

Title:

Identification and characterization of near-fatal asthma phenotypes by cluster analysis

Short title: Near-fatal asthma phenotypes by cluster analysis

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ABSTRACT

Background: near-fatal asthma (NFA) is a heterogeneous clinical entity and several profiles of patients have been described according to different clinical, pathophysiological and histological features. However, there are no previous studies that identify in a unbiased way - using statistical methods such as clusters analysis – different phenotypes of near-fatal asthma. Therefore, the aim of the present study was to identify and to characterize phenotypes of near fatal asthma using a cluster analysis.

Methods: over a period of two years, 33 Spanish hospitals enrolled 179 asthmatics admitted for an episode of near-fatal asthma. A cluster analysis using two-steps algorithm was performed from data of 84 of these cases.

Results: the analysis defined three clusters of patients with NFA: cluster 1, the largest, including older patients with clinical and therapeutic criteria of severe asthma; cluster 2, with an high proportion of respiratory arrest (68%), impaired conciousness level (82%) and mechanical ventilation (93%); and cluster 3, which included younger patients, characterized by an insufficient anti-inflammatory treatment and frequent sensitization to *Alternaria alternata* and soybean.

Conclusions: these results identify specific asthma phenotypes involved in NFA, confirming in part previous findings observed in studies with a clinical approach. The identification of patients with a specific NFA phenotype could suggest interventions to prevent future severe asthma exacerbations.

KEY WORDS: asthma, cluster analysis, mechanical ventilation, near-fatal asthma, phenotypes.

INTRODUCTION

The World Health Organization estimated 225,000 deaths caused by asthma worldwide in 2005 (1), projecting about 430,000 by 2030 (2). Patients who die from asthma (fatal asthma) as well as those who suffer life-threatening exacerbations (near-fatal asthma) can be considered as part of the same group (3, 4). Although some authors have described near-fatal asthma (NFA) as a single phenotype (5), there are numerous studies defining different subtypes of patients according to the etiology, pathogenesis and clinical course of this type of asthma (6, 7). The use of statistical techniques such as cluster analysis has identified, in less severe forms of asthma, different phenotypes of this and other respiratory diseases (8-10). However, to our knowledge, there are no previous studies of this type in NFA.

The “Multicentric Life-Threatening Asthma Study” (MLTAS) was designed to identify and describe different clinical profiles of NFA. Its findings have provided information on different subgroups of patients with NFA and highlighted the influence that some clinical, psychological and physiological conditions have on NFA patients (11-14). The technique of clusters analysis provides us with a new approach to the evaluation of MLTAS data. Hence, the aim of the current study was to explore the information previously collected, in a non-biased way, in order to complete our findings based on clinical observations and to reveal new aspects about the heterogeneity of NFA.

METHODS

Study design

Our dataset included baseline data from patients with asthma (n= 179) recruited from the MLTAS. A detailed description of methods used has been published previously (11). Briefly, a descriptive and prospective multicentric study was carried out in 33 hospitals throughout Spain. These centers provided health care to 15,000,000 inhabitants, i.e. 40% of the total Spanish population. Patients were enrolled from April 1997 until March 1999. The Ethics Committee of each hospital approved the study. Informed consent was obtained from patients or their relatives.

Patients

Asthmatics of both sexes aged ≥ 15 years were prospectively and consecutively included. All patients fulfilled the American Thoracic Society diagnostic criteria for asthma (15). A NFA episode was defined as a severe asthma exacerbation accompanied by at least one of the following: 1) respiratory arrest; 2) requirement for mechanical ventilation (MV); and 3) hypercapnia (arterial carbon dioxide tension of >50 mmHg) and/or acidosis (pH of <7.30). Exclusion criteria were the concomitant presence of different acute diseases such as heart disease or pulmonary embolism, suspected of inducing the exacerbation.

Variables measured

All patients completed a 72-item enrollment form specifically designed for the study. This information was divided into five areas: 1) demographic and sociocultural variables; 2) clinical and functional characteristics of asthma; 3) clinical condition on hospital arrival; 4) in-hospital progression of the NFA attack; and 5) spirometric and immunological studies (prick-test, RAST). Information on pharmacological therapy for asthma and their compliance was obtained directly from patients, regardless of the prescribed treatment.

Additionally, patients completed two psychological self-administered questionnaires (16, 17). The Spanish validated version of the Toronto Alexithymia Scale (16) was used to determine the presence of alexithymia, a personality trait defined by the difficulty to identify, distinguish and describe emotions and bodily sensations such as dyspnea (18).

Furthermore, psychiatric disorders were determined from a separate self-reported questionnaire, the 28-item version of the General Health Questionnaire (GHQ), also validated in its Spanish version (17, 19).

Variable reduction

The entire MLTAS dataset provided information about 74 items, that were reduced to 44 variables before cluster analysis use (Table 1). Thus, variables relating to the asthma treatment, atopy, and sensitization to allergens were recoded, grouping their content by categories (e.g. inhaled glucocorticoids, pollens). In cases of redundant

information, such as pulmonary function values, only data with a high clinical significance was selected (eg. FEV₁). On the other hand, variables with minimal differences among patients, such as those related with hospital drug treatment of acute asthma, were also ruled out. Finally, by cluster analysis requirements, we excluded outliers and patients who had incomplete data in any of the variables studied.

Statistical analysis

Cluster algorithm was applied to identify relatively homogeneous groups of cases based on selected characteristics. Clustering divides the data into n groups such that the within-group sum-of-squares is minimized. Number of groups was calculated previously by complete hierarchical clustering analysis. We applied the *two-step* clustering method, that offers the possibility to handle both continuous and categorical variables, as in our case (20). We standardized the observations to have zero mean and unit standard deviation. Then, quantitative variables with different scale units and nominal scaled variables may be simultaneously analyzed.

Data were analyzed with "SPSS Statistics 15.0 for Windows" (SPSS Inc., Chicago, IL). A descriptive analysis of all variables was performed. The values were expressed as mean and standard deviations or percentages. Quantitative variables of 3 clusters were compared using ANOVA or, when its distribution was not normal, using the Kruskal-Wallis test. Qualitative variables were analyzed using Chi-square or Fisher exact test. Statistically significant differences were those that presented a p -value < 0.05 .

RESULTS

Over two years of data collection, 179 NFA episodes were recorded (15-83 years, 61% women). Complete information was available for all variables in 84 cases. There were not statistically significant differences between the groups of cases included and excluded for the analysis about several demographic and clinical variables (Table 2).

The results of cluster analysis obtained from those 84 patients allowed to distinguish a three-cluster model of asthmatics with NFA, whose characteristics are shown in Tables 3-5.

Cluster 1

Thirty-three patients were grouped into this cluster (39%), in which women predominated (82%). Patients of this cluster were older compared with patients of clusters 2 and 3. The mean age at onset of asthma (35.9 years) was significantly higher than cluster 2 and 3. In addition, educational level of cluster 1 was the lowest of the 3 groups. This cluster had the highest prevalence of severe persistent asthma (82% of patients) defined by GINA criteria (21), and there were no cases of intermittent or mild persistent asthma. The FEV₁ mean value in this group also was the lowest, although this difference was not statistically significant. As regards to asthma medications, almost all patients (91%) were taking inhaled corticosteroids (ICS), combined with salmeterol or formoterol in 70% of cases. A 21% of patients also used systemic glucocorticoids and a 30% received ipratropium bromide. This cluster was also characterized by higher ratios of hospital admissions and visits to an emergency department after a severe asthma exacerbation. Finally, 49% of patients had previously presented at least one episode of NFA. All this despite being the group that had the highest frequency of regular medical monitoring (82%) and written asthma action plans (45%). On the other hand, this group showed the lowest proportion of patients with allergic sensitization (42%) but the highest percentage of previous history of nasal polyps (15%), psychiatric comorbidity (64%) and alexithymia (49%).

Cluster 2

A third of patients (n=28) were assigned to Cluster 2. The mean age was intermediate between clusters 1 and 3 and this group showed the highest proportion of intermediate and higher level of education (39%). In most demographic, psychological and therapeutic variables, patients of this cluster were placed halfway between clusters 1 and 3. Regarding asthma treatment, only 50% of patients were receiving ICS, with a mean doses (523 mcg/day of budesonide) between cluster 1 and cluster 3. The most obvious feature of this subgroup was the presence of a high percentage of impaired consciousness level (82%) and respiratory arrest (68%) on

arrival at hospital. Accordingly, they showed the highest levels of respiratory acidosis (mean pH: 7,09) and hypercapnia (mean PaCO₂: 78 mmHg), and 93% of them needed mechanical ventilation (p<0,001).

The degree of sensitization to allergens was similar between Clusters 2 and 3, and there were also no significant differences between the 3 clusters with respect to a known history of nonsteroidal antiinflammatory drugs (NSAIDs) intolerance.

Cluster 3

Twenty-three patients were assigned to Cluster 3. This cluster was younger (mean age: 42,4 years) and showed an earlier onset of asthma. This group also had the highest percentage of male (74%) and the lower incidence of psychiatric comorbidity. The patients of clusters 2 and 3 were current smokers much more frequently than cluster 1.

The proportion of sensitization to certain allergens involved in previous studies with NFA, such as soybeans or spores of *Alternaria alternata* (22, 23) were higher in this cluster (26%) compared with the other groups.

Other main features of this subgroup were: 1) only 4% of patients showed a periodic medical monitoring of their asthma; 2) only 30% of them received ICS treatment; and 3) none of patients followed a written action plan for asthma during the NFA attack.

DISCUSSION

The concept of asthma has evolved substantially in recent decades. At present, is understood as a multidimensional disorder with different phenotypes (24). Consequently, for many years has been an increasing interest in the characterization of different clinical, biological or genetic asthmatic subtypes, which has resulted in different asthma phenotypes and endotypes (8-10, 25-26). This heterogeneity of asthma can also be observed in NFA. In fact, it has been described different forms of clinical and pathology presentation (6, 7). Cluster analysis has identified different phenotypes of asthma and other respiratory diseases (8-10). But, to our knowledge, this is the first cluster analysis to explore, specifically, different phenotypes of NFA.

The MLTAS was designed to identify and characterize the different clinical subtypes of NFA asthma. A further analysis of the MLTAS data using cluster analysis technique has enabled us to identify three clusters of asthmatics with NFA that shared phenotypic features (Table 6).

Patients included in Cluster 1 appear to be with more severe asthma according GINA guidelines and asthma medications requirements. In this subgroup there are concentrated numerous factors previously identified as risk factors for NFA: 1) previous visits to emergency care or hospitalizations for acute asthma, 2) previous history of NFA episodes, and 3) previous history of asthma exacerbations that required MV (6, 26). They also showed a higher incidence of psychiatric and psychological disorders, a common feature in NFA (12, 27). It is possible that this fact, together with the lower educational level of this group, could explain the low use of written asthma plans (21%), despite being the patients with the best medical follow-up. In this sense, our results require recall, once again, the importance of preventive health strategies and extreme care to patients with a history of NFA (or risk factors for this type of asthma), in order to prevent further exacerbations.

Asthmatics of Cluster 2 had an intermediate position with respect to the other clusters in many of variables. In issues such as clinical and gasometric findings at the time of admission to hospital, the most obvious feature of this cluster was the large proportion of patients with decreased level of consciousness and respiratory arrest, accompanied by increased respiratory acidosis and hypercapnia. In an acute asthmatic attack, the rapid shallow breathing associated with the increased elastic and resistive inspiratory load increases the work of breathing and consequently the energy demands. This fact, together with the fatigue caused by hypoxemia in both diaphragm and abdominal muscles (28), could lead to the suffocation of the patient. This mechanism, rather than cardiac arrhythmias, seems to be responsible of the deaths from asthma (29). Hypoxemia also causes a decrease in the perception of dyspnea, while hypercapnia produces a cognitive impairment (30). Poor perception of the severity of an asthma attack has been proposed as a mechanism underlying treatment delay (31), with a consequent increase in morbidity and mortality of asthma (32). However, this was not the case in our study. Patients in Cluster 2 showed a minor delay in arriving at the hospital [159 (159) minutes], compared to

Cluster 1 [445 (573) minutes] and Cluster 3 [471 (675); $p=0,025$]. The transfer, furthermore, occurred in ambulance in greater proportion than in the other two groups (64% vs. 39% and 17%; $p=0,005$). In any case, the effect that respiratory failure can produce in the worsening of asthmatic exacerbations and in the decrease in the perception of their symptoms supports the oxygen therapy as soon as possible during acute severe asthma to correct hypoxemia. And, in asthmatics with a blunted perception of dyspnea, frequent measurements of airway narrowing, such as peak-flow monitoring, are required to assess the patient's real condition (31).

Finally, patients in Cluster 3 were characterized by a different profile of sensitization to certain allergens, such soybean and *Alternaria alternata*, compared to the rest of asthmatics. They were younger and, unlike the other clusters, the vast majority of them (73%) were men. Both demographic characteristics were similar to the findings of some previous studies of NFA related with these aeroallergens. Download of soybean in the city's port was the cause of the "epidemics" of NFA described in Barcelona in the 80s of the last century (22). Between August 1981 and September 1987, 26 outbreaks of asthma exacerbations, which affected 687 patients and caused 1,155 hospital admissions, were detected. These patients required admission to an intensive care unit in 11.9% of cases, and 8.5% needed mechanical ventilation. Often, patients had sudden-onset asthma attacks, especially the men, arriving at the hospital in agonizing situation. Surprisingly, many of them recovered quickly and they could be extubated within hours (33). Other Spanish and American port cities have been the scene of similar outbreaks (34).

Regarding *A. alternata*, sensitized patients were also significantly younger in previous studies, although women were predominant (14, 23). Although their hospital admission length was shorter, as in the present study, they showed a remarkable number of deaths or severe neurological sequelae

On the other hand, it is noteworthy that more than 50% of patients in this cluster did not have any medical follow up of their asthma, only 4% had a regular control and none followed a written asthma action plan during de NFA attack. Related to this, 70% of these patients were not on corticosteroid medication. These factors, along with smoking, make it more difficult to control asthma, increasing their mortality and

the risk of NFA episodes (4, 26). This group of asthmatics, and possibly some patients of the Cluster 2, have similar characteristics to the NFA patients studied by Romagnoli et al (5). They compared 24 patients with a history of NFA, 64 with severe asthma and 67 with moderate asthma. His main finding was the observation that the NFA patients received treatment with inhaled glucocorticoids in a much smaller proportion than the other two groups

Our study presented some limitations. In addition to the lack of parameters of cellular inflammation, obesity, a significant factor in the development and control of asthma (8), was not recorded. At the moment in which we designed the MLTAS, this circumstance was not as well recognized. Another limitation of this study was the relatively high number of cases of the original database that could not be included in the cluster analysis because their information was partially incomplete. Although there were no significant differences in demographic variables, severity of asthma, lung function, allergen sensitization or development of the NFA episodes between the rejected and the included cases (Table 2), it is possible that the reduction in the number of patients has limited the statistical significance of some of the differences observed between the 3 clusters. Finally, it would have been desirable to confirm prospectively our model of NFA clusters. In practice, such confirmation would not be feasible, given the changes occurred in our country in terms of asthma management from the time of our data were collected (35). At present, as a result of closer adherence to the clinical practice guideline recommendations, is likely that the profile of patients in Cluster 3 and a part of the Cluster 2 were less common.

In summary, the results of this study are consistent with a large body of previous clinical works that suggest that NFA presents a heterogeneous nature. The use of cluster analysis allowed us to confirm, in a non-biased way, several risk factors of NFA previously reported. Among them, some variables related with a more severe asthma, a high use of health resources and the absence of an adequate treatment and monitoring of asthma, including a very limited use of asthma action plans. Finally, our finding on the presence of a phenotype of NFA related to the sensitization to soybean and *A. alternata* suggests the existence of a specific pathogenic mechanism. The recognition of different profiles in NFA patients should ideally involve improvements in the design of specific therapeutic strategies for each

NFA phenotype, adapting the management of patients to their specific characteristics, as well as to correct their shortcomings.

AUTHOR'S CONTRIBUTIONS:

- José Serrano-Pariente: design of the work; acquisition, analysis and interpretation of the data for the work; writing the article; guarantor of the paper.
- Gustavo Rodrigo: critical revision of the work and writing the article.
- José Antonio Fiz: design of the statistical analysis and interpretation of the data of the study; revision of the work.
- Astrid Crespo: interpretation of the data and critical revision of the work.
- Vicente Plaza: conception and design of the study; acquisition, analysis and interpretation of the data for the work; writing the article.
- Members of Spanish High Risk Asthma Research Group: acquisition of the data for the work.

REFERENCES

- 1.- World Health Organization. WHO Programmes and projects. Chronic respiratory diseases. Asthma. URL: <http://www.who.int/respiratory/asthma/en/>. Date last accessed: October 30 2013.
- 2.- World Health Organization. Projections of mortality and burden of disease, 2004-2030. URL: http://www.who.int/entity/healthinfo/global_burden_disease/Dth6_2030.xls. Date last accessed: October 30 2013.
- 3.- Richards GN, Kolbe J, Fenwick J, Rea HH. Demographic characteristics of patients with severe life threatening asthma: comparison with asthma deaths. *Thorax* 1993;48:1105-1109.
- 4.- Campbell DA, McLennan G, Coates JR, Frith PA, Gluyas PA, Latimer KM et al. A comparison of asthma deaths and near-fatal asthma attacks in South Australia. *Eur Respir J*. 1994 Mar;7(3):490-7.
- 5.- Romagnoli M, Caramori G, Braccioni F, Ravenna F, Barreiro E, Siafakas NM et al. Near-fatal asthma phenotype in the ENFUMOSA Cohort. *Clin Exp*

- Allergy*, 2007;37:552–557.
- 6.- Strunk RC, Nicklas RA, Milgrom H, Davis ML, Iklé DN. Risk factors for fatal asthma. En: Sheffer AL, ed. Fatal asthma. New York, Marcel Dekker Inc.; 1998. p. 31-44.
 - 7.- Lugogo NL, MacIntyre NR. Life-threatening asthma: pathophysiology and management. *Respir Care*. 2008;53:726-35.
 - 8.- Moore WC, Meyers DA, Wenzel SE, Teague WG, Li H, Li X et al. Identification of Asthma Phenotypes Using Cluster Analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med*, 2010;181:315–323.
 - 9.- Bochenek G, Kuschill-Dziurda J, Szafraniec K, Plutecka H, Szczeklik A, Nizankowska-Mogilnicka E. Certain subphenotypes of aspirin-exacerbated respiratory disease distinguished by latent class analysis. *J Allergy Clin Immunol*. 2014 Jan;133(1):98-103.
 - 10.- Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE et al. Cluster Analysis and Clinical Asthma Phenotypes. *Am J Respir Crit Care Med*, 2008;178:218–224.
 - 11.- Plaza V, Serrano J, Picado C and Sanchis J on behalf of the High Risk Asthma Research Group. Frequency and clinical characteristics of rapid-onset fatal and near-fatal asthma. *Eur Respir J*. 2002 May;19 (5):846-52.
 - 12.- Serrano J, Plaza V, Sureda B, de Pablo J, Picado C, Bardagí S et al. Alexithymia: a relevant psychological variable in near-fatal asthma. *Eur Respir J* 2006;28:296–302.
 - 13.- Martínez-Moragón E, Plaza V, Serrano J, Picado C, Galdiz JB, López-Viña A, et al. Near-fatal asthma related to menstruation. *J Allergy Clin Immunol* 2004;113:242-4.
 - 14.- Plaza V, Serrano J, Picado C, Cosano J, Ancochea J, de Diego A et al. Clinical characteristics of the fatal and near-fatal asthma in *Alternaria alternata* sensitized patients. *Med Clin (Barc)*. 2003 Nov 29;121(19):721-4.
 - 15.- American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. *Am Rev Respir Dis* 1987; 136: 225–244.
 - 16.- Rodrigo G, Lusiardo M, Normey L. Alexithymia: reliability and validity of the Spanish version of the Toronto Alexithymia Scale. *Psychother Psychosom* 1989;51:162–168.

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- 17.- Lobo A, Pérez Echeverria MJ, Artal J. Validity of scaled version of the General Health Questionnaire (GHQ-28) in a Spanish population. *Psychol Med* 1986; 16: 135–140.
 - 18.- Sifneos PE. The prevalence of “alexithymic” characteristics in psychosomatic patients. *Psychother Psychosom* 1973; 22: 255–262.
 - 19.- Goldberg D. Use of the general health questionnaire in clinical work. *BMJ* 1986; 293:1188–1189.
 - 20.- Bacher J, Wenzig K, Vogler M. SPSS TwoStep Cluster - a first evaluation. Universität Erlangen-Nürnberg, Wirtschafts- und Sozialwissenschaftliche Fakultät, Sozialwissenschaftliches Institut Lehrstuhl für Soziologie (Ed.): Nürnberg, 2004 (Arbeits- und Diskussionspapiere / Universität Erlangen-Nürnberg, Sozialwissenschaftliches Institut, Lehrstuhl für Soziologie 2004-2). URL: <http://nbn-resolving.de/urn:nbn:de:0168-ssoar-327153>. Date last accessed: February 2015.
 - 21.- Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. NHLBI/WHO workshop report. Publication No. 95–3659. Bethesda, MD, National Institutes of Health, National Health, Lung and Blood Institute, 1995.
 - 22.- Antó JM, Sunyer J, Rodriguez-Roisin R, Suarez-Cervera M, Vazquez L. Community outbreaks of asthma associated with inhalation of soybean dust. Toxicoepidemiological Committee. *N Engl J Med*. 1989 Apr 27;320(17):1097-102.
 - 23.- O'Hollaren MT, Yunginger JW, Offord KP, Somers MJ, O'Connell EJ, Ballard DJ et al. Exposure to an aeroallergen as a possible precipitating factor in respiratory arrest in young patients with asthma. *N Engl J Med*. 1991 Feb 7;324(6):359-63
 - 24.- Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. *Nat Med*. 2012 May 4;18(5):716-25.
 - 25.- Lötvall J, Akdis CA, Bacharier LB, Bjerner L, Casale TB, Custovic A et al. Asthma endotypes: A new approach to classification of disease entities within the asthma syndrome. *J Allergy Clin Immunol* 2011;127:355-60.
 - 26.- Strunk RC. Identification of the fatality-prone subject with asthma. *J Allergy Clin Immunol*. 1989 Feb;83(2 Pt 1):477-85.
 - 27.- Campbell DA, Yellowlees PM, McLennan G, Coates JR, Frith PA, Gluyas PA

- et al. Psychiatric and medical features of near fatal asthma. *Thorax*. 1995 Mar;50(3):254-9.
- 28.- Verges S, Bachasson D, Wuyam B. Effect of acute hypoxia on respiratory muscle fatigue in healthy humans. *Respir Res*. 2010 Aug 11;11:109-117.
- 29.- Molfino NA, Nannini LJ, Martelli AN, Slutsky AS. Respiratory arrest in near-fatal asthma. *N Engl J Med*. 1991 Jan 31;324(5):285-8.
- 30.- Eckert DJ, Catcheside PG, Smith JH, Frith PA, McEvoy RD. Hypoxia suppresses symptom perception in asthma. *Am J Respir Crit Care Med*. 2004 Jun 1;169(11):1224-30.
- 31.- Kikuchi Y, Okabe S, Tamura G, Hida W, Homma M, Shirato K et al. Chemosensitivity and perception of dyspnea in patients with a history of near-fatal asthma. *N Engl J Med*. 1994 May 12;330(19):1329-34.
- 32.- Johnson AJ, Nunn AJ, Somner AR, Stableforth DE, Stewart CJ. Circumstances of death from asthma. *Br Med J (Clin Res Ed)*. 1984 Jun 23;288(6434):1870-2.
- 33.- Ferrer A, Torres A, Roca J, Sunyer J, Antó JM, Rodriguez-Roisin R. Characteristics of patients with soybean dust-induced acute severe asthma requiring mechanical ventilation. *Eur Respir J*. 1990 Apr;3(4):429-33.
- 34.- White MC, Etzel RA, Olson DR, Goldstein IF. Reexamination of epidemic asthma in New Orleans, Louisiana, in relation to the presence of soy at the harbor. *Am J Epidemiol*. 1997 Mar 1;145(5):432-8.
- 35.- Bellido Casado J, Plaza V, Bardagí S, Cosano J, López Viña A, Martínez Moragón E et al. [Is the incidence of near-fatal asthma decreasing in Spain?]. *Arch Bronconeumol*. 2006 Oct;42(10):522-5.

Table 1.- Variables included in the cluster analysis

Sex
Age
Level of education
Smoking
GHQ score
Psychiatric comorbidity
TAS score
Presence of alexithymia
Asthma severity (GINA)
FEV1 (post NFA episode)
Age at onset of asthma
Presumptive NSAID intolerance
History of atopy
History of rhinosinusitis
Medical care for asthma
Number of prior hospitalizations for asthma
Past mechanical ventilation for asthma
Hospitalization for asthma in the past 12 months
Past ED visits for asthma in the past 12 months
Past NFA attacks
Past hospitalization for asthma
Treatment for asthma:
Inhaled corticosteroids dose (mcg/d of budesonide)
Long-acting beta agonist (formoterol, salmeterol)
Oral corticosteroids
Theophylline
Ipratropium bromide
Trigger of the NFA episode
Sudden onset of near-fatal asthma episode (<2 hours)
Impaired consciousness level on hospital admission
Tracheal intubation required
Respiratory arrest
Hours under mechanical ventilation
pH on arterial blood gas analysis on hospital admission
PaCO ₂ on arterial blood gas analysis
Written asthma action plan followed
Season of the NFA episode
Days in hospital
Days in ICU
Total dose of systemic steroids in first 5 days in hospital (mg prednisone)
Medical complications during hospitalization
Eosinophil count cells on hospital admission
Number of positive skin prick-tests per patient
Sensitization to <i>Alternaria alternata</i>
Sensitization to fungi

GHQ: General Health Questionnaire (19). TAS: Toronto Alexithymia Scale (16). GINA: classification from the Global INitiative for Asthma (21). FEV₁: forced expiratory volume in the first second. NSAID: nonsteroidal antiinflammatory drug. ED: Emergency Department. NFA: near-fatal asthma, PaCO₂: partial pressure of carbon dioxide.

Table 2.- Comparison between cases included in the cluster analysis and excluded patients who had incomplete data in any of the variables studied

	Included (n=84)	Excluded (n=93)	p
Age, years	51.5 (19.9)	49.9 (18.5)	0.578
Female, %	60	58	0.879
Age at onset of asthma, years	28.5 (19)	32.5 (20.5)	0.138
Level of education, %:			
basic (<8 yrs of schooling)	18	17	0.989
primary	54	55	
intermediate	20	21	
higher	8	7	
Smoking, %:			
Current smoker	18	25	0.469
Ex-smoker (>6 month)	20	22	
Never smoker	62	53	
Psychological status:			
Psychiatric comorbidity (GHQ $\geq$ 7), %	52	49	0.654
Alexithymia (TAS-26 > 73), %	37	36	0.970
Asthma severity (GINA), %:			
Intermittent	2	2	0.953
Mild Persistent	2	3	
Moderate Persistent	41	43	
Severe Persistent	55	51	
FEV ₁ post-NFA attack, %	77 (24)	73 (24)	0.331
Treatment for asthma:			
Inhaled Corticosteroids, %	62	52	0.222
ICS dose (mcg/day of budesonide)	744 (748)	631 (756)	0.277
Written asthma action plan followed, %			
Yes	14	12	0.856
No	30	33	
Without action plan	55	56	
Eosinophil count cellsx10 ⁶ .L ⁻¹	394 (417)	553 (614)	0.074
Atopy, %	45	39	0.532
At least one positive skin-prick test, %	61	51	0.136

GHQ: General Health Questionnaire (19). TAS-26: Toronto Alexitimia Scale (16). GINA: classification from the Global INitiative for Asthma (21); ICS: inhaled corticosteroids; FEV₁: forced expiratory volume in one second, expressed as percentage of reference value; NFA: near-fatal asthma; atopy: presence of rhinosinusitis and/or conjunctivitis and/or eczema.

Table 3.- Demographic data and psychiatric comorbidity

	Total n=84	Cluster 1 n=33	Cluster 2 n=28	Cluster 3 n=23	p
Age, years	51.5 (19.8)	59.2 (17.2)	49.9 (20.3)	42.4 (19.3)	0.006
Female, %	60	82	61	26	<0.001
Age at onset of asthma, years	28.5 (19)	35.9 (17.8)	25.3 (18.9)	22 (18.2)	0.013
Level of education, %:					
basic (<8 yrs of schooling)	72	88	57	65	0.024
primary	7	6	4	13	
intermediate	13	3	28	9	
higher	8	3	11	13	
Smoking, %:					
Current smoker	18	3	29	26	0.015
Ex-smoker (>6 month)	20	15	21	26	
Never smoker	62	82	50	48	
Psychological status:					
Psychiatric comorbidity (GHQ≥7), %	52	64	50	39	0.187
GHQ score	8.4 (7.4)	10.8 (7.8)	8.1 (7.2)	5.4 (6)	0.023
Alexithymia (TAS-26 > 73), %	37	49	25	35	0.042
TAS-26 score	68 (14)	74 (13)	63 (15)	65 (13)	0.005

GHQ: General Health Questionnaire (19). TAS-26: Toronto Alexitimia Scale (16).

Table 4a.- Clinical characteristics of asthma (I)

	Total n=84	Cluster 1 n=33	Cluster 2 n=28	Cluster 3 n=23	p
Asthma severity (GINA), %:					
Intermittent	2	0	7	0	<0.001
Mild Persistent	2	0	4	4	
Moderate Persistent	41	18	46	65	
Severe Persistent	55	82	43	30	
Treatment for asthma:					
Inhaled Corticosteroids, %	61	91	50	30	<0.001
ICS dose (mcg/day of budesonide)	744 (748)	1224 (670)	523 (633)	323 (610)	<0.001
LABA, %	46	79	43	4	<0.001
ICS+LABA,%	37	70	29	0	<0.001
LABA alone, %	10	9	14	4	0.519
Teophylline, %	14	15	18	9	0.677
Ipratropium bromide, %	20	30	18	9	0.139
Systemic corticosteroids, %	13	21	7	9	0.255
Written asthma action plan followed, %					
Yes	14	21	18	0	0.152
No	30	24	29	39	
Patients without action plan	56	55	54	61	
Hospital frequentation:					
Past hospitalization for asthma, %	57	79	57	26	<0.001
Number of hospitalizations for asthma per patient	2.2 (3.6)	3.5 (4.1)	2.1 (3.8)	0.5 (1)	<0.001
Past endotracheal intubation for asthma,%	10	12	11	4	0.723
Past near-fatal crisis, %	27	49	18	9	0.002
Hospitalization for asthma in the past year, %	24	39	18	9	0.020
Past ED visits for asthma in the last year, %	51	61	54	35	0.156
Medical care for asthma, %:					
Regular	41	82	21	4	<0.001
Irregular	32	18	43	39	
None	27	0	36	57	

GINA: classification from the Global INitiative for Asthma (21); ICS: inhaled corticosteroids; LABA: long acting β -agonists; ED: emergency department.

Table 4b.- Clinical characteristics of asthma (II)

	Total n=84	Cluster 1 n=33	Cluster 2 n=28	Cluster 3 n=23	p
Presumptive NSAID intolerance, %	16	18	14	13	0.976
Alergologic status:					
At least one positive skin-prick test, %	62	42	71	78	0.011
Number of positive skin-prick tests per patient	1.35 (1.35)	0.94 (1.37)	1.39 (1.13)	1.87 (1.42)	0.020
Sensitized to <i>A. alternata</i> or soybean, %	12	6	7	26	0.048
FEV ₁ post-NFA attack, %	77 (24)	69 (25)	82 (19)	81 (26)	0.067
Atopy, %	45	39	54	44	0.530
Previous history of nasal polyps, %	10	15	7	4	0.460
Previous history of sinusitis, %	16	12	18	17	0.801

NSAID: nonsteroidal anti-inflammatory drug; FEV₁: forced expiratory volume in the first second, expressed as percentage of reference value; NFA: near-fatal asthma; atopy: presence of rhinitis and/or conjunctivitis and/or eczema.

Table 5.- Characteristics of near-fatal asthma attacks and hospital course

	Total n=84	Cluster 1 n=33	Cluster 2 n=28	Cluster 3 n=23	p
Rapid-onset crisis (<2 hours), %	14	9	18	17	0.574
Impaired consciousness level, %	39	15	82	22	<0.001
Respiratory arrest, %	26	9	68	0	<0.001
Tracheal intubation required, %	42	24	93	4	<0.001
Arterial blood gas analysis:					
pH	7.20 (0.13)	7.26 (0.08)	7.09 (0.16)	7.26 (0.07)	<0.001
PaCO ₂ , mmHg	65 (24)	60 (15)	78 (35)	57 (11)	0.012
Eosinophil count cellsx10 ⁶ .L ⁻¹	394 (417)	381 (363)	288 (339)	543 (533)	0.194
> 500 eosinophil x10 ⁶ .L ⁻¹), %	35	39	21	44	0.193
> 300 eosinophil x10 ⁶ .L ⁻¹), %	45	52	32	52	0.233
Hospital course:					
Days in hospital	11.2 (9.2)	14 (12.6)	11.5 (5.4)	6.7 (4.2)	<0.001
Admission in ICU, %	55	49	96	13	<0.001
Days in ICU	2.6 (5.6)	3 (8)	4 (3.6)	0.4 (1.2)	<0.001
Major consequences, %	24	33	25	9	0.102
Total dose of systemic steroids in first 5 days, mg prednisone	538 (259)	574 (293)	582 (272)	435 (150)	0.078

PaCO₂: arterial carbon dioxide tension; Eosinophil count cells: values from first hemogramme on hospital admission. ICU: intensive care unit; days in ICU and hours under mechanical ventilation were calculated only in patients with ICU admission or tracheal intubation required.

Table 6.- Main characteristics of near-fatal asthma phenotypes

	Cluster 1	Cluster 2	Cluster 3
Demographic characteristics	Older More frequent female Lowest level of education Most common cluster	frequently current smokers	Younger More frequent male frequently current smokers
Psychiatric comorbidity	++	++	+
Asthma characteristics	Late onset Very frequent severe persistent asthma* Frequent regular medical care Very frequent past hospitalization for asthma	intermediate position between clusters 1 and 3	Early onset Very infrequent regular medical care
Medication	91% with ICS 21% OC	only 50% with ICS	only 30% with ICS
FEV ₁ mean (SD)	69 (25)	82 (19)	81 (26)
At least one positive skin-prick test	42%	71%	78%
sensitized to <i>Alternaria alternata</i> or soybean	6%	7%	26%
NFA attack characteristics	longer hospitalization	Frequent impaired consciousness level and respiratory arrest Very frequent tracheal intubation required Highest hipercapnia	shorter hospitalization

*classification from the Global Initiative for Asthma (21); ICS: inhaled corticosteroids; OC: oral corticosteroids; LABA: long acting β -agonists; FEV₁: forced expiratory volume in one second, expressed as percentage of reference value; NFA: near-fatal asthma.