Current Allergy & Clinical Immunology

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Sponsorship & Support

Current Allergy & Clinical Immunology is the official journal of the Allergy Society of South Africa and is produced as a service for health care workers to improve understanding and communication in the field of allergy. Publication of the journal is made possible by the generous financial and other support offered by the following pharmaceutical and diagnostic companies.

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AstraZeneca • Boehringer Ingelheim • Cipla Medpro • GlaxoSmithKline • Laboratory Specialities • Miele • MSD • Nestlé • Novartis • Schering-Plough • UCB
It was a great privilege to be asked to edit this first issue of *Current Allergy & Clinical Immunology* for 2006 with allergy testing as the theme.

Allergy testing remains a very controversial area of clinical medicine and we have tried to cover as many important issues as possible. There seem to be two camps of thought: the ‘testers’ who routinely test all patients with symptoms of allergy and the ‘treaters’ who prefer to treat pharmacologically without allergy testing. I have attempted to provide as much evidence base as possible in favour of using validated tests for routine allergy diagnosis and hope that after reading this issue that many of you will be converted to being ‘testers’.

Most importantly, this is the first issue of *Current Allergy & Clinical Immunology* to be CPD accredited. At the end of the journal we have provided a series of CPD questions which can be answered interactively on the ALLSA website at www.allergysa.org. Successful candidates will have CPD points directly credited electronically to the HPCSA.

In this issue Koshak’s original Saudi Arabian study highlights the allergic nature of asthma, the importance of allergy testing and the predictive value of total IgE and Phadiatop in identifying atopic asthma. This theme is continued in my article on cost-effective allergy diagnosing, looking at the combined predictive value of using both Phadiatop and fx5 food allergy screens, and the number of test allergens testing positive. We also explore the impact of the allergen load on clinical symptoms. Potter clearly defines the role of the cellular allergen stimulation test (CAST) in identifying allergens for which we previously had no reliable tests. Lopata discusses the more complex and specialised allergy tests available, as a prelude to his new regular feature on allergy testing which will continue in future issues of this journal. We also include our first ALLSA Position Statement on Skin-Prick Testing which will act as a basis for clinical practice. In contrast, the article on controversial complementary and alternative allergy tests clearly shows that these so-called ‘allergy and intolerance tests’ play no useful role in allergology, and should be avoided as they can only lead to misdiagnoses and delay effective treatment.

We continue our regular clinical features – Clinical Allergy Images edited by Du Toit, Allergies in the Workplace edited by Jeebhay and Todd, Skin Focus by Docrat and ABC of Allergology by Morris – and introduce a new feature, Snippets from Other Journals, compiled by Puterman.

Remember to diarise the forthcoming 2006 ‘All 4 Kids’ ALLSA Congress due to take place in conjunction with SAPA at Sun City in early September 2006.

Finally I would like to thank my brother Dr Hugh Morris, MMed (Path), MRC Path (UK), for his superb practical input into this issue, who recently passed away following a cycling accident.

**Adrian J Morris**

*Guest editor*

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*Current Allergy & Clinical Immunology* has been accredited for CPD points in the Clinical category, so you can now earn 2 CPD points for Individual Learning. CPD accreditation is only available through the online service; no faxed or mailed responses will receive CPD credits. To obtain CPD credits:

1. Read the journal
2. Answer the questionnaire on p.51 by accessing the online CPD accreditation on the ALLSA website at www.allergysa.org/cpd or follow the links from the home page www.allergysa.org.
3. To register, you will need to enter your name, personal details, HPCSA number and a password.
4. Once you have registered, you will receive an email confirming your registration. You can either answer the questionnaire immediately or log on at a later date to answer the questionnaire. Please note that each questionnaire has a closing date – the closing date for submission of the March 2006 questionnaire is 31 May 2006.
5. Follow the instructions given on the questionnaire page and online.
6. After you have submitted your answers, they will be marked immediately, and you will be informed of the results and the number of points earned.
7. At any time you will be able to see your current CPD credits from the journal by logging on.
Do in vitro IgE tests have a role in identifying atopic asthma?

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ABSTRACT
Background: Optimal management of asthma mandates the identification of an IgE-mediated sensitisation to allergen (atopy).
Objective: To explore the role of in vitro IgE tests in the identification of atopic asthma (AA).
Setting: Allergy Clinic, King Abdulaziz University Hospital (KAUH), Jeddah, Saudi Arabia.
Methods: This was a prospective study of 191 adult asthmatics. A positive reaction to common inhalant allergens (sensitisation) using skin-prick tests (SPTs) identified AA versus non-atopic asthma (NAA) patients. Patients also underwent in vitro IgE tests: total serum IgE, and specific multi-allergen IgE test (Phadiatop) using the Immuno-CAP system.
Results: A total of 171 adult asthmatics were included, ranging in age from 12 to 64 years old (mean=32 years ±13 SD; 64% were females). Moderate-persistent or mild-persistent asthma occurred in 59% and 38.3% respectively. Atopy, identified by positive SPTs, was present in 86%. Mean total IgE was higher in AA than in NAA patients: 722 ± 888 SD versus 43 ± 49 SD (df=1, p<0.05). Total IgE was elevated (>190 IU/ml) in 70% of the AA group versus none of the NNA group. A significant linear trend was detected for means of total IgE levels of asthma severity (F=8.2, p<0.01). Phadiatop was positive in 88% of the AA group versus 2% of the NAA; there was a significant correlation between positive SPT and Phadiatop (df=1, p<0.001). Positive Phadiatop had a sensitivity of 88% and specificity of 87.5% in detecting allergen sensitisation.
Conclusion: Sensitisation to common inhalant allergens by SPT or Phadiatop was high in asthmatics at KAUH. Based on sensitivity and specificity, in vitro allergy tests (Phadiatop more than total IgE) can be utilised as complementary tools in the identification of AA. Strategies to modulate allergen sensitisation may improve the care of patients with AA.

INTRODUCTION
Asthma, the commonest recurrent respiratory disease, is characterised by chronic inflammation of the airways, which is frequently aggravated by exposure to inhalant allergens. These can activate an IgE-antibody-mediated allergic reaction (type 1 hypersensitivity or atopy). Recent asthma guidelines have made advances in clinical and laboratory assessment, management, and prevention of asthma. In conjunction with the clinical evaluation, optimal assessment of asthma includes recommendations for allergy testing to identify allergen sensitisation, particularly in uncontrolled asthma.

The skin-prick test (SPT) is considered the golden standard in the identification of allergen sensitisation and can help in establishing the diagnosis of atopic asthma (AA) versus non-atopic asthma (NAA). Unfortunately, although SPT is the most accurate, sensitive and cost-effective technique in the identification of allergen sensitisation, it needs a specialised medical care set-up (e.g., allergy clinic). When such a facility is not available, in vitro allergy testing may be an alternative to SPT in the identification of allergen sensitisation and AA.

An increase in the total serum IgE has been documented in approximately two-thirds of adults with asthma. Although measuring total IgE is not recommended routinely, increased levels support the diagnosis of asthma rather than other respiratory illnesses, and suggest the possible role of an allergen-induced immunological reaction.

Specific multi-allergen in vitro tests of IgE antibodies to a mixture of common inhalant allergens have been developed to screen patients with atopic illnesses. Further identification of sensitisation to each calibrated allergen requires a more explicit allergy work-up, such as SPT or specific IgE antibodies to each allergen. The increased awareness of asthma in the Arabian peninsula and the availability of advanced laboratory techniques stimulated research of the possible role of allergy testing in the assessment of asthma. Among health care providers, there is an underestimation of the role of in vitro allergy tests in the identification of allergen sensitisation and in differentiating between AA and NAA. Hence, the purpose of this study was to explore the characteristics of in vitro IgE tests in the identification of AA at King Abdulaziz University Hospital (KAUH).

METHODS
Subjects
This was a prospective cross-sectional study of 191 chronic asthmatics, older than 12 years old. Subjects with the diagnosis of bronchial asthma based on history and physical examination were sequentially selected from patients visiting the allergy outpatient clinic at KAUH. The clinical assessment of asthma severity was conducted according to asthma guidelines. Subjects were classified in terms of asthma severity into four groups: mild intermittent, mild persistent, moderate persistent, and severe persistent. Patients with other medical illnesses identified by history or physical examination or those on any chronic oral medication were excluded. Verbal consent was obtained by explaining the study purpose to the candidates. This study was carried out during the period January 1997 to April 2000.

In vivo allergy tests
The diagnosis of AA was identified by the presence of a positive reaction to one or more common inhalant allergens using the in vivo standard SPT on the patient’s forearm. The allergen extracts were obtained from Greer Laboratories, United States of America.

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The inhalant allergen panel included: tree pollen: Acacia, Atriplex canescens, Cupressus arizonica, Eucalyptus globulus, Prosopis juliflora; weed pollen: Artemisia tridentata, Amaranthus hybridus, Ambrosia trifida, Chenopodium album, Plantago lanceolata, Salsola; grass pollen: Cynodon dactylon, Phelum pratense; moulds: Alternaria alternata, Aspergillus mix, Candida albicans, Cladosporium herbarum, Fusarium moniliforme, Penicillium notatum, Rhizopus nigricans; cat hair; mixed feathers (chicken, duck, goose); house-dust mites (HDMs): Dermatophagoides pteronyssinus (Dp), Dermatophagoides farinae (Df), cockroach mix (Periplaneta americanaus, Blatella germanica).

A positive SPT was any reaction showing ≥3 mm wheal with erythema to one or more allergens. A solution of 0.1% histamine solution was used as a positive control, and a wheal size reaction of ≥5 mm was considered adequate. Antihistamines or other drugs that might inhibit the SPT were stopped for the appropriate duration in relation to the effect of each medication.

**In vitro allergy tests**

Venous blood samples were drawn for measurement of the total serum IgE level and specific multi-allergen IgE antibodies. The original method for obtaining an IgE count, the radio-allergosorbent test (RAST), has evolved from a radio-immunoassay to a test that involves enzymatic or fluorometric processes. Total serum IgE, and specific IgE antibodies to common inhalant allergens were measured by the radio-immunoassay fluorescent CAP system, Phadiatop (Phadia, Sweden) which is available in the clinical immunology laboratory at KAUP. The normal range of total serum IgE is 10-190 IU/ml serum; an elevated IgE >190 kU/l. The Phadiatop test is a multi-allergen in vitro test that contains a mixture of several allergens bound in the matrix to detect the most common specific IgE types present in serum. It is reported as either a positive or negative result for a statistically significant level of specific IgE, but does not detect the presence of a particular specific IgE type. Additionally, in order to explore the correlation between SPT and in vitro specific IgE antibodies, the Phadiatop test was also performed on rinitis cases with negative SPT.

**Data analysis**

Frequency tables, correlation analyses by chi-square test, and test of linearity by ANOVA were carried out using an SPSS statistical program (Version 12).

**RESULTS**

Twenty asthmatics were excluded from the study because of incomplete data; 171 cases fulfilling the clinical diagnosis of asthma completed the study. Their ages ranged from 12 to 64 years (mean = 32 ±13 SD); 110 (64.3%) were female. Levels of clinical severity were moderate persistent in 86 asthmatics (50.3%) followed by mild persistent in 65 asthmatics (38%) (Fig. 1). AA identified by positive SPT (sensitisation) was detected in 147 asthmatics (86%).

The different characteristics of in vitro allergy tests among all asthmatics are demonstrated in Table I. Using the ANOVA test, a significant difference was detected between the mean total IgE among AA versus NAA (df=1, p<0.05). Total serum IgE was elevated (>190 IU/ml) in 102 of AA cases (69.4%), and none in NAA. Additionally, using the ANOVA test, a significant linear trend was detected between means of total serum IgE and each group of asthma severity (F=8.2, p=0.003) (Fig. 2).

**DISCUSSION**

Although a remarkable scientific effort has been invested to improve understanding of the pathophysiology, diagnosis and treatment of asthma, less effort has been given to the clinical utilisation of laboratory tests. A presumptive diagnosis of asthma based on clinical assessment and empirical management with beta-agonist (bronchodilators) and/or inhaled corticosteroids is a reasonable and effective approach in many patients. However, in patients with significant symptoms that are not controlled with these standard measures, specific allergy testing may be warranted to establish the correct diagnosis of AA and identify the offending allergens.
SPT was positive in 85% of the adult asthmatic cases tested in the allergy clinic at KAUH, which is higher than the range (29%–77%) in internationally reported asthma population studies. SPT reports from other cities in Saudi Arabia showed positive reactions in more than half the patients with a history of respiratory allergy and asthma. The higher rates of sensitisation to inhalant allergens at KAUH needs future exploration, especially when avoidance and anti-inflammatory medications at KAUH. Based on sensitivity and specificity, the Phadiatop test can be used as an alternative and specific in differentiating individuals who are sensitised to common inhalant allergens from those who are not. The in vitro multi-allergen IgE test is recommended as an aid in diagnostic and referral decisions, and in mass-screening programmes for patients suspected of having an inhaled allergic diathesis. A positive Phadiatop test requires further investigations in order to explore each possible offending specific allergen by either SPT or antigen-specific IgE antibodies test. In vitro specific IgE antibodies to inhalant allergens are not affected by skin reactivity or medications, have no risk of systemic reaction, are less traumatic and better tolerated. However, in vitro testing is less sensitive than SPT; the results are not available immediately, and it becomes more costly when a large panel of allergens is tested. A positive Phadiatop test in the face of a negative SPT can be due to exposure to hidden or unknown inhalant allergens, intake of medication that might have interfered with SPT reactivity, and weak reactions to SPT (erythema only or a wheal <3 mm) that require the use of more sensitive tools like the intradermal skin test.

In Table I, the characteristics of in vitro allergy tests in atopic asthma versus non-atopic asthma are summarised. There was a significant correlation between higher total IgE level and in vivo SPT results, which is compatible with the literature. The Phadiatop test has been shown to be highly sensitive and specific in differentiating individuals who are sensitised to common inhalant allergens from those who are not. The in vitro multi-allergen IgE test is recommended as an aid in diagnostic and referral decisions, and in mass-screening programmes for patients suspected of having an inhaled allergic diathesis.

### Table I. Characteristics of in vitro allergy tests in atopic asthma versus non-atopic asthma

<table>
<thead>
<tr>
<th>Character</th>
<th>All asthma cases</th>
<th>Atopic asthma (AA)</th>
<th>Non-atopic asthma (NAA)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total number</td>
<td>Positive SPT</td>
<td>Negative SPT</td>
</tr>
<tr>
<td>Age range (years)</td>
<td>(Mean ±SD)</td>
<td>(Mean ±SD)</td>
<td>(Mean ±SD)</td>
</tr>
<tr>
<td>Female</td>
<td>108 (63%)</td>
<td>93 (64%)</td>
<td>15 (63%)</td>
</tr>
<tr>
<td>Range of total IgE (IU/ml)</td>
<td>0 - 5000</td>
<td>0 - 5000</td>
<td>0 - 162</td>
</tr>
<tr>
<td>Mean ±SD Total IgE</td>
<td>650 ± 88SD</td>
<td>722 ± 888SD</td>
<td>43 ± 49SD</td>
</tr>
<tr>
<td>Normal IgE</td>
<td>69 (40%)</td>
<td>45 (31%)</td>
<td>24 (100%)</td>
</tr>
<tr>
<td>Elevated IgE</td>
<td>102 (60%)</td>
<td>102 (69%)</td>
<td>0</td>
</tr>
<tr>
<td>Negative Phadiatop</td>
<td>38 (22%)</td>
<td>17 (12%)</td>
<td>21 (88%)</td>
</tr>
<tr>
<td>Positive Phadiatop</td>
<td>133 (78%)</td>
<td>130* (88%)</td>
<td>3 (2%)</td>
</tr>
</tbody>
</table>

* df=1, p<0.05 Significant in AA versus NAA
** df=1, p<0.001 Significant in AA versus NAA

In conclusion, the prevalence of allergic sensitisation to inhaled allergens, intake of medication that might have interfered with SPT reactivity, and weak reactions to SPT (erythema only or a wheal <3 mm) that require the use of more sensitive tools like the intradermal skin test. A positive SPT or in vitro IgE test suggests mainly sensitisation to the tested allergen, which may or may not have any clinical correlation. Occasionally, in order to confirm the clinical impact of an allergen in exacerbating asthma symptoms, further in vivo allergy testing, such as bronchoprovocation with the suspected allergen, may be conducted. Once a clinically relevant allergen is identified, applying targeted avoidance strategies can lead to better symptom control and should be an integral part of management and prevention plans of asthma. Furthermore, specific allergy testing provides guidance about which allergens to include in allergen immunotherapy, which is a therapeutic option in AA especially when SPT reactivity, and weak reactions to SPT (erythema only or a wheal <3 mm) that require the use of more sensitive tools like the intradermal skin test. A positive SPT or in vitro IgE test suggests mainly sensitisation to the tested allergen, which may or may not have any clinical correlation. Occasionally, in order to confirm the clinical impact of an allergen in exacerbating asthma symptoms, further in vivo allergy testing, such as bronchoprovocation with the suspected allergen, may be conducted. Once a clinically relevant allergen is identified, applying targeted avoidance strategies can lead to better symptom control and should be an integral part of management and prevention plans of asthma. Furthermore, specific allergy testing provides guidance about which allergens to include in allergen immunotherapy, which is a therapeutic option in AA especially when SPT reactivity, and weak reactions to SPT (erythema only or a wheal <3 mm) that require the use of more sensitive tools like the intradermal skin test.

In conclusion, the prevalence of allergic sensitisation to common inhalant allergens using either SPT or multi-allergen IgE antibodies was a common feature in asthmatics at KAUH. Based on sensitivity and specificity, in vitro IgE tests (multi-allergen IgE antibodies more than elevated total IgE) can be utilised as a complementary allergy test to in vivo SPT in the search for allergen sensitisation in patients with asthma. The higher the total serum IgE, the more likely the presence of atopy. Additionally, the Phadiatop test can be used as an alternative allergy test in helping to identify patients with AA, particularly when SPT is not readily available. Strategies directed to modulate allergen sensitisation, as identified by appropriate allergy tests, may improve the care of patients with AA.
Declaration of conflict of interest
The author has no conflict of interest.

REFERENCES

NEWS
ALLSA JOURNAL CLUB PRESENTATIONS GET A BOOST
Prof Cas Motala receiving a laptop computer from Mr Grant Taylor of Boehringer Ingelheim. This generous donation of a computer to ALLSA will enable the presenters of Journal Club talks to enhance their presentations. For details of the Journal Club programme for 2006, contact ALLSA office 021-447-9019.
The GlaxoSmithKline Research Fund has been made available to The Allergy Society of South Africa by GlaxoSmithKline for the purpose of promoting research in the field of asthma and allergic rhinitis.

Each Research Grant will be a maximum of R50 000

The GlaxoSmithKline Research Grant is tenable at any recognised local University or research institution approved by the Selection Committee.

Medical Graduates of Southern African medical schools or graduates who have been domiciled in South Africa for a minimum of three years, who are registered with the Health Professions Council and are members of the Allergy Society of South Africa will be eligible to apply for the GlaxoSmithKline Research Grants.

Applications will be considered for research projects relating to asthma and allergic rhinitis, whether basic or applied; however conventional drug trials will not be acceptable.

Closing date for application
31 May 2006

Application details can be obtained from the ALLSA office
Please visit the ALLSA website at www.allergysa.org/awards to submit your electronic application

Please note that only electronic submissions will be processed

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IS ALLERGY TESTING COST-EFFECTIVE?

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ABSTRACT
This article reviews the evidence for and against specific IgE testing in allergy management prior to pharmacotherapy (‘testers’ versus ‘treaters’). While the value of combining results of both Phadiatop inhalant and fx5 food allergy screening may improve our ability to predict clinical allergic asthma, rhinitis and eczema, evidence suggests that the cumulative load of environmental allergens to which an individual is sensitised may help to determine when allergen tolerance or clinical allergic diseases such as asthma and rhinitis are likely to occur.

‘TESTERS’ VERSUS ‘TREATERS’
Medical opinions are divided between the ‘testers’ who investigate before therapy is instituted and ‘treaters’ who do not investigate to save costs. The ‘treaters’ have suggested that allergy testing is not always necessary in patients with allergy symptoms and prefer to treat with pharmacotherapy without identification of specific triggers. An example of this is a recent editorial in this journal in which Laloo expressed the view that specific IgE testing is overused and most diagnoses and therapeutic decisions are not influenced by this test. The controversy is whether specific allergy testing is an essential diagnostic resource or an unnecessary expense.

‘Testers’ will argue that it is incorrect to blindly engage in various pharmacotherapies and that these trials of therapy will outweigh the initial cost of allergy diagnostic testing. ‘Testers’ will argue further that treatment can then be more focused and this could include specific allergen avoidance, appropriate pharmacotherapy and occasionally desensitisation immunotherapy. This is supported by rhinologists who will stress that even in mild to moderate hay fever it is essential to identify specific seasonal triggers in order to plan prophylactic treatment each year. Atopic patients endure mite and pet exposure which triggers their persistent symptoms of asthma, rhinitis and eczema, and targeted lifestyle changes can lead to a significant improvement in symptoms. A recent general practice study conducted in The Netherlands revealed that asthmatic patients were highly unlikely to be told whether their asthma was allergic or non-allergic suggesting that no diagnostic testing was done. In fact very few persistent asthmatics ever see an allergist or have allergen skin-prick testing done, despite half of all asthma sufferers being sensitised to house dust mites. Nasser points out that allergic sensitisation is central to the underlying mechanisms of atopic asthma judging from the success of anti-IgE therapy (Xolair) in patients with severe persistent asthma.

Although theoretically only a controlled allergen challenge can confirm the causal relationship between allergen exposure and clinically relevant allergic symptoms, in routine day-to-day allergy practice, it is common to use a positive skin-prick test or the presence of serum specific IgE antibodies to relevant environmental allergens plus a suggestive clinical history as proof of allergy-induced disease. Moreover, the higher the level of specific IgE antibodies present, the stronger the association with clinical allergic disease. According to the European Academy for Allergology and Clinical Immunology (EAACI), it is essential to establish an early diagnosis of allergy in young children with precise identification of the offending allergens. In addition, there may be merit in periodically quantifying the levels of specific IgE so as to reassess clinical reactivity and perhaps detect development of allergen tolerance.

Symptoms do not always mean allergy
The real value to patients of having a ‘tester’ as opposed to a ‘treater’ as their medical advisor lies in the following data. In infants with atopic dermatitis approximately one-third will have a specific food allergy as an eczema trigger, while at 4 years of age, 43% of children with eczema will have developed allergies to house-dust mites (Fig. 1), grass pollen and cats. Asthma that commences in early life is often atopic and associated with IgE sensitisation to common foods (particularly egg) and inhalant allergens (predominantly house-dust mite and pet).

However, not all early wheezing is associated with allergy and only about one-third of infants with virus-induced wheeze are allergic. The majority (70%) of young children with wheeze will in fact be symptom-free by school age. Here negative results to allergy testing are helpful in determining those children unlikely to develop asthma and in reassuring their parents of this low risk. The converse is true in older children; about two-thirds will have a specific allergy as a cause for their persistent wheezing or cough. Non-allergic causes of asthma-like symptoms in children should be considered and these include gastro-oesophageal...
reflux disease (GORD), infective rhinosinusitis, vocal cord dysfunction and the highly prevalent ‘crèche syndrome’ with its troublesome post-viral cough.

**Allergy testing helps predict the ‘allergic march’**

It is common for children to progress over time from one allergic manifestation to another in a predictable manner. The path of the ‘allergic march’ begins with food-related allergies and eczema in infancy and progresses to predominant inhalant allergens with wheezing, asthma and rhinitis in the middle childhood years. Symptoms of asthma often settle by adolescence but tend to recur again in middle age. Food-allergic children may show declining levels of food specific IgE and subsequently develop tolerance to many foods by about the age of 5 years, particularly if their food specific IgE antibody levels were initially low.

Concomitant factors that promote the ‘allergic march’ in children include a combination of:

- Less early exposure to infectious diseases (a cornerstone of the ‘hygiene hypothesis’)
- Prolonged indoor environmental exposure
- Adopting a sedentary lifestyle.

Platts-Mills’ feels that the current predisposition to minimal outdoor physical activity during childhood (with TV, computer games and fear of crime) leads to obesity which is strongly associated with the development of asthma. The value of seeing a ‘tester’ is that the information from investigations will help predict which patients with this type of lifestyle are at risk of developing allergic diseases.

**Allergy testing is now recommended from infancy**

All patients with severe, persistent or recurrent allergy-like symptoms and those with a need for ongoing ‘prevention’ treatment should be tested for specific allergies irrespective of their age. Children may be allergy tested from 4 months of age or even younger, particularly if food allergies are suspected to cow’s milk, hen’s egg, and peanut allergens. There is no longer a lower age limit for performing skin-prick tests or specific IgE antibody estimation. Specific IgE is produced by the fetus during the last trimester of pregnancy and is well established in the neonatal period. The lower age limit of 3 years for allergy testing which was incorrectly promoted in the medical literature was without any evidence base.

Young children may present with many allergic signs and symptoms such as eczema, rhinitis, asthma and food allergy and it is imperative to identify specific trigger allergens as early as possible. Individuals with insect venom allergy, latex allergy and oral allergic symptoms as a result of cross-reactivity between pollens and fruits will also benefit from confirmation of their specific IgE-mediated allergic hypersensitivity.

Studies show that elevated specific IgE antibodies to allergens such as hen’s egg and cow’s milk in infancy can predict sensitisation to inhalant allergens and the development of allergic asthma by 7 to 10 years of age. However it is imperative that any allergy testing should be preceded by a comprehensive allergy history to guide the practitioner in identifying the trigger allergens. Tests that measure specific antibodies should be chosen on the basis of local and seasonal allergen knowledge and should focus on those local allergens that are statistically more likely to cause symptoms.

The extent of each allergy test profile will depend on the individual’s age, geographic region, positive family allergy history and the character of their symptoms. Allergy testing should help identify infants at risk for the development of subsequent allergic diseases and also guide specific treatments such as secondary allergen avoidance, effective pharmacotherapy and specific allergen immunotherapy.

**ALLERGY TESTING AND ITS PREDICTIVE VALUE**

**Which allergy test?**

Allergy testing using the allergen skin-prick method with commercial allergens is simple and relatively inexpensive. However, allergens need to be carefully stored; have a limited shelf-life and testing needs to be conducted by a practitioner experienced in interpreting the wheal and flare reactions. Serum specific IgE antibody testing is arguably more cost-effective at the initial assessment of the allergic patient who presents with persistent respiratory, dermatological and food-related symptoms.

The ImmunoCAP® or CAP RAST multi-channel analysing system (Fig. 2) is now widely accessible via pathology laboratories throughout Southern Africa. These tests have replaced the earlier RASTs (radio-allergo sorbent tests) which utilised a radio-label to measure specific IgE to various inhalant and food allergens in the patient’s serum. The ImmunoCAP is highly reliable for identifying typical IgE-mediated allergy when accurate skin-prick testing (SPT) is not readily available. A number of ImmunoCAP screening panels have been developed for local inhalant allergens such as house-dust mites, pet danders, local pollens and mould spores, and also for common offending food allergens. Both SPT and ImmunoCAP RAST have good positive predictive values (can identify those with a specific allergy) and negative predictive values (can identify those with no allergy). One should not forget the value of a negative allergy test, which can liberate the anxious patient and the parent from unnecessary house-dust mite or pet avoidance practices and dietary manipulation.

**Accurately predicting the probability of an allergic disease**

Elevated total serum IgE is a non-specific phenomenon and is of minimal value in identifying a specific allergy. Total IgE normally increases with age from infancy to plateau in the teenage years and may be non-specifically raised with extensive eczema. Furthermore, a
normal total IgE (less than 100kU/l in adults) does not rule out specific allergy but makes it less likely, especially if the level is below 10kU/l.

While the higher the level of serum specific IgE antibodies, the stronger the likelihood of clinical allergic disease, the clinical relevance of specific IgE values less than 3.5kU/l (RAST grade 2) is of limited value. These slightly raised levels of specific IgE to common food and inhalant allergens are common, especially in early childhood and may have no clinical significance.

Blood testing using the Phadiatop (Phadia) is an excellent baseline inhalant allergen screen if no particular allergen is initially suspected. This screen in South Africa includes allergens such as house-dust mite (*Dermatophagoides pteronyssinus*), cat dander, dog dander, horse hair, tree pollen (silver birch), grass pollen (Bermuda and timothy), mould spores (cladosporium) and weed pollen (mugwort).

The fx5 paediatric food allergen screening panel (Phadia) includes cow’s milk, hen’s egg, wheat flour, soy protein, cod fish and peanut. These six food allergens account for over 90% of relevant paediatric food-allergy-related problems.

Wickman et al. in the Scandinavian BAMSE birth-cohort study demonstrated that the presence of IgE antibodies greater than 3.5 kU/l for both Phadiatop and fx5 measured in combination in 4-year-old children could indicate a 97.4% predictive likelihood of a suspected allergic disease (asthma, rhinitis, eczema or food allergy) (Fig. 3). In the same study, the presence of IgE antibodies greater than 3.5 kU/l to either Phadiatop or to fx5 used as a single test was less efficient in predicting any allergic disease (71%). Custovic et al. in the Manchester Asthma and Allergy Study found a similar predictable value for asthma development if a summation of house-dust mite and cat allergen specific IgE levels was utilised and not merely the identification of antibodies.

Wickman et al. then looked at sensitisation to 14 individual allergens contained in the screens including Phadiatop inhalants (*D. pteronyssinus*, cat, dog, horse, silver birch, timothy, cladosporium and mugwort) and fx5 foods (cow’s milk, egg white, wheat, soy protein, codfish and peanut). They noted that if the sum of allergen specific IgE antibody levels to their selected profile of 14 allergens was greater than 34 kU/l or more than 4 of the 14 allergens tested were positive, then this indicated a 75% or greater probability of an allergic disease being present or developing (Figs 4 & 5).13

Thus testing a certain profile of airborne and food allergens and utilising the sum of IgE antibody levels in combination with the number of allergens that elicit a positive test result may represent a more efficient diagnostic tool than using individual positive IgE antibody results only.

Sampson et al. looked at individual food allergens in an attempt to quantify specific IgE cut-off points for allergy diagnosis in children in the USA (Table I). They have produced data on specific IgE levels for cow’s milk, hen’s egg, cod fish and peanut, above which food allergy has a 95% probability.

**IMPACT OF THE ALLERGEN ‘LOAD’**

Some patients may be sensitised to an allergen on testing but paradoxically remain asymptomatic, suggesting the involvement of both tolerance mechanisms and a threshold above which clinical disease will manifest. Others, at modest levels of pollen exposure, will experience upper respiratory, ocular and nasal symptoms only, but at higher ambient pollen levels will in addition experience lower respiratory symptoms with wheeze and develop asthma.

Furthermore, patients may be asymptomatic on exposure to a specific allergen, but become symptomatic when concurrently exposed to additional allergens to which they are sensitised. Thus several different aller-

![Fig. 3. Probability of development of at least one of four allergic diseases (asthma, eczema, allergic rhinitis and food allergy)](image)

![Fig. 4. Probability of allergic disease based on sum of allergen specific IgE levels.](image)

![Fig. 5. Probability of allergic disease based on number of positive allergen tests.](image)
Allergens (the allergen load [Fig. 6]) may act synergistically to exceed an individual’s reaction threshold. But if the allergen load is reduced through avoidance of one or more of the allergens (to which they are sensitised), they may experience fewer symptoms and a reduced need for pharmacotherapy.

To further illustrate this point, consider an individual sensitised to both cat and grass pollen, who may have no symptoms on cat exposure in winter, but in summer with the higher pollen load displays troublesome symptoms. To further illustrate this point, consider an individual sensitised to both cat and grass pollen, who may have no symptoms on cat exposure in winter, but in summer with the higher pollen load displays troublesome symptoms.

The clinical course of asthma is usually characterised by periods of symptom-control and is then interrupted by unexplained asthma exacerbations. Using knowledge of local ‘allergen load’ may help us predict these exacerbations and any sudden deterioration in asthma.

It is therefore fundamentally important to test and identify the exact nature of allergens to which the individual has allergic sensitisation, so that planning and allergen avoidance can be implemented to reduce the allergen load and improve overall rhinitis, asthma and even eczema management.

**Declaration of conflict of interest**

The author has no conflict of interest.

**Practice points**

- Children with persisting/recurrent/severe allergy symptoms should all be allergy tested.
- Many infant wheezers do not have allergies or asthma and will outgrow their symptoms.
- A negative allergy test will liberate the individual and their caregivers from unnecessary avoidance measures.
- Infants tend to develop transient food allergies while older children develop persistent inhalant allergies.
- In sensitised individuals, the cumulative sum of the allergen ‘load’ will determine when symptoms occur.
- The more allergens that test positive and the greater the sum of specific IgE antibodies present, the greater the probability of an allergic disease being present.
- In children, specific food allergies can now be predicted using cut-off points for specific IgE, thus reducing the need for food challenge testing.

**Table I. Food specific IgE concentrations (RAST) predictive of clinical reactions**

<table>
<thead>
<tr>
<th>Food allergen</th>
<th>Decision point (kU/l)</th>
<th>Positive predictive value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cow’s milk</td>
<td>• &lt; 2 years 5</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>• &gt; 2 years 15</td>
<td>95</td>
</tr>
<tr>
<td>Hen’s egg</td>
<td>• &lt; 2 years 2</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>• &gt; 2 years 7</td>
<td>98</td>
</tr>
<tr>
<td>Peanut</td>
<td>14</td>
<td>100</td>
</tr>
<tr>
<td>Tree nut</td>
<td>−15</td>
<td>−95</td>
</tr>
<tr>
<td>Fish</td>
<td>20</td>
<td>100</td>
</tr>
<tr>
<td>Wheat</td>
<td>26</td>
<td>74</td>
</tr>
<tr>
<td>Soya</td>
<td>30</td>
<td>73</td>
</tr>
</tbody>
</table>

Reproduced from: Sampson et al.\(1^6\)

**Fig. 6. Allergen load.**

**REFERENCES**

ADDITIONAL TESTS

Non-IgE-mediated reactions to foods and drugs account for the majority of adverse reactions encountered in clinical practice. Until recently sensitivity to many environmental agents could only be confirmed by challenge tests, which are usually tedious and in some instances could be dangerous. The cellular antigen stimulation test (CAST) is useful for detecting non-IgE-mediated sensitivity to food additives, preservatives and drugs. It can also confirm IgE-mediated sensitivity, but in general, specific IgE tests, such as skin-prick tests and the CAP RASTs are more efficient in this regard.

Cut-off values for the CAST for sulphites have been confirmed by double-blind placebo-controlled food challenges in the Allergy Diagnostic and Clinical Research Unit at the University of Cape Town. If selected by careful history taking CASTs can be a cost-effective diagnostic clinical tool.

Adverse reactions to food additives are occurring with increasing frequency in recent times, often manifesting as isolated episodes of angioedema and broncho-spasm, but also as triggers of exacerbations in patients with chronic urticaria.

It is usually by careful history taking and keeping a diary of exposure in relation to clinical exacerbation that a dietary ingestant is identified as the possible culprit for the adverse reaction. Until recently, there was no laboratory test available to evaluate clinical sensitivity to non-IgE-mediated triggers of adverse reactions not only to food additives, but also to drugs, occupational antigens and substances in certain foods.

Allergy diagnostic tests based on the in vitro reaction of blood basophils to allergens have been of research interest for many years. However the basophil histamine release assay, although sensitive and practical, is a tedious one and has been difficult to standardise. In recent years, however, the CAST-ELISA (Bühlmann Laboratories, Switzerland) has gained acceptance as an important test in the allergy diagnostic arena, if properly selected and interpreted. This article focuses on the principles of the cellular antigen stimulation test (CAST), the selection of patients and interpretation of the results.

**PRINCIPLE OF THE CAST**

The CAST depends on the exposure of interleukin 3 (IL-3) primed fresh basophils to different concentrations of an allergen, drug or chemical. Basophils which are sensitive to such exposure release sulphido leukotrienes into the media. These released leukotrienes are measured by an ELISA test: the CAST thus measures both IgE- and non-IgE-mediated leukotriene release in the ELISA.

Cut-off values for non-specific leukotriene release have been determined by exposing (±20) healthy (non-allergic and non-sensitive) adult individuals to the agents, determining background release in this way. Patients who are clinically sensitive have leukotriene levels above the normal controls.

**THE FLOW CAST**

With developments in flow cytometry it is possible to measure upregulation of membrane markers of basophil activation (GP53 alias CD63) when basophils are exposed to allergens, drugs or other ‘chemicals’. This has resulted in the development of a flow-cytometric allergen stimulation test (FAST) now available as the Flow-CAST (Bühlmann Laboratories) or BASO Test (Becton-Dickinson).

The FAST may be used either utilising whole blood, or with leukocytes isolated by buffy coat centrifugation on sedimentation over dextran. The use of whole blood in this assay has the advantage of simpler manipulations (fewer centrifugation steps) but has lesser basophil recovery, interference with serum components, high activation in controls and interference by aggregated platelets also carrying CD63 markers and measured by FACS counting.

Although the flow CAST is a sophisticated technique for measuring basophil activation upon allergen/chemical stimulation it requires expensive equipment (FACS machine) and highly trained laboratory technologists.

Thus the CAST ELISA has gained more widespread acceptance as a practically useful diagnostic tool, although the CAST ELISA is a highly specialised test to establish and maintain in the clinical laboratory. Some laboratories in Europe combine the CAST with the flow CAST in a single stimulation assay (CAST COMBI) to enhance sensitivity to the assay in evaluation of drug allergies.

**THE CAST ASSAY**

There are three procedural parts to the CAST assay.

**Isolation of leukocytes**

Dextran is added to the patient’s blood in order to increase blood viscosity at 18-28°C for 90 minutes after which the erythrocytes are sedimented. The supernatant containing the leukocytes is then transferred and subjected to a brief centrifugation to remove the thrombocytes and the pellet suspended in stimulation buffer containing IL-3.

**Cell stimulation**

Cells are stimulated for 40 minutes at 37°C with an anti-IgE receptor antibody (stimulation control) or with no antibody (background) or ‘allergen’ in different concentrations. The supernatant is frozen or tested immediately for serum leukotriene (sLT) concentration in an ELISA.

**Leukotriene determination**

The ELISA is performed using precoated microtitre plates. Sixteen wells per assay are used for the stan-
INTERPRETATION OF RESULTS OF THE ASSAY

For food and inhalation allergens, insect allergens and latex, Bühlmann have proposed that individuals with a net sLT stimulation yield higher than 200 pg/ml should be regarded as positive for the allergen tested.

Owing to the small increases of sLT with drug allergens, chemical allergens and food additives, Bühlmann have established an individual technical cut-off value for each allergen. These values represent the mean +3 standard deviations from up to 20 stimulated samples from normal blood donors.

The technical cut-off values are listed in Table I. Note that these are all above 40 pg/ml. It is important to understand that positive and negative predictive values for true clinical sensitivity for values above the technical cut-off values have not yet been determined. Thus the results of the CAST need to be carefully evaluated.

The results of the CAST need to be carefully evaluated in relation to the clinical context of exposure in relation to reaction when found to be above or close to the technical cut-off value, to interpret the clinical significance of the result.

VALIDATION OF THE CLINICAL USEFULNESS OF THE CAST

In view of the uncertainties surrounding the significance of a previous cut-off value of 200 pg/ml for the sulphite CAST, our department undertook an evaluation of the CAST in a cohort of 20 patients who had suspected sensitivity to sulphites, comparing the result of the CAST with the result of a double-blind placebo-controlled food challenge (DBPCFC) in each of the subjects.

Patients eliminated sulphites 48 hours prior to the challenge and then received 1, 5, 10, 15, 25, 50, 75, 100, 150 and 200 mg potassium metabisulphite diluted in preservative-free apple juice (30 ml) for each challenge. They received either a placebo or a sulphite challenge (24 hours apart). Sulphites were ingested at 10-minute intervals and vital signs (PEFR, pulse, BP and clinical symptoms) were monitored.

For this study, the significance of values specifically below 200 pg/ml (negative CASTs) which were obtained in 20 adult subjects previously clinically considered to be ‘sulphite sensitive’ (but not confirmed by the previous cut-off value) were studied.

Ten of 14 patients with ‘negative CASTs’ (below 200 pg/ml) had a positive challenge, while 6 patients with previous values above 200 pg/ml were also studied and 5 of these had a positive challenge.

Our laboratory found that sLT values above 40 pg/ml correlate extremely well with positive challenges to sulphites (83% overall). However, there are indeed subjects who are sensitive to sulphites whose basophils do release lesser amounts of sLT on stimulation with sulphites in vitro. Fine tuning of the concentrations used in the assays or priming of the cells may improve this in the future.

RECOMMENDATIONS FOR USE OF THE CAST IN CLINICAL PRACTICE

1. The CAST is recommended as a useful test in the evaluation of non-IgE-mediated ‘sensitivities’ in clinical practice.

2. Although the CAST also reliably measures IgE-mediated sensitivities to inhalants, foods, insects and occupational allergens, the CAST is a more expensive test and not more sensitive than the CAP RAST for this indication. It is not recommended as a first-line test for IgE-mediated sensitivities in the South African context.

3. The CAST is most useful in the clinical evaluation of food additive and preservative sensitivity (e.g. sulphites, sodium benzoates and food colourants). The cut-off value for sulphite sensitivity (40 pg/ml) has been validated using DBPCFC at the Allergy Diagnostic and Clinical Research Unit of the University of Cape Town Lung Institute. For other additives the Bühlmann technical cut-off values should be interpreted in the clinical context.

4. In view of the poor sensitivity of specific IgE testing for drug allergy and non-steroidal anti-inflammatory drug sensitivity, the CAST ELISA or flow CAST may have a specific investigative application in this context. Studies by Sanz et al. showed that combining the FAST with the CAST improved the sensitivity of the CAST, confirming sensitivity in 47% of cases who had positive skin tests to benzylpenicillin and amoxicillin and confirmed the specificity in 93% of patients who had negative skin tests and tolerated beta-lactams.

5. It has been suggested that the CAST may be useful in evaluating patients with clinical latex sensitivity who are skin test and RAST negative and the Allergy Diagnostic and Clinical Research Unit (ADCRU) is currently investigating this in a cohort of latex-sensitive health care workers.

6. A possible future application of the CAST is to measure the response of patients undergoing allergen immunotherapy. Preliminary data indicate that patients’ basophils lose their sensitivity to allergen stimulation fairly early during allergen immunotherapy so this test may serve to identify responders and non-responders. This idea needs to be evaluated in prospective studies in the future.

REQUESTING A CAST

A limited number of laboratories conduct the CAST in South Africa. On selecting a CAST, a full history of specific exposure in relation to clinical symptoms should be provided to the laboratory in order to select the most likely ‘allergen’ in a cost-effective way.

A fresh sample of EDTA blood is required (2 x 4 ml specimens) and this should reach the laboratory in the morning on which the test is to be conducted, preferably within 3 hours of taking the blood sample. Patients should be off antihistamines and antileukotrienes for 48 hours prior to the test. It is also preferable to investigate patients 3 weeks after a severe adverse reaction. We prefer the patient to be brought to the laboratory where blood is taken freshly and the patient can also be interviewed to assist intelligent selection of the most appropriate CAST reagent. It is important to ensure that patients are not on oral or injected steroids for 2 weeks prior to conducting a CAST on their basophils.

The result of a CAST is usually available within 24 hours and it is our policy to discuss each result with the
### Table I. Technical cut-off values for CAST

<table>
<thead>
<tr>
<th>Code</th>
<th>Allergen</th>
<th>Concentration in cell stimulation</th>
<th>Technical cut-off pg/ml sLT</th>
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</thead>
<tbody>
<tr>
<td><strong>Antibiotics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BAG2-C1</td>
<td>Penicillin G 500 µg</td>
<td>500 µg</td>
<td>50</td>
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<tr>
<td>BAG2-C2</td>
<td>Penicillin V 500 µg</td>
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<td>40</td>
</tr>
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<td>BAG2-C11</td>
<td>PPL (benzylpenicilloypolylysine) 5 µg</td>
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<td>BAG2-C12</td>
<td>MDM (minor determinant mixture) 100 µg</td>
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<td>100</td>
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<tr>
<td>BAG2-C203</td>
<td>Ampicillin 2 mg</td>
<td>2 mg</td>
<td>70</td>
</tr>
<tr>
<td>BAG2-C204</td>
<td>Amoxicillin 200 µg</td>
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<td>100</td>
</tr>
<tr>
<td>BAG2-C3</td>
<td>Cephalosporin C 20 µg</td>
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<tr>
<td>BAG2-C31</td>
<td>Cefamandole 500 µg</td>
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<tr>
<td>BAG2-C32</td>
<td>Cefazolin 500 µg</td>
<td>500 µg</td>
<td>80</td>
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<td>BAG2-C33</td>
<td>Cefuroxime 500 µg</td>
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<td>Sulfamethoxazole 20 µg</td>
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<td>Trimethoprim 20 µg</td>
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<td>BAG2-C81</td>
<td>Ciprofloxacin 20 µg</td>
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<td><strong>Analgesics</strong></td>
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<td>BAG2-C51</td>
<td>Lys-Aspirin 500 µg</td>
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<td>BAG2-C52</td>
<td>Diclofenac 5 µg</td>
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</tr>
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<td>BAG2-C53</td>
<td>Ibuprofen 20 µg</td>
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<td><strong>Food Additives</strong></td>
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<td>BAG2-C111</td>
<td>Sodium benzoate 500 µg</td>
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<td>BAG2-C112</td>
<td>Sodium nitrate 20 µg</td>
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<td>BAG2-C113</td>
<td>Potassium metabisulfite 10 µg</td>
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<td>Sodium salicylate 200 µg</td>
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<td>Food Colorant Mix I 20 µg</td>
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<td>Food Colorant Mix II 5 µg</td>
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<td>Tartrazine 1 mg</td>
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<td>BAG2-CE104</td>
<td>Quinoline Yellow 100 µg</td>
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<td>Sunset Yellow Fcf 100 µg</td>
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<tr>
<td>BAG2-CATR</td>
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<td>BAG2-CLJD</td>
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<td>BAG2-CMIV</td>
<td>Mivacurium 200 µg</td>
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<tr>
<td>BAG2-CPAN</td>
<td>Pancuronium 200 µg</td>
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<td>BAG2-CPRO</td>
<td>Propofol 200 µg</td>
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<td>BAG2-CROC</td>
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<td>BAG2-CSUX</td>
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<td>BAG2-CVEC</td>
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<td>BAG-K79</td>
<td>Phtalic acid / anhydride 200 µg</td>
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<td>BAG-K80</td>
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<td>BAG-K82</td>
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<td>BAG-K87</td>
<td>A-Amylase 20 µg</td>
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patient and to provide specific written information to facilitate avoidance of the allergen/preservative/additive/drug to which the patient is found to be sensitive.

Declaration of conflict of interest

The author has no conflict of interest as he received no personal remuneration or conference funding. Buhlmann Laboratories (Basel, Switzerland) funded the sulphite studies conducted on the CAST test at the UCT Lung Institute (by way of provision of reagents and contributing to the technologist’s salary).

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WIPO Congress in Tenerife

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Specialised *in vitro* diagnostic methods in the evaluation of hypersensitivity—an overview

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Division of Immunology, Allergy Section in the Institute of Infectious Diseases and Molecular Medicine (IIDMM), Faculty of Health Sciences (NHLS), University of Cape Town, South Africa

**ABSTRACT**

Hypersensitivity reactions can be differentiated into IgE- and non-IgE-mediated allergic and also non-allergic reactions. In this article we explore currently available tests used to distinguish non-IgE conditions. Testing involves not only estimation of the different antibody types but also cellular activation and inflammatory markers.

Allergic diseases, including reactions to foods, represent increasing health problems worldwide, and symptoms may not be easily distinguished from other disorders. The term hypersensitivity is defined as a reaction that induces reproducible symptoms and signs, initiated by exposure to a defined stimulus at a dose tolerated by normal subjects. Hypersensitivity can be differentiated into IgE and non-IgE allergic and non-allergic hypersensitivity, which does not involve the immune system. Therefore, different tests must be used to distinguish between these conditions. An allergic hypersensitivity is usually IgE-mediated but may involve IgG and IgA antibodies as well as other immune cells (Table I).

**Allergen markers**

Most patients are sensitised to more than one allergen which might trigger clinical symptoms and often it is difficult to distinguish the major offender. In addition, the symptoms are not only dependent on IgE antibodies but also on a number of other confounding factors. These can include inflammation, presence of infection, physical and psychological stress and hormonal influences. The gold standard for food allergy or intolerance is the double-blind placebo-controlled food challenge (DBPCFC). However, this technique does not distinguish between allergic and non-allergic hypersensitivity involving different antibody types, cellular immune mechanisms and reactions based on intolerance. With these issues in mind *in vitro* assays need to determine the mechanisms behind the symptoms. In this article we explore currently available tests and highlight their applications and limitations.

**Table I: Tests for the presence of allergic sensitisation and identification of offending allergens**

<table>
<thead>
<tr>
<th>Test aims to identify</th>
<th>Principle of the test</th>
<th>Basic technology</th>
<th>Major test system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of sensitisation to specific allergen</td>
<td>IgE/IgA/IgG antibodies tests to allergens from one allergen source or one single allergen component</td>
<td>Different assays using a solid phase to bind allergen-specific antibodies and detect with anti-IgE/IgA/IgG reagents</td>
<td>UniCAP</td>
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<td>Presence of inflammation mediators from different cells</td>
<td>Histamine from basophils/mast cells</td>
<td>Solid phase with attaching antibody and labelled anti-mediator reagents</td>
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<tr>
<td></td>
<td>Tryptase from mast cells</td>
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<tr>
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<td>Leukotrienes and prostaglandins</td>
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<td>UniCAP</td>
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<tr>
<td></td>
<td>Eosinophil mediators such as ECP</td>
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<td>ELISA</td>
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<tr>
<td></td>
<td>Lymphocyte mediators such as cytokines</td>
<td></td>
<td>ELISA</td>
</tr>
<tr>
<td>Cellular immune response</td>
<td>T-cell proliferation</td>
<td>Cell cultivation with specific allergen/antigen stimulation; analysis of cell proliferation</td>
<td>Tissue culture</td>
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<td></td>
<td>Basophil activation</td>
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<td>CAST Flow cytometry</td>
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</tbody>
</table>

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measured in nasal secretions and indicate active allergy defense mechanism. Antibodies of the IgE type are produced as part of the body's complex immune reaction to a foreign antigen, with the help of helper T cells. During an immune reaction to a foreign antigen, antibodies called specific IgE antibodies are produced. They bind to receptors on mast cells andbasophils. Upon re-exposure to the same antigen, specific IgE antibodies bind to the antigen, triggering mast cell activation and releasing mediators such as histamine, tryptase, and other vasoactive substances. This results in allergic symptoms, including systemic anaphylaxis. The presence of specific IgE antibodies in serum can reflect the extent of exposure to that antigen. IgE antibodies can be quantified via the ImmunoCAP system or the micro-arrays system. The IgE antibody response can be quantified to all available ImmunoCAP allergens; however, only a few allergens have been reported in their allergen microarray, has emerged as a promising approach to high-throughput large-scale profiling of allergen interactions for simultaneous monitoring of IgE and IgG antibodies directed against a variety of allergy-eliciting molecules. The major benefit of this technology lies in its ability to screen for several hundred allergens simultaneously while employing only minute amounts of the patient's serum (20 µl).

CELLULAR MARKERS

During the allergic reaction new and preformed mediators are released from cells, such as mast cells and eosinophils, into the tissue or blood and these can be quantified. These include histamine, tryptase, leukotrienes, prostaglandins and eosinophilic cationic protein.

Tryptase and histamine

Mast cells play a key role in allergic reactions and the numbers increase under inflammatory conditions. After activation, they release a range of mediators, including tryptase and histamine, which in turn can lead to allergic symptoms, including systemic anaphylaxis. Activation follows an anaphylactic reaction triggered by food, drugs or insect venom. Histamine in contrast to tryptase is a very unstable marker and degrades very fast (within minutes!). Therefore an elevated level of serum tryptase is a more reliable indicator for anaphylactic reactions, while an elevated level of serum histamine indicates mast cell activation.

Eosinophil cationic protein (ECP)

ECP is a highly cytotoxic protein found in eosinophil granules. Eosinophils are the main cells responsible for producing the inflammation characteristic of asthma by degranulation in the lung tissue during activation. This can increase hypersensitivity and lead to chronic inflammatory diseases of the airway. Elevated levels of ECP can be quantified in serum, bronchial alveolar fluid and induced sputum. High levels indicate inflammation, which is a risk factor for uncontrolled asthma. The measurement of ECP in serum can be used to monitor inflammation in asthma, guide corticosteroid treatment and expose non-compliant patients. Elevated ECP levels have also been observed in children with cow's milk allergy. Values over 15 µg/l should be considered elevated, but patients should act as their own control during treatment and follow-up if possible.

ANTIBODY MARKERS

Specific IgG antibodies

During an immune reaction to a foreign antigen, antibodies are produced as part of the body's complex immune response. Antibodies of the IgG type are typical in type I allergic reactions; however, high titres of antigen-specific IgG and IgA antibodies are also observed. In autoimmune disorders, these antibodies are directed against self-antigens (autoantigens). The presence and level of specific IgG antibodies in serum can reflect the extent of exposure to that antigen. IgG antibodies can be quantified via the ImmunoCAP system or the micro-arrays system. The IgG antibody response can be quantified to all available ImmunoCAP allergens; however, only a few allergens have been evaluated and respective cut-off values determined (Table II).

Measuring specific IgG antibodies may provide valuable information in different areas of allergology.

Allergic diseases

- Marker for exposure in different lung diseases, including aspergillosis, aspergillus and allergic alveolitis to bird allergens. The latter can be regarded as positive when values exceed 30 mg/l.

Food allergy

- Presence of IgG is a sign of exposure (also of particular interest for cross-reactivity to foods which are not usually consumed by these individuals, e.g. kiwi, avocado)
- Diagnostic importance for certain food antigens, e.g. gluten in coeliac disease (see below)

Immunotherapy

- Monitoring success of immunotherapy with inhalant allergens and hymenoptera venoms (increase indicates positive response to therapy)

Autoimmunity

- Elevated levels of antibodies to thyroid peroxidase (TPO) and thyroglobulin (TG)

Elevated IgG antibodies have also been detected in cow’s milk allergy (CMA), which is a very complex disease with diverse clinical manifestation and allergen recognition. Bovine milk contains about 3.5% protein of which casein constitutes 80% while whey proteins and minor allergens constitute 20%. Furthermore, casein can be divided into four fractions while the major whey proteins are alpha-lactalbumin and beta-lactoglobulin. The latter is acid-stable and likely to remain stable in the gut providing a specific source of allergens.
Specific IgA antibodies

IgA antibodies are part of the mucosal immune defence system of the body and present in blood as well as in secretions such as saliva and mucus. Increased levels of specific IgA antibodies to food antigens vary considerably according to exposure and geographical area but are not directly linked to an allergic disease. However, elevated levels may indicate increased exposure as a result of damage to the intestinal mucosa, which is frequently seen in coeliac disease (CD).12

In comparison with antibody-mediated hypersensitivity, there are no in vitro diagnostic assays to predict cell-mediated hypersensitivity. The only exception is CD, which is an autoimmune disorder of the small intestine resulting from inappropriate T-cell-mediated immune responses against gliadin. Gliadin is the alcohol-soluble fraction of gluten found in nutrients such as wheat, barley, rye and oats. A special enzyme called tissue transglutaminase catalyses the transformation of gliadin, which in turn activates gladin-specific T-cells. This suggests an active role for this enzyme in the inflammatory response to gluten-containing grains. The measurement of elevated levels of specific IgA and IgG (in IgA-deficient patients) antibodies to gliadin are highly sensitive and specific and can also be used to monitor elimination diets as gliadin specific IgA disappears. Suggested cut-off values for gliadin specific IgA and IgG antibodies are about 2.0 mg/l and 18 mg/l respectively, but should be validated against levels in normal healthy individuals in a given geographic area.

In contrast, food hypersensitivity to wheat is a different disease which is mediated via IgE antibodies, and several wheat allergens may be implicated.

IMMUNOBLOT

Sometimes patients present with a clear history of allergic sensitisation but commercially available assays do not detect elevated specific antibodies. In this situation when sensitisation to an unknown allergen source is suspected, immunoblotting (also called Western blotting) should be conducted. Protein extracts of the offending allergen source are separated by gel-electrophoresis (in an electrical field) according to molecular size, the allergens are then transferred to a membrane (blotting) and detected with serum IgE antibodies from sensitised patients.13 This method can be very sensitive; however, the evaluation of the results requires a sound knowledge of molecular allergens and it is advisable to compare results with those in non-sensitised individuals.

BASOPHIL ACTIVATION

The purpose of this test is to mimic in vitro the contact between allergens and circulating basophils. The release of histamine and tryptase can be measured using the ImmunoCAP system and the release of leukotrienes (which are more stable biological markers) via the cellular antigen stimulation test (CAST). In recent years an increasing number of studies have demonstrated that flow cytometry is a reliable tool for monitoring basophil activation on allergen challenge by detecting surface expression of protein markers such as CD63 and CD203c.14 The assay is relatively fast with results produced within 1-2 hours, and requires about 5 ml of fresh whole blood. Protein allergens or drugs can easily be tested; however, healthy control subjects have to be included and assessed for each allergen and concentration tested.

CONCLUSIONS

Confirmation of immunological hypersensitivity reactions rely in the laboratory setting on the detection of allergen specific antibodies. IgE antibodies play a pivotal role in these reactions, but allergen specific IgA and IgG have been useful markers for detecting conditions such as CD and allergic alveolitis respectively. Nevertheless, the evaluation of food allergy based on these antibody types remains questionable. The assessment of in vivo activation of cells and mediator release are important indicators used to confirm that allergic asthma, rhinitis and anaphylaxis have indeed taken place. Furthermore, T-cell and basophil activation can be utilised in vitro under controlled conditions to identify allergic reactions to food additives, clinically relevant cross-reactivity and true latex allergy. Future developments include novel sensitive and specific tests for routine allergy diagnosis such as the allergen microarray, while cellular tests are likely to remain specialised tests for the evaluation of specific clinical cases.

Declaration of conflict of interest

The author has no conflict of interest.

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REFERENCES

ALLSA POSITION STATEMENT:
ALLERGEN SKIN-PRICK TESTING

Prepared by Dr Adrian Morris
Reviewed by Prof Paul Potter (ALLSA) and Dr Richard Lockey (AAAAI)

ABSTRACT
Allergen skin-prick testing is described as the 'cornerstone' of allergy diagnosis and has become highly standardised over the years. This position statement addresses important issues such as standardised allergens and test materials, testing procedure, technique, interpretation, reproducibility and safety of allergen skin-prick testing as recommended in clinical allergy practice in South Africa.

INTRODUCTION
Allergen skin testing was first used by Dr Charles Blackley to diagnose pollen as the cause of his hay fever in 1873. In 1924 the current skin-prick test (SPT) method was introduced and in 1975 Prof. Jack Pepys proposed the modified skin-prick testing method.1 Today the allergen extracts and lancet are standardised and this technique for diagnosing immediate IgE-mediated allergy is used universally.

Allergen skin testing is an extremely safe procedure and only one death as a result of skin-prick testing has ever been recorded.2,3 Therefore there is a theoretical possibility of this test inducing an anaphylactic reaction in highly allergic individuals. Mild systemic reactions with itching and generalised rashes have also been recorded but are unusual and occur in 1:3000 patients tested by SPT.3

AGE OF PATIENTS
There is no lower limit for allergen skin-prick testing, and consensus indicates that the tests are of value from 4 months of age.4 However, infants and the elderly tend to have a less reactive skin with fewer mast cells than older children and adults.5 In the past, the lowest age limit was incorrectly set at 3 years.

TEST SITE
The usual site for testing is the inner (volar) aspect of the forearm between the wrist and elbow. This sensitive area of skin reacts well if the allergens are placed 2-3 cm apart. They should not be placed closer than 5 cm to the wrist or less than 3 cm from the elbow crease as skin sensitivity to skin testing varies two-fold between the elbow and wrist.6 The skin of the upper back can also be used if there is dermatitis on the forearms, or in children with small forearms. The individual allergen test sites should be marked in two columns about 3 cm apart, with a felt tipped or ballpoint pen at 2-3 cm intervals. Any number from 1 to 40 allergens may be tested in a single session7 (the average being 6-12).

THE LANCET
A special standardised lancet should be used with a 1 mm pointed tip and blunt shoulder to prevent excessive trauma to the skin. The lancet is pressed through the drop of allergen at 90 degrees to the skin allowing puncturing of the skin. Lancets should be replaced after each allergen pricked, or thoroughly wiped with alcohol to prevent cross-contamination of allergens. The lancet should always be discarded after performing the histamine control prick. A conventional hypodermic needle should not be used instead of the standardised lancet as this will cause varying skin penetration and the puncture depth will be difficult to control.8

Intradermal (ID) skin testing employing the injection of allergen into the subcutaneous tissue should not be confused with standardised skin-prick testing. This ID method used to test venom and drug allergy usually injects a far higher amount of allergen. It has a much greater risk of inducing anaphylaxis, and has been reported to have induced a number of anaphylactic deaths over the last century.9

ALLERGEN SOLUTIONS
Purified standardised allergens which are commercially prepared should be used for inhalant allergen testing and these usually include house-dust mite, cat dander, dog dander, tree pollens, grass pollens and mould spores. In order to stabilise the allergen extract, glycerol is added in a strength of 50% of volume. Additional inhalants may be added to the panel of allergens used and will depend on the age of the child, the allergy case history and the geographic region.

Common standardised food allergens include cow's milk, hen's egg, wheat flour, soy, codfish and peanut. Other standardised food allergens include various nut and shellfish allergens. Fruit or vegetable allergens are best tested using the fresh fruit employing the prick-prick method of puncturing the fruit with the lancet, or dipping the lancet into the food and then pricking the skin with the fresh fruit residue.10 Because these fresh allergens are not standardised and the extract used has unknown allergen content, the prick-prick method carries a higher theoretical risk of inducing a systemic reaction.9 For safety reasons, some investigators suggest first applying the wet food/fruit to the intact skin for some minutes before performing the prick-prick test.10,11

All SPTs should include a positive and negative control test to assess normal skin reactivity for the person being tested. The negative SPT is performed using buffered saline in the glycerol base used to preserve the other allergen substances. No wheal reaction should be recorded with the negative control unless the person suffers from dermatographia. The positive control employs a drop of histamine 10 mg/ml or occasionally codeine. This test should induce a wheal and flare reaction and the wheal should be at least 3 mm in diameter. A smaller wheal or no wheal at all at the positive control site should alert the tester to the possibility of concomitant medication. Drugs such as antihistamines, antidepressants or topical steroids will suppress the control test and the rest of the allergens tested cannot be interpreted because of this overall suppression.10,12

Standardised allergen extracts for skin-prick testing are widely available and distributed in South Africa by companies such as ALK-Abello (Denmark), Stallergenes
(France), Allergopharma (Germany) and Leti (Spain) or their local agents.

THE PROCEDURE

The patient should have the skin test procedure carefully explained before skin testing commences and any concerns or questions need to be addressed. The procedure is unlikely to be painful or induce vasovagal syncope if empathetically discussed. Children under 16 years should be accompanied by a parent or guardian. Verbal consent should be obtained from all patients including children old enough to understand the procedure; otherwise their parents should give consent.

A droplet of each purified allergenic extract is placed on the cleansed volar aspect of the forearm at 2-3 cm intervals (Fig. 1). The lancet is pressed through the droplet perpendicular to the skin for one second to puncture the skin at 90 degrees and no blood should be drawn. The ‘modified’ skin-prick method (as described by Pepys and Mygind) whereby the skin is pricked at 55 degrees and then lifted with the lancet tip, leads to variable skin penetration and is not recommended.1,6

One normally starts with the negative control and finishes with the positive control. After all the droplets have been penetrated at 90 degrees by the lancet and the skin gently punctured, the excess allergen droplets are carefully blotted (not wiped) away using a clean absorbent paper towel (cotton wool should not be used). The test results are then interpreted 15-20 minutes after puncturing the skin.11

The practice of performing the double skin-prick testing method using two duplicate tests of each allergen at the same session is not widely practised as this increases the allergen load and may cause unnecessary discomfort.13

INTERPRETING THE RESULTS

Interpreting the results of SPTs should be done by a doctor or nurse with experience of the procedure to ensure reproducibility and accuracy. The same amount of pressure should be applied with each skin puncture, and the wheal and flare reaction is then measured, with special attention to the diameter of the wheal measured in millimetres. The mean of the longitudinal and vertical wheal diameter is used if the wheal is not concentric. However ‘pseudopodia’ extensions should not be measured. The older assessment using 0 to ++++ is no longer recommended and wheals are now universally measured in millimetres.13

The SPT results are measured using a ruler or calibrated see-through gauge and recorded in the patient’s notes in millimetres of wheal diameter. Sometimes a transparent adhesive tape is placed over the wheal and the wheal size traced and then stuck into the patient’s clinical notes. Irritant delayed reactions which are not indicative of immediate hypersensitivity may occur on the skin 3-5 hours after skin-prick testing.

A positive result to a specific allergen or mix is indicated by a mean wheal diameter measuring 3 mm or more greater than the negative control (Fig. 2). A diameter of 3 mm is equivalent to a surface area of 7 mm² (some practitioners use area of wheal instead of wheal diameter). To clarify this, if the negative control is 0 mm then 3 mm or greater wheal for the test allergen represents a positive test but if the negative control measures 2 mm then a positive test would be a wheal of 5 mm or more.

The presence of the wheal indicates that the person has been sensitised to that specific allergen while the associated flare or erythema is not used as a gauge of allergic sensitisation. Sensitivity to testing increases with the potency of the extract and the pressure applied with the lancet. However, with experience and, after taking an exhaustive allergy history, most well-trained allergists will be able to give a good predictive diagnosis after assessing the skin test results in conjunction with the clinical history.11,12,14

While Sporik’s studies15 of children with food allergens such as egg, milk and peanut have suggested that a wheal greater than a certain size may indicate the presence of food allergy, the severity of an allergic reaction cannot be accurately predicted by the size of the wheal alone. For example, some patients with anaphylactic sensitivity to insect venom, latex, antibiotics and local anaesthetics may have wheal size as small as 3 mm while others may conversely have wheals of 10 mm or greater to inhalant and other food allergens but manifest little or no allergic signs if they are exposed to these allergens.

Fig. 1. Procedure of skin-prick testing.

Fig. 2. Results of skin-prick testing.
For IgE-mediated food allergy in children, in conjunction with Sporik’s work (Table I), Eigermann and Sampson16 and Hill et al.11 have introduced cut-off points for positive SPTs above which food allergy has a 95% probability. These probabilities have been reproduced by Roberts and Lack18 using ‘likelihood ratios’.

### Table I. Skin prick testing: 100% positive predictive value (PPV) for food allergy

<table>
<thead>
<tr>
<th>Food allergen</th>
<th>100% PPV &lt; 2 yrs (Wheat diameter)</th>
<th>100% PPV &gt; 2 yrs (Wheat diameter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cow’s milk</td>
<td>6 mm &gt;8 mm</td>
<td></td>
</tr>
<tr>
<td>Hen’s egg</td>
<td>5 mm &gt;7 mm</td>
<td></td>
</tr>
<tr>
<td>Peanut</td>
<td>4 mm &gt;8 mm</td>
<td></td>
</tr>
</tbody>
</table>

Source: Sporik et al.13

### CONTRAINDICATIONS TO SKIN-PRICK TESTING

Do not apply skin-prick tests to patients when there is a convincing history of anaphylaxis to the test allergen. This is particularly important in nut, latex, horse, drug or severe food allergy. Patients with ongoing food allergic symptoms should not be skin tested until their symptoms are stable.11 In these cases it is far safer to perform a RAST (ImmunoCAP, Pharmacia) on a venous blood sample to confirm the allergy. Bear in mind that patients may test negative to an allergen that caused their anaphylaxis for up to 6 weeks after the reaction as a result of a relative depletion of specific IgE during this 6-week refractory period (this refractory period also applies to RAST results).11

### FACTORS THAT INFLUENCE RESULTS

Stop all antihistamine medication for at least 3 days prior to the SPT. Also, stop other medication such as tricyclic antidepressants, mast cell stabilisers, ranitidine, anti-emetics or beta-blockers as well as topical antihista-mines, immunomodulatory creams and topical steroids for one week before the test. Oral steroids and asthma inhalers should not be stopped. If the person has extensive dermatitis, and no clear skin is available for testing then RAST testing should be performed instead. Dermatographism will make skin testing difficult to interpret as all the test sites are likely to react non-specifically with a wheal and flare reaction. Skin responses are lower in the morning than in the afternoon because of circadian rhythm. Wheal size diminishes in ageing skin, which is more easily traumatised as a result of atrophy with bleeding and tends to form marked postpuncture vesicles. The menstrual cycle may influence results and increased wheal response on day 12-16 of the menstrual cycle may be evident.6

### SAFETY OF SKIN-PRICK TESTING

Skin-prick testing is an extremely safe procedure according to the Royal College of Pathologists (UK) and the American Academy of Asthma, Allergy and Immunology.14 According to the medical literature, only one fatal reaction has ever been confirmed following skin-prick testing and this occurred after testing with 90 commercial allergens.23 However, studies indicate ID skin testing carries a greater risk of inducing a generalised systemic reaction.14,25 Mild systemic reactions with itching have occasionally been reported with allergen skin-prick testing but this responded promptly to removal of the allergen from the skin and simple antihistamine medication. Mild reactions are more likely to occur in infants under 6 months of age, children with a convincing history of anaphylaxis, and in those with severe food allergies when non-standardised fresh food extracts are used for testing.13 The duplication of skin tests at the same session increases allergen load and potential for enhanced generalised reactions.

Lin et al.21 investigated 10 400 standardised allergen SPTs and found that no adverse reactions were reported. In the largest study of skin-prick testing reactions ever recorded (over 18 000 patients on whom 497 656 individual skin tests to various allergens were performed), only 5 mild systemic reactions were recorded.22 These all responded promptly to antihistamine medication within 1 hour. However skin-prick testing should not be confused with ID testing and injection desensitisation immunotherapy which both carry a greater risk of inducing systemic allergic reactions.11,14,20 Lockey et al.22,25 retrospectively reported 6 deaths associated with skin tests between 1964 and 1993, but all occurred in patients using the ID injection method and not standardised skin-prick testing. Even though skin-prick testing is safe, the theoretical risk of a reaction necessitates that antihistamine medication and adrenaline should be readily available when performing allergen skin-prick testing on adults and children. Children should be weighed prior to testing and the appropriate dose of adrenaline (10 µg/kg intramuscular) noted in case a generalised reaction occurs. Unlike injection immunotherapy, the patient does not need to wait for an extended period after the testing. The wheal and flare reaction is initially assessed at 15-20 minutes and again at 30 minutes, after which the skin is cleaned with alcohol or soap and the patient may then safely leave the clinic.23,24 Despite the greater risk of adverse reactions in the under-6-month age group, delaying the allergy investigation is not recommended since early diagnosis will spare children unnecessary suffering from their symptoms of allergy.13

### REPRODUCIBILITY AND ACCURACY

The competence of the person performing the test is paramount and the technique employed should be consistent across all test sites.17 Although the technique appears quite simple, its interpretation requires a thorough clinical allergy history and an experienced practitioner.15,25 Standardised allergens should be used wherever possible except for testing with fresh fruit and vegetable extracts using the prick-prick method. The standardised allergens used should be checked for expiry date (all should be clearly labelled) and stored between testing at 2-8°C in a refrigerator. If fresh food extracts are used, these should be prepared freshly every day and discarded after use.6 Provided all the above precautions are followed, these tests are very accurate, give immediate results, and there should be no risk of any adverse reaction occurring.10

### Declaration of conflict of interest

The author has no conflict of interest.

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Many unconventional allergy tests are available which purport to diagnose a number of maladies. Tests range from electrodermal tests to trace metal estimation in hair samples. These unvalidated tests are promoted by complementary and alternative medicine (CAM) practitioners. Superficially many of these tests sound plausible, but are based on unproven theories and explained with simplistic physiology. Most of these tests diagnose non-existent illnesses; are a waste of money, and divert attention from actual allergies, thus delaying conventional treatment that may offer genuine allergy relief.

CAM practitioners base their allergy tests on controversial theories about what might cause allergies. Examples include:
- Chemical fumes from cleaning solvents, petrol, paints and perfumes
- Electromagnetic radiation from power lines and electronic devices
- Food with traces of colourings, antibiotics, pesticides and preservatives
- Micro-organisms such as Candida albicans and exotic parasites
- Prescription and over-the-counter medication
- Multiple foods such as wheat, yeast, sugar and coffee
- Endogenous hormones particularly progesterone.

WHO ‘TESTS’ THEIR TESTS?
CAM practitioners cite anecdotal case reports and clinical studies published in fringe medical journals. Individuals may well develop non-specific irritant reactions and side-effects to medication or vaso-active amines occurring in foods but this is of a non-allergic nature. Environmental or multiple chemical sensitivities, systemic candidiasis, attention deficit disorder (ADDH) and chronic fatigue are commonly diagnosed as resulting from ‘allergies’ to various environmental chemicals and naturally occurring fungi and parasites. Although Candida can cause vaginitis and oral thrush, there is no convincing evidence that systemic infections are related to allergy. Exotic parasite infestations are diagnosed on a droplet of blood with no convincing supportive evidence. Few of these tests are ever validated, checked or run with control samples. None is routinely recalibrated or appraised with recognised scientific checks of equipment.

A recent article in Britain’s Daily Mail newspaper (19/11/05) reported on an adolescent girl who tested ‘positive’ to 33 toxic chemicals found in household cleaners, foods and the modern ‘environment’. This caused enormous consternation to her caregivers but when one considers the accuracy of these tests and whether traces of chemicals in hair samples or other body fluids have any health implications at all, the unnecessary anxiety generated by these ‘tests’ becomes apparent.

Once many of these fictitious conditions are diagnosed, the naive patient is then put onto various elimination diets, rotation diets and many unnecessary vitamin and trace element supplements. Herbal remedies such as echinacea (now banned in USA), spirulina, grape seed oil, nettle, vitamin C and more recently flax seed oil are prescribed and symptom improvement may be related to undisclosed ‘salting’ with steroids in these so-called natural remedies. The illegal addition of corticosteroids to these ‘natural and traditional’ remedies gives them obvious therapeutic effect but may result in dangerous side-effects if used for prolonged periods of time. Warner is of the opinion (and this is also the author’s experience) that health journalists are unlikely to investigate or expose these pseudoscientific tests as fallacious for fear of alienating their ‘complementary and alternative medicine’ readership. Some of these CAM allergy tests may someday be proved to be safe and efficacious, but to date no convincing studies have proved any of their efficacies in diagnosing allergies.

This article reviews the common ‘allergy tests’ used by complementary and alternative medical practitioners.

SOME COMMON TESTS

The leucocytotoxic test (Bryan’s test)
Bryan’s leucocytotoxic test was originally developed in 1956 by Black, and further elucidated by Bryan in 1960. The basis of the test is that if the patient’s white blood cells are mixed with the offending allergen, they swell. The test then measures any swelling of the leukocytes and if a certain threshold of swelling is measured, using a Coulter counter, a positive result is recorded. Studies to date have shown poor correlation between this test and clinical allergy. The marketers, who rely on anecdotal evidence of efficacy, do not mention these disappointing clinical studies. A large number of allergens are tested for and patients are usually positive to a number of foods, additives and other agents. Personal communication with Kalatos in Australia and Steinman in South Africa plus Lieberman’s study in USA confirm that preliminary studies on the ALCAT test found no diagnostic accuracy. At present the test is also marketed under the name ‘Nutron’. Despite claims to the contrary, no large studies have ever shown the test to be accurate despite its having been available for over 50 years!
The original protagonists of the ALCAT test (which includes the leucocytotoxic test and Nutron test) contended only a few non-peer-reviewed congress abstracts as evidence that it worked, while the antagonists (personal communication with the leading opinion leaders in the field of food allergy such as Bindlev-Jensen, Potter and Katelaris) have substantial data on record to show a poor diagnostic accuracy. The lack of mainstream acceptance of these tests is often blamed on a ‘conspiracy’ by the larger multinational diagnostic companies trying to remove the defenceless opposition from the market. This perception is not a true reflection of the situation.

The IgG ELISA allergy test

Another allergy test of questionable accuracy is the IgG ELISA test. This test measures IgG antibodies to various foods which should not be confused with IgE antibody testing in conventional RAST and UniCAP. Most people develop IgG antibodies to foods they eat and this is a normal non-specific response. There is no convincing evidence to suggest that this test has any allergy diagnostic value. In fact, the IgG response may even be protective and prevent the development of IgE allergy. IgG4 antibodies produced after high level cat allergen exposure in childhood confer cat allergy protection and not sensitisation.

Applied kinesiology (muscle testing)

Applied kinesiology was developed in the USA by Goodhart in 1964 and relies on energy fields within the body to diagnose allergy and intolerance. Kinesiology is popular among chiropractic practitioners in the South Africa. In this test, the practitioner tests the patient’s muscle strength when the allergen is placed in a vial in front of them. The shoulder strength (deltoid muscle) is usually tested for weakness. The patient holds out an arm and the practitioner applies a counter pressure – if the patient is unable to resist the counter pressure, the test is considered positive to that allergen. The antidote to the allergy is then also held in front of the patient and if their weakness is reversed – this indicates it is the correct antidote. There are a number of variations to the technique of muscle testing and many practitioners complement the test by holding a magnet in front of the patient. There is no convincing evidence that this test has any useful role to play in allergy diagnosis.

VEGA testing (electrodermal testing)

This test was developed by German physician Dr Reinhold Voll in 1958. The VEGA test (or electrodermal test) involves measuring electromagnetic conductivity in the body using a Wheatstone bridge galvanometer. The patient has one electrode placed over an acupuncture point and the other electrode is held while a battery of allergens and chemicals are placed in a metallic honeycomb. A fall in the electromagnetic conductivity or a ‘disordered reading’ indicates an allergy or intolerance to that allergen. Newer transistorised/computerised versions of the original VEGA or Voll test are called DermaTron, BEST, Quantum and LISTEN Systems which have a similar application and give more rapid results. Some claim to test for 3 500 allergens in 3 minutes! Katelaris et al. performed independent double-blind testing, comparing VEGA testing with conventional testing in known allergy sufferers, and the VEGA tests had no reproducibility or diagnostic accuracy at all. The manufacturers aggressively promote the test and offer free training courses for potential ‘allergy’ diagnosticians.

Hair analysis testing in allergy

Hair is analysed for allergies in two ways. First of all, the hair is tested for toxic levels of heavy metals such as lead, mercury and cadmium and then deficiencies of selenium, zinc, chromium, manganese and magnesium. There is no scientific evidence to support the hypothesis that these heavy metals have any bearing on allergic diseases. Hair samples are usually sent away for analysis and numerous studies have failed to find any accuracy in hair analysis diagnosing allergies. Another hair test is called dowsing. The dowser swings a pendulum over the hair and an allergy is diagnosed if an altered swing is noted.

Auriculocardiac reflex

Suspected allergens are placed in filter papers over the skin of the forearm. A bright light is shone through the ear lobe or back of the hand. At the same time the pulse is assessed. If the filter paper contains an allergen to which the patient is allergic, the pulse increases by 12 or more beats per minute. To date, no scientific data are available to validate this test.

Provocation-neutralisation tests

The allergen is applied sublingually, or by skin injection. Increasing test doses are given until a wheal appears on the skin (provocation dose); the dose is then decreased until the wheal disappears. This is the neutralisation dose which is used to treat the allergy and ‘desensitise’ the patient. This test has also not been validated by studies and has no diagnostic reliability in allergy or treatment.

Nampudripad’s allergy elimination technique (NAET)

NAET has to be the most unsubstantiated allergy treatment proposed to date. It consists of a combination of methods of diagnosing and treating allergy such as kinesiology, VEGA testing and acupuncture. It was proposed in 1983 by American chiropractor Devi Nampudripad, hence its name. The premise is that allergy (contrary to our current understanding) is due to some form of internal energy blockage triggered by abnormal energy fields in the brain. Nampudripad proposed that after 20 or so treatments she can programme the brain and body energy flow and eradicate all allergies and many other diseases affecting mankind. However, as a cause of allergies, energy flow and electrical fields in the body have not ever been proven.

Live blood analysis

With the aid of a simple microscope and a short course in microscopy, many CAM practitioners are now professing to be able to diagnose all sorts of chronic ailments including allergies. The finger is pricked and a fresh blood specimen is examined under the light
microscope for blood cell "deterioration", rare parasites, or coagulation disorders. It is impossible to determine parasitaemia, bacteraemia or coagulation abnormalities on a drop of blood, without specialised stains and testing methods.

**Stool analysis and microscopy for yeasts and parasites**

Fringe laboratories in the USA operate a postal service, analysing stool samples for bizarre metabolites and an array of exotic parasites and organisms that are purposed to cause non-specific symptoms supposedly related to lifestyle allergies. Great Smokies Laboratories in the USA will do a full assessment of those children with exotic micro-organisms, bizarre biochemicals and proteins on a stool sample and send a ‘comprehensive’ report of these.

**BEWARE OF ANECDOTAL AND UNSUBSTANTIATED ALLERGY TESTS**

There are a plethora of so-called tests for ‘intolerances’ including urine, stool and saliva as well as bioresonance (vibrational medicine) and iridology. These tests are often promoted as ‘wonder’ diagnoses and anecdotal stories of lifelong allergies finally being accurately diagnosed abound. It would be naïve for any medical practitioners to accept these individual anecdotal reports of diagnostic efficacy without any scientifically validated studies to prove their worth. We often read about similar tests in the media and unsuspecting patients flock to part with their hard-earned money. Conventional medical practitioners may be accused of bias against these supposedly simple and ‘cheap’ tests and feel pressurised to try them out. On the other hand, a convincing CAM practitioner armed with an impressive allergy-diagnosing ‘contraption’ can talk even the most sensible patient into believing their pseudo-scientific allergy-diagnosing ‘contraption’ can talk even the most sensible patient into believing their pseudo-scientific explanations and anecdotal reports of allergy cures. Once patients realise that they have been incorrectly diagnosed, they may feel embarrassed, put the matter down to bad experience and hardly ever complain about the treatment or costs involved. For more information on these dubious visits test the Quackwatch website at www.quackwatch.com.

**Declaration of conflict of interest**

The author has no conflict of interest.

**REFERENCES**


**Product News**

**IgE testing in persistent cough**

IgE testing is helpful for GPs in determining those young children with persistent cough who will and will not develop asthma at age of 6 years.

Cough is the main complaint in at least 13% of general practice consultations for children from birth to 4 years of age. Clinical parameters alone cannot identify the subgroup of children for whom the risk of developing asthma is high, and therefore if a special investigation could be found to have a high predictive effect, this would be of great benefit to the clinician.

A study in The Netherlands of 752 children visiting 72 GPs, found that IgE testing was helpful for GPs in determining those young children with persistent cough who will and will not develop asthma at age of 6 years. The aim of the study was to investigate the diagnostic added value of allergen-specific IgE measurements to predict development of asthma at the age of 6 in young children with persistent cough. A structured questionnaire and a blood sample at inclusion were used to construct a simple scoring formula including age at inclusion (3-4 years), wheezing, and family history of pollen allergy. A follow-up examination with lung function tests and questionnaires was performed at the age of 6 years.

Serum total IgE and specific IgE for cat, dog, and house-dust mites were determined. The children with an IgE-positive status were matched to those with a negative status defined by age, sex, region (rural versus urban) and IgE antibody testing, and using the baseline criteria the researchers could categorise children who wheeze into low- and high-risk groups. Clinical parameters alone cannot identify the subgroup of children who wheeze into low- and high-risk groups. The study concluded that the assessment of specific IgE to Serum total IgE and specific IgE for cat, dog, and house-dust mites were determined. The children with an IgE-positive status were matched to those with a negative status defined by age, sex, region (rural versus urban) and IgE antibody testing, and using the baseline criteria the researchers could categorise children who wheeze into low- and high-risk groups. Clinical parameters alone cannot identify the subgroup of children who wheeze into low- and high-risk groups. The study concluded that the assessment of specific IgE to
TONGUE VARIANTS WHICH HAVE AN ATOPIC ASSOCIATION

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Helen Fisher, Clinical Research Nurse
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There is a vast spectrum of clinical disorders which present with an abnormal appearance of the tongue. Many of the benign tongue variants are more common in, but not unique to, atopic individuals. These variants enjoy bizarre and descriptive names, such as black hairy tongue, geographic tongue or fissured (scrotal) tongue.1 This article deals with the latter two conditions, both of which represent abnormalities of the papillae.

Geographic tongue (Fig.1)

Background: Geographic tongue, also called benign migratory glossitis, was first described in 1955 and occurs in approximately 3% of the population. It occurs in all age groups but is more common in adults; the incidence in females is approximately twice that of males.2,3

Presentation: Patients and/or their family members may report that the tongue has an abnormal appearance which resembles that of a ‘map’ or burn injury. The lesions classically wax and wane over time with occasional periods of complete remission, hence the term migratory glossitis. Although generally painless, patients with a geographic tongue may occasionally present with a burning sensation which is noted with hot or spicy foods. Adult patients may occasionally be concerned about a diagnosis of oral cancer, despite reporting that they have noted these lesions over many years.

Clinical findings: The top layer of the ‘skin’ of the tongue is unevenly shed leading to the classic manifestation of an area of erythema, with atrophy of the filiform papillae of the tongue, surrounded by a serpiginous, white hyperkeratotic border and degeneration of the overlying mucosa. The tongue exhibits a well-demarcated area of erythema, primarily affecting the dorsum, and often extending to involve the lateral borders of the tongue. Similar lesions may be present concurrently on other aspects of the tongue or other mucosal sites, e.g. geographic lip (Fig. 2). There is no loss of the sense of taste, or dexterity of the tongue. There is, however, a measurable decrease in the tongue’s sense of touch. Importantly, most people with geographic tongue are otherwise healthy.

Aetiology: Geographic tongue tends to run in families but has been associated with a number of other genetic medical conditions, including atopic conditions, psoriasis and diabetes. A polygenic mode of inheritance has been suggested because of clustering in families. Associations with specific human leukocyte antigens have been reported. In young women, geographic tongue may be brought on or exacerbated by taking oral contraceptives. Geographic tongue has been
reported with increased frequency in patients with fissured tongue (see below). Weaker links have been reported to anaemia, seborrhoea, and eating spicy foods.

**Treatment:** Geographic tongue lesions heal spontaneously, and although benign, this condition may last for years and often recurs. Although no treatment is generally recommended, several treatments have been tried, including topical Retin-A and treatments for thrush. Patients who experience pain and burning may experience relief when treated with antihistamines.

**Fissured tongue or scrotal tongue (Fig. 3)**

**Background:** Fissured tongue, also called scrotal tongue, is a not uncommon finding in the general population. As with geographic tongue, fissured tongue is found in all age groups but with an increased incidence in adults. It is slightly more common in males.

**Presentation:** The condition is usually noted as an incidental finding. Fissured tongue is characterised by grooves that vary in depth and are noted along the dorsal and lateral aspects of the tongue. The lesions are usually asymptomatic unless debris is trapped within the fissures or when it occurs in association with geographic tongue. Fissured tongue may also be seen in Down syndrome and the Melkersson-Rosenthal syndrome.

**Clinical findings:** Fissured tongue affects the dorsum and often extends to the lateral borders of the tongue. The depth of the fissures varies but has been noted to be up to 6 mm in diameter. When particularly prominent, the fissures or grooves may be interconnected, separating the tongue dorsum into what may appear to be several lobules. The presence of fissured tongue, in association with persistent or recurring lip or facial swelling and intermittent seventh (facial) nerve paralysis (Bell’s palsy), is diagnostic of Melkersson-Rosenthal syndrome. Histological examination exhibits non-caseating granulomatous inflammation. The facial paralysis is indistinguishable from Bell’s palsy, and it may be an inconsistent and intermittent finding with spontaneous resolution. Oro-facial granulomatosis in the paediatric population may be an initial manifestation of Crohn’s disease and so careful surveillance is recommended for these patients.4

**Aetiology:** A definitive aetiology for fissured tongue is not yet known. A polygenic or autosomal dominant mode of inheritance is suspected as this condition is seen with increased frequency in families with an affected proband. A biopsy is rarely indicated as the clinical findings are characteristic. Histological examination reveals an increase in the thickness of the lamina propria, loss of filiform papillae, hyperplasia of the rete pegs, neutrophilic microabscesses within the epithelium, and a mixed inflammatory infiltrate in the lamina propria.

**Treatment:** No definitive therapy or medication is required. If symptomatic, patients are encouraged to brush the dorsum of the tongue to eliminate debris that may serve as an irritant. Complications are not associated with fissured tongue per se but are noted in association with the manifestations of Melkersson-Rosenthal syndrome.

**REFERENCES**

GROVER’S DISEASE – TRANSIENT ACANATHOLYTIC DERMATOSIS

Grover’s disease, or transient acantholytic dermatosis, is a pruritic eruption affecting fair-skinned men older than 40 years. The lesions occur on the trunk as crops of discrete papulovesicles and scaly papules (Fig. 1). Precipitating factors include exercise, heat and sweating, as well as exposure to ultraviolet or ionising radiation.

Differential diagnosis

Grover’s disease may mimic other dermatological conditions. These include Darier’s disease, miliaria rubra (heat rash), papular urticaria and insect bite reaction, dermatitis herpetiformis, pityrosporum folliculitis and drug reaction.

Special investigations

Skin biopsy establishes the diagnosis. Microscopically there is focal acantholytic dyskeratosis. Acantholysis is the separation of cells in the epidermis.

Course and prognosis

Although Grover’s disease is known as transient acantholytic dermatosis and may last a few weeks to months (with a self-limiting course), some cases are persistent.

Management

Patients should avoid strenuous exercise and exposure to sunlight.

Topical therapy

Calamine lotion with 1% menthol and 1% phenol relieves itching. Topical steroids may be used for initial control.

Oral therapy

Oral therapy is reserved for extensive and severely pruritic cases. Oral steroids (prednisone 40 mg daily) are tapered once itching and inflammation is controlled over a period of 4 weeks. Isotretinoin 40 mg daily for 2 weeks and then 10 mg a day for 10 weeks is helpful. Oral vitamin A at a dose of 50 000 units 3 times a day for 2 weeks, and then decreasing to 15 000 units daily for 10 weeks has also been used. Dapsone has been beneficial in some patients.

Phototherapy with UVB is useful for recalcitrant cases of Grover’s disease.

FURTHER READING


ACKNOWLEDGEMENT

I would like to acknowledge the help that I have received from our secretary Miss F Zain who has diligently typed and checked all the Skin Focus articles published over many years.
OCCUPATIONAL ALLERGY IN THE FISH PROCESSING INDUSTRY – TOWARDS PREVENTIVE STRATEGIES

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‘Seafood’ refers to any aquatic organism that is intended for human or animal consumption.1 Recent years have seen a growing demand for seafood, which has led to increased production. While adverse reactions (toxic and allergic) to seafood have been reported by a growing number of consumers, allergic reactions in particular have also been documented to occur in the occupational setting as a result of exposure to all three major seafood groupings (Table I).2,3

Table I. Classification of seafood groups causing occupational allergies

<table>
<thead>
<tr>
<th>Phylum</th>
<th>Class</th>
<th>Family (common name)</th>
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<tbody>
<tr>
<td>Arthropoda</td>
<td>Crustacea</td>
<td>Crabs, lobsters, prawns, shrimp</td>
</tr>
<tr>
<td>Mollusca</td>
<td>Gastropoda</td>
<td>Abalone</td>
</tr>
<tr>
<td></td>
<td>Bivalvia</td>
<td>Clams, oysters, mussels, scallops</td>
</tr>
<tr>
<td>Cephalopoda</td>
<td>Squid</td>
<td>Squid (cuttlefish)</td>
</tr>
<tr>
<td>Pisces (sub-phylum)</td>
<td>Osteichthyes</td>
<td>Salmon, plaice, tuna, hake, cod, herring, sardine, trout, anchovy, yellow fin</td>
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<tr>
<td>Chordata</td>
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The seafood industry and working populations at risk

Occupational exposure to seafood allergens occurs mainly in the food and fishing industry.4,5 Workers in a number of these industries are exposed to seafood, especially those involved in either manual or automated processing of crabs, prawns, mussels, fish and fishmeal. Other occupations associated with seafood exposure include oyster shuckers, laboratory technicians and researchers, jewellery polishers, restaurant chefs, fishmongers and fishermen.6 The Food and Agriculture Organisation (FAO) of the United Nations estimated that in 2002, fishery and aquaculture production activities produced direct employment and revenue for 38 million people worldwide (www.greenfacts.org/fisheries). The number of fishers and fish farmers has been growing at an average rate of 2.6% per year since 1990. Among these workers 52% worked aboard fishing trawlers, 32% were involved in aquaculture production (marine and freshwater) and 16% worked inland as capture fishers or in other land-based activities such as processing. It is estimated that more than 90% of the world fishers and fish farmers are from developing countries, producing 60% of the over 100 million tons of world fish.5 In many countries, labour in the fishing industry tends to be divided along gender lines with men almost exclusively going out to sea to catch the fish and women doing the majority of on-land processing.6 Most of these workers are seasonal workers. The degree of exposure is likely to be highest during the harvest season when most of the processing occurs.

Seafood processing plants vary in technological levels, with some of the smaller workplaces relying entirely on manual handling of the seafood and larger companies using modern, highly automated processes. There is great variation in processing procedures for the different types of seafood.5 Common processing techniques employed for the major seafood groupings and sources of potential exposure to seafood products are outlined in Table II. There is great variability of exposure within and among various jobs involved in seafood processing with reported airborne environmental allergen concentrations ranging from 1 to 5 061 ng/m³.7

Constituents of seafood

The allergic and inflammatory reactions to seafood experienced by workers in the seafood processing industry are the result of exposure to the seafood itself (Table I) (muscle and connective tissue, exoskeleton, blood, fish juice, skin, skin slime/mucin, gut) or to the various non-seafood components present in the product. Fish juice contains high molecular weight proteins (meat, skin, skin slime/mucin, gut), biogenic amines, histamine and cadaverine, degradation compounds in old fish, and digestive enzymes (pepsin and trypsin), all capable of causing adverse reactions in exposed individuals. The major fish allergens are parvalbumins, in crustaceans tropomyosin is most common and molluscs contain various unknown allergens.5,6 Non-seafood components include various contaminants such as parasites (e.g. Anisakis simplex); protochlorodes (e.g. Hoya) and algae (e.g. dinoflagellates Hematodinium); coral and sponges (e.g. marine soft sponge and red soft coral); marine or bacterial toxins (e.g. histamine); chemical additives (e.g. sodium metabisulphite) and spices (e.g. mustard, paprika, flour additives, garlic); and hidden ingredients (e.g. casein) in canned or processed fish products.5,9,10

High-risk work processes, sources of exposure and routes of entry

The production of seafood aerosols during processing has been identified as a potential high-risk activity for allergic sensitisation by high molecular weight seafood proteins through inhalation. These processes include degutting, heading and cooking/boiling of fish, mincing of seafood, fishmeal milling/bagging and cleaning of the processing line and storage tanks with high-pressured water (Fig. 1) (Table II).5 Occupational asthma is commonly related to crustaceans (e.g crabs and prawns) and fishmeal production. Skin-related allergic symptoms may be due to direct contact with the actu-

...
al seafood, vegetable additives (e.g. spices) or a systemic response to inhalational exposures. Occupational skin exposure occurs mainly as a result of unprotected handling of various fish and their products at various stages in the production process (Fig. 2).

Allergic health effects associated with seafood

Occupational seafood allergy can manifest as rhinitis, conjunctivitis, asthma, urticaria and protein contact dermatitis (Table III). Systemic anaphylactic reactions have also been reported. Another condition known to be associated with occupational exposure to seafood is extrinsic allergic alveolitis. The overall proportion of adult asthma (new and reactivated disease) attributable to occupational exposure is estimated to be 10%. The reported prevalence of occupational asthma among seafood workers varies from 7% to 36%.

The major skin manifestations associated with seafood are contact urticaria and eczematous contact dermatitis of various types. Contact urticaria is associated with direct contact with raw seafood proteins. At least 75% of eczematous dermatitis in the fish-processing industry is of an irritant nature commonly caused by contact with water and fish products (fish juice, slime, skin, fillet). Contact with the proteinaceous material also causes a chronic recurrent dermatitis commonly known as protein contact dermatitis (PCD). However, biochemical sensitisers (e.g. garlic, onion, spices) added to seafood can also cause a delayed allergic contact dermatitis. In the seafood industry, the reported prevalence of occupational PCD is between 3% and 11%.

Findings of a study investigating occupational fish allergy among workers along the West Coast of South Africa

The South African seafood industry employs over 28 000 mainly female seasonal workers involved predominantly in bony fish (hake, pilchard and anchovy) processing activities. A study investigating the risk of occupational allergy associated with pilchard and anchovy processing on the West Coast of South Africa found that workers were at substantial risk of inhaling aerosolised fish antigens that resulted in an increased risk of developing occupational asthma. High fish antigen levels, ranging from 81 to 75 748 ng/m³, were encountered during fishmeal production and bagging activities. A high correlation was found between ambient pilchard and anchovy antigen concentrations (Pearson r = 0.71, p<0.001).
The study also found that workers were at risk of developing occupational allergies, with rhinconjunctivitis (2.6%) being more prevalent than asthma (1.8%) and PCD or urticaria (1%). A dose-response relationship was demonstrated between the ambient level of fish antigen exposure at the time of symptom onset and the risk of such work-related asthma symptoms. Workers with work-related asthma symptoms had a twofold increased likelihood of being exposed to pilchard antigen concentrations >30 ng/m³ at the time of symptom onset and was demonstrated between the ambient level of fish processing plants include:

- Asthma
- Hypersensitivity pneumonitis (extrinsic allergic alveolitis)
- Anaphylaxis (rare)
- Rhinitis, conjunctivitis
- Asthma
- Hypersensitivity pneumonitis (extrinsic allergic alveolitis)
- Urticaria, angioedema and protein contact dermatitis
- Contact irritant dermatitis
- Contact allergic dermatitis

<table>
<thead>
<tr>
<th>Pathological mechanism</th>
<th>Occupational disease outcomes</th>
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<tr>
<td>General systemic response</td>
<td>Anaphylaxis (rare)</td>
</tr>
<tr>
<td>Allergic/toxic inflammatory lung reactions</td>
<td>Rhinitis, conjunctivitis</td>
</tr>
<tr>
<td>Allergic/toxic inflammatory skin reactions</td>
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<td>Contact irritant dermatitis</td>
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<td>Contact allergic dermatitis</td>
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Prevention of occupational seafood allergies – a focus on fish processing

In the light of the findings in the South African study reporting substantial exposure to fish antigens and related adverse health outcomes, it is evident that preventive measures need to be instituted to reduce morbidity and other adverse social outcomes (e.g. workplace absenteeism, job loss, decreased productivity, loss of earnings, increased health care expenditure) associated with occupational asthma and dermatitis among fish-processing workers. Firstly, regulatory exposure standards for fish allergens should be developed in the long term since none currently exists internationally. This requires standardisation of immunoassays for the evaluation of allergen exposure that can be implemented by most laboratories. In the meantime the most practicable strategy would be to identify departments and activities with high aerosol exposure (fishmeal bagging, gutting machine) during the initial risk-assessment process. Baseline and follow-up exposure measurements can be used to assess the effectiveness of local extraction ventilation systems using total particulate as a proxy for fish allergen levels (since there exists some degree of correlation between these two measures). Employer compliance and law enforcement of the Regulations for Hazardous Biological Agents (HBA) under the Occupational Health and Safety Act (OHSA) in South Africa are also crucial to this strategy. Key aspects that also apply to food-processing plants include:

- Regular biennial risk assessment and categorisation of workplace by employers
- Employees to follow safe procedures for HBA disposal and decontamination and to report all incidents of accidental exposure to HBA
- Employer to provide information and training to employees on potential risks of HBA and risk-reduction measures
- Regular exposure monitoring and medical surveillance of employees
- Workplace health and safety committee approved protocol for procedures dealing with abnormal results
- A requirement to follow the hierarchy of control measures using standard and transmission-based precautions.

Secondly, workplace interventions and control measures need to be implemented to reduce the emission of bio-aerosols in fish-processing plants. Process separation or enclosure, and the use of local extraction ventilation systems for processes and equipment (gutting machine, steam exhaust box and fishmeal bagging) are activities needing special emphasis. Workplace practices such as broom sweeping especially in the fishmeal bagging plants should be prohibited and vacuum cleaners or wet mopping implemented instead. Where there is significant potential for skin contact with the hazardous agent (fish skin, cutting, spice mixing), appropriate gloves (cotton-lined to prevent excessive sweat retention) with long plastic sleeves should be worn. Puncture wounds and lacerations should be treated expeditiously to prevent infection and skin exposure to allergens in fish juice. An appropriate combination of emollients and moisturisers can be used prophylactically to protect skin barrier function and help prevent the development of irritant contact dermatitis.

Thirdly, ongoing industrial hygiene and medical surveillance is required to assess the effectiveness of interventions. Although exposure monitoring of total dust particulate as opposed to allergen levels has its limitations in that dust levels may only partially correlate with the actual allergen concentrations, it may be the only realistic exposure measure. For this as well as other reasons, medical surveillance programmes have an important role to play. Such programmes should include annual symptom screening questionnaires, skin-prick testing with fish extracts and clinical skin examination. Where these screening activities offer evidence of possible work-related health problems, additional tests (e.g. spirometry and challenge tests, skin-patch tests with fresh fish and blood tests for specific IgE) can be used to confirm the presence of adverse health outcomes such as occupational asthma or contact dermatitis. The following guidelines used for management of other occupational allergies could be used to deal with abnormal results obtained from medical screening, surveillance and individual case management:

- Asthmatics sensitised to seafood should change to non-seafood work
- Asthmatics without sensitisation to seafood should be relocated to less exposed seafood tasks
- Workers with rhinitis and sensitisation should be investigated closely and relocation to less exposed tasks should be considered
- Workers sensitised to seafood but without respiratory symptoms should be re-examined annually
- Workers with rhinitis only but without sensitisation to seafood allergens do not warrant re-examination unless symptoms worsen.
Finally, education and training programmes for employers, workers and occupational health service providers are required. Essential components of such programmes should include knowledge of allergic diseases and their end-points, competence and skills to monitor allergic diseases and prevent them, as well as provision of information for those workers at risk in the fish-processing industry.

**Future research directions**

Future research needs to be directed at the detailed biochemical analysis of the offending fish allergens causing occupational allergies. This will contribute to the development of more sensitive and specific diagnosis techniques for evaluating affected workers. Furthermore, more user-friendly methods for the environmental detection of fish allergens that have more widespread application in the workplace need to be developed. The influence of other possible contributory factors to allergic responses such as endotoxin, histamine and parasites needs closer investigation, especially among fishmeal processors.

**REFERENCES**


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We look forward to your joining us.

Kind regards
Sharon Kling
(Convenor)

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Although allergic diseases are on the rise and present a major health problem, many people are incorrectly labelled or self-diagnosed as being allergic or food intolerant.

It is all too easy to assume that any persistent non-specific symptom must be an allergy. The lay media and growing Internet culture breed self-diagnosis, and alternative allergy practices thrive on making diagnoses of food allergies, environmental intolerances and chemical sensitivities to a wealth of common substances. Very often these can never be substantiated or absolutely disproved. Non-specific symptoms linked to poor lifestyle such as tiredness, poor concentration, weight gain, food cravings, mood swings and polymyalgia are not allergy related.

Allergic diseases should be diagnosed by a qualified doctor and not a lay practitioner armed with a short correspondence course in health, nutrition or allergy. Syndromes such as fibromyalgia, chronic candidiasis, myalgic encephalomyelitis, reactive hypoglycaemia, attention deficit disorder/hyperactivity (ADDH) and depression are not allergic in nature. Diagnostic labels of allergy tend to stick for life without reappraisal. For example, most transient viral rashes in childhood are unrelated to penicillin co-prescribed at the time, but often mislabelled as penicillin allergy. Similarly, vomiting attacks after eating spoilt fish are more likely to be food poisoning and not due to ‘iodine’ allergy.

Diagnosing allergy needs to be an investigative process which involves a comprehensive allergy history exploring onset of symptoms and their causal relationship to allergen exposure. In addition, looking at lifestyle, current medical history and family history of allergies plus concomitant allergen exposure will all help trace the offending allergen. This should be followed by reliable and validated allergen testing and may even necessitate formal allergen challenge testing. Treatment recommendations should be based on scientifically validated allergy management as outlined in the Good Allergy Practice guidelines (Table I).

Very often, non-specific and transient symptoms receive a reflex response of ‘it must be some sort of allergy’ from the busy physician. Unsubstantiated statements like these can lead to unnecessary and lifelong allergen avoidance. It is extremely important to confirm a suspected allergy by antigen testing either in vivo or in vitro and if no reliable test exists, then serious consideration should be given to a graded allergen challenge in hospital if necessary.

If a patient presents with a number of allergy-like symptoms but no causative allergen is identified with testing or on challenge, then it is important to inform the patient that an allergic disease is unlikely to be present. A ‘grey area’ occurs with delayed hypersensitivity reactions, which may occur some time after exposure and are not identified by specific IgE allergy testing. These conditions are not common, despite the media interest and the pattern of symptoms should facilitate the correct diagnosis. Bizarre and atypical symptoms may often be attributed to allergic diseases by self-professed intolerance ‘experts’. Lactose intolerance causes primarily gastrointestinal (GI) symptoms and not rashes! Gluten intolerance causes primarily malnutrition, fatigue, anaemia or rashes. Conditions not related to allergy are listed in Table II.

### Table I. Good Allergy Practice – Principles

| * Symptoms and signs of allergy are based on sound scientific evidence. |
| * Testing, including skin testing and immunological blood tests, should be validated and reproducible. |
| * Treatment should be evidence-based and universally accepted by allergy opinion leaders. |
| * The vast majority of allergic reactions involve IgE immediate hypersensitivity but delayed hypersensitivity (IgG and cell-mediated) does occur. |
| * There is a familial predisposition to develop allergies (called atopy). |
| * Allergic conditions include: anaphylaxis, hay fever, perennial rhinitis, allergic asthma, skin allergies, food allergy and intolerance, allergies to venoms, drugs, and occupational allergies. |

### Table II. Conditions unrelated to allergy

| Obesity or weight gain |
| Fibromyalgia and repetitive strain injury (RSI) |
| Multiple sclerosis |
| Parkinson’s disease |
| Myalgic encephalomyelitis |
| Postviral fatigue syndrome |
| Food phobia and aversion |
| Anxiety or panic attacks |
| Reactive hypoglycaemia |
| Depression |
| Insomnia |
| Rheumatoid arthritis |
| Candida vaginitis and systemic candidiasis |
| Irritable bowel syndrome |
| Crohn’s disease |
| Nocturnal enuresis |
| Attention deficit disorder/hyperactivity |
| Autism |
| Hyperosmia on exposure to volatile chemicals and odours |

Correspondence: Dr A Morris, 2 Burnham Rd, Constantia 7800.
Tel 021-797-7980, email adrianm1@telkomsa.net
Food-related symptoms may occasionally be T-cell- or IgG-mediated in children, particularly with cow’s milk-induced oesophagitis and delayed infantile eczema. Trial-and-error challenges will reproduce symptoms and identify the causal allergen. Food-additive reactions to colouring and preservatives remain controversial and additive allergy testing is unreliable. Thus the medical literature is filled with contradictory case studies and the very existence of this form of allergy remains debatable.

In the final analysis, a healthy, nutritious diet, free of excessive additives, together with plenty of exercise will go a lot further to improve overall health, rather than exhaustive allergy testing and unnecessary elimination diets or supplements. The input of a suitably qualified dietician is worth its weight in gold in resolving nutritional issues.

In these times of medicolegal litigation and liability claims, practitioners are loath to readily discount an allergic disease. However, if the symptoms don’t fit a recognised allergic pattern and the appropriate tests are negative, then it is prudent to inform patients that their symptoms are unlikely to be due to an allergy (Table III). A patient with a condition spuriously diagnosed as allergy will not respond well to conventional allergy medication and is therefore highly likely to seek further advice and treatment from ‘alternative’ practitioners.

Many complementary or holistic centres ‘identify’ previously undetected intolerances to numerous foods and environmental chemicals. The diagnosis is accompanied by a superficially plausible explanation of symptoms reinforced and illustrated with simplified physiology.

If a diagnosis of allergy appears unlikely, and all the parameters point away from this diagnosis, inform the patient that no allergy is likely to exist. Excessive allergy testing for the sake of screening will only raise the level of anxiety and serve little purpose at the end of the day.

REFERENCES


Table III. Allergy or no allergy – that is the question!

- Symptoms should fit a well-documented allergic condition.
- Typical physical signs should be present at examination.
- History should implicate well-defined allergens.
- Testing should confirm diagnostic hypothesis (skin, blood or challenge testing).
- Repeated allergen challenge should trigger reproducible symptoms and allergen withdrawal should improve these symptoms.
- Conventional allergy treatment should ameliorate symptoms.

If not – then review the diagnosis! It may not be an allergy.

**XYZAL® (LEVOCETIRIZINE) REDUCES THE COST OF PERSISTENT ALLERGIC RHINITIS**

Using the once-daily antihistamine Xyzal® (levocetirizine) reduces the cost of persistent allergic rhinitis to employers and to society, and significantly improves symptoms and quality of life for patients, in comparison to no treatment. The costs of untreated persistent allergic rhinitis are substantial – to patients, to healthcare providers, to employers, and to society as a whole, commented Professor Jean Bousquet, lead author of this important paper. 'The results of this innovative study show that these costs can be significantly reduced through long-term treatment with levocetirizine.'

XPERT is the first clinical study to follow from the reclassification of allergic rhinitis by the Allergic Rhinitis and its Impact on Asthma (ARIA) project, in collaboration with the World Health Organization, in 2001.

Persistent allergic rhinitis is now defined as allergic rhinitis with symptoms (runny nose, itchy eyes and nose, sneezing and blocked nose) that occur more than four days per week and last for more than four consecutive weeks. The new cost analysis of XPERT showed that levocetirizine treatment led to significant reductions in medical resources required to treat persistent allergic rhinitis, compared with no treatment (nasal cromoglycates, -40%; ocular cromoglycates -55%; additional medications, -59%), and in additional medications required to treat comorbidities.

Time lost from work and usual daily activities (such as leisure activities and unpaid work) was significantly greater for patients whose persistent allergic rhinitis was not treated, compared with those who took levocetirizine. Professor Bousquet pointed out that ‘given the burden associated with persistent allergic rhinitis, treatment with levocetirizine could substantially improve the life of those who suffer from the disease.’

References available on request. Contact Louise Rabie 011-481-3000.

Xyzal® 5mg tablets are available in packs of 30.

Registration Number: 365/7.1/0425
Allan S Puterman
The January 2006 edition of the Journal of Allergy and Clinical Immunology (JACI) has as its main theme the recent FDA ‘black box’ warning on drugs used by allergists, especially the long-acting β₂-agonists (LABA). There are at least seven articles on this matter including reviews, editorials and perspectives. The reader is exposed to the meanings and mechanisms of the black box warning and the functions of the FDA. An understanding of β₂-receptor function, mechanisms and genetic variability is highlighted. The review summary by Harold S Nelson concludes that LABAs should only be administered accompanied by therapy with inhaled corticosteroids. In this combination there is no evidence of deleterious effects from the use of the LABAs.

The use of magnesium sulfate in acute asthma: rapid uptake of evidence in North American emergency departments
Rowe BH, Camargo CA (J Allergy Clin Immunol 2006; 117: 53-58)
This article reminds us that intravenous magnesium sulphate is a possible treatment modality in patients with acute severe asthma. Observational cohort study data were collated from 9 745 emergency department patients with asthma. Of these patients, 240 received magnesium sulphate. Although there is no comment on the efficacy of this treatment, the authors conclude that physicians in emergency departments across North America and Canada accept the efficacy of this treatment in acute asthma. Further, it is readily available and appropriately restricted to use in patients with severe acute asthma.

Bidirectional interactions between viral respiratory illnesses and cytokine responses in the first year of life
A very complex article detailing results of nasopharyngeal viral analysis and blood cytokines from 285 children enrolled in the study. The children were enrolled at birth and routine blood and nasopharyngeal samples collected at predetermined intervals as well as during wheezing episodes. Of clinical interest, 89 children (31%) had 179 wheezing episodes. Viruses were identified in 118 (66%) of these wheezing episodes, most often rhinovirus (n = 59) and RSV (n = 51). Wheezing episodes were associated with a unique developmental pattern of IL-13 and IFN-γ cytokine response profiles which will continue to be tracked.

Response profiles to fluticasone and montelukast in mild to moderate persistent childhood asthma
This large group of asthma researchers from the Childhood Asthma Research and Education Network of the National Heart, Lung and Blood Institute have sought to determine intra-individual and interindividual response profiles to an inhaled corticosteroid (ICS) and a leukotriene receptor antagonist (LTRA).

One hundred and forty four children (6-17 years) with mild to moderate persistent asthma were enrolled. The study was multicentre, randomised, double-masked, 2-sequence, and 16-week crossover. The ICS fluticasone propionate (100 µg twice daily) or the LTRA montelukast (5-10 mg) were administered using only as needed bronchodilators.

Clinical, pulmonary, and inflammatory responses to these controllers were evaluated.

The results confirmed that improvements in most clinical asthma control measures occurred with both controllers. However, clinical outcomes, pulmonary responses and inflammatory biomarkers improved significantly more with fluticasone than with montelukast.

Exhaled nitric oxide (eNO) a biomarker for allergic inflammation was also measured. Within participants, patients with higher baseline eNO levels responded better to ICS than LTRA.

The authors concluded that asthma control, assessed by use of several clinical, pulmonary and inflammatory responses, improved consistently and significantly more with an ICS than with montelukast. Further eNO might be a useful marker to identify children who can achieve a greater improvement with an ICS compared with an LTRA.
It is hard to believe that we are already into the first quarter of the new year! I hope you had a good holiday season, and are raring to go in 2006! The past year was an excellent year for ALLSA, as reviewed in the Chairman’s report in the November edition of Current Allergy & Clinical Immunology. I would like to take advantage of this opportunity to thank Cas Motala for his inspirational leadership during 2005. He continues to represent us at international level, and has valuable connections with the World Allergy Organisation. He also maintains excellent relationships with the pharmaceutical industry. Last year he put a great deal of effort into achieving tax exemption status for ALLSA, so that the funds we have at our disposal can be put to good use in furthering education and research in allergy in South Africa.

What of 2006? Our first activity will be the Diploma in Allergology, with the clinicals being hosted by the University of Pretoria, thanks to Robin Green. We have 5 candidates for this examination, clearly indicating that the Diploma is becoming a sought-after qualification. The Allergy Masterclass for 2006 will be held in Cape Town on 20 May, as Gauteng have a few inter-city meetings on the cards for this year, and also host the Congress. Please see elsewhere in this journal for the application form and provisional programme for the Masterclass.

ALL 4 KIDS, the combined ALLSA and SA Paediatric Association Congress, will be held in Sun City in September. André van Niekerk is the ALLSA convenor and congress co-chair. Already the line-up of international and local speakers promises a congress of the very highest quality, and the allergy section boasts speakers of the calibre of Michael Kaliner, Allen Kaplan and Gideon Lack. Kindly diarise the date: 7-10 September.

A major focus for this year is the revision of both the adult and the children’s asthma management guidelines. To this end it is heartening to report improved liaison between ALLSA and NAEP (Andrew Halkas is the official ALLSA representative on NAEP Council), and between ALLSA and SATS (Elvis Irusen and Heather Zar are both ALLSA Excom and also SATS Council members). Kindly also diarise World Asthma Day on 2 May.

It gives me great pleasure to congratulate Mike Levin on achieving his doctoral degree in linguistics, pointing out the language barriers that exist between doctors and our non-English speaking patients. His article appeared in this journal last year and won him the Editors’ award for the best publication in 2005. His research was partially supported by an ALLSA research award. Congratulations too on the arrival of your daughter Amara, Mike!

Finally, I would like to make an appeal to our members to submit letters and articles to this journal. Current Allergy & Clinical Immunology, our flagship, makes a very important contribution to allergy in SA. The editors and guest editors do a marvellous job with review articles, but they need input from our members. Please see the Contents page for details regarding contributions.

Sharon Kling
Secretary

NASONEX IS NOW INDICATED FROM THE AGE OF 2 YEARS!

Nasonex Aqueous Nasal Spray is indicated for use in adults, adolescents and children between the ages of 2 and 11 years to treat the symptoms of seasonal allergic or perennial allergic rhinitis.

In patients who have a history of moderate to severe symptoms of seasonal allergic rhinitis, prophylactic treatment with Nasonex Aqueous Nasal Spray is recommended prior to the anticipated start of the pollen season.

Dosage and directions for use

Adults and adolescents: The usual recommended dose for prophylaxis and treatment is two sprays (50 µg/spray) into each nostril once daily (total dose 200 µg). Once symptoms are controlled, dose reduction to one spray into each nostril (total dose 100 µg) may be effective in some patients for maintenance.

Children between the ages of 2 and 11 years: The usual recommended dose is one spray (50 µg/spray) in each nostril once daily (total dose 100 µg).

For more information contact Gary Vine, Schering-Plough (Pty) Ltd, 011-922-3300.
Support your society, as it supports the study and practice of allergology in South Africa.

ALLSA remains one of the world’s most pro-active and innovative allergy societies. Our pioneering website and patient information resources have spurred other national societies to follow suit.

ALLSA relies on an active membership base to continue to provide excellent resources to healthcare workers in Southern Africa. We welcome new members from all over Southern Africa and membership is open to all healthcare workers with an interest in allergology. Our current membership includes medical practitioners (general practitioners, physicians, pulmonologists, ENT specialists, dermatologists, ophthalmologists, paediatricians and anaesthetists), nurses, dieticians, medical technologists, pharmaceutical industry staff and medical students.

Membership currently costs only R120 annually; this tax-deductible contribution to ALLSA is valued by our society which then ploughs these contributions back into providing new resources for members and the public.

Members enjoy a number of privileges which include:

- The highly rated ALLSA journal – *Current Allergy & Clinical Immunology*, which is edited by Profs Weinberg and Zar and published quarterly.
- Patient information guides and leaflets on all the common allergic disorders and allergen avoidance measures.
- Access to database of international allergy research journals and journal searches.
- Discounted ALLSA congress registration fees for our annual congress.
- Regional allergy courses, meetings and journal clubs.
- Support with examination preparation for the Diploma in Allergology of the Colleges of Medicine of SA.
- Access to allergy research funding and annual ALLSA research awards of up to R50 000 per research study.

For more details on membership and privileges please contact Ruwayda Adams on tel 021-447-9019, fax 021-448-0846, or e-mail enquiries to allsa@mweb.co.za.

Please cut out the membership application form and post together with your cheque or postal order made payable to the Allergy Society of South Africa. Please ensure the full society name appears on the cheque; the initials ‘ALLSA’ are unfortunately not acceptable to the bank. If you pay by direct debit, please ensure the bank slip includes your surname and birth date (Smith 12/06/63); this should be faxed to ALLSA at 021-448-0846.

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**ALLSA Membership Application**

**R150 annual subscription**

Dr/Sr/Mr/Mrs/Ms: ____________________________________________

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Date of birth: ____________________________________________

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Special Interests: ____________________________________________

Comments: ____________________________________________

Post to: Allergy Society of South Africa, PO Box 88, Observatory 7935

**Direct debit details:**

Standard Bank: Rondebosch

Sort Code: 02-50-09

Account Number: 07 149 1821

Cheques and postal orders payable to **Allergy Society of South Africa**

Please include surname and birth date on direct debit order and fax bank slip to 021-448-0846
MSD and the Allergy Society of South Africa take pleasure in announcing a new research award for 2006

R25 000 will be made available for the MSD-ALLSA Research Award in 2006. The award will be granted for an asthma-related project in Southern Africa.

Closing date for application
31 May 2006

Application details can be obtained from the ALLSA office

Please visit the ALLSA website at www.allergysa.org/awards to submit your electronic application.

Please note that only electronic submissions will be processed

ALLSA NATIONAL OFFICE
P.O. Box 88
Observatory
7935

TELEPHONE & FAX ENQUIRIES
Fax: (021) 448 0846
Tel: (021) 447 9019

E-mail: allsa@mweb.co.za
R25 000 will be made available in 2006. The purpose of the award is to support local research into allergic conditions of Southern Africa. Preference will be given to supporting non-established researchers demonstrating research potential.

Closing date for application
31 May 2006

Application details can be obtained from the ALLSA office

Please visit the ALLSA Website at www.allergysa.org/awards to submit your electronic application

(Please note only electronic submissions will be processed)

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CPD QUESTIONNAIRE

Earn 2 CPD points after you have read the journal by completing the following questionnaire online on the ALLSA website at www.allergysa.org/cpd or follow the links from the home page www.allergysa.org. To earn points, you will need to register and fill in personal details (make sure you have your HPCSA number handy and decide on a password beforehand). Once you have registered, you can answer the questionnaire. Please note that there is only one correct answer per question, and you will have only one opportunity to submit the questionnaire, so please check answers carefully. You will be able to change answers if you click the wrong one by mistake, but once you click ‘Submit Answers’ the test will be submitted and marked. Points will be submitted electronically to the HPCSA. The closing date for submission of this questionnaire is 31 May 2006.

IS ALLERGY TESTING COST-EFFECTIVE?
1. True or false? Allergy testing in infancy is inaccurate and should be deferred until at least the age of 3 years or older.
   a) True
   b) False

2. True or false? The presence of IgE antibodies greater than 3.5 kU/l for both Phadiatop and f5 measured in combination in 4-year-old children indicates a 97.4% predictive likelihood of a suspected allergic disease (asthma, rhinitis, eczema or food allergy).
   a) True
   b) False

3. True or false? In children, a specific IgE level to peanut which is 14 kU/l or greater has a 100% predictive value for diagnosing peanut allergy.
   a) True
   b) False

4. Choose ONE correct answer: The f5 food allergy screen (Phadia) consists of the following food allergens:
   a) Cow’s milk, hen’s egg, wheat flour, soy protein, codfish and peanut
   b) Soya milk, hen’s egg, corn flour, lentil bean, codfish and peanut
   c) Cow’s milk, hen’s egg, wheat flour, tomato, codfish and peanut
   d) Soya milk, hen’s egg, corn flour, tomato, dogfish and peanut
   e) Cow’s milk, strawberry, wheat flour, soya bean, codfish and lentil.

CLINICAL INDICATIONS AND INTERPRETATION OF THE CAST
1. Choose ONE correct answer: The CAST determines:
   a) Leukotriene release
   b) Leukotriene and histamine release
   c) Tryptase release
   d) Catecholamine release
   
2. Choose ONE correct answer: The CAST is ideally suited to testing:
   a) Bee venom hypersensitivity
   b) Inhalant allergies
   c) Allergy to food preservatives
   d) Milk intolerance
   e) Dermatographism is present.

3. Choose ONE correct answer: The following is required for CASTs:
   a) Fresh serum
   b) Fresh EDTA whole blood
   c) Heparinised whole blood
   d) Clotted blood

SPECIALISED IN VITRO DIAGNOSTIC METHODS IN THE EVALUATION OF HYPERSENSITIVITY – AN OVERVIEW
1. Choose ONE answer: During the allergic reaction new and pre-formed mediators are released from cells, such as mast cells and eosinophils. Choose the INCORRECT one:
   a) Tryptase
   b) Histamine
   c) IgE antibody
   d) Eosinophil cationic protein

2. True or false? During an immune response to a foreign antigen, antibodies are produced as part of the body’s defence mechanism. The IgG antibody response can be quantified using the ImmunoCAP, however it is only validated for some allergens.
   a) True
   b) False

POSITION STATEMENT: SKIN-PRICK TESTING
1. True or false? A wheal of 5 mm to hen’s egg skin-prick test has a 100% positive predictive value for egg allergy at age 7 years.
   a) True
   b) False

2. True or false? Allergen skin-prick testing (SPT) is a much safer procedure than intradermal (ID) skin testing.
   a) True
   b) False

3. Choose ONE incorrect statement. Skin-prick testing should not be performed when:
   a) There is a history of anaphylaxis to test solution.
   b) The child is under one year of age.
   c) Patient is currently on antihistamine medication.
   d) Extensive eczema is present at test site.
   e) Dermatographism is present.

4. Choose ONE incorrect statement:
   a) Skin testing may be performed on the volar aspect of the forearm.
   b) The lancet should have a 5 mm tip and blunted shoulder.
   c) The allergens should be placed 2-3 cm apart.
   d) The wheal reaction must be measured after 15-20 minutes.
   e) Allergens should be stored between 2 and 8°C.

COMPLEMENTARY AND ALTERNATIVE ALLERGY TESTS
1. Choose ONE answer that is not an example of a complementary and alternative medicine (CAM) allergy test:
   a) Electrodermal (VEGA) test
   b) Applied kinesiology
   c) CAST
   d) Auriculocardiac test
   e) Hair analysis

2. Choose ONE correct answer: Applied kinesiology testing involves:
   a) Skin electromagnetic measures
   b) Testing muscle strength
   c) Specific IgE antibodies
   d) Specific IgG antibodies
   e) Applying fresh allergen to the skin.

ABC OF ALLERGOLOGY
1. True or false? Obesity, fibromyalgia, anxiety and hypoglycaemia may have an underlying allergic cause.
   a) True
   b) False

2. True or false? Delayed hypersensitivity reactions are related to specific IgE antibodies causing mast cell degranulation.
   a) True
   b) False

ALLERGIES IN THE WORKPLACE
1. Choose ONE correct answer: Work-related asthma symptoms are commonly reported among workers in the fish processing industry involved in all, EXCEPT ONE of the following activities:
   a) degutting of fish
   b) boiler room (local dust)
   c) fishmeal milling and bagging
   d) fish filleting

2. Choose ONE correct answer: The common causes of dermatitis among workers in the fish processing industry are the following, EXCEPT ONE of the following:
   a) water
   b) fish and fish products (fish juice, slime/mucin, skin, fillet, gut)
   c) additives (e.g. garlic, onion, spices)
   d) glues and inks used for can labelling
Instructions for Authors

Current Allergy & Clinical Immunology publishes articles concerned with the understanding and practice of allergic diseases or clinical immunology.

Material submitted for publication to Current Allergy & Clinical Immunology is accepted on condition that it has not been published elsewhere. The management reserves the copyright of the material published. All named authors must give consent to publication. Current Allergy & Clinical Immunology does not hold itself responsible for statements made by contributors.

Original research, review articles, case reports, brief research reports or photographs may be submitted. Letters to the editor are welcome and if suitable will be published in a correspondence section.

All articles will be subject to peer review. Electronic submission is preferable. However, if authors are unable to submit electronically then the article may be posted to the correspondence address listed at the end of these instructions.

Manuscript preparation

1. Articles may be submitted electronically online at www.allergysa.org/articles or follow the links from the homepage www.allergysa.org. To register, you need to enter your name, personal details, HPCSA number and a password. Once you have registered, you will receive an email confirming your registration. You can either submit your article immediately or log on at a later date. Authors should state their full name, qualifications, institutional affiliation and provide a corresponding address and email on the title page. Articles should be a maximum of 3500 words with no more than 3 figures and 3 tables. Short reports should be a maximum of 1000 words with a maximum of 2 tables or illustrations.

2. Each article should be accompanied by a summary of not more than 200 words (50 words for short reports). A structured abstract is required for original research papers.

3. Authors are requested to declare conflict of interest and source of funding relating to the article. Authors should disclose any relationship within the last 2 years with pharmaceutical companies in the following categories if pertinent to the article: research grants, educational support (sponsorship at conference), advisory boards, speaker, consultant or shares in companies. This must be stated at the end of the manuscript before the references. Details of ethical approval obtained must be included in all original research articles.

4. All abbreviations should be spelt out when first used in the text and thereafter used consistently.

5. Scientific measurements should be expressed in SI units.

6. Tables should be labelled with Roman numerals, thus: I, II, III, etc. and illustrations with Arabic numerals, thus: 1, 2, 3, etc. Tables and figures should be submitted as part of the manuscript file. Please do not submit photographs in Powerpoint and MS Word format – a high-resolution jpg is required. Photographs should be submitted separately from the manuscript file and clearly labelled.

7. Where identification of a patient is possible from a photograph the author must submit a consent to publication signed by the patient, or by the parent or guardian in the case of a minor.

8. If any tables or illustrations submitted have been published elsewhere, written consent to republication should be obtained by the author from the copyright holder and the author(s).

References

1. References should be inserted in the text as superior numbers, and should be listed at the end of the article in numerical order.

2. References should be set out in the Vancouver style, and only approved abbreviations of journal titles should be used; consult the January issue of Index Medicus (No. 1 Part 1) for these details. Names and initials of all authors should be given unless there are more than six, in which case the first three names should be given followed by ‘et al.’ First and last page numbers should be given.

Example:


3. References for books should include author, title, town, publisher and date.

Example:


4. ‘Unpublished observations’ and ‘personal communications’ may be cited in the text, but not in the reference list. Articles accepted but not yet published can be included as references followed by ‘(in press)’.

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