

Allergens and Thunderstorm Asthma

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Thunderstorm-related asthma is increasingly recognized in many parts of the world. This review focuses on important advances in the understanding of the mechanism of the role of allergens, in particular fungal spores such as *Alternaria*, in asthma epidemics associated with thunderstorms. From our observations, we have proposed that the prerequisites for this phenomenon are as follows: 1) a sensitized, atopic, asthmatic individual; 2) prior airway hyperresponsiveness before a sudden, large allergen exposure; 3) a large-scale thunderstorm with cold outflow occurring at a time and location during an allergen season in which large numbers of asthmatics are outdoors; and 4) sudden release of large amounts of respirable allergenic fragments, particularly fungal spores such as *Alternaria*.

Introduction

Asthma associated with thunderstorms has been reported in several countries. Packe and Ayres [1,2] first noted the association of thunderstorms with large numbers of patients presenting with acute asthma attacks after thunderstorms in Birmingham, England, in 1983. They described a concurrent increase in airborne spores of *Didymella exitialis* and *Sporobolomyces* fungi. Since then, many episodes of thunderstorm asthma have been noted around the world (Table 1), including the United Kingdom [2,3,4•,5–8], Australia [9–12], Canada [13], and the United States [14]. Several meteorologic and aerobiologic mechanisms were proposed to explain this phenomenon [15,16•,17].

Common to all epidemics of thunderstorm-related asthma is a significant increase in atmospheric allergen load. The patients affected are invariably atopic, and seasonal aeroallergens play a critical role in these events. The original studies proposed a role for grass pollen in sensitized individuals in these asthma epidemics. How-

ever, increasing evidence suggests that other seasonal allergens are responsible for at least some of these epidemics. Fungal spores such as *Alternaria*, *Cladosporium*, and *Didymella* [4••] and weed pollens such as *Parietaria* [15] were implicated. This review discusses the role of allergens in thunderstorm-related asthma.

Airway Hyperresponsiveness and Priming

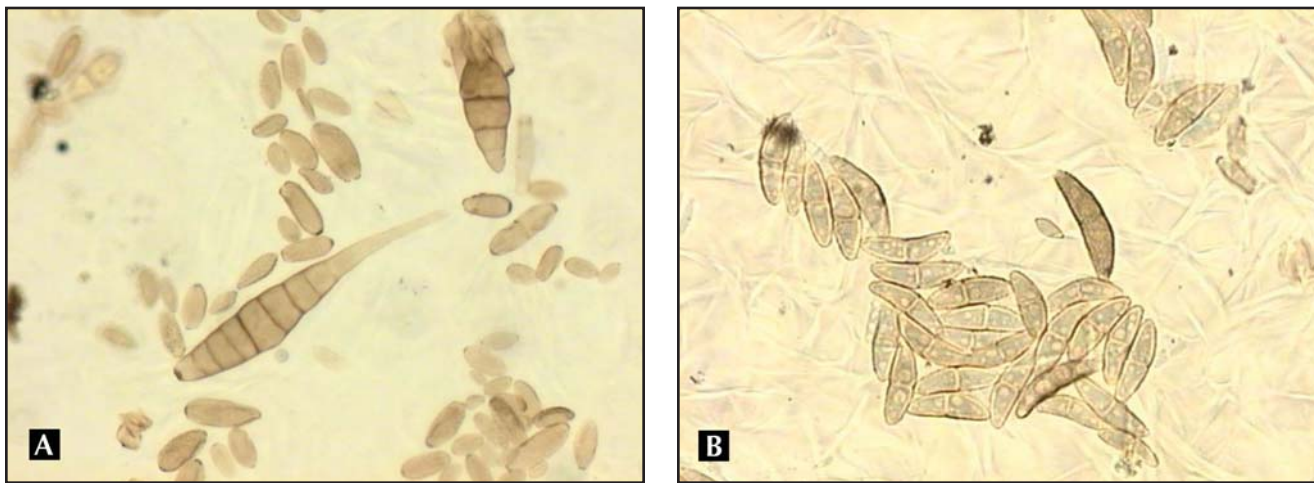
Airway hyperresponsiveness, the exaggerated narrowing of the airways after the inhalation of irritant or allergenic stimuli, is a key feature of asthma. The sudden and severe asthma attacks characteristic of epidemic thunderstorm asthma suggest exposure to a large allergen load on previously primed bronchial airways. Several bronchial priming factors have been proposed, including viral infections, sudden changes in temperature, grass pollen, fungal spores, elevated ozone levels or air pollution, poor compliance with inhaled corticosteroids, poor asthma management plans, rainfall, high humidity, low/high wind speed, high air pressure, and high and low temperature [4••,8,10,15,17,18]. A background of primed, hyper-responsive airways, even in mild to moderate asthma, results in sudden, severe attacks in sensitized individuals. Our observations are that airways of doubly sensitized patients are primed, or hyperresponsive, during the summer grass pollen season and are thus vulnerable to the subsequent fungal spore season. Unusually high counts of fungal spores or other allergens resulting from sudden surges with thunderstorms cause this “second hit,” and severe exacerbations follow, causing asthma epidemics and even death.

Respirable Particles

An important feature of allergens is their respirability. Grass pollen ruptures on exposure to moisture, resulting in the release of highly allergenic and small, easily respirable starch particles. Moisture causes rupture of pollen grains via osmotic shock. The fragmentation of pollen grains into small particles ($\leq 5 \mu\text{m}$) exacerbates asthma because these particles are sufficiently small to enter into the smaller airways [18,19]. In the Cambridge epidemic, an association of increased asthma admissions with levels of broken *Alternaria* levels in the atmosphere was demonstrated. This phenomenon is described after harvesting or mass lawn mowing, which leads to shearing of the spores growing on the base of grass or cereal crops.

Table 1. Thunderstorm asthma studies

Dates	Location	Studies
July 6–7, 1983	United Kingdom	Packe and Ayres [1], 1985
June 20, 1984	United Kingdom	Alderman et al. [3], 1986
November 11, 1984	Australia	Egan [12], 1985
November 8–9, 1987	Australia	Bellomo et al. [9], 1992
November 29–30, 1989	Australia	Bellomo et al. [9], 1992
June 24–25, 1994	United Kingdom	Celenza et al. [8], 1996; Davidson et al. [6], 1996; Venables et al. [5], 1997; Hajat et al. [7], 1997
October 30–31, 1997	Australia	Girgis et al. [10], 2000
July 31–August 1, 2000	Canada	Wardman et al. [13], 2002
July 29, 2002	United Kingdom	Pulimood et al. [4••], 2007
1993–2004	United States	Grundstein et al. [14], 2008

**Figure 1.** Torpedo-shaped *Alternaria* (A) and *Didymella* (B) spores.

Torpedo-shaped *Alternaria* spores (Fig. 1A) are large and more likely to penetrate the small airways after they are broken. Germination of fungal spores on exposure to moisture could also result in increased allergenicity. This could be explained by exposure to moisture in the upper and lower respiratory tract or exposure to rainfall associated with thunderstorms. *Parietaria* spp also demonstrate a release of smaller respirable particles on exposure to moisture. The pattern of rupture of the *Parietaria* pollen on exposure to moisture is similar to that of grass pollen [20]. Rainfall associated with thunderstorms therefore appears to play an important role in promoting respirability of allergens [14,19,21].

Allergens

Grass pollen

Several studies reported that grass pollen allergy is a marker for thunderstorm-related asthma exacerbations [4••,9,10,22]. Grundstein et al. [14] stratified thunderstorms by rainfall amount and found associations between asthma attendances and thunderstorms with recorded rainfall but not for thunderstorms with no

recorded rainfall. Although rainfall may cleanse the air of larger particles such as intact pollen grains and fungal spores [23], the rupture of pollen grains in rainwater may yield an increase in respirable particles. Suphioglu [18] and Schappi et al. [24] observed a 50-fold increase in respirable particles following rainfall events. The fragmentation of pollen grains may occur not only when they are in contact with rain droplets but also possibly within clouds [25] and on the plants [19]. Taylor et al. [26] showed that the release of subcellular pollen components after a cycle of humidifying, wetting, and drying of flowering grasses demonstrates how light rainfall, dew, fog, and watering of lawns can rupture pollen grains within the anthers. After drying, disturbances such as wind, recreational activities, and lawn mowing can trigger the release of allergen-loaded particles of respirable size as a free aerosol, creating a potential trigger for asthma [26].

Although grass pollen may be responsible for some of the epidemics described in the literature, individual fungal spore levels and patient sensitization to fungi have not always been studied [9,11]. We reported a case-control study in which almost all participants were doubly sensitized to grass and *Alternaria alternata*, suggesting

that for epidemics of thunderstorm asthma, a “second hit” is required [4••]. Epidemics of asthma in the United Kingdom are infrequent, even though thunderstorms and rainfall are common several times each year during the grass pollen season in May and June. It is therefore unlikely that grass pollen is solely responsible for epidemics of thunderstorm asthma. A Canadian study reported a strong association between emergency department visits for asthma and thunderstorms that could not be explained by an increase in grass pollen counts but suggested that the mechanism may be through an increase in fungal spore counts [27].

Pollen allergens such as Hor v 4, Jun a 2, Pla a 2, Cry j 2, Bet v 7, and Tri a 25 have homologues in fungi. This raises the interesting possibility that pollen and fungal allergens could cross-sensitize in a synergistic manner, giving rise to the complex interactions observed in thunderstorm asthma. Details on a range of pollen-specific allergens are available on the Allergome website (<http://www.allergome.org>).

Fungal spores

Fungi are saprobic and, more rarely, parasitic organisms that are responsible for most of the aerobic decay of plant materials and are present in air throughout the world, often as the dominant biologic component. More than 80 fungal genera are associated with allergic respiratory symptoms. The allergens from *Aspergillus fumigatus*, *Cladosporium herbarum*, and *A. alternata* are the best characterized. Most isolated allergens are proteins or glycoproteins with molecular weights of 6 to 90 kDa. Although in some cases carbohydrate portions of fungal extracts show allergenic activity, most IgE-binding activity is associated with the protein component [28]. Mold sensitivity is associated with increased asthma severity, death, hospital admissions, intensive care admissions in adults, and increased bronchial reactivity in children [29–31]. Aerobiology studies show an association of asthma admissions with thunderstorms and increased fungal spores, as well as with grass pollen in the atmosphere [27].

In the United States, commercially available fungal allergen extracts are of variable quality and lack standardization [32] because of inherent difficulties with manufacturing [33]. Therefore, investigators have questioned whether the reported reactivity of asthmatic patients to multiple mold allergens is caused by genuine sensitization to individual fungi or to IgE cross-reactivity between products of different fungal species. Purified allergen preparations of *C. herbarum* were superior to the crude allergen extracts. The allergen contents of the purified extract differed with respect to total allergenic potency and allergenic composition [32]. Therefore, with increasing standardization and purification, a clearer picture of the pattern of fungal sensitization will emerge.

Humidity coupled with higher winds triggers increased spore production and dissemination. Airborne fungal spores are smaller than pollen grains, ranging between

2 and 50 μm in diameter (with most spores falling into the 2- to 10- μm range), and thus readily penetrate into the lower airways [28]. Moisture also may activate certain fungal species to release respirable-sized particles, including spores.

Alternaria

Alternaria spp sensitivity ranged from 3.3% in a large study of Italian children to 5.5% in a cohort of Isle of Wight children [34,35]. In other European studies, about 3% of patients in Portugal and 20% of patients in Spain with allergic respiratory symptoms had a positive skin test reaction to *Alternaria* or *Cladosporium* spp [36]. In a study of more than 17,000 US citizens, positive skin test responses to *Alternaria* occurred in 3.6% of the population [37], whereas another study showed responses as high as 12.9% [38]. Our results indicate that about one third of controls with seasonal asthma were sensitized to *Alternaria* spp [4••]. In a large-scale study of children with asthma residing in US inner cities, 38.3% of the 12,086 asthmatic children had positive skin tests to *Alternaria* spp. Up to 70% of patients with fungal allergy have skin test reactivity to *Alternaria* spp. In the United States, up to 80% of individuals with confirmed asthma have demonstrated positive reactions to one or more fungi [39]. Advances in molecular biology have led to a better understanding of fungal allergens and their relationship to allergic disease. Several major allergens were identified and characterized from *Alternaria* spp [40]. One of these, Alt a 1, is secreted or released from growing germ tubes, particularly from ungerminated spores, as with *Aspergillus* [41]. This could explain the role of rainfall and the effect of moisture in causing exacerbations by promoting germination.

The severity of asthma is strongly linked to *Alternaria* sensitivity [42]. *Alternaria* produces potent T-helper type 2–like adjuvant effects in the airways, encouraging immune deviation to an allergic response.

Spores such as *Cladosporium* and *Alternaria* spp are found in higher concentrations during dry weather. When preceded by long dry spells, thunderstorms could result in an increase in both dry and wet weather allergens caused by associated rainfall. Thunderstorm epidemics of asthma are positively correlated with an increase in ambient fungal spores [4••,27,43]. Threshold concentrations for triggering allergic symptoms are estimated at 100 spores/ m^3 for *Alternaria* spp and 3000 spores/ m^3 for *Cladosporium* spp [44]. There is no agreed upon threshold concentration for *Didymella* spp.

The Cambridge study looked at environmental factors, aerobiology, hospital episode statistics, and a patient population presenting to a tertiary center in the United Kingdom. The outbreak reported a significant association of thunderstorm-associated asthma with *A. alternata* sensitivity in grass pollen-sensitive patients. There was an increase in atmospheric *Alternaria* levels and a strong association with broken *Alternaria* levels and asthma admissions. A prolonged grass pollen season leads to bronchial hyperresponsiveness in individuals doubly sen-

sitized to grass pollen and *Alternaria* spp. A large-scale thunderstorm occurring at the time of harvesting with high levels particularly of fragmented fungal spores can trigger an asthma epidemic. An important phenomenon observed in the Cambridge study was that almost all patients were allergic to grass pollen, but to demonstrate a significant association with the thunderstorm epidemic, the additional sensitivity to fungal spores was required. Some patients had life-threatening symptoms, and the only asthma death in Cambridge for that year occurred at the time of the thunderstorm [4••].

The torpedo-shaped spores appear to become more respirable after they are fragmented. The breakage of spores may be caused by crop harvesting at the time of thunderstorms [4••]. Broken *Alternaria* is associated with increased asthma admissions. Observational data from Naples and Cambridge suggest that patients who are outdoors and thus exposed to the elements and to spores are most likely to be affected severely. It is likely that the first component of the “double hit” includes priming by prior allergen exposure, a viral infection at the time of a storm, or even exposure to other pollutants in an urban atmosphere (eg, diesel fumes).

Cladosporium

A cross-sectional study of 1132 adults with asthma found that sensitization to *A. alternata* (odds ratio, 2.03) or *C. herbarum* (odds ratio, 3.2) is a significant risk factor for severe asthma (odds ratio for both, 2.34) in several European countries and in Australia, New Zealand, and Portland, Oregon, in the United States [45]. Girgis et al. [10] showed that 61% of thunderstorm-related asthma patients were sensitized to *Cladosporium*, compared with 35% of controls but were unable to show that *Alternaria* sensitization was increased. However, their controls included all individuals who had attended for asthma in the 4 months before the outbreak; therefore, this group was more likely to have been on prophylactic-inhaled corticosteroids, reducing the likelihood of developing thunderstorm-related asthma [10]. Neither study produced adequate data on environmental levels of grass pollen or fungal spores at the time of the asthma outbreak.

The Cambridge study suggested cross-sensitization between fungal spores. Sixteen of 23 patients and 7 of 11 controls with thunderstorm-related asthma exhibited *Cladosporium* spp sensitivity. Only 1 of the 33 participants reporting thunderstorm-related asthma was not sensitized to either *Alternaria* or *Cladosporium* spp, clearly demonstrating the impressive value of skin testing to *Alternaria* and *Cladosporium* spp in identifying cases of thunderstorm-related asthma [4••].

Didymella

The release of *D. exitialis* (Fig. 1B) and *Sporobolomyces* in response to rapid changes in humidity was noted previously. Lewis et al. [21] reported an increase in *Didymella* spore counts associated with thunderstorm outbreaks of

asthma. Packe and Ayres [1,2,46] reported using skin prick test solutions for sensitization to *D. exitialis*. Their results argue against an important role for fungal spores such as *Didymella* or *Sporobolomyces* spp (or both) in thunderstorm epidemics. However, Packe and Ayres [2,46] did not test for *Alternaria*. Reagents for allergy skin testing to *Didymella* are not commercially available, accounting for the lack of data on sensitization rates [2,46]. *D. exitialis* shares many antigens with *Alternaria* spp, and the very high levels of *Didymella* spp released after rainfall in the Cambridge study may have also contributed to some asthma attendances [4••]. Unfortunately, it was not possible to test this theory on skin testing. It is worth noting that previous experienced investigators found that *Didymella* spp sensitization was exceptionally uncommon; therefore, routine testing for this fungal mold was discontinued many years ago (Frankland, personal communication). Broken *Alternaria* was highly correlated with *Didymella* and *Cladosporium* spp counts and significantly associated with asthma admissions. It is worth noting that on the day of the thunderstorm epidemic in Cambridge, the nearby city of Derby recorded the highest spore count of *Didymella* since recording started in 1970. Therefore, it is possible that sensitization to other fungal species will be increasingly recognized as allergens are better characterized and as improved methods for testing purified components become available [42].

Parietaria

Parietaria spp are urticaceae weeds that are widespread in the Mediterranean area, in which a spring and summer pollen season is in part contemporaneous with that of grasses. In Naples, exposure to *Parietaria* spp pollen was associated with a report of thunderstorm asthma [15]. This observational study of seven patients demonstrated *Parietaria* sensitivity in the absence of grass pollen sensitivity. Meteorologic details of the storm are unavailable from the published letter, but aerobiology data suggest that the concentration of *Parietaria* pollen was particularly high, with a peak of 144 grains/m³ being recorded on June 3, whereas airborne concentrations of grasses and *Alternaria* spp were very low. The outbreak of asthma was not of epidemic proportions described in other locations, but exacerbations appeared to be of similar severity to cases seen in Cambridge [15,47]. Patients sensitized to *Parietaria* who were indoors with the windows closed during the night of June 4 did not experience symptoms, suggesting that significant direct exposure to the elements was required for exacerbation.

Climate Change and Thunderstorms

An improved understanding of the causes and implications of thunderstorm asthma is essential for directing public health policy, which may be particularly relevant in the context of climate change. Seasonal aeroallergens vary by region and geography, but climate change has altered plant

distribution and, consequently, allergen distribution [48]. The scale and season of plant flowering are influenced. Earlier budburst results in increased seasonal allergen release. Natural events such as El Niño also have resulted in the early release of tree pollens. For example, permanent changes in vegetation in the past 10 years resulting from extensive wildfires are likely to affect aeroallergen loads. In the United Kingdom and possibly in the United States, epidemic asthma is likely to occur more frequently in future seasons if the trend over the past 35 years for an earlier and longer *Alternaria* season continues [49].

Thunderstorms are a common occurrence in the United States and are forecast to increase in cities such as Atlanta, Dallas, and New York because of climate change [50]. In their study from Atlanta, Grundstein et al. [14] reported a 3% increase in asthma visits to emergency departments on days after thunderstorms. They also showed that thunderstorms stratified for rainfall and wind gusts were associated with increased asthma visits, possibly triggered by increased spore production and dissemination of aeroallergens. Therefore, climate change affecting the frequency of thunderstorms and the type and concentration of aeroallergens in some areas will likely influence the occurrence of thunderstorm asthma epidemics [51].

Climatic factors associated with thunderstorms

Taylor and Jonsson [25] proposed a mechanism by which updrafts entrain pollen grains into the high humidity of a cloud base in which the grains rupture, and downdrafts transport the fragments to ground level in dry, cold outflows extending about 5 km ahead of the rainfall. This proposed allergen circulation likely also applies to fungal spores. This process would explain why many of the individuals in our study developed symptoms before rainfall started and why many claim the ability to foretell the imminent arrival of a thunderstorm by worsening of their asthma. Large-scale thunderstorms with associated outflows occur on average less than twice per year in the United Kingdom, and even fewer occur during the daytime, when the population is exposed to aeroallergens. This may explain why asthma epidemics occur infrequently.

Several climatic factors associated with thunderstorms also were proposed as directly influencing asthma exacerbations. Photochemically generated irritant gases such as nitrogen oxide increase during thunderstorms and lead to increased ozone levels, which contribute to increased airway hyperreactivity. Other possible factors associated with a sudden increase in asthma symptoms include a preceding dry spell followed by winds that cause a sudden rise in allergens, an increase in lightning strikes [11], a sudden decrease in temperature, and an increase in humidity [8]. However, Grundstein et al. [14,16•] suggested that existing studies are limited by the use of meteorologic data with poor spatial resolution and a lack of appropriate air quality data to definitively support or refute a specific meteorologic hypothesis.

Farming Practice

Farming practice also may contribute to the rise in fungal spore levels before thunderstorms. *Alternaria*, *Cladosporium*, and *Didymella* spp grow on cereal crops and grass. Hyde and Williams [52] suggested that *Alternaria* spores are present in large numbers, especially during harvesting, and may be inhaled whole or as fragments. Corden et al. [49] frequently observed bursts of *Alternaria* spores during grass mowing and harvesting and microscopic evidence of *Alternaria* spores broken into fragments, presumably caused by mechanized harvesting [49]. Over many years of microscopic examination of air flora, they reported that *Alternaria* was the only fungal spore that was found broken. Friesen et al. [53] observed that harvesting liberated immense numbers of fungal spores, many of which were carried large distances by wind currents. Furthermore, in response to a Met Office forecast of heavy rain or thunderstorms, cereal farmers in the United Kingdom will bring forward harvesting to save their crop. This leads to increased concentrations of airborne *Cladosporium* spp and both broken and complete spores of *Alternaria* spp. In our study, unbroken *Alternaria* counts did not correlate with asthma admissions, supporting the hypothesis that several factors are required before epidemic asthma occurs during thunderstorms. Somewhat surprisingly, grass pollen counts were negatively associated with asthma admissions, with a 13% reduction in asthma admissions per 100–pollen grain increase/m³. The statistical analysis from June to August incorporated the peak grass pollen season, and we therefore concluded that grass pollen is unlikely to be an independent etiologic factor in thunderstorm asthma [4••].

Conclusions

From the literature and our own observations, we have proposed a list of necessary prerequisites for thunderstorm asthma as follows:

- Sensitized atopic asthmatic individuals
- Prior airway hyperresponsiveness before a sudden, large allergen exposure
- A large-scale thunderstorm with cold outflow occurring at a time and location during an allergen season in which large numbers of asthmatics are outdoors
- Sudden release of large amounts of respirable allergenic fragments, particularly fungal spores such as *Alternaria*

The vast majority of asthmatics who develop symptoms during thunderstorms are atopic. Therefore, the primary mechanism is allergen-induced acute bronchospasm. The most important mechanisms associated with large thunderstorms are the sudden surge in allergens (particularly easily respirable fragmented *Alternaria* spores), a high

concentration of fungal spores, and their transportation over large distances. Other associated factors, such as ozone and a sudden reduction in temperature, may contribute to bronchial hyperresponsiveness. Although grass pollen sensitivity is not an independent predictor of thunderstorm-related asthma, by causing bronchial hyperresponsiveness, it acts as a co-factor in *Alternaria* allergic hay fever sufferers by lowering the threshold at which severe acute asthma develops.

Vulnerable groups of asthma patients can be identified from previous asthma exacerbations and skin test results. Collaboration between the meteorologic and aeroallergen counting centers should allow prediction of future epidemics and warn at-risk groups in time. It is also likely that epidemic thunderstorm asthma will occur more frequently in future seasons if the trend over the past 35 years for an earlier and lengthening *Alternaria* season continues [50]. A further challenge will be to assess whether prophylactic therapy with high-dose inhaled or oral corticosteroids or specific immunotherapy to *Alternaria* can prevent these potentially life-threatening attacks of asthma.

Disclosure

No potential conflicts of interest relevant to this article were reported.

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