequent asthma exacerbations in adult subjects; these associations remained after adjustment for age, gender, race and baseline FEV₁. An unscheduled health care visit for asthma and treatment with oral corticosteroids in the previous year were significantly

associated with subsequent development of an asthma exacerbation ($p < 0.01$ and $p < 0.0001$, respectively). 71% of adults who experienced an exacerbation reported an unscheduled health care visit for asthma in the previous year, compared with 59% of subjects who did not have an exacerbation. Use of short acting beta-2 agonists more than twice per week was 81% in both groups and did not differ between adults who did and did not experience an exacerbation. Over 80% of adults in each of the two groups were being treated with ICS/LABA with no significant difference between groups.

Discussion

In our analysis of children and adults with sub optimally controlled asthma despite use of inhaled corticosteroids, we identified factors associated with an increased risk of subsequent asthma exacerbations. The rate of severe asthma exacerbations among our study participants was high; 37% of children and 27% of adults developed an exacerbation over the 24-week treatment period. It is noteworthy that the majority of participants did not suffer an exacerbation despite absence of well-controlled asthma at study baseline. Since the majority of asthmatics in the United States do not have well-controlled asthma⁴, identification of risk factors for asthma exacerbations in this population has the potential to guide treatment decisions and reduce asthma morbidity and mortality. Our post-hoc analysis of geographically diverse, well-characterized uncontrolled asthmatics enrolled into two prospective clinical trials demonstrates that in children and adults, history of an asthma exacerbation within the previous year is a strong predictor for future exacerbations. This finding is consistent with several previously published observational studies²³⁻²⁷.

We report several differences in characteristics associated with exacerbations between children and adults and identify additional risk factors for exacerbation in uncontrolled asthmatics. In our study, lower pre-bronchodilator FEV₁ was associated with subsequent exacerbation in adults, but not children. This finding may reflect airway remodeling as a contributor to increased risk of asthma exacerbations, a phenomenon recognized among even well controlled older adults, as recently reported by Dunn, et al²⁸. In children, pre and post-bronchodilator FEV₁/FVC ratio, but not FEV₁, was a predictor of exacerbations. FEV₁/FVC ratio has been shown in other studies to be a better marker of asthma severity and control than FEV₁ percent predicted in children^{29,30}, perhaps related to the fact that children with asthma have not had significant airway remodeling with permanent decrement in FEV₁. Use of more than one asthma controller therapy in children was associated with significantly higher rates of exacerbation during the 24-week observation period ($p < 0.04$), possibly reflecting baseline disease severity. However, the potential effects of long acting beta agonists on increased asthma exacerbations and increased bronchial hyper-responsiveness, as reported in several studies, must also be considered as a contributor to the increased numbers of exacerbations in these children^{31,32}. Not surprisingly, this relationship did not exist in adults since the majority of adults in our study were receiving ICS/LABA combination therapy at baseline. Use of short acting beta agonists however was inversely associated with asthma exacerbations in children and not associated with exacerbations in adults. One possible explanation for this finding is that children and/or their guardians who were more aware of asthma symptoms and more likely to act upon them were at lower risk for exacerbation.

Asthma questionnaire scores, including ACQ, ASUI, AQLQ and ACT were predictive of future exacerbations in adults but not children, perhaps due to relative inability of children to articulate symptoms of poor asthma control or quality of life. Conversely, in adults, worse scores on the ASUI, ACQ and AQLQ were associated with asthma exacerbations.

The Gaining Optimal Control of Asthma Study demonstrated that most patients with poorly controlled asthma could achieve adequate control through intensification of controller therapy ⁵. Though all patients with uncontrolled asthma would likely benefit from more aggressive treatment, such treatment is typically not utilized by patients in the real world setting. Lack of adequate treatment is due to a combination of factors including under-recognition of poor control by clinicians and patients ⁶, poor adherence to asthma controller therapy or unwillingness of patients with asthma to take medications due to concerns about safety. Improved methods for identifying patients at risk of asthma exacerbation are critical for reduce morbidity and mortality from the disease.

Our post-hoc analysis differed from previously published reports in that we did not identify body mass index, smoking status, second hand smoke exposure and race as risk factors for subsequent asthma exacerbations. Our results may also differ from previous studies in that our cohort was geographically and socioeconomically diverse^{33,34, 35}. One potential weakness of our study the fact that our study is limited to inclusion of risk factors collected during the parent clinical trials as well as the absence of specific biomarker data including fractional exhaled nitric oxide and sputum eosinophil measures. A major strength of our study is the fact that a diverse range of asthma patients is included, with different geographic, racial and socioeconomic status. Baseline asthma characteristics were well defined during enrollment of subjects into the parent clinical trials. In addition, through similar study designs and eligibility criteria, we were able to compare risk factors between children and adults. Our findings may help clinicians identify patients who are at higher risk for exacerbations and thus candidates for more aggressive asthma controller therapy. Additionally, use of these metrics may reduce escalation of treatment in those patients who are unlikely to develop exacerbations.

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Table 1
Baseline characteristics of childhood participants in the Study of Acid Reflux in Children with Asthma (SARCA)

Characteristic	Exacerbators [†]			Non- Exacerbators			P Value [*]
	N	Mean (95% CI)	N	Mean (95% CI)	N	Mean (95% CI)	
Age	110	10.9 (10.3,11.5)	185	11.6 (11.2,12.0)			0.04
Gender							0.24
Male	73	66%	110	59%			
Female	37	34%	75	41%			
Race							0.56
White	47	43%	68	37%			
Black	52	47%	94	51%			
Other	11	10%	23	12%			
Exposed to 2nd hand smoke							0.75
Yes	34	31%	54	29%			
No	76	69%	131	71%			
Age at asthma onset (years)	110	2.9(2.4,3.4)	185	3.7(3.2,4.1)			0.09
Number years with asthma	110	8.0(7.3,8.7)	185	8.0(7.4,8.5)			0.98
BMI (kg/m ²)	110	22.4(21.2,23.7)	185	22.5(21.7,23.4)			0.48
Baseline pre-BD FEV1 (L)	110	2.1(2.0,2.3)	185	2.3(2.2,2.4)			0.11
Baseline pre-BD FEV1 (%)	110	91.7(88.4,95.1)	185	92.3(90.2,94.5)			0.45
Baseline pre-BD FVC (L)	110	2.8(2.6,3.0)	185	2.8(2.7,2.9)			0.45
Baseline pre-BD FVC (%)	110	102.6(99.9,105.2)	185	99.8(97.7,101.9)			0.20
Baseline FEV1/VC (pre-BD)	110	77.1(75.1,79.1)	185	80.8(79.6,82.1)			<0.01
FEV1/FVC (post BD)	105	81.9(80.2,83.7)	181	86.0(84.8,87.1)			<.0001
% bronchodilator change	105	10.2(7.6,12.8)	181	9.3(7.9,10.7)			0.64
ACQ6 ^{††}	110	1.1(1.0,1.3)	185	1.2(1.1,1.3)			0.44
ACQ7 ^{†††}	110	1.2(1.0,1.3)	185	1.2(1.1,1.3)			0.60
ASUI (range 0 to 1) ^{†††}	110	0.82(0.79,0.85)	185	0.83(0.81,0.85)			0.43
AQLQ ^{†††}	110	5.4(5.2,5.7)	184	5.5(5.3,5.6)			0.95
ACT(range 5 to 25) ^{†††}	42	18.9(17.7,20.1)	94	19.0(18.3,19.8))			0.86

Characteristic	Exacerbators [†]			Non- Exacerbators			P Value [*]
	N	Mean (95% CI)		N	Mean (95% CI)		
cACT (range 0-27) ^{†††}	68	19.4(18.4,20.3)		90	20.1(19.3,21.0)		0.17
PC ₂₀ methacholine	73	2.8(1.8,3.7)		136	3.1(2.4,3.7)		0.55
Unscheduled healthcare visits for asthma in the past year	91	83%		127	69%		<0.01
Oral corticosteroid in the past year	88	80%		112	61%		<0.001
SABA>=2/week	71	65%		148	80%		<0.01
ICS/LABA	73	66%		100	54%		0.04

^{*} P-value from Fisher's test

[†] Exacerbations are the subset of participants who required steroids or an urgent visit

^{††} Lower values indicate less severe asthma

^{†††} Higher values indicate less severe asthma

BMI: Body mass index; FEV₁: forced expiratory volume in 1 second; FVC: forced vital capacity; BD: bronchodilator; ACQ6: Asthma Control Questionnaire question 6; ACQ7: Asthma Control Questionnaire question 7; ASUI: Asthma Symptom Utility Index; AQLQ: Asthma Quality of Life Questionnaire; PC20: provocative concentration causing a 20% drop in FEV₁; SABA: short acting beta-agonist

Table 2
Baseline Characteristics of adult participants in the Study of Acid Reflux in Adults with Asthma (SARA)

Characteristic	Exacerbators [†]			No- Exacerbators			P Value [*]
	N	Mean (95% CI)		N	Mean (95% CI)		
Age (years)	108	43.3(40.7,45.9)		294	41.1(39.6,42.6)		0.09
Gender							0.52
Male	32	30%		97	33%		
Female	76	70%		197	67%		
Race							0.34
White	56	52%		167	57%		
Black	41	38%		109	37%		
Other	11	10%		18	6%		
Smoking Status							0.75
Current	--	--		--	--		
Former	18	17%		53	18%		
Never	90	83%		241	82%		
Exposed to 2nd hand smoke							0.88
Yes	30	28%		84	29%		
No	78	72%		210	71%		
Age at asthma onset (years)	108	18.2(14.9,21.5)		294	15.9(14.1,17.8)		0.23
Number years with asthma	108	25.1(21.9,28.3)		294	25.2(23.4,26.9)		0.77
BMI (kg/m ²)	108	31.8(30.1,33.5)		293	32.0(31.1,33.0)		0.63
Baseline pre-BD FEV ₁ (L)	108	2.3(2.1,2.4)		293	2.5(2.4,2.6)		0.02
Baseline pre-BD FEV ₁ (%)	108	74.2(71.4,77.0)		293	77.8(76.0,79.6)		0.02
Baseline pre-BD FVC (L)	108	3.3(3.1,3.4)		293	3.4(3.3,3.5)		0.17
Baseline pre-BD FVC (%)	108	86.1(83.4,88.8)		293	87.5(85.8,89.3)		0.25
Baseline FEV ₁ /FVC (pre-BD)	108	70.5(68.5,72.5)		293	72.7(71.7,73.7)		0.10
FEV ₁ /FVC (post BD)	107	73.5(71.6,75.4)		292	75.8(74.8,76.8)		0.07
% bronchodilator change	107	10.2(8.6,11.7)		292	10.9(9.2,12.7)		0.62
ACQ6 ^{††}	108	1.9(1.7,2.1)		294	1.6(1.5,1.7)		0.01
ACQ7 ^{††}	108	2.1(1.9,2.2)		294	1.8(1.7,1.9)		<0.01

Characteristic	Exacerbators [†]			No- Exacerbators			P Value *
	N	Mean (95% CI)		N	Mean (95% CI)		
ASUI ^{†††}	108	0.71(0.68,0.74)		294	0.77(0.75,0.79)		<0.001
AQLQ ^{†††}	108	4.3(4.0,4.5)		294	4.8(4.7,4.9)		<0.001
PC ₂₀	33	3.1(1.8,4.4)		142	3.3(2.6,4.0)		0.66
Unscheduled healthcare visits in the previous year	77	71%		158	54%		<0.01
Oral corticosteroid use in the previous year	80	74%		120	41%		<0.0001
SABA >=2/week	88	81%		238	81%		0.90
ICS/LABA	90	83%		234	80%		0.40

* P-value from Fisher's test

[†] Exacerbations are the subset of participants who required steroids or an urgent visit

^{††} Lower values indicate less severe asthma

^{†††} Higher values indicate less severe asthma

BMI: Body mass index; FEV₁: forced expiratory volume in 1 second; FVC: forced vital capacity; BD: bronchodilator; ACQ6: Asthma Control Questionnaire question 6; ACQ7: Asthma Control Questionnaire question 7; ASUI: Asthma Symptom Utility Index; AQLQ: Asthma Quality of Life Questionnaire; PC₂₀: provocative concentration causing a 20% drop in FEV₁; SABA: short acting beta-agonist.