

Trends in hospitalizations for anaphylaxis, angioedema, and urticaria in Australia, 1993-1994 to 2004-2005

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Background: Recent investigations in developed countries have found marked increases in the prevalence of allergic conditions. **Objective:** We sought to examine recent time trends in the prevalence of anaphylaxis, angioedema, and urticaria by describing trends and age and sex differentials in hospitalizations for these conditions in Australia.

Methods: Data on hospital admissions and deaths for anaphylaxis, angioedema, and urticaria were extracted for the periods 1993-1994 to 2004-2005 and 1997-2004, respectively. For hospital admissions, age-standardized rates were calculated. Time trends and sex differences were quantified by using negative binomial models.

Results: During the study period, there was a continuous increase in the rate of hospital admissions for angioedema (3.0% per year), urticaria (5.7% per year), and, most notably, anaphylaxis (8.8% per year). There was a particularly steep increase in the incidence of hospitalization for food-related anaphylaxis among children aged less than 5 years. Admissions for non-food-related anaphylaxis occurred predominantly in adults, particularly those more than 35 years of age. Among children, admission rates were higher in boys, but the sex difference was reversed among adults. Over an 8-year period, there were 106 deaths associated with anaphylaxis or angioedema.

Conclusion: Hospitalization rates for allergic conditions are on the increase, but the nature and causative factors differ between adults and children. The relation of these changes to those in the prevalence of specific allergen sensitization in the community requires further investigation in population studies.

Clinical implications: Among older persons, angioedema is becoming an increasing problem. Among children, hospitalization because of food-induced anaphylaxis is a growing concern. (*J Allergy Clin Immunol* 2007;120:878-84.)

Key words: Allergic reaction, hospitalization, mortality, anaphylaxis, food, urticaria, angioedema, trends, Australia

There has been increasing concern in many westernized countries about the hazard of food-related anaphylaxis, predominantly in school-aged children.^{1,2} Allergies to peanuts or tree nuts have been a particular focus of concern.^{3,4} These are the most common cause of severe food-related anaphylaxis and death in children, and unlike most other childhood food allergies, the majority of cases of peanut allergy persist into adulthood.⁵ Severe anaphylactic reactions have the potential to be fatal. Combined results from 2 small studies of deaths caused by food-induced anaphylaxis in the United States showed that 87% of the fatalities were due to peanuts or tree nuts, and 94.5% occurred in persons aged less than 35 years.^{6,7}

Recent investigations conducted in the United Kingdom have found marked increases in hospitalizations for anaphylaxis and for the related conditions of urticaria and angioedema since 1990.⁸ The authors proposed that the increases could be a result of increasing exposure to environmental risk factors (eg, peanuts, other foods, or latex), a lower threshold for sensitization to these allergens in the population, or both. Similar findings have been reported in the United States⁹ and Australia.¹⁰

Although these conditions are a particularly serious problem for children and young adults, they can affect persons of all ages. In older persons drug reactions are a relatively more common trigger, and food reactions are less common.¹¹

Among children, immediate hypersensitivity to inhalant allergens and conditions associated with this state, asthma, and rhinitis are more common in boys than in girls.¹² However, the sex predisposition for anaphylaxis, angioedema, and urticaria is not well described.

The objective of this analysis was to examine recent time trends in the prevalence of these allergic conditions by describing trends in hospital admissions and deaths associated with anaphylaxis, angioedema, and urticaria in Australia. A further objective was to characterize the epidemiology of these conditions by examining age and sex differentials, both in the rates of hospital admission and in the trends over time.

METHODS

Hospitalization data were obtained from the National Hospital Morbidity Database¹³ held at the Australian Institute of Health and

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Abbreviations used

ACE: Angiotensin-converting enzyme
ICD: International Classification of Diseases
ICD-9-CM: ICD-9–Clinical Modification
ICD-10-AM: ICD-10–Australian Modification

Welfare. Data were available in 1-year periods from July 1 to June 30 for each year. The data span 2 different versions of International Classification of Diseases (ICD) coding. The ICD-9–Clinical Modification (ICD-9-CM) was used to classify hospital admissions from 1993 through 1997, whereas the ICD-10–Australian Modification (ICD-10-AM) was introduced from 1998 onward. We included all hospital admissions in Australia from 1993-1994 to 2004-2005 in which the principal diagnosis was grouped under the broad categories of angioedema (ICD-9-CM codes 995.1 and 277.6; ICD-10-AM codes T78.3 and D84.1), anaphylaxis (ICD-9-CM codes 995.0, 995.6, and 999.4; ICD-10-AM codes T78.2, T88.6, T78.0, and T80.5), or urticaria (ICD-9-CM codes 708 and 698.2; ICD-10-AM codes L50 and L28.2). For the separate analyses of anaphylaxis due to food or nonfood causes, the data were limited to the period 1994-1995 to 2004-2005 because the classification of the type of anaphylaxis was unreliable in data for 1993-1994.

Mortality data were obtained from the National Mortality Database, which is also held at the Australian Institute of Health and Welfare.¹⁴ Data (in calendar years) were extracted from 1997 through 2004 where anaphylaxis (ICD-10 codes T78.0, T78.2, and T88.6), angioedema (ICD-10 code T78.3), or both were listed anywhere on the death certificate.

Age-standardized rates were calculated by standardizing to the age distribution of the Australian population in mid-2001, which was obtained from the Australian Bureau of Statistics.¹⁵ Rates were compared by estimating rate ratios by using generalized linear models with a negative binomial error structure.¹⁶ Models were fitted with the Proc GENMOD procedure in SAS Version 9.1 (SAS Institute, Inc, Cary, NC).¹⁷

RESULTS

Between 1993-1994 and 2004-2005, there were 47,958 hospital admissions for anaphylaxis, angioedema, or urticaria in Australia (Table I). Overall, there were more female than male patients admitted with these conditions. The median age of persons admitted was highest for angioedema (53 years) and lowest for anaphylaxis caused by food (23 years). Death was coded as the mode of separation in 0.17% of all hospitalizations for these conditions.

All allergic conditions

Between 1993-1994 and 2004-2005, there was a continuous increase in the rate of hospital admissions for angioedema, urticaria, and, most notably, anaphylaxis (Fig 1). The number of hospital admissions for these allergic conditions as a proportion of the total number of hospital admissions in Australia increased from 0.05% in 1993-1994 to 0.08% in 2004-2005.

The rate of hospitalizations for angioedema increased from 4.5 per 100,000 population in 1993-1994 to 6.8 per

100,000 population in 2004-2005, representing an average annual increase of 3.0%. In the same period, hospitalizations for urticaria increased from 5.6 to 10.3 per 100,000 population, representing an average annual increase of 5.7%.

The most dramatic increase in hospital admissions for allergic conditions between 1993-1994 and 2004-2005 was seen in those admitted for anaphylaxis, among whom hospitalizations almost tripled from 3.7 to 10.8 per 100,000 population. This is equivalent to an average annual increase of 8.8% in the rate of hospital admissions for anaphylaxis.

Urticaria

Hospital admissions for urticaria were approximately 3 times higher in children aged 0 to 4 years than for any other age group (Fig 2). Between 1993-1994 and 2004-2005, there were significant increases in the rate of hospital admissions for urticaria in all age groups. Overall, the rate of hospitalization approximately doubled over this period. The greatest increase was in those aged 15 to 34 years (7.8% per year).

Among children aged 0 to 14 years, rates of admission for urticaria were higher in boys than in girls, whereas in those aged 15 years and older, rates of admission were higher in female than in male subjects (Table II).

Angioedema

The rate of hospitalization for angioedema was highest in persons aged 65 years and older and lowest in children aged 5 to 14 years (Fig 3). Although the rate of hospital admissions for angioedema remained relatively constant for most age groups between 1993-1994 and 2004-2005, the rate in persons aged 65 years and older doubled from 10 to 20 per 100,000 population. This represented an average annual increase of 5.6% in the rate of admissions for angioedema in this older age group. For those aged 15 to 34 years, the average annual increase was 4.3%. There was no significant change in the rate of hospital admissions for angioedema in those aged less than 15 years or 35 to 64 years.

The differences between male and female subjects were similar to those seen for urticaria. Among children aged 0 to 14 years, rates of admission for angioedema were higher in boys than in girls, whereas in those aged 15 years and older, rates of admission were higher in female than in male subjects (Table II).

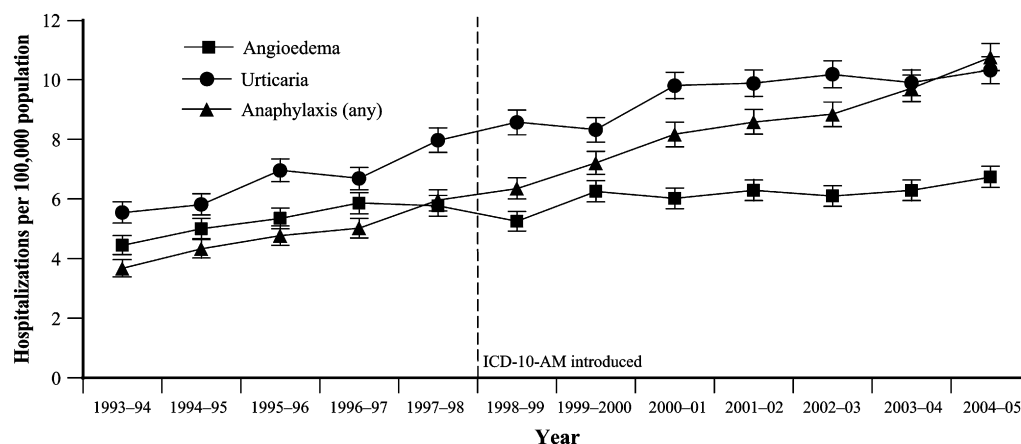
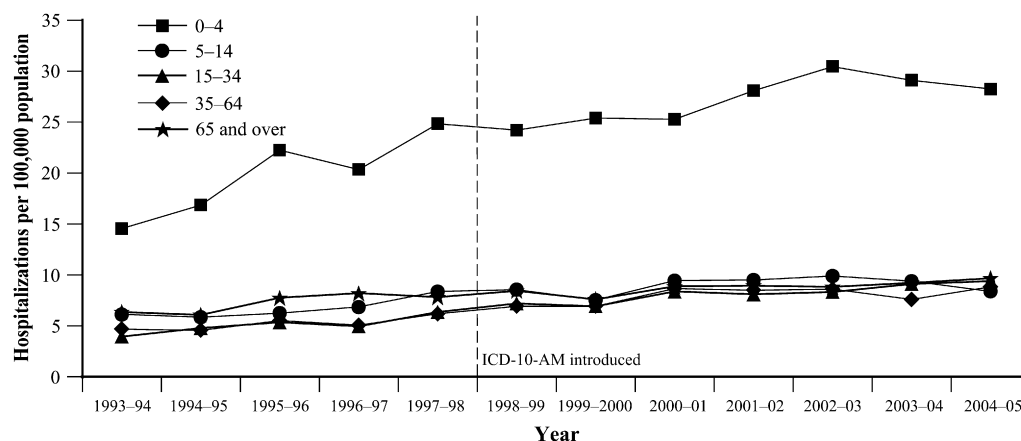
Anaphylaxis

Hospital admissions for anaphylaxis in Australia increased markedly between 1993-1994 and 2004-2005 across all age groups, particularly in those aged 0 to 4 years. In this age group hospitalizations for anaphylaxis increased from 4.1 to 19.7 per 100,000 population over the 12-year period. The increase in this age group was mainly attributable to an increase in admissions for anaphylaxis caused by food, as opposed to other causes (data not shown). In contrast, the vast majority of persons

TABLE I. Hospital admissions for anaphylaxis, angioedema, and urticaria, Australia, 1993-1994 to 2004-2005

	Angioedema	Urticaria	Anaphylaxis (food)	Anaphylaxis (nonfood)	Total
No. of admissions	13,012	19,032	5515	10,399	47,958
Male sex	43%	45%	49%	43%	45%
Median age (y [interquartile range])	53 (31-70)	29 (7-50)	23 (5-40)	42 (26-58)	37 (17-58)

Note: Median age (in years) is calculated from a subset of total hospital admissions (45,862 records) in which specific age data (as opposed to only the 5-year age group) were available: 12,381 for angioedema, 18,075 for urticaria, 5386 for anaphylaxis (food), and 10,020 for anaphylaxis (nonfood).

**FIG 1.** Age-standardized rate of hospital admissions per 100,000 population for angioedema, urticaria, and anaphylaxis, Australia, 1993-1994 to 2004-2005.**FIG 2.** Hospital admissions for urticaria by broad age group, Australia, 1993-1994 to 2004-2005.

aged 65 years and older who were admitted to hospital for anaphylaxis were admitted for causes other than food.

Anaphylaxis attributed to nonfood triggers. The rate of hospital admissions for anaphylaxis due to nonfood causes was highest for those aged 35 years and older, whereas children had the lowest rates (Fig 4). Overall, admissions for anaphylaxis attributed to nonfood triggers had an average annual increase of 8.5% between 1994-1995 and 2004-2005. The rate of increase did not differ significantly between age groups.

Among children aged 0 to 14 years, rates of admission for anaphylaxis not related to food were higher in boys than in girls, whereas in those aged 15 years and older, rates of admission were higher in female than in male subjects (Table II).

Anaphylaxis attributed to food. Between 1994-1995 and 2004-2005, admissions for anaphylaxis caused by food had an average annual increase of 13.2%. This was the most substantial increase observed for all the allergic conditions investigated. The rate increased across all age groups but was much greater among those aged 0 to 4

TABLE II. Sex differences in rates of hospitalization for anaphylaxis, angioedema, and urticaria, Australia, 1993-1994 to 2004-2005

Age group (y)	Rate ratio male: female sex (95% CI)			
	Angioedema	Urticaria	Anaphylaxis (food)	Anaphylaxis (nonfood)
0-4	1.47 (1.21-1.78)	1.36 (1.25-1.48)	Not applicable*	1.52 (1.19-1.96)
5-14	1.34 (1.12-1.61)	1.32 (1.20-1.46)	1.54 (1.30-1.81)	1.56 (1.26-1.94)
15-34	0.66 (0.61-0.71)	0.72 (0.67-0.77)	0.72 (0.62-0.83)	0.68 (0.60-0.76)
35-64	0.75 (0.70-0.81)	0.60 (0.56-0.65)	0.74 (0.63-0.88)	0.68 (0.61-0.75)
≥65	0.81 (0.74-0.88)	0.66 (0.61-0.71)	1.00 (0.78-1.27)	0.87 (0.81-0.94)

*Rate ratio changed significantly over the study period.

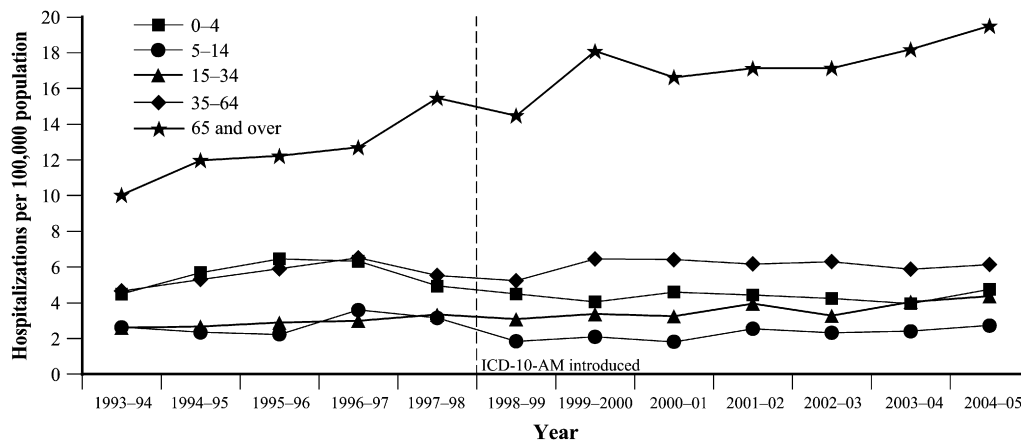


FIG 3. Hospital admissions for angioedema by broad age group, Australia, 1993-1994 to 2004-2005.

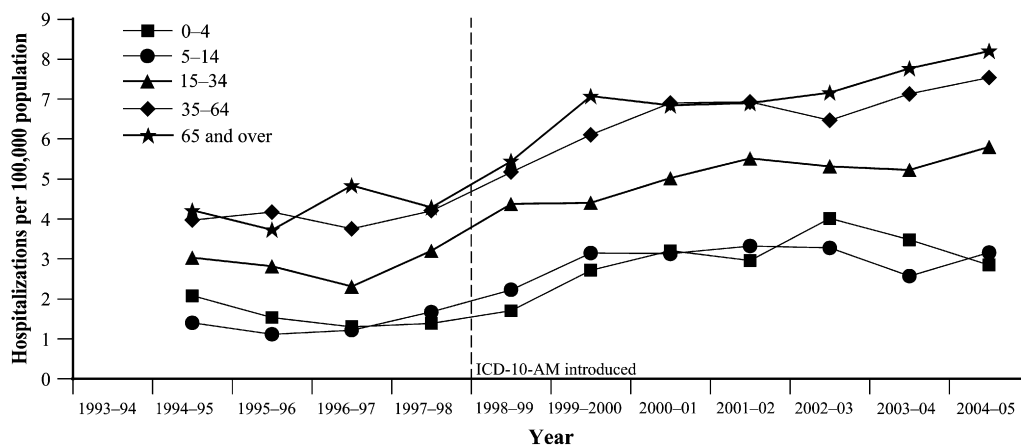


FIG 4. Hospital admissions for anaphylaxis due to nonfood causes by broad age group, Australia, 1994-1995 to 2004-2005.

years, among whom a 5.5-fold increase in the rate of admission was observed over the study period (Fig 5). Furthermore, the average annual increase in this age group was greater in boys (18.0%; 95% CI, 15.3% to 20.7%) than in girls (10.7%; 95% CI, 6.0% to 15.6%).

There was no sex difference in the rate of increase in hospital admissions for anaphylaxis caused by food among those aged 65 years and older. The rate of increase diminished with increasing age.

Deaths caused by allergic conditions

Between 1997 and 2004, there were 106 deaths in Australia in which anaphylaxis or angioedema was certified as the underlying or an associated cause of death. The number of deaths involving these conditions remained relatively constant between 1997 and 2001 at approximately 10 deaths per year. Between 2002 and 2004, the number of deaths doubled, and in 2004, there were 20 deaths associated with anaphylaxis or angioedema.

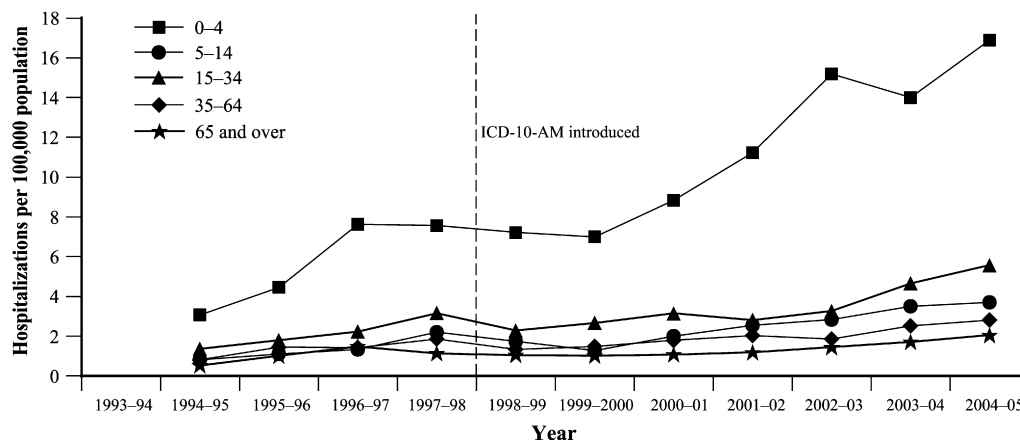


FIG 5. Hospital admissions for anaphylaxis caused by food by broad age group, Australia, 1994-1995 to 2004-2005.

Between 1997 and 2004, male subjects accounted for just over one half of deaths (52%) in which anaphylaxis or angioedema were listed anywhere on the death certificate. Six deaths occurred in children aged 0 to 14 years, 10 deaths occurred in young adults aged 15 to 34 years, 41 deaths occurred in persons aged 35 to 64 years, and 49 deaths occurred among those aged 65 years and older.

The majority of these deaths (62) were associated with anaphylaxis, unspecified but excluding those caused by vaccine or food. Six deaths involved anaphylaxis attributed to an adverse food reaction. Eighteen deaths involved anaphylaxis caused by "adverse effect of correct substance correctly administered," and 23 deaths were partly attributed to angioedema or "giant urticaria." Some deaths had more than one of these conditions listed on the death certificate, and thus these groups are not mutually exclusive.

DISCUSSION

Between 1993-1994 and 2004-2005, we observed increases in hospital admissions for urticaria, angioedema, and anaphylaxis in Australia that were consistent with trends observed in the United Kingdom^{18,19} and in the United States.⁹ We particularly observed a large increase in admissions for angioedema in older adults and a steep increase in admissions for food-related anaphylaxis in children, which are similar to trends reported elsewhere.^{8,19} Among children, rates of admission for these conditions were substantially higher in boys than in girls, which is in keeping with the similar sex difference in the prevalence of atopic conditions in this age group. However, among adults, the sex differential was reversed, with higher rates of admission among women than men for most conditions.

The increase observed in admissions for urticaria, anaphylaxis, and angioedema is in contrast to the trend observed in admissions for asthma. Over a similar time period (1993-1994 to 2003-2004), hospital admissions for

asthma in Australia decreased by 43% among children aged 0 to 14 years and by 17% among those aged 15 years and older.²⁰ There are no nation-wide data on time trends in the prevalence of atopy. However, we have previously shown, in a population-based study of children aged 8 to 11 years living in Belmont, New South Wales, Australia, that the prevalence of atopy, as measured on the basis of skin prick test results, did not change over the period 1992-2002.²¹

The main limitation of this study is that hospital admissions only represent a small proportion of incident cases of these conditions. Patients presenting with episodes of anaphylaxis, angioedema, and urticaria would not be included in our estimations if they resolved spontaneously, if the person died on the way to the hospital, or if he or she was successfully treated elsewhere (eg, at home), by a general practitioner, or in the emergency department. Studies of anaphylaxis cases from one emergency department in Brisbane, Australia, found that 94% of cases in adults²² and 93% of cases in children²³ were managed solely in the emergency department. Similar findings have been reported overseas.²⁴ This implies that hospital admission data include less than 10% of cases of anaphylaxis that are actually presented to the hospital.

Although the use of hospitalization data will represent only a small proportion of incident cases of these allergic diseases, the large increases in admissions observed are likely to reflect either an increase in the incidence of these conditions or an increase in their severity over the study period. It is unlikely that the increase is due to changes in the criteria for admitting persons to the hospital with these conditions. The increase in admissions is also unlikely to be attributable to changes in classification associated with the introduction of ICD-10-AM during the study period. The time trends were gradual over the study period, and there was no sudden change in admission rate for any of the conditions during or after the changeover from ICD-9-CM to ICD-10-AM in 1998.

Our data do not provide any direct evidence about the cause of the increase in admission rates. It seems unlikely

that rapid change over such a short time interval could be explained by changes in recognition or diagnostic labeling. The increase in food-related anaphylaxis in children and non-food-related anaphylaxis and angioedema in older adults suggests that more than one causative factor is involved.

Angiotensin-converting enzyme (ACE) inhibitors and aspirin are 2 pharmacologic agents that can trigger angioedema and, in the case of aspirin, anaphylaxis. ACE inhibitors are now widely used as treatment for hypertension, heart failure, and the prevention of diabetic renal disease. Low-dose aspirin is now widely used for prevention of arterial vascular occlusion, particularly in patients with coronary, cerebral, or peripheral vascular disease. Their use has increased substantially over the study period,²⁵⁻²⁷ and in one study more than 60% of persons admitted to the hospital with angioedema had comorbid conditions that were likely to be treated with ACE inhibitors.⁹ An ecologic study of South Australian public hospitals demonstrated that the large increase in the number of discharges coded as angioedema observed after 1991-1992 coincided with the steep increase in prescriptions for ACE inhibitors.²⁸ The doubling in the rate of admissions for angioedema in those aged 65 years and older in our study supports this finding because persons in this age group would be more likely to be taking medications to control blood pressure, such as ACE inhibitors. Furthermore, data collected on prescription of drugs from a sample of general practitioner encounters across Australia also showed a doubling of prescriptions for the ACE inhibitor ramipril between 2000-2001 to 2004-2005²⁹ and more frequent prescription of perindopril from 2001-2002 to 2005-2006.³⁰

The data used in this study are based on routinely reported hospitalization data and hence reflect the diagnoses reached by the treating clinician. It is possible that some cases diagnosed as urticaria and angioedema had unrecognized features of anaphylaxis, and hence the rates of anaphylaxis might be underestimated. Unfortunately, we have no opportunity to investigate the validity of the final recorded diagnosis. Efforts toward a universally accepted definition of anaphylaxis, including specific clinical criteria for accurate diagnosis, are being pursued by several bodies from the United States, Australia, and Europe.³¹ It is hoped that these criteria will enable the capture of more than 95% of cases of anaphylaxis.

We observed higher rates of admissions for allergic conditions in young boys aged 0 to 14 years and in women aged 15 years and older. Although we were unable to determine the specific food causing the admissions to the hospital, others have shown that peanut and tree nut allergy is more common in boys aged younger than 18 years and in adult women.³² This age-related sex difference is similar to that observed in the prevalence of asthma and in rates of hospital admission for asthma.²⁰ Similar patterns are also seen in the prevalence of hay fever and atopy, although male subjects have higher total IgE concentrations than female subjects across all ages.³³ An English study of emergency admissions for anaphylaxis

showed that female subjects of child-bearing age were at increased risk of anaphylaxis admission (rate ratio, 1.38; 95% CI, 1.27-1.50).¹⁹ Although it is tempting to suggest these differences are attributable to the action of sex steroids, there is little direct evidence to support this assertion.

Our data show that death from anaphylaxis and related conditions is rare. However, it is possible that some deaths caused by anaphylaxis have been incorrectly attributed to asthma.³⁴ This would result in an underestimation of the true death rate caused by anaphylaxis. Although there was an increase in the last 2 years, the numbers are small and not reliable for assessing time trend over such a short period.

Allergic disease, particularly food allergy, is becoming an increasingly important health problem in Australia and many other developed countries. At present, the only way to prevent allergic reactions to foods is to avoid ingesting them. Food allergen avoidance has a significant effect on individuals and families and can cause emotional distress and disruption or avoidance of social interactions. Our Australian data confirm other reports that hospitalization rates for anaphylaxis, urticaria, and angioedema are on the increase. The relation of these changes in hospitalization rates to changes in the prevalence of food and nonfood allergen sensitization in the community remains uncertain and requires further investigation in population studies.

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