Original Article

Causes of death in asthma patients enrolled in the Bahia State Program for the Control of Asthma and Allergic Rhinitis*

Adelmir Souza-Machado[1], Carolina Souza-Machado[2], Daisy Freitas Silva[3], Eduardo Vieira Ponte[4], Alvaro A. Cruz[5]

Abstract

Objective: To report demographic and clinical characteristics of patients with asthma who evolved to death, as well as to describe the conditions related to this outcome in a subgroup of patients admitted to the Program for the Control of Asthma and Allergic Rhinitis in Bahia (ProAR). **Methods:** A descriptive, retrospective, observational study. Data from clinical charts and death certificates of 16 patients of 930 subjects with severe asthma monitored at the ProAR Central Reference Center from December 2003 to June 2006 were reviewed. **Results:** Of the 930 patients participating in the program, 16 (1.72%) died. Of these, there were 10 males and 6 females, ranging in age from 39 to 74 years (median, 55 years); 12 (75%) of the patients were black. Time since diagnosis ranged from 1 to 68 years (median, 30 years). In 43.8 and 53.8%, respectively, there was a personal or family history of atopy. Ex-smokers (<10 pack-years) accounted for 37.5% of the cases. Causes of death listed on the death certificates were as follows: asthma or asthma exacerbations in 8 (50%); respiratory failure in 3 (18.75%); acute heart infarction in 2 (12.5%); hepatitis in 1 (6.25%); hypovolemic shock in 1 (6.25%); and cardiorespiratory arrest in 1 (6.25%). Of the 16 deaths, 13 (81.25%) occurred inside hospitals. **Conclusion:** Asphyxia and cardiovascular diseases were the most common attributed causes of mortality in this subgroup of patients with severe asthma. Hospital-based mortality, male gender, advanced age, long-term disease and fixed airflow obstruction were the aspects most frequently observed in the cases studied.

Keywords: Mortality; Rhinitis/treatment; Asthma/treatment; Cardiovascular diseases.

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1. Ph.D. Adjunct Professor of Pharmacology at the *Escola Bahiana de Medicina e Saúde Pública* – EBMSP, Bahia School of Medicine and Public Health – Salvador (BA) Brazil.
2. Assistant Professor at the *Universidade Católica do Salvador* – UCSAL, Catholic University of Salvador – Salvador (BA) Brazil.
3. Nursing student at the *Universidade Católica do Salvador* – UCSAL, Catholic University of Salvador – Salvador (BA) Brazil.
4. PhD student in the Postgraduate Course in Medicine and Health at the *Universidade Federal da Bahia* – UFBA, Federal University of Bahia – Salvador (BA) Brazil.
5. Ph.D. Adjunct Professor at the Bahia School of Medicine, *Universidade Federal da Bahia* – UFBA, Federal University of Bahia – Salvador (BA) Brazil.
Correspondence to: Adelmir Souza-Machado. Centro de Saúde Carlos Gomes, Rua Carlos Gomes 270, 7º andar, ProAR, CEP 40060-330, Salvador, BA, Brasil.
Tel/Fax 55 71 3321-8467. E-mail: adelmirm@terra.com.br
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Introduction

Asthma is a chronic respiratory disease that is common in adults and children, resulting in substantial morbidity and high mortality rates.[1,2] However, the risk of mortality is reduced through appropriate pharmacological interventions.[3] It is estimated that 10% of patients with asthma present severe manifestations of the disease. Severe asthma results in a disproportional burden, with direct expenditures for health care and indirect financial losses in the work environment and nuclear families of these patients.[1,4] However, the cruelest consequence of severe asthma is the personal and family suffering caused by recurrent asphyxia.

It has been observed that the rates of asthma-related mortality do not increase in parallel with increases in its prevalence.[1,2,4] The countries in which higher mortality rates are reported are those in which there is little or no access to treatment for asthma. According to data obtained from the Brazilian Unified Health System, asthma is the fourth leading cause of hospitalization in Brazil and was responsible for 329,182 hospitalizations nationwide in 2004, 969 of those patients evolving to death.[5]

In contrast to what has been observed in other countries, such as Finland and Canada,[6,7] a nationwide asthma control program has not yet been established in Brazil. Isolated initiatives in some Brazilian cities and states have been offering assistance to patients of various ages suffering from asthma of various degrees of severity.[8] In 2003, the *Programa de Controle da Asma e da Rinite Alérgica na Bahia* (ProAR, Program for the Control of Asthma and Allergic Rhinitis in Bahia) was implemented. The main objective of the program is to coordinate measures for the prevention and treatment of bronchial asthma and allergic rhinitis within the Unified Health System in the state of Bahia, Brazil, guaranteeing regular access to medication, free of charge, and seeking to improve the quality of life of asthma patients by reducing the number of hospitalizations and emergency room visits, as well as the asthma-related mortality rate.[9]

In Brazil, there have been few studies evaluating asthma-related mortality in terms of its characteristics and the conditions under which such mortality occurs.[10] Considering the influence of severe persistent asthma on various health markers and the scarcity of local data that would enable the adequate monitoring of the progression of the disease, the objectives of the present study were to report demographic and clinical characteristics of patients with asthma who evolved to death, as well as to describe the causes and conditions related to this outcome in this subgroup of patients.

Methods

ProAR enrollment criteria

In accordance with the ProAr enrollment criteria, patients with severe asthma, of either gender, who were nonsmokers, were over 12 years of age, and were admitted to/monitored at the ProAR Referral Center – *Universidade Federal da Bahia* (UFBA, Federal University of Bahia), Salvador, Brazil, were enrolled in the study.[9] Individuals without asthma and diagnosed with chronic obstructive pulmonary disease or other pulmonary diseases were referred to the General Pulmonology Outpatient Clinic at the UFBA *Hospital Universitário Professor Edgard Santos* (University Hospital Professor Edgard Santos) and were therefore excluded from the final analysis.

ProAr monitoring routines

After being enrolled in the Program, patients were submitted to regular visits with the attending physician every 30 and 60 days, in accordance with the criteria established in the III Brazilian Consensus on Asthma Management [11] and in the World Health Organization report entitled 'Allergic Rhinitis Initiative and its Impact on Asthma'.[12] Instructions on the use of medications and training in the use of inhaler devices were provided at enrollment and reinforced during every medical visit by the pharmaceutical treatment team. Control on the use of medications and treatment compliance were supervised by a nurse and by the ProAr team of pharmacists. In addition, health education activities were offered to patients and their families every other week.

Study design and mortality data collection

This was a descriptive, retrospective, observational study in which data were collected from the clinical charts and death certificates of 16 patients with asthma monitored at the ProAr Referral Center who ultimately died between December of 2003 and June of 2006. Primary and secondary causes

related to mortality, as well as place and time of death, were collected from the death certificates. Demographic and clinical characteristics, as well as details regarding asthma treatment, were collected from the ProAr outpatient clinical charts.

Ethical aspects

The Ethical Committee of the Bahia School of Medicine approved the study design. All of the patients enrolled in the Program, or their legal representatives, were informed that data regarding the monitoring and treatment in ProAR might be used in studies, but that anonymity was guaranteed, and all gave written informed consent at enrollment.

Results

ProAR treatment profile

Patients with severe asthma (n = 1730) were monitored by a multidisciplinary health care team and received free medication for asthma from December of 2003 to June of 2006. During this period, 930 patients were provided medical care at the ProAr Referral Center. The main characteristics of treatment at the ProAR Referral Center are listed in Table 1.

Characteristics of the patients with severe asthma who died

Between December of 2003 and June of 2006, 16 (1.72%) of the 930 ProAr patients died. Of those 16, 10 were male and 6 were female. Ages ranged from 39 to 74 years (median, 55 years). Of the total, 12 (75%) were of African descent. Former smokers (<10 pack-years) accounted for 37.5% of the deaths. Regarding professional activity, 6 (37.5%) patients were unemployed and were supported by family members, 4 (25%) were retired, and the remaining patients pursued the following occupations: machine operator (n = 1); secretary (n = 1); carpenter (n = 1); nursing assistant (n = 1); general service assistant (n = 1); and painter (n = 1). Time since medical diagnosis of the disease ranged from 1 to 68 years (median, 30 years). A personal and family history of atopy was found, respectively, in 7/16 (43.8%) and 7/13 (53.8%; no data available for 3 patients). The follow-up period from admission to the ProAR Outpatient Clinic to the time of death ranged from 3 to 22 months (median, 9 months). Causes of death reported on the death certificates were: asthma or asthma exacerbations, in 8 patients (50%); respiratory failure, in 3 patients (18.75%); acute myocardial infarction, in 2 patients (12.5%); hepatitis, in 1 patient (6.25%); hypovolemic shock caused by digestive tract hemorrhage, in 1 patient (6.25%); and cardiorespiratory arrest, in 1 patient (6.25%). Of the 16 patients, 13 (81.25%) died inside hospitals, mainly in emergency rooms, although one of those deaths occurred in an infirmary and one in an intensive care unit. The 3 remaining patients died in their homes. Other characteristics can be seen in Table 2.

Table 1 - Medical visits at the ProAr Referral Center from December of 2003 to June of 2006.

Profile of ProAR outpatient visits	n
Total of medical visits (first and subsequent)[a]	7506
Follow-up visits (subsequent to enrollment)	6240
Screening visits	1482
Patients enrolled in the program (HUPES)[b]	930
Patients who were monitored for the confirmation of diagnosis	342
Outpatient clinic discharge	4
Deaths	16

ProAR: Program for the Control of Asthma and Allergic Rhinitis in Bahia; and HUPES: Hospital Universitário Professor Edgard Santos (Professor Edgard Santos University Hospital); [a]HUPES Outpatient Clinic Magalhães Neto, Federal University of Bahia School of Medicine of Bahia; and [b]Severe persistent asthma diagnosed by a physician (clinical and spirometric evaluation).

Time of the year when the patients with severe asthma died

No differences were identified regarding the time of the year when the patients died, although most of the deaths occurred in the fourth and second trimesters: five between October and December; four between April and June; three between January and March; and three between July and September. This information was unavailable for one of the deaths. Of the 16 patients who died, 12 (75%) had been enrolled during the first 12 months after the implementation of the Program. As previously mentioned, 13 (81.2%) of the 16 died in hospitals or in health care centers or facilities. We found that 4 (25%) of the patients died on a Monday; 68.8% of the patients died between 12 am and 12 pm, and 31.2% of the patients died between 12 pm and 12 am.

Table 2 - General characteristics of patients with asthma who died.

Patients	Gender	Age (years)	Δ asthma (years)	Visits to emergency rooms (12 months)	Oral corticosteroid courses (12 months)	Cause of death[a]
1[b]	M	70	67	100	2	ARF
2[b]	M	39	4	2	6	Asthma
3	M	74	68	1	1	Hepatitis
4[b]	F	58	18	30	continuous[c]	ARF
5[b]	M	48	20	8	10	Asthma
6[b]	F	44	40	30	2	CRA
7	M	53	20	0	0	Asthma
8	F	65	45	20	0	AMI
9	M	48	4	36	0	Asthma
10	F	45	1	70	0	AMI
11	M	48	8	10	4	ARF
12[b]	M	60	55	30	5	Shock
13	F	72	30	8	0	Asthma
14	M	66	60	4	0	Asthma
15	F	44	34	0	continuous[c]	Asthma
16	M	57	30	10	2	Asthma
%25	-	47.25	15.5	3.5	0	-
%50	-	55	30	10	1.5	-
%75	-	65.25	47.5	30	3.5	-

M: male; F: female; Δ asthma: duration of the disease diagnosed by a physician; ARF: acute respiratory failure; AMI: acute myocardial infarction; CRA: cardiorespiratory arrest; and Shock: hypovolemic shock due to upper digestive tract hemorrhage; [a]Place of death: home, in 3 patients (patients 6, 8 and 10), intensive care unit, in 1 (patient 2), infirmary in 1 (patient 14), and the emergency room, in 11 (patients 1, 3-5, 7, 9, 11-13, 15 and 16); [b]Former smokers (<10 pack-years); and [c]Continuous prednisone use at 20 mg/day.

Clinical parameters on the severity of asthma in the patients who died

In the 12 months prior to the enrollment of these patients to ProAR, 14 (87.5%) reported frequent emergency room visits (median, 10 visits/year) and hospitalizations due to asthma (median, 1.5 hospitalizations/year). Only one of the patients (patient 15) had reported a near-fatal asthma attack. Patients 2, 4, 8 and 9 had not been hospitalized due to asthma or any other disease during the same period; patients 2 and 4 did not even report having made any emergency room visits.

Clinical manifestations suggesting rhinitis and gastroesophageal reflux were identified in 8 (50%) of the patients; 2 (12.5%) of the patients (patients 3 and 12) had no complaints of rhinitis or reflux. There were 7 patients (43.7%) who were diagnosed with systemic arterial hypertension, 2 (12.5%) who were diagnosed with diabetes mellitus and 3 (19%) who were considered overweight (body mass index > 30 kg/m^2). Diagnoses of osteoporosis, cataract, ventricular tachycardia, hepatitis and deep vein thrombosis were each observed in at least 1 patient (6.25%).

Pulmonary function at baseline and at the time of death

Pulmonary function parameters at enrollment in the ProAR are shown in Table 3. Of the16 patients, 2 were unable to perform spirometry during the 3-month follow-up period leading up to the time of death. Of the 13 patients being treated in health care facilities at the time of death, only 1 (7.7%) was submitted to pulmonary function tests, blood gas analysis and pulse oximetry.

Drug treatment for asthma and rhinitis

The patients reported that, during the 12-month period preceding enrollment in the Program, they had used, although irregularly and intermittently, various treatments for asthma: oral or inhaled

Table 3 - Pulmonary function parameters of patients with asthma who died.

Patient	FVC	FEV_1	FEV_1/FVC	$FEF_{25-75\%}$	ΔFEV_1(%)	FEV_1%
1	-	-	-	-	-	-
2	-	-	-	-	-	-
3	3.57	0.99	73	0.18	4	47
4	1.76	1.78	81	1.96	1	36
5	1.65	1.17	71	0.15	6	35
6	1.54	1.07	69	0.64	2	38
7	4.53	2.19	80	3	4	70
8	4.07	2.31	57	1.03	23	88
9	2.07	0.68	33	0.26	-1	25
10	1.28	0.99	86	0.78	8	49
11	0.82	0.39	48	0.07	-4	13
12	2.14	0.89	42	0.31	5	36
13	1.6	0.83	52	0.41	0	62
14	2.22	1.15	52	-	13	46
15	1.78	0.69	39	0.17	5	27
16	4.53	2.19	48	0.81	4	70
%25	1.7	1.12	53.5	0.16	2.5	35.5
%50	1.9	1.0	54.5	0.4	4.0	42.0
%75	2.2	1.32	75	0.97	4.5	40.2

Notes: Patients 1 and 2 were not submitted to spirometry due to functional incapacity and inability to perform maneuvers; FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; $FEF_{25-75\%}$: forced expiratory flow between 25% and 75% of FVC; and ΔFEV_1 (%): percent variation of FEV_1 after administration of salbutamol (400 μg).

β_2-agonists were used by 83%; aminophylline was used by 33%; inhaled corticoids were used by 17%; and daily oral corticosteroids were used by 12.5%. The use of systemic antihistamine drugs and nasal topical corticoids during the period prior to enrollment was not reported. Regarding courses of oral corticosteroids, 15 patients reported their use during asthma exacerbations (variation, 0-10; median, 2 courses). Patients 4 and 15 used oral prednisone daily (mean dose, 20 mg).

Patients were treated with formoterol (12-24 μg/day) and budesonide (400-800 μg/day) by dry powder inhaler; for symptom relief, nasal budesonide (64-128 μg/dose/day) and fenoterol (200 μg/dose) were prescribed to the patients enrolled in the Program. Of the 16 patients who died, 5 (31.25%) had been noncompliant with the recommended treatment for asthma and rhinitis; in 3 (18.75%) cases, there was no record regarding treatment compliance.

Regardless of the prescribed treatment, 7 (43.7%) patients reported symptoms suggestive of asthma and rhinitis in their final outpatient visit; 9 (56.3%) reported no symptoms.

Discussion

In the present study, the authors reported the principal demographic and clinical characteristics of 16 patients with severe asthma who died. Males of African descent, older than 55 years of age, after 30 years of disease and personal history of atopy were predominant. Asthma and respiratory failure were the principal causes of death. Most of the patients died in health care facilities, principally in emergency rooms.

It is estimated that 10% of all patients with asthma suffer from the severe form of the disease. This subgroup of patients with asthma present a high risk of exacerbations, hospitalizations and death due to asphyxia.[1,4] Studies have shown that asthma-related mortality is more common in females, in individuals older than 55 years of age and in ethnic minorities, such as African-Americans and Hispanics.[1-4] The mortality rate is three times higher among individuals of African descent than among Caucasians.[1,4,13-15] The higher proportion of males in the cases of death identified in the ProAR cohort might be related to the fact that all causes

of death, and not only those related to asthma, that is, the incidence of comorbidities, the severity of each comorbidity and other factors related to treatment compliance of patients with chronic diseases, were included. Other studies corroborate these results.[13-15] It has been reported that all-cause mortality is higher among patients with asthma. In studies on mortality among patients with asthma, respiratory causes predominate, especially asthma, followed by ischemic heart diseases.[10,15] In the present study, we found that other markers of asthma severity, such as hospitalizations, emergency room visits and corticosteroid courses, were similar when compared to controls in the ProAR cohort (data not shown). [9] In general, in addition to the very severity of the disease, certain factors, such as inadequate and irregular medical monitoring, the lack of a written plan of action and noncompliance with treatment, can contribute to the fatal outcome.

Asthma is a chronic inflammatory disease that can evolve to imperfect remodeling, destruction of airways and parenchyma causing pulmonary function impairment, which is aggravated by the age of patients and the duration of the disease.[16,17] In the present study, asthma-related mortality mostly occurred in individuals over 50 years of age who suffered from asthma and fixed airflow obstruction for a prolonged time. Clinical manifestations suggestive of gastroesophageal reflux and rhinitis were found in 50% of the patients. Various findings have confirmed the hypothesis that asthma and rhinitis are expressions of a single systemic disease whose severity progressively increases.[18,19] Concomitant rhinitis and asthma accentuates the severity of asthma and imposes increasing risks of cause-specific complications to patients.[18,19] Other studies have shown that rhinitis and asthma can also influence the evolution of cardiovascular manifestations.[20]

As previously mentioned, most of the patients died in emergency rooms. One of the deaths occurred in an infirmary and one in an intensive care unit due to asthma and hepatitis-related complications, respectively. Deaths from asthma and respiratory failure in emergency rooms may be related to the inability of staff to recognize the severity of the exacerbation, noncompliance with the action plan, limited access to health services, delays in therapeutic interventions and lack of simplified treatment protocols.[14,21-27] In addition, the judicious evaluation of patient histories, the risks associated with the disease and the determination of pulmonary function parameters are frequently ignored. We highlight the fact that six patients in this series reported no hospitalizations; two of these reported no visits to emergency rooms until the time of death. This can also mean that patients have a poor perception of the severity of asthma, not accurately identifying the bronchial obstruction, resulting in a delay in seeking medical attention.[22,25] Poor perception of the severity of bronchial obstruction can be considered as the major subjacent cause of fatal exacerbations in patients with asthma. Patients with asthma whose perception is poor are at risk of underestimating their disease and receiving insufficient treatment.[21-25]

It has been reported that asthma-related deaths are more common on weekends and at night; curiously, deaths from acute myocardial infarction are more common on Mondays and in the morning.[13,14] In this series of cases, deaths predominantly occurred on Mondays from 12 am to 12 pm, which suggests that there was a delay in seeking medical attention. We found no evidence of a relationship between higher incidence of mortality and lower physiological production of endogenous cortisol.

Objective measures of pulmonary function, such as peak expiratory flow and forced expiratory volume in one second, are useful predictive factors for hospital admission of patients with asthma.[26,27] Peak expiratory flow, measured serially (at 15 min and 4 h after the initiation of treatment) in the emergency room, is a good prognostic marker of the outcome of the asthma attack.[27] Signs and symptoms guide therapeutic procedures, but repeated measurements of pulmonary function parameters contribute to the evaluation of the intensity of bronchial obstruction and the response to the recommended treatment.[27] Simple resources for the determination of pulmonary function parameters are unavailable in most Brazilian hospitals, particularly in our state. This might have been one of the factors that made the evaluation of these patients more difficult and contributed to their not being hospitalized, which would account for the fact that a great number of the deaths occurred in emergency rooms.

A subgroup of patients with severe asthma remains symptomatic, despite using inhaled corti-

costeroids in high doses combined with long-acting β_2-agonists and other asthma medications, such as oral corticosteroids.[1,4,21] The lack of asthma control in this subgroup of patients can be attributed to various factors: denial or underestimation of the disease by the patients; insufficient treatment for the severity of the disease; lack or incorrect use of asthma medications; limited access to health care services; presence of comorbidities; and factors inherent to the disease.[21-28]

Some authors have found that the use of inhaled corticoids is inversely proportional to the risk of death from asthma.[3] In the present study, we found that mortality was more common during the first 12 months of treatment for asthma, which suggests that the anti-inflammatory treatment period might have been cumulatively insufficient. Surprisingly, 9 (56.3%) of the asthma patients who died reported no symptoms during the medical visits preceding their deaths. Poor perception of the severity of asthma is not uncommon. In a study conducted by Neffen et al.,[29] although the patients self-evaluated the disease as 'well controlled', only 2.4% met the well-defined criteria for disease control.[29]

Filling out death certificates is not an easy task. Imprecision in completing the fields (cause of death) is common. In Brazil, asthma-related mortality is statistically underestimated, increasing by nearly 50% when deaths in which asthma is mentioned in any of the fields on the death certificate are included. The incidence of records for asthma as a secondary cause of death is higher in Brazil than in Australia, England and the United States.[10,13,14] In the present study, only the primary cause of death was considered and registered exactly as stated on the death certificates; interpretations and extrapolations on the causes of death, such as 'cardiorespiratory arrest', 'bronchospasm' and 'chronic obstructive pulmonary disease' were avoided. Severe asthma is expressed in various phenotypes, such as fixed airflow obstruction, exaggerated lability of the disease and resistance to corticosteroids.[16] Asthma can be confused with chronic obstructive pulmonary disease and be mistakenly reported, especially in elderly patients or those with fixed airflow obstruction.

The present study has limitations due to its descriptive, retrospective design and because there is high imprecision in the completion of death certificates in Brazil.[10] However, information on the causes of deaths was collected from official documents that are used in the national statistical analyses. The relevance of this study lies primarily in its originality and the details provided regarding the deaths of patients with asthma in a cohort established on the basis of an asthma control program in Brazil. Regional characteristics and realities should be considered for each state. However, the aspects shown in this study can be considered as representative of Brazil as a whole.

In summation, the deaths of patients with severe asthma were mainly due to asphyxia and cardiovascular diseases in a hospital environment. Male gender, advanced age, long-term disease and fixed airflow obstruction were frequent findings in the majority of the deaths. A better understanding of the prognostic factors of this disease can contribute to the prevention of some fatal events. However, phenotypical characterization in isolation is still an imprecise method for the understanding of the asthma syndrome. Adequate identification of at-risk patients, diagnosed with severe, labile asthma that is difficult to control still represents a void in the precise management of these diseases. Comorbidities can worsen the prognosis of asthma and vice-versa.

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