# Certain subphenotypes of aspirin-exacerbated respiratory disease distinguished by latent class analysis

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**Background: Aspirin-exacerbated respiratory disease (AERD) is recognized as a distinct asthma phenotype. It usually has a severe course accompanied by chronic hyperplastic eosinophilic sinusitis with nasal polyps, blood eosinophilia, and increased concentrations of urinary leukotriene $E_4$ ($LTE_4$). More insightful analysis of individual patients shows this group to be nonhomogeneous.**

**Objective: We sought to identify any likely subphenotypes in a cohort of patients with AERD through the application of latent class analysis (LCA).**

**Methods: Clinical data from 201 patients with AERD (134 women) were collected from questionnaires. Standard spirometry, atopy traits, blood eosinophilia, and urinary $LTE_4$ concentrations were evaluated. LCA was applied to identify possible AERD subphenotypes.**

**Results: Four classes (subphenotypes) within the AERD phenotype were identified as follows: class 1, asthma with a moderate course, intensive upper airway symptoms, and blood eosinophilia (18.9% of patients); class 2, asthma with a mild course, relatively well controlled, and with low health care use (34.8% of patients); class 3, asthma with a severe course, poorly controlled, and with severe exacerbations and airway obstruction (41.3% of patients); and class 4, poorly controlled asthma with frequent and severe exacerbations in female subjects (5.0% of patients). Atopic status did not affect class membership. Patients with particularly intensive upper airway symptoms had the highest levels of blood eosinophilia and the highest concentrations of urinary $LTE_4$.**

**Conclusions: LCA revealed unique AERD subphenotypes, thus corroborating the heterogeneity of this population. Such discrimination might facilitate more individualized treatment in difficult-to-treat patients. (J Allergy Clin Immunol 2014;133:98-103.)**

***Key words:*** *Aspirin, aspirin-exacerbated respiratory disease, asthma phenotype, latent class analysis, nonsteroidal anti-inflammatory drugs*

*Abbreviations used*

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| AERD: | Aspirin-exacerbated respiratory disease |
| cysLT: | Cysteinyl leukotriene |
| ED: | Emergency department |
| ICU: | Intensive care unit |
| LCA: | Latent class analysis |
| $LTE_4$: | Leukotriene $E_4$ |
| NAEPP EPR3: | National Asthma Education and Prevention Program Expert Panel Report 3 |
| NSAID: | Nonsteroidal anti-inflammatory drug |
| TENOR: | The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens |

Aspirin-exacerbated respiratory disease (AERD) is a distinct clinical syndrome characterized by chronic eosinophilic inflammation of the upper and lower airways with symptoms that are exacerbated by aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs).[1-3] It is generally recognized as severe asthma with a predilection for female subjects that develops in line with a characteristic sequence of symptoms.[2] The majority of patients have chronic hyperplastic eosinophilic sinusitis with nasal polyps characterized by rapid regrowth, resulting in multiple sinus surgeries.[4]

Atopy is rather frequent in this population.[4,5] Most patients with AERD synthesize excessive amounts of cysteinyl leukotrienes (cysLTs) in a stable condition, which is reflected by increased urinary leukotriene $E_4$ ($LTE_4$) concentrations when compared with those seen in asthmatic patients who tolerate aspirin well.[6]

In view of this relatively distinct clinical and pathophysiologic presentation, AERD is regarded as one of the specific asthma phenotypes.[7] When individual cases are more insightfully analyzed, however, this group no longer appears to be so homogenous, differing in terms of specific clinical and laboratory parameters.

Clinical studies carried out to date on numerous groups of patients with AERD have analyzed the prevalence or mean values of several parameters and subsequently proposed the average clinical picture of this asthma phenotype.[2,4] Another approach compared a large group of patients with AERD with patients with aspirin-tolerant asthma in terms of several differentiating clinical variables.[8]

The present study aimed to identify and describe the likely subphenotypes within a cohort of patients representing the AERD phenotype by applying advanced statistical modeling methods. As opposed to the previously referenced variable-oriented studies, the present study was focused on patients. Hence we applied latent class analysis (LCA) to group together patients with AERD who were similar to each other in terms of the selected clinical variables.

With regard to respiratory diseases, this statistical approach had been applied in large populations, which effectively helped to

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Supported by a grant from the Polish Ministry of Science and Higher Education and Jagiellonian University (K/ZDS/001022).

Disclosure of potential conflict of interest: The authors have been supported by a grant from the Polish Ministry of Science and Higher Education (no. K/ZDS/001022).

Received for publication February 23, 2013; revised June 15, 2013; accepted for publication July 9, 2013.

Available online August 27, 2013.

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0091-6749/$36.00



http://dx.doi.org/10.1016/j.jaci.2013.07.004

identify several wheezing and asthma phenotypes.[9-11] Another methodology (ie, a hierarchic cluster analysis) facilitated the identification of distinct clinical phenotypes in asthmatic adults and children.[12-14]

## METHODS

### Subjects studied

The participants were recruited from consecutive patients given a diagnosis of AERD at the Department of Internal Medicine, Jagiellonian University Medical College, Krakow, Poland. The recruitment phase spanned from June 2008 to September 2010. In total, 201 patients were enrolled. They remained without any asthma exacerbations in the 4 weeks preceding the study and received asthma medications as currently prescribed by their physicians. All patients signed informed consent forms approved by the Jagiellonian University Ethics Review Committee.

The AERD diagnosis was made before the study. It was based on a typical history confirmed by a positive oral or inhaled aspirin challenge result.[15] In 42 patients with severe steroid-dependent asthma, the diagnosis had to be based exclusively on the unequivocal clinical picture and a history of asthma attacks after ingestion of NSAIDs. Because of both low $FEV_1$ and the nonfeasibility of reducing the dosage of oral corticosteroids, these patients never qualified for the aspirin challenge.[15]

### Data collection

Patients' data were collected from a specifically structured questionnaire. Participants underwent a demographic and detailed medical history interview. The current level of asthma severity was based on the National Asthma Education and Prevention Program Expert Panel Report 3 (NAEPP EPR3).[16] Asthma control was assessed by using the Asthma Control Test. Standard spirometry and skin prick tests were performed. Blood eosinophilia, total IgE levels, and baseline urinary $LTE_4$ concentrations were measured (see the Methods section in this article' Online Repository at www.jacionline.org).

### Analytic strategy and selection of variables

Latent class models were fitted to the clinical and laboratory variables assessed in the study.[17] This statistical modeling technique was used to estimate the number of classes of underlying categorical latent variables with a finite number of mutually exclusive levels, which simultaneously considered the relationships between the respective numbers of variables under consideration. Two types of parameters were estimated: the prevalence of each latent class (ie, *a priori* probability that a selected subject was in each class) and the conditional probabilities describing the distribution of the responses to each question within each class. Identification of the optimal model was done in a stepwise manner (see the Methods section and Table E1 in this article' Online Repository at www.jacionline.org). The best-fitting 4-class model was finally determined. Each subject was allocated to a single latent class based on the maximum-probability assignment rule (ie, to the class with the highest *a posteriori* probability of membership; see the Methods section and Table E2 in this article' Online Repository at www.jacionline.org).

The applied procedure demonstrated that the membership probability was more than 0.8 for 160 (79.6%) patients and more than 0.9 for 124 (61.7%) patients. Only for 10 (5.0%) patients was the highest membership probability less than 0.6, thus indicating its more ambiguous nature.

Because LCA requires categorization and independence of the considered variables, the following variables relevant to the study were analyzed: asthma age of onset; body mass index; current level of asthma control; asthma-related emergency department (ED) visits, hospitalizations, and stays in the intensive care unit (ICU) through the entire time of asthma duration; upper airway symptoms, occurrence of nasal polyps, and history of polypectomies as indicators of chronic rhinosinusitis; $FEV_1$ percent predicted; $\Delta FEV_1$ after bronchodilator; skin prick test responses; total IgE levels; and blood eosinophilia (detailed in the Methods section in this article' Online Repository).

Sex effects and asthma duration were additionally estimated as covariates. The class membership probabilities were estimated separately for male and female patients by using sex as a categorical covariate.

After identifying the 4 final classes, the mean values of the logarithmically transformed urinary $LTE_4$ concentrations were calculated and compared among the classes. In each class treatment of asthma (divided into 4 categories) was assessed, and the proportion of patients using each category of treatment was computed. Finally, the current level of asthma severity was analyzed. In each class the proportion of patients representing each level of asthma severity was computed as well (see the Methods section in this article' Online Repository).

### Statistical analysis

The statistical software SAS version 9.1 (SAS Institute, Cary, NC) was used to calculate the descriptive statistics and to carry out all analyses, including LCA (PROC LCA version 1.2.7).[18] One-way ANOVA was applied to assess the difference in the logarithmically transformed $LTE_4$ measurements among the 4 classes. The statistical significance was set to an $\alpha$ level of .05. The odds ratio of being in a given class relative to the fixed reference class for a 1-year increase within asthma duration was estimated by using logistic regression, with the latent class as the dependent variable and asthma duration as the independent variable.

## RESULTS

The clinical characteristics for the entire AERD cohort are presented in Table I. The main characteristics of the respective classes are summarized below (detailed in Table II and Table E3 in this article' Online Repository at www.jacionline.org).

Thirty-eight (18.9%) patients (mean age, 41.4 $\pm$ 11.5 years) were allocated to class 1, which was defined as having "asthma with a moderate course, intensive upper airways symptoms, and blood eosinophilia." This class contained the highest proportion of patients with chronic rhinosinusitis, as determined by upper airway symptoms and the occurrence of nasal polyps. The frequency of asthma-related ED visits was equally distributed within the 3 established intervals. Only half of the patients had a high frequency of hospitalizations, whereas the other half displayed low numbers. Stays in the ICU were very rare. Asthma was partially controlled in half of the patients and uncontrolled in one third, even though 87% of patients were treated with oral corticosteroids, inhaled corticosteroids, or both (Fig 1). Mild asthma was established in 34% of patients, moderate in 29%, and severe only in 10.5% (Fig 2). The highest proportion of patients had increased blood eosinophil counts. This class was also unique in its significantly highest urinary $LTE_4$ concentration (Fig 3).

Seventy (34.8%) patients (mean age, 50.1 $\pm$ 13.4 years) were grouped into class 2, which was defined as having "asthma with a mild course, relatively well controlled, with low health care use." This group comprised the highest proportion of male patients. The frequency of asthma-related ED visits and hospitalizations was the lowest. This class had the best asthma control, even though 25.7% of patients remained without any corticosteroid treatment (Fig 1). These patients had milder asthma because 35.7% had intermittent and 25.7% had mild disease (Fig 2). The urinary $LTE_4$ concentration was comparable with that in class 3 patients, although significantly lower than in class 1 patients (Fig 3).

Eighty-three (41.3%) patients (mean age, 52.7 $\pm$ 10.2 years) were allocated to class 3, which was defined as having "asthma with a severe course, poorly controlled, with severe exacerbations and airway obstruction." Female patients outnumbered male