



Near-fatal asthma: a heterogeneous clinical entity

José Serrano-Pariente^a and Vicente Plaza^b

Purpose of review

The aims of the present review were to describe the heterogeneous nature of near-fatal asthma (NFA) and to summarize the distinctive phenotypes identified in this subtype of asthma.

Recent findings

Clinical, physiological, and histological studies have shown a large number of triggers, pathological mechanisms, and risk factors associated with NFA. Based on the demographic and clinical characteristics of the patients, the circumstances surrounding the asthma exacerbation and some distinctive features of the disease, several clinical profiles of asthma patients with NFA have been described. Recent data show new associations between some gene expression patterns and fatal asthma, as well as with some biological markers related to inflammatory or immunologic mechanisms in the airways. Also, the use of statistical methods, such as cluster analysis, allowed identifying and confirming different phenotypes of life-threatening asthma patients.

Summary

NFA is a heterogeneous clinical entity, in which different patients' clinical profiles may coexist [e.g. rapid-onset NFA, NFA in patients with dyspnea hypoperception or sensitized to certain pneumoallergens (*Alternaria alternata*, soybean), NFA related to the menstrual cycle, brittle asthma]. Knowledge of these phenotypes as well as adequate and specific management strategies can reduce morbidity and mortality in patients suffering from NFA.

Keywords

asthma exacerbation, cluster analysis, fatal asthma, near-fatal asthma, phenotypes

INTRODUCTION

In special circumstances asthma may be a life-threatening disease. WHO statistics showed that in 2005, 225 000 people worldwide died as a result of their asthma [1], rising to 428 000 annual deaths by 2030 [2]. These patients dying of asthma and those with severe asthma exacerbation episodes at risk of death suffer in fact from the same type of asthma, a condition called near-fatal asthma (NFA), life-threatening asthma, or critical asthma syndrome [3–5]. Although a formal unique definition of NFA is lacking, criteria used for the identification of these types of exacerbations usually include some of the following events: dyspnea that prevents speech, decreased level of consciousness, hypercapnia (in general, $\text{PaCO}_2 > 45\text{--}50\text{ mmHg}$), admission to an ICU, respiratory or cardiopulmonary arrest, orotracheal intubation, and mechanical ventilation. In some cases, other patients have been included in this category, such as those with history or two or more episodes of pneumothorax or pneumomediastinum as a complication of an acute severe asthma attack, patients with two or more hospital admissions for asthma despite treatment with

systemic glucocorticoids, and asthma exacerbations with acidosis.

Despite the fact that some authors have described NFA as a single phenotype [6], numerous clinical, physiological, and histopathological studies [7–14] allowed distinguishing different profiles of patients with NFA based on demographic characteristics, triggers of asthma attacks, pathogenesis of the disease or comorbidities, and clinical presentation of exacerbations. Recently, as in other less severe forms of the disease [15], some studies [16,17] have confirmed the heterogeneity of this

^aPneumology Department, Hospital Comarcal d'Inca, Inca, Islas Baleares and ^bDepartment of Respiratory Medicine, Hospital de la Santa Creu i Sant Pau, Institut d'Investigació Biomèdica Sant Pau (IIB Sant Pau), Universitat Autònoma de Barcelona; Department of Medicine, Barcelona, Spain

Correspondence to José Serrano-Pariente, Pneumology Department, Hospital Comarcal d'Inca, Carretera Vella de Llubí s/n, E-07300 Inca, Islas Baleares, Spain. Tel: +34 971 888500; fax: +34 971 888600; e-mail: jserrano@separ.es

Curr Opin Allergy Clin Immunol 2017, 17:28–35

DOI:10.1097/ACI.0000000000000333

KEY POINTS

- Asthma continues to be an avoidable cause of death, especially in young asthmatics.
- Like other less severe forms of asthma, NFA is a very heterogeneous disease that includes different patient profiles.
- There are multiple demographic, clinical, physiological, biological, and histological factors that have allowed recognizing different NFA phenotypes. Recent studies using cluster analysis reaffirm that some of these phenotypes exist.
- Adequate therapeutic management of asthma and some specific preventive strategies can reduce morbidity and mortality of NFA.

type of asthma using statistical methods such as cluster analysis. The present review summarizes the main findings of studies examining the nature of NFA, especially the most recent data, and describes the different phenotypes that have been identified in this subtype of asthma. Knowledge and identification of their particular features have been crucial to design specific prophylactic strategies to prevent further exacerbations [18]. Of note, it should be remembered that increasing the efficacy in the therapeutic management of NFA literally means to save lives and to avoid severe sequelae [19].

ASTHMA HETEROGEITY

The Global Initiative of Asthma (GINA) currently defines asthma as a heterogeneous disease usually characterized by chronic airway inflammation [20]. The term ‘asthma’ includes a variety of clinical symptoms, such as dyspnea, cough, or wheezing in patients with variable airflow limitation or bronchial hyperresponsiveness. According to different demographic, clinical, and functional characteristics, patients with asthma can be grouped into different clinical profiles, the so-called phenotypes [21]. On the other hand, there are different types of asthma according to etiological and physiopathological mechanisms of the disease, the so-called endotypes [22]. Therefore, the current concept of asthma should be understood as a syndrome that encompasses different entities, with some similar clinical and functional manifestations, but with distinct causes and pathogenetic mechanisms [23]. Coinciding with this ‘new’ approach to asthma, intense research activity focused on the characterization of severe asthma and the identification of different phenotypes [24] including NFA [6] has been maintained for more than 1 decade with

different programs both in the United States (Severe Asthma Research Program) and Europe [European Network For Understanding Mechanisms Of Severe Asthma (ENFUMOSA), Longitudinal Assessment of Clinical Course and BIOMarkers in Severe Chronic AIRway Disease, and Unbiased Biomarkers for the Prediction of Respiratory Disease Outcome].

In relation to the severity of asthma, severe asthma and NFA are not synonymous.

Although episodes of NFA (and asthma-related deaths) are more common in patients with severe asthma, patients with mild and moderate asthma can also suffer from NFA. The Estudio del Asma Grave en Latinoamérica y España (EAGLE) project, a case-control study in which 2593 clinical records of asthma patients with an exacerbation episode requiring hospitalization were analyzed, showed that 4.9% of patients with mild-moderate asthma required ICU admission, 2.1% intubation and mechanical ventilation, 1.3% had cardiopulmonary arrest, and 0.4% died during hospital admission [25].

FATAL AND NEAR-FATAL ASTHMA

Death from asthma has been known to occur since its original descriptions in ancient times [26]. In the second century CE, the Greek physician Aretaeus of Cappadocia who studied in Alexandria and practiced in Rome is credited with an accurate description of the paroxysm of asthma and emphasized that the patient could die if the symptoms persist. Much more recently, since the mid-XX century, the characteristics of patients who have died of asthma (fatal asthma) have been described in detail. Initial studies focused on establishing the clinical profile of these asthma patients and the circumstances surrounding death [27]. Subsequent studies aimed to investigate the characteristics of patients suffering from asthma attacks severe enough to put their life at risk (NFA). Similarities between both subgroups of patients lead to conclude that they had the same type of asthma, distinguished only by differences in the stages of the exacerbation episode [3,4].

Some characteristics of the patients or the asthma disease may be risk factors for NFA, including history of ICU admission because of asthma exacerbation and the need of mechanical ventilation [28] or previous treatment with oral steroids. A greater blood gases impairment (hypercapnia and acidosis) and the presence of pulmonary hyperinflation on admission are also circumstances associated with NFA, which should be considered by attending physicians in the emergency department.

Family history of fatal asthma is another factor that should be considered at the time of evaluating the risk for NFA in a patient with asthma. Teerlink

et al. [29] examined evidence for a heritable component to asthma mortality using a unique data resource consisting of death certificates linked to the genealogical database Utah Population Database. They analyzed 1553 individuals whose death certificate listed asthma as a cause of death in a registry of all Utah deaths since 1904. According to the genealogical index of familiarity, the relative risk of dying of asthma was 1.60 in first-degree relatives of cases and 1.34 in second-degree relatives.

In Western countries, asthma-related mortality is currently restricted to low rates. However, in young asthmatics, uncontrolled asthma continues to be an avoidable cause of sudden death. In a recent nationwide study in Denmark [30[¶]], through the review of death certificates, 625 sudden unexpected death cases in individuals 1–35 years from 2000 to 2006 were found. Of those, 49 persons with uncontrolled asthma were identified. Symptoms prior to death were reported in 84% of these cases, although only 57% of patients sought medical care [30[¶]]. According to a nation United Kingdom database analysis, between 2000 and 2005, the mortality rate was 1063 from 250 043 asthma admissions (0.43%) [31]. More recently, the National Review of Asthma Deaths published in 2014 a confidential enquiry report in which the characteristics of the 195 persons who died from asthma in the United Kingdom during 1 year (between 2012 and 2013) and the circumstances related to death were described in detail [32^{¶¶}]. Nearly half (41%) died at home, one-quarter (23%) on the way to hospital, and one-third (30%) in hospital. In children, 80% of those under 10 years and 72% of those aged 10–19 years died before they reached hospital. During the final asthma attack, 45% of people died without seeking medical assistance or before emergency medical care could be provided, and exacerbation factors or triggers were recorded in only 51% of cases.

In Spain, some promising data from a multicenter study [33] showed a progressive reduction in the incidence of NFA episodes between late 1990s and early 2000s. Nevertheless, NFA has not been eradicated. A recent retrospective review of all admissions because of asthma exacerbation in a single hospital recorded 400 NFA episodes between 2000 and 2010, with a mortality rate of 3.1%. In this particular study [34], no signs of a decreasing trend for the decade analyzed were found.

NEAR-FATAL ASTHMA PHENOTYPES

Observations of the initial clinical studies of NFA revealed that risk factors for this type of asthma were numerous and very heterogeneous. Together with

distinctive clinical, functional, and therapeutic variables, these risk factors include dissimilar variables, such as education, psychological, social, and economic factors [7,35]. Thus, different subgroups of NFA have been described according to the rapidity of onset of exacerbations [8,9,36–38] or the presence of some functional or psychological alterations, such as a decreased perception of dyspnea or anomalies in the ventilatory response to hypoxemia and hypercapnia [10,11]. Recently, NFA has also been related with patterns of gene expression (transcriptomic endotypes of asthma) in the sputum and blood, and some biological mechanisms of inflammatory or immunological type [39[¶]]. In patients with fatal asthma, increased release of mediators of acute airway inflammation by lymphocytes present in lung tissue, like granule-secreted enzymes (granzymes) and perforins has been observed [40,41]. Also, increased expression of the proinflammatory cytokine IL-8 and its receptor, and CD8(+) T cells in lung tissue from patients who died of fatal asthma has been reported [42]. Additionally, increased expression of Toll-like receptors and thymic stromal lymphopoietin may contribute to the acute inflammation in fatal asthma patients [43].

Phenotypes of NFA can be classified according to the characteristics of patients, asthma disease itself, and exacerbations.

Near-fatal asthma phenotypes according to the characteristics of patients

Age and sex

In young men, NFA attacks of sudden onset (1–3 h) such as those elicited by exposure to aeroallergens are frequent. These patients do not always suffer from particularly severe asthma, and recovery is usually rapid [44]. Among older patients, however, deaths are more common in women [4]. On the other hand, in young women, a strong relationship between the menstrual rhythm during childbearing age and the development of NFA attacks has been observed [45].

Altered perception of dyspnea

Some patients with asthma have an altered perception of dyspnea in the presence of increased airflow resistance [10]. Reduced chemosensitivity to hypoxia and hypercapnia and blunted perception of dyspnea may predispose patients to fatal asthma attacks [11]. Altered perception of symptoms may explain a delay in seeking medical care as a feature of the final event in a high percentage of asthma deaths in NFA cases [4].

Psychological factors and psychiatric comorbidity

Denial of illness together with depression, anxiety, and alexithymia (a personality trait defined by the difficulty to identify, distinguish, and describe emotions and bodily sensations such as dyspnea) are especially frequent in patients with NFA [10,12,13,46]. Psychiatric disorders may contribute to the development of asthma exacerbations altering the behavior of patients regarding their disease and/or affecting the perception or recognition of certain symptoms [10], which greatly hinders the therapeutic management of asthma in these patients.

Poor adherence to treatment

Several studies [6,7,16[■],29,47] have shown a surprisingly lack of adequacy of treatment to clinical practice guidelines on asthma management in patients with NFA. Although occasionally this fact may be attributable to healthcare professionals taking care of the patients, it is frequently related to the patients' poor adherence to anti-inflammatory treatment. In the ENFUMOSA cohort [6], of the 24 patients with an NFA episode in the previous 5 years, only 37.5% received inhaled corticosteroids (ICS). Moreover, 58.8% of patients treated with long-acting β_2 -adrenergic agonists were not receiving ICS simultaneously. In the National Review of Asthma Deaths report [32[■]] from the United Kingdom, although 86% of patients had ICS inhalers prescribed at the time of death, either as stand alone or in combination, 38% were known to have been issued fewer than four inhalers and 80% with fewer than 12 preventer inhalers in the previous year. By contrast, with respect to short-acting β_2 -adrenergic agonists, 39% had been prescribed more than 12 short-acting reliever inhalers in the year before they died, whereas 6 (4%) had been prescribed more than 50 reliever inhalers. On the contrary, appropriate asthma treatment improves prognosis and the future clinical course of NFA. In the study of Rodríguez-Trigo *et al.* [19], 53 patients who had experienced a near-fatal attack of asthma were treated according to the GINA guidelines and followed for a mean of 49 months (intervention group). They were compared with 40 NFA patients who had not been managed according to the GINA guidelines and who were followed for a mean of 51 months (historic control group). Statistically significant reductions were found in the mortality rate (0 vs. 15%), number of new NFA attacks (89% reduction), and need for new hospital admissions for asthma (85% reduction) in favor of the intervention group.

Near-fatal asthma phenotypes according to the characteristics of asthma

Asthma severity

Patients with NFA usually show a prior history of numerous emergency and hospital admissions for asthma attacks, including the need for mechanical ventilation [7,35,36,48]. It is also common that many patients receive intense antiasthma treatments, with many drugs and at high doses [16[■],47,48]. However, it should be noted that NFA is not exclusive of severe asthma and that patients with moderate, mild, or intermittent asthma can also have this type of exacerbations [16[■],17,25,36,48].

Pulmonary function

NFA has been related to two circumstances regarding pulmonary function of the patients. First, a great lability of spirometric values (the so-called brittle asthma) is common among asthmatics [49]. Moreover, it has been associated with the presence of an intense bronchial hyperresponsiveness [50].

Etiopathogenetic mechanisms of asthma

Asthma patients with NSAID intolerance may develop extremely severe exacerbations when treated with these drugs [14,51]. NSAID hypersensitivity or aspirin-exacerbated respiratory disease has unique pathophysiological features [52] with distinct clinical presentation and has been proposed as a real endotype of asthma [22]. It has been estimated that 15% of severe asthmatics are aspirin sensitive, a double prevalence than in the remaining asthmatics. In some clinical series, up to 14% of sudden onset NFA episodes have been attributed to the ingestion of these drugs [36].

Near-fatal asthma phenotypes according to the characteristics of the exacerbation

Asthma triggers

NFA attacks can be triggered by many possible factors, including exposure to different allergens, such as soybean and castor bean seeds, fungi such as *Alternaria alternata*, and some foods. Outbreaks of asthma in Barcelona during the 1980s were caused by the inhalation of soybean dust released to the atmosphere during the unloading of soybean in the city harbor [53]. Between 1981 and 1987, 26 outbreaks of asthma were detected, with 687 patients affected and causing 1155 admissions to the emergency services, with 11.9% of patients requiring admission to the ICU and 8.5% requiring

mechanical ventilation. The epidemic attacks of asthma had characteristic features, namely, a sudden onset, an often greater than usual severity, and rapid recovery [44]. Installing filters on silos to prevent airborne dissemination of allergenic soybean particles eliminated outbreaks of asthma caused by inhalation of the dust [18].

Exposure to airborne spores of the common mold *A. alternate* has been implicated as a possible trigger of life-threatening asthma attacks in young patients [54]. As in the case of soybean-related asthma outbreaks, asthmatics sensitized to this fungus typically have a faster recovery after attacks. However, they can also die or develop severe neurological sequelae in a greater proportion (15%) than the remaining patients with NFA [55].

Rapidity of onset of asthma attack

Rapidity of onset of NFA attacks allows distinguishing a rapid-onset asthma attack developing in an interval between 1 and 3 h, and a slow-onset asthma attack developing more gradually over the course of days or weeks. The proportion of each type of exacerbation varies largely across the different studies, in part because of differences in the definitions of both NFA and sudden crisis used by the authors. Overall, rapid-onset asthma attacks account for 8–29% of cases [36,56,57], but the percentage may reach up to 58% of asthma crises in clinical series of fatal asthma [58]. Table 1 shows differences between rapid-onset and slow-onset NFA [8,36–38,44,56,59,60].

CLUSTER ANALYSIS OF NEAR-FATAL ASTHMA PHENOTYPES

In recent years, different statistical techniques have been extensively used to discriminate mathematically different subgroups of asthma patients [15,61,62]. These methods (such as cluster analysis or latent class analysis) use grouping algorithms of patients based on the variables analyzed, and have the theoretical advantage of being ‘unbiased’ at the time of selecting demographic, therapeutic, functional, or histological characteristics, among others, that may define the different asthma phenotypes.

In the case of NFA, results of two multicenter studies using cluster analysis for the identification and characterization of NFA phenotypes have been recently published. In the first study, the Spanish High Risk Asthma Research Group [16^a] performed a cluster analysis using two-steps algorithm from data of 84 asthmatics admitted for an episode of NFA. 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 a high proportion of respiratory arrest (68%), impaired consciousness level (82%), and mechanical ventilation (93%); and cluster 3, which included younger patients, characterized by a more frequent sensitization to *A. alternata* and soybean (26%) but a lower use of ICS (30%) as compared with the remaining clusters. In summary, results of this study showed factors related to a higher degree of intrinsic asthma severity in clusters 1 and 2. Consequently, the characteristics of clusters

Table 1. Differential characteristics between rapid-onset and slow-onset near-fatal asthma

	Rapid-onset NFA	Slow-onset NFA
Characteristics of patients	More frequent in young males	More frequent in women
Triggers	Respiratory allergens Environmental pollutants Emotional stress NSAID intake	Respiratory tract infections
Clinical differences	Higher hypercapnia and acidosis Absence of lung sounds Generally a more rapid recovery	Higher number of previous emergency room visits and hospital admissions
Histological findings	Airway permeability Greater tightening of the muscular layer Neutrophils exceed eosinophils in the airways submucosa Higher proportion of mast cell degranulation	Mucous plugs Lung hyperinsufflation Loss of airway epithelial layer Mucous gland hyperplasia Eosinophils exceed neutrophils in the airways submucosa

NFA, near-fatal asthma.

Table 2. Main characteristics of near-fatal asthma phenotypes identified by cluster analysis

	Cluster 1	Cluster 2	Cluster 3
Patient characteristics	Older More frequent female Lowest level of education Frequent psychiatric comorbidity	Frequently current smokers Frequent psychiatric comorbidity	Younger More frequent male Frequently current smokers
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
Allergic and functional characteristics	At least one positive skin-prick test: 42% Sensitized to <i>Alternaria alternata</i> or soybean: 6% FEV ₁ mean (SD): 69% (25)	At least one positive skin-prick test: 71% Sensitized to <i>Alternaria alternata</i> or soybean: 7% FEV ₁ mean (SD): 82% (19)	At least one positive skin-prick test: 78% Sensitized to <i>Alternaria alternata</i> or soybean: 26% FEV ₁ mean (SD): 81% (26)
Therapeutic characteristics	ICS: 91% Oral corticosteroids: 21%	ICS: 50%	ICS: 30%
NFA attack characteristics	Longer hospitalization	Frequent impaired consciousness level and respiratory arrest Very frequent mechanical ventilation required Highest hypercapnia	Shorter hospitalization

FEV₁, forced expiratory volume in 1 s, expressed as percentage of reference value; ICS, inhaled corticosteroids; NFA, near-fatal asthma.

1 and 2 may be viewed as indicators of a higher risk for NFA. Of note, inadequate asthma management is a differentiating feature of cluster 3, which reinforces that adequate asthma treatment is a key factor for the prevention of NFA.

In the second study, carried out by Sekiya *et al.* [17] in Japan, 175 life-threatening asthma exacerbations were analyzed, and five clusters of patients were defined: younger-onset asthma with severe baseline asthma symptoms; female-predominant elderly asthma; allergic asthma without baseline ICS treatment; male-predominant chronic obstructive pulmonary disease-overlapped elderly asthma; and asthma with almost no baseline symptoms.

Therefore, the results of both studies confirm some of the findings previously obtained in clinical studies, including the high percentage of patients meeting criteria of very severe asthma and history of frequent exacerbations, although NFA can also develop in asthmatics with a previously mild disease or a very few symptoms. These studies also reaffirm the relationship between NFA and sensitization to some allergens, and finally, highlight the dramatic influence of an inappropriate asthma treatment in patients with NFA.

The main characteristics of NFA phenotypes shown by cluster analysis are summarized in Table 2.

CONCLUSION

Exacerbation episodes of NFA occur in very different circumstances, favored by many risk factors and by a considerable number of physiopathological mechanisms. Numerous clinical, physiological, genetic, immunological, histopathological, and statistical studies have confirmed the existence of different phenotypes in patients suffering from this modality of very severe asthma. Fortunately, adequate treatment of the disease following the recommendations of clinical practice guidelines, and implementation of specific preventive strategies have demonstrated that it is possible to reduce the morbidity and mortality of NFA.

Acknowledgements

We thank Marta Pulido, MD, for editing the manuscript and editorial assistance.

Financial support and sponsorship

None.

Conflicts of interest

J.S-P. declares that in the last 3 years he has received honoraria for speaking at sponsored meetings from GlaxoSmithKline and Boehringer Ingelheim; and as a consultant for Mundipharma, Novartis and Chiesi. He has also received help assistance to meeting travel from Chiesi and received funding/grant support for research projects from AstraZeneca.

V.P. declares that in the last 3 years he has received honoraria for speaking at sponsored meetings from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Merck, Mundipharma, and Pfizer; and as a consultant for Mundipharma, Orion, and Teva. He has also received help assistance to meeting travel from Boehringer Ingelheim and Chiesi, and received funding/grant support for research projects from a variety of government agencies and not-for-profit foundations, as well as from Chiesi and Menarini.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. World Health Organization. WHO Programmes and projects. Chronic respiratory diseases. Asthma. Available at: <http://www.who.int/respiratory/asthma/en/>. [Accessed August 2016]
2. World Health Organization. Projections of mortality and burden of disease, 2004–2030. Available at: http://www.who.int/entity/healthinfo/global_burden_disease/Dth6_2030.xls. [Accessed August 2016]
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, et al. A comparison of asthma deaths and near-fatal asthma attacks in South Australia. *Eur Respir J* 1994; 7:490–497.
5. Kenyon N, Zeki AA, Albertson TE, Louie S. Definition of critical asthma syndromes. *Clin Rev Allergy Immunol* 2015; 48:1–6.
6. Romagnoli M, Caramori G, Braccioni F, et al. Near-fatal asthma phenotype in the ENFUMOSA Cohort. *Clin Exp Allergy* 2007; 37:552–557.
7. Strunk RC. Identification of the fatality-prone subject with asthma. *J Allergy Clin Immunol* 1989; 83:477–485.
8. Wasserfallen JB, Schaller MD, Feihl F, Perret CH. Sudden asphyxic asthma: a distinct entity? *Am Rev Respir Dis* 1990; 142:108–111.
9. Sur S, Crotty TB, Kephart GM, et al. Sudden-onset fatal asthma: a distinct entity with few eosinophils and relatively more neutrophils in the airway submucosa? *Am Rev Respir Dis* 1993; 148:713–719.
10. Gibson GJ. Perception, personality, and respiratory control in life-threatening asthma. *Thorax* 1995; 50 (Suppl 1):S2–S4.
11. Kikuchi Y, Okabe S, Tamura G, et al. Chemosensitivity and perception of dyspnea in patients with a history of near-fatal asthma. *N Engl J Med* 1994; 330:1329–1334.
12. Yellowlees PM, Ruffin RE. Psychological defenses and coping styles in patients following a life-threatening attack of asthma. *Chest* 1989; 95:1298–1303.
13. Miller BD. Depression and asthma: a potentially lethal mixture. *J Allergy Clin Immunol* 1987; 80:481–486.
14. Picado C, Castillo JA, Montserrat JM, Agusti-Vidal A. Aspirin-intolerance as a precipitating factor of life-threatening attacks of asthma requiring mechanical ventilation. *Eur Respir J* 1989; 2:127–129.
15. Moore WC, Meyers DA, Wenzel SE, 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.
16. Serrano-Pariente J, Rodrigo G, Fiz JA, et al. Identification and characterization of near-fatal asthma phenotypes by cluster analysis. *Allergy* 2015; 70:1139–1147.
- The use of cluster analysis confirmed the heterogeneity of NFA already described in previous clinical studies.
17. Sekiya K, Nakatani E, Fukutomi Y, et al. Severe or life-threatening asthma exacerbation: patient heterogeneity identified by cluster analysis. *Clin Exp Allergy* 2016; 46:1043–1055.
18. Antó JM, Sunyer J, Reed CE, et al. Preventing asthma epidemics due to soybeans by dust-control measures. *N Engl J Med* 1993; 329:1760–1763.
19. Rodríguez-Trigo G, Plaza V, Picado C, Sanchis J. [Management according to the Global Initiative for Asthma guidelines of patients with near-fatal asthma reduces morbidity and mortality]. *Arch Bronconeumol* 2008; 44:192–196.
20. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2016. Available at: www.ginasthma.org. [Accessed August 2016]
21. Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. *Nat Med* 2012; 18:716–725.
22. Lötvall J, Akdis CA, Bacharier LB, et al. Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. *J Allergy Clin Immunol* 2011; 127:355–360.
23. Chung KF, Adcock IM. Clinical phenotypes of asthma should link up with disease mechanisms. *Curr Opin Allergy Clin Immunol* 2015; 15:56–62.
- An interesting review of the underlying pathogenetic mechanisms driving severe asthma phenotypes identified by cluster analysis. Understanding these mechanisms may lead to better patient-oriented therapeutic approaches.
24. Kupczyk M, Wenzel S. U.S. and European severe asthma cohorts: what can they teach us about severe asthma? *J Intern Med* 2012; 272:121–132.
25. Rodrigo GJ, Plaza V, Neffen H, et al. Relationship between the characteristics of hospitalised acute asthma patients and the severity of their asthma. A case-control study. *Allergol Immunopathol (Madr)* 2009; 37:225–229.
26. Karamanou M, Androutsos G, Aretaeus of Cappadocia and the first clinical description of asthma. *Am J Respir Crit Care Med* 2011; 184:1420–1421.
27. Bullen SS. Correlation of clinical and autopsy findings in 176 cases of asthma. *J Allergy* 1952; 23:193–203.
28. Turner MO, Noertjojo K, Vedral S, et al. Risk factors for near-fatal asthma. A case-control study in hospitalized patients with asthma. *Am J Respir Crit Care Med* 1998; 157:1804–1809.
29. Teerlink CC, Hegewald MJ, Cannon-Albright LA. A genealogical assessment of heritable predisposition to asthma mortality. *Am J Respir Crit Care Med* 2007; 176:865–870.
30. Gullach AJ, Risgaard B, Lynge TH, et al. Sudden death in young persons with uncontrolled asthma: a nationwide cohort study in Denmark. *BMC Pulm Med* 2015; 15:35.
- The study based on a review of death certificates of sudden unexpected deaths in individuals aged 1–35 years in Denmark from 2000 to 2006, shows that in persons with uncontrolled asthma the cause of death was predominantly sudden cardiac death followed by fatal asthma attack.
31. Watson L, Turk F, James P, Holgate ST. Factors associated with mortality after an asthma admission: a national United Kingdom database analysis. *Respir Med* 2007; 101:1659–1164.
32. Royal College of Physicians. 'Why asthma still kills' - The National Review of Asthma Deaths (NRAD) Confidential Enquiry report, May 2014. Available at: <https://www.rcplondon.ac.uk/projects/outputs/why-asthma-still-kills>. [Accessed August 2016]
- The most recent, exhaustive, and ambitious report analyzing the circumstances surrounding fatal asthma.
33. Bellido-Casado J, Plaza V, Bardagi S, et al. Is the incidence of near-fatal asthma decreasing in Spain? *Arch Bronconeumol* 2006; 42:522–525.
34. Gonzalez-Barcala FJ, Calvo-Alvarez U, Garcia-Sanz MT, et al. Characteristics and prognosis of near-fatal asthma exacerbations. *Am J Med Sci* 2015; 350:98–102.
35. McFadden ER Jr, Warren EL. Observations on asthma mortality. *Ann Intern Med* 1997; 127:142–147.
36. Plaza V, Serrano J, Picado C, Sanchis J; High Risk Asthma Research Group. Frequency and clinical characteristics of rapid-onset fatal and near-fatal asthma. *Eur Respir J* 2002; 19:846–852.
37. Elliot JG, Abramson MJ, Drummer OH, et al. Time to death and mast cell degranulation in fatal asthma. *Respirology* 2009; 14:808–813.
38. Hyzy RC, Travis WD, Hanna E, et al. Slow-onset asthma deaths have more eosinophils and health care utilization than rapid-onset deaths. *Respir Med* 2008; 102:1819–1826.
39. Yan X, Chu JH, Gomez J, et al. Noninvasive analysis of the sputum transcriptome discriminates clinical phenotypes of asthma. *Am J Respir Crit Care Med* 2015; 191:1116–1125.
- Description of three patterns of gene expression for transcriptomic endotypes of asthma in sputum and blood associated with NFA, severe, and milder asthma.
40. Annoni R, Silva LF, Nussbaumer-Ochsner Y, et al. Increased expression of granzymes A and B in fatal asthma. *Eur Respir J* 2015; 45:1485–1488.
41. O'Sullivan S, Cormican L, Faul JL, et al. Activated, cytotoxic CD8(+) T lymphocytes contribute to the pathology of asthma death. *Am J Respir Crit Care Med* 2001; 164:560–564.
42. Oda H, Kawayama T, Imaoka H, et al. Interleukin-18 expression, CD8(+) T cells, and eosinophils in lungs of nonsmokers with fatal asthma. *Ann Allergy Asthma Immunol* 2014; 112:23–28.
43. Ferreira DS, Annoni R, Silva LF, et al. Toll-like receptors 2, 3 and 4 and thymic stromal lymphopoietin expression in fatal asthma. *Clin Exp Allergy* 2012; 42:1459–1471.

44. Picado C. Barcelona's asthma epidemics: clinical aspects and intriguing findings. *Thorax* 1992; 47:197–200.
45. Martínez-Moragón E, Plaza V, Serrano J, *et al.* Near-fatal asthma related to menstruation. *J Allergy Clin Immunol* 2004; 113:242–244.
46. Serrano J, Plaza V, Sureda B, *et al.* Alexithymia: a relevant psychological variable in near-fatal asthma. *Eur Respir J* 2006; 28:296–302.
47. Johnson AJ, Nunn AJ, Somner AR, *et al.* Circumstances of death from asthma. *Br Med J (Clin Res Ed)* 1984; 288:1870–1872.
48. Rea HH, Scragg R, Jackson R, *et al.* A case-control study of deaths from asthma. *Thorax* 1986; 41:833–839.
49. Ayres JG, Miles JF, Barnes PJ. Brittle asthma. *Thorax* 1998; 53:315–321.
50. Pouw EM, Koeter GH, de Monchy JG, *et al.* Clinical assessment after a life-threatening attack of asthma; the role of bronchial hyperreactivity. *Eur Respir J* 1990; 3:861–866.
51. Ledford DK, Wenzel SE, Lockey RF. Aspirin or other nonsteroidal inflammatory agent exacerbated asthma. *J Allergy Clin Immunol Pract* 2014; 2:653–657.
52. Steinke JW, Wilson JM. Aspirin-exacerbated respiratory disease: pathophysiological insights and clinical advances. *J Asthma Allergy* 2016; 9:37–43.
53. Antó JM, Sunyer J, Rodríguez-Roisin R, *et al.* Community outbreaks of asthma associated with inhalation of soybean dust. *Toxicoepidemiological Committee. N Engl J Med* 1989; 320:1097–1102.
54. O'Hollaren MT, Yunginger JW, Offord KP, *et al.* Exposure to an aeroallergen as a possible precipitating factor in respiratory arrest in young patients with asthma. *N Engl J Med* 1991; 324:359–363.
55. Plaza V, Serrano J, Picado C, *et al.* [Clinical characteristics of the fatal and near-fatal asthma in *Alternaria alternata* sensitized patients]. *Med Clin (Barc)* 2003; 121:721–724.
56. Kolbe J, Fergusson W, Garrett J. Rapid onset asthma: a severe but uncommon manifestation. *Thorax* 1998; 53:241–247.
57. Kallenbach JM, Frankel AH, Lapinsky SE, *et al.* Determinants of near fatality in acute severe asthma. *Am J Med* 1993; 95:265–272.
58. Sears MR, Rea HH, Beaglehole R, *et al.* Asthma mortality in New Zealand: a two year national study. *N Z Med J* 1985; 98:271–275.
59. Kunitoh H, Yahikozawa H, Kakuta T, *et al.* Fatal and near fatal asthma. *Ann Allergy* 1992; 69:111–115.
60. Reid LM. The presence or absence of bronchial mucus in fatal asthma. *J Allergy Clin Immunol* 1987; 80:415–416.
61. Weinmayr G, Keller F, Kleiner A, *et al.* Asthma phenotypes identified by latent class analysis in the ISAAC phase II Spain study. *Clin Exp Allergy* 2013; 178:218–224.
62. Haldar P, Pavord ID, Shaw DE, *et al.* Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008; 178:218–224.