CHEST Online Supplement

Risk Factors and Predictive Clinical Scores for Asthma Exacerbations in Childhood

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e-Appendix

Methods

Study Population

Children who participated in this study were index cases for a family-based study of the genetics of asthma in Costa Rica. Of 7,130 schoolchildren whose parents returned the screening survey, 2,594 (36.4%) had asthma (physician-diagnosed asthma and at least 2 respiratory symptoms or an asthma attack in the previous year). Of these, 616 (23.6%) unrelated children had Costa Rican ancestry and were willing to participate in the study. There was no significant difference in sex or grade in school for children who did and did not participate. Written parental consent and written assent were obtained. The study was approved by the Institutional Review Boards of the Hospital Nacional de Niños (San José, Costa Rica) and Brigham and Women's Hospital (Boston, MA).

Pulmonary function tests

Subjects were instructed to avoid short-acting bronchodilators for at least four hours before testing. After baseline spirometry, subjects were given 200μg of albuterol via metered-dose inhaler using a spacer, and spirometry was repeated 15 minutes later to assess response to bronchodilator administration.

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Methacholine challenge testing

The protocol consisted of 5 breaths of saline solution followed by one breath of a 1 mg/mL methacholine solution, 1 and 4 breaths of a 5 mg/mL methacholine solution, and one breath of a 25 mg/mL methacholine solution. Inhalations were taken from a DeVilbiss 646 nebulizer (Sunrise Medical, Carlsbad, CA). After each level, spirometry was performed at 180, 210 and 240 seconds.

IgE levels and eosinophil count

Serum total and allergen-specific IgE levels were determined using a UniCAP 250 (Pharmacia & Upjohn, Kalamazoo, MI), with samples measured in duplicate. Serum was assayed for IgE to three allergens: cockroach (*Blatella germanica*), dust mite (*Dermatophagoides pteronyssinus*), and *Ascaris lumbricoides*. Eosinophil count was measured in peripheral blood by a Coulter-counter technique. IgE levels and eosinophil counts were $\log_{10}$-transformed for data analysis.

Clinical score

Variable selection: All variables that were significantly associated with the EP3-based (main) definition of asthma exacerbations in the univariate analysis were included. Using principal components analysis (PCA), factors or clusters of variables were identified. Decision was made *a priori* to only select factors with an Eigenvalue greater than 1 (see **e-Table 3** and **e-Figure 1**). In order to create a tool applicable in any setting by general practitioners and pediatricians, we decided *a priori* to exclude pulmonary function tests and laboratory results from the clinical score. The remaining factors (factors 4-10 in the table) were used to build a clinical score.

Variable reduction: Some of the identified variables were combined into one question either to simplify the process or because separate responses would not be available for replication in CAMP: “maternal history of eczema” and “paternal history of hay fever” were combined into “parental history of atopy” (in CAMP, parental eczema and/or hay fever were asked in one question, and this was the variable included in the analysis); “current smoke exposure” and “smoke exposure during infancy” were combined into one item. While some of these steps depend on subjective decisions by the investigators, they were based on prior knowledge on the matter, and they were made before evaluating the score in the validation sets.

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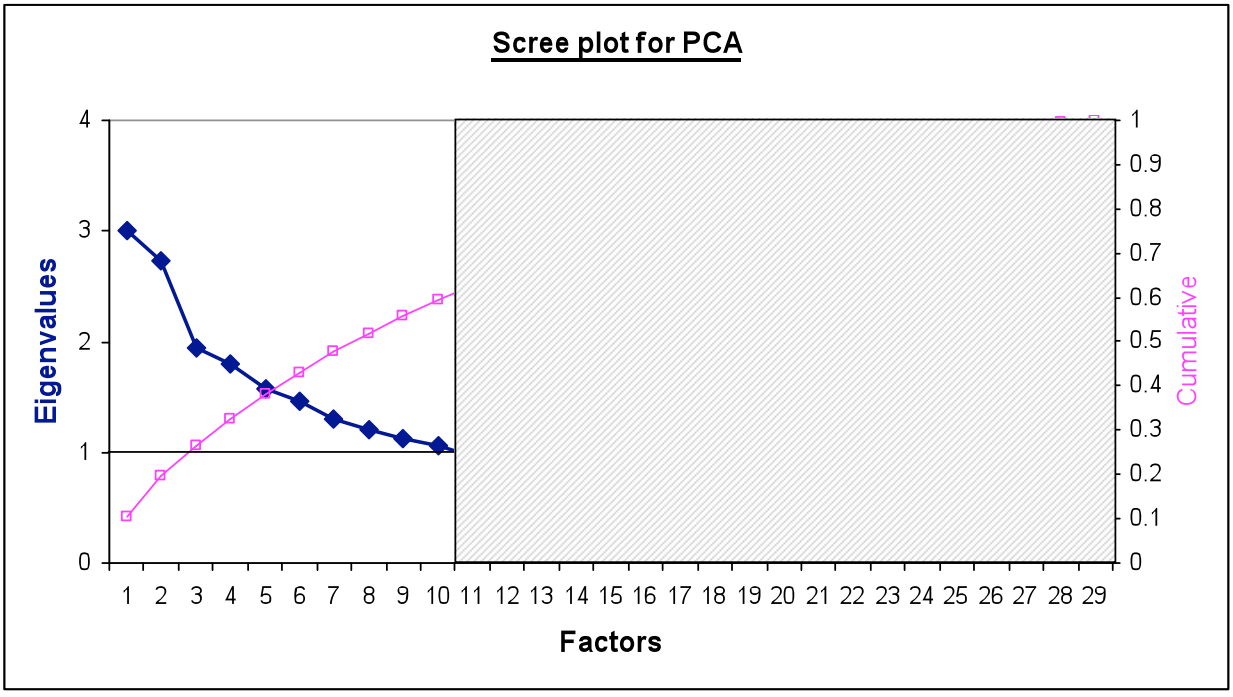
From PCA, each variable should be accompanied by a corresponding weight. However, all variables were assigned the same weight (in this case 0 for "no" and 1 for "yes") to improve simplicity and reduce the time required to administer the questionnaire. Finally, in a fashion similar to backward selection in logistic regression, the score was tested for the EP3 outcome, removing one variable at a time, and those variables found to not improve the performance or predictability were removed. The resulting 17 items for the final score are shown in **Figure 1** in the main manuscript.

Score validation: No further modifications were introduced once we moved from the exploratory subset to the validation set in Costa Rica or the CAMP trial cohort. Evaluation of the clinical score was then performed using both the EP3 and the ATS/ERS definitions in the Costa Rica validation set and in CAMP.

e-Figure 1. Scree plot for principal components analysis



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e-Table 1. Variable definitions

Variable name	*Definition*
Main outcome:	
Asthma exacerbation	1) EP3 definition: The NAEPP/NHLBI published the Expert Panel Report 3 (EP3) Guidelines for the Diagnosis and Management of Asthma in 2007. It defines several criteria for assessment of asthma control, among which is the number of exacerbations requiring systemic steroids per year: ≥2 indicates not well controlled. We therefore defined an exacerbation as any hospitalization and/or ≥ 2 acute care visits in the last 12 months. 2) ATS/ERS definition: In accordance to ATS/ERS consensus guidelines, a severe asthma exacerbation was defined as any hospital admission, acute/urgent visit, and/or oral steroid burst for asthma in the last 12 months. This definition was used only in the validation phases of the study. *Note:* Acute visits included emergency rooms, urgent care centers, and acute doctor's office visits related to exacerbations. For Costa Rica, it also included acute nebulization rooms.
Predictor variables:	
Anti-inflammatory medications	Reported use of inhaled steroids and/or leukotriene inhibitors
Bronchodilator response	FEV_1 increase ≥ 200mL or ≥ 12% over baseline
Doctor visits for asthma	Reported non-acute, scheduled doctor visits for asthma
Ever hospitalized for asthma	Ever admitted to the hospital for asthma (in Costa Rica, this variable excluded subjects admitted in the last year), as reported by the parents.
High eosinophil count	Peripheral blood eosinophil count ≥ 500 cells/mm^3
High IgE level	Serum total IgE level ≥ 100 IU/mL
Parental education level	Highest education level reported by either mother or father (highest of the two if both available)
PD_{20} / PC_{20}	Methacholine dose (for Costa Rica) or concentration (CAMP) that produced a 20% decrease in FEV_1 compared to baseline (best FEV_1 after inhalation of saline solution)
Positive methacoline test	FEV_1 decrease of 20% or more below baseline (best FEV_1 after inhalation of saline solution)
Positive allergen-specific IgE	Serum IgE ≥ 0.35 IU/mL for the specific allergen
Positive skin test	Wheal ≥ 3 mm larger than saline control
Prematurity	Birth before 37 weeks gestational age, as reported by parents
Treatment group	Treatment groups from the CAMP trial (placebo, nedocromil, or inhaled steroids)

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e-Table 2. Baseline characteristics in Costa Rica and CAMP

	Exploratory set (n=465)	*Validation set (n=150)*	*p**
Mean age in years (SD)	8.99 (1.81)	9.21 (1.90)	0.20
Male gender (%)	279 (60.0)	90 (60.0)	1.00
Parental educ. high school or higher (%)	235 (50.5)	75 (50.0)	0.93
Ever hospitalized for asthma (%)	195 (41.9)	56 (37.3)	0.34
Ever ICU for asthma (%)	8 (1.7)	2 (1.3)	1.00
Mean number of ER visits previous year	1.80	1.79	0.92
Mean number of doctor visits last yr	3.82	3.69	0.73
≥2 oral steroid bursts last year (%)	35 (7.5)	13 (8.7)	0.73
Doctor-diagnosed eczema (%)	24 (5.2)	9 (6.0)	0.68
Doctor-diagnosed hay fever (%)	127 (27.3)	42 (28.0)	0.92
High eosinophil count (%)	255 (54.9)	74 (49.3)	0.26
High IgE (%)	368 (79.1)	107 (71.3)	0.06
Short acting β_2 (%)	367 (78.9)	124 (82.7)	0.35
Inhaled steroids (%)	167 (35.9)	57 (38.0)	0.69
Leukotriene inhibitors (%)	21 (4.5)	2 (1.3)	0.08
Xanthines (%)	20 (4.3)	7 (4.7)	0.82
Father's history of: asthma (%)	106 (23.0)	31 (21.0)	0.66
eczema (%)	18 (3.9)	7 (4.7)	0.64
hay fever (%)	111 (24.1)	41 (27.5)	0.45
Mother's history of: asthma (%)	139 (30.0)	48 (32.0)	0.68
eczema (%)	25 (5.4)	12 (8.0)	0.24
hay fever (%)	135 (29.0)	40 (26.9)	0.68
Dyspnea walking up slight level (%)	366 (78.7)	124 (82.7)	0.35
Tightness walking up slight level (%)	332 (71.4)	115 (76.7)	0.25
Symptoms ≥ 3 months/year (%)	279 (60.0)	90 (60.0)	1.00
Smoke exposure, before 2yrs of age (%)	142 (30.6)	50 (33.6)	0.54
Smoke exposure, current (%)	128 (27.6)	41 (27.5)	1.00
Mean FEV_1/FVC pre-albuterol (SD)	82.5 (7.4)	82.4 (7.1)	0.86
Post-albuterol FEV_1 % increase (SD)	6.1 (9.9)	5.1 (8.5)	0.29
Mean PD_{20}/PC_{20}[c] from saline (SD)	2.42 (2.92)	2.50 (3.16)	0.82
Mean total clinical score (SD)	6.85 (2.2)	6.82 (2.1)	0.90
-Reported symptoms	3.8	3.8	0.26
-Healthcare utilization	1.1	1.0	0.10
-Medical history	0.8	0.8	0.61
-Current medications	1.2	1.2	0.70
Hospitalization and/or ≥2 acute visits (%)	324 (69.7)	104 (69.3)	0.94
-Any hospitalization (%)	27 (5.8)	8 (5.3)	0.83

*P-value for comparison between exploratory and validation sets in Costa Rica; Fisher's exact test (binary variables) or t-test (continuous variables).

e-Table 3. Principal components analysis: Factor loadings of clinical variables in Costa Rica[a]

	Factor[b]									
Variable	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Height (cm)	**0.94***	0.05	0.05	-0.01	-0.04	0.03	0.07	0.10	0.00	0.00
FEV_1 pre-bronchodilator (L)	**0.88***	-0.21	0.02	-0.01	-0.05	0.05	-0.03	0.00	0.08	0.06
Age (yrs)	**0.88***	0.04	0.08	-0.03	-0.07	0.04	0.06	-0.01	-0.13	-0.03
FEV_1/FVC (% change)	-0.04	**0.80***	0.04	-0.08	-0.02	0.03	0.11	0.02	0.06	0.09
Bronchodilator response	-0.05	**0.72***	0.12	-0.12	0.18	-0.03	0.08	-0.04	-0.04	0.07
Gender	0.19	0.32	0.08	0.23	0.01	-0.04	-0.28	-0.31	0.13	-0.20
FEV_1/FVC pre-bronchodilator (L)	0.03	**-0.77***	-0.07	-0.17	0.02	-0.01	-0.02	-0.14	0.07	0.16
Positive IgE to dust mite	0.07	0.10	**0.77***	0.00	-0.07	-0.03	0.01	0.15	0.04	0.04
Eosinophils (cells/mm^3)	-0.05	0.03	**0.75***	-0.05	0.11	-0.02	0.04	-0.01	0.12	0.08
Positive IgE to ascaris	0.14	0.09	**0.62***	0.07	0.08	-0.01	0.06	0.05	-0.18	-0.06
Symptoms with exercise	0.04	-0.02	0.02	**0.73***	0.03	-0.02	0.16	0.00	-0.13	0.05
Shortness of breath with activity	-0.01	-0.02	-0.03	**0.66***	0.00	0.09	0.03	0.20	-0.22	0.07
Symptoms with cold air	-0.08	0.04	0.20	**0.60***	0.02	0.00	0.10	-0.21	0.09	0.08
Symptoms with colds or flu	-0.01	-0.01	-0.08	**0.51***	0.08	0.02	-0.07	0.02	0.16	-0.03
Courses of steroids last year	0.05	0.08	0.09	0.00	**0.84***	-0.01	0.02	-0.04	-0.04	0.03
Doctor visits last year	-0.19	0.08	0.09	0.16	**0.81***	0.03	0.11	0.10	0.05	0.09
Smoke exposure, current	0.03	0.02	-0.04	0.05	0.01	**0.90***	0.03	0.02	-0.02	-0.02
Smoke exposure, infancy	0.07	-0.01	-0.03	0.02	-0.04	**0.86***	-0.04	0.00	-0.11	0.01
History of bronchiolitis or	0.05	0.16	-0.12	0.07	0.08	-0.05	**0.67***	-0.03	-0.02	0.00
Ever hospitalized for asthma	-0.01	0.11	0.26	0.10	0.11	0.09	**0.57***	-0.01	-0.10	0.03
Ever ICU for asthma	0.10	-0.09	0.22	0.07	-0.13	0.00	**0.47***	-0.07	0.28	-0.03
Short-acting β_2 agonists	0.01	0.09	0.21	0.15	0.01	-0.05	0.09	**0.70***	0.13	-0.13
Maternal history of eczema	-0.12	0.00	-0.03	0.11	-0.03	-0.04	0.18	**-0.64***	0.12	-0.10
Parental education	0.01	-0.02	0.05	-0.05	-0.05	-0.15	-0.03	-0.09	**0.77***	0.18
Inhaled steroids	-0.12	0.17	-0.02	0.07	0.17	0.13	0.26	0.31	**0.43***	-0.15
Leukotriene inhibitors	-0.05	-0.11	-0.16	-0.04	**0.38***	-0.11	-0.07	0.07	**0.39***	-0.14
Symptoms with dust	0.04	-0.03	0.15	0.11	0.05	0.05	0.01	-0.04	0.04	**0.79***
Paternal history of hay fever	0.03	-0.01	-0.19	-0.04	-0.07	-0.22	**0.40***	0.00	0.02	**0.44***
Symptoms over 3 months per year	-0.19	0.17	-0.05	0.17	0.28	0.04	-0.22	0.32	0.09	**0.41***
Variance	2.630	2.063	1.903	1.828	1.739	1.687	1.487	1.374	1.288	1.201

Laboratory values and pulmonary function tests obtained by research team during study visit. Past family, medical, and respiratory histories as reported by parents in study questionnaire; unless specifically stated, questions referred to the 12 months prior to the interview. [a]Principal components analysis with varimax (orthogonal) rotation. [b]Factors 4-10 used in clinical score. [c]Reported history of bronchiolitis and/or pneumonia during the first 2 years of life. [*]Significant loading.

e-Table 4. Score model characteristics in both samples

	Costa Rica[a]	CAMP 1-year	CAMP 2-years
Odds / risk ratio (95%CI)[b]	1.71 (1.5-1.9)	1.24 (1.2-1.3)	1.25 (1.2-1.3)
P-value	<0.0001	<0.0001	<0.0001
C-statistic[c]	0.78	0.69	0.66
Goodness of fit[d]	0.61	0.70	0.11

[a]Costa Rica sample as a whole (n=615). [b]Adjusted logistic regression using score as a continuous variable rather than categories. Costa Rica adjusted for age, gender, and parental education. CAMP adjusted for age, gender, race, and treatment arm. [c]C-statistic is equivalent to the area under the curve (AUC) in an ROC curve. [d]Hosmer-and-Lemeshow goodness of fit (GOF).

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