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# Characteristics and prognosis of near-fatal asthma exacerbations.

--Manuscript Draft--

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| **Abstract:** | BACKGROUND: Asthma remains a major public health concern because of its high prevalence and the costs it generates. Near-fatal asthma (NFA) episodes represent the most severe forms of the disease after fatal asthma, with significant variations in their incidence between different populations.<br>OBJECTIVE: To analyze the episodes of NFA over a period of 11 years in our hospital<br>METHODS: We retrospectively reviewed all admissions due to asthma exacerbation in our hospital between 2000 and 2010 for patients over 18 years old.<br>RESULTS: The study included 400 NFA episodes of 285 patients (74% women; mean age 66 years). Of these patients, 228 (80%) had a single episode of NFA and 57 had more than one episode during the study period. We observed no clear upward or downward trend during the study period. Readmitted patients had more comorbidities, poorer lung function, more severe forms of asthma and more admissions in the year before the index admission. There was a mortality rate of 3.1%. Over 20% of patients were not given controller treatment and over 40% of patients were not treated with inhaled corticosteroids.<br>CONCLUSIONS: NFA episodes are still prevalent in our population of asthma patients. Reasons for this could be related to improper management in the stable phase, as suggested by the low rate of patients treated with ICS. It also seems necessary to optimize patient management during hospitalization, since stays appear prolonged in comparison to studies in other countries. |

TITLE: Characteristics and prognosis of near-fatal asthma exacerbations. An 11 year survey.

SHORT TITLE: Near-fatal asthma exacerbations.

ABSTRACT:

BACKGROUND: Asthma remains a major public health concern because of its high prevalence and the costs it generates. Near-fatal asthma (NFA) episodes represent the most severe forms of the disease after fatal asthma, with significant variations in their incidence between different populations.

OBJECTIVE: To analyze the episodes of NFA over a period of 11 years in our hospital

METHODS: We retrospectively reviewed all admissions due to asthma exacerbation in our hospital between 2000 and 2010 for patients over 18 years of age.

RESULTS: The study included 400 NFA episodes of 285 patients (74% women; mean age 66 years). Of these patients, 228 (80%) had a single episode of NFA and 57 had more than one episode during the study period. We observed no clear upward or downward trend during the study period. Readmitted patients had more comorbidities, poorer lung function, more severe forms of asthma and more admissions in the year before the index admission. There was a mortality rate of 3.1%. Over 20% of patients were not given controller treatment and over 40% of patients were not treated with inhaled corticosteroids.

CONCLUSIONS: NFA episodes are still prevalent in our population of asthma patients. Reasons for this could be related to improper management in the stable phase, as suggested by the low rate of patients treated with ICS. It also seems necessary to optimize patient management during hospitalization, since stays appear prolonged in comparison to studies in other countries.

KEY WORDS: Asthma; near-fatal; exacerbations; prognosis; hospital admissions.

## INTRODUCTION:

Asthma remains a major public health concern because of its high prevalence and the costs it generates, especially in poorly controlled patients[1,2]. In our population a slight downward trend in asthma mortality has been observed[3], although hospital admissions continue to rise, especially in women[4].

Near-fatal asthma (NFA) episodes are relatively infrequent events that represent the most severe forms of the disease after fatal asthma[5-7].

Significant variations have been observed in the incidence of NFA between different populations, although in most studies NFA admissions constitute between 10% and 21% of all asthma admissions[5,6,8,9]. The definition of NFA is inconsistent across studies[5,6,8-10]. Furthermore, the definition of an intensive care unit (ICU) and the availability of beds in these units vary between countries[11]. These differences make it difficult to extrapolate results across countries.

The aim of our study was to analyze the episodes of NFA over a period of 11 years in our hospital. We recorded patient demographics, clinical characteristics on admission, disease management in stable condition and the clinical course of episodes of severe exacerbation. Documenting the incidence of episodes of NFA may be helpful to identify weaknesses in the healthcare system and to make proposals for improvement.

MATERIAL AND METHODS:

We retrospectively reviewed all admissions due to asthma exacerbation in our hospital between 2000 and 2010 for patients over 18 years old. The data were obtained by two members of the research team by medical record review (UCA, MTGS). Discrepancies in data analysis and interpretation were resolved by consensus with the other members of the group.

Admissions due to other specific causes of asthma exacerbation, such as pulmonary embolism or pneumonia, were excluded.

NFA was defined based on the need for mechanical ventilation, ICU admission, respiratory arrest, hypercapnia with $PaCO_2$ greater than 50 mmHg or acidosis with a pH lower than 7.30, according to the criteria used by Plaza et al.[10]. Hospital stay was defined as the period from patient arrival at the hospital emergency department to discharge.

Our analysis included clinical characteristics exhibited at the time of the first NFA episode. Blood gas data were taken from the first arterial blood gas test available after patient arrival at the hospital emergency department.

Comorbidities were evaluated according to the Charlson index only. We did not collect data on the specific pathologies for all the patients admitted during the 11-year study period.

The etiology of asthma exacerbation was established on the basis of clinical criteria and the results of physical examinations and complementary tests, by consensus of the research team. Cases of respiratory infection presenting new or worsening cough, new or worsening dyspnea and fever >38ºC, or a temperature that was abnormal for that individual, in the absence of other sources of infection[12]. Specifically, bacterial infection was considered probable if the patient also presented increased amount of sputum or purulence, and probably viral in the absence of these criteria[13].

The period of admission was stratified according to season: Spring, Summer, Autumn and Winter, which include respectively April to June, July to September, October to December and January to March.

STATISTICAL ANALYSIS:

The data were tested for normal distribution using Kolmogorov-Smirnov test.

Categorical variables are expressed as frequencies and absolute values. Continuous variables with a normal distribution are expressed as mean ± standard deviation (SD). The median and interquartile range (IQR) were used for non-Gaussian data distribution.

Student t test was used for the comparison of the continuous variables with a normal distribution. Mann Whitney U test was used when these variables had a non-parametric distribution. Categorical variables were compared using Chi-squared test.

Temporal trends in hospital admissions were explored using a Poisson generalized additive model

All statistical analyzes were performed using SPSS 15.0 for Windows, Version 15.0 (SPSS Inc., Chicago, Illinois,USA).

The study was approved by the Research Ethics Committee of our institution.

RESULTS:

The study included 400 NFA episodes of 285 patients (74% women; mean age 66 years). Of these patients, 228 (80%) had a single episode of NFA and 57 had more than one episode during the study period (Table 1).

There was wide variation in the annual proportion of NFA episodes of all asthma-related admissions; from a maximum of 24.6% in 2001 to 12.6% in 2003. We observed no clear upward or downward trend during the study period (Fig 1).

Of these patients 43% were obese and 25% were smokers or ex-smokers (Table 1). Readmitted patients had more comorbidities, poorer lung function, more severe forms of asthma and more admissions in the year before the index admission (Table 1). In over 70% of cases, exacerbation was caused by viral infection (Table 2). No seasonal predominance of episodes was observed (Table 2). Patients with repeated episodes of NFA were less likely to enter the ICU or exhibit acidosis (Table 2)

Over 20% of patients were not given controller treatment and over 40% of patients were not treated with inhaled corticosteroids (ICS) (Table 3). At discharge 15% of patients did not take single or combined ICS (Table 4). Mean hospital stay was long and did not vary between the first admission or readmission, with an average of 15.5 days and a median of 12 days (Table 2). There was a mortality rate of 3.1% (Table 2).

The nine patients who died, 6 women and 3 men, were older than those who survived: mean age 76 versus 67 years, respectively (data not shown).

DISCUSSION:

NFA episodes were relatively common in our study population: during 11 years we identified 400 episodes, representing 19% of all asthma admissions in our hospital. Although comparison with other populations is difficult because the criteria used to define NFA are inconsistent, the rate of serious episodes was higher than in most recent studies[5,6,9,14]. There is only one study, in a Japanese population, where the rate of severe episodes, defined by the need for mechanical ventilation, was greater than in our population[8]. The large number of severe episodes is alarming, since these are high-risk situations. In addition, throughout the study period there was no reduction in the frequency of these events. This contrasts with trends in other populations. For example, in an English multicenter study analyzing ICU admissions between 2002 and 2011, a significant upward trend in admissions for asthma exacerbation was observed[11]. By contrast, studies in U.S. hospitals show a favorable downward trend, with a decreasing number of severe exacerbations of asthma[7,15]. Improved controller treatment could be one of the determinants of better evolution of these patients, as reflected in the study of Kao et al with increased use of ICS[7]. However, differences in the clinical practice of each community, in the healthcare systems management or in the availability of ICU beds are some of the factors that may influence these results[7,11,15].

Smoking did not appear to be a particularly important factor among patients with episodes of NFA in our population, since 25% of these were smokers or former smokers. This is a lower rate than that reported by most authors concerning episodes of severe asthma exacerbations[5,10,16-18]. It is also lower than that reported for the whole Spanish population with asthma, where smokers and former smokers account for 37% of all asthmatics[19].

Regarding controller treatment, we would highlight the low proportion of patients treated with ICS prior to admission, only 59%. However, this is comparable to rates of controller ICS reported by other authors in similar studies: 43% in a New York (USA) population reported by Dhuper et al and in a Houston population reported by Kao et al, up to 78% in a study by Eisner et al in California[5,7-9,15,16,20]. ICS seems advisable considering that 79% of the patients we studied had moderate or severe asthma[21]. This could be one of the causes of the relatively high frequency of episodes of NFA in our community, since the beneficial effect of ICS on asthma prognosis is well-known[22].

Hospital stay of our patients was longer than that of similar patients in other studies[6-8,11,16,23]. This is in agreement with the results of a recent study of hospital admissions for asthma exacerbation in our community, which also reflect higher average stays than in other populations[4]. More advanced age or higher comorbidity in our patients could at least partly explain the longer hospital stays, as these two factors are known to play a role in the worst cases of asthma exacerbation[24-26].

During the study period 9 patients died, representing 3.1% of patients admitted for NFA episodes (2.25% of the episodes, if we include readmissions). This is similar to rates reported in the literature[7,9,16,27]. Han et al. in a USA hospital population reported no deaths in 2000 and 2001, but these studies only included 19 patients[15]. In another study in a Japanese hospital there were no deaths reported, but unlike our study, patients suffering hemodynamic instability, coma or undergoing mechanical ventilation for cardiorespiratory arrest were excluded[8].

ICU admission was much higher in the single admission group versus the readmitted group. We believe that there are 3 main factors that could partly explain this finding. First, fewer readmitted patients had acidosis (33.6% versus 45% of single admissions), and the presence

of acidosis could be a criterion for ICU admission. Second, the group of readmitted patients presented worse baseline lung function (FEV1 48% versus 64% in the single admission group, and third, the greater comorbidity (Charlson index of 0 in only 3% of readmitted patients versus 25% in single admissions) could have meant they were not considered eligible for ICU admission due to poor prognosis[28].

Repeated admissions occurred in patients with higher baseline asthma severity, more comorbidities, worse lung function and more admissions in the year prior to the index admission. These findings are consistent with those reported by other investigators[2,5,20,26,28,29]. The results of the present study suggest that asthma care in our region could be improved and the incidence of NFA reduced. Proposals for improvement include the need to identify factors related with poor disease control, implement patient educational programs, and establish regular outpatient consultation for the management of difficult-to-control cases[19,31,32].

LIMITATIONS:

Our study has certain limitations common to retrospective studies in general, and some patient variables could not be ascertained in all cases. Moreover, the data came from a single hospital, so the results may not adequately reflect the situation in other medical centers. Asthma diagnosis was based on the discharge report produced by the specialist doctor who treated the patient, with review of medical records by our research team (including pulmonologists, internists, and radiologists). However, no additional complementary tests were performed to confirm asthma diagnosis, which means some misdiagnosis is possible.

Other important factors, not considered in the present study, may have contributed to the proportion of NFA episodes, such as viral infection prevalence, pollution or climate changes.

Comparisons with other studies should be taken with caution, given the differences in inclusion criteria between studies and the characteristics of the different populations.

CONCLUSIONS:

In conclusion, NFA episodes are still prevalent in our population of asthma patients. Reasons for this could be related to improper management in the stable phase, as suggested by the low rate of patients treated with ICS. It also seems necessary to optimize patient management during hospitalization, since stays appear prolonged in comparison to studies in other countries.

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Figure Legends:

Figure1.-In percentage of all asthma hospital admissions

Trend of near-fatality asthma (NFA), by year.

Figure 1
Click here to download Figure: Figure_1.jpg

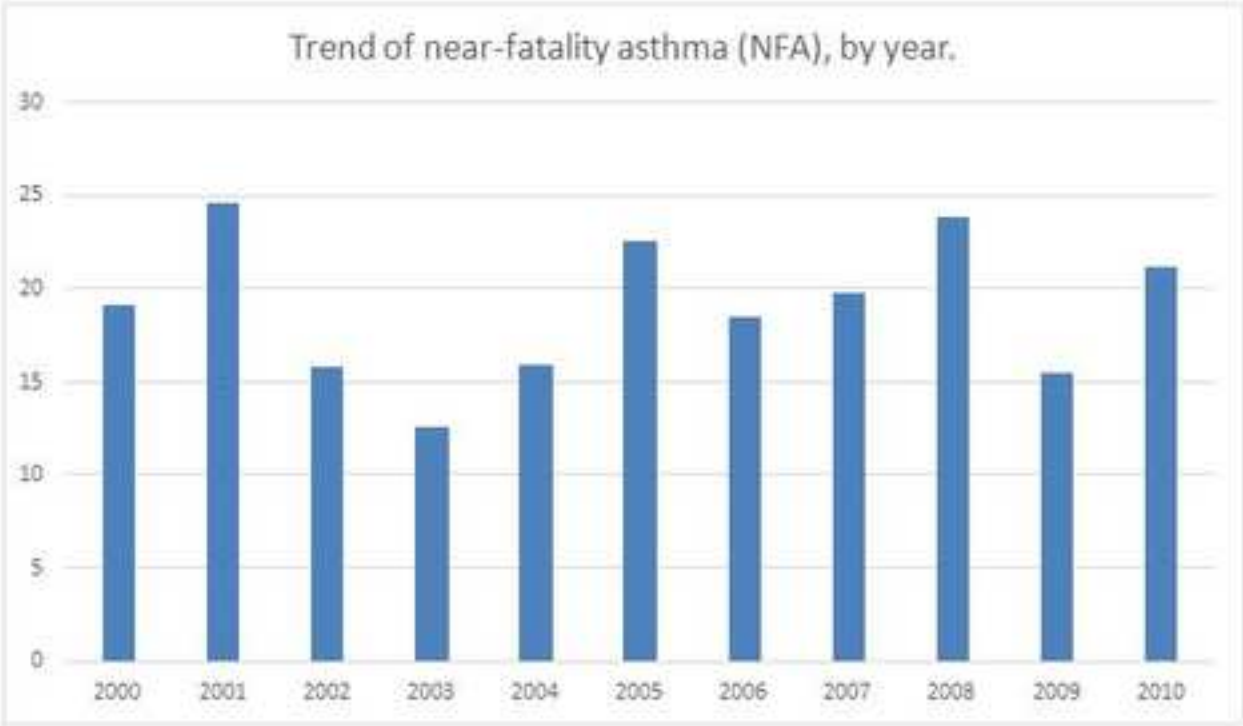


Figure1.-In percentage of all asthma hospital admissions

Table 1. Patient characteristics.

Comparison between patients with a single hospital admission versus readmitted patients (only first admission)

| | Total patients | Single admission | Readmitted | P |
|---|---|---|---|---|
| Total, n (%) | 285 | 228 (80%) | 57 (20%) | |
| Age, mean (SD) | 66.4 (17.3) | 66.2 (17.9) | 67.5 (14.7) | NS |
| Gender, n (%) | | | | NS |
| Male | 75 (26.3) | 64 (28.1) | 11 (19.3) | |
| Female | 210 (73.7) | 164 (71.9) | 46 (80.7) | |
| FEV1%, mean (SD) | 61.2 (24.0) | 64.2 (23.8) | 48.0 (20.5) | 0.003 |
| Obesity | | | | NS |
| Normal weight | 28 (24.3) | 24 (25.0) | 4 (21.1) | |
| Overweight | 37 (32.2) | 31 (32.3) | 6 (31.6) | |
| Obesity | 50 (43.5) | 41 (42.7) | 9 (47.4) | |
| Smoking | | | | NS |
| Never smoker | 213 (74.7) | 169 (74.1) | 44 (77.2) | |
| Former smoker | 26 (9.1) | 20 (8.8) | 6 (10.5) | |
| Current smoker | 46 (16.1) | 39 (17.1) | 7 (12.3) | |
| Charlson index, n (%) | | | | 0.001 |
| 0 | 60 (21.1) | 58 (25.4) | 2 (3.5) | |
| 1 | 105 (36.8) | 75 (32.9) | 30 (52.6) | |
| 2 | 62 (21.8) | 50 (21.9) | 12 (21.1) | |
| ≥ 3 | 58 (20.4) | 45 (19.7) | 13 (22.8) | |
| Asthma severity, n (%) | | | | 0.000 |
| Intermittent | 26 (9.1) | 25 (11) | 1 (1.7) | |
| Mild | 25 (8.8) | 23 (10.1) | 2 (3.5) | |
| Moderate | 46 (16.1) | 41 (18.0) | 5 (8.8) | |
| Severe | 133 (46.7) | 90 (39.5) | 43 (75.4) | |
| Unclassified | 55 (19.3) | 49 (21.5) | 6 (10.5) | |
| Emergency last year, n (%) | | | | NS |
| 0 | 170 (59.6) | 140 (61.4) | 30 (52.6) | |
| 1 – 3 | 103 (36.3) | 81 (35.5) | 22 (38.6) | |
| ≥4 | 12 (4.2) | 7 (3.1) | 5 (8.8) | |
| Hospital admissions last year, n (%) | | | | 0.002 |
| 0 | 190 (66.7) | 160 (70.2) | 30 (52.6) | |
| 1 | 62 (21.8) | 49 (21.5) | 13 (22.8) | |
| ≥2 | 33 (11.6) | 19 (8.3) | 14 (24.6) | |

SD: standard deviation; NS: non-significant.

Body mass index data available for 115 patients.

Table 2. Characteristics of exacerbations.

Comparison between patients with a single hospital admission versus readmitted patients (all admissions).

| | Single admission | Readmitted | P |
|---|---|---|---|
| Total admissions | 285 | 115 | |
| Hospital stay, mean (SD) | 15.9 (13.5) | 14.5 (9.6 ) | NS |
| Season, n (%) | | | NS |
| Spring | 77 (27.0) | 27 (23.5) | |
| Summer | 40 (14.0) | 22 (19.1) | |
| Autumn | 86 (30.2) | 27 (23.5) | |
| Winter | 82 (28.8) | 39 (33.9) | |
| Day of admission, n (%) | | | NS |
| Monday-Thursday | 172 (60.4) | 67 (58.3) | |
| Friday-Sunday | 113 (39.6) | 48 (41.7) | |
| ICU, n (%) | | | 0.005 |
| No | 199 (69.8) | 95 (82.6) | |
| Yes | 86 (30.2) | 20 (17.4) | |
| Death, n (%) | | | NS |
| No | 278 (97.5) | 113 (98.3) | |
| Yes | 7 (2.5) | 2 (1.7) | |
| Exacerbation aetiology | | | NS |
| Unknown, n (%) | 34 (11.9) | 10 (8.7) | |
| Virus, n (%) | 197 (69.1) | 89 (77.4) | |
| Bacteria, n (%) | 44 (15.4) | 14 (12.2) | |
| Other, n (%) | 10 (3.5) | 2 (1.7) | |
| Arterial blood gases | | | |
| pH at admission, mean (SD) | 7.33 (0.13) | 7.35 (0.09) | 0.037 |
| pH at admission, categorised | | | 0.032 |
| Normal (7.35-7.45), n (%) | 126 (44.7) | 67 (59.3) | |
| Acidosis, less than 7.35, n (%) | 128 (45.4) | 38 (33.6) | |
| Alkalosis, more than 7.45, n (%) | 28 (9.9) | 8 (7.1) | |
| PaCO2 at admission, mean (SD) | 58.7 (17.6) | 61.8 (15.1) | NS |

NS: non-significant; ICU: Intensive Care Unit; SD: Standard Deviation

Table 3. Baseline treatment before admission.

Comparison between patients with a single hospital admission versus readmitted patients (only first admission)

| | Single admission | Readmitted | P |
|---|---|---|---|
| Controller treatment | | | NS |
| Treated | 177 (77.6) | 47 (82.5) | |
| Not treated | 51 (22.4) | 10 (17.5) | |
| Beta-2 agonists | | | NS |
| Yes | 38 (16.7) | 14 (24.6) | |
| No | 190 (83.3) | 43 (75.4) | |
| ICS | | | NS |
| Yes | 20 (8.8) | 10 (17.5) | |
| No | 208 (91.2) | 47 (82.5) | |
| Combination ICS+B2A | | | NS |
| Yes | 115 (50.4) | 23 (40.4) | |
| No | 113 (49.6) | 34 (59.6) | |
| LTRA | | | 0.019 |
| Yes | 19 (8.3) | 11 (19.3) | |
| No | 209 (91.7) | 46 (80.7) | |
| OCS | | | NS |
| Yes | 31 (13.6) | 4 (7.0) | |
| No | 197 (86.4) | 53 (93.0) | |
| Theophylline | | | NS |
| Yes | 19 (8.3) | 6 (10.5) | |
| No | 209 (91.7) | 51 (89.5) | |
| DOT | | | NS |
| Yes | 30 (13.2) | 3 (5.3) | |
| No | 198 (86.8) | 54 (94.7) | |

NS: non-significant; ICS: Inhaled Corticosteroids; B2A: Beta-2 agonists; LTRA: leukotriene receptor antagonist; OCS: Oral corticosteroids; DOT: Domiciliary Oxygen Therapy.

Table 4. Treatment at hospital discharge.

Comparison between patients with a single hospital admission versus readmitted patients (only first admission)

| | Single admission | Readmitted | P |
|---|---|---|---|
| Controller treatment | | | 0.10 |
| Treated | 208 (91.2) | 57 (100) | |
| Not treated | 20 (8.8) | 0 | |
| Beta-2 agonists | | | NS |
| Yes | 25 (11.0) | 3 (5.3) | |
| No | 203 (89.0) | 54 (94.7) | |
| ICS | | | NS |
| Yes | 21 (9.2) | 8 (14.0) | |
| No | 207 (90.8) | 49 (86.0) | |
| Combination ICS+B2A | | | NS |
| Yes | 158 (69.3) | 46 (80.7) | |
| No | 70 (30.7) | 11 (19.3) | |
| LTRA | | | 0.013 |
| Yes | 15 (6.6) | 10 (17.5) | |
| No | 213 (93.4) | 47 (82.5) | |
| OCS | | | NS |
| Yes | 154 (67.5) | 35 (61.4) | |
| No | 74 (32.5) | 22 (38.6) | |
| Theophylline | | | NS |
| Yes | 16 (7.0) | 4 (7.0) | |
| No | 212 (93.0) | 53 (93.0) | |
| DOT | | | NS |
| Yes | 33 (14.5) | 6 (10.5) | |
| No | 195 (85.5) | 51 (89.5) | |

NS: non-significant; ICS: Inhaled Corticosteroids; B2A: Beta-2 agonists; LTRA: leukotriene receptor antagonist; OCS: Oral corticosteroids; DOT: Domiciliary Oxygen Therapy.

# Characteristics and Prognosis of Near-fatal Asthma Exacerbations; An 11-year Survey

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ABSTRACT:

BACKGROUND: Asthma remains a major public health concern because of its high prevalence and the costs it generates. Near-fatal asthma (NFA) episodes represent the most severe forms of the disease after fatal asthma, with significant variations in their incidence between different populations.

OBJECTIVE: To analyze the episodes of NFA over a period of 11 years in our hospital

METHODS: We retrospectively reviewed all admissions due to asthma exacerbation in our hospital between 2000 and 2010 for patients over 18 years of age.

RESULTS: The study included 400 NFA episodes of 285 patients (74% women; mean age 66 years). Of these patients, 228 (80%) had a single episode of NFA and 57 had more than one episode during the study period. We observed no clear upward or downward trend during the study period. Readmitted patients had more comorbidities, poorer lung function, more severe forms of asthma and more admissions in the year before the index admission. There was a mortality rate of 3.1%. Over 20% of patients were not given controller treatment and over 40% of patients were not treated with inhaled corticosteroids.

CONCLUSIONS: NFA episodes are still prevalent in our population of asthma patients. Reasons for this could be related to improper management in the stable phase, as suggested by the low rate of patients treated with ICS. It also seems necessary to optimize patient management during hospitalization, since stays appear prolonged in comparison to studies in other countries.

KEY WORDS: Asthma; near-fatal; exacerbations; prognosis; hospital admissions.

INTRODUCTION:

Asthma remains a major public health concern because of its high prevalence and the costs it generates, especially in poorly controlled patients[1,2]. In the present population, a slight downward trend in asthma mortality has been observed[3], although hospital admissions continue to rise, especially in women[4].

Near-fatal asthma (NFA) episodes are relatively infrequent events that represent the most severe forms of the disease after fatal asthma[5-7].

Significant variations have been observed in the incidence of NFA between different populations, although in most studies NFA admissions constitute between 10% and 21% of all asthma admissions[5,6,8,9]. The definition of NFA is inconsistent across studies[5,6,8-10]. Furthermore, the definition of an intensive care unit (ICU) and the availability of beds in these units vary between countries[11]. These differences make it difficult to extrapolate results across countries.

The aim of this study was to analyze the episodes of NFA over a period of 11 years. The authors recorded patient demographics, clinical characteristics on admission, disease management in stable condition and the clinical course of episodes of severe exacerbation. Documenting the incidence of episodes of NFA may be helpful to identify weaknesses in the healthcare system and to make proposals for improvement.

MATERIAL AND METHODS:

All admissions due to asthma exacerbation in our hospital between 2000 and 2010 for patients over 18 years old were retrospectively reviewed. The data were obtained by 2 members of the research team by medical record review (UCA, MTGS). Discrepancies in data analysis and interpretation were resolved by consensus with the other members of the group.

Admissions due to other specific causes of asthma exacerbation, such as pulmonary embolism or pneumonia, were excluded.

NFA was defined based on the need for mechanical ventilation, ICU admission, respiratory arrest, hypercapnia with $PaCO_2$ greater than 50 mmHg or acidosis with a pH lower than 7.30, according to the criteria used by Plaza et al[10]. Hospital stay was defined as the period from patient arrival at the hospital emergency department to discharge.

The analysis included clinical characteristics exhibited at the time of the first NFA episode. Blood gas data were taken from the first arterial blood gas test available after patient arrival at the hospital emergency department.

Comorbidities were evaluated according to the Charlson index only. The authors did not collect data on the specific pathologies for all the patients admitted during the 11-year study period.

The etiology of asthma exacerbation was established on the basis of clinical criteria and the results of physical examinations and complementary tests, by consensus of the research team. Cases of respiratory infection presenting new or worsening cough, new or worsening dyspnea and fever >38ºC, or a temperature that was abnormal for that individual, in the absence of other sources of infection[12]. Specifically, bacterial infection was considered probable if the patient also presented increased amount of sputum or purulence, and probably viral in the absence of these criteria[13].

The period of admission was stratified according to season: Spring, Summer, Autumn and Winter, which include respectively April to June, July to September, October to December and January to March.

STATISTICAL ANALYSIS:

The data were tested for normal distribution using Kolmogorov-Smirnov test.

Categorical variables are expressed as frequencies and absolute values. Continuous variables with a normal distribution are expressed as mean ± standard deviation (SD). The median and interquartile range (IQR) were used for non-Gaussian data distribution.

Student t test was used for the comparison of the continuous variables with a normal distribution. Mann Whitney U test was used when these variables had a non-parametric distribution. Categorical variables were compared using Chi-squared test.

Temporal trends in hospital admissions were explored using a Poisson generalized additive model.

All statistical analyzes were performed using SPSS 15.0 for Windows, Version 15.0 (SPSS Inc., Chicago, Illinois,USA).

The study was approved by the Research Ethics Committee of the author's institution.

RESULTS:

The study included 400 NFA episodes of 285 patients (74% women; mean age 66 years). Of these patients, 228 (80%) had a single episode of NFA and 57 had more than one episode during the study period (Table 1).

There was wide variation in the annual proportion of NFA episodes of all asthma-related admissions; from a maximum of 24.6% in 2001 to 12.6% in 2003. No clear upward or downward trend during the study period was observed (Fig 1).

Of these patients 43% were obese and 25% were smokers or ex-smokers (Table 1). Readmitted patients had more comorbidities, poorer lung function, more severe forms of asthma and more admissions in the year before the index admission (Table 1). In over 70% of cases, exacerbation was caused by viral infection (Table 2). No seasonal predominance of episodes was observed (Table 2). Patients with repeated episodes of NFA were less likely to enter the ICU or exhibit acidosis (Table 2)

Over 20% of patients were not given controller treatment and over 40% of patients were not treated with inhaled corticosteroids (ICS) (Table 3). At discharge 15% of patients did not take single or combined ICS (Table 4). Mean hospital stay was long and did not vary between the first admission or readmission, with an average of 15.5 days and a median of 12 days (Table 2). There was a mortality rate of 3.1% (Table 2).

The nine patients who died, 6 women and 3 men, were older than those who survived: mean age 76 versus 67 years, respectively (data not shown).

DISCUSSION:

NFA episodes were relatively common in our study population: during 11 years we identified 400 episodes, representing 19% of all asthma admissions in the hospital. Although comparison with other populations is difficult because the criteria used to define NFA are inconsistent, the rate of serious episodes was higher than in most recent studies[5,6,9,14]. There is only 1 study, in a Japanese population, where the rate of severe episodes, defined by the need for mechanical ventilation, was greater than in the population in this study[8]. The large number of severe episodes is alarming, since these are high-risk situations. In addition, throughout the study period there was no reduction in the frequency of these events. This contrasts with trends in other populations. For example, in an English multicenter study analyzing ICU admissions between 2002 and 2011, a significant upward trend in admissions for asthma exacerbation was observed[11]. By contrast, studies in U.S. hospitals show a favorable downward trend, with a decreasing number of severe exacerbations of asthma[7,15]. Improved controller treatment could be one of the determinants of better evolution of these patients, as reflected in the study of Kao et al with increased use of ICS[7]. However, differences in the clinical practice of each community, in the healthcare systems management or in the availability of ICU beds are some of the factors that may influence these results[7,11,15].

Smoking did not appear to be a particularly important factor among patients with episodes of NFA in our population, since 25% of these were smokers or former smokers. This is a lower rate than that reported by most authors concerning episodes of severe asthma exacerbations[5,10,16-18]. It

is also lower than that reported for the whole Spanish population with asthma, where smokers and former smokers account for 37% of all asthmatics[19].

Regarding controller treatment, the authors would highlight the low proportion of patients treated with ICS prior to admission, only 59%. However, this is comparable to rates of controller ICS reported by other authors in similar studies: 43% in a New York (USA) population reported by Dhuper et al and in a Houston population reported by Kao et al, up to 78% in a study by Eisner et al in California[5,7-9,15,16,20]. ICS seems advisable considering that 79% of the patients we studied had moderate or severe asthma[21]. This could be one of the causes of the relatively high frequency of episodes of NFA in our community, since the beneficial effect of ICS on asthma prognosis is well-known[22].

Hospital stay of the patients in this study was longer than that of similar patients in other studies[6-8,11,16,23]. This is in agreement with the results of a recent study of hospital admissions for asthma exacerbation in this community, which also reflect higher average stays than in other populations[4]. More advanced age or higher comorbidity in these patients could at least partly explain the longer hospital stays, as these 2 factors are known to play a role in the worst cases of asthma exacerbation[24-26].

During the study period 9 patients died, representing 3.1% of patients admitted for NFA episodes (2.25% of the episodes, if we include readmissions). This is similar to rates reported in the literature[7,9,16,27]. Han et al in a U.S. hospital population reported no deaths in 2000 and 2001, but these studies only included 19 patients[15]. In another study in a Japanese hospital there were no

deaths reported, but unlike this study, patients suffering hemodynamic instability, coma or undergoing mechanical ventilation for cardiorespiratory arrest were excluded[8].

ICU admission was much higher in the single admission group versus the readmitted group. The authors believe that there are 3 main factors that could partly explain this finding. First, fewer readmitted patients had acidosis (33.6% versus 45% of single admissions), and the presence of acidosis could be a criterion for ICU admission. Second, the group of readmitted patients presented worse baseline lung function (FEV1 48% versus 64% in the single admission group, and third, the greater comorbidity (Charlson index of 0 in only 3% of readmitted patients versus 25% in single admissions) could have meant they were not considered eligible for ICU admission due to poor prognosis[28].

Repeated admissions occurred in patients with higher baseline asthma severity, more comorbidities, worse lung function and more admissions in the year prior to the index admission. These findings are consistent with those reported by other investigators[2,5,20,26,28,29]. The results of the present study suggest that asthma care in our region could be improved and the incidence of NFA reduced. Proposals for improvement include the need to identify factors related with poor disease control, implement patient educational programs, and establish regular outpatient consultation for the management of difficult-to-control cases[19,31,32].

LIMITATIONS:

This study has certain limitations common to retrospective studies in general, and some patient variables could not be ascertained in all cases. Moreover, the data came from a single hospital, so the results may not adequately reflect the situation in other medical centers. Asthma diagnosis

was based on the discharge report produced by the specialist doctor who treated the patient, with review of medical records by our research team (including pulmonologists, internists, and radiologists). However, no additional complementary tests were performed to confirm asthma diagnosis, which means some misdiagnosis is possible.

Other important factors, not considered in the present study, may have contributed to the proportion of NFA episodes, such as viral infection prevalence, pollution or climate changes.

Comparisons with other studies should be taken with caution, given the differences in inclusion criteria between studies and the characteristics of the different populations.

CONCLUSIONS:

In conclusion, NFA episodes are still prevalent in this population of asthma patients. Reasons for this could be related to improper management in the stable phase, as suggested by the low rate of patients treated with ICS. It also seems necessary to optimize patient management during hospitalization, since stays appear prolonged in comparison to studies in other countries.

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Figure Legends:

Figure1.-In percentage of all asthma hospital admissions

Trend of near-fatality asthma (NFA), by year.