

Short communication

Sensitivity to fungal allergens is a risk factor for life-threatening asthma

Background: Previous studies have suggested that sensitivity to *Alternaria* and *Cladosporium* may be risk factors for life-threatening asthma. We have investigated this by studying the relationship between skin tests for fungal spores and admission to an intensive care unit (ICU) for asthma.

Methods: Skin prick tests for fungal spores (*Alternaria tenuis*, *Cladosporium cladosporioides*, *Helminthosporium maydis*, and *Epicoccum nigrum*), cat dander, house-dust mite (*Dermatophagoides pteronyssinus*), and a seven-grass mix were performed in three groups of patients: patients admitted to an ICU with an attack of asthma; those who had received emergency treatment for asthma but had not been admitted to an ICU, and those who had never required emergency treatment for their asthma.

Results: Twenty of 37 patients (54%) admitted to the ICU had a positive skin test for one or more fungal allergens compared with 15/50 patients (30%) in each of the other groups ($P=0.005$). The ICU patients were no more likely to have positive skin tests for the grass mix, cat dander, or house-dust mite than the other patients.

Conclusions: A positive skin test for fungal allergens is a risk factor for admission to an ICU with an acute attack of asthma.

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Key words: asthma; fungal allergens.

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Accepted for publication 20 December 1999

Although fatal asthma is uncommon, it is of concern because it can occur in young people, and it is potentially preventable (1). Patients who are admitted to an intensive care unit (ICU) usually have life-threatening attacks and are similar in their characteristics to those who die from asthma (2). Study of these patients provides the opportunity to identify risk factors for life-threatening asthma (3). Sensitivity to fungal allergens may be one such risk factor. O'Hollaren et al. (4) reported that 10 out of 11 subjects from the Midwest of the USA who had a respiratory arrest due to asthma were skin-test-positive for *Alternaria alternata*. In contrast, only 31% of a control group of asthmatics who had not had a respiratory arrest were skin-test-positive for *Alternaria*. In another study, the odds of death due to asthma in 5–34-year-olds in Chicago were 2.16 times higher on days when mould spore counts were 1000 spores per cubic metre or more (5). In South Africa, Roux et al. (6) compared 21 children who had been admitted to the ICU at least twice in the same or adjacent months in different years with another group who had been admitted to the ICU on more than one occasion but without any seasonal pattern. In this retrospective case control study, the seasonal group were significantly

likely to have positive skin tests for the fungal allergen *Cladosporium*. Both *Alternaria* and *Cladosporium* have dry-weather air spores which are dispersed into the atmosphere when there is an increase in wind speed and a fall in relative humidity (7). We wished to determine whether sensitivity to dry-weather spores such as *Alternaria* or *Cladosporium* was associated with an increased likelihood of admission to the ICU in New Zealand. Other dry-weather air spores that have been identified as allergens (7) and are part of the air spora in Auckland include *Helminthosporium* and *Epicoccum* (8).

Material and methods

Subjects

Subjects were studied only if they were between the ages of 18 and 50 years. All of the subjects lived in the Auckland metropolitan area. The study was approved by the North Health Ethics Committee.

Three groups of subjects were studied:

- 1) *Community*: Subjects with asthma who had never been admitted to hospital because of their asthma

and who had never required treatment with nebulized bronchodilators for acute exacerbation of their asthma.

- 2) *Hospital*: Subjects who had been admitted to hospital with acute exacerbation of asthma, or who had required treatment with nebulized bronchodilators for acute exacerbation at an accident and emergency department. None of these subjects had been admitted to an ICU with asthma.
- 3) *Intensive care*: Subjects who had been admitted to an ICU with an acute, severe attack of asthma.

The first group of patients were identified by computerized disease registers maintained by four general practitioners (GP), all of whom practised within the catchment area for Auckland Hospital. Subjects on the asthma register between the ages of 18 and 50 years were sent a letter signed by the GP inviting them to take part in the study. Those who responded were not included in this group if they had ever been admitted to hospital with asthma, if they had ever attended an accident and emergency department because of their asthma, or if they had visited their GP with exacerbation of asthma and received treatment with nebulized bronchodilators.

Patient Information Services at Auckland Hospital provided a printout of all patients admitted to Auckland Hospital with acute exacerbation of asthma for the previous 2 years. If the subjects were between the ages of 18 and 50 years, a letter was sent to the last known address (as recorded in the hospital notes) inviting them to take part. Subjects were not included in this group if they had ever been admitted to an ICU with asthma.

Subjects who had been admitted to the ICU at Auckland Hospital in the previous 5 years were identified from a computerized database maintained by this department. Subjects between the ages of 18 and 50 years were sent a letter inviting them to take part. Where possible, those who did not respond to the letter were contacted by telephone. Subjects identified from the GP disease registers or the list of hospital admissions were included in the ICU group if they reported a previous admission to any ICU with asthma. Details were recorded of the subject's medication and any other medical diagnoses including eczema and hay fever.

A power calculation was performed based on the assumption that 50% of the subjects in the ICU group and 20% in the community group would have a positive skin test for a fungal allergen. This showed that if $\alpha=0.05$ and $\beta=0.2$, we would need 36 subjects in each group. We opted to study 50 subjects in each group, but we were able to identify only 37 subjects who had been admitted to an ICU and who were available for skin testing. Fifty subjects were studied in the two other groups.

The baseline characteristics of the subjects are listed in Table 1. The proportion of women was similar in the community and intensive care groups (60.0% and 64.9%, respectively), but there were more women in the hospital group (80.0%). The mean age was similar in all three groups.

Skin testing

The allergens, obtained from Bayer Corp (Elkhart, IN, USA), were a seven-grass mix (perennial rye, timothy, sweet vernal, meadow fescue, redtop, orchard, and Kentucky bluegrass 1:20 w/v), *Alternaria tenuis* (also known as *Alternaria alternaria*) 1:10 w/v, *Cladosporium cladosporioides* 1:10 w/v, *Helminthosporium maydis* 1:10 w/v, *Epicoccum nigrum* 1:10 w/v, *Dermatophagoides pteronyssinus* 30 000 AU/ml, and standardized cat hair and pelt 10 000 BAU/ml. Negative (50% glycerol) and positive controls (histamine 10 mg/ml) were also used. All subjects provided written informed consent. Skin testing was not performed if the subject had used oral antihistamines within the previous 48 h. Such subjects were rescheduled for skin testing at a later date.

Skin prick testing was performed as previously described (9). Drops of the allergens and the positive and negative controls were placed on the volar aspect of forearm skin 2 cm apart. The positive control was placed near the wrist while the negative control was nearer the elbow. A standardized lancet (Prick Lancetter, Hollister-Stier) was passed through each drop of allergen in order to break the epidermis. A separate lancet was used with each allergen. The drop of allergen was then wiped away with a tissue. The wheal size was measured 15 min later. The largest diameter of the wheal was measured with a transparent plastic ruler. The skin prick test was regarded as positive if the wheal diameter was greater than 2 mm. One person performed all of the skin tests.

Statistical analysis

A logistic regression was performed with SAS (Proc Reg) (10). The analysis investigated whether the patient category (community, hospital, or intensive care) had

Table 1. Baseline characteristics of subjects

	No. of subjects	Mean age (years) ³	Male:female
ICU	37	36.0 ± 9.8	13/24
Hospital ¹	50	32.5 ± 8.5	10/40
Community ²	50	35.9 ± 9.8	20/30

¹This group includes subjects who had been admitted to hospital with asthma or who had been treated in an emergency department for an acute attack of asthma. None of these subjects had been admitted to an ICU with an attack of asthma.

²This group includes subjects with asthma who had never been treated with nebulized bronchodilators for an acute attack of asthma in a doctor's surgery or emergency department, or as a hospital inpatient.

³Values are expressed as mean ± SD.

any influence on the response to fungal allergens. Covariates were sex, diagnosis of eczema or hay fever, and reactions to grass pollen, cat dander, and house-dust mite.

Results

The results of the skin tests are shown in Table 2. Of the intensive care subjects, 54.1% were skin-test-positive for one or more of the fungal allergens, compared with 30.0% for the community and hospital groups. The difference between the ICU patients and those in the other two groups was statistically significant ($P=0.005$).

The intensive care patients were not, however, more likely to respond to allergens other than the fungi. Only 59.5% of the intensive care patients were skin-test-positive for the grass mix, compared with 76% in the hospital group and 72% in the community group. Similarly, only 51.4% of the intensive care patients responded to cat dander, compared with 58% of the community subjects and 62% of the hospital subjects. The proportion of subjects responding to *D. pteronyssinus* was similar in all three groups.

The mean wheal diameter was calculated for each allergen for the subjects with positive skin tests. There was no difference between the three groups in the mean wheal diameter for any of the allergens (Table 3).

Discussion

In this case control study, we found that subjects who had been admitted to the ICU with severe, potentially life-threatening asthma were significantly more likely to have one or more positive skin tests for fungal dry-weather spores. Indeed, positive skin tests for fungi occurred almost twice as frequently in the subjects in the ICU group. This difference does not reflect an increase in sensitization to all inhalant allergens. The

Table 2. Percentage of positive skin tests for different allergens

	Hospital	Community	ICU
<i>Alternaria</i>	26.0%	24.0%	40.5%
<i>Cladosporium</i>	14.0%	14.0%	24.3%
<i>Epicoccum</i>	20.0%	2.0%	21.6%
<i>Helminthosporium</i>	14.0%	8.0%	21.6%
All fungi	30.0%	30.0%	54.1%
Grass mix	76.0%	72.0%	59.5%
Cat dander	62.0%	62.0%	51.4%
<i>D. pteronyssinus</i>	90.0%	84.0%	89.2%

Subjects admitted to the ICU were significantly more likely ($P=0.005$) to have one or more positive skin tests for fungal allergens than the subjects who had been treated in hospital or at an emergency department for an acute attack of asthma (hospital group) or subjects who had never required treatment with nebulized bronchodilators for acute exacerbation of asthma (community group).

Table 3. Mean wheal diameter (mm) of skin prick tests

	Hospital	Community	ICU
<i>D. pteronyssinus</i>	9.4	9.4	9.1
Grass mix	8.2	7.7	8.1
Cat dander	5.4	5.3	5.6
<i>Alternaria</i>	3.5	4.6	3.9
<i>Cladosporium</i>	3.6	3.4	3.0
<i>Helminthosporium</i>	3.4	3.3	2.5
<i>Epicoccum</i>	4.1	3.0	2.8

The mean wheal diameter was calculated for each allergen in the subjects with positive skin tests. There was no significant difference between the three groups (hospital, community, and ICU) in the mean wheal diameter for any allergen.

patients admitted to the ICU were no more likely to have positive skin tests to grass pollen, cat dander, or *D. pteronyssinus* than the other subjects.

This is a retrospective study; thereafter, we cannot be certain that all of the subjects were sensitized to fungal allergens at the time they were admitted to the ICU, but it is unlikely that many of the subjects became sensitized after their life-threatening attack but before they were skin-tested.

Our finding of an association between life-threatening asthma and sensitization to fungal allergens is consistent with previous reports. O'Halloren et al. found that subjects who had a respiratory arrest were more likely to have a positive skin test to *Alternaria* than other subjects with asthma (4). Targonski et al. reported that deaths from asthma in Chicago were more common on days with very high fungal spore counts (5). These observations beg the question of why sensitization to fungal spores is a risk factor for life-threatening attacks. Fungal spores are smaller in size than pollen grains, and this fact will favour deposition of spores in the airways (7). Bronchial provocation tests performed with *Alternaria* are more likely to produce late asthmatic responses than those performed with grass pollen (10). In addition, the spore counts in the atmosphere are usually many times higher than pollen counts. Certainly, spore counts for *Alternaria* and *Cladosporium* and other fungi can fluctuate dramatically from one day to another (4, 11). One can speculate that a sudden and dramatic increase in fungal spores could predispose to severe, acute attacks of asthma in those who are sensitized to these spores.

Other studies provide evidence that dry-air spores may be implicated in acute attacks of asthma. In Melbourne, Australia, Abramson et al. (12) found a positive relationship between spore counts for *Alternaria* and attendances at emergency departments 2 days later ($r=0.51$, $P<0.05$). Similarly, there was a relationship between *Cladosporium* spore counts and visits to the emergency department 3 days later ($r=0.66$, $P<0.01$). We found an increase in the frequency of positive skin tests in the patients who had been admitted to ICU, but not in the other individuals who had required emergency treatment for

their asthma. One can speculate that if we had been able to relate spore counts to ICU admissions, we would have seen a stronger relationship than that seen with emergency department visits in the Melbourne study.

Indirect evidence for a relationship between sensitization to *Alternaria* and acute attacks of asthma comes from the work of Peat et al. (13). They studied the prevalence of asthma and allergic sensitization in schoolchildren (5–8 years of age) in different regions in New South Wales, Australia. In the three coastal regions, the prevalence of positive skin tests for *Alternaria* ranged from 4.0% to 7.7%, compared with 15.2% to 23.1% for the three inland regions ($P < 0.001$). In contrast, sensitization to house-dust mite was higher in coastal areas (28.6–34.4%) than the inland areas (12.7–26.4%). The prevalence of current asthma was significantly lower in the inland regions, but, despite this, the inland regions had significantly higher rates of overnight hospitalization, emergency department visits, and urgent doctor visits. These findings suggest an association between sensitization to *Alternaria* and acute attacks, but they do not prove it.

In Brisbane, Australia, the relationship between attendances at the emergency department and the weather has been studied (14). An increase of admissions occurred in the autumn in association with winds blowing from the south. This change in wind direction was associated with clear skies and falls in temperature and humidity. Similar weather changes have also been

associated with emergency department attendances in Bermuda (15). These observations are of interest because clear days with brisk winds and low relative humidity are ideal for dispersion of dry-air spores such as *Alternaria* and *Cladosporium* (7, 16).

Further studies need to be conducted in subjects sensitized to dry-air spores such as *Alternaria* and *Cladosporium* to determine whether or not they are at increased risk of acute, severe attacks of asthma with this pattern of weather. If this were found to be the case, the knowledge would be useful in clinical practice. Subjects who had a history of severe attacks of sudden onset and a positive skin test for one or more dry-air spores could be warned about the weather conditions associated with abrupt increases in spore count. They could then monitor their asthma more carefully in these circumstances, and, if appropriate, take additional treatment for their asthma at this time.

Acknowledgments

We thank Elizabeth Robinson for performing the statistical analysis; Drs Tom Marshall, Paul Crozier, Lesley Hoy, and Douglas Gillanders for help with identifying the subjects from general practice; and Dr Stephen Streat for assistance in identifying the subjects who had been admitted to the intensive care unit (Department of Critical Care Medicine) at Auckland Hospital. Andrew Udy was a summer student supported by the Asthma and Respiratory Foundation of New Zealand.

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