Artigo original

Asthma as a Cause of Death

Asma como Causa de Morte

Thais Mauad, Diogenes Seraphim Ferreira[1]

RESUMO

Mortes causadas por asma são incomuns, mas, mesmo assim, respondem por cerca de 287.000 óbitos anuais mundialmente. Embora as taxas de mortalidade por asma venham diminuindo em diversos países, há grande disparidade na mortalidade por asma no mundo. A maior parte das mortes está relacionada ao manejo clinico subótimo.

Fatores frequentemente envolvidos com asma quase fatal e fatal incluem história prévia de crises quase fatais, intubação/ventilação mecânica prévia, hospitalização ou admissão em UTI, falta de adesão ao tratamento, percepção falha de dispneia, distúrbios psicológicos e nível socioeconômico baixo. Na autópsia, os pulmões de pacientes que morreram de asma estão geralmente hiperinflados e os brônquios maiores e menores ocluídos por muco. Os achados histológicos incluem descolamento epitelial, espessamento da lâmina *reticularis* da membrana basal, glândulas submucosas e músculo liso aumentados e composição alterada da matriz extracelular nas vias aéreas grandes e pequenas. A inflamação brônquica é generalizada, sendo proeminente na camada adventícia das pequenas vias.

Os mecanismos que levam à morte na asma não estão claros. O espasmo potente da musculatura lisa e a produção excessiva de muco parecem ser os eventos chave que culminam em morte. Uma exacerbação aguda pode ser mortal em pacientes com asma mal controlada e subtratada e que tenham alterações estruturais nas vias aéreas pré-existentes.

Descritores: Asma/mortalidade; Asma/patologia; Asma/prevenção & controle.

ABSTRACT

Death attributable to asthma is considered uncommon. However, worldwide, there are approximately 287,000 such deaths every year. Although asthma mortality rates are decreasing in many countries, there is a great disparity among countries in terms of asthma mortality in the world. Most asthma deaths are related to suboptimal disease management.

Factors frequently associated with near-fatal and fatal asthma include a previous near-fatal asthma exacerbation, previous intubation/mechanical ventilation, asthma-related admission to the hospital or ICU, lack of treatment adherence, poor perception of dyspnea, psychological disorders and low socioeconomic status. At autopsy, the lungs from patients who died of asthma are usually hyperinflated. The large and small bronchi are occluded with mucus. Histological findings include epithelial detachment, thickening of the *lamina reticularis* of the basement membrane, enlarged submucosal glands, greater airway smooth muscle area, and altered extracellular matrix composition in the large and small airways. Bronchial inflammation is present throughout, with prominent inflammation in the adventitial layer of the small airways.

The mechanisms of death from asthma remain unclear. Pronounced airway smooth muscle constriction and excessive mucous discharge are likely to be key events. In patients with poorly controlled, undertreated, severe asthma, with pre-existing structural alterations in the airways, an acute exacerbation can be deadly.

Keywords: Asthma/mortality; Asthma/pathology; Fatal asthma.

1. Department of Pathology, University of São Paulo School of Medicine, São Paulo, Brazil.
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Correspondence to: Thais Mauad. Department of Pathology. University of São Paulo School of Medicine. Av. Dr. Arnaldo 455, CEP: 01246-903. São Paulo, SP, Brazil. Tel. 55 11 3061-7173, Fax 55 11 3061-8521. E-mail: tmauad@usp.br.

INTRODUCTION

Fatal asthma is defined as a severe asthma exacerbation resulting in death (1). Near-fatal and fatal asthma may be seen as a continuum of a very severe asthma exacerbation, which would likely result in fatality if appropriate and timely management were not available.

Many countries have experienced decreases in asthma mortality in the last two decades, especially countries where the use of inhaled corticosteroids increased. Nevertheless, it was estimated that, in 2004, asthma accounted for about 287,000 deaths yearly worldwide (2). Data from the World Health Organization show large discrepancies in asthma mortality among countries, the rates being lower in Europe and North America, whereas rates are higher in Africa, Central Asia, and Central (3).

EPIDEMIOLOGY

Although the mechanisms leading to death from asthma have been not fully elucidated, fatal asthma is frequently associated with suboptimal management and delays in obtaining treatment during the final attack (3).

Asthma mortality risk increases with age, and the mortality rate is approximately 10 times higher among persons over 65 years of age than among those under 34 years of age (4). However, there has been inaccurate reporting of mortality data for the older age groups, because of confusion with other respiratory ailments or concurrent medical conditions (5). In contrast, the rate of false-positive asthma diagnosis is quite low for individuals in the 5- to 34-year age bracket. Therefore, comparisons are typically made relative to the population of asthma sufferers with that age bracket.

Since the 1960s, there have been two epidemics of fatal asthma. During the 1960s, asthma mortality spiked in England, Wales, Scotland, Ireland, Norway, New Zealand, and Australia (6-8). Between 1959 and 1966, the age-adjusted mortality rate (for 5- to 34-year age group) rose from 0.7 to 2.2 per 100,000 population, a threefold increase, in England and Wales (6). This epidemic of fatal asthma was attributed to the use of high doses of the poorly selective beta-agonist isoprenaline (7). The increase in sales of this bronchodilator coincided with the increase in deaths observed in the countries where it was sold. Countries where highly concentrated isoprenaline was not available during that decade—the United States and West Germany—were spared (7). However, there is controversy over this claim, and other factors have been proposed as contributors to the increased deaths, such as undertreatment of asthma and increased prevalence or increased severity of the disease (9,10).

A second epidemic was observed in New Zealand in the second half of the 1970s. The age-adjusted asthma mortality rate in New Zealand was 1.4/100,000 population in 1975 and rose to 4.1/100,000 population in 1979 (11). The increase in asthma mortality was attributed to the use of fenoterol (12). As safety warnings were issued and fenoterol sales dropped, the number of asthma deaths in the country also fell (13).

Since the late 1980s, there has been a consistent reduction in asthma mortality in many countries (14). Improved management of asthma is the most likely reason for this reduction, because the use of inhaled corticosteroid therapy is associated with a reduced risk of death from asthma (15,16) and the use of this medication has been associated with decreased asthma mortality in various countries (17,18).

FACTORS ASSOCIATED WITH NEAR-FATAL AND FATAL ASTHMA

Many factors associated with near-fatal and fatal exacerbations of asthma have been identified (Chart 1). The risk factors most often implicated in near-fatal asthma or fatal asthma include a history of mechanical ventilation, as well as admission to the hospital or ICU for an asthma attack (19-21).

Chart 1 - Risk factors for near-fatal and fatal asthma.

Previous near-fatal asthma exacerbation
Previous intubation and mechanical ventilation for asthma
Previous ICU admission for asthma
Previous hospital admission for asthma
Lack of adherence to asthma treatment
Poor perception of dyspnea
Psychological problems and psychiatric diseases
Low socioeconomic status
Allergen exposure (Alternaria, soybean)
Intolerance to aspirin and nonsteroidal anti-inflammatory drugs
Smoking

Concern about the safety of long-acting β_2 agonist therapy was raised in the 1990s when asthma-related death was found to be three times more likely among patients taking salmeterol than among those taking albuterol, despite the fact that the difference was not statistically significant (22). The Salmeterol Multicenter Asthma Research Trial (SMART) demonstrated a fourfold increase in asthma deaths associated with salmeterol use (23). A post hoc analysis suggested the risk was related to the lack of use of inhaled corticosteroids, which was also less common among African-Americans. This prompted the United States Food and Drug Administration to issue a public health advisory in 2005 stating that long-acting β_2 agonists can "increase the chance of severe asthma episodes and death when such episodes occur" (24). A second safety warning, issued in 2010, stated the ongoing concern regarding the safety of long-acting β_2 agonists (25). Various meta-analyses provided evi-

dence that the combination of inhaled corticosteroids and long-acting β_2 agonists can be used safely (26-28), which conforms to the recommendations of current asthma treatment guidelines (29,30).

Many factors related to treatment adherence have been identified in cases of near-fatal and fatal asthma. Such factors include the underuse of inhaled corticosteroids (20,31) and delay in initiating oral corticosteroids during an acute attack (20). Lack of appropriate medical care (32), limited use of primary care services (33), and failure to keep appointments (34) have also been identified in affected individuals. It has been also suggested that a blunted perception of dyspnea can predispose some asthma sufferers to a life-threatening attack. (35).

Adverse psychological factors have also been associated with near-fatal and fatal asthma. These include having been diagnosed with a psychiatric disorder, most commonly depression or a behavioral disorder, especially denial (36). However, in one systematic review of psychological risk factors associated with near-fatal and fatal asthma, it was not possible to conclude that such factors increased the risk of near-fatal asthma/fatal asthma, because of a lack of consistency across studies, in terms of the methodology employed in the psychological assessments (37).

Patients of lower socioeconomic status seem to be at increased risk of death from asthma (38). This association might be related to limited access to health care services and lower compliance with prescribed treatment regimens.

Intolerance to aspirin and nonsteroidal anti-inflammatory drugs can cause severe asthma exacerbations (39). Aspirin intolerance has been shown to be more common among patients with a history of near-fatal asthma attacks than among those without (40). In one study, Alternaria sensitivity was identified as a major risk factor for near-fatal asthma (41). In another investigation, high levels of exposure to mold spores were associated with an increased risk of death from asthma (42).

Smoking has been associated with near-fatal asthma and fatal asthma in some studies (32,43). However a systematic review (21) did not find a significant association between smoking and near-fatal asthma/fatal asthma.

PATHOLOGICAL ASPECTS OF FATAL ASTHMA

The lungs of patients that have died from asthma are hyperinflated and might not collapse when the chest cavity is opened at autopsy. The atelectatic areas observed on the pleural surface represent areas of collapse distal to bronchial obstruction by mucous plugs. Lung sections typically show occlusion of the larger and smaller bronchi by tenacious mucus or mucous plugs (Figure 1).

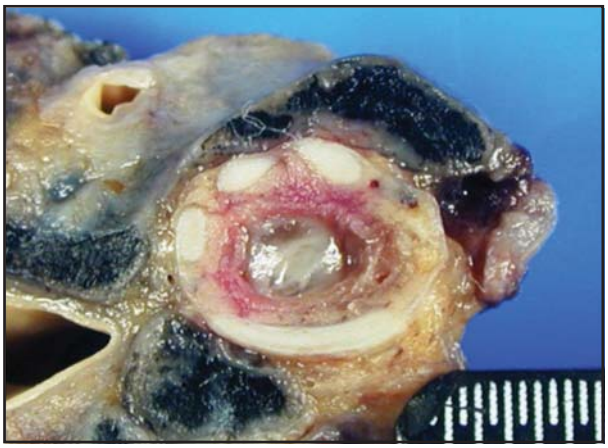

Figure 1 - Cross-section of a large, cartilaginous bronchus. The lumen is filled with a viscous mucous plug.

Scale bar = 0.5 cm.

Luminal obstruction by exudates composed of mucus and cells is a major contributing cause to a fatal event in most asthma patients. In cases of fatal asthma, Aikawa et al. reported an increase in the mucus occupying ratio, especially in the peripheral airways (44). The analysis of the mucus of a single patient that died of asthma showed a high mucin content, with proteins of extreme size and low charge density, which could explain the solidity of the plugs observed in status asthmaticus (45).

In fatal asthma, there is extensive sloughing of the epithelium to the airway lumen. Epithelial detachment can have deleterious consequences, such as increased exposure of the mucosal nerve endings to irritant factors, enhanced penetration of allergens, and reduced mucociliary clearance (44,46). In addition, the epithelial disruption observed in fatal asthma can lead to greater retention of mucus through impairment of mucociliary clearance, and the inflammatory cell debris can impair clearance by increasing mucus viscosity (47). Histological samples of large airways in fatal asthma are shown in Figures 2 and 3.

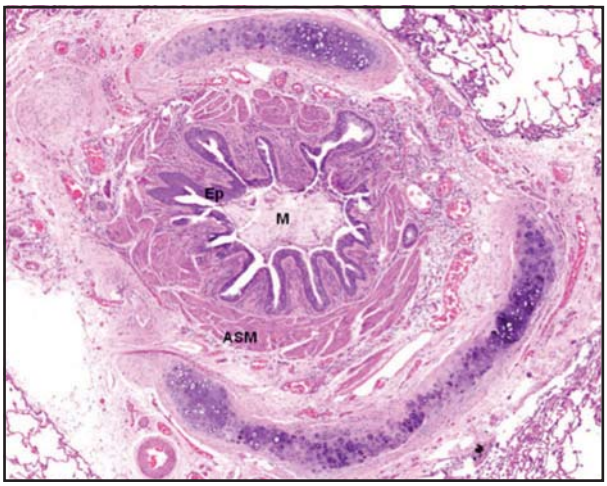

Figure 2 - Large airway of a patient who died from a fatal asthma attack, showing a mucous plug within the airway lumen, epithelial folding, and thickened ASM layer.

Hematoxylin and eosin staining. Ep, epithelium; and M, mucus. Scale bar = 500 µm.

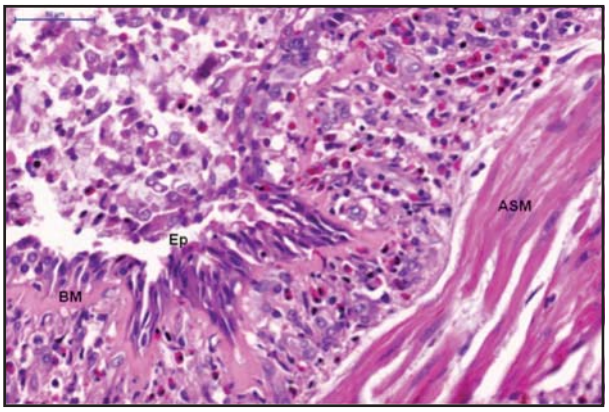

Figure 3 - Bronchial mucosa of a patient who died from a fatal asthma attack, showing epithelial damage and basement membrane thickening. The lamina propria is thickened with abundant inflammation, as is the ASM layer.
Hematoxylin and eosin staining. BM, basement membrane; Ep, epithelium. Scale bar = 50 µm.

Submucosal glands are enlarged in patients with asthma, contributing to a hypersecretory state (48). In cases of fatal asthma, there is a disproportionate increase in smooth muscle actin in the myoepithelial cells of the bronchial mucous glands, which could be at least partially responsible for the abundant mucous discharge that is characteristic of a fatal asthma attack (49).

Hyaline thickening of the basement membrane has been described in cases of fatal asthma (50). In such cases, there is thickening of the subepithelial *lamina reticularis* that underlies the true basal lamina of the bronchial epithelium, and this is therefore referred to as pseudo-thickening (46). This thickening is caused by the deposition of several extracellular matrix components. There have been no studies comparing the varying degrees of asthma severity in terms of basement membrane thickening. Due to its constant accessibility in bronchial biopsies, this airway compartment has been used as a marker of remodeling (46).

An increase in airway smooth muscle (ASM) area is the structural change that most consistently correlates with parameters of obstruction and disease severity. In addition, the role of the ASM as an immunomodulator, like that of the airway epithelium, has received considerable attention in recent years (46,51).

Patients with asthma have proportionally greater ASM area than do those without asthma and those with COPD (52). The increased ASM area observed in cases of fatal asthma is due to hyperplasia, hypertrophy, or increased extracellular matrix deposition (53,54). It occurs throughout the tracheobronchial tree and is the major contributor to the increased area of the inner airway wall in asthma (55).

An increase in the quantity of elastic fibers and fibronectin within the ASM has been described in the large airways of patients with fatal asthma and might contribute to altered muscle mechanics. In addition, an increase in the expression of matrix metalloproteinases 9 and 12 by ASM cells shows that the ASM participates in the remodeling process in asthma (56). James et al. analyzed the stereological properties of ASM thickness in a large number of autopsies and concluded that the ASM layers were thickest in the most severe cases of asthma (57). It is of note that neither ASM thickness nor the degree of ASM hyperplasia/hypertrophy was found to correlate with patient age or disease duration, suggesting that the structural alterations in the ASM layer occur early in the course of asthma (57).

The outer layer of the small airways is intimately connected to the alveolar parenchyma by the alveolar attachments. The elastic load provided by the lung parenchyma is transmitted to the airways through the alveolar attachments, resulting in a mechanical interdependence between airways and parenchyma. Studies on fatal asthma tissue have provided important information about this compartment. The quantity of altered alveolar attachments is increased in fatal asthma, and that increase is accompanied by a decrease in the number of elastic fibers and in the proteoglycans decorin/lumican, as well as by an increase in collagen type III content in the outer walls (58-60). These structural alterations could impair the tethering forces and could explain some functional abnormalities, such as the loss of the bronchodilator effect of deep breathing in spontaneous bronchoconstrictive episodes, the loss of elastic recoil, and the increased airway closure described in cases of severe asthma.

In fatal asthma, there is a marked congestion of the bronchial blood vessels. Two separate studies revealed that the larger blood vessels occupy a greater area in cases of fatal asthma than in other cases of asthma and control cases, although the total number of vessels was not increased (52,61).

Various studies have assessed the quantity and extent of inflammation in fatal asthma. Such studies have contributed to the notion that inflammation in asthma extends to the distal lung and to the upper respiratory tract (62-64). Inflammatory (and structural) alterations at this level could influence the mechanisms of airway parenchyma interdependence and could alter small airway function.

Innate immune stimuli, such as exposure to viruses or air pollution, might be involved in the pathogenesis of asthma exacerbations. Fregonese et al. found that the expression of the anaphylatoxin receptors C3ar and C5ar was higher in lung tissue obtained from patients who died from a fatal asthma attack than in biopsy samples obtained from patients with mild asthma and from controls, suggesting that triggers that activate the complement system are involved in the mechanisms of a fatal asthma attack (65).

A distinct phenotype of fatal asthma, related to the time of onset of the last crisis, has been recognized. Patients that died shortly after the onset of the attack (within the first 2-3 h) presented more neutrophils than eosinophils in the large and small airways

(66). Faul et al. studied five cases of sudden death from asphyxia during an asthma attack (< 1 h after the onset of the attack) and showed that all five patients had a high proportion of CD8+ T cells in the airways (64). Sudden-onset asthma attacks are most often triggered by nonsteroidal anti-inflammatory drugs and inhalation of fumes, whereas slow-onset asthma attacks are most often associated with suspected respiratory infections (1).

Viral infections are likely to be implicated in near-fatal/fatal asthma exacerbations. However, previous studies of tissue samples obtained from patients who died from a fatal asthma attack have shown that the levels of respiratory virus nucleic acids did not differ from that observed in control samples (67,68). However, it possible that, in fatal asthma, there is an aberrant T-cell response to viral infection. O'Sullivan et al. detected an aberrant T cell population with higher expression of perforin (a marker of cytotoxicity), interleukin 4, and interferon gamma in patients that have died from asthma (68).

In summary, the alterations observed in the lungs of patients that have died from asthma probably represent the adverse combination of a severe, acute exacerbation (triggered by any one of a number of factors) and a poorly controlled, undertreated, severe form of the disease with pre-existing structural alterations in the airways.

REFERÊNCIAS

1. Plaza V, Serrano J, Picado C, Sanchis J. Frequency and clinical characteristics of rapid-onset fatal and near-fatal asthma. Eur Respir J 2002;19(5):846-52.
2. World Health Organization. The global burden of disease : 2004 update. Geneva: World Health Organization; 2008.
3. Masoli M, Fabian D, Holt S, Beasley R. The global burden of asthma: executive summary of the GINA Dissemination Committee report. Allergy 2004;59(5):469-78.
4. Moorman JE, Rudd RA, Johnson CA, King M, Minor P, Bailey C, et al. National surveillance for asthma--United States, 1980-2004. MMWR Surveill Summ 2007;56(8):1-54.
5. Sears MR, Rea HH, de Boer G, Beaglehole R, Gillies AJ, Holst PE, et al. Accuracy of certification of deaths due to asthma. A national study. Am J Epidemiol 1986;124(6):1004-11.
6. Speizer FE, Doll R, Heaf P. Observations on recent increase in mortality from asthma. Br Med J 1968;1(5588):335-9.
7. Stolley PD. Asthma mortality. Why the United States was spared an epidemic of deaths due to asthma. Am Rev Respir Dis 1972;105(6):883-90.
8. Gandevia B. The changing pattern of mortality from asthma in Australia. 2. Mortality and modern therapy. Med J Aust 1968;1(21):884-91.
9. Benatar SR. Fatal asthma. N Engl J Med 1986;314(7):423-9.
10. Buist AS. Is asthma mortality increasing? Chest 1988;93(3):449-50.
11. Jackson RT, Beaglehole R, Rea HH, Sutherland DC. Mortality from asthma: a new epidemic in New Zealand. Br Med J (Clin Res Ed) 1982;285(6344):771-4.
12. Crane J, Pearce N, Flatt A, Burgess C, Jackson R, Kwong T, et al. Prescribed fenoterol and death from asthma in New Zealand, 1981-83: case-control study. Lancet 1989;1(8644):917-22.
13. Crane J, Pearce N, Burgess C, Jackson R, Beasley R. End of New Zealand asthma epidemic. Lancet 1995;345(8955):984-5.
14. Wijesinghe M, Weatherall M, Perrin K, Crane J, Beasley R. International trends in asthma mortality rates in the 5- to 34-year age group: a call for closer surveillance. Chest 2009;135(4):1045-9.
15. Ernst P, Spitzer WO, Suissa S, Cockcroft D, Habbick B, Horwitz RI, et al. Risk of fatal and near-fatal asthma in relation to inhaled corticosteroid use. JAMA 1992;268(24):3462-4.
16. Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. N Engl J Med 2000;343(5):332-6.
17. Melissinos CG, Gourgoulianis K, Adamidis SC. Inhaled drug consumption and asthma mortality in Greece. Chest 1995;107(6):1771-2.
18. Neffen H, Baena-Cagnani C, Passalacqua G, Canonica GW, Rocco D. Asthma mortality, inhaled steroids, and changing asthma therapy in Argentina (1990-1999). Respir Med 2006;100(8):1431-5.
19. Turner MO, Noertjojo K, Vedal S, Bai T, Crump S, Fitzgerald JM. Risk factors for near-fatal asthma. A case-control study in hospitalized patients with asthma. Am J Respir Crit Care Med 1998;157(6 Pt 1):1804-9.
20. Kolbe J, Fergusson W, Vamos M, Garrett J. Case-control study of severe life threatening asthma (SLTA) in adults: demographics, health care, and management of the acute attack. Thorax 2000;55(12):1007-15.
21. Alvarez GG, Schulzer M, Jung D, Fitzgerald JM. A systematic review of risk factors associated with near-fatal and fatal asthma. Can Respir J 2005;12(5):265-70.
22. Castle W, Fuller R, Hall J, Palmer J. Serevent nationwide surveillance study: comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. BMJ 1993;306(6884):1034-7.
23. Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest 2006;129(1):15-26.
24. US Food and Drug Administration. FDA Public Health Advisory: Serevent Diskus (salmeterol xinafoate inhalation powder), Advair Diskus (fluticasone propionate & salmeterol inhalation powder), Foradil Aerolizer (formoterol fumarate inhalation powder). www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm162678.htm. Date last updated: May, 2006. Date last accessed: March 30, 2012.
25. US Food and Drug Administration. FDA Drug Safety Communication: New safety requirements for long-acting inhaled asthma medications called Long-Acting Beta-Agonists (LABAs). www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm200776.htm. Date last updated: February, 2010. Date last accessed March 30, 2012.

26. Welsh EJ, Cates CJ, Poole P. Combination inhaled steroid and long-acting beta2-agonist versus tiotropium for chronic obstructive pulmonary disease. Cochrane Database Syst Rev;5:CD007891.
27. Jaeschke R, O'Byrne PM, Mejza F, Nair P, Lesniak W, Brozek J, et al. The safety of long-acting beta-agonists among patients with asthma using inhaled corticosteroids: systematic review and metaanalysis. Am J Respir Crit Care Med 2008;178(10):1009-16.
28. Bateman E, Nelson H, Bousquet J, Kral K, Sutton L, Ortega H, et al. Meta-analysis: effects of adding salmeterol to inhaled corticosteroids on serious asthma-related events. Ann Intern Med 2008;149(1):33-42.
29. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2011. www.ginasthma.org. Date last updated: December, 2011. Date last accessed: March 30, 2012.
30. National Heart, Lung and Blood Institute. National Asthma Education and Prevention Program. Guidelines for the Diagnosis and Management of Asthma (EPR-3). www.nhlbi.nih.gov/guidelines/asthma/. Date last updated: July, 2007. Date last accessed: March 30, 2012.
31. Romagnoli M, Caramori G, Braccioni F, Ravenna F, Barreiro E, Siafakas NM, et al. Near-fatal asthma phenotype in the ENFUMOSA Cohort. Clin Exp Allergy 2007;37(4):552-7.
32. Harrison B, Stephenson P, Mohan G, Nasser S. An ongoing Confidential Enquiry into asthma deaths in the Eastern Region of the UK, 2001-2003. Prim Care Respir J 2005;14(6):303-13.
33. Sturdy PM, Butland BK, Anderson HR, Ayres JG, Bland JM, Harrison BD, et al. Deaths certified as asthma and use of medical services: a national case-control study. Thorax 2005;60(11):909-15.
34. Burr ML, Davies BH, Hoare A, Jones A, Williamson IJ, Holgate SK, et al. A confidential inquiry into asthma deaths in Wales. Thorax 1999;54(11):985-9.
35. Kikuchi Y, Okabe S, Tamura G, Hida W, Homma M, Shirato K, et al. Chemosensitivity and perception of dyspnea in patients with a history of near-fatal asthma. N Engl J Med 1994;330(19):1329-34.
36. Kolbe J, Fergusson W, Vamos M, Garrett J. Case-control study of severe life threatening asthma (SLTA) in adults: psychological factors. Thorax 2002;57(4):317-22.
37. Alvarez GG, Fitzgerald JM. A systematic review of the psychological risk factors associated with near fatal asthma or fatal asthma. Respiration 2007;74(2):228-36.
38. Grant EN, Lyttle CS, Weiss KB. The relation of socioeconomic factors and racial/ethnic differences in US asthma mortality. Am J Public Health 2000;90(12):1923-5.
39. 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(2):127-9.
40. Yoshimine F, Hasegawa T, Suzuki E, Terada M, Koya T, Kondoh A, et al. Contribution of aspirin-intolerant asthma to near fatal asthma based on a questionnaire survey in Niigata Prefecture, Japan. Respirology 2005;10(4):477-84.
41. O'Hollaren MT, Yunginger JW, Offord KP, Somers MJ, O'Connell EJ, Ballard DJ, et al. Exposure to an aeroallergen as a possible precipitating factor in respiratory arrest in young patients with asthma. N Engl J Med 1991;324(6):359-63.
42. Targonski PV, Persky VW, Ramekrishnan V. Effect of environmental molds on risk of death from asthma during the pollen season. J Allergy Clin Immunol 1995;95(5 Pt 1):955-61.
43. Marquette CH, Saulnier F, Leroy O, Wallaert B, Chopin C, Demarcq JM, et al. Long-term prognosis of near-fatal asthma. A 6-year follow-up study of 145 asthmatic patients who underwent mechanical ventilation for a near-fatal attack of asthma. Am Rev Respir Dis 1992;146(1):76-81.
44. Aikawa T, Shimura S, Sasaki H, Ebina M, Takishima T. Marked goblet cell hyperplasia with mucus accumulation in the airways of patients who died of severe acute asthma attack. Chest 1992;101(4):916-21.
45. Sheehan JK, Richardson PS, Fung DC, Howard M, Thornton DJ. Analysis of respiratory mucus glycoproteins in asthma: a detailed study from a patient who died in status asthmaticus. Am J Respir Cell Mol Biol 1995;13(6):748-56.
46. Mauad T, Bel EH, Sterk PJ. Asthma therapy and airway remodeling. J Allergy Clin Immunol 2007;120(5):997-1009; quiz 1010-1.
47. Kuyper LM, Pare PD, Hogg JC, Lambert RK, Ionescu D, Woods R, et al. Characterization of airway plugging in fatal asthma. Am J Med 2003;115(1):6-11.
48. Carroll NG, Mutavdzic S, James AL. Increased mast cells and neutrophils in submucosal mucous glands and mucus plugging in patients with asthma. Thorax 2002;57(8):677-82.
49. Green FH, Williams DJ, James A, McPhee LJ, Mitchell I, Mauad T. Increased myoepithelial cells of bronchial submucosal glands in fatal asthma. Thorax 2010;65(1):32-8.
50. Dunnill MS. The pathology of asthma, with special reference to changes in the bronchial mucosa. J Clin Pathol 1960;13:27-33.
51. An SS, Bai TR, Bates JH, Black JL, Brown RH, Brusasco V, et al. Airway smooth muscle dynamics: a common pathway of airway obstruction in asthma. Eur Respir J 2007;29(5):834-60.
52. Kuwano K, Bosken CH, Pare PD, Bai TR, Wiggs BR, Hogg JC. Small airways dimensions in asthma and in chronic obstructive pulmonary disease. Am Rev Respir Dis 1993;148(5):1220-5.
53. Bai TR. Evidence for airway remodeling in chronic asthma. Curr Opin Allergy Clin Immunol 2010;10(1):82-6.
54. James AL, Elliot JG, Jones RL, Carroll ML, Mauad T, Bai TR, et al. Airway Smooth Muscle Hypertrophy and Hyperplasia in Asthma. Am J Respir Crit Care Med. Epub ahead of print March 8, 2012. doi:10.1164/rccm.201110-1849OC.
55. James AL, Wenzel S. Clinical relevance of airway remodelling in airway diseases. Eur Respir J 2007;30(1):134-55.
56. Araujo BB, Dolhnikoff M, Silva LF, Elliot J, Lindeman JH, Ferreira DS, et al. Extracellular matrix components and regulators in the airway smooth muscle in asthma. Eur Respir J 2008;32(1):61-9.
57. James AL, Bai TR, Mauad T, Abramson MJ, Dolhnikoff M, McKay KO, et al. Airway smooth muscle thickness in asthma is related to severity but not duration of asthma. Eur Respir J 2009;34(5):1040-5.
58. Mauad T, Silva LF, Santos MA, Grinberg L, Bernardi FD, Martins MA, et al. Abnormal alveolar attachments with

decreased elastic fiber content in distal lung in fatal asthma. Am J Respir Crit Care Med 2004;170(8):857-62.
59. de Medeiros Matsushita M, da Silva LF, dos Santos MA, Fernezlian S, Schrumpf JA, Roughley P, et al. Airway proteoglycans are differentially altered in fatal asthma. J Pathol 2005;207(1):102-10.
60. Dolhnikoff M, da Silva LF, de Araujo BB, Gomes HA, Fernezlian S, Mulder A, et al. The outer wall of small airways is a major site of remodeling in fatal asthma. J Allergy Clin Immunol 2009;123(5):1090-7, 1097 e1.
61. Carroll NG, Cooke C, James AL. Bronchial blood vessel dimensions in asthma. Am J Respir Crit Care Med 1997;155(2):689-95.
62. Carroll N, Cooke C, James A. The distribution of eosinophils and lymphocytes in the large and small airways of asthmatics. Eur Respir J 1997;10(2):292-300.
63. de Magalhaes Simoes S, dos Santos MA, da Silva Oliveira M, Fontes ES, Fernezlian S, Garippo AL, et al. Inflammatory cell mapping of the respiratory tract in fatal asthma. Clin Exp Allergy 2005;35(5):602-11.
64. Faul JL, Tormey VJ, Leonard C, Burke CM, Farmer J, Horne SJ, et al. Lung immunopathology in cases of sudden asthma death. Eur Respir J 1997;10(2):301-7.
65. Fregonese L, Silvestri M, Sabatini F, Defilippi AC, Rossi GA. Severe and near-fatal asthma in children and adolescents. Monaldi Arch Chest Dis 2001;56(5):423-8.
66. Sur S, Hunt LW, Crotty TB, Gleich GJ. Sudden-onset fatal asthma. Mayo Clin Proc 1994;69(5):495-6.
67. Macek V, Dakhama A, Hogg JC, Green FH, Rubin BK, Hegele RG. PCR detection of viral nucleic acid in fatal asthma: is the lower respiratory tract a reservoir for common viruses? Can Respir J 1999;6(1):37-43.
68. O'Sullivan S, Cormican L, Faul JL, Ichinohe S, Johnston SL, Burke CM, et al. Activated, cytotoxic CD8(+) T lymphocytes contribute to the pathology of asthma death. Am J Respir Crit Care Med 2001;164(4):560-4.