# Current Allergy & Clinical Immunology

## Contents

### Guest Editorial
- **54** Congress issue: food allergy, drug allergy and anaphylaxis
  - C Motala

### Review Articles
- **56** Food protein-induced enterocolitis syndrome
  - L-A van der Poel, A Fox, G du Toit
- **58** Oral allergy syndrome - what's new?
  - H Steinman
- **64** Penicillin allergy in children
  - S Karabus, C Motala
- **67** Anaphylaxis in infants: can recognition and management be improved?
  - F E R Simons
- **71** H1 antihistamines in allergic disease
  - C Motala
- **75** Asthma exacerbations - a review
  - N Chetty

### Allergies in the Workplace
- **84** Allergic contact dermatitis in the food industry - from agriculture to food processing and manufacture: A case study of a dairy farmer
  - A Burdzik

### ABC of Allergology
- **89** Allergy examination
  - S Emanuel, D Hawarden

### Evidence-Based Health Care
- **91** Dietary exclusions for established atopic eczema
  - T Young

### Chairmen’s Report
- **93** S Kling

### Product News
- **82, 95, 96, 97, 99**

### CPD Questionnaire
- **100** Earn 3 CPD points

### 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.

The Allergy Society of South Africa gratefully acknowledges support from these companies:

- Abbott
- AHN Pharma
- AstraZeneca
- Boehringer Ingelheim
- Cipla Medpro
- GlaxoSmithKline
- Laboratory Specialities
- Miele
- MSD
- Nestlé
- Novartis
- Schering-Plough

---

**Editors**
- Prof. Eugene G Weinberg
- Prof. Heather J Zar

**Founding Editor**
- Prof. Paul C Potter

**Production Editor and Advertising Executive**
- Anne Hahn

**Editorial Advisory Board**
- Dr C Buys (Namibia)
- Dr G du Toit
- Prof. R Green
- Prof. M Haus
- Prof. M J eebhay
- Dr N Khumalo
- Dr S Kling
- Dr A Lopata
- Dr A Manjra
- Dr A Morris
- Prof. C Motala
- Dr C Obihara (The Netherlands)
- Prof. P Potter
- Dr A Puterman
- Prof. G Todd

**Contributions**
The editors encourage articles, letters, news and photographs relating to the field of allergy and clinical immunology. Enquiries should be addressed to: The Editors, Current Allergy & Clinical Immunology, Allergy Society of South Africa, PO Box 88, Observatory 7935 South Africa.

Tel: 021 447 9019,
Fax: 021 448 0846,
Website: [www.allergysa.org](http://www.allergysa.org)

E-mail: mail@allergysa.org

Accredited by the Department of Education

The views expressed in this publication are those of the authors and not necessarily those of the sponsors or publishers. While every effort has been made to ensure that the contents of this journal are both accurate and truthful, the publisher and editors accept no responsibility for inaccurate or misleading information that may be contained herein.

Cover: Fresh fruit

Courtesy: Dr H Steinman

Printed by Tandym Print
Repro by C2 Digital

ISSN 1609-3607
Allergic diseases, including asthma, rhinitis, conjunctivitis, dermatitis and food allergies, are major contributors to morbidity and sometimes cause mortality in the developed world. Also, their incidence and severity are still rising. Over the past decades, genetics together with both basic and clinical immunology have made great strides in understanding the disease processes in allergy. The articles in this edition of Current Allergy & Clinical Immunology include aspects of food allergy, drug allergy and anaphylaxis, in line with the themes of this year’s ALLSA congress.

There have been significant advances in the understanding of food proteins and recognition of gastrointestinal syndromes in food allergy. Van der Poel et al. briefly discuss food protein-induced enterocolitis syndrome (FPIES), a potentially life-threatening condition due to non-IgE-mediated food allergy (cow’s milk and soya proteins are the common causes), with emphasis on correct diagnosis, management and prognosis. IgE antibodies to aeroallergens may cross-react with protein in fresh fruit and vegetables to cause symptoms that include oral pruritus, swelling of the lips, tongue and throat – the oral allergy syndrome (OAS). Steinman discusses new information about plant proteins including profilins, lipid transfer proteins and pathogenesis-related proteins, as well as the growing list of pollen-food syndrome associations, and the potential role of immunotherapy in the treatment of OAS.

Drug allergy remains one of the most challenging areas in the field of allergology. This is partly related to the number of new drugs emerging on the market each year, but also to the various routes of administration, the presence of allergenic excipients in drugs and the misuse of antibiotics in general. Allergic reactions to the penicillins and cephalosporins remain the most common drug allergies. Penicillin allergy continues to be misdiagnosed. Karabus and Motala outline a practical approach to the diagnosis of penicillin allergy and its management.

Anaphylaxis is the most serious form of an allergic reaction, with food allergens being the most common cause of this disorder. Simons presents an excellent overview of anaphylaxis in children including a case report, aetiology, differential diagnosis and management of this life-threatening condition. The use of self-injected adrenaline as first-aid treatment for anaphylaxis is emphasised. H1-antihistamines remain first-line medication in the treatment of allergic rhinoconjunctivitis and urticaria. Motala discusses the mechanism of H1-antihistamines and advantages of the second-generation antihistamines over their predecessors in the long-term management of allergic diseases.

Cas Motala
Guest editor
Associate Professor, Paediatric Medicine, School of Child & Adolescent Health, University of Cape Town & Red Cross War Memorial Children’s Hospital, Rondebosch, Cape Town, South Africa
FOOD PROTEIN-INDUCED ENTEROCOLITIS SYNDROME (FPIES) – A REVIEW

Lauri-Ann van der Poel, MB ChB, MRCPCH
Adam Fox, MA, MSc, MBBS, DCH, FRCPCH, FHEA, Dip Allergy
George du Toit, MB BCh, DCH, FCP(SA), FRCPCH, Dip Allergy, FAAAI
MRC & Asthma UK Centre in Allergic Mechanisms of Asthma, Division of Asthma Lung Biology, Guy’s and St Thomas’ NHS Foundation Trust, Kings College, London, UK

ABSTRACT

Food protein-induced enterocolitis syndrome (FPIES) is an under-recognised and frequently misdiagnosed syndrome – characterised by severe protracted diarrhoea and/or vomiting and frequently associated with additional symptoms such as pallor and/or lethargy – which has its onset soon after the ingestion of the particular food protein. FPIES represents a severe cell-mediated, gastrointestinal food hypersensitivity. Although typically ascribed to cow’s milk and soy, FPIES has been described after the ingestion of a wide range of food proteins.

This brief review aims to summarise current knowledge of food protein-induced enterocolitis syndrome (FPIES).

PRESENTATION AND PREVALENCE

The presentation of FPIES varies from mild (e.g. non-dehydrating vomiting and/or diarrhoea) to severe and potentially life-threatening symptoms. Symptom progression may occur rapidly to a state of dehydration. Hypovolaemic shock is associated in up to 20% of cases. A combination of vomiting, lethargy and resulting acidosis understandably – and necessarily – leads to the primary diagnosis of sepsis. In this clinical scenario, the dietary history may not receive prominence with the result that the syndrome recurs with each subsequent ingestion of the food protein. Failure to recognise the association with diet may lead to multiple intensive or high-care admissions due to supposed recurrent sepsis.

It is unclear whether prior ingestion of the food protein is required in order to induce the FPIES ‘sensitivity’ or if symptoms can occur de novo. FPIES has only been described in childhood, and in particular, early childhood (at the time of introduction of complementary feeds, i.e. breast-milk alternatives and/or solid foods). The prevalence and incidence of FPIES are not known. Attempts to determine them are hampered by the variable presentation, under-recognition of the syndrome, infrequently performed diagnostic challenges and, perhaps, the rarity of the condition.

DIAGNOSIS

The FPIES diagnosis is a clinical one; equivocal scenarios require resolution by modified oral food challenge (OFC) tests. Standard OFCs are modified in anticipation of rapid-onset vomiting and/or diarrhoea. Therefore, intravenous cannulation is necessary prior to commencement, as are stepwise challenge increments. Lengthy intervals between incremental food doses are mandatory. It is also wise to prepare intravenous bolus replacements, anti-emetics and steroid medications.

The FPIES diagnostic criteria include the onset of predominantly gastrointestinal (GI) symptoms in young infants (usually before 9 months of age), which are consistently present on repeat ingestion of the trigger food. Recurrent vomiting usually occurs within 1-2 hours. Removal of the offending food protein from the diet leads to rapid and complete resolution of symptoms within 24-48 hours. Additional pathognomonic features include a raised white blood cell count with a predominance of neutrophils. This finding necessarily blurs the clinical picture, raising the clinician’s suspicion of sepsis. The presence of bloody diarrhoea may also lead to suspicion of infectious diarrhoea, coagulation defects or intussusception in those who fail to appreciate the significance of the temporal association with a new food. The absence of fever, presence of eosinophilic debris in the stools and negative stool cultures can help differentiate these conditions. Characteristically, inflammatory markers are not raised. Biopsies show crypt abscesses, diffuse inflammatory cell infiltrates with plasma cells in the colon, and oedema with mild villous injury in the small intestine. FPIES may occasionally present with insidious chronic diarrhoea, vomiting and failure to thrive.

Patients with FPIES classically return negative allergy tests (specific-IgE and/or skin-prick testing). Endoscopy is often unhelpful as infants may remain well between challenges. Atypical cases have been described with detectable specific IgE to the causal protein and with a more prolonged course of allergy. However, given the high population prevalence of IgE-mediated food allergy (between 4% and 6% in young children in developed countries), it is not surprising that a proportion of children with FPIES have concomitant IgE-mediated food allergy.

Studies suggest that atopy patch testing (APT) can aid prediction of tolerance and thus avoid unnecessary food challenges. Indeed, Fogg et al. demonstrate in 19 children with FPIES that APT returns a remarkably high sensitivity and specificity.

DIFFERENTIAL DIAGNOSIS

Acute infective conditions remain the primary differential diagnosis, e.g. sepsis and/or gastroenteritis. Conditions such as milk-protein-induced proctocolitis, enteropathy and eosinophilic gastroenteropathies may also present with similar, overlapping features. FPIES represents the severe end of the spectrum of food allergy that affects only the gut. Table I outlines the comparative features of FPIES, gastroenteritis and IgE-mediated food allergy.

ROUTE OF EXPOSURE AND TYPICAL FOOD PROTEIN TRIGGERS

The route of allergen exposure is usually by ingestion. There are no reports of FPIES in exclusively breastfed infants. This is in contrast to IgE-mediated food allergies where acute skin reactions and even non-IgE-
mediated conditions, such as dietary protein-induced proctocolitis, have been attributed to food protein passage through breast milk.2

Milk and soy are most frequently implicated; it is not uncommon for infants to react to both (50%).1 Many solid food allergens have also been implicated in FPIES.2 Cross-reactivity is high, e.g. when one fin-fish species is implicated, children may react to other fin-fish. Table II lists case reports which reflect the food proteins regarded as responsible for inducing FPIES.

**MANAGEMENT**

While the pathophysiological immune basis for FPIES is poorly understood, the cornerstone of management of children with FPIES is careful exclusion of the causal food protein (and cross-reactive foods). The prognosis of the condition is favourable. Modified incremental OFCs will be necessary to verify the diagnosis if the presentation is equivocal, and to determine whether tolerance to the candidate food protein has developed. Symptoms resolve dramatically after avoidance of the causal food protein (and cross-reactive foods). The prognosis of the condition is favourable.

**REFERENCES**

**ORAL ALLERGY SYNDROME – WHAT’S NEW?**

Harris Steinman, MB ChB, DCh(SA)

Food & Allergy Consulting Services, Milnerton, Cape Town, South Africa

**ABSTRACT**

Oral allergy syndrome/pollen-food syndrome (OAS/PFS) affects up to 70% of patients with birch-pollen allergy. Prevalence is likely to continue to increase as the prevalence of inhalant allergies rises. Homologous proteins in fruits, vegetables, and pollen of grasses, trees, and weeds are responsible for PFS. Component-resolved diagnosis (CRD) with recombinant allergens may assist with the diagnosis of this condition in the future. As there is currently no proven therapy for this syndrome, cooking and avoidance of offending fruits and vegetables are the only options.

**INTRODUCTION**

Individuals with pollen allergy often report adverse effects after the ingestion of a wide variety of foods from plants. This association has in recent years gained greater recognition because of the increasing prevalence of pollen allergy.2 The clinical effects are usually restricted to the oral cavity and include oral pruritus, swelling of the lips, tongue and throat, hoarseness, pharyngitis, and laryngeal oedema. These localised symptoms, caused by fruit, vegetables and spices, have been termed oral allergy syndrome (OAS).2,24 Immunoglobulin E (IgE) antibodies to the aeroallergen cross-react with the proteins in fresh fruit and vegetables to cause symptoms. Symptoms that patients experience are usually mild and do not require immediate medical attention. However, some patients experience more severe and systemic reactions, such as severe laryngeal oedema, urticaria, asthma, or even food-induced anaphylaxis, though this is quite rare except in mugwort-celery-spice syndrome.2,9 This variation has resulted in a debate over whether such reactions may be considered a severe form of OAS or whether, as other authors contend, OAS includes only mild symptoms.

Further, whereas the term OAS has been used by some authors to describe oral symptoms caused by any food allergen, and not necessarily related to pollen allergy, others have argued that the term pollen-food syndrome (PFS) should be used to highlight the association between pollen-sensitisation and oral symptoms, since this is less ambiguous.2,12,11

As OAS/PFS symptoms are in most instances mild, the prevalence is difficult to assess. Estimates of the percentage of patients with pollen allergy who also suffer from PFS vary from 47% to 70%, and this is thought to be the most common food allergy in adolescents and adults.12

Although most scientific evidence is related to co-sensitisation with birch pollen, a tree sparsely found in South Africa (where it is planted mainly as an ornamental), many other sources of pollen are likely to contain one or more of the cross-reactive panallergens, and therefore similar clinical effects may be seen locally. Further, allergenic weed sources can be found in the botanical families of Asteraceae (mugwort, ragweed, sunflower, feverfew), Amaranthaceae (goosefoot, Russian thistle), Urticaceae (wall pellitory), Euphorbiaceae (castor bean, mercury pollen, latex tree), Plantaginaceae (plantain), and Cannabaceae (Japanese hop pollen), with mainly plants of the Asteraceae family giving rise to OAS/PFS, particularly in Europe.2,13 In Australia and Mediterranean countries, 20-40% of pollen-allergic patients are found to be allergic to plantain (Plantago lanceolata).2

**ASSOCIATIONS**

Although individuals may experience oral symptoms following ingestion of fruit and vegetables without underlying pollen allergy, in the majority of cases the initial event is sensitisation to pollen, and then there is subsequent development of cross-reactivity to food allergens, so that patients often develop pollen allergies before the development of oral symptoms.10 In Europe, sensitisation to birch pollen is a very common contributor.14

The association of oral symptoms and pollen allergy results from cross-reactivity of pollen-specific IgE with homologous food allergens.10 Prior to the identification of these proteins, the association between different families of plants was not well understood. The pollens and foods involved are usually not botanically related but contain conserved homologous proteins, as there are shared epitopes (binding sites) in the primary and tertiary structures of pollen and food allergens.2 Several clinical syndromes have been described25 as resulting from these associations, e.g. between birch pollen and fruit, in particular apple,16 between ragweed pollen and melon and/or bananas,17 between birch and/or mugwort pollen and celery (the so-called ‘mugwort-celery-carrot-spice syndrome’),18-20 between latex and fruit (latex-fruit syndrome),21,26 between plantain and cocksfoot (orchard) grass (Dactylis glomerata) pollen and melon;27 and a number of other associations among aeroallergens and plant proteins, depending on the particular cross-reactive allergens.

The plant proteins involved in OAS and PFS have been shown to belong to plant protein families, including those of profilins, pathogenesis-related proteins (PRs), and lipid transfer proteins (LTPs). There are a few well-described associations between aeroallergens and the fruits that elicit OAS symptoms. Appreciating the pattern of sensitisation to these foods and to pollen may assist in the deduction of the responsible panallergens, and thereby assist with predicting the range of food that may affect an individual. Only the most common relevant panallergens are reviewed below, and it should be kept in mind that other allergen families, e.g. calcium-binding proteins (polcalins), are occasionally responsible for PFS.2 With the development of recombinant allergens, component-resolved diagnosis (CDR) may assist in the prediction and management of OAS/PFS.24

**Profilin**

Profilin is a monomeric, actin-binding protein that regulates the organisation of the actin filaments to form the actin cytoskeleton in plants.25 Profilins are present in a

---

Correspondence: Dr Harris Steinman, Food & Allergy Consulting Services, PO Box 565, Milnerton 7435. E-mail harris@zingsolutions.com

58 Current Allergy & Clinical Immunology, June 2009 Vol 22, No. 2
broad range of pollens and foods, including trees, grasses and weeds. Sensitisation to profilin occurs in approximately 20% of pollen-allergic patients, and patients sensitised to pollen profilins react to a broad range of inhalant and food allergens.10,25,26

An example is the birch pollen allergen Bet v 2. Patients who are sensitised to Bet v 2 often have symptoms upon ingesting apple, pear, carrot, and celery.1 Patients with allergies to grass pollen profilin often have oral symptoms in response to eating celery and carrots.1

In mugwort-celery-spice syndrome, patients sensitised to mugwort cross-react to profilins in celery and spices of the Apiaceae, or Umbelliferae, family (carrots, caraway seeds, parsley, coriander, aniseed or fennel seeds).1,9

However, there is a wide range of homology between profilins from different fruits and vegetables; therefore, cross-reactivity is more likely to occur among foods with high degrees of profilin homology than among those with low homology.

Pathogenesis-related proteins (PRs)
PR proteins are involved in the defence systems of higher plants and are induced upon infection, wounding or environmental stresses (e.g., drought, flooding, freezing temperature, and ozone).27 They are classified into 14 families based on similarities such as in their amino acid sequence or enzymatic activities.27 Importantly, these proteins are stable at low pH and resistant to proteolysis. Not all PR families contain allergens: plant-derived allergens have sequence similarities to PR families 2,3,4,5,8,10, and 14.27,28 Approximately 25% of characterised allergens are PRs.29

As PR proteins are influenced by a number of factors, they may vary depending on the environmental conditions in which the plant grows, and on the particular cultivar of the fruit. Even ripeness and storage conditions affect PR content, with more mature plants having more.27 Geographical and dietary factors also play a role in sensitisation to fruit or vegetables containing PRs.15 For example, allergy to Rosaceae family fruits is attributed to grass pollen sensitisation in southern Europe and to birch pollen sensitisation in northern Europe.2,30,31

The PR family consists of, among others, the beta 1,3 glucanases (the PR-2 family), the class I, II, and IV chitinases (the PR-3 family), thaumatin-like proteins (PR-5), class III chitinases (PR-8), Bet v 1 homologues (PR-10) and LTPs (PR-14).

The PR-2 family consists of beta 1,3 glucanases, which catalyse the hydrolytic cleavage of 1,3 beta-D-glucosidic beta 1,3 glucans, abundant components of the plant cell wall.30 These allergens have been isolated from banana, potato, tomato and latex (Hev b 2), and are thought to be responsible for the cross-reactivity between these foods and latex in the latex-food syndrome seen in some patients.1,17,27

The PR-3 family consists of the class I, II, and IV chitinases. However, only class I chitinases have been associated with allergy.1,28 These proteins hydrolyse chitin found in the exoskeletons of insects and the cell walls of fungi. Banana, avocado and chestnut have allergens with sequence similarity to the class I chitinases, and the class I chitinases have an N-terminal hevein domain that is shared by latex prohevein (Hev b 6.01).1,17,34 The PR-3 allergens are thought to be responsible for the cross-reactivity between the above foods and latex in latex-food syndrome.34

The PR-5 family contains the thaumatin-like proteins. Although not fully understood, thaumatin-like proteins are thought to have antifungal properties, to rapidly accumulate in high levels during stress on the plant, and to give plants resistance to freezing and drought.1 Thaumatin-like proteins have been characterised from apple (Mal d 2), cherry (Pru av 2), bell pepper (Cap a 1) and mountain cedar pollen (Jun a 3).1,27

The PR-8 family of proteins consists of class III chitinases. These are usually minor allergens.1 This group includes the latex allergen hevamine27,28 and a chitinase from cucumber.29

The PR-10 family consists of the Bet v 1-homologues, i.e. proteins that have an amino acid sequence homology with the allergen Bet v 1 from birch pollen, a protein with unknown function.27,28 As with other PRs, their expression is induced upon environmental stress, wounding or infection.28 They are probably the most important PR proteins involved in OAS/PFS, with approximately 70% of birch-pollen-allergic individuals being affected by OAS/PFS as a result of IgE cross-reactivity between Bet v 1 and its food homologues.27,28

PR-10 homologues are found in many members of the Rosaceae and Prunoideae fruits, and of the Apiaceae vegetables.2,4,28 The best known Bet v 1 homologue is Mal d 1, a major allergen in ripe apples, resulting in oral symptoms in birch-pollen-allergic patients. Other Bet v 1-homologues include Pru av 1 from cherry, Pru ar 1 from apricot, Pyr c 1 from pear, Api g 1 from celery, Dau c 1 from carrot, and Cor a 1 from hazelnut.4 These proteins share a high degree of amino acid sequence similarity (28-67%) with the major birch allergen Bet v 1.25,28,29

The PR-14 family comprises the LTPs. LTPs transfer phospholipids from liposomes to mitochondria and have antimicrobial activities.2 LTPs are important allergens of the Prunoideae family (peaches, apricots, plums, cherries) and the Rosaceae family (apples, pears), and are usually found in the peel.2 Significantly different from the protein families involved in OAS/PFS where a pre-existing pollen allergy sensitisation is found, LTPs often cause food allergy to fruit in the absence of pollen allergy. For example, hypersensitivity to peach, the most frequent fruit allergy in Spain, is clinically not associated with any kind of particular pollen allergy,31 even though there seems to be a higher prevalence of asthma in pollen-allergic patients with peach allergy.32 There are exceptions. For example, the LTP from mugwort pollen has been shown to cross-react with peach LTP and may be involved in the mugwort-peach allergy association frequently seen in the Mediterranean. Mugwort is not found in South Africa. Individuals who are allergic to LTPs in fruit have been shown to have a higher rate of anaphylaxis (36%) than those sensitised to PR-10 fruit allergens (18%).1,20,29

Current Allergy & Clinical Immunology, June 2009 Vol 22, No. 2 59
Cross-reactive carbohydrate determinants

The role of cross-reactive carbohydrate determinants (CCDs) remains controversial. Glycoproteins contain N-linked carbohydrate groups, which induce IgE, leading to cross-reactivity between foods and pollens. 24-26 CCDs are found in, among others, celery, tomato, potato and peanut, and in ragweed, timothy grass and birch pollen. However, debate continues over whether these CCDs can cause clinical symptoms. 24,28,29 For example, in a study of patients with grass-pollen allergy who are clinically asymptomatic to ingested peanut but have positive serum IgE to peanut but negative reactions to a skin-prick test for peanut, the patients were found to have IgE to the CCDs of peanut. The cross-reactive IgE had low biological activity. In contrast, in a study of celery-allergic patients, 25% were shown to have IgE to CCDs. 28 In a study of the sera of 10 tomato-allergic patients, 4 with IgE to CCDs showed biological activity in the basophil histamine release assay with tomato glycoproteins only but failed to react to nonglycosylated recombinant tomato proteins. 29

IgE antibodies directed toward glycans appear to show the widest pattern of cross-reactivity among allergenic extracts and are often responsible for observed in vitro cross-reactions within PFS. 24 Further research may elucidate the reasons for conflicting evidence and the causes of the variability of biological activity of CCDs. 24,26 Importantly, many glycoproteins carry only one IgE-binding glycan and therefore cannot cross-link IgE bound to receptors; nor can they activate mast cells and basophils, whereas other glycoproteins have been identified that contain more than one N-linked glycan. 30

As plant proteins are characterised in more detail, it will become easier to identify potential cross-reactions. However, not all patients with cross-reactive antibodies will actually experience symptoms; i.e. the IgE cross-reactivity will be either clinically manifest or irrelevant. Clinical manifestations seem to be influenced by a number of factors, including the host’s immune response, allergen exposure, and the individual allergen itself. 2 For example, and importantly, amino acid sequence homology among members of each protein family group varies, which influences the cross-reactivity patterns seen and the likelihood of symptomatic cross-reactivity. For example, in the PR-14 family of LTPs, there is in general a high sequence homology among the allergen members, suggesting a high probability of cross-reactivity among members, and this is confirmed clinically, whereas in the profilin protein family a much wider range of homology exists among members, and therefore cross-reactivity among some plants containing profilin is not certain. Other factors that influence cross-reactivity among family members are the degree of ripeness of the fruit or vegetable, storage conditions, and a number of other factors that influence the expression of the allergen; levels of cross-reactivity may even vary among cultivars. 44

Food-allergic patients may be sensitised to more than one allergen found in a specific food, complicating cross-reactivity. For example, a high prevalence of OAS/FPS occurs to ingestion of apple in birch polysensitised individuals as a result of the cross-reactivity between Mal d 1 from apple and Bet v 1 from birch pollen; however, apple-allergic individuals may be monosensitised or polysensitised to any number of apple allergens, e.g. to Mal d 1 (PR-10), Mal d 2 (PR-5), Mal d 3 (PR-14), Mal d 4 (profilin), or any other apple allergen or combination of allergens. 45

CLINICAL MANIFESTATIONS

The clinical effects are usually restricted to the oral cavity and include oral pruritus, swelling of the lips, tongue and throat, hoarseness, pharyngitis, and laryngeal oedema. The most common complaint among patients is an itching or tingling of the mouth after ingestion of fresh fruit or vegetables. 2 Patients may also experience angio-oedema localised to the mouth. Some studies have shown that a few patients will develop some abdominal cramping or discomfort after ingestion, but rarely vomiting or diarrhoea. 3 Anaphylaxis may uncommonly occur in association with OAS/FSP (as opposed to anaphylaxis without this association). Anaphylaxis is particularly more likely with LTP-containing foods. Almost all patients will have some degree of allergic rhinitis or conjunctivitis because the IgE antibodies to an allergen are cross-reacting with the fruit or vegetable proteins.

Reactions may vary depending on the allergen responsible for symptoms. Patients allergic to profilin may report that ingesting a cooked fruit or vegetable does not elicit symptoms, whereas cooked fruit or vegetables containing heat-stable allergens, e.g. LTPs, may still result in symptoms.

DIAGNOSIS

The diagnosis is based almost entirely on the patient’s history. A history of allergy to aeroallergens and then tingling or itching of the mouth after eating fresh fruits or vegetables is enough to make the diagnosis of OAS in almost all cases. The OAS reaction is usually immediate and can occur as soon as the fruit or vegetable is put into the mouth. The reactions are usually the same if the patient eats the same fruit or vegetable again, but there may be a dose threshold. Most symptoms should be confined to the oropharynx.
Although commercial extracts of most fruits and vegetables are available for tests, these extracts are highly heat-labile and easily degradable, often losing their potency and sensitivity by the time they are used in skin-prick tests. This has led to the use of the prick-to-prick method, in particular if initial skin-prick tests are negative despite a persuasive clinical history. The procedure is to prick the fresh fruit with the lancet and then immediately use the same lancet for the skin-prick test with fresh nut or apple.29 Studies have confirmed that commercial extracts are not as good as fresh fruit in skin-prick testing.

If systemic reactions such as urticaria, wheezing, and anaphylaxis occur in association with OAS/PFS, this suggests the involvement of an LTP allergen. Potential cross-reactivity with other LTP-containing foods should be explored, and in this instance coexisting pollen allergy may not be related to a cross-reactive allergen (with the exception of mugwort). However, systemic reactions may occur to a food without oral symptoms, and if an individual is polysensitised to a number of allergens in a food, then atypical clinical patterns may emerge. A thorough history should be obtained to ensure that the patient has no signs of a more serious IgE-medi- ated food allergy. Patients should be questioned about what foods were ingested around the same time; excluding those foods as the cause of the reaction would be appropriate. This may include skin-prick testing, specific IgE antibody testing, and food challenge. The development of recombinant allergens representa- tive of cross-allergenic allergens has resulted in the evolvement of component-resolved diagnosis (CRD), in which sensitisation to single allergens can be tested, enabling improved evaluation of OAS/FCS and cross-reactivity. Table I lists examples of useful recombinant allergens that have been developed. Besides prick-to-prick tests, patterns of co-sensitisation have been proposed as guides in the diagnosis of OAS/FPS. For example, in a study of grass-pollen- and birch-pollen-allergic patients with confirmed oral allergy symptoms to apple, hazelnut or mugwort, a diagnosis was best obtained through a case history and skin-prick tests with fresh fruit, and skin-prick tests had a negative predictive value of greater than 89%. When a skin-prick test with fresh nut or apple cannot be performed, histamine release is a diagnostic alternative. However, other studies have shown that skin-prick tests and in vitro IgE levels are poor predictors of clinical sensiti- vity.

Double-blind, placebo-controlled food challenges (DBPCFC) are considered the gold standard in the diagnosis of food allergy. However, using DBPCFC to diagnose OAS/FPS has various constraints, including the fact that storage ripening processes affect the level of allergen present, and that levels of the same pan-allergen vary between varietals. Food-in-a-capsule challenges are also problematic, as the food bypasses the oral mucosa and the allergen may be degraded in the stomach by digestion.

**TREATMENT**

Most patients with OAS will avoid the fruit(s) or vegetable(s) eliciting their symptoms. If the patient wishes to tolerate the localised symptoms and there is no suggestion of systemic symptoms, it is safe to continue eating the food. A survey of allergists concerning management of OAS found no consensus: some recommended complete avoidance of the offending foods, others did not advocate food restrictions, and 38% personalised recommendations according to the individual, sometimes advocating the avoidance of cross-reactive foods.

However, since cross-reactivity may depend on the heat-stability of the responsible cross-reactive allergen, cooking alone may be sufficient to deactivate the responsible panallergen. However, in patients with concomitant eczema, ingestion of cooked birch-pollen-related foods, while not inducing OAS, still caused atopic eczema to worsen, suggesting that T-cell cross-reactivity between Bet v 1 and related food allergens occurs independently of IgE cross-reactivity in vitro and in vivo. Therefore, ingestion of cooked fruits and vegetables may cause perennial activation of pollen-specific T cells and B cells, leading to maintenance of perennially increased allergen-specific IgE levels, and thereby symptoms, in pollen-allergic patients outside the pollen season.

Although the same panallergen may be present in a range of foods, homology may still vary, resulting in clinical cross-reactivity between some members and not others. Studies assessing cross-reactivity in the Rosaceae family of fruits found that from 46% to 63% of patients with confirmed PFS to one fruit had clinical reactivity to other Rosaceae fruits; the authors recommended that if a reported reaction is confirmed, tolerance to other Rosaceae fruits, particularly apricot, apple, and plum, should be evaluated, unless the patient has eaten them without symptoms after the initial reaction.

It is inappropriate to take an antihistamine prior to eating a culprit food, as this would mask symptoms beyond the oropharynx, they should avoid the food as if they have classic IgE-mediated food allergy. The hypothesis that immunotherapy for pollen allergy may reduce or abolish symptoms of OAS/FPS, as a result of cross-reactivity among panallergens, has been addressed in a number of studies, with varying results. A study of birch-pollen-allergic individuals with symptoms to apple who were treated with subcutaneous immunotherapy reported a significant reduction or disappearance of oral symptoms to apples (84%), with a concomitant reduction in reactivity to skin-prick tests to apple. Similarly, a study reported that immunotherapy resulted in birch-allergic patients being able to eat significantly more apple or hazelnut with no resulting symptoms. However, the amount of apple or hazelnut tolerated remained small. In contrast, other studies have demonstrated no improvement following immunotherapy (except for pollen-related symptoms of rhinoconjunctivitis). Results of an immunotherapy

### Table I. Diagnostic recombinant allergens

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Panallergen</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>rBet v 1 PR-10</td>
<td>LTP</td>
<td>Birch tree</td>
</tr>
<tr>
<td>rAra h 8 PR-10</td>
<td>Peanut</td>
<td>Soy</td>
</tr>
<tr>
<td>rApi g 1.01 PR-10</td>
<td>Celery</td>
<td>Peach</td>
</tr>
<tr>
<td>rCor a 1 PR-10</td>
<td>Hazel nut</td>
<td>Peach</td>
</tr>
<tr>
<td>rGly m 4 PR-10</td>
<td>Soy</td>
<td>Birch tree</td>
</tr>
<tr>
<td>rPru p 1 PR-10</td>
<td>Peach</td>
<td>Timothy</td>
</tr>
<tr>
<td>rBet v 2 Profilin</td>
<td>Peach</td>
<td>Wall pellitory</td>
</tr>
<tr>
<td>rAra h 9 LTP</td>
<td>Peanut</td>
<td>Hazel nut</td>
</tr>
<tr>
<td>rCor a 8 LTP</td>
<td>Hazel nut</td>
<td>Peach</td>
</tr>
<tr>
<td>rPar j 2 LTP</td>
<td>Wall pellitory</td>
<td>Peach</td>
</tr>
</tbody>
</table>

DBPCFC: double-blind, placebo-controlled food challenge

OAS: oral allergy syndrome

PFS: perennial food syndrome

CRD: component-resolved diagnosis

DBPCFC: double-blind, placebo-controlled food challenge

IgE: immunoglobulin E

Table I lists examples of useful recombinant allergens that have been developed.
study of birth subcutaneous immunotherapy for apple allergy reported the possible induction of OAS in 2 of 12 study participants as a result of immunotherapy.53

Disclosure of interest

Consultant to Phadia, Sweden.

REFERENCES

Penicillin-allergy in children

S Karabus, MB ChB, MRCP(UK), FCPaeds(SA), Dip Allergology (SA)
C Motala, MB ChB, FCPaeds(SA), FACAAI, FAAAAI
Allergy Clinic, Division of Paediatric Medicine, School of Child & Adolescent Health,
University of Cape Town & Red Cross War Memorial Childrens’ Hospital, Cape Town, South Africa

ABSTRACT
It is not uncommon to see skin rashes during a course of treatment with penicillin and penicillin-based antibiotics. This is often assumed to be due to penicillin allergy although in most cases no testing is performed to verify the diagnosis. Many children are simply labelled ‘penicillin allergic’, a label which they carry into adulthood which may deny them the benefit of treatment with the most appropriate group of antibiotics. Penicillins are the most widely used antibiotics for common infections as well as being the antibiotics which most often cause allergic reactions. The incidence of self-reported penicillin allergy is 1-10% but most of these patients will test negative. Misdiagnosis of penicillin allergy may result in the unnecessary use of more expensive and less effective antibiotics as well as the emergence of multidrug-resistant organisms. History alone is unreliable in the diagnosis of penicillin allergy. Skin testing (skin-prick and intradermal testing) remains standard practice for the evaluation of patients with immediate hypersensitivity reactions (IgE-mediated) to penicillin. Skin testing combined with a thorough history, determination of specific IgE antibody level and, if indicated, a drug provocation test (DPT) should diagnose the majority of children with penicillin allergy. Patients with proven penicillin allergy can undergo desensitisation if they require penicillin therapy and no alternative is available. Accurate diagnosis of penicillin allergy is essential to avoid the morbidity, mortality and economic cost associated with unnecessary withholding of this drug in non-allergic patients.

BACKGROUND
In the paediatric population it is not uncommon to see a skin rash during a course of treatment with a penicillin antibiotic. This is often assumed to be due to penicillin allergy. In most of these cases no testing is performed to verify the diagnosis and many children are simply labelled as ‘penicillin allergic’. They end up carrying this label into adulthood which may therefore be denied the benefit of treatment with the most appropriate group of antibiotics.

Penicillin and penicillin-based antibiotics are the most widely used antibiotics for common infections. They are also the antibiotics which most often cause allergic reactions with the frequency of life-threatening anaphylaxis estimated to be 0.01%-0.05%. The incidence of self-reported penicillin allergy varies between 1% and 10% but more than 80-90% of these have no evidence of IgE antibodies to penicillin on skin-testing. Penicillin-based antibiotics are usually less expensive and have fewer side-effects than alternative broad-spectrum antibiotics. They are also more effective for certain infections. This is especially important for patients on long-term penicillin prophylaxis (e.g. rheumatic heart disease) or treatment (e.g. bacterial endocarditis).

CLASSIFICATION
There are a number of ways to classify drug allergies. From a clinical perspective a practical method is to divide adverse drug reactions according to the time interval between exposure and onset of reaction – immediate, accelerated and delayed reactions. Immediate hypersensitivity reactions (IgE-mediated) occur up to 1 hour after exposure to the offending agent. Non-immediate reactions include accelerated reactions (1-72 hours) and delayed reactions (>72 hours). Immediate reactions may present with anaphylaxis, urticaria, angio-oedema and bronchospasm; accelerated/delayed reactions may manifest as serum sickness, interstitial nephritis, haemolytic anaemia, morbilliform eruptions and Stevens-Johnson syndrome.

DIAGNOSIS (Fig. 1)

History
The diagnosis of penicillin allergy begins with a detailed history. A personal or family history of drug allergies may be relevant as this may predispose to penicillin allergy whereas a history of atopy does not. The signs, symptoms and severity of the reaction and any previous reactions should be documented. For example, urticaria and bronchospasm would suggest an IgE-mediated immediate drug reaction. The dose and route of administration are also important. Prolonged parenteral administration is more likely to cause a hypersensitivity reaction than the oral or topical route. A concomitant viral illness is important as this may cause a rash that is mistaken for penicillin allergy. The maculopapular rash induced by ampicillin or amoxicillin given to a child with Epstein-Barr virus infection may also be mistaken for a drug allergy.

Physical examination
The clinical examination should focus on the skin, mucous membranes and the chest. On the skin one should distinguish between an urticarial and a morbilliform or maculopapular rash. Mucous membrane

Fig. 1. Basic algorithm for drug allergy testing.
involvement may indicate Stevens-Johnson syndrome or toxic epidermal necrolysis. The presence of wheezing or stridor should be noted on examination of the respiratory system.

**Investigations**

Penicillin is metabolised into major (penicilloyl) and minor (penilloate and penilloate) antigenic determinants. It is essential to test sensitivity to both minor and major determinants, as testing only for major determinants would miss at least 10% of penicillin-sensitive subjects.

- **Blood tests**
  During an acute hypersensitivity reaction a serum tryptase level should be performed. This is a sensitive and specific test of mast-cell activation. Ideally blood is taken at 0, 1 and 6 hours after the reaction and placed in a lithium-heparin tube. A peak at 1 hour with a fall to normal levels within 12-24 hours is diagnostic of mast-cell degranulation and an IgE-mediated reaction.

  A CAP-RAST for IgE antibodies to amoxicillin, ampicillin, penicillin V, penicillin G and cefaclor is available to aid in the diagnosis. The blood should be taken from 6 weeks after the acute reaction has taken place in order to get the most accurate results. The sensitivity is approximately 80-90% but it does not test for the minor determinants of penicillin.

  More recently the CAST (cellular antigen stimulation test) has become available. This test measures the in vitro production of sulphidoleukotrienes by leukocytes when stimulated by the specific drug. The sensitivity and specificity are approximately 46% and 85% respectively.

- **Skin tests** (Fig. 2)
  The skin-test panel should include a positive (histamine 10 mg/ml) and a negative (0.9% saline) control as well as a major determinant mixture and minor determinant mixture. Amoxicillin (20-25 mg/ml) should be added to the skin-test panel as its side chain is not included in the above two mixtures. If the offending drug is something other than one of these, it should be added to the panel with the understanding that the negative predictive value of such a test is unknown. A wheal 3 mm or more greater than the negative control is considered a positive test result.

  Skin-prick testing (SPT) is a reliable and relatively safe procedure for detecting IgE-mediated penicillin allergy. It has a specificity approaching 100% for IgE-mediated allergy. The sensitivity is relatively low (50-70%) (Table I). Anaphylaxis has never been reported in a skin-test-negative individual challenged with the medication. SPT is not indicated if the history suggests a non-IgE-mediated hypersensitivity reaction such as Stevens-Johnson syndrome or serum sickness. In these patients, penicillin should be avoided indefinitely.

**Drug provocation test (DPT)**

If the penicillin skin tests are negative and the IgE antibody levels are normal, a DPT should be performed in a setting where resuscitation equipment and trained personnel are available. A suggestive history of allergy together with a positive CAP-RAST and/or a positive skin test is sufficient for the diagnosis of penicillin allergy without the need to perform a DPT. A DPT is not recommended if there is a history of anaphylaxis.

**MANAGEMENT**

Initial management of acute penicillin allergy consists of discontinuing the drug and treating the clinical reactions, e.g. anaphylaxis, urticaria or wheeze. Subsequent management entails confirming the diagnosis, strict avoidance of the offending drug and patient education (including the use of injectable adrenaline for prevention of anaphylaxis). A Medic Alert bracelet should also be obtained.

Desensitisation to the drug (either by the oral or intravenous route) should be considered in children with IgE-mediated reactions if no alternative treatment to penicillin is available. Desensitisation must be conducted in an intensive care unit by experienced personnel. The aim of desensitisation is to convert a patient who is highly allergic to penicillin to a state in which they can tolerate the drug. The basic principle is to start with a minute dose, then double it every 15 minutes until a full dose is reached. Various desensitisation protocols are available (Tables II and III). Penicillin therapy must be commenced immediately after completing desensitisation (tolerance is only temporary). Desensitisation must be repeated if a course of penicillin is required again. Minor adverse reactions may occur after this procedure in a third of cases but no fatal or life-threatening

<table>
<thead>
<tr>
<th>Step</th>
<th>Penicillin (mg/ml)</th>
<th>Amount (ml)</th>
<th>Dose given (mg)</th>
<th>Cumulative dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5</td>
<td>0.1</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
<td>0.2</td>
<td>0.1</td>
<td>0.15</td>
</tr>
<tr>
<td>3</td>
<td>0.5</td>
<td>0.4</td>
<td>0.2</td>
<td>0.35</td>
</tr>
<tr>
<td>4</td>
<td>0.5</td>
<td>0.8</td>
<td>0.4</td>
<td>0.75</td>
</tr>
<tr>
<td>5</td>
<td>0.5</td>
<td>1.6</td>
<td>0.8</td>
<td>1.55</td>
</tr>
<tr>
<td>6</td>
<td>0.5</td>
<td>3.2</td>
<td>1.6</td>
<td>3.15</td>
</tr>
<tr>
<td>7</td>
<td>0.5</td>
<td>6.4</td>
<td>3.2</td>
<td>6.35</td>
</tr>
<tr>
<td>8</td>
<td>5</td>
<td>12</td>
<td>12</td>
<td>12.35</td>
</tr>
<tr>
<td>9</td>
<td>5</td>
<td>24</td>
<td>12</td>
<td>24.35</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
<td>5</td>
<td>25</td>
<td>49.35</td>
</tr>
<tr>
<td>11</td>
<td>50</td>
<td>50</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>12</td>
<td>50</td>
<td>100</td>
<td>200</td>
<td>400</td>
</tr>
<tr>
<td>13</td>
<td>50</td>
<td>4</td>
<td>200</td>
<td>400</td>
</tr>
<tr>
<td>14</td>
<td>50</td>
<td>8</td>
<td>400</td>
<td>800</td>
</tr>
</tbody>
</table>

Observe patient for 30 minutes, then give full therapeutic dose by the desired route.

Modified from Sullivan TJ.

*Interval between doses is 15 minutes.

Fig. 2. Skin-prick test.
reactions have been reported to date. It is important to note that desensitisation will not prevent non-IgE reactions such as serum sickness, haemolytic anaemia or interstitial nephritis from occurring.

**CROSS-REACTIVITY WITH OTHER ANTIBIOTICS**

Up to 20% of patients with penicillin allergy may develop an adverse reaction to cephalosporins \(^{12}\) (particularly with 1st and 2nd generation agents). The rate of cross-reactivity between the 3rd and 4th generation cephalosporins is much lower. Cross-reactivity between these drugs is believed to be due to the drugs having similar R-group side chains and not due to the β-lactam ring itself (Fig. 3). For example, amoxicillin shares a side-chain with cefadroxil, cefotaxime with ceftriaxone, and ampicillin with both cefalexin and cefacor. It is recommended that penicillin-allergic patients who require a cephalosporin should undergo SPT. If this is negative, a cephalosporin can safely be administered \(^a\) with less than 1% risk of a mild systemic reaction.

In a patient with a known allergy to a cephalosporin, substitution with a cephalosporin with a different side-chain is usually safe.

Cross-reactivity between penicillin and carbapenems is also reported: 50% with imipenem \(^{16}\) and 10% with meropenem. \(^{17}\) based on history and SPT. In studies where DPTs were also done, cross-reactivity was reportedly <1%. \(^{18}\)

**CONCLUSIONS**

Allergic reactions to penicillin (anaphylaxis in particular) are relatively infrequent in the paediatric population. The majority of children with the label of penicillin allergy can safely take this drug without fear of an allergic reaction. Misdiagnosis of penicillin allergy may result in the unnecessary use of more expensive and less effective antibiotics as well as the emergence of multidrug-resistant organisms. History alone (usually poorly documented and often vague) is unreliable in the diagnosis of penicillin allergy. SPT remains the standard practice for the evaluation of patients with immediate hypersensitivity reactions (IgE-mediated) to penicillin. SPT combined with a thorough history, determination of specific IgE antibody level and, if indicated, a DPT should diagnose the majority of children with penicillin allergy. Patients with proven penicillin allergy can undergo desensitisation if they require penicillin therapy and no alternative is available. Accurate diagnosis of penicillin allergy is essential to avoid the morbidity, mortality and economic cost associated with unnecessary withholding of this drug in non-allergic patients.

**Declaration of conflict of interest**

The authors declare no conflict of interest.

**REFERENCES**


---

**Table III.** Penicillin intravenous desensitisation protocol with drugs added by piggyback infusion

<table>
<thead>
<tr>
<th>Step*</th>
<th>Penicillin (mg/ml)</th>
<th>Amount (ml)</th>
<th>Dose given (mg)</th>
<th>Cumulative dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>2</td>
<td>0.1</td>
<td>0.2</td>
<td>0.02</td>
<td>0.03</td>
</tr>
<tr>
<td>3</td>
<td>0.1</td>
<td>0.4</td>
<td>0.04</td>
<td>0.07</td>
</tr>
<tr>
<td>4</td>
<td>0.1</td>
<td>0.8</td>
<td>0.08</td>
<td>0.15</td>
</tr>
<tr>
<td>5</td>
<td>0.1</td>
<td>1.6</td>
<td>0.16</td>
<td>0.31</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>0.32</td>
<td>0.32</td>
<td>0.63</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>0.64</td>
<td>0.64</td>
<td>1.27</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>1.2</td>
<td>1.2</td>
<td>2.47</td>
</tr>
<tr>
<td>9</td>
<td>10</td>
<td>0.24</td>
<td>2.4</td>
<td>4.87</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>0.48</td>
<td>4.8</td>
<td>10</td>
</tr>
<tr>
<td>11</td>
<td>10</td>
<td>1</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>12</td>
<td>10</td>
<td>2</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>13</td>
<td>100</td>
<td>0.4</td>
<td>40</td>
<td>80</td>
</tr>
<tr>
<td>14</td>
<td>100</td>
<td>0.8</td>
<td>80</td>
<td>160</td>
</tr>
<tr>
<td>15</td>
<td>100</td>
<td>1.6</td>
<td>160</td>
<td>320</td>
</tr>
<tr>
<td>16</td>
<td>1000</td>
<td>0.32</td>
<td>320</td>
<td>640</td>
</tr>
<tr>
<td>17</td>
<td>1000</td>
<td>0.64</td>
<td>640</td>
<td>1280</td>
</tr>
</tbody>
</table>

Observe patient for 30 minutes, then give full therapeutic dose by the desired route.

Modified from Sullivan TJ. \(^4\)

\(\times\) Interval between doses is 15 minutes.

---

Fig. 3. Classes of β-lactam antibiotics.
ANAPHYLAXIS IN INFANTS: CAN RECOGNITION AND MANAGEMENT BE IMPROVED?

F Estelle R Simons, MD, FRCPC
Section of Allergy and Clinical Immunology, the Department of Pediatrics and Child Health and the Department of Immunology, Canadian Institutes of Health Research National Training Program in Allergy and Asthma, Faculty of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada

The true rate of occurrence of anaphylaxis in infants, defined arbitrarily as age newborn to 2 years, inclusive, is unknown; however, most anaphylaxis case series and anaphylaxis epidemiologic studies in individuals of all ages include infants, some as young as 1 month of age.1-3 Fatalities in anaphylaxis, although rare in infancy, do occur, and even the first episode can be fatal.4,5

CASE REPORT
A 9-month-old boy with a 2-week history of cough and wheeze suddenly developed choking, coughing, labored breathing, and apnea, followed by a respiratory arrest at home. He was resuscitated by his father and brought to a community hospital within 6 minutes. On arrival, he was afebrile, limp, and cyanotic, with decreased air entry, deep retraction, and generalized inspiratory and expiratory rhonchi. He had red, scaly areas of skin on his face, chest, and extremities, with superimposed raised red areas 0.5 to 1 cm in diameter on his face and chest. His weight was 9 kg; heart rate, 152/min; respiratory rate, 38/min; and blood pressure, 80/50 mm Hg. He was given supplemental oxygen, intubated, ventilated, and transferred to a pediatric intensive care unit with the diagnosis of bronchiolitis, which was epidemic in the region at the time. Chest radiograph revealed minimal peribronchial thickening. The rapid antigen detection assay for respiratory syncytial virus was negative. He responded to albuterol and was extubated within 12 hours. In view of the atypical clinical picture for bronchiolitis and the rapid improvement, the diagnosis was reconsidered.

An allergy/immunology specialist was consulted, and additional history was obtained. The infant had been almost exclusively breast-fed since birth; however, on one occasion, he had developed generalized hives soon after ingesting a cow’s milk formula supplement. Minutes before his respiratory arrest, he had tasted ice cream for the first time. His eosinophil count was 1.08 X 10^9/L. Cow’s milk specific IgE was 3.6 kU/L. The allergist’s diagnoses were anaphylaxis to cow’s milk, asthma, and atopic dermatitis. Four weeks later, the skin prick test to cow’s milk was strongly positive (weal 10 mm greater than control). Long-term risk reduction measures initiated included strict avoidance of cow’s milk and related products, and optimized asthma and atopic dermatitis management. An Anaphylaxis Emergency Action Plan was developed. An epinephrine autoinjector 0.15 mg was prescribed despite recognition that this dose was not ideal for a 9-kg infant. Education sessions were held with his parents.

WHAT TRIGGERS ANAPHYLAXIS IN INFANTS?
Food is the most common trigger of anaphylaxis in this age group.6,10 through direct ingestion, breast milk, or accidental ingestion (eg, a crawling infant finds and tastes a food item); of note, skin contact with food or food-based skin care products or inhalation of aerosolized food particles potentially sensitizes an infant but seldom causes anaphylaxis. Caregivers may be unaware of the infant’s initial exposure to the food. Common culprits are cow’s milk or egg, but any food can be a trigger, including those presumed innocuous (eg, cow’s milk substitutes, hypoallergenic formulas6-8), those not traditionally given to infants (eg, sesame),9 or those not previously identified as being allergenic in individuals of any age (eg, caribou and whale meats).10

Less common triggers include medications (eg, β-lactam antibiotics, antipyretics such as ibuprofen, neuromuscular blockers), natural rubber latex (nipples, pacifiers, toys), insect stings, inhalant allergens, vaccinations for prevention of infectious diseases, and non-immune triggers such as cold exposure. Idiopathic anaphylaxis has been reported in infants.11,12

WHICH INFANTS ARE AT INCREASED RISK FOR ANAPHYLAXIS?
Clinical risk factors and comorbid diseases that increase the risk of anaphylaxis and of fatality in anaphylaxis have not yet been optimally defined in infants. Atopy; common infant respiratory diseases such as bronchiolitis, asthma, and croup; and urticaria pigmentosa/mastocytosis are likely to be important. Comorbidities in caregivers – for example, depression, or use of sedatives, ethanol, or recreational drugs – might impede recognition of anaphylaxis in the infant for whom they are responsible.13

HOW CAN RECOGNITION OF ANAPHYLAXIS IN INFANTS BE IMPROVED?
Physicians need to have a high index of suspicion to diagnose anaphylaxis promptly in infants, because it may be difficult to recognize in this age group for a variety of reasons. Parents, caregivers, and even health care professionals may not be aware of the possibility that anaphylaxis can occur in infancy. Many anaphylaxis episodes in infancy are “first” episodes. Subjective symptoms of anaphylaxis such as itching cannot be described by infants (Table I). Some signs of anaphylaxis (for example, regurgitation and loose stools after feeding) also occur in healthy infants. The differential diagnosis of anaphylaxis is age-dependent (Table II). Laboratory tests to support the clinical diagnosis of anaphylaxis may or may not be helpful.11 Histamine levels need to be measured in a blood sample obtained within 1 hour of symptom onset. Total tryptase levels need to be measured in a sample obtained within 3 hours of symptom onset. Even if the sample is optimally timed, tryptase levels are seldom elevated in food-induced anaphylaxis. Moreover, if fatality occurs and an elevated postmortem tryptase level is found, interpretation can be difficult because elevated tryptase levels have also been reported in some infants with sudden infant death syndrome.14

WHAT ARE THE BARRIERS TO OPTIMAL MANAGEMENT OF ANAPHYLAXIS IN INFANTS?
Acute management in health care settings
The universal principles of prevention, prompt diagnosis, rapid assessment (airway, breathing, circulation,
responsiveness, skin, and weight), and prompt treatment apply. The evidence base for the treatment of anaphylaxis in infants is largely empirical. Epinephrine is the initial medication of first choice; however, the recommended initial dose of 0.01 mg/kg intramuscularly is based entirely on tradition, because no prospective epinephrine clinical pharmacology study has been conducted in infants with, or at risk of, anaphylaxis. If intravenous epinephrine is needed, care should be taken to calculate the dose accurately, dilute the epinephrine solution accurately, and avoid an overly rapid infusion rate. If epinephrine overdose occurs, infants cannot report symptoms; signs include pallor, tremor, and pulmonary edema that, like anaphylaxis itself, may be manifest by cough and respiratory distress. In addition to epinephrine, supplemental oxygen should be given. The airway should be established and maintained. An intravenous line should be established. Continuous monitoring should be instituted. Additional medications should be administered as needed. 

### Anaphylaxis signs in infants:

<table>
<thead>
<tr>
<th>Anaphylaxis symptoms that infants cannot describe</th>
<th>Anaphylaxis signs that are potentially difficult to interpret in infants, and why</th>
<th>Anaphylaxis signs in infants: obvious but may be nonspecific</th>
</tr>
</thead>
<tbody>
<tr>
<td>General: feeling of warmth, weakness, anxiety, apprehension, impending doom</td>
<td>General: nonspecific behavioral changes such as persistent crying, fussing, irritability, fright</td>
<td>Skin/mucous membranes: rapid onset of hives (potentially difficult to discern in infants with acute atopic dermatitis; scratching and excoriations, as such, will be absent in young infants); angioedema (face, tongue, oropharynx)</td>
</tr>
<tr>
<td>Skin/mucous membranes: itching of lips, tongue, palate, uvula, ears, throat, nose, eyes, and so forth; mouth-tintling or metallic taste</td>
<td>Skin/mucous membranes: flushing (may also occur with fever, hyperthermia, or crying spells)</td>
<td>Skin/mucous membranes: rapid onset of hives (potentially difficult to discern in infants with acute atopic dermatitis; scratching and excoriations, as such, will be absent in young infants); angioedema (face, tongue, oropharynx)</td>
</tr>
<tr>
<td>Respiratory: nasal congestion, throat tightness; chest tightness; shortness of breath</td>
<td>Respiratory: hoarseness, dysphonia (common after a crying spell); drooling, increased secretions (common in infants)</td>
<td>Respiratory: rapid onset of coughing, choking, stridor, wheezing, dyspnea, apnea, cyanosis</td>
</tr>
<tr>
<td>Gastrointestinal: dysphagia, nausea, abdominal pain/cramping</td>
<td>Gastrointestinal: splitting up/regurgitation (normal in infants, especially if breast-fed); colicky abdominal pain</td>
<td>Gastrointestinal: sudden, profuse vomiting</td>
</tr>
<tr>
<td>Cardiovascular: feeling faint, presyncope, dizziness, confusion, blurred vision, difficulty in hearing, palpitations</td>
<td>Cardiovascular: hypotension; measured with an appropriate size blood pressure cuff, low systolic blood pressure for infants is defined as less than 70 mmHg from age 1 month to 1 year, and less than (70 mmHg 1 + [2 x age in y]) in the first and second years of life; tachycardia, defined as greater than 120-130 beats per minute from the third month to second year of life inclusive; loss of bowel and bladder control (ubiquitous in infants)</td>
<td>Cardiovascular: weak pulse, arrhythmia, diaphoresis/swearing, pallor, collapse/unconsciousness</td>
</tr>
<tr>
<td>Central nervous system: headache</td>
<td>Central nervous system: drowsiness, somnolence (common in infants after feeds)</td>
<td>Central nervous system: rapid onset of unresponsiveness, lethargy, or hypotonia; seizures</td>
</tr>
</tbody>
</table>

*More than 1 body system involved.*

### Long-term risk reduction

Assessment. Most episodes of anaphylaxis in infants are IgE-mediated. Sensitization to allergens – for example, to foods – can be determined by using skin prick tests or by quantitative measurement of allergen-specific IgE levels. Selection of allergens for testing should be based on the history. Positive skin tests have a different appearance in infants compared with older individuals. Like elevated allergen-specific IgE levels, they denote sensitization, but are not themselves diagnostic of anaphylaxis or any other allergic disease. In infants with food allergy, physician-monitored oral incremental challenges may be helpful if the diagnosis is in doubt or if there is minimal or no evidence of sensitization to the suspect allergen. A challenge is strictly contraindicated in an infant such as the one reported here, who has a strong clinical history of anaphylaxis and is highly sensitized to the suspect allergen. Equipping the infant’s caregivers for management of anaphylaxis in the community. Risk reduction involves vigilant allergen avoidance, which can be stressful for families. Relevant comorbidities in the infant and the caregiver should be managed optimally. Caregivers should be equipped with injectable epinephrine for first aid treatment in the context of an Anaphylaxis Emergency Action Plan, which can be downloaded from www.aaaai.org and readily adapted for use in infants.

### Epinephrine

Most infants weigh less than 15 kg. No epinephrine autoinjector currently available provides a dose of <0.15 mg. Presenting a dilemma for physicians prescribing epinephrine autoinjectors for this vulnerable population (see Case Report). Although experienced pediatric nurses draw up and measure infant doses from an ampule of epinephrine rapidly and accu-
Table III. Differential diagnosis of anaphylaxis in infants

<table>
<thead>
<tr>
<th>Skin: urticaria; urticaria pigmentosa/mastocytosis, hereditary angioedema</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory (upper or lower respiratory tract): obstruction, congenital (e.g., laryngeal web, vascular ring, malacia) or acquired (e.g., aspiration of foreign body, croup, bronchiolitis, asthma); asphyxiationsuffocation; breath-holding</td>
</tr>
<tr>
<td>Gastrointestinal tract: obstruction, congenital (e.g., pyloric stenosis, malrotation) or acquired (e.g., intussusception)</td>
</tr>
<tr>
<td>Shock: septic, cardiovascular, hypovolemic</td>
</tr>
<tr>
<td>Central nervous system: seizure, post-ictal state, stroke, trauma, child abuse, increased intracranial pressure</td>
</tr>
<tr>
<td>Metabolic disorders</td>
</tr>
<tr>
<td>Infectious diseases: eg, pertussis, gastroenteritis, meningitis</td>
</tr>
<tr>
<td>Ingestion of poison or toxin (eg, food, drug, plant); drug overdose</td>
</tr>
<tr>
<td>Munchausen syndrome by proxy</td>
</tr>
<tr>
<td>Sudden infant death syndrome</td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>

* Peanuts and tree nuts account for one third of foreign body aspirations, as well as being common triggers of anaphylaxis.

† Infants with gastrointestinal anaphylaxis present with abdominal pain, cramps and vomiting with or without diarrhea minutes to a few hours after ingestion of the culprit food.

H₁-antihistamines

In anaphylaxis, H₁-antihistamines might relieve skin symptoms and signs but they do not relieve upper or lower airway obstruction or shock. They therefore are not drugs of choice, are not life-saving, and do not replace epinephrine.

The onset of action of orally administered H₁-antihistamines takes at least 1 to 2 hours. First-generation H₁-antihistamines in usual doses potentially cause sedation and unresponsiveness that can impede the recognition of anaphylaxis, and they can also lead to respiratory arrest in infants.19,23

Medical identification

At-risk infants who are in the care of a babysitter or other third party should be protected by wearing accurate medical identification,14 such as a T-shirt or Velcro patch on clothes (Velcro USA Inc, Manchester, NH) with a specific allergy alert message, for example, “Do not give cow’s milk to this baby.” Medical identification bracelets made of cloth are available for older infants.

Anaphylaxis education. Caregivers of infants report high anxiety levels with regard to taking responsibility for the recognition and management of an anaphylaxis episode, particularly the possibility of having to inject epinephrine.13,14 Individualized instruction and coaching help to diminish this anxiety.

SUMMARY

Anaphylaxis is likely underrecognized in infancy. Many episodes are ‘first’ episodes. Infants cannot report symptoms. Diagnosis therefore depends on a high index of suspicion and on physical signs. The differential diagnosis of anaphylaxis in infancy includes age-unique entities such as congenital or metabolic disorders, child abuse, Munchausen syndrome by proxy, and sudden infant death syndrome. Management is based on empirical evidence. A prospective systematic study of anaphylaxis in infancy is needed.

Acknowledgement

I gratefully acknowledge the assistance of Ms Lori McNiven.

This article was published in journal of Allergy and Clinical Immunology 2007; vol 120, pp 537-540, Simons FER, Anaphylaxis in infants: can recognition and management be improved? Copyright American Academy of Allergy, Asthma & Immunology (2007). Reprinted with permission of the author and copyright holder.

Declaration of conflict of interest

The author declares no conflict of interest.

REFERENCES


**H₁ ANTIHISTAMINES IN ALLERGIC DISEASE**

Cas Motala, MB ChB, FCPaeds(SA), FACAAI, FAAAAI
Allergy Clinic, Division of Paediatric Medicine, School of Child & Adolescent Health, University of Cape Town & Red Cross War Memorial Children’s Hospital, Rondebosch, Cape Town, South Africa

**ABSTRACT**

Histamine (one of the key mediators released from mast cells and basophils), plays a major role in the pathophysiology of allergic diseases, including rhinitis, urticaria, asthma and anaphylaxis. Histamine exerts its effects through its interaction with one of four distinct receptors (H₁, H₂, H₃, H₄). In allergic disease, it is the H₁ antihistamines which are of primary benefit, although H₂ antihistamines may also play a therapeutic role.

H₁ antihistamines remain first-line medications for the treatment of allergic rhinoconjunctivitis and urticaria. Second-generation antihistamines are preferred to their predecessors because of better benefit-risk ratios. The newer antihistamines are not only more potent, but also have anti-allergic and anti-inflammatory properties. Although they are more expensive than the traditional antihistamines, the cost is substantially offset by their superior efficacy and safety profile when used in recommended dosages.

**CLASSIFICATION**

H₁ antihistamines are classified into the older, or first-generation, antihistamines, and the newer, or second-generation, antihistamines. The main differences between the two generations of drugs are their propensity to cause central nervous system (CNS) side-effects. The commonly used members of these drug classes are listed in Table I. The highly lipophilic nature of the first-generation antihistamines allows them to penetrate well into the CNS where they induce sedation. The potential to enhance the central effects of alcohol and other CNS sedatives further limits such use. In addition, many of these drugs also have actions which reflect their poor receptor selectivity, including an anticholinergic effect and blockade of both α-adrenergic and 5-hydroxytryptamine receptors (muscarinic effect) Tachyphylaxis is also a problem with the use of the older antihistamines.

**MECHANISM OF ACTION**

H₁ antihistamines are not receptor antagonists as previously thought, but are inverse agonists. When neither histamine nor antihistamine is present, the active and inactive states of the H₁ receptor are in equilibrium or a balanced state. Histamine combines preferentially with the active form of the receptor to stabilise it and shift the balance towards the activated state and stimulate the cell (Fig. 1). Antihistamines stabilise the inactive form and shift the equilibrium in the opposite direction. Thus, the amount of histamine-induced stimulation of a cell or tissue depends on the balance between histamine and H₁ antihistamines.

Histamine effects stimulated through the H₁ receptor include pruritus, pain, vasodilatation, vascular permeability, hypotension, flushing, headache, tachycardia, bronchoconstriction, and stimulation of airway vagal afferent nerves and cough receptors as well as decreased atrioventricular-node conduction. Although most of the effects of histamine in allergic diseases are mediated by H₁ receptor stimulation, certain effects such as hypotension, tachycardia, flushing, headache, itching and nasal congestion are mediated through both H₂ and H₃ receptors.

In the CNS, the effects histamine exerts through H₂ receptors include cycle of sleep and waking, food intake, thermal regulation, emotion and aggressive behaviour, locomotion, memory and learning. First-generation H₂ antihistamines, such as chlorphenamine, diphenhydramine, hydroxyzine and promethazine, penetrate readily into the brain, in which they occupy 50-90% of the H₂ receptors. The result is CNS sedation. In contrast, second-generation H₂ antihistamines penetrate the CNS poorly, as they are actively pumped out by P-glycoprotein, an organic anion transporting protein that is expressed on the luminal surfaces of vascular endothelial cells in the blood vessels that constitute the blood-brain barrier. Their propensity to occupy H₂ receptors in the CNS varies from 0% for fexofenadine to 30% for cetirizine. Thus, second-generation H₂ antihistamines are relatively free of sedating effects.

Through H₂ receptors histamine has various effects on the immune system, including the maturation of dendritic cells and modulation of the balance of helper T-cell type 1 (Th1) and Th2 towards Th1. Histamine also induces the release of pro-inflammatory cytokines (pro-inflammatory activity). Because histamine has such effects on allergic inflammation and the immune system, treatment with H₂ antihistamines reduces the expression of pro-inflammatory cell adhesion molecules and the accumulation of inflammatory cells, such as eosinophils and neutrophils. Major clinical effects of H₂ antihistamines are seen in suppression of the early response to allergen challenge in the conjunctiva, nose, lower airway and skin.

---

**Table I. Common H₁-receptor antagonists**

<table>
<thead>
<tr>
<th>Class</th>
<th>First generation</th>
<th>Second generation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxyzine</td>
<td>Cetirizine</td>
<td></td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>Loratadine</td>
<td></td>
</tr>
<tr>
<td>Chlorpheniramine</td>
<td>Desloratadine</td>
<td></td>
</tr>
<tr>
<td>Promethazine</td>
<td>Fexofenadine</td>
<td></td>
</tr>
<tr>
<td>Levoxetirizine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Two earlier developed agents, astemizole and terfenadine, were withdrawn in 1998 because of cardiac toxicity adverse effects.

Correspondence: Prof CasMotala, cassim.motala@uct.ac.za
PHARMACOKINETIC PROPERTIES

H1-receptor antagonists are well absorbed from the gastrointestinal tract after oral administration. Their onset of effect occurs within 1-3 hours; their duration of action varies from several hours to 24 hours, (second-generation drugs being generally around 24 hours) (Table II). First-generation antihistamines and some of the second-generation agents are oxidatively metabolised by the hepatic cytochrome P450 system, the exceptions being levocetirizine, cetirizine, and fexofenadine. Levocetirizine and cetirizine are excreted largely unchanged in urine and fexofenadine is excreted mainly in the faeces but also the urine. Hepatic metabolism has several implications: prolongation of the serum half-life in patients with hepatic dysfunction and those receiving concomitant cytochrome P450 inhibitors, such as ketoconazole and erythromycin. Also, longer duration of action is found in elderly patients who have reduced liver function. In these patients there is a possibility of precipitating serious unwanted cardiac or CNS effects. Concomitant administration of probenecid reduces the total body and renal clearance of fexofenadine. The bioavailability of fexofenadine may be altered by simultaneous consumption of grapefruit juice (reduced rate and absorption of the drug by almost 30%); however, grapefruit juice does not affect the absorption of other second-generation antihistamines. Although topical intranasal and ophthalmic H1 antihistamines differ in their pharmacokinetics, most of the topical preparations need to be administered twice daily because of the washout from the nasal mucosa or conjunctiva.

CLINICAL USES IN ALLERGIC DISEASE

H1 antihistamines currently constitute the largest class of medications used in the treatment of allergic disorder, allergic rhinoconjunctivitis and urticaria in particular. Formulations and dosages of the newer antihistamines are listed in Tables III and IV.

Allergic rhinoconjunctivitis

In patients with allergic rhinitis (AR) both first- and second-generation H1 antihistamines have proven to be highly effective in relieving sneezes, itching, and nasal discharge but not nasal blockage. First-generation H1 antihistamines have an unsatisfactory benefit-to-risk ratio in allergic rhinoconjunctivitis. In seasonal and perennial rhinitis, the evidence base for their use is small. Dosage recommendations are empirical. In seasonal AR, there is a large evidence base for the use of second-generation oral H1 antihistamines such as cetirizine, desloratadine, fexofenadine, loratadine. Efficacy has been well documented in hundreds of randomised, double-blind, placebo-controlled, parallel-group clinical trials involving thousands of participants. In perennial AR, the evidence base for second-generation H1 antihistamines use is growing and the efficacy of cetirizine, desloratadine, fexofenadine, loratadine, and levocetirizine has been documented. Regular daily administration is associated with a significant decrease in symptoms and nasal mucosal inflammation compared with ‘as needed’ or ‘on demand’ use. H1 antihistamines provide relief of allergic rhinitis comparable to that provided by intranasal cromolyn sodium 4% and are generally found to be less potent than intranasal corticosteroids in the treatment of AR symptoms. Leukotriene receptor antagonists (LRAs) may also be effective in certain patients with AR if combined with an antihistamine. In allergic conjunctivitis, the ocular symptoms induced by allergens, such as itching, tearing and reddening are reduced by administration of H1 antihistamines either systemically or topically as eye drops such as azelastine, ketotifen, levocabastine and olopatadine. Topical application usually results in faster onset of action – within 5 minutes – than oral administration.

Table II. Pharmacokinetics of second-generation oral H1 antihistamines (mean ± SD)

<table>
<thead>
<tr>
<th>H1 antihistamines (metabolite)</th>
<th>T_{max} (h) after a single dose</th>
<th>Terminal elimination half-life (T_{1/2}, h)</th>
<th>% eliminated unchanged in the urine/faeces</th>
<th>Duration of action (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetirizine</td>
<td>1.0 ± 0.5</td>
<td>6.5-10</td>
<td>60/10</td>
<td>≥24</td>
</tr>
<tr>
<td>Loratadine</td>
<td>1.2 ± 0.3</td>
<td>7.8 ± 4.2</td>
<td>Trace</td>
<td>24</td>
</tr>
<tr>
<td>Desloratadine</td>
<td>1-3</td>
<td>27</td>
<td>0</td>
<td>≥24</td>
</tr>
<tr>
<td>Fexofenadine</td>
<td>2.6</td>
<td>14.4</td>
<td>12/80</td>
<td>24</td>
</tr>
<tr>
<td>Levocetirizine</td>
<td>0.8 ± 0.5</td>
<td>7 ± 1.5</td>
<td>86</td>
<td>≥24</td>
</tr>
</tbody>
</table>

Adapted from Simons et al.
Acute and chronic urticaria

H1 antihistamines are first-line medications in acute and chronic urticaria and very effective in providing symptomatic relief. The evidence base for the use of H1 antihistamines in acute urticaria remains small; however, recently, in a prospective, randomised, double-blind, placebo-controlled, 24-month-long study, high-risk children given cetirizine had significantly fewer episodes of acute urticaria than did those given placebo.21 Although the evidence base for the use of first-generation H1 antihistamines in chronic urticaria also remains surprisingly small by current standards, that for second-generation H1 antihistamines (e.g. fexofenadine) has increased considerably during the past few years.22-23 In chronic urticaria, H1 antihistamines should optimally be given on a regular basis to prevent hives from appearing, rather than ‘as needed’.

Atopic dermatitis

In atopic dermatitis (AD), itching is one of the major symptoms and the resultant scratching usually causes worsening of the lesion. H1 antihistamines may relieve itching and reduce scratching. Relief of itching by H1 antihistamines is often incomplete in AD, because the itching produced by mediators other than histamine is not down-regulated. H1 antihistamines appear to relieve itching mainly through their CNS effects and thus first-generation H1 antihistamines (sedating) such as hydroxyzine and diphenhydramine are more effective for relief of itching in this disorder than are the second-generation H1 antihistamines (non-sedating).24 However, recent studies have shown that second-generation medications such as cetirizine and loratadine may also relieve itching in AD.25-27 In higher doses, cetirizine has been demonstrated to have a topical glucocorticoid-sparing effect in AD.

Anaphylaxis

Adrenaline is the first-line treatment in anaphylaxis. Antihistamines are considered adjunctive treatment for relief of itching, urticaria, rhinorrhea, and other symptoms.28 Because first-generation H1 antihistamines such as chlorpheniramine, diphenhydramine, and hydroxyzine have high aqueous solubility and are available in parenteral formulations for injection, they continue to be widely used in the treatment of anaphylaxis. Most of the second-generation H1 antihistamines have low aqueous solubility and none is available in formulation for injection. Antihistamines also have a potential role in prevention of anaphylaxis. In anaphylaxis, many of the effects of histamine, such as vasodilation and hypotension, occur as a result of its effects at both H1 and H2 receptors.29-30 H1 and H2 antihistamines given concomitantly decrease the frequency and severity of these reactions, and routine prophylaxis with these medications has been proposed.29 The prophylaxis pretreatment or treatment with both an H1 and H2 antihistamine may be more effective than pretreatment with an H1 antihistamine alone. Second-generation H1 antihistamines, administered orally, prevent allergic reactions in patients receiving immunotherapy.30

Asthma

In asthma, current evidence does not support the use of antihistamines for treatment. However, second-generation antihistamines are reported to reduce symptoms of allergic asthma in certain patients and exacerbation of asthma in adult patients with AR. The amount of improvement produced by H1 antihistamines in asthma is modest.31

USE IN PREGNANCY AND LACTATION

Chlorpheniramine, one of the first-generation antihistamines, is reportedly safe in pregnancy. There is little information on the use of the new antihistamines during pregnancy although cetirizine and loratadine are considered relatively safe for use during pregnancy (FDA category B).32-34 H1 antihistamines are excreted in small amounts in breast milk (<0.1% of a maternal dose). Breast-fed infants whose mothers have ingested first-generation antihistamines may experience irritability, drowsiness or respiratory depression;35 no symptoms have been attributed to second-generation antihistamines to date.

ADVERSE EFFECTS

The adverse effects of first-generation H1 antihistamines, mainly on the CNS, including drowsiness, impaired driving performance, fatigue, lassitude, and dizziness, are well documented. Other side-effects (anticholinergic) include dry mouth, urinary retention, gastrointestinal upset and appetite stimulation. Although the new-generation antihistamines are relatively free of serious CNS effects, a small number of individuals may experience sedation with these agents. Minor side-effects such as nausea, light-headedness, drowsiness, headaches, agitation and dry

<p>| Table III. Formulations and dosages of second-generation oral antihistamines |
|-------------------------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Generic name</th>
<th>Formulation</th>
<th>Recommended dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetirizine</td>
<td>10 mg</td>
<td>Table</td>
</tr>
<tr>
<td>Loratadine</td>
<td>10 mg</td>
<td>Table</td>
</tr>
<tr>
<td>Desloratadine</td>
<td>5 mg</td>
<td>N/A</td>
</tr>
<tr>
<td>Fexofenadine</td>
<td>60 mg</td>
<td>N/A</td>
</tr>
<tr>
<td>Levocetirizine</td>
<td>5 mg</td>
<td>N/A</td>
</tr>
</tbody>
</table>

<p>| Table IV. Second-generation topical antihistamines |
|-------------------------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Generic name</th>
<th>Formulation</th>
<th>Recommended dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azelastine</td>
<td>Nasal soln 0.1%</td>
<td>Adult &amp; paediatric ≥12 yr: 2 sprays/nostril bd</td>
</tr>
<tr>
<td>Ketotifen</td>
<td>0.025% ophthalmic soln</td>
<td>Adult &amp; paediatric ≥3 yr: 1 drop/eye bd</td>
</tr>
<tr>
<td>Levocabastine</td>
<td>Nasal spray 50 mg/puff</td>
<td>Adult: 2 sprays/nostril bd – qid</td>
</tr>
<tr>
<td>Olopatadine</td>
<td>0.1% ophthalmic soln</td>
<td>Adult &amp; paediatric ≥3 yr: 1 drop/eye bd</td>
</tr>
</tbody>
</table>

Current Allergy & Clinical Immunology, June 2009 Vol 22, No. 2 73
mouth have been reported occasionally with the new antihistamines. Weight gain (due to increased appetite) has also been reported in a few patients treated with cetirizine. Hypersensitivity reactions, including skin rashes and angio-oedema may also occur. In recommended dosages, the new antihistamines are generally safe. Toxicity associated with the new antihistamines is usually related to increased drug levels (due to over-dosage or impaired metabolism). Symptoms of overdose include drowsiness and agitation (especially in children).

First-generation H1 antihistamines may cause tachycardia, supraventricular arrhythmia, and prolongation of the QT interval in a dose-dependent manner. Two second-generation antihistamines, astemizole and terfenadine, were withdrawn from the market because of their cardiac toxic effects (torsades de pointes and other potentially fatal ventricular arrhythmias). Cetirizine, levocetirizine fexofenadine, loratadine and desloratadine appear to be free from cardiac toxicity even at higher than recommended doses.18,37

Declaration of conflict of interest

The author declares no conflict of interest.

REFERENCES


10. Banfield C, Gupta S, Marino M, Lim J, Affrime M. Grapefruit juice associated with the new antihistamines, astemizole and terfenadine, were withdrawn from the market because of their cardiac toxic effects (torsades de pointes and other potentially fatal ventricular arrhythmias). Cetirizine, levocetirizine fexofenadine, loratadine and desloratadine appear to be free from cardiac toxicity even at higher than recommended doses.18,37
INTRODUCTION

One of the commonest reasons why patients present to primary care physicians and to emergency departments is because of an exacerbation of their asthma symptoms. Knowledge of the factors contributing to such exacerbations helps the physician to understand why these episodes occur, thereby enabling more effective work-up and management.

Various reasons why patients who are steroid-naive or well controlled on inhaled corticosteroids develop an exacerbation of their asthma symptoms include respiratory infections (viral, bacterial, atypical), allergens (aeroallergens, food additives and food allergens), exposures (occupational sensitisers, environmental, drugs), and miscellaneous factors (β-adrenergic receptor polymorphisms and non-respiratory factors) (Fig. 1). These trigger factors result in multicellular inflammation, bronchial hyperresponsiveness and airflow obstruction.

INFECTIONS

Viral infections

Viral infections of the respiratory tract are associated with 80-85% of asthma exacerbations with two-thirds of these infections being due to picornaviruses (mainly rhinoviruses). Coronavirus, the next most common virus, causes a less severe exacerbation while influenza, parainfluenza, adenovirus and respiratory syncytial virus occur in a proportion of patients. Human metapneumovirus (HMPV), a paramyxovirus closely related to respiratory syncytial virus (RSV) has been associated with acute wheezing exacerbations especially in infants and young children. Up to 12% of all lower respiratory tract infections may be due to HMPV in this age group. In South African children, the prevalence of HMPV was found to be 8.3% among those presenting with acute wheezing, while 7.4% were infected with human bocavirus and 2.4% with human coronavirus. In addition, viruses and aeroallergens may have a synergistic effect on individuals with asthma, thus having a greater effect on the exacerbation rate together than either factor alone.

Respiratory syncytial virus

Respiratory syncytial virus (RSV) is an important cause of viral bronchiolitis in infants and young children, but their role in the pathogenesis of asthma and asthma exacerbations remains unclear. RSV infects almost 100% of children by 2 years of age. There are 2 subgroups of RSV-induced bronchiolitis, an eosinophil-positive group (with significantly raised eosinophil and interleukin-5 (IL-5) levels and raised IL-5/interferon (IFN)-γ ratios in bronchoalveolar lavage fluid) which results in a T-helper (Th) 2 type response, and an eosinophil-negative group (with an absence of the Th2 cytokine profile). Since childhood asthma also induces a strong Th2 immune response, it is likely that infants with eosinophil-positive RSV-induced bronchiolitis, go on to develop childhood asthma. RSV is the predominant pathogen in wheezing infants younger than 2 years of age.

Rhinovirus

Rhinovirus (RV) is the most commonly recovered virus from the lower respiratory tract in acute exacerbations of asthma in children over the age of 2 years. It was previously thought that RV primarily caused an infection in the upper respiratory tract, but we now know

Correspondence: Dr N Chetty, PO Box 561067, Chatsworth 4030. Tel 031-403-8613, fax 031-403-8614, e-mail nchetty@worldonline.co.za
that optimal replication of RV occurs between 33°C and 35°C, and thermal mapping of the airways in humans confirms that the temperatures found in the trachea and subsegmental bronchi will allow RV to replicate effectively in the lower respiratory epithelium.1 There are currently about 150 serotypes of RV and the majority (>90%) of the serotypes bind to intercellular adhesion molecule 1 (ICAM 1). The major human RV receptor is ICAM-1, and the gene for this receptor is located on chromosome 19.20 RV infection of the lower respiratory tract markedly increases cell surface expression of ICAM-1 in bronchial and respiratory epithelial cells by induction of ICAM-1 promoter activity involving upregulation of NF-κB, together with increasing ICAM-1 mRNA transcription.11 The net result is an increased RV infiltration of epithelial cells of the lower respiratory tract.

IFNs are antiviral proteins with an important role in the innate immune response to viral infections. Asthmatic bronchial epithelial cells have a deficient innate immune response to infection with RV in that they produce more than 2.5 times less IFN-β protein, and this impairs the infected cell’s ability to undergo apoptosis, thereby allowing increased viral replication to occur.12 Patients with allergic asthma also produce significantly lower amounts of IFN-α following viral infections.13 Deficient induction of IFN-α by RV in asthmatic bronchial epithelial cells has also been demonstrated.14 This paves the way for rhinoviral infection of the respiratory epithelial cells.

The next step is activation of the respiratory epithelial cells to produce pro-inflammatory mediators. RV infection results in an increased mRNA expression and translation of IL-6, IL-8, IL-16, eotaxin and RANTES (Regulated on Activation, Normal T cell Expressed and Secreted). IL-6 and IL-8 are pro-inflammatory cytokines. IL-8 is a potent chemotactic for neutrophils. Neutrophils predominately more frequently than eosinophils as the major inflammatory cell in sputum from patients with asthma in acute exacerbations following viral infections.15 RANTES is a chemokine with chemotactic activity for eosinophils, monocytes and T-lymphocytes. IL-16 activates eosinophils and is a chemotactic for lymphocytes.16 Generation of these cytokines results in deterioration of lung function.

Bacterial infections

Clinical and experimental studies indicate that sinonasal inflammation can result in worsening of lower airways disease, induced by post-nasal drip, nasobronchial reflux of inflammatory mediators. Organisms which may be cultured in maxillary sinus aspirates include Moraxella catarhalis, nontypeable Haemophilus influenzae and streptococcal pneumonia. Effective medical and surgical treatment of sinusitis may result in clinical improvement of the asthma symptoms.17 Furthermore, chronic sinusitis has been suggested as playing a causal role in difficult-to-control asthma.

Asthma is an independent risk factor for invasive pneumococcal disease. The respiratory airways of asthmatics display goblet cell hyperplasia, which results in increased production of mucus. Alterations in the secreted mucus results in abnormalities in viscosity and in the mucociliary clearance of the airways which can serve as a focus for localised infection that can develop into invasive bacterial infection.18

Atypical bacterial infections

Mycoplasma pneumoniae and Chlamydoaphila pneu-
moniae are significantly related to wheezing in children, especially in those with a history of recurrent episodes.19 This suggests a potential role for these pathogens in the exacerbation of childhood asthma. In children with wheezing, the incidence of M. pneu-
moniae and C. pneumoniae infections increases with age and occurs mainly after 5 years of age.20 Telithromycin, a new ketolide antibiotic, as well as macrolide antibiotics, has shown benefit in adults with acute exacerbations of asthma.20,21 Although the exact mechanism of the benefit is unclear, the findings suggest that atypical bacterial infections may be related to acute asthma exacerbations. However, it needs to be remembered that the ketolide and macrolide antibiotics have also been shown to have immunomodulatory effects both in vitro and in vivo, on the migration of neutrophils and production of pro-inflammatory cytokines.22,23 Therefore, more research and understanding are needed to define the precise roles of atypical bacteria in asthma exacerbations and the anti-inflammatory role of ketolide and macrolide antibiotics in this condition. The anti-inflammatory properties these antibiotics are considered to possess may actually be a secondary effect to an antimicrobial action to as yet unidentified respiratory tract bacteria.

ALLERGENS

Aeroallergens

Epidemics of asthma exacerbations have been observed following thunderstorms, with the strongest association in late spring and summer. A marked increase in the ambient concentration of grass pollen grains has been implicated in this condition.24 Thunderstorms are also associated with increased levels of Alternaria and Cladosporium species and sensitisation to these moulds correlates with asthma exacerbations and hospitalisations.25 Sensitisation to mites, cat and cockroach has been found to be a significant risk factor for worsening asthma symptoms. However, there is no clearly established quantitative relationship between current exposure to these perennial allergens and asthma exacerbations.2

Food additives and food allergens

Sulphites are antioxidants that are used as preservatives in foods and drugs, especially in injected and inhaled medications, and as antimicrobial agents in wine. They are used on dehydrated vegetables, dried fruits and in fruit drinks. Sulphiting agents include sulphur dioxide, sodium sulphite, and potassium and sodium salts of bisulphite and metabisulphite. Exposure to sulphites in an asthmatic who is sensitive to these agents may result in significant bronchospasm. Although injectable adrenaline (Epi-pen) contains sodium metabisulphite as an antioxidant, it may still be safely used if a patient experiences a severe systemic reaction as a consequence of sulphite exposure. Tartrazine, a synthetic yellow food dye has not been shown to cause asthma exacerbations, even among aspirin-sensitive asthmatics.

Asthma alone is an infrequent manifestation of food allergy. The major foods incriminated in the production of asthma in children are milk, eggs, soy, wheat, peanut, fish, tree nuts and shellfish. Acute respiratory symptoms to these antigens are an IgE-mediated reaction. More often, there are associated cutaneous, gastrointestinal and cardiac symptoms resulting in anaphylaxis.

EXPOSURES

Occupational sensitisers

Occupational asthma (OA) refers to bronchial inflammation directly resulting from the inhalation of dusts,
gases, fumes or vapours at the workplace. This results in variable airflow obstruction and bronchial hyper-reactivity, after a latent period of exposure to such agents.

Allergic OA is caused by high molecular weight (HMW) allergens and some low molecular weight (LMW) allergens. HMW allergens are mainly proteins derived from animals (e.g. animal protein in laboratory settings), plants (e.g. coffee bean dust in food processing), foods (e.g. flour in bakeries) and enzymes (e.g. protease and amylase in detergent manufacture). Sensitisation to these agents elicits a Th2 immune response with the production of specific IgE. Some LMW agents, such as antibiotics (e.g. penicillins in the pharmaceutical industry), metals (e.g. platinum salts, chrome and nickel in the metal-refining industry) or isocyanates (e.g. in the spraypainting industry) also elicit a Th2 immune response.

Non-allergic OA occurs as a result of high level exposure to potent respiratory irritants in the workplace. This results in non-immunological bronchial inflammation with resultant bronchoconstriction termed reactive airways dysfunction syndrome (RADS). Typically, there is no latent period prior to the presentation of bronchial symptoms. Industrial agents which are known to cause RADS include chlorine, sulphuric acid and toluene disocyanate used in the production of polyurethane products.26

Environmental exposures

Exercise, cold air, environmental pollutants and tobacco smoke are recognisable factors associated with aggravation of asthma symptoms.

Exercise-induced asthma usually results in transient narrowing of the airways following the cessation of vigorous exercise. The ‘thermal hypothesis’ proposes that cooling of the airways is followed by rapid rewarming resulting in reactive hyperaemia of the bronchial microcirculation and oedema of the airway wall, thus causing bronchoconstriction after exercise.27 Exercise-induced bronchospasm (EIB) phenotype is characterised by increased production of cysteinyl leukotrienes which may be mediated by sensory nerves. EIB may on occasion result in a severe bronchospasm and has been associated with sports-related deaths.

Cold air results in reflex bronchoconstriction and has been used as a diagnostic test for demonstrating bronchial hyper-reactivity.

Outdoor air pollution results in increased risk for asthma exacerbations. Polluted air may contain a mixture of ozone, nitrogen dioxide, sulphur dioxide, lead, carbon monoxide and particulate matter. Vehicular exhaust emissions contain ultrafine particulate matter, carbon, nitrogen dioxide and carbon monoxide and even short-term exposure to such emissions is associated with neutrophilic inflammation of the airways.28 Tobacco smoke exposure has been associated with asthma exacerbations and has been identified as a significant risk factor for asthmatic children, requiring intubation.29 According to a recent Institute of Medicine report, smoking in the home is causally related to exacerbations of asthma in preschool-aged children.30 Various mechanisms result in a state of corticosteroid resistance in asthmatics who smoke. Furthermore, cigarette smoking causes a downregulation of the β-adrenergic receptor function which impairs the clinical response to β2-agonists, thus potentiating an exacerbation.31

Drugs

Aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) and β-blockers have been associated with asthma exacerbations. Aspirin-induced asthma is a clinical syndrome which involves intolerance to aspirin and other NSAIDs which inhibit cyclo-oxygenase. This results in alterations in arachidonic acid metabolism and an overproduction of leukotrienes resulting in asthmatic attacks when these drugs are ingested. Beta-blockers in general and non-selective β-blockers (e.g. propanolol) in particular have the potential for worsening bronchospasm and inhibiting therapeutic responses to inhaled β-agonists.

MISCELLANEOUS

Beta-adrenergic receptor polymorphisms

Polymorphisms of the β2-adrenergic receptor can affect regulation of the receptor.32 Patients who are homozygous for arginine at codon 16 of the receptor (Arg/Arg) have worsening of their lung function with regular versus as-needed use of inhaled β2-adrenergic agonists. This effect is not observed in asthmatics homozygous for glycine (Gly/Gly) or in patients with the Arg/Gly genotype. The first prospective clinical trial, stratified by genotype, confirmed that genotype at the 16th amino-acid position of the β-adrenergic receptor affects the long-term response to albuterol use and suggested that bronchodilator treatments avoiding albuterol may be appropriate for patients with the Arg/Arg genotype.33 A similar result was demonstrated when long-acting β-agonists were studied. Relative to patients with the Gly/Gly genotype at position 16 of the β-adrenergic receptor, Arg/Arg genotype patients have an impaired therapeutic response to salmeterol in either the absence or presence of concurrent inhaled corticosteroid use.34

The prevalence of the Arg/Arg genotype in asthmatic patients in South Africa is unknown while a sixth of USA asthmatic patients have this genotype, and the frequency is even greater in individuals of African decent.35 Much debate has been initiated following the results of these trials with some researchers showing that response to salmeterol does not vary between β-adrenergic receptor genotypes after chronic dosing with an inhaled corticosteroid.36 Therefore, more research is needed in this area to clarify the relationship between β-adrenergic receptor genotypes and regular bronchodilator usage.

Non-respiratory factors

There is a strong association between gastro-oesophageal reflux, psychological dysfunctioning, obstructive sleep apnoea and recurrent exacerbations of asthma. Pathological gastro-oesophageal reflux is considered a potential trigger of asthma. Mechanisms of this acid-induced bronchoconstriction include a vagally mediated reflex and microaspiration. A subgroup of patients gains improved control of asthma with treatment of gastro-oesophageal reflux. Although psychological dysfunctioning has been strongly associated with recurrent asthma exacerbations, more studies are needed to clarify whether psychological disturbances are the cause or consequence of the loss of control in asthma. Snoring and obstructive apnoea may trigger nocturnal asthma attacks. In some unstable asthmatic patients, improvement in asthma control has occurred after nasal continuous positive airway pressure.37
CONCLUSION
In the majority of patients, asthma can be reasonably well controlled with inhaled anti-inflammatory drugs. A proportion of patients however suffer from frequent exacerbations of the condition, leading to emergency outpatient treatment or hospitalisation. Understanding the various factors affecting such exacerbations may result in improved management and prevention of such exacerbations.

Declaration of conflict of interest
The author declares no conflict of interest.

REFERENCES

Don’t miss the ALLSA AGM, 10 July 17h15!
Do visit the ALLSA stand at the Congress for back copies of the journal, patient information sheets and to renew your membership or join ALLSA
ABSTRACTS
ALLERGY SOCIETY OF SOUTH AFRICA (ALLSA) CONGRESS,
DURBAN, 10-12 JULY 2009

Abstracts are listed alphabetically within each section according to the name of the presenter of the paper. Please consult the congress programme for more details.

ORAL PRESENTATIONS

HIGH EXHALED NITRIC OXIDE (ENO) IS ASSOCIATED WITH WORK-RELATED RESPIRATORY ALLERGY IN NON-ATOPIC BAKERS
R Baityie1, 2, MF Jeebhay2
1Department of Environmental and Occupational Studies, Faculty of Applied Sciences, Cape Peninsula University of Technology, Cape Town, South Africa
2Centre for Occupational and Environmental Health Research, School of Public Health and Family Medicine, University of Cape Town, South Africa

Background: The aim of this study was to evaluate the determinants of elevated (>35 ppb) exhaled nitric oxide (ENO) for various clinically relevant endpoints in baker’s allergy and asthma.

Methods: A cross-sectional study of 544 bakers was conducted in 31 bakeries using an interviewer-administered questionnaire. Skin-prick tests (SPT) tested for skin reactivity to common aeroallergens. Specific IgE to wheat (β6) and rye (β5) was quantified using ImmunoCAP (Phadia). A hand-held portable sampling device (NIOX MINOX) was used to determine ENO levels during the work shift according to ATS/ERS recommendations (2005).

Results: The mean age of workers was 33 years, 57% were female, 43% current smokers and 38% were atopic (SPT positive to common allergens). Work-related (WRS) ocular-nasal symptoms (42%) were more prevalent than asthmas (25%) symptoms. A higher proportion of workers were sensitised to wheat (41%) than rye (35%). Probable baker’s asthma (WRS, sensitisation and previous history of a positive methacholine challenge test) was estimated in 5%. The mean eNO was 24 ppb, with 18% having moderately increased (21-35 ppb) and 17% high (>35 ppb) levels. High eNO was significantly (p < 0.05) associated with male gender (OR=1.7), current smokers (OR=0.6), exercise (OR=2.6), recent chest infection (OR=2.3), atopy (OR=4.6), doctor diagnosed asthma (OR=2.7) and hay fever (OR=2.6). A strong positive correlation (r=0.72, p < 0.001) was observed between eNO and specific IgE to either wheat or rye in non-atopic workers. In multivariate models (adjusted for gender, smoking and recent chest infection) non-atopic workers with high eNO (>35 ppb), were twice as likely to report work-related chest symptoms (OR=3.0) and even more likely to report hay fever (OR=2.8) or doctor diagnosed asthma (OR=4.6). These non-atopic workers with high eNO were also more likely to have increased IgE to wheat (OR=7.2) or rye (OR=8.6), baker’s rhinitis (OR=7.2) and a clinical diagnosis of baker’s asthma (OR=11.2).

Conclusion: This is the first study to demonstrate an association between eNO, work-related symptoms, IgE reactivity to flour dust allergens and baker’s rhinitis and asthma. High eNO (>35 ppb) could be used as a marker for work-related respiratory allergy among non-atopic bakers.

SOUTH AFRICAN PRIMARY IMMUNODEFICIENCY - THE REGISTRY AND THE WAY FORWARD
Monika Esser
Immunology Unit, NHLS Tygerberg Hospital, Cape Town, South Africa

Although IgA deficiencies have been reported as frequently as 1/300 people, primary immunodeficiency diseases (PIDs) are regarded a rare group of genetic diseases. However population prevalence of diagnosed PID in the USA by telephonic audit of 10 000 households in 2007 revealed a prevalence of 1/1 200 persons including severe immunodeficiencies. Delayed diagnosis is still common even in better resourced countries, mostly because of lack of awareness. In South Africa data of almost 90 patients have been recorded on the PID Registry at Tygerberg Hospital since November 2006. Patient enrollment is slow at about 30 new registrations per annum despite visits to hospitals in Johannesburg and Durban by the registry administrator. A wide spectrum of immunodeficiencies is reflected including a number of autoinflammatory diseases and suspected genetic susceptibility to tuberculosis. Diagnosis is at an average age of 10 years with a range of 6 months to 60 years. Antibody deficiencies still constitute the largest single group as in international registries and the majority of patients are on intravenous immunoglobulin therapy. In the past 6 months 3 new patients were diagnosed with severe combined immunodeficiencies; this may reflect an improving awareness. Almost 90% of patients are from the Western Cape and Gauteng, which probably correlates with availability of PID diagnostic facilities in these regions and also dense population. Black patients are still totally underrepresented at just over 4%, most likely because of lack of access to diagnostic facilities and treatment. Collaboration with other African countries, especially the North African regions has been established, where consanguinity reflects in a higher prevalence of PID than in western countries. Workshops in Africa on immune diagnostics and treatment with locally applicable guidelines for recognition of PID in developing countries are being established subsequent to the first African PID Congress ASDI in October 2008.

SUMMARY FINDINGS OF SKIN-PRICK TEST RESULTS FROM AN ALLERGY PRACTICE IN BOTSWANA
Shiang-Ja Kang, Loeto Mazhani, Diana Dickinson, Andrew Steenhoff
Riverwalk, Gabane, Botswana

Objective: Aeroallergen sensitisation patterns have been reported for South Africa and Zimbabwe. Similar Botswana studies are lacking. We review aeroallergen skin-prick test (SPT) results for Botswana, and compare these with those of neighbouring countries. Sensitisation to common foods was also examined.

Methods: All patients who had SPT from October 2008 to May 2009, at a private allergy practice in Gabane, Botswana, were included. Positive reaction was defined as a 3 mm wheal greater than negative control. Depending on clinical presentation, testing panel included: trees (plane, oak, acacia), grass (Bermuda, Timothy, maize), weed (English plantain), moulds (malt, Alternaria, Aspergillus), cat, dog, dust mites, Blomia tropicalis, cockroach, milk, soya, egg white, wheat, peanut.

Results: Fifty-five patients were analysed, 6 of whom underwent food testing only. The mean age was 10.5 years (SD 11.8; range: 4 months - 51 years), 67% were male and 75% were black. Grass pollen sensitisation was most common followed by Alternaria (29%), dog (20%), acacia tree (20%), weed (20%), cat (19%), cockroach (12%) and dust mites (6%). For foods, egg was most common (6/10) followed by peanut (4/8) and milk (1/8). No patients reacted to Blomia, oak, soya or wheat. Rhinitis was the commonest presentation (71%), followed by asthma (42%) and eczema (38%). Asthmatics were more likely to be cockroach allergic than non-asthmatics (p=0.02). Rhinitis patients were more likely to be grass allergic (p=0.01). Conjunctivitis sufferers were more likely to be sensitised to Bermuda grass (p=0.03). All food allergy patients had eczema.

Conclusion: Bermuda grass is the commonest aeroallergen causing rhinoconjunctivitis in Botswana. Unlike Zimbabwe and Cape Town, dust mite sensitisation is uncommon. Cockroach sensitisation is significant in asthmatics, similar to urban populations in the USA. Egg and peanut were the commonest food allergies. Larger population studies are needed to confirm these findings.
EFFECT OF AIR POLLUTANTS/ALLERGENS MEDIATED OXIDATIVE STRESS ON BRONCHIAL ASTHMA

KSA Mosandu1, ED Dabula, Z Novak2
1Chemical Pathology Department, MEDUNSA, University of Limpopo, South Africa
2University of Szeged, Paediatric Department, Szeged, Hungary

Background: Exposure to noxious mutagenic pollutants and allergens can activate neutrophils and macrophages to produce reactive oxygen species (ROS) and reactive nitrogen species (RNS). The subsequent oxidative stress induced in this way may increase the risk of developing exacerbated conditions of asthma through the promotion of T-cell response. The purpose of this study is to investigate the implication of pollutants and allergens in the exacerbation of asthmatic conditions and the involvement of oxidative stress.

Methods: Lung function was evaluated using spirometric measures in 60 asthmatic children (6-14 years old) with clinical history of asthma. Total equivalent antioxidant capacity (TEAC), superoxide dismutase (SOD) and glutathione peroxidase (GPx) were evaluated using kits commercially available from Randox-Company. Malondialdehyde (MDA) was estimated by thiobarbituric acid reaction.

Results: A general lung obstruction profile was detected in all our patients (from mild to severe) corresponding to the clinical score ranging from 3 to 18 and confirmed by FEV1 (forced expiratory volume) % ranging from 71% to 75% and by the measured ratio of FEV1/FVC (forced volume calculated). Haematological results displayed a high level of eosinophils (7.8-20%) for the majority of patients corresponding to the IgE values exceeding 500 kU/l. Positive Phadiatop has been observed in these patients who also displayed low values of TEAC and GPx (<1.42 mmol/l and <700 U/ml, respectively) and high values of 8 isoprostane (>7.5 pg/ml) in contrast with high levels of MDA (>3.5 mmol/l). However, exacerbated conditions of asthma were clinically confirmed only in 18 patients (clinical score: 6 - 8) with FEV1/FVC ratio ranging from 43% to 75%

Conclusion: Exacerbations of asthma are a consequence of hyperproduction of eosinophils and IgE by oxidative stress generated by the combustion products acting as adjuvants in the immune system of those patients sensitised to the observed allergens.

MITE AND COCKROACH SENSITISATION IN PATIENTS WITH ALLERGIC RHINITIS IN THE FREE STATE

RY Sreedat, J Claassen, AJ Claassen, G Joubert
Universitas Hospital, University of the Free State, Bloemfontein, South Africa

Aim and objectives: Previous studies on patients with allergic rhinitis living in the Free State province of South Africa showed that grass pollen and house-dust mites were the predominant allergens with house-dust mite sensitisation being less prevalent than in the coastal areas and a low rate of sensitisation to the storage mite Lepidoglyphus destructor. No studies have been conducted on sensitisation to the other storage mites, spider mites or cockroaches. The aim of this study was to determine the prevalence of sensitisation to various house-dust mites, storage mites, spider mites and cockroaches in patients with allergic rhinitis living in the Free State.

Methods: Fifty consecutive patients with moderate-severe persistent allergic rhinitis who were attending the ENT clinic at Universitas Hospital underwent skin-prick testing and/or ImmunoCAP RAST testing for common allergens, house-dust mites, storage mites, spider mites and cockroaches.

Results: Forty-six per cent of patients were sensitised to one of the house-dust mites, with house-dust mite sensitisation being significantly more common in patients who had previously lived at the coast. Storage mites were not common allergens, while 46% of patients were sensitised to the spider mite T. urticae. B. germanica was the cockroach species most commonly sensitised on ImmunoCAP RAST testing, with 38% of patients being sensitised.

Conclusions: House-dust mites, T. urticae and the cockroach B. germanica appear to be important allergens in the Free State province of South Africa. Storage mite sensitisation is not common.

WORK-RELATED ALLERGY AND ASTHMA IN SPICE MILL WORKERS – THE IMPACT OF PROCESSING DRIED SPICES ON IgE Reactivity

A van der Walt1, AL Lopata,2,3 NE Nieuwenhuizen,3 MF Jeebhay1
1Centre for Occupational and Environmental Health Research, School of Public Health and Family Medicine, University of Cape Town, South Africa
2School of Applied Science, Allergy Research Group, RMIT University, Melbourne, Australia
3Allergy and Asthma Research Group, Division of Immunology, Institute of Infectious Diseases and Molecular Medicine, University of Cape Town, South Africa

Background: Three spice mill workers developed work-related asthma and allergy after prolonged exposure to high levels (>10 mg/m3) of inhalable spice dust. Patterns of sensitisation to a variety of spices and putative allergens were identified.

Methods: Work-related allergy and asthma were assessed on history, clinical evaluation, pulmonary function and fractional exhaled nitric oxide (FeNO). Specific IgE reactivity to a range of common inhalant, food and spice allergens was evaluated using ImmunoCAP and allergen microarray. The presence of non-IgE mediated reactions was determined by basophil stimulation (CAST-ELISA). Specific allergens were identified by immunoblotting to extracts of raw and dried processed garlic, onion and chili pepper.

Results: Asthma was confirmed in all 3 subjects, with work-related patterns prominent in worker 1 and 3. Strong specific IgE responses to multiple spices and pollen were observed in worker 1 and 2, and weak responses in worker 3, who was sensitised exclusively to garlic and chili pepper. Microarray analysis demonstrated prominent profilin reactivity in both atopic workers 1 and 2. Immunoblotting demonstrated a 50 kDa cross-reactive allergen in garlic and onion, and allergens of approximately 40 kDa and 52 kDa in chili pepper. Dry powdered garlic and onion demonstrated greater IgE binding.

Conclusions: This study demonstrated IgE reactivity to multiple spice allergens in workers exposed to high levels (>10 mg/m3) of inhalable spice dust. Processed garlic and onion powder demonstrated stronger IgE reactivity than the raw plant. Astery and polysensitisation to various plant profilins, alluding to pollen-food syndrome, represents additional risk factors for sensitiser-induced work-related asthma in spice mill workers.
THE CURIOUS CASE OF CURVULARIA IN CAPE TOWN
Dilys Berman-Uys
Allergy Diagnostic Clinical Research Unit, UCT Lung Institute, Cape Town, South Africa

Curvularia is an allergenic fungal spore that peaks during autumn. The total fungal spore load from a Burkard 7-day recording volumetric spore trap, mounted on a roof close to the University of Cape Town Lung Institute in Mowbray, was quantified from June 2008 to April 2009. The range was 8 - 5,618 spores/cubic metre air. The proportion of the total fungal spore load for Curvularia varies according to the geographic location. Documented ranges are 0.87% to 9.8%. Seasonal changes in Cape Town generally start in February, depending on the weather parameters. The Curvularia catch increased at the onset of autumn, and the proportion of Curvularia spores in the total fungal spore load rose from 0.3% for the period June 2008 to January 2009, to 12.1% for the autumn months February - April 2009. Curvularia counts of this magnitude have not been measured at three previously sampled sites in Cape Town. This finding indicates that Curvularia may be an important allergen in this area. A small prospective study could be undertaken, by adding this fungal spore allergen to the skin-prick or Immunocap testing panels in local hospitals to determine the incidence of Curvularia sensitivitiy in the local population.

DENTITRIFICATION BETWEEN TRUE LATEX ALLERGY AND CROSS-REACTIVITY IN SOUTH AFRICAN DENTAL WORKERS
TS Singh,1 A Lopata,2 DO Mabe,1 ME Raand CROSS-REACTIVITY IN SOUTH AFRICAN DENTAL WORKERS
1National Institute for Occupational Health, NHLS, Immunology and Microbiology, Johannesburg, South Africa
2Division of Immunology, IIDMM, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa

The findings of this study demonstrated that Hev b 5, 6.01, 6.02 and 8 can be reliably used in the diagnosis of true latex allergy among South African dental workers. Sensitisation and asymptomatic latex sensitisation and the remaining 19 were identified as false-positive responses to latex as a result of cross-reactivity due to sequence homologies between allergens from different sources has been reported. It is important to discriminate between true allergy and asymptomatic sensitisation for the treatment and management of latex sensitive individuals.

Aim: The aim of this study was to determine the role of single recombinant Hevea brasiliensis latex allergens and cross-reacting carbohydrate determinants (CCDs) in the diagnosis of latex allergy in South African dental workers.

Methods: This study investigated 41 composite latex (k82) positive individuals from a previous study of 421 dental workers. Clinical symptoms to latex were identified through a self-administered questionnaire. Sensitivity to eight single recombinant Hevea brasiliensis latex allergens (Hev b 1, 3, 5, 6.01, 6.02, 8, 9, and 11) was tested. Allergens from MUXF3 and HRP markers were included in order to detect sensitisation to CCDs. The IgE reactivity to these markers was analysed with the Pharmacia ImmunoCap system.

Results: Hev b 1, 3, 9 and 11 allergens showed little or no value in the evaluation of clinical sensitisation. The clinically significant latex allergens identified were Hev b 5, 6.01, 6.02 and 8. Of the 41 latex sensitised individuals tested, 22 showed true latex allergy, 7 had asymptomatic latex sensitisation and the remaining 19 were identified as false-negative responses to latex as a result of cross-reactivity to carbohydrate epitopes.

Conclusion: The findings of this study demonstrated that Hev b 5, 6.01, 6.02 and 8 can be reliably used in the diagnosis of true latex allergy among South African dental workers.

PRODUCT NEWS

Long-chain polyunsaturated fatty acids influence the immune system of infants
Gottrand F. EA 3925, IFR 114, Faculty of Medicine and University of Lille 2, Lille, France. fgottrand@chu-lille.fr

Several events occur during the first months of life that allow the immune system to become competent and functional. The aim of this article is to review the rationale and evidence of an influence of (n-3) long-chain PUFA (LCPUFA) on the immune system of infants. The (n-3) LCPUFA exert their immunomodulatory activities at different levels. The (n-3) LCPUFA metabolites induce eicosanoid production, alter gene expression, and modify lipid raft composition, altering T-cell signalling; all contribute to immunological functional changes. However, the roles of these mechanisms and the types of T or other immunological cells involved remain unclear at present. Moreover, the effect of (n-3) LCPUFA on the immune system of infants may vary according to dose, time of exposure, and profile of the immune system (T-helper, Th1/Th2). Most of the interventional studies in infancy have been performed for the prevention of allergy. They all confirmed influence on T-cell function and cytokine profiles, but clinically beneficial effects are more conflicting. Supplementation of the matenal diet in pregnancy or early childhood with (n-3) LCPUFA is potentially a noninvasive intervention strategy to prevent the development of allergy, infection, and possibly other immune-mediated diseases. However, any long-term in vivo effects on (n-3) LCPUFA early in life for immunomodulatory defense in infants and later on immune status and health remain to be assessed.

J Nutr 2008; 138(9): 1807S-1812S.

For more information please contact Nestle Consumer Services on 0860 09 67 89
ALLERGIES IN THE WORKPLACE

ALLERGIC CONTACT DERMATITIS IN THE
FOOD INDUSTRY - FROM AGRICULTURE
TO FOOD PROCESSING AND MANUFACTU RE: A CASE STUDY OF A DAIRY
FARMER
Amy Burdzik, MB ChB
Centre for Occupational and Environmental Health Research, University of Cape Town, South Africa

ABSTRACT
Agriculture and food production have a high prevalence of occupational skin disease when compared with other industries. This article discusses contact dermatitis in a farmer. The discussion outlines the three main different allergic skin conditions: allergic contact dermatitis, protein contact dermatitis and contact urticaria, as well as diagnosis and management of work-related allergic skin disease, with emphasis on the allergens found in different parts of the food industry. It highlights the need for health care practitioners to consider occupational causes for all skin conditions and to take a detailed occupational history.

INTRODUCTION
Occupational allergy is defined as an allergy caused by exposure to a substance in the workplace. Allergies at work can affect various organ systems, leading to several different clinical syndromes including allergic contact dermatitis, contact urticaria, occupational rhinitis and asthma, and even anaphylaxis. Occupational skin diseases, and contact dermatitis in particular, are some of the commonest health problems caused by work, accounting for around 30% of reported, compensatable occupational diseases in several European countries. The incidence rate is believed to be around 0.5-1.9 per 1 000 workers per year. In agriculture and the food industry, many different allergens can lead to allergic contact dermatitis, ranging from chemicals and pesticides used on farms to foodstuffs, preservatives and additives used during food processing.

Worldwide more than one billion people are employed in agriculture, and around 7.5% of South Africa’s workforce is employed in the industry. An additional 22 million people are employed in the food and drink industry globally, although in South Africa, employment in this sector fell by 19% between 1999 to 2004. This number reflects formal employment, so there are likely to be many more people employed informally and in small businesses throughout the country.

A high burden of occupational skin disease in this sector translates into large costs, both to the individual and to employers in terms of days lost from work, and adjustments necessary in the workplace. Early recognition of allergic contact dermatitis may lead to improved outcomes for the individual in a condition which has been thought to have a relatively poor prognosis for full recovery. Therefore, the health care practitioner needs to be aware of possible occupational causes for all skin disease.

CASE REPORT
A 53-year-old manager of a dairy farm presented with an 8-month history of a burning, erythematous rash, particularly on his face and forearms. It had started 4 months after moving to a new dairy farm, although he had performed a similar role on several different farms. Prior to this episode, he had suffered from cracked fingers in 2006, and seen a dermatologist. He had been patch tested using commercially available allergens in 2006 and had a positive reaction of questionable relevance to Quaternium 15. His rash had resolved with use of steroid creams and had not recurred. He had no history of atopy, eczema or asthma, and no other chronic medical conditions.

A course of potent topical steroid had not controlled a recent flare, but he mentioned that while he had been on holiday in Australia his rash had resolved spontaneously, only to recur on the airplane back to South Africa. He lives on the dairy farm in a recently built house.

On examination, he had chronic eczematous skin changes on both wrists and over the knuckles. There were cracks in the web spaces of his fingers, and erythema and scaling of the upper arms. The rest of his examination was unremarkable. The clinical picture was compatible with dermatitis.

A workplace visit was conducted to assess exposures. As one of two managers, his role is mainly supervisory, but he may perform any part of the milking process as needed. There are 600 cows on the farm and they are milked 3 times a day. The udders are sprayed with a disinfectant prior to being attached by rubber tubing to milking machines (Fig. 1). Following milking, the cow’s teats are treated with a teat dip to prevent infection, and they then walk across a formaldehyde-impregnated mat to disinfect their hooves. Any cows with health problems are assessed by the farm managers, and may then be treated with a laxative, stool hardener or antibiotic. Artificial insemination is also performed by the managers.

The milk is stored in large stainless steel vats. These are cleaned with industrial chemicals. Periodically, the cows are treated for ticks. Following milking, the cows return to open sheds for feeding with a grain mix that is manufactured on the farm (Fig. 2).

CAUSES OF SKIN DISEASE IN AGRICUL TURE AND THE FOOD INDUSTRY
There are many skin disorders associated with farming, food production and processing. Infections such as milker’s nodule and or, which present as papules on the hands and fingers, are caused by parapox viruses carried by cows and sheep respectively. Most workers know what the cause is and seldom seek medical help for the conditions especially as they become immune. Microsporum and dermatophyte infections are carried by dogs, cattle and horses and these can infect humans causing inflammatory dermatophytosis. Other
important zoonoses include systemic diseases such as brucellosis and anthrax. Skin cancers are more common in susceptible outdoor workers. This article focuses on causes of dermatitis in the industry.

Irritants are a common cause of dermatitis. Irritant dermatitis is related to wet work, exposure to detergents and cleaning agents, hand cleaners and abrasives, and tends to have a more gradual onset with repeated exposure to one or several irritants.

Allergic contact dermatitis is a delayed hypersensitivity inflammatory reaction. It follows previous sensitisation to an agent which is usually a low-molecular-weight hapten. The substance is small enough to penetrate the stratum corneum and is taken up by Langerhans cells which then present it as an antigen to T-lymphocytes in the lymph nodes and skin. Antigen-specific T-lymphocytes enter the blood stream and circulate to the skin. During the next exposure to the substance, there is a cytokine-induced inflammatory reaction, and dermatitis generally develops within 12 to 48 hours. It may be difficult to distinguish allergic contact dermatitis from irritant contact dermatitis. If dermatitis corresponds to the site of contact and develops within 12-48 hours of minimal exposure it is likely to be allergic in origin.

Irritant contact dermatitis was thought to be more common than allergic contact dermatitis, but recent studies have argued that allergic contact dermatitis, or a combination of both, may be found to occur as frequently as irritant dermatitis, depending on how thoroughly a doctor investigates when looking for the allergen and the type of occupation. Kucenic and Belsito found that nearly 50% of contact dermatitis in some professions was allergic in nature.

Since the late 1970s, a separate entity known as protein contact dermatitis has been described. Clinically it is similar to other types of contact dermatitis, but a distinguishing feature is an immediate itch and urticaria developing within minutes of contact, especially on already damaged skin. Proteins which cause protein contact dermatitis are larger than the low-molecular-weight haptens usually associated with allergic contact dermatitis, and are normally divided into four groups - vegetable/fruit/spice; animal; grains; and enzymes. These are all present in the food industry. It is a rare entity, and there are minimal epidemiological data for incidence or prevalence in different industries. Usually patch testing with the agents will be negative, but a skin-prick or 'scratch' test (when the raw food is applied to a scratch rather than intact skin) will give a wheal and flare reaction. Because the causative agents are large proteins which would not normally penetrate skin, it is thought that skin needs to be damaged, either through irritation or atopic dermatitis, before it can develop. Contact urticaria may be immune-mediated (by IgE) or not, and in some cases the mechanism of action is not yet understood. Abnormal skin, for instance from an irritant dermatitis, may predispose to sensitisation.

Some of the more common substances reported to cause contact urticaria and contact dermatitis in the food and agriculture industry are listed in Tables I and II.

**Table I. Substances known to cause contact urticaria in agriculture and the food industry**

| Animal proteins | Milk, cheese, eggs, beef, liver, lamb, chicken, turkey, seafoods (fish, prawns, shrimp, oyster) |
| Plant proteins (fruit and vegetables) | Asparagus, apple, banana, beans, cabbage, castor bean, celery, garlic and onion, kiwi fruit, lemon and lime, mushrooms, mango, parsley, parsnip, peach, potato, soybean, strawberry, thyme, tomato, watermelon |
| Grains, nuts and spices | Almond, buckwheat, cashew nuts, cayenne pepper, cinnamon acid and cinnamic aldehyde, curry, flour, maize, menthol, rice, vanilla, wheat |
| Enzymes and additives | Benzoic acid, sodium benzoate, sorbic acid, tartrazine |

* Adapted from Tantersampan & Maibach, Ale & Maibach.

**Agriculture**

The agricultural industry has the highest reported rates of occupational skin disease in the USA. Allergic contact dermatitis has been described for pesticides, disinfectants, rubber chemicals and feed additives (minerals, antibiotics, antioxidants). Animal dander (cows, sheep) can also be a sensitiser. In a Finnish study, cow dander was the commonest cause of contact urticaria followed by rubber, flour grains and feed. Cow’s milk and hen’s eggs may cause contact urticaria, as may various other plant and animal proteins as listed in Table I. Pesticides, especially fungicides, are known allergens. Fertilisers may contain phosphated compounds as well as cobalt and nickel, which can cause contact dermatitis.
Beekeepers develop allergic contact dermatitis following exposure to propolis. This resinous substance from trees (often poplar) is incorporated into the hive as a sealant by bees, and is widely used in cosmetics and toothpaste. ‘Hoppicker’s dermatitis’ describes a condition thought to be related to resin on hops plants when they are picked for brewing beer.

Green coffee beans are a well-known cause of occupational allergy. Contact dermatitis from lettuce is reported in occupational and non-occupational settings. Celery has been described as a cause of phytophotodermatitis. This is due to high quantities of psoralens followed by sun exposure leading to dermatitis.

Bakers and confectioners

Baker’s asthma due to flour allergy is a well-described clinical entity. Flour and grains may also cause protein contact and allergic contact dermatitis. Mites and pesticides contaminating stored grain are further sources of exposure. Enzymes, such as α-amylase which is used to improve baking quality, are allergens and ‘flour whiteners’ (e.g. benzoyl peroxide) have been found to cause dermatitis.

Aside from grains, bakers are also exposed to numerous spices. The five spices which most commonly cause contact dermatitis in the USA are capscicum, cinnamon, cloves, nutmeg and vanilla. Capsicum is also an irritant—so strong that it is used in teargas. Cinnamon is used as a flavourant not only in baking, but also in toothpaste, chewing gum and spiced cola soft drinks or alcoholic beverages. Cinnamic aldehyde is used in sunscreens, and has some cross-reactivity with balsam of Peru, which may be found in fragrances and tested for with commercially available allergens.

Nutmeg and clove are frequently used in cooking and baking. Clove oil is also used to flavour toothpaste and mouthwashes. Vanilla may cause contact dermatitis in workers involved in cultivation, trade and industrial use of vanilla. These workers may report additional symptoms of rhinitis, asthma and vertigo in a syndrome known as ‘vanillism’. Contact urticaria (and contact dermatitis) to turmeric (curcumin) has been reported recently.

Chefs and cooks

Chefs and cooks are exposed to a wide variety of both irritants and allergens. Frequent hand-washing, and exposure to irritant and abrasive food products such as citrus fruits, can be contributory factors. Garlic and onion are common contact allergens. Other foods reported to cause contact dermatitis are listed in Table II.

Food additives such as dyes, preservatives, stabilisers and antioxidants cause dermatitis. Although it is rare, a dye used to colour oranges, cheese, jam and fish known as Citrus Red No. 2, can cause contact dermatitis. Tartrazine and Sunset Yellow dyes may cause contact urticaria. Benzoyl acid and sorbic acid which are used as preservatives produce non-immunological contact urticaria.

Contact urticaria has been reported to milk as well as cheeses. The major allergens is thought to be casein. Contact urticaria to parmesan cheese has recently been reported. Italian cheesemakers wrap their cheese in rags. These have been found to support growth of the Rhizoglyphus mite, which is a known sensitizer.

Non-food exposures include latex gloves and nickel in cooking utensils.

Butchers, poultry processors and seafood workers

In poultry processing, most dermatitis is irritant, as a result of the frequent wet work. Contact urticaria results from direct animal protein contact (blood, skin, meat and viscera) on already damaged skin. Butchers have similar contact. Urticaria has been reported after exposure to beef, lamb and calf liver. Seafood processing workers have a particularly high prevalence of occupational allergy. A recent study found a prevalence of protein contact dermatitis (diagnosed by a history of recurrent skin problems and a positive skin-prick test) of between 1% and 2%. This is thought to be due to high-molecular-weight proteins generating an IgE response.

DIAGNOSIS AND MANAGEMENT

Early diagnosis is key, as prolonged exposure is more likely to lead to intractable dermatitis which persists after removal from exposure. Prognosis worsens with chronicity, treatment delay, underlying atopic dermatitis and poor understanding of the condition by the worker. Avoidance of exposure is the mainstay of treatment. Before this can be done, the allergen needs to be identified. Because of the numerous exposures listed, this may be difficult, and relies heavily on an extensive, detailed and informed history. Patch testing with commonly implicated allergens or agents specific for the individual job or task may be helpful. These commercially available allergens may identify a cause in up to 80% of cases. For contact urticaria and protein contact dermatitis, a scratch test may be necessary if the patch test is negative.

Avoidance of workplace visit is mandatory as patients may not recall or even be aware of all of their exposures when questioned in the office. Material Safety Data sheets from the workplace provide some information, but by law do not need to declare substances which make up less than 1% of the product. Therefore, an allergen
may be present in a product but not declared. A patch test with the products identified from the workplace visit may be required. Patch testing needs to be performed by an expert with full knowledge of the risks, particularly when testing non-standard agents which may be dangerous. Interpretation of the results of these patch tests requires expertise as they may illicit false-positive or immunoreactive reactions if not tested appropriately.

Patients need to be informed of their allergy and likely sources of the allergen. They should be encouraged to read product constituents and, if possible, informed about use of alternative products and where the allergen may be encountered outside of the workplace.

Previously, occupational contact dermatitis was thought to have a very poor prognosis, but a recent review has shown that 78-84% of people recover without significant impairment. However, people sensitised to common ubiquitous allergens, especially, may suffer significant disability and recurrent disease as they will struggle to avoid exposure from these widely occurring substances. A change of occupation is not usually necessary and does not influence prognosis in most cases. A ‘holiday from work’ or temporary job change should be considered for very severe allergy in cases where the allergen cannot be avoided in the workplace, and for people with a skin barrier defect who would frequently be exposed to irritants.

Treatment of allergic contact dermatitis after allergen avoidance is as for other types of dermatitis. Saary et al. found good quality studies showing benefit of treatment with potent and moderately potent topical steroids. Unfortunately, there is limited information about prevention of allergic contact dermatitis in the workplace.

Case study evaluation

In the case of the farmer, no definitive diagnosis for his dermatitis has been made. As noted above, the number of exposures is vast. He is in contact with cow dander, pesticides, fungicides, cleaning agents, medications, animal feed and rubber. He lives in a newly built house with exposure to paint, new carpets and cleaning products. The history of recurrence of his symptoms on the airplane suggests a link to cleaning products, an insecticide sprayed prior to departure or even products in the upholstery or paint.

The previous positive reaction to Quaternium 15 needs to be revalidated relevant to his current dermatitis and exposures. Quaternium 15 is a formaldehyde-releasing preservative used in cosmetics, moisturisers and soaps, as well as in disinfectants and other industrial agents such as adhesives, polishes and paints. The farmer is exposed to disinfectants used to clean the milk tanks, as well as disinfectants used on the cows’ udders. We will need to perform a patch test with commonly available allergens to assess whether it is positive again, as well as a patch test with specific allergens found on the farm, and then decide which results are relevant to his presentation. A prick test with cow dander is necessary. If positive, a change of occupation or work holiday will be required, as cow dander is ubiquitous on the farm. If he is allergic to other products, such as disinfectants, medications or food additives, a change of those products will end his exposure and lead to improvement in his dermatitis.

Conclusion

Occupational contact dermatitis is a common occupational illness, and is particularly prevalent in agriculture and the food-processing industries. Allergic contact dermatitis may be more common than we anticipate, so it is useful to perform patch tests on patients with suspected contact dermatitis to rule out potential allergens even if the dermatitis is thought to be mostly irritant. Although there are many unusual allergens, patch testing with commercially available allergens may reveal allergens such as nickel, rubber and some spices.

All health practitioners should bear this in mind when assessing dermatitis, and should remember the possible work-related causes of the condition, especially in cases which appear to be refractory to treatment or when there is a clear history of symptoms worsening with work and clearing on vacation, as with our patient. Allergen avoidance and early treatment should lead to a good outcome in most cases and allow the individual to continue in his or her chosen occupation.

Declaration of conflict of interest

The author declares no conflict of interest.

REFERENCES

20. Diba VC, English JSC. Contact allergy to green coffee bean dust in a coffee processing plant worker. Contact Dermatitis 2002; 47: 56.

PATIENT INFORMATION SHEETS - ANOTHER ALLSA MEMBERSHIP BENEFIT

Did you know that membership of ALLSA entitles you to receive copies of our Patient Information Sheets which provide information on various aspects of allergy in an easy-to-understand format for your patients?

Topics covered include:
- Allergen Immunotherapy
- Allergic Reactions to Honey Bee and Wasp Stings
- Allergic Rhinitis
- Bedding Protectors and Allergy Control
- Cockroach Allergy
- Coeliac Disease
- Contact Dermatitis
- Drug Allergy
- Egg Allergy
- Fish Allergy
- Food Additives and Preservatives
- Food Allergy
- House-Dust Mite Allergy
- Latex Allergy
- Milk Allergy/Intolerance
- Mould Allergy
- Peanut Allergy
- Pet Allergy
- Seafood Allergy
- Soya Allergy
- Treatment of Allergic Eczema
- Urticaria and Angioedema
- Vacuuming and Allergy Control
- Wheat Allergy

Patient information sheets can be ordered in batches of 50 from the ALLSA office, tel 021-447-9019, email mail@allergysa.org

There is no charge for the leaflets, but we do charge for postage.
Travis is 14 years old. He has suffered from asthma and allergic rhinitis since he was a toddler. He had severe eczema as an infant which is now localised to the flexural surfaces of his limbs.

Dr Do-a-lot prepares to examine him.

She asks Sister Sweet to measure his height and weight on the way to the examination room.

She notices that his appearance and posture have been affected by his chronic condition.
He is small, thin, and round-shouldered, with a pigeon chest.
His face is elongated which makes him look sad, and he is mouth-breathing.
His speech has a nasal quality.
He performs an allergic salute as he steps up onto the scale and twitches his nose.
Features that may be present in the physical examination of an allergic patient

- Pale complexion
- Hyperaemic conjunctivae
- Conjunctival pavement slabbing
- Sinusitis
- Dry cracked lips
- Lip licking dermatitis
- Eczema
- Dry skin or eczema around the eyes and at the hairline
- Hyperinflated chest
- Wheeze on expiration may be heard
- Postnasal drip
- Lymphoid hyperplasia of the posterior pharyngeal wall
- A geographical tongue is said to be more common in allergic children
- Swollen, often pale, inferior turbinates
- Nasal crease
- Nasal secretions
- Deviated nasal septum
- Dennie’s lines
- Allergic shinners
- Tearing
- Conjunctival pavement slabbing
DIETARY EXCLUSIONS FOR ESTABLISHED ATOPIC ECZEMA

Taryn Young, MB ChB, FCPHM, MM ed
RYTD Consultancy, Pinelands, Cape Town, South Africa

Aims
This feature on evidence-based health care (EBHC) aims to present useful practice-related information on topics relevant to readers of Current Allergy & Clinical Immunology. The treatment of topics is not comprehensive. The main aim is to illustrate selected aspects of the EBHC process viz. (i) identifying the best evidence and (ii) applying valid and relevant evidence in clinical practice. The box titled ‘Some terms explained’ enlarges on the technical terms mentioned in the text and marked with an asterisk (*).

Background
Atopic eczema affects up to 20% of children worldwide. It is caused by a combination of genetic and environmental factors. Although there is currently no cure for atopic eczema, a wide range of treatments are used to control the symptoms. One such approach is a dietary one, whereby certain foods such as cows’ milk are excluded on the basis that they are thought to cause eczema to worsen.

So what is the question?
What are the effects of dietary exclusions for the treatment of established atopic eczema?

The type of evidence to look for, and where to look for it
The best evidence will come from randomised controlled trials (RCTs). If more than one trial has been conducted, the most reliable evidence, if available, is a systematic review of all relevant RCTs. The Cochrane Collaboration (www.cochrane.org) conducts systematic reviews of the effects of healthcare interventions following rigorous methods and processes to reduce bias. Results from systematic reviews are published in The Cochrane Library (http://www.thecochranelibrary.com/) and the Cochrane Database of Systematic Reviews has an impact factor* of 4.654.

What was found?
You found a recent systematic review examining the effects of dietary exclusions for the treatment of established atopic eczema.

What did the authors do?
The authors conducted a comprehensive search and identified 12 RCTs of which 9 were included. Data extraction and assessment of the risk of bias of included studies were done independently by two authors. For studies with a similar type of intervention, authors performed a meta-analysis, to calculate a weighted treatment effect across trials, using a random effects model. They expressed the results as risk ratio and 95% confidence intervals (CI) for dichotomous outcomes* and mean differences and 95% CI for continuous outcomes*. The results were also expressed as number needed to treat where appropriate, for a range of plausible control event rates. Heterogeneity* was assessed using I² (Box 1). Where it was not possible to perform a meta-analysis the data was summarised for each trial.

Box 1. Identifying and measuring heterogeneity

1. Inspect the forest plot
If CIs for the results of individual studies (generally depicted graphically using horizontal lines) have poor overlap, this generally indicates the presence of statistical heterogeneity.

2. Statistical test for heterogeneity
The chi-squared (χ², or chisq) test is included in the forest plots in Cochrane reviews. It assesses whether observed differences in results are compatible with chance alone. A low P value (or a large chi-squared statistic relative to its degree of freedom) provides evidence of heterogeneity of intervention effects (variation in effect estimates beyond chance). Care must be taken in the interpretation of the chi-squared test, since it has low power in the (common) situation of a meta-analysis when studies have small sample size or are few in number. This means that while a statistically significant result may indicate a problem with heterogeneity, a non-significant result must not be taken as evidence of no heterogeneity. This is also why a P value of 0.10, rather than the conventional level of 0.05, is sometimes used to determine statistical significance.

3. I² statistic
Some argue that, since clinical and methodological diversity always occur in a meta-analysis, statistical heterogeneity is inevitable. Therefore the test for heterogeneity is irrelevant to the choice of analysis; heterogeneity will always exist whether or not we happen to be able to detect it using a statistical test. Methods have been developed for quantifying inconsistency across studies that move the focus away from testing whether heterogeneity is present to assessing its impact on the meta-analysis. A useful statistic for quantifying inconsistency is the I². A rough guide to interpretation is as follows:
- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.
**Results and conclusion**

The studies fell into three main categories – egg and cow’s milk exclusion diets; few foods diet and elemental diet. Only two studies were considered sufficiently similar to pool. There may be some benefit in using an egg-free diet in infants with suspected egg allergy who have positive specific IgE to eggs. Little evidence supports the use of various exclusion diets in unselected people with atopic eczema, but that may be because they were not allergic to those substances in the first place. Lack of any benefit may also be because the studies were too small and poorly reported. Future studies should be appropriately powered focusing on participants with a proven food allergy. In addition a distinction should be made between young children whose food allergies improve with time and older children/adults.

**REFERENCES**


*Some terms explained*

**Journal impact factor (IF):** The IF is a tool for ranking, evaluating, and comparing journals. It is calculated based on a 2-year period and is a measure of the frequency with which the ‘average article’ – usually articles, reviews, proceedings or notes; not editorials and letters to the Editor – in a journal has been cited in a particular year. The IF is calculated by dividing the number of IF year citations by the source items published in that journal during the previous 2 years.

\[
\text{IF} = \frac{\text{(the number of IF year citations)}}{\text{(the source items published in that journal during the previous 2 years)}}
\]

**Dichotomous (binary) data:** Data that can take one of two possible values, such as dead/alive, smoker/non-smoker, present/not present.

**Continuous data:** Data with a potentially infinite number of possible values within a given range.

Height, weight and blood pressure are examples of continuous variables.

**Heterogeneity:** Inevitably, studies brought together in a systematic review will differ. Any kind of variability among studies in a systematic review may be termed heterogeneity. Variability in the participants, interventions and outcomes studied may be described as clinical diversity (sometimes called clinical heterogeneity), and variability in study design and risk of bias may be described as methodological diversity (sometimes called methodological heterogeneity). Variability in the intervention effects being evaluated in the different studies is known as statistical heterogeneity, and is a consequence of clinical or methodological diversity, or both, among the studies. Statistical heterogeneity manifests itself in the observed intervention effects being more different from each other than one would expect as a result of random error (chance) alone.3

---

**2-DAY WORKSHOP: THE ESSENTIALS FOR CRITICAL READING AND INTERPRETATION OF MEDICAL LITERATURE**

Are you trying to keep up with new developments in your field but are put off by p values, confused about relative risks and 95% confidence intervals, and completely thrown by cohort and case-control studies? Do you end up reading the conclusions of the abstract of a research article?

RYTD Consultancy will be offering 2-day workshops in 2009 on "The essentials for critical reading and interpretation of medical literature". The course provides a valuable opportunity to learn key concepts to enable critical reading of medical literature.

The full course is accredited for 11 CPD points with the HPCSA.

Who can attend? The course is open to doctors, nurses, occupational therapists, physiotherapists, speech therapists, pharmacists and dentists working in all levels of health care.

Course content: Essential epidemiology and biostatistics, basic research methodology and the approach to use when reading a paper.

For more information contact Dr Taryn Young, RYTD Consultancy.

RYTD Consultancy
P O Box 38580
Pinelands 7430
South Africa
Fax: +27 86 531 8671
Cell: + 27 82 8959 656
Email: info@rytdconsult.co.za

Enhancing your capacity to make the right health care decisions
It is hard to believe that the triennium of the current ALLSA Excom has already come to an end. I clearly remember the wonderful 2006 congress at Sun City, during which I was elected chairman. I was overwhelmed at the privilege and by the trust placed in me, and this feeling continues to this day. It is an honour to have been ALLSA Chair during the 20th year and now the ‘coming of age’ of our organisation. The Allergy Society of South Africa was established by very visionary people in 1988, and it is fitting that, 21 years on, we are on the brink of having our first subspecialists registered and will be embarking on subspecialist training. What is also unique about this is that allergology will be based not only on paediatrics and internal medicine, but also on family medicine. I would like to pay tribute to our founder members, to the Excoms through the years, to the Journal editors and contributors, to all our loyal members, and to our office and support staff.

I believe that the last 3 years have been a watershed year in our Society, and would like to briefly discuss the highlights. I have to point out that our achievements have built on the legacy of past Excoms and have also involved considerable work and input from ALLSA members working outside the Excom.

**Allergology Subspecialist Registration**

There is no doubt that the greatest achievement of this Society is the recognition of allergology as a subspecialty. The most recent hard work was done by Paul Potter and Cas Motala, but many years ago the ground work was laid by Eugene Weinberg, Paul Potter, Cas Motala and Matt Haus. We managed to build on this and achieved recognition of the Diploma in Allergology. I believe that the popularity of this diploma has contributed to academic allergology, and I wish to pay tribute to Matt Haus and Bruce Sparks for helping us to get it through the Colleges of Medicine and subsequently through the HPCSA. The groundwork of support and the excellent training programme at Red Cross Children’s Hospital resulted in allergy spreading around the country. We now have centres of excellence in Gauteng (Steve Biko Academic Hospital and Pretoria University – Robin Green) and KwaZulu-Natal (Ahmed Manjra) in addition to the ongoing expertise in Cape Town.

**Governance Charter**

ALLSA has taken the lead in establishing a Governance Charter for the Society. Cas Motala and Tom Sutcliffe devoted many hours to this document, which I think is an excellent addition to the Constitution and which will continue to guide us in matters of governance. The current Excom all contributed ideas and suggestions, and it will be available to members at the Durban Congress for perusal and comment.

**ALLSA Position Statements**

This Excom has been brave in promoting ‘good allergy practice’ and putting position statements on the ALLSA website. We have come in for a fair amount of criticism as a result, but I think it is in line with our stated Vision and Mission for the Society. Thank you to the expert ALLSA members who assisted in drafting these position statements.

**Subcommittees and portfolios**

I will now give brief report backs on the activities of the various subcommittees and portfolios of the ALLSA Excom.

**Membership and website**

Our membership has remained reasonably steady, and we have some ideas to recruit young members from universities. The award-winning website is excellent - thanks to Di Hawarden, Ruwayda Adams and Daniel Braude for all their hard work.

**Research**

Mohamed Jeebhay (Chair), Cas Motala and Heather Zar have implemented innovative changes to the application and assessment processes of the research awards. Some outstanding projects have been funded by ALLSA grants, and we anticipate feedback at congresses and as reports in the Journal.

**Education**

Robin Green has spearheaded a number of initiatives, including a series of lectures in allergy in Gauteng, and promoting the Diploma in Allergology among paediatricians and registrars. He has organised the Diploma examination panels very efficiently, and has involved new examiners in the past few examinations. We have had three outstanding congresses over the past years: one combined with the South African Thoracic Society and two combined with the South African Paediatric Association. In all three, our members made excellent contributions to the science and the social events, we had high calibre international speakers, and brilliant local faculty. The international speakers were Gideon Lack (UK), Mike Kaliner and Allen Kaplan (USA) in 2006, Jean Bousquet (France), Andrew Bush and Adnan Custovic (UK), Hugo Neffen (Argentina), Soren Pedersen (Denmark) and Andrea Apter (USA) in 2007, and Tom Platts-Mills (USA) and Susan Prescott (Australia) in 2008. This year’s congress will host Estelle Simons (Canada) and George du Toit (ex SA, now in the UK) as the guest speakers. The newest initiative is a comprehensive update of the Handbook of Allergy, with Cas Motala and Paul Potter as co-editors.

**Policy and Advocacy**

This subcommittee, ably led by Andrew Hallas, has been involved in establishing guidelines for our interaction and relationship with health care funders. The most recent initiatives involve prescribed minimum benefits for treatment of asthma in children and guidelines for appropriate allergy testing. Harris Steinman is ALLSA’s representative on FLAG, but he is also a major advocate for honest advertising and does not shy away from difficult situations – for this we thank him.
Our Childhood Asthma Guidelines are being finalised as I write this, and will be presented at the congress. Thank you to Cas for driving the process and to all the contributors for your hard work.

Current Allergy & Clinical Immunology
Heather Zar, Eugene Weinberg and Anne Hahn have continued to produce an outstanding Journal that carries both review articles and original allergy research. It is an excellent resource, and has received international as well as national acclaim. The Editors have been prepared to be innovative in terms of content and presentation, and for this we laud them.

International
Cas Motala served South Africa, Africa and World Allergy in an exemplary fashion as a Director on the WAO Board, and for this we thank him. He has been succeeded by Paul Potter, who has already contributed to a number of WAO position papers and who we know will continue to represent allergy in South Africa in his usual inimitable fashion. Heather Zar was a member of the GINA Panel that developed the most recent guidelines for management of asthma in children under the age of 5 years.

We would also like to thank the World Allergy Organisation for their support of our congresses by sponsoring speakers and/or GLORIA symposia.

Conclusion
I look back over the last 3 years with pride, yet with a deep sense of humility and gratitude. I have worked with the most amazing Executive Committee and ALLSA office staff. We have experienced some incredibly difficult problems and have dealt with unpleasant situations, yet I could always call on the wisdom and support of the Excom members. Cas continues to be a wise head and a major guiding hand, and I have to single him out for special thanks.

I also want to thank Heather Zar for her tireless work for ALLSA. Heather is not standing for re-election, and we will miss her input on the Excom, but she will continue to co-edit the Journal, and we look forward to working with her in her new capacity of President of the South African Thoracic Society.

Our congresses were successful for several reasons, but I have to thank the organising and scientific committees, and also the UCT Conference Management Centre and Sue McGuiness Communications and Event Management. In particular, Sue McGuiness brings a particular brand of professionalism and expertise to congress and event management that will prove hard to surpass, and the organisational and financial success of these events are in no small measure due to her. Our last congress coincided with a very difficult time for her, and we really appreciate the manner in which she handled everything.

Ahmed Manjra, the lone ranger in Durban, has done it again – a wonderful congress with an excellent scientific programme – thanks, Ahmed.

Ruwayda Adams – how do I even begin to thank her? The smoothly purring engine of the ALLSA machine ensures the seamless running of the Society. She has been ably assisted by Shahnaz Arnold, and the always-friendly Jan Aprill keeps the office organised. Anne Hahn continues to do the most brilliant production editorial work on the Journal. Thank you to all of you.

And last, but certainly not least, our partners in the pharmaceutical and medical device industry deserve our heartfelt thanks. It has been their support that has enabled us to further allergy research in South Africa (GlaxoSmithKline, UCB, MSD and Cipla), organise congresses, run workshops, publish the Journal, and provide patient information sheets. We acknowledge the governance and economic restraints under which they operate and we wish to ensure them that we appreciate their help, support and friendship.

Lastly, the ALLSA Excom appreciates that the majority of our membership base is in Gauteng. We wish to thank our loyal members and assure those outside the Western Cape that we are looking at ways of ensuring access to allergy journals and other resources for them.

I want to wish you all a wonderful ALLSA Congress in Durban. Enjoy the scientific content as well as the social events and the networking, and take time to explore the wonderful city.

To the incoming ALLSA Chairman and Excom: I wish you all the best for a very enjoyable and successful triennium!

Sharon Kling
Chairman
PRODUCT NEWS

ACCURATE ALLERGEN IDENTIFICATION
NOW A REALITY

Labspec (Pty) Ltd is pleased to announce the launch of a national allergen-testing awareness campaign across South Africa, to let consumers and medical practitioners alike know that highly accurate, specific allergen identification is now within everyone’s reach.

Being able to identify exactly which allergen elicits an allergic response within an individual, may result in more specific treatment, an accurate overview of any lifestyle changes that may need to be made in the affected individual, and ultimately, enhanced quality of life.

As a subsidiary of Phadia, the world leader in diagnostics, Labspec is committed to helping medical practitioners make accurate diagnoses and sound management decisions.

We at Labspec have also initiated a national print media campaign both to consumers and medical staff, and a dedicated sales force will highlight the benefits to paediatricians and general practitioners across the country.

Possibly the best part of requesting a Labspec allergen test, is the fact that the procedure is covered by most medical aids, thereby making the decision of whether to be tested or not, an easy one.

Please contact Labspec on 011-792-6790/1/2/3, or visit www.labspec.co.za.

Contact:
Charles Duff 011-792-6790/1/2/3
Maria Ramsay 082-410-6053
Angela Neveling 083-407-7654
jacque Larsen 083-273-2604

A PHADIA COMPANY

GIVING TODDLERS A HEAD START IN LIFE

Abbott, leaders in Science-Based Nutrition, are proud to announce the launch of Isomil 3 Advance Plus, the first soy-based follow-on formula to contain the essential long-chain polyunsaturated fatty acids, arachidonic acid (ARA) and docosahexaenoic acid (DHA).

The importance of DHA and ARA, naturally found in breast milk and added to infant formulas to support brain development, was recognised by the rapid accretion of these fatty acids in the infant brain. Reports of enhanced intellectual development in breastfed children and the recognition of the physiological importance of DHA in visual and neural systems, led to clinical trials that evaluated whether infant formulas supplemented with DHA and ARA would enhance visual and cognitive development.

Evidence for a beneficial effect of ARA plus DHA supplementation on central nervous system (CNS) development is strong. A randomised study evaluated visual and cognitive development in infants at 34 and 39 months of age and compared infants fed standard formula, formula supplemented with DHA or formula supplemented with DHA and ARA. This study, with the longest follow-up period reported to date, showed that DHA and ARA supplementation support visual and cognitive development in infants from birth to children 39 months of age.

Isomil 3 Advance Plus is a milk- and lactose-free, soy-based formula that is specifically designed for children from 1 year of age who have IgE-mediated cow’s milk allergy, are lactose intolerant or suffer from digestive symptoms such as gas, diarrhoea or regurgitation.

In addition to the patented combination of DHA and ARA, Isomil 3 Advance Plus contains:
• Taurine and choline, which together with DHA and ARA are required for brain development.
• Soy protein isolate, equivalent to animal protein in quality and a rich source of nucleotides, required for normal immune development.
• A vegetable oil blend that optimizes calcium and fat absorption and is associated with a lower incidence of gastrointestinal intolerance than infant formula containing animal fats or palm olein oil.

Isomil 3 Advance Plus is a nutritionally complete, follow-on soy formula for growing toddlers from 1 year of age. It has been tested in clinical trials and is the scientifically supported soy formula with the patented EYE Q system of brain nutrients that support brain development.

Isomil 3 Advance Plus is competitively priced and is available at pharmacies, supermarkets and baby stores. For more information on Isomil 3 Advance Plus, please contact the brand manager, Yvonne MacLeod, at Abbott Nutrition, tel 011-858-2000.

4. Isomil® 3 Advance Plus Product Monograph.

MIELE LAUNCHES TOP-CLASS RANGE OF VACUUM CLEANERS

A fact of modern life is the increase in allergies, with more and more adults and children suffering from asthma, rhinitis and hay fever. Allergies are made worse by household pets, and dust mites in carpets, mattresses and soft furnishings. In response to the growing need for appliances that can help alleviate the problems suffered by allergy sufferers Miele have developed a number of features and accessories to ensure excellent levels of cleanliness in the home.

The S5281 MedicaAir Vacuum Cleaner is supplied with all the features and accessories to meet the specific needs of allergy sufferers. The unit is equipped with an innovation that offers additional security and comfort; the Allergotec Sensor floorhead for visible hygienic cleanliness.

Miele offers a choice of three filters placed behind the motor. Because of the airtight design, any air leaving the vacuum cleaner only leaves via the final filter. The Miele Super AirClean filter removes nearly 94% of the particles as small as 0.3 µ and, for this reason is the most suitable for everyday households. The Miele Active AirClean filter incorporates the Super AirClean filter and is designed for customers who have to vacuum up items with unpleasant odours. A tight-fitting filter cassette with a rubber seal prevents any air escaping. The active charcoal component absorbs and neutralises odours. The Miele Active HEPA filter solves the problems of allergy sufferers. The Active HEPA filter retains 99.5% of particles.

For the true pet lover – the S5261 in Capri Blue and S5361 in Tauberry Red are Miele’s Cat & Dog range of vacuum cleaners. Stubborn pet hairs do not stand a chance with the Miele Cat & Dog’s Turbo Brush. This special floorhead is driven by the suction of the cleaner and rotates evenly to pick up hair and dirt from most types of carpets, while the smooth running floor head SBD takes care of most hard floor surfaces. The Miele Cat & Dog vacuum cleaner is specially fitted with an ActiveAirClean filter. The activated charcoal filling ensures any smell arising from the contents of the dustbag is absorbed before it leaves the cleaner and that the exhausted air is always fresh too.

BOEHRINGER INGELHEIM LAUNCHES INFLANAZE® 100

It is with great pleasure and excitement that Boehringer Ingelheim, a leader in respiratory care, announces the launch of Inflanaze® 100.

Allergic rhinitis is a highly prevalent chronic respiratory disease that impacts significantly on the quality of life of patients.¹ The prevalence of allergic rhinitis is rising with a huge indirect and direct economic burden.² In addition nearly 80% of asthmatic patients have coexisting allergic rhinitis.³ Topical corticosteroids are highly effective first-line treatment of allergic rhinitis.⁴ Budesonide is comparatively an effective corticosteroid which is well tolerated for all classifications of allergic rhinitis.⁵ Inflanaze® 100, 100µg budesonide per metered spray, provides another option for healthcare professionals to treat this common respiratory disease. Inflanaze® 100 provides high dose budesonide for the allergic rhinitis patient and allows tapering down of medication to the lowest dose adequate to control symptoms. With its less number of sprays per day, the new 100 dosage allows for better patient compliance.⁶ It is registered from the age of 6 years allowing for use in children.

Inflanaze® 50 and 100 possess a broad actuator making the administration of medication to children and patients who struggle to use nasal sprays easy and comfortable. Inflanaze® 100 contains 200 doses, contains no alcohol and has potassium sorbate as its preservative.⁷ This product addition shows that Boehringer Ingelheim, with its wide range of medication for asthma and allergic rhinitis, is committed to optimising respiratory care.

References:
5. Inflanaze® 100 Package Insert.
6. Data on File

For full prescribing information refer to the package insert.
NOPQ
MSD (Pty) Ltd is proud to announce the introduction of SINGULAIR 4 mg. Studies have shown that asthma in children under the age of six is on the increase worldwide.1 SINGULAIR 4 mg is the first asthma controller therapy, that is not a steroid, to be approved in South Africa for children as young as 2 years old.2

Studies have shown improvements in symptom and activity scores from as early as day one, affirming the efficacy of SINGULAIR 4 mg in this age group.3 The current guidelines for treatment of asthma in children, as compiled by the Allergy Society of South Africa (ALLSA), call for the introduction of a leukotriene antagonist as a controller agent in this age group at step 2, after the use of short-acting reliever medication has proven to be inadequate in controlling asthma symptoms. In other words using leukotriene antagonist as a first line controller agent.4 At present, of the leukotriene receptor antagonists, only SINGULAIR is indicated for use in children under the age of 12.5

SINGULAIR 4 mg is indicated for the prophylactic treatment of mild to moderate asthma in the 2-5 year old age group. SINGULAIR 4 mg is presented in a 28-day pack and one tablet should be taken once daily at bedtime.2 To date worldwide use is more than 2.2 million children in more than 90 countries. This puts SINGULAIR in the unique position of being the only controller therapy to be registered and indicated for asthmatic patients from 2 years old and up.2

REFERENCES:
2 Data on File.

Foratec HFA

Foratec HFA is another exciting addition to Cipla’s range of respiratory products, emphasising our commitment to offering solutions for Total Asthma Control!

Foratec HFA (formoterol fumarate 12µg) is:
- a long-acting β2-agonist, giving up to 12 hours bronchodilation
- as fast-acting as salbutamol, between 1-3 minutes
- the only available formoterol fumarate MDI
- a 120-dose MDI; 2 months’ supply (at 1 puff b.d.)
- CFC-free, re-enforcing our global commitment to preserving our planet within our sphere of influence
- indicated as add-on therapy to inhaled corticosteroids in patients with chronic persistent asthma (GINA step 3)3 and for prophylaxis and treatment of symptoms in patients with COPD,
- priced at R69.60 SEP (excl VAT), the most cost-effective long-acting β2-agonist in SA!5

Isn’t this enough reason to prescribe Foratec HFA?

Cipla offers you Total Asthma Control through choice of molecules, choice of devices and a choice to treat cost-effectively!

Prescribing information available on request. Please contact Elizma Kemp on 021-917-5620.

1. Foratec HFA Package Insert
5. SEP (excl. VAT) as per PCD, July 2008
Support your society, it supports 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 R200 annually; this is a tax-deductible expense.

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. This journal is available on-line.
• Access to ALLSA’s comprehensive allergy website at www.allergysa.org.
• On-line CPD accreditation.
• Patient information guides and leaflets on common allergic disorders.
• 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 mail@allergysa.org

Please cut out the membership application form and post together with your payment.

---

**ALLSA Membership Application**

**R200 annual subscription**

Dr/Sr/Mr/Mrs/Ms: .................................................................

Address: ........................................................................

....................................................................................

E-mail address: ............................................................

Phone: ................................................................. Fax: .................................................................

Speciality: .................................................................

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 payable to **Allergy Society of South Africa**

For direct deposits: Kindly fax your bank deposit slip as proof of payment (Fax No. 021-448-0846)
AstraZeneca is proud to introduce a new design for Symbicord boxes and packaging. The purpose of the packaging change is to standardise the colours and design globally, so that wherever in the world you may be, the Symbicord packaging will look the same.

In line with these changes, we are also keeping these colours for our promotional and educational material, so that the design is standardised throughout. The new look is bold, positive, professional and modern, with an emphasis on clinically relevant and clear information. The approach is future-focused, to reflect the constant innovation and challenging of conventions that is the basis of our approach to medicine at AstraZeneca.

Please note that the ingredients and doses of Symbicord will remain the same.

In conjunction with the new look, AstraZeneca intends to introduce user-friendly educational and support material to assist and support people with asthma.

The new material is aimed at providing the busy physician and his/her patients with the tools that they need so that people with asthma can take responsibility for their own asthma control.

**Symbicord® Turbuhaler® 80:4.5 µg/dose (Inhaler),** Reg No. 35/21.5.1/0404. Each delivered dose contains as active constituents: Budesonide 80 micrograms and formoterol fumarate dihydrate 4.5 micrograms.

**Symbicord® Turbuhaler® 160:4.5 µg/dose (Inhaler),** Reg No. 35/21.5.1/0405. Each delivered dose contains as active constituents: 160 micrograms and formoterol fumarate dihydrate 4.5 micrograms.

**Symbicord® Turbuhaler® 320:9 µg/dose (Inhaler),** Reg No. 38/21.5.1/0187. Each delivered dose contains as active constituents: Budesonide 320 micrograms and formoterol fumarate dihydrate 9 micrograms.

**NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:**

AstraZeneca Pharmaceuticals (Pty) Limited, 5 Leeuwkop Road, Sunninghill, 2157, South Africa. Reg No. 9205854/07. Tel: +27 11 797 6000. Fax: +27 11 797 6001. www.astrazeneca.co.za

---

**Asthma limits the full potential of millions of South Africans**

As a long term condition, asthma affects people of all ages and all walks of life. The provision of good asthma care provided by highly motivated professionals eases what many consider to be a burden. The right care changes lives and makes it possible for people with asthma to live a normal, healthy and active life.

The NAEP is striving to improve the health and well being of people living with asthma and is here to help you with:

- Dissemination and interpretation of accredited Asthma Treatment Guidelines
- Free asthma information
- Accredited education programmes for health professionals

**Become a professional member today. Encourage your patients to become members.**

Tel: (011) 643 2755 • Fax: (011) 678 3069 • E-mail: naepm@netactive.co.za

www.asthma.co.za
Penicillin allergy is more common in young children than adults? a) True b) False

The closing date for submission of this questionnaire is 31 August 2009.

FOOD-PROTEIN-INDUCED ENTEROCOLITIS SYNDROME (FPIES)
1. True or false: FPIES is an IgE-mediated food allergy disorder affecting the gastrointestinal tract? a) True b) False
2. True or false: FPIES can occur in exclusively breast-fed infants? a) True b) False
3. Choose ONE correct answer: FPIES may resolve in 90% of cases after: a) 3-6 months b) 24-36 months c) >5-10 years d) >10 years
4. Choose ONE correct answer: The most common causative food of FPIES in infants is: a) egg white b) wheat c) cow’s milk d) peanut

ORAL ALLERGY SYNDROME (OAS) – WHAT’S NEW?
1. True or false: Symptoms of OAS are caused by cross-reactivity of IgG4 antibodies to aeroallergens with proteins in fresh fruit/s and vegetable/s? a) True b) False
2. True or false: Plant proteins involved in OAS belong to plant protein families including profilins, pathogenesis-related proteins and lipid transfer proteins? a) True b) False
3. Choose ONE correct answer: The diagnosis of OAS is based primarily on: a) Skin-prick testing b) Specific IgE c) Patient’s history d) Atopy patch test
4. Choose ONE correct answer: Symptoms of OAS can be prevented by: a) Pre-treatment with antihistamine b) Intranasal steroids c) Cooking of offending foods d) Antileukotrienes

PENICILLIN ALLERGY
1. True or false: Penicillin allergy is more common in young children than adults? a) True b) False

Anaphylaxis in infants: can recognition and management be improved?
1. True or false: Skin contact with food or food-based skin products or inhalation of aerolised food particles potentially sensitises an infant but seldom causes anaphylaxis? a) True b) False
2. True or false: Drugs are the most common triggers of anaphylaxis in infants? a) True b) False
3. Choose ONE correct answer: Which laboratory test supports the clinical diagnosis of anaphylaxis? a) urine histamine b) serum tryptase c) full blood count d) lymphocyte subsets?
4. Choose ONE correct answer: The first-line treatment for anaphylaxis is: a) nebulised B2 agonist inhalation b) diphenhydramine c) intramuscular adrenaline d) intravenous hydrocortisone

H1 ANTIHISTAMINES IN ALLERGY DISEASE
1. True or false: H1 antihistamines are specific antagonists of the H1 receptor? a) True b) False
2. True or false: Second-generation H1 antihistamines are less or non-sedating because they do not cross the blood-brain-barrier? a) True b) False
3. Choose ONE correct answer: Simultaneous consumption of grapefruit juice may alter the bioavailability of: a) chlorpheniramine b) cetirizine c) fexofenadine d) desloratadine.
4. Choose ONE correct answer: Dose-dependent cardiac toxic effects may occur with the following H1-antihistamine: a) fexofenadine b) levocetirizine c) loratadine d) diphenhydramine.