

Clinical Commentary Review

Epidemic Thunderstorm Asthma: Lessons Learned from the Storm Down-Under

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Epidemic thunderstorm asthma (ETSA) is a global health problem that can strike without sufficient warning and can have catastrophic consequences. Because of climate change, future events are likely to become more common, more disastrous, and more unpredictable. To prevent loss of life and avoid surge events on health care infrastructure, identifying at-risk individuals and their potential biomarkers is the most prophylactic approach that can be taken to mitigate the deadly consequences of ETSA. In this review, we provide an update on the clinical mechanism, global prevalence, and characteristics of those patients moderately or severely at risk of ETSA. Identifying these patient characteristics will aid clinical professionals to provide suitable and personalized treatment plans and, in turn, avoid future loss of life. © 2020 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). (J Allergy Clin Immunol Pract 2020;■:■-■)

Key words: Epidemic thunderstorm asthma; Grass pollen; Allergens; Allergic rhinitis; Sensitization; Allergen-specific IgE; Melbourne; Risk factors; Biomarkers; Asthma treatment

Epidemic thunderstorm asthma is characterized by the emergence of acute asthma presentations after a thunderstorm. For example, on November 21, 2016, sensitized individuals in

Melbourne were impacted by the most significant epidemic thunderstorm asthma event in recorded history. Thousands were hospitalized for severe respiratory presentations, a majority of whom were found to suffer from allergic rhinitis or asthma, and the death of 10 patients have been associated with the event. Asthma-related hospital admissions rose by almost 1000% during the 12-hour storm, an unprecedented number that the health infrastructure was not prepared to handle.¹ Although multiple epidemics have been observed across developing countries worldwide, thunderstorm asthma events have occurred most frequently in Melbourne, Australia, with at least 7 separate epidemics recorded.² Events have been observed across other states, but they are far less common and pose less of a risk to public health compared with those in Melbourne.

CLINICAL MECHANISMS

The interactions between aeroallergens and meteorological factors that occur during these epidemic thunderstorm asthma (ETSA) events contribute to an increased severity of asthmatic symptoms within sensitized populations.³ The arrival of thunderstorms has been strongly linked with increased levels of allergenic particles.⁴ Thunderstorm outflow concentrates airborne allergens, such as pollen, near ground level,⁵ increasing the risk of exposure for predisposed individuals.⁶ Pollen is well documented to be present during ETSA events,⁷ with grass pollen identified as a major factor to trigger asthmatic symptoms.⁸ Other aeroallergens, such as fungal spores, have also seen huge atmospheric increases during thunderstorms and may also have an impact on respiratory health.^{9,10}

Intact pollen grains are too large to normally reach the lower airways. However, pollen can naturally swell and rupture from osmotic shock when exposed to high levels of moisture during thunderstorms,¹¹ releasing hundreds of fine allergenic starch granules of respirable size (Figure 1) into the atmosphere.^{12,13} Recently, it has been shown that concentrations of pollen fragments are at their highest, and remain high, during convective thunderstorms.¹⁴ These particulates can be small enough to travel past the pharynx, reach the lower respiratory tract, and trigger asthmatic symptoms.^{15,16}

Thunderstorm asthma epidemics usually occur during late spring where pollen concentrations are highest. All 7 Melbourne epidemics occurred in November, when ryegrass pollination was at its peak.¹⁷ The distribution of grass pollens is dependent on the weather, and Melbourne's high susceptibility to ETSA may be influenced by local weather patterns interacting with the environment. Hot northern winds tend to push aeroallergens from large grasslands down south toward a sensitized urban population.⁷ Thunderstorms aid in the dispersion of intact and ruptured pollen grains, leading to sensitized individuals inhaling

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No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication July 31, 2020; revised October 6, 2020; accepted for publication October 18, 2020.

Available online ■■

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2213-2198

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<https://doi.org/10.1016/j.jaip.2020.10.022>

Abbreviations used

ETSA- Epidemic thunderstorm asthma

FeNO- Fractional exhaled nitric oxide

ICS- Inhaled corticosteroids

INCS- Intranasal corticosteroids

RAST- Radioallergosorbent test

SLIT- Sublingual immunotherapy

high atmospheric levels of allergens within a short period of time.¹⁸ The climate in Australia experiences many spatial and temporal variations that influence weather parameters such as temperature and rainfall. These changes can occur seasonally, annually, or over long periods of time.¹⁹ Abnormal weather patterns have become more common due to climate change,²⁰ which may be responsible for the increased frequency and severity of extreme weather health events²¹ such as epidemic thunderstorm asthma. The global impact of climate change has been well studied in the Northern Hemisphere, with limited long-term data on its projected ecological impact in the Southern Hemisphere.²²

A POTENTIAL GLOBAL PROBLEM

ETSA events are not unique to Australia (see Figure 2). Although infrequent, they are a global phenomenon, with 26 known events reported worldwide, and unlike ETSA events in Australia, are rarely responsible for a large number of asthma exacerbations. Exceptions include the 1994 London epidemic, the 2013 Iran epidemic, and the 2016 Saudi Arabia epidemic. Past ETSA events include those listed in Table I. The prevalence of atopic conditions in populations from industrialized countries has been associated with increased air pollutants.⁴⁷ Thunderstorms occur more frequently in temperate climates, like Europe or the Middle East, or subtropical environments, like Australia.^{48,49} All documented thunderstorm asthma events, as shown in Table I and Figure 2, also coincided with their respective country's spring and summer pollen seasons.⁵⁰ A combination of a susceptible population, extreme weather patterns, and high aeroallergen concentration results in these unique asthma epidemics. Thunderstorm-associated asthma presentations have been observed in Mexico,⁵¹ the USA,⁵² and Greece,⁵³ but no specific events have yet to be confirmed and documented.

The allergenic triggers vary from country to country. ETSA events are largely triggered by major community allergens. For example, grass pollen is the dominant ETSA trigger in Australia,^{37,39-42,44} *Conocarpus erectus* is the suspected trigger during ETSA events in Iran,⁵⁴ and *Olea europaea* and *Parietaria sp.* in Italy.^{33,34}

WHO IS MOST AT RISK OF ETSA?

It is estimated that between 20% and 70% of individuals with asthma are undiagnosed and are not receiving treatment.⁵⁵ This is cause for concern, especially when attempting to identify the subset of individuals who are at risk of ETSA. This is particularly true for patients with ETSA, because these individuals may not have previously suffered from asthma.^{39,45} However, almost all patients hospitalized suffered from allergic rhinitis or pollen sensitization, and some patients presented signs of having undiagnosed asthma.⁴⁵ Generally, all individuals who attended



FIGURE 1. Clinical mechanism of epidemic thunderstorm asthma (ETSA). ETSA events largely coincide with peak pollen season. High concentrations of aeroallergens (both pollen and fungal) are swept via high winds toward a population of at-risk individuals. Larger and intact pollen grains are trapped by the mucosal linings of the upper airways (1). However, during an ETSA event, high humidity levels cause the pollen to expand and rupture as a result of osmotic shock. This releases an abundance of respirable allergenic particles that are small enough to reach the lower airways (2), triggering an asthmatic response.

emergency departments during the 2016 ETSA event in Melbourne displayed the following characteristics.

Individuals with moderate risk

Asthmatic history. Compared with common asthma exacerbations, individuals who have been impacted by the 2016 Melbourne epidemic have experienced ongoing symptoms. Approximately 80% of patients with ETSA were observed to suffer from persistent asthmatic symptoms, 28% on a weekly basis, with an inability to adequately self-manage.⁵⁶ This was observed even among patients with a history of well-controlled asthma, as individuals who were normally able to treat their chronic condition were unable to ease their breathlessness. Also of interest, 63% of patients with no prior history of asthma reported developing symptoms during the months after exposure to an epidemic thunderstorm event.⁵⁶

Ethnicity. Few studies had accounted for ethnicity when investigating ETSA events. Independent from other risk factors, Asian ethnicity has been found to considerably increase the risk of susceptibility to thunderstorm asthma.⁵⁷ Atopic conditions are

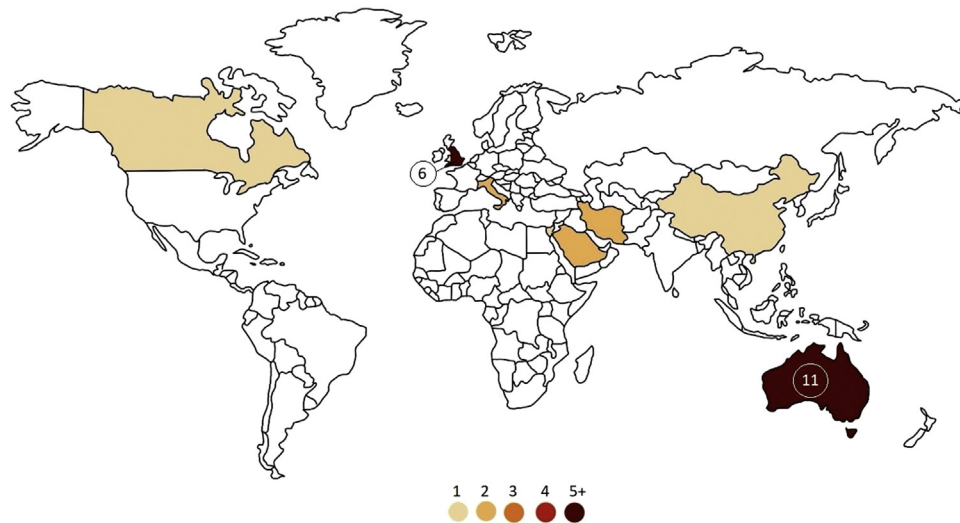


FIGURE 2. Global prevalence of epidemic thunderstorm asthma (ETSA). Number of documented ETSA events, per country, since 1983. An ETSA event is described as acute exacerbation of asthmatic symptoms in patients, often leading to an influx of presentations to the emergency department, during or after a thunderstorm.

more prevalent among Australians with Asian descent, with allergic rhinitis twice as common compared with non-Asians. Asthma severity was also shown to increase among Asian immigrants as their length of stay increased.⁵⁸ Interestingly during the 2016 ETSA event in Melbourne, although patients of Asian descent were less likely to be admitted to hospital compared with their non-Asian counterparts, this trend reversed if those with Asian heritage were born in Australia.¹⁷ Critically, 25% of the Melbourne population is of Asian descent; 6 of the 10 patients who died after the 2016 Melbourne epidemic were of Asian ethnicity.⁷

Seasonal allergy. Patients most at risk of ETSA include those with existing sensitivity to ryegrass,^{59,60} a history of allergic rhinitis, and are unlikely to be using inhaled asthma medications.⁵⁹ Sensitivity to ryegrass pollen was the leading contributor to an individual's susceptibility to ETSA. Specifically, a high radioallergosorbent test (RAST) for grass pollen is a strong indicator of heightened risk of ETSA in individuals with seasonal allergies.⁶⁰ Of importance, some studies report ryegrass pollen sensitization of all individuals presenting to emergency during ETSA, further indicating the importance of ryegrass sensitization as the leading contributor of susceptibility to ETSA.⁶¹ Although allergy to ryegrass appears to dominate among patients with ETSA, many patients also had sensitivities to other seasonal grass species including elevated IgE for Bermuda grass (94%), and positive skin prick tests for Bahia grass (94%) and Timothy grass (91%).⁶¹

Medication use. During the 1997 Wagga Wagga epidemic, the usage of inhaled corticosteroids (ICS) among patients with asthma was low, but patients who had used ICS before the 1997 Wagga Wagga epidemic experienced less severe symptoms, highlighting the importance of prior asthma management to minimize susceptibility during ETSA.³⁹ More recently, risk factors associated with medication use included individuals taking beta-blockers, but not those taking nonsteroidal anti-inflammatory drugs, which have been identified in patients with ETSA.¹

Individuals severely at risk

Of those individuals who attended emergency departments during the 2016 ETSA event in Melbourne, a substantial proportion reacted severely and required hospital admission. These severely at-risk individuals displayed the following characteristics.

Asthma. Not all individuals who suffered during ETSA had a history of asthma. However, during an ETSA event, individuals more likely to suffer severely and require hospital admission were those who had a doctor-diagnosed history of their asthma,⁵⁹ were aware of their asthma,⁵⁹ displayed asthmatic symptoms prior to,⁵⁹ and importantly, if they were admitted to hospital in the previous 12 months.¹⁷ Of particular concern, 58% of asthmatic patients with ETSA either lacked an asthma action plan or had poorly controlled symptoms (55%), and in 68% of cases, preventative corticosteroids were either underused or not prescribed.¹⁷ Many individuals experienced progressively declining asthma control and persistent symptoms after an ETSA event.⁵⁶

Allergen specific IgE. Of importance, individuals hospitalized during ETSA had elevated titers of IgE. Of particular interest, 100% of hospitalized individuals had high levels of ryegrass allergen specific IgE. These same individuals were also allergic to Bermuda grass (96%), with some individuals demonstrating some sensitivity toward common fungal allergens from the genera *Alternaria* and *Cladosporium*.⁵⁹ More specifically, in addition to overall elevated ryegrass pollen specific IgE, patients with ETSA are also more likely to demonstrate serum specific IgE to the major ryegrass allergen Lol p 5.⁶² This is a significant observation as Lol p 5 is located within starch granules inside pollen grains.^{11,63} These granules are released into the air on rupturing during certain atmospheric conditions, such as ETSA.^{11,13,64} Thus, detection of allergen specific IgE toward Lol p 5 may add to the repertoire of biomarkers to assess an individual's risk and vulnerability to future ETSA events.

TABLE I. Global occurrences of thunderstorm asthma events: location, date, and number of individuals affected during the documented ETSA event

Location	Date	No. of individuals affected	Reference
Asia			
Saudi Arabia	November 2, 2002	No data	23
Ahvaz, Iran	November 2, 2013	2000	24
Israel	October 25, 2015	No data	25
Ahvaz, Iran	October 28, 2015	33	26
Kuwait, Saudi Arabia	December 1, 2016	844	27
Yulin, China	September 11, 2018	391	12
Europe			
Birmingham, England	July 6, 1983	106	28
Nottingham, England	June 20, 1984	19	29
UK	July 22, 1989	32	30
London, England	June 24, 1994	640+	31
Cambridge, England	July 29, 2002	57	32
Naples, Italy	June 4, 2004	7	33
Puglia, Italy	May 27, 2010	20	34
London	July 23, 2013	40	35
Australia			
Melbourne	November 11, 1984	85	36
Melbourne	November 8, 1987	154	37
Melbourne	November 29, 1989	277	37
Tamworth	November 1, 1990	110	38
Wagga Wagga	October 30, 1997	215	39
Newcastle	October 27, 1998	6	40
Melbourne	November 19, 2003	70	41
Melbourne	November 25, 2010	36	42
Melbourne	November 8, 2011	30	43
Canberra	October 27, 2014	15	44
Melbourne	November 21, 2016	~10,000	45
North America			
Canada	July 31, 2000	157	46

ETSA, Epidemic thunderstorm asthma.

IDENTIFYING AND MANAGING THE PATIENT IN ETSA

A comprehensive approach toward management and prevention of ETSA includes: (i) environmental and public health strategies, with forecasting and early warning to reduce exposure; and (ii) reduction in individual susceptibility through primary and secondary prevention.

In regions with thunderstorm asthma history and risk, thunderstorm forecasts together with pollen counts can be combined in a risk matrix to issue public health warnings.^{65,66} These include taking proper precautions to remain indoors, take preventive inhaled steroids, and have ready access to bronchodilator inhalers. This forecasting also enables health and emergency service systems to be on alert and suitably prepared.

Thunderstorm asthma is characterized by airway inflammation with IL-5-mediated sputum eosinophilia and eosinophil degranulation.⁴⁰ ICS are first-line medications for patients with asthma that have been demonstrated to improve airway responsiveness and inflammation.⁶⁷ As already mentioned above, a case control study after the Wagga Wagga episode in 1997 found a lower rate of ICS use in thunderstorm cases.³⁹ Most reports of ETSA found that those affected were not on ICS,^{34,37,39,40,46} and this was a factor in ambulance calls,⁶⁸

emergency department presentations,^{7,45,60,61} and admissions to respiratory wards.^{7,17} A number of factors may contribute to this, including the following: (i) most ETSA-affected individuals had predominantly allergic rhinitis with no prior diagnosis of asthma or were not aware of asthma symptoms; (ii) they had less severe or intermittent asthma for which regular ICS may not have been indicated, or (iii) they were nonadherent to regular ICS use despite having persistent asthma. Hence, the evidence supports regular ICS use for those with diagnosed asthma, or a history of thunderstorm asthma, throughout the susceptible grass pollen season of spring and early summer months. The recent change in Global Initiative in Asthma guidelines for a combination of low-dose ICS with fast onset long-acting bronchodilator (formoterol) on an “as needed” basis in step 1 of therapy would be a suitable option for these patients with intermittent or infrequent asthma symptoms.¹

As ETSA airway inflammation is an archetypal type 2 inflammation,⁴⁰ the measurement of the type 2 biomarker fractional exhaled nitric oxide (FeNO) to guide therapy and dose of inhaled steroids would be appropriate in these patients if available. There are no prospective studies in ETSA to confirm this, but elevated FeNO measurements in those who have experienced ETSA⁶¹ support this approach.

As previously mentioned, almost all patients hospitalized with ETSA suffered from allergic rhinitis and pollen allergy even if there was no history of diagnosed asthma. Adequate control of allergic rhinitis is recommended for control of asthma.⁶⁹⁻⁷² A meta-analysis⁷³ and systematic review⁷⁴ of the role of intranasal corticosteroids (INCS) in asthma demonstrated improved asthma outcomes with the use of INCS compared with placebo, despite a lack of further improvement with INCS as an addition to ICS. Hence, identification of undiagnosed asthma symptoms in those with allergic rhinitis and adequate treatment of allergic rhinitis in those without a history of asthma are both important factors in reducing the risk of ETSA.

Apart from the pharmacological approaches above, desensitization with specific allergen immunotherapy⁷⁵ induces long-term immune tolerance to the responsible allergen. Sublingual immunotherapy (SLIT) for grass pollen allergy has shown to ease asthmatic symptoms for susceptible individuals who were exposed to an ETSA event compared with individuals taking ICS alone. Of those treated with SLIT (Oralair; manufactured by Stallergenes, London, UK) before the 2016 ETSA event in Melbourne, allergic individuals either had no asthma symptoms (71%) or exacerbation of their asthma (0%), compared with 24% and 41%, respectively, of individuals who did not receive preventative SLIT before the ETSA event.⁷⁵ Patients undergoing SLIT before the pollen season have fewer allergic symptoms, and even fewer again if repeat treatments are given over 2 consecutive pollen seasons.⁷⁶ Patients with allergic rhinitis receiving SLIT over 3 years demonstrate a decrease in airway inflammation, allergen specific T^{REG}-cell proliferation, increased serum allergen specific IgG, and lasting levels of IgG₄⁺ memory B cells, indicating a persistent and lasting protective immune response attributed to repeat SLIT of ryegrass pollen allergen.⁷⁶ This suggests a primary and secondary role for allergen immunotherapy in reducing the risk of ETSA.

CONCLUSIONS

ETSA is a global health issue that will most likely become more frequent and severe over the coming years due to climate change. Australia, being the country hit hardest and most often by these events, should prepare for future epidemics to avoid burdening our current health infrastructure. It is crucial for health professionals to identify potential biomarkers and risk factors in affected individuals. These may include existing sensitivity to seasonal allergenic grasses, prior history of allergic rhinitis, overall elevated titers of IgE, elevated grass pollen specific IgE, serum specific IgE to major grass allergens, such as Lol p 5 from ryegrass and its cross-reactive analogues in other grasses, and high RAST or positive skin prick tests to seasonal allergens. Determining these factors will help patients receive appropriate and effective treatment methods and reduce the aftermath of the 2016 Melbourne epidemic from happening again.

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