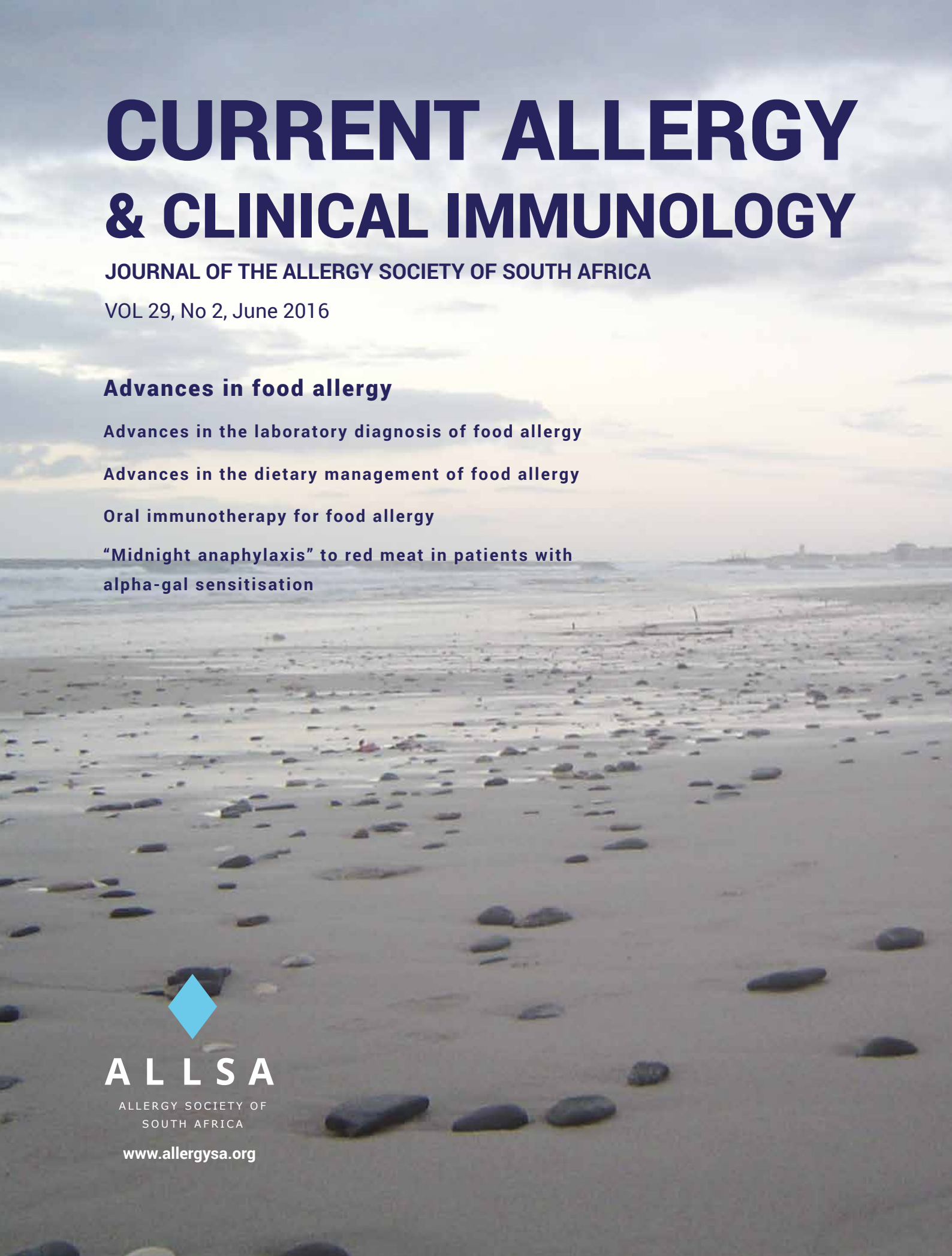

CURRENT ALLERGY & CLINICAL IMMUNOLOGY

JOURNAL OF THE ALLERGY SOCIETY OF SOUTH AFRICA

VOL 29, No 2, June 2016

Advances in food allergy

Advances in the laboratory diagnosis of food allergy

Advances in the dietary management of food allergy

Oral immunotherapy for food allergy

"Midnight anaphylaxis" to red meat in patients with alpha-gal sensitisation

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JOURNAL OF THE ALLERGY SOCIETY OF SOUTH AFRICA

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GUEST EDITORIAL

What an honour it is to be Guest Editor for this second 2016 edition of *Current Allergy and Clinical Immunology* with the theme 'Advances in Food Allergy'. In this edition, the 'advances' in the world of food allergy have been divided up into advances in laboratory diagnosis, advances in dietary management and advances in oral immunotherapy as a possible 'treatment' for food allergy. We also take a glimpse at newly recognised forms of food allergy, with the example of alpha gal allergy causing a delayed reaction to red meat.

Pretoria-based Cathy van Rooyen and Sylvia van den Berg are well known to us as expert pathologists specialising in allergy and immunology. They enlighten us with their update on laboratory diagnosis of food allergy, focusing on the role of component-resolved diagnostics in a variety of food allergies. Molecular allergology can be applied to help differentiate between true food allergy and cross-reactivity and, sometimes, in predicting allergy severity or persistence. The increasing availability and role of cellular allergen tests is also discussed.[1]

We are delighted that Rosan Meyer, South African-born dietician and our international guest speaker at last year's ALLSA congress, has contributed her review of 'advances in dietary management of food allergy'. A paediatric dietician currently based at the Imperial College in London, Rosan has teamed up with Adriana Lozinsky, who works in paediatric gastroenterology in São Paulo, Brazil. They update us on diagnostic elimination diets, the dietary management of eosinophilic oesophagitis and FPIES, and on the introduction of allergenic solids.[2]

There is a great deal of excitement – but also much uncertainty in the food allergy world – about the oral immunotherapy for food allergy, also known as 'specific oral tolerance induction' (SOTI). We are honoured to have Anna Nowak-Węgrzyn, renowned paediatric allergist from the Icahn School of Medicine at Mount Sinai, New York, as lead author of an update on oral immunotherapy in this issue. Anna has teamed up with Dr Stephanie Albin to write a comprehensive and enlightening review article which highlights the advances in and reservations about oral immunotherapy. The general recommendation is that oral immunotherapy is still a research tool which cannot yet be recommended as routine practice.[3]

In parallel with advances in the diagnosis and treatment of food allergies, in the past decade 'new' types of food allergy have been recognised. One such new allergy is delayed allergy to red meat as a result of alpha gal (alpha galactose 1,3 galactose) allergy, first published in 2009 with the identification of 'clusters' of such allergy occurring in the United States. This unique type of allergy to a carbohydrate moiety has also been identified in South Africa and, together with two colleagues from George, we have described typical cases, followed by an overview of this syndrome.

In addition to the guest review articles in this edition, we have our regular features of occupational allergies, a case series on food-additive allergy, the educational and entertaining ABC series, and an ethics article to provide some food for thought.

Your guest editor
Claudia Gray

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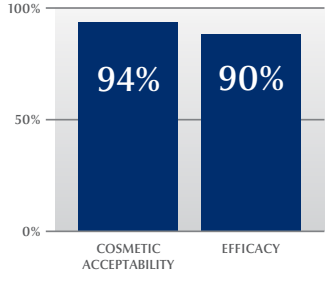

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CHAIRMAN'S REPORT

Di Hawarden

Greetings to all the readers of *Current Allergy and Clinical Immunology*.

I would like to report back on our successful contribution to world allergy week, which took place from 4-10 April 2016. The theme for 2016 was Pollen Allergies – Adapting to a changing climate. This year we partnered with ThermoFisher and a number of radio interviews were conducted, as well as a television interview.

MEDIA EXPOSURE

TV: Dr Marinda McDonald on Die Groot Ontbyt (Kyknet)

RADIO: 702 Interview
Pretoria FM
Groot FM Interview
Tygerberg in Cape Town

Live Reads on: Mix FM
East Rand Stereo
OFM
Algoa

Thank you to all the ALLSA members that made themselves available to be interviewed, and to Prea Pillay from Thermo-Fisher for co-ordinating this event.

DIPLOMA ALLERGOLOGY

May 2016

Exams were held in Johannesburg, and co-ordinated by Dr Debbie White. Examiners included Dr Omolemo Kitchin, Dr Vis Naidoo, Dr Tamara Kerbelker and Dr Tamatha Urquhart.

Five candidates wrote and all passed.

- Dr CX Dearden
- Dr W Dicks
- Dr E Kiragu
- Dr O Odusote
- Dr AC Swartz

Congratulations to you all.

ALLSA CONGRESS 2016

The 25th annual congress of the Allergy Society will take place in Cape Town from 15-18 September 2016.

You will have seen that the theme is Allergy….or not? This year we look at the conditions that may mimic allergy, making the diagnosis more difficult. We have three International speakers, a stimulating selection of topics for the plenary sessions, and some great workshops.

We are very excited to have Dr David Klatzow, renowned forensic scientist and author to give the opening address at our 25th annual ALLSA congress. This exciting event takes place on Friday, 16th November. Don't forget to register for the congress before 21st July to take advantage of the early registration fee. We look forward to welcoming you to the new Century City Convention Centre. Visit the congress website for the programme and registration form.

http://allergysa.org/AnnualCongress/Register

I would like to thank Ruwayda Adams for keeping our society and our office running, and Robyn Marais for steering the journal. We would not manage without you. Enjoy this copy of the journal which was expertly guest-edited by Dr Claudia Gray.

Happy Reading
Di

16270

Are the symptoms really signs of allergy?

Nasal congestion/sneezing, itchy/watery eyes and nose:

- **65%** of patients diagnosed as having allergic rhinitis and prescribed antihistamine may not be allergic. [1, 2]

Wheezing, coughing, breathing problems:

- **90%** of children and **60%** of adults with asthma have allergy. [3-5]

Dry skin, pruritus, scratching:

- **90-70%** of infants and young children with eczema have underlying allergy. [3, 6]

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Phadiatop® measures IgE antibodies to a well-balanced mixture of common inhalant allergens. These tests help you to:

- differentiate IgE mediated atopic allergy from other allergy-like symptoms [7-13]
- identify patients that need Specific IgE testing for allergen identification and continued allergy care [7-13]

Reveal the secrets behind the allergy-like symptoms

A single blood test that helps you to rule in or rule out allergy

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As a further commitment to providing quality medical care to all South Africans, Cipla Medpro has granted an amount of **R20 000** to the Allergy Society of South Africa for research in the field of asthma and allergic rhinitis.

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

CLOSING DATE FOR APPLICATIONS
31 OCTOBER 2016

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

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Guest Review

ADVANCES IN THE LABORATORY DIAGNOSIS OF FOOD ALLERGY

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S van den Berg | MBChB, MMedClin Path, FRC Path (Clin) DTM&H
Allergy, Immunology & Virology Pathologist, Ampath, and Extraordinary Lecturer, Department of Paediatrics, University of Pretoria
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SUMMARY
A great number of advances have been made in the diagnostic tools and testing methods available for food-allergy diagnosis. Improved and new methodologies have become available not only to identify the presence of a food allergy, but also to aid in determining the severity of an allergy, the likelihood of its resolution and potential cross-reactivity with other allergens. Cross-activity may include that between biologically related and unrelated foods or even between inhalant allergens. These testing methods may also improve patient outcomes by helping clinicians to provide accurate dietary advice and reduce the need for food challenges.

This article has been peer reviewed.

INTRODUCTION

Suspected food allergy is a common problem in primary care and its diagnosis and subsequent management may often be challenging. This may have an impact on a patient's quality of life and nutritional state, owing to the unnecessary avoidance of certain foods. It may also lead to severe or even life-threatening allergic reactions if certain allergens are not identified and avoided.

Before discussing advances in the diagnosis of food allergy, it is essential to acknowledge that a good patient history by an astute clinician will always remain the cornerstone of allergy diagnosis. The history, aided by a physical examination, should indicate which allergy tests are ordered. Although there have been many advances in laboratory testing for food allergy, these tests should be used only after careful consideration of the patient history and by using a step-wise diagnostic approach. Clinicians should try to answer the following questions before ordering allergy tests:

- Is the patient allergic?
- Does allergy contribute to the patient's symptoms?
- What are the most likely clinically relevant allergens?
- What is the suspected mechanism of allergy (IgE- or non-IgE-mediated)?

Initial testing may include skin-prick or ImmunoCap® IgE tests for one or more specific allergens or an appropriate screening test for food allergens. If a food-screening test is positive, individual foods contained in the mix should be requested.

Additional testing should be considered when more specific information may improve patient management or when the clinician suspects an allergy but the test results are not confirmatory. Advanced diagnostic testing for food allergy may therefore be able to assist clinicians in the optimal management of patients with more complicated allergic reactions.

ADVANCED DIAGNOSTIC TESTS FOR FOOD ALLERGY

COMPONENT-RESOLVED DIAGNOSTICS

With the advent of component allergy testing, it has now become possible to predict allergen cross-reactivity, help predict the severity of reactions, help to offer dietary advice (some allergic patients may tolerate heated or processed foods or even peeled fruit) and reduce the need for food challenges. Component allergy testing may also predict the likelihood that a patient may outgrow a food allergy.[1–3]

WHAT ARE ALLERGEN COMPONENTS?

- Natural allergen sources may contain many different proteins (components), only a few of which are allergenic.[2,3]

TABLE I: SUMMARY OF RELEVANT INFORMATION GAINED BY TESTING FOR CROSS-REACTIVE POLLEN AND FOOD COMPONENTS

	CCD	PROFILIN	PR-10	LTP
Severity of reaction	±	+	++	+++
Localisation of cross-reactive allergen	N/A	Throughout	Pulp of fruit	Peel of fruit
Stability to heat and digestion	N/A	Labile	Labile	Stable

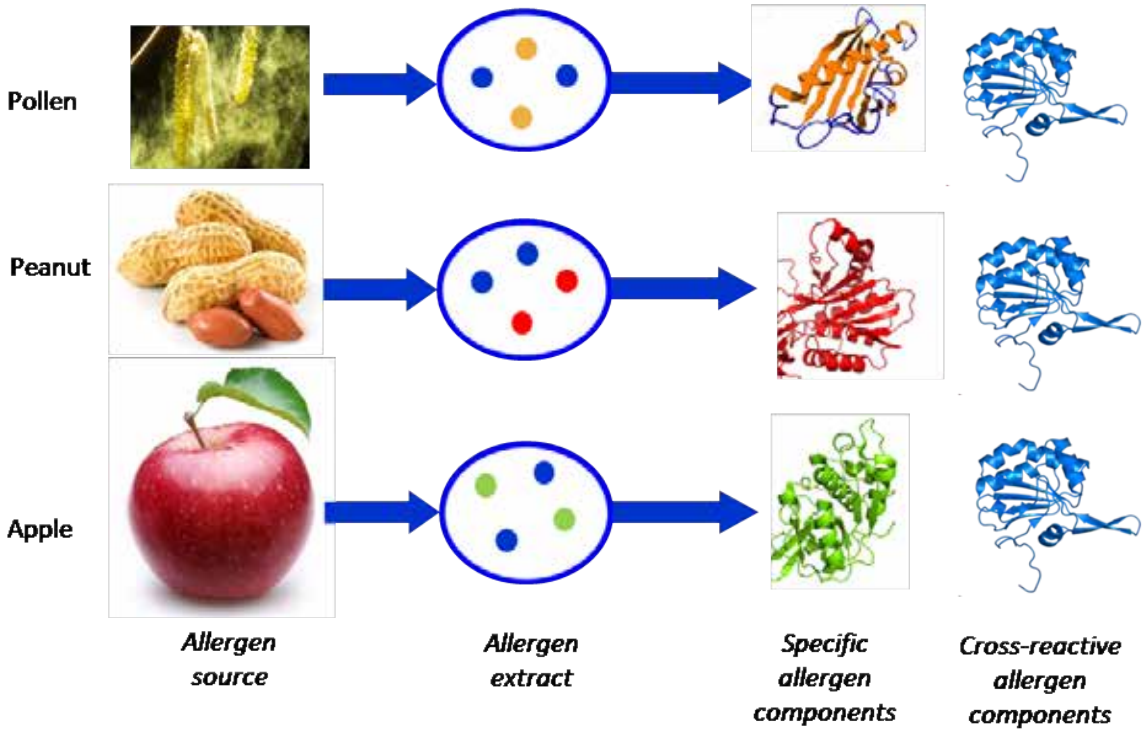

Figure 1: Some allergen components are species-specific and some are cross-reactive

- Some of these protein components are species-specific, but some occur in multiple allergen sources (cross-reactive components).[2,3]
- The allergen component names include their scientific acronym and number (e.g. *Ara h 2* means the second allergen from *Arachishypogaea* or the peanut).[2,4]

APPLICATIONS WHERE COMPONENTS MAY ADD CLINICAL VALUE TO FOOD-ALLERGY DIAGNOSIS

1. POLLEN-FOOD SYNDROME

- Patients have positive food-allergy tests when sensitised to cross-reactive components that occur in pollens as well as in foods of plant origin.[5,6]
- Food–pollen sensitisation may or may not be clinically relevant. The clinical relevance may be predicted by knowledge of the allergenicity of certain protein groups, for example, cross-reactive carbohydrate determinant (CCD)(least allergenic) < Profilin < pathogenesis-related protein group 10 (PR-10) < lipid transfer protein (LTP). Patients with CCD sensitisation should not be advised to avoid those cross-reactive foods to which they tested positive, because CCD sensitisation does not usually cause symptoms.[1]
- Sensitisation to some food–pollen cross-reactive components, most notably profilin and PR-10, are the cause of oral allergy syndrome (OAS) symptoms. Symptoms are usually confined to itching or swelling of the oropharynx, but in rare circumstances systemic reactions may occur.[5,6]
- Some of these food–pollen cross-reactive component proteins are heat labile (profilin, PR-10) and some are heat stable (LTP), which is important in helping to advise whether a patient should try cooking their food.
- Some proteins are localised to certain areas in fruits, for example PR-10 in the pulp of fruit and LTP in the peel of fruit. Patients with LTP allergy can be advised to try to eat peeled fruit (see Table I).
- Sensitisation to cross-reactive pollen components should be suspected when allergy tests to several foods of plant origin are positive.[2] The typical sensitisation pattern to alert to the presence of cross-reactive components is when allergy tests to soy, wheat and peanut are positive in combination. This should prompt testing to CCD, profilin, PR-10 and LTP. Please see laboratory data in Table II to illustrate this.

TABLE II: LABORATORY DATA (2013) INDICATING THE HIGHEST LEVELS (%) OF SOY, WHEAT AND PEANUT SENSITISATION IN AREAS WITH THE HIGHEST POLLEN SENSITISATION

SENSITISATION	KZN	WESTERN CAPE	EASTERN CAPE	FREE STATE	GAUTENG	LIMPOPO	MPUMALANGA	NORTH WEST
Grass pollen	27	61	38	80	56	53	41	77
Wheat	20	44	40	62	49	44	54	56
Soya	18	31	27	51	40	35	43	44
Peanut	32	47	41	58	51	49	45	57

TABLE III: SUMMARY OF THE MAIN EGG-ALLERGEN COMPONENTS

EGG WHITE				EGG YOLK
Ovomucoid Gal d 1	Ovalbumin Gal d 2	Conalbumin Gal d 3	Lyzozyme Gal d 4	Egg serum albumin Gal d 5
• Highly allergenic • Heat stable • Associated with more persistent egg allergy	• Heat labile • If positive, may still tolerate baked egg			• Occurs in egg yolk, chicken meat and feathers • Associated with bird-egg syndrome

TABLE IV: SUMMARY OF MAIN MILK ALLERGEN COMPONENTS

MILK				
CASEIN Bos d 8	ALACTALBUMIN Bos d 4	B-LACTOGLOBIN Bos d 5	BOVINE SERUM ALBUMIN Bos d 6	LACTOFERRIN Bos d LACTOFERRIN
• Heat stable • Most important allergen • Associated with more severe and persistent allergy • Cross-reacts between mammals (e.g. goat's milk, sheep's milk, cow's milk)	• Main whey proteins • Heat labile • Patients with an allergy to whey protein react more severely to fresh milk. May tolerate boiled/baked milk, long-life milk, hard cheese and yoghurt		• Occurs in milk and beef/red meat • Heat labile; patient may tolerate well-cooked milk and dairy • Cross-reaction with other mammals	• Heat labile • May be used as a preservative in beef and nasal sprays

2. EGG ALLERGY:

- The main and most important egg allergen component is ovomucoid, an egg-white protein.[1,2,7]
- Ovomucoid is highly allergenic, heat stable and predicts more persistent allergy.[1,2]
- *Clinical implication*: Patients who have a clinically confirmed (by history or challenge) egg allergy and test positive to ovomucoid are more likely allergic to all forms of egg, including baked egg, and may have a more prolonged allergy. Patients with egg allergy who do not test positive to ovomucoid may be able to tolerate extensively heated egg, for example egg used in cakes and biscuits (see Table III).

3. MILK ALLERGY

- The main and most important milk allergen component is casein.[1–3]
- Casein is highly allergenic, heat stable and predicts persistent allergy.[1–3]
- Casein cross-reacts between mammals, for example cow, sheep and goat's milk.
- *Clinical implication:* Patients who have a clinically confirmed milk allergy and test positive to casein may need to avoid all dairy products (including the baked form). They may have more severe clinical reactions to milk. Patients with milk allergy who do not have a casein allergy may be able to tolerate boiled or long-life milk, hard cheeses, coffee creamer or goat's milk (see Table IV).

4. FISH ALLERGY

- The main and most important fish allergen component is parvalbumin.[1–3]
- Parvalbumin is highly allergenic, heat stable and predicts more severe and persistent allergy.[1–3]
- Parvalbumin is broadly cross-reactive and is a marker for general fish sensitisation.[1–3]
- *Clinical implication*: Patients who have a clinically confirmed fish allergy (by history or challenge) and test positive to parvalbumin usually need to avoid all fish species. However, the parvalbumin content of different fish species may vary, for example lower levels in tuna. Patients not allergic to parvalbumin should consider allergy tests to unrelated fish species to identify possible safe alternatives (see Table V).[2,8]

5. SHELLFISH ALLERGY

- True shellfish allergy is best indicated by the shrimp allergen component Pen m 2, an arginine kinase.[3,9,10]
- The main and most important cross-reactive allergen component in shellfish is tropomyosin, a muscle protein.[1,3,9,10]
- Pen a 1 is a tropomyosin and a major allergen in shrimp. This protein is very heat stable and cross-reacts with other tropomyosins found in crustaceans (prawns, crayfish, crab), arachnids (house dust mite), insects (cockroach) and molluscs (squid).[3,9,10]
- *Clinical implication*: Patients who have a clinically confirmed shellfish allergy (by history or challenge) and test positive to tropomyosin usually need to avoid all crustaceans. They may also react to tropomyosin in molluscs such as squid and in anasakis, a fish parasite. Clinical reactivity to tropomyosin from aero-allergens such as house dust mite and cockroach may also be seen. Primary sensitisation to tropomyosin

TABLE V: SUMMARY OF MAIN CROSS-REACTIVE FISH ANS SHELLFISH ALLERGEN COMPONENTS

FISH		SHELLFISH
Cod parvalbumin Cyp c 1	Carp parvalbumin Gad c 1	Tropomyosin Pen a 1
• Heat stable • Broad cross-reactivity; marker for general fish sensitisation • Parvalbumin content of different fish species may vary, for example lower levels in tuna		• Heat-stable muscle protein • Found in crustaceans, molluscs, insects and mites with clinical cross-reactivity

TABLE VI: STORAGE PROTEINS PRESENT IN VARIOUS NUTS AND SEEDS

FOOD ALLERGEN	2S ALBUMIN	7/8S GLOBULIN	11S GLOBULIN
Hazelnut	Y	Y	Y
Almond	Y	N	Y
Brazil nut	Y	N	Y
Cashew nut	Y	Y	Y
Pistachio nut	Y	Y	Y
Chickpea	Y	N	Y
Garden pea	N	Y	N
Lentil	N	Y	N
Peanut	Y	Y	Y
Soyabean	Y	Y	Y
Sesame seed	Y	Y	Y
Sunflower seed	Y	N	N
Pecan nut	Y	N	N
Walnut	Y	Y	Y
Buckwheat	Y	Y	Y

may originate from foods or aero-allergens containing tropomyosin (see Table V).[4]

6. MEAT ALLERGY

- Patients with red meat allergy may be sensitised to α-Gal, a sugar structure found on the glycoproteins of non-primate mammals.[3,4,11,12]
- IgE antibodies to α-Gal may be associated with severe allergic symptoms and with delayed-type anaphylaxis.[3,11]
- Sensitisation to α-Gal may be induced by tick bites.[3,4,11]
- Bovine serum albumin (BSA) is a heat-labile allergen present both in milk and beef which may cause cross-reactivity between different mammalian meats.[3]

7. NUT AND SEED ALLERGY

- Storage proteins are the dominant allergens in nuts, seeds, fruit stones and kernels.[1,13]
- The main storage proteins are designated according to molecular weight and are grouped in 7/8S and 11S globulins and 2S albumins.[1]
- These proteins are very stable to heat and digestion, therefore sensitised patients may also react to cooked and processed nuts/seeds.[1,13]
- Sensitisation to storage proteins is regarded as an important risk factor for severe systemic reactions, particularly if sensitisation to more than one storage protein in a particular allergenic source is identified.[1,13]
- The 2S albumin seems to be the dominant allergen with the highest risk for severe systemic reactions in tree nut, seed and peanut allergies.[1,14–16]

7.1 PEANUT ALLERGY

- The main and most important peanut allergen components are Ara h 1, Ara h 2, Ara h 3 and Ara h 6 storage proteins.[1,2]
- These storage proteins are heat stable and may predict severe and persistent allergy.[1,2]
- Storage proteins may cross-react with other nuts, seeds and legumes.[1,2]
- Sensitisation to peanut storage proteins, particularly Ara h 2, is most frequently associated with peanut anaphylaxis.[1,2]
- *Clinical implication*: Patients who have a clinically proven peanut allergy (by history or challenge) and who test positive to Ara h 2 need to avoid all peanuts and cross-reactive nuts and seeds. Patients not allergic to Ara h 2 who do not have a clinical history of anaphylaxis do not need to implement such strict avoidance measures, for example avoidance of foods produced in a factory that uses nuts or requesting products produced in a nut-free environment. Sensitisation to pollen cross-reactive components can lead to the over-diagnosis of peanut allergy and unnecessary avoidance. Many individuals sensitised to the peanut may be tolerant to it, therefore food challenges are recommended if the clinical history is unclear.

8. WHEAT ALLERGY:

- The most important wheat allergen component is Omega-5-gliadin.[1,2,17,18]
- Omega-5-gliadin predicts true wheat allergy in children and is associated with wheat-dependent, exercise-induced anaphylaxis (WDEIA).[1,2,17,18]
- Alpha Amylase/TI or Tri-a aA TI sensitisation may be associated with respiratory allergy symptoms after exposure to inhaled wheat flour (Baker's asthma).[1]
- *Clinical implication:* Patients who have clinically confirmed wheat allergy with a positive component test to omega-5-gliadin need to avoid all wheat products. Patients who are sensitised to pollen cross-reactive components are often wheat tolerant and do not necessarily need to avoid wheat. LTP allergy may also be associated with WDEIA, therefore sensitisation to food-pollen cross-reactive components should be

TABLE VII: SUMMARY OF MAIN PEANUT ALLERGEN COMPONENTS

PEANUT				
Storage proteins	Profilin	PR-10	LTP	CCD
Ara h 1 Ara h 2 Ara h 3 Ara h 6	Ara h 5	Ara h 8	Ara h 9	CCD
• Stable to heat and digestion • Associated with a risk of anaphylaxis • Cross-reactivity with other nuts and seeds	OAS	OAS	Risk of anaphylaxis, mainly in Mediterranean countries	Pollen cross-reactivity Avoidance not necessary

TABLE VIII: SUMMARY OF MAIN WHEAT ALLERGEN COMPONENTS

WHEAT						
Ω 5 Gliadin	αβɣω Gliadins	Alpha amylase/TI	Profilin	PR-10	LTP	CCD
Tri-a 19		Tri-a aA TI			Tri a 14	
Risk marker for systemic reactions Wheat allergy persistence Wheat-dependent, exercise-induced anaphylaxis	Marker of severe reactions Marker of wheat allergy persistence	Baker's asthma to inhaled wheat flour	OAS	OAS	Associated with wheat-dependent, exercise-induced anaphylaxis	Pollen cross-reactivity Avoidance not necessary

identified in these patients.

9. SOY ALLERGY

- The most important soy allergens are Gly m 5 and Gly m 6 seed-storage proteins.[1,2,14]
- These allergens indicate primary sensitisation to soy and are also high-risk markers for more severe allergic reactions to soy.
- Pollen-sensitised individuals may also react to Gly m 4, the PR-10 in soy. These patients may experience severe OAS or even systemic reactions.[1,2,14,19]
- *Clinical implication:* Patients who have a clinically confirmed soy allergy (by history or challenge) and test positive for Gly m 5 and Gly m 6 should avoid all soy products. Asymptomatic sensitisation to Gly m 5 and Gly m 6 may occur, therefore food challenges are recommended if the clinical history is unclear. Patients who are sensitised only to pollen cross-reactive components are usually soya tolerant. Most commercial allergy tests for soy extracts contain low levels of Gly m 4, therefore pollen-sensitised patients with a suspicion of soy allergy should be tested separately to Gly m 4.

SPECIFIC IGE TESTING TO ALLERGEN COMPONENTS

Testing for IgE-mediated components can be requested individually (ImmunoCap® IgE to specific allergen components) or to multiple allergen components simultaneously (immuno solid-phase allergen chip (ISAC) allergen microarray testing).[2,3,8] The choice of test will depend on the availability of allergens, the patient history and financial considerations.

CELLULAR ALLERGY TESTS

The most prominent cellular allergy tests for the diagnosis of food allergy measure basophil reactivity to allergens. Basophils have IgE receptors on their cell surfaces, therefore they may be activated via cross-linking specific IgE in the patient's serum or directly in an IgE-independent manner.[20,21] Whereas protein allergens are usually required for IgE binding, basophils may also be activated directly by small molecular-weight allergens.[22] Certain foods, colourants, preservatives and food additives may induce non-IgE-mediated basophil activation. Basophil-mediated allergy may include either an immediate or a delayed allergic response. Symptoms of basophil-mediated allergy may include sino-pulmonary respiratory symptoms, gastrointestinal symptoms and urticaria.

Basophil-mediated allergy can be measured by a basophil activation test (BAT) or the commercially equivalent cellular allergen stimulation test (CAST®).[23,24] The first-generation CAST® test was a CAST®-ELISA, where sulfidoleukotrine release from activated basophils was measured by ELISA technology. This assay was very time-consuming and had to be performed within four hours of venepuncture, making it impractical for routine laboratory diagnostics. The next-generation assays use flow-cytometry (flow-CAST® or other in-house flow-cytometry based BATs) to identify particular basophilic activation markers after stimulation by a particular allergen.[15,16] These assays are more suited to routine use, as specimens can be processed for up to 24 hours after collection. A wide range of commercial allergens are available, which include foods, food-allergen components, colourants, preservatives and food additives. A commercial food allergen screen containing milk, egg white, wheat, soy, peanut, hazelnut, codfish and shrimp is also available.[24]

Studies of the sensitivity and specificity of BAT in patients with food allergy have yielded varied results, due to the diversity of available food allergens.[25] In individual patients, BAT has confirmed the diagnosis of primary food allergy to multiple different food allergens.[15] In two specific studies of patients with apple allergy and carrot, celery and hazelnut allergy, the sensitivity of BAT was shown to be 85–90% and the specificity 80–90%. However, these are research studies that do not necessarily translate into clinical practice.[16]

TABLE IX: SUMMARY OF THE MAIN SOY ALLERGEN COMPONENTS

SOY					
Storage proteins		Profilin	PR-10	LTP	CCD
Gly m 5	Gly m 6		Gly m 4		
• Associated with more severe reactions • Heat stable		OAS	May cause severe reactions	May cause severe reactions	Pollen cross-reactivity Avoidance usually not necessary

IgE testing to food allergens by skin-prick testing or specific IgE testing (e.g. ImmunoCap®) is still the gold standard for detecting IgE-mediated allergy to foods. There is no indication to use a BAT for detecting allergen-specific IgE in lieu of current testing methods. The usefulness of BAT for the diagnosis of food allergy lies in its capabilities of detecting non-IgE-mediated basophil activation to foods and food additives such as colourants and preservatives. Recently, BAT has also been found to be useful in differentiating true peanut allergy from false positives and predicting a more severe peanut allergy.[26] The clinical implication is that BAT should be considered when the clinician suspects an allergy, but the results of IgE-mediated tests do not confirm this or when the patient history is suggestive of an allergy to a food additive. Where available, BAT can be used as an adjunctive *in vitro* test in the diagnostic workup of patients with food allergy.[8] As with all test results, these results should be correlated with the clinical history. Food challenges should be performed to confirm the clinical significance if the patient history is unclear.

CONCLUSION

The clinical history should always be the first starting point in allergy diagnosis. The likelihood of allergy, the pathogenic mechanism as well as the most appropriate allergen selection should be considered when allergy tests are requested. Screening or allergen-specific tests should be used to make the initial diagnosis and identify the offending allergens. More specialised tests should be used to predict the severity of allergy, identify the primary sensitiser and relevant cross-reactivity, and predict the likelihood of allergy resolution. Clinicians should be aware of the different testing modalities available and their uses and limitations. As the field of allergy diagnostics is rapidly expanding and becoming more technologically advanced, clinicians may need to rely more on advice about testing and interpretation from specialists in the field.

DECLARATION OF CONFLICT OF INTERESTS

The authors are employed by AMPATH Pathologists, a private provider of diagnostic testing for allergy.

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Guest Review

ADVANCES IN THE DIETARY MANAGEMENT OF FOOD ALLERGY

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SUMMARY

Food allergies have increased in the past 20 years. Research into dietary management has also escalated, playing an integral role from diagnosis to management and, more recently, including tolerance induction and prevention. This overview article is aimed at reviewing recent advances in the dietary management of both Immunoglobulin E (IgE)-mediated and non-IgE-mediated food allergy, focusing on new research related to dietary elimination, food challenges, prevention in sensitised children through early introduction and tolerance induction through dietary manipulation of foods. The review concludes that the time for dietary elimination in non-IgE-mediated allergies and the type of elimination diet in EoE are now better understood and favour the SFED.

Key words: food allergy; dietary management; diagnostic elimination diet; food challenges; oral tolerance

This article has been peer reviewed.

INTRODUCTION

Published data indicates that there has been an increase in the prevalence of food allergies in the past 20 years.[1] In fact, food allergy has been described as the 'second wave' of the allergy epidemic, the first being the increase in asthma, allergic rhinitis and inhalant sensitisation.[2] In some developed countries the prevalence of food allergy in infancy has reached 10 per cent and evidence is emerging that rates are also rapidly increasing in developing countries.[1,3] In line with the increased prevalence, there has also been an escalation in research on dietary management, which plays an integral role from diagnosis (i.e. diagnostic elimination diet and food challenges) to management and, more recently, tolerance induction and prevention. Although many dietary interventions require further studies prior to their implementation into day-to-day practice, there have been some advances that may already be worth considering in the dietary management of the food-allergic child. This overview article is aimed at critically reviewing recent advances in the dietary management of both Immunoglobulin E (IgE)-mediated and non-IgE-mediated food allergy, focusing on new research related to dietary elimination (including diagnostic diets), food challenges, secondary prevention in sensitised children through early introduction and tolerance induction through dietary manipulation of foods.

DIAGNOSIS OF FOOD ALLERGY

The length of time required for a diagnostic dietary elimination diet for children with non-IgE-mediated gastrointestinal food allergies has long been debated. The recommended time for a diagnostic elimination diet has varied according to different publications, ranging from 2 to 4 weeks and some proposing 8–12 weeks, in particular, for eosinophilic oesophagitis (EoE). A recent study by Chebar-Lozinsky et al[4] prospectively recruited a group of children with mixed non-IgE-mediated gastrointestinal allergies and assessed symptom improvements at four and eight weeks through a previously published symptoms questionnaire.[5,6] In that study the vast majority of cases significantly improved after four weeks on the elimination diet; only 1.6% had improved further at the eight-week mark. It is, however, important to note that this study did not aim to establish histological improvements in children with EoE; this population may therefore require a longer time on the elimination diet before this is achieved.

- A four-week diagnostic elimination diet is sufficient for the majority of children with non-IgE-mediated gastrointestinal food allergies.
- The elimination diet should be guided by a suitably qualified dietician to ensure optimal elimination.

DIETARY ELIMINATION

An elimination diet forms the mainstay of dietetic management for both IgE- and non-IgE-mediated food allergy.[7] Most notably, the greatest advances in dietary management have occurred in emerging food-allergic conditions, including EoE and Food Protein-induced Enterocolitis Syndrome (FPIES).[8–11] In EoE, the treatment is focused on clinical and histological remission and the main options are based on dietary exclusions and/or topical steroids.[12] Three dietary approaches have been studied: the elemental diet (amino acid formula (AAF)), empiric elimination diet (EED) and directed elimination diet (DED). The elemental diet was the first dietary intervention studied in EoE and remains the most effective for clinical and histological remission, with improvement rates usually around 90%.[13,14] However, the high cost, poor palatability and increased need for a nasogastric tube (45–85%) has led to alternative dietary approaches, including the empirical or directed approach, being introduced.[14,15] It is, however, important that clinicians understand the effectiveness of these approaches. The most studied EED is the six foods elimination diet (SFED),[14,15] which includes the avoidance of dairy, soya, egg, wheat, nuts and fish/shellfish. Studies have shown a clinical and histological remission rate around 70–80% and the most common food triggers identified by sequential food challenges have been cow's milk, wheat, egg and soya.[10,14,15] Moreover, the majority of the patients responsive to SFED have just one to two causative food allergens, with nuts (6%) and seafood (0%) being the least likely causative foods.[10] For this reason, a four foods elimination diet (FFED) (cow's milk, egg, soya and wheat) was developed and studied among patients with EoE. Molina-Infante et al[16] studied the impact of FFED in adults with EoE and found an improvement rate of 54%. In paediatrics only one study has been performed with the FFED, has been published in abstract format, and has found a 74% remission rate.[17] Kargawalla et al[10] found that in 74% of children cow's milk was the main causative food, and in a retrospective study the same group found that 65% histological remission occurred if only cow's milk was removed.[18] Similar results were found by Kruszewski et al,[19] with a 64% histological remission on a cow's milk elimination diet only, but importantly the quality of life was better in those who were on the cow's milk elimination diet only compared to those on Fluticasone. Although the SFED remains the most successful described in the scientific literature, it is important to note that in the majority of children cow's milk will be the main culprit and nuts and seafood are rarely a problem in EoE. Wheat, according to a recent review, should also not be expanded to other gluten-containing foods (i.e. rye, oat and barley), as there is insufficient evidence at this stage and it would impose further unnecessary dietary elimination.[20]

The DED is centred on the removal of specific food allergens from the patients' diet based on a suggestive history of food sensitisation supported by positive results of a skin-prick test and/or a patch test.[21] Spergel et al[22] found in their paediatric cohort an 89% and 72% symptom and histological improvement respectively; however, these data have not been reproduced by other centres and significant concerns exist regarding the reliability of the atopy patch test, which is not recommended for routine practice in the diagnosis of food allergy.[23,24] In addition, Henderson et al[14] found this method to lead to remission in only 65% of cases compared to 81% remission with the SFED.

FPIES is a non-IgE-mediated allergy that is characterised by profuse, repetitive and severe vomiting usually one to four hours after the ingestion of the offending allergen.[25] Caubet et al[8] reported from the largest FPIES cohort to date that 65% of children reacted to one food only, 26% to two foods and 9% to three or more foods. Although there is agreement in studies that cow's milk is the most common liquid FPIES allergen, there is disagreement on the rate of soya allergy in children with FPIES. Studies performed in United States found that 30–50% of the children with FPIES react to both cow's milk and soya;[8,11] however, other studies from Australia, Europe and Israel had significantly lower levels of soya FPIES,[26–28] which is an important consideration, especially in resource-poor environments where soya may offer a cost-effective alternative to cow's milk.

FPIES through breast milk is reported in single cases only;[29] consequently, guidelines do not suggest routine avoidance of the culprit food in breastfeeding mothers.[30] In cases where breast milk is not available, the majority of guidelines recommend the use of a hypoallergenic formula [extensively hydrolysed or AAF] and an AAF in particular if growth faltering is involved;[30] however, it is clear from the data that in some children soya may be considered. Although avoidance of the offending allergen remains the cornerstone of liquid FPIES management, the difficulty often lies in the introduction of complementary foods, as almost one-third of children with liquid FPIES will also have solid FPIES. A joint publication of authors from Europe, Israel and the United States indicates the avoidance of grains, legumes and poultry until six months

- The elemental diet has the best efficacy in EoE, however, is difficult to implement.
- Although the SFED has to date the best efficacy, it is important to note that nuts and seafood are rare causative allergens in EoE, hence an FFED may offer a good alternative.
- Cow's milk protein is the most common cause of liquid FPIES but not all countries report a high level of soya FPIES – this will need to be established in each child.
- The pre-emptive elimination of foods beyond six months is not recommended in FPIES.

of age, but after this introduction should occur either as a hospital-based challenge or at home.[9] Venter and Groetch have published a useful practical weaning guide for FPIES; however, this will need to be adjusted to every individual child depending on the culprit allergen.[31] No current evidence supports the introduction of baked milk for children with cow's milk FPIES; however, if the child is already tolerating baked milk products without symptoms, these can be continued.

FOOD CHALLENGES

Although oral food challenges have been well established in IgE-mediated food allergies, practice has varied significantly between centres. This has been recognised by both the American Academy of Allergy Asthma and Immunology and the European Academy of Allergy and Clinical Immunology with the publication of the PRACTALL consensus report on food challenges in 2012.[32] On the basis of an extensive literature review, a general challenge schedule comprising 3, 10, 30, 100, 300, 1 000 and 3 000 mg of food protein at intervals of at least 20 minutes was recommended. However, the authors do acknowledge that for low-protein foods (i.e. fruit and vegetables) other amounts will be required for challenges to deliver a reasonable amount of food and highlight the importance of considering the food matrix with food challenges.[32]

Advances have also been made in food challenges for children with non-IgE-mediated gastrointestinal allergies. Nowak-Wegzryn et al[33] published their challenge guidelines for FPIES in 2009, which have since been internationally accepted as the standard challenge protocol for this allergy. These guidelines indicate that the challenge dose should be calculated based on gram of food protein per kilogram of body weight, with a usual dosing ranging between 0.15 g and 0.3 g protein/kg body weight and up to a maximum of 10 g. Dosages should be provided within 30–45 min intervals.[33] For children without FPIES, but other non-IgE-mediated cow's milk protein-related gastrointestinal food allergies, Venter et al[34] published a milk ladder approach for home reintroduction. This approach is based on the extent of milk heating and fermentation, which has an impact on both the conformational epitopes and the peptide length.[35,36] Whether this approach can also be used for other common non-IgE mediated allergens (i.e. soya, egg, wheat) has been studied by Meyer et al and their findings are due to be published in 2016. It is crucial, however, that IgE-mediated allergy is ruled out prior to embarking on any home introduction of allergens.

- PRACTALL challenge guidelines should be used for IgE-mediated food allergy challenges.
- The dose for FPIES food challenges is based on protein/kg: 0.15–0.3 g protein/kg.
- The home challenge ladder for non-IgE-mediated
- IgE-mediated food allergies need to be excluded before embarking on home challenges.

EARLY INTRODUCTION

In 2015 Du Toit et al published their study on the early introduction of peanut protein in high-risk infants (LEAP study).[37–39] Enrolment criteria included children between 4 and 11 months of age with egg allergy and/or eczema and the eligible cases were randomly assigned to either receiving 6 g of peanut protein per week or no peanut protein at all. The total reduction of peanut allergy at 60 months in the early introduction cohort was 86%. Within this cohort, there was sub-group of children who were already sensitised to peanut (defined as 1–4 mm skin-prick test size) and who had a prevalence of peanut allergy of 10.6% in the peanut consumption group versus 35.5% in the non-peanut consumption group. Subsequently international guidelines have been published, recommending the early introduction of peanuts following the protocol from this study in children who have eczema with/without egg allergy and also in those who have an SPT of 1–4 mm to peanut protein. According to these guidelines, the clinician may wish to perform an observed peanut challenge for those with evidence of a positive peanut SPT (1–4 mm) to determine whether they are clinically reactive before initiating at-home peanut introduction. It is at all times important that clinicians consider the safety of peanut protein introduction in the sensitised group.[39] We are awaiting the results of the PRONUT study (NCT01744990) for guidance on the early introduction of tree nuts.

- Early introduction of peanut protein is now recommended in children with eczema/egg allergy/SPT 1–4 mm of peanut protein.
- It is important to consider the safety of the peanut protein introduction in the sensitised cohort and therefore the clinician may wish to consider a supervised peanut challenge prior to at-home introduction.
- The peanut introduction protocol of the LEAP study is recommended.

TOLERANCE INDUCTION THROUGH PROBIOTICS

The involvement of the gut bacterial flora has long been recognised as a factor that may contribute to the development of food allergy.[40] Significant research has occurred in the domain of allergy prevention, but in recent years studies have also focused on using probiotics in tolerance induction in children allergic to cow's milk. Canani et al have published several articles on the acquisition of tolerance in children with both IgE- and non-IgE-mediated cows' milk protein allergy, using an extensively hydrolysed formula (EHF) supplemented by Lactobacillus rhamnosus GG (LGG).[41,42] Although several methodological concerns remain regarding these studies, including that all data

were produced by a single centre, no adverse events were reported, therefore EHF with LGG is already in use in many European countries. The addition of LGG is proving to be a novel approach to assisting tolerance induction; however, this requires further research.

- EHF with LGG is safe for children with food allergies to use, but further research is required to support its efficacy in tolerance induction.

CONCLUSION

Many advances have been made in the management of food allergy, from diagnosis to the induction of tolerance. The time for dietary elimination in non-IgE-mediated allergies and the type of elimination diet in EoE are now better understood and favour the SFED. However, there is a drive towards eliminating fewer foods in children with EoE. Although further research is required with regard to the early introduction of other allergens in the cohort sensitised to food allergens, data from the LEAP study have indicated a clear benefit for early the introduction of peanuts in an already sensitised cohort.

Further data are required to confirm the impact of the addition of LGG to EHF, but this certainly opens up a new avenue for tolerance induction. The dietary management of food allergy is a fast-evolving area that requires clinicians to keep abreast of new research to ensure that children receive optimal clinical care.

DECLARATION OF CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUN PHARMA

Guest Review

ORAL IMMUNOTHERAPY FOR FOOD ALLERGY

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ABSTRACT

The IgE-mediated food allergy associated with risk for fatal anaphylaxis has been the subject of multiple immunotherapy studies in the past decade. The growing body of evidence suggests that for IgE-mediated food allergy immunomodulation through food immunotherapy is possible; however, the extent of protection provided by such treatment is highly variable. The capacity for food immunotherapy to restore permanent oral tolerance to food has not been demonstrated conclusively. In this review we discuss the most relevant studies of food oral immunotherapy.

Key words: food immunotherapy; food oral immunotherapy; food sublingual immunotherapy; oral tolerance, desensitisation

This article has been peer reviewed.

INTRODUCTION

Food allergies affect an estimated 5% of adults and 8% of young children in countries with Western lifestyles and appear to be on the increase in developing countries.[1–3] Peanuts, tree nuts, cow's milk, eggs, soya beans, wheat and seafood are responsible for more than 90% of food allergies in children. In adults, peanuts, tree nuts and seafood are the primary food allergens causing anaphylaxis.[4] Whereas childhood food allergy to cow's milk, eggs, soya beans and wheat typically resolve with time, peanut, tree nut and seafood allergies tend to be life-long.[5] Peanuts in particular have garnered significant attention, as they are the leading trigger of food allergy fatalities;[6,7] and data indicate that peanut allergy has at least doubled in the past two decades.[8,9]

The current standard management of food allergy involves the avoidance of the food, prompt recognition and treatment of allergic reactions, and nutritional support.[4,10,11,12] No therapies have been proven to accelerate the development of oral tolerance or provide effective protection from accidental exposures.[13] However, novel allergen-specific and allergen non-specific approaches to food allergy therapy are being developed and studied.[14]

While various routes of immunotherapy are being explored, oral immunotherapy (OIT) has emerged as the most actively investigated novel therapy for food allergy.[15] A first case of successful egg OIT was reported in 1908.[16] The renewed interest in the OIT emerged in the 1990s, starting with small, uncontrolled studies in Europe that provided a proof of concept for larger controlled clinical trials.[17–34] Whereas multiple studies have been published to date, the interpretation of the results is affected by significant heterogeneity in the design that hampers the ability to compare the results directly.[35–38]

BAKED MILK AND EGG DIET AS AN ALTERNATIVE OIT

The introduction of extensively heated (baked) milk and egg into the diet of milk- and egg-allergic children induces immunologic changes comparable to OIT.[39] Children with transient egg and milk allergy produce IgE antibodies directed primarily against conformational epitopes that are destroyed with high temperature, enzymatic digestion or food processing.[40,41] Heated egg-white proteins undergo enhanced gastric digestion, and ovomucoid bound to grain matrices in baked products forms insoluble complexes, which decreases allergenicity.[42,43] Two large clinical trials have investigated tolerance to extensively heated (baked into wheat muffins and waffles) milk and egg in children.[44,45] In both studies, tolerance to baked milk and egg was determined in the majority (approximately 75%) of children during a physician-supervised oral food challenge. Additional studies have confirmed that baked milk and egg diets are tolerated by the majority of milk- and egg-allergic children.[46–49]

Compared to the children who continued strict dietary avoidance according to the current standard of care, children ingesting baked milk or egg developed tolerance to unheated milk and egg at an accelerated rate.[50,51,52]

These findings suggest that for the majority of milk- and egg-allergic children who can tolerate milk or egg in baked products, strict avoidance of baked products is unnecessary and may account for the delayed acquisition of tolerance to unheated milk or egg.[53] The results of these baked milk and egg trials have changed the paradigm of the current management of milk and egg allergy, allowing for a more personalised approach based on the reactivity to baked milk and egg.[4,12,54–56]

Initial assessment of the reactivity to baked milk and egg is usually done during a physician-supervised oral food challenge because a subset of children with a more severe allergy may react with anaphylaxis to the first introduction of baked milk or egg. However, if the child has already been ingesting baked products in the diet, it is appropriate to continue home introduction. Serologic and skin-prick test-based cut-off levels have been proposed for baked milk and egg, but these values require further validation before introduction into clinical practice.[47,57–61]

The baked egg and milk diets add complexity compared to strict allergen avoidance, but can improve patient lifestyle. Nutritional counselling is important to facilitate adherence to the guidelines for baked-food preparation at home and buying commercial baked-food products. The incorrect preparation of baked foods or purchase of foods that contain unbaked milk and egg may put patients at risk for acute allergic reactions.[62,63]

OIT MECHANISM

OIT uses the pathways operative in oral tolerance, the default immune response in the gut to the ingested food protein antigens.[21,64,65] The aim of OIT is to first achieve desensitisation and then to re-establish permanent oral tolerance. Desensitisation is a state of temporary antigen hypo-responsiveness (increased threshold) that depends on the regular ingestion of the food. Dosing interruption may lead to the loss of the protective effect of desensitisation. So-called augmentation factors such as viral infection, exercise, use of NSAIDs or menstruation can trigger reactions to the previously tolerated maintenance dose.[66,67] The exact mechanism of desensitisation is not known; the associated immunologic changes include the decreased reactivity of mast cells (measured with skin-prick test reactivity) and basophils, increased food-specific serum and salivary IgG_4 and IgA antibodies and, initially, increased but eventually decreased serum food-specific IgE antibodies.[68–70] Similarly, the mechanism of permanent tolerance is not known, but may involve the development of regulatory T-cells followed by anergy and/or the deletion of food allergen-specific effector T-cells.[21,70–73]

Oral tolerance is defined as the ability to ingest the food without symptoms despite prolonged periods of avoidance or irregular intake. The permanence of protection is usually tested with the intentional interruption of OIT dosing for at least 4–12 weeks followed by a 'tolerance' food challenge.[28,74] To date, no adequately controlled rigorous trials of OIT have demonstrated the development of permanent tolerance (or even long-term desensitisation) due to therapy as opposed to natural acquisition. Individualised up-dosing and maintenance dosing as well as the prolonged administration of egg OIT may be necessary to enhance sustained unresponsiveness for some subjects with egg allergy.[29,75] In a long-term study of peanut OIT, 24 subjects were treated up to five years with maintenance daily doses of 4 000 mg peanut protein.[76] Twelve (50%) of the 24 passed a peanut challenge to 5 000 mg of peanut protein one month after stopping OIT and were considered to have achieved sustained unresponsiveness and added unrestricted peanut to their diet. With a shorter duration of peanut OIT, after 24 months of daily dosing with 4 000 mg of peanut protein, 20 out 23 (87%) treated subjects became desensitised, as determined by a peanut challenge.[72] However, after three months of strict peanut elimination, seven (30%) only passed the peanut challenge with 4 000 mg of peanut protein. Following an additional three months of peanut avoidance (a total of six months after discontinuation of peanut OIT), three of the seven subjects (3/23; 13%) remained tolerant to peanut during the final peanut challenge.

Therefore, it may be possible to improve rate of tolerance with a longer duration of OIT, comparable to the standard duration of subcutaneous immunotherapy (SCIT) for aeroallergens or venom (usually three to five years) and with higher maintenance dosing.[77]

SELECTION OF PATIENTS FOR FOOD ORAL IMMUNOTHERAPY

OIT clinical trials have been conducted in healthy children and young adults. For safety reasons, most studies excluded subjects with a history of severe anaphylaxis and more than mild persistent asthma. For efficacy concerns, some studies required reactions to a relatively low threshold at the baseline food challenge to show the treatment effect, preselecting the subjects less likely to outgrow food allergy spontaneously but also less likely to respond to OIT. While it is always the case that food OIT may induce tolerance in those who would develop spontaneous tolerance, evidence shows that immunotherapy could still be beneficial and potentially might accelerate the process in this context.[28,74] More accurate diagnostic tests, including molecular allergy diagnostic tests, may facilitate the preselection of subjects with a favourable profile regarding response to OIT, as well as to help identify subjects who are not likely to outgrow the allergy spontaneously.[13,75,78]

OIT DOSING SCHEDULE

During OIT, food is mixed with a vehicle and eaten in gradually increasing doses. Dose escalations occur in a controlled setting, usually every two weeks.[13,38] Most studies include an initial rapid dose escalation day that is

followed by further dose escalation in the clinic on a bi-weekly schedule until the maintenance dose is achieved. Daily ingestion of tolerated doses during the build-up and maintenance phases occurs at home. The need for daily dosing may affect long-term adherence as well as incidental dosing interruptions due to illness or travel. Therefore, less frequent intervals for maintenance dosing in OIT are attractive. A small clinical trial of milk OIT suggested that twice-weekly maintenance dosing is as safe and efficacious as daily maintenance dosing.[79] If these findings are confirmed by large clinical trials and with different foods, twice-weekly maintenance dosing will represent a practical approach to long-term food OIT.

FOOD ORAL IMMUNOTHERAPY SUCCESS RATES

Figure 1 presents the different phases of OIT as well as the general trends of immunologic change seen in OIT. It is unclear which factors determine a response to OIT. It is possible that desensitisation failure is associated with the most severe food allergy phenotype, as opposed to desensitisation success that may be associated with a milder, transient phenotype and higher chances of spontaneous resolution of food allergy.[13,76] This is particularly important in milk and egg allergy that have a high likelihood of spontaneous resolution.[28,74] In general, lower pre-treatment serum levels of specific egg and peanut IgE antibodies are associated with better response rates and enhanced sustained unresponsiveness.[76,80]

OIT SAFETY

OIT is associated with acute adverse allergic reactions in virtually all patients, which are more common during dose escalation than during maintenance (see Table I).[66,67,81,82] Most of the adverse reactions are mild and limited to the oropharynx. However, systemic reactions are seen and may occur at previously tolerated doses in the presence of augmentation factors, even during the maintenance phase.[66] Outside of acute allergic reactions, many patients complain of chronic gastrointestinal symptoms (abdominal pain, nausea, vomiting, diarrhoea) that may lead to discontinuation of OIT.[23,25,26] Gastrointestinal side-effects affect a majority of patients, and those undergoing OIT may be at higher risk (estimated at up to 2%) for developing eosinophilic esophagitis than the general allergic population.[25,83–86] Compared to sublingual and epicutaneous immunotherapy, OIT is associated with higher rates of systemic adverse events but also with higher efficacy.[87–89]

DISCONTINUATION OF OIT

The discontinuation (drop-out) rates from OIT trials range between 10% and 20%.[20,71] About 5–10% discontinue due to failure to progress to the minimum tolerated dose during the initial rapid dose escalation day, and subsequent discontinuations can be related to adverse reactions, such as gastrointestinal symptoms.

Figure: 1 OIT time course and immunologic changes

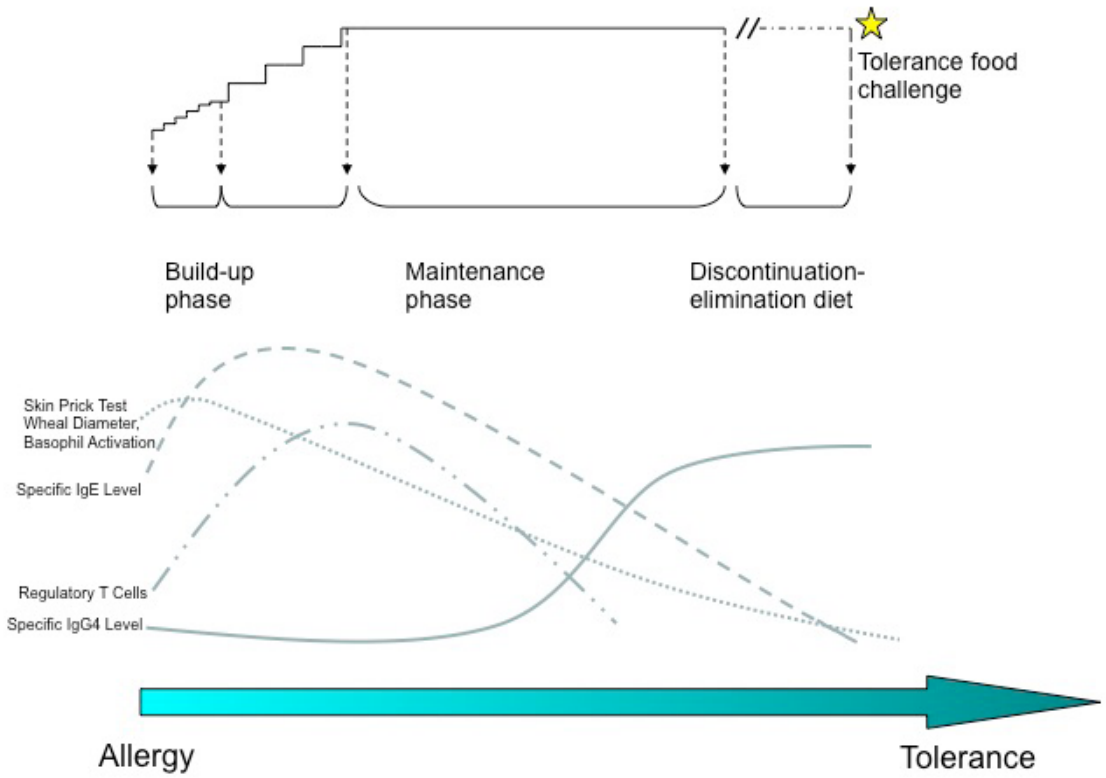

TABLE I: ADVERSE REACTIONS REPORTED FROM SELECTED CLINICAL TRIALS OF FOOD OIT

Author (year)	Patients in the active arm	Age	Food	Duration	% doses associated with AE in the active group	
Longo (2008), Italy	30	7–15 years	Milk	1 year	Rush escalation Mouth/lip/tongue pruritus or swelling: 100%; Abdominal pain: 75%; Erythema/urticaria: 48%; Mild asthma: 35%; Epinephrine used in four patients	Maintenance (at home): Emergency department admission and epinephrine treatment: two patients; no details on other AEs
Jones (2009), United States	29	57.5 months (12–111 mo)	Peanut	3 years	Initial dose escalation Any symptoms: 92%; Mild sneezing/itching/ laryngeal symptoms: 69%; Mild/moderate nausea or abdominal pain: 44%; Mild diarrhoea/emesis: 21% Needing epinephrine: four patients (10%)	Build up phase and maintenance phase Any symptoms: 46%; Upper respiratory: 1.2% Skin: 1.1% Treatment with epinephrine after home dosing: two subjects, each had one episode
Blumchen (2010), Germany	23	3.2–14.3 years	Peanut	9 weeks	Initial dose escalation Any symptoms: 7.9%; Gastrointestinal: 3.5%; Skin: 3.2%; Respiratory: 2.8%; Upper respiratory: 1.6% No treatment with epinephrine	Build-up phase and maintenance phase Any symptoms: 2.6%; Gastrointestinal: 0.9%; Skin: 0.4%; Respiratory:1.3% Upper respiratory: 0.2%; No treatment with epinephrine; four subjects were discontinued due to asthma worsening
Anagnostou (2014), United Kingdom	49	7–16 years	Peanut	6 months	The entire course of OIT Oral pruritus: 6.3%; Abdominal pain: 2.6%; Nausea: 2.2%; Vomiting: 0.75%; Diarrhoea: 0.03%; Urticaria: 0.16%; Angioedema: 0.4%; Erythema: 0.23%; Rhinitis: 0.37%; Wheezing: 0.41%; Laryngeal oedema: 0.01%; Use of inhaled bronchodilator: 0.35%; Use of intramuscular epinephrine: 0.01%	

OIT AND QUALITY OF LIFE

Results from uncontrolled studies suggest that OIT may improve some aspects of life quality such as dietary and social limitations, risk of accidental exposure, and anxiety.[90,91,92] The true impact of OIT on quality of life remains to be determined.

SELECTED CLINICAL TRIALS OF FOOD OIT

Although numerous studies of food OIT have been conducted to date, only a few adhered to a rigorous design, as recently critically reviewed by meta-analyses.[36,37,39,93] There is tremendous heterogeneity regarding study design, inclusion criteria, dosing schedule, duration of therapy and the approach to evaluating the persistence of the protection following discontinuation of OIT. Table II summarises selected clinical trials of food OIT.

ORAL IMMUNOTHERAPY COMBINED WITH ANTI-IGE MONOCLONAL ANTIBODY

Anti-IgE monoclonal antibody is a non-allergen-specific treatment that has been successfully tested as a monotherapy for peanut allergy. In one study, subjects treated with the highest dose of anti-IgE showed an increased dose threshold response for peanut after four months.[94] Pre-treatment with anti-IgE monoclonal antibody has been shown to be effective and the improved safety of food OIT likely by lowering circulating IgE and down-regulating expression of the IgE receptor on antigen presenting cells. Two small pilot studies of milk and peanut OIT combined with omalizumab reported a markedly increased safety of OIT.[22,95] These results have been confirmed by a large, double-blind, placebo-controlled trial with subjects randomised to omalizumab or placebo.[96] Open-label milk OIT was initiated after four months of omalizumab/placebo with escalation to maintenance over 22–40 weeks, followed by daily maintenance dosing through to month 28. At month 28, omalizumab was discontinued, and subjects passing an oral food challenge (OFC) continued OIT for 8 weeks, after which OIT was discontinued with a re-challenge at month 32 to assess

sustained unresponsiveness.

Fifty-seven subjects (7–32 years) were randomised, with no significant baseline differences in age, milk-specific IgE levels, skin-test results, or OFC results. At month 28, 24 (88.9%) omalizumab-treated subjects and 20 (71.4%) placebo-treated subjects passed the 10 g 'desensitisation' OFC (p = 0.18). At month 32, sustained unresponsiveness was demonstrated in 48.1% in the omalizumab group and 35.7% in the placebo group (p = p.42). Adverse reactions were markedly reduced during OIT escalation in omalizumab-treated subjects for percentages of doses per subject, provoking symptoms (2.1% vs 16.1%, p = 0.0005), dose-related reactions requiring treatment (0.0% vs 3.8%, p = 0.0008) and doses required to achieve maintenance (198 vs 225, p = 0.008). In this first randomised, double-blind,

TABLE II: SELECTED CLINICAL TRAIS IN FOOD ORAL IMMUNOTHERAPY

STUDY/SUBJECTS	SUCCESS RATE	IMMUNOLOGIC CHANGES	SIDE-EFFECTS/COMMENTS
PEANUT OIT			
Blumchen, 2010[20] n = 23; age 3–14 years Subjects underwent a rush protocol for 1 week and then received OIT for 8 weeks. Goal maintenance dose: 500 mg peanut protein daily.	Twenty-two out of 23 (96%) subjects finished the initial rush protocol, but 17 of these subjects did not achieve the goal dose of 500 mg of peanut with rush therapy (they continued on individualised long-term build-up protocols to reach 500 mg). Only 14 subjects out of 22 (64%) reached a maintenance dose of at least 500 mg of peanut and completed OIT. The median tolerated dose after completion of OIT was 1 g of peanut.	After OIT, all subjects had reductions in IL-5, IL-4, and IL-2 (P < 0.001). After discontinuing OIT for 2 weeks, peanut-induced IL-5, IL-4 and IL-2 secretion were stable in most of the subjects. After OIT, there was a small reduction of peanut SPT wheal diameter (P < 0.05). After discontinuing OIT for 2 weeks, this reduction was no longer evident. After OIT, peanut-specific IgG4 levels increased (P < 0.001). After discontinuing OIT for 2 weeks, there was a small decrease in specific IgG4 levels (P < 0.001). Peanut-specific IgE levels as well as total IgE levels did not change with OIT.	The dropout rate of this study was 35% (8 out of 23 subjects). In 4 subjects, OIT was discontinued by the study physician because of adverse allergic reactions. Two subjects dropped out because of compliance, 1 because of a severe infection and 1 was a partial responder who did not qualify for the final challenge. Adverse reactions were frequent, particularly during the rush protocol. Of 317 total doses of OIT during the rush protocol, 25 doses (7.9%) were associated with objective symptoms. Of 637 doses of OIT during the long-term build-up protocol, 160 doses (2.6%) were associated with objective symptoms.
Varshney, 2011[71] n = 28; age 1–16 years Subjects were randomised 19:9 to OIT or placebo for 48 weeks. Goal maintenance dose: 4 000 mg peanut protein daily.	During the initial day of ra pid dose escalation, 26 out of 28 (93%) subjects reached the maximum cumulative dose of 12 mg of peanut protein or placebo. Sixteen subjects received the full course of peanut OIT and all tolerated 5 g of peanut protein following OIT.	Compared to placebo, peanut OIT group showed reductions in SPT size (P < 0.001), IL-5 (P = 0.01), and IL-13 (P = 0.02), and increases in peanut-specific IgG4 (P < 0.001). The ratio of forkhead box protein 3 (FoxP3) (high): FoxP3(intermediate) CD4+ CD25+ T cells increased at the time of OFC (P = 0.04) in peanut OIT subjects.	Adverse reactions were common, but most reactions were mild. In the active arm, 9 out of 19 subjects (47%) experienced adverse reactions during the initial day escalation. During the build-up phase, adverse reactions occurred following 1.2% of 407 build-up doses. None of the placebo subjects required treatment during initial day escalation or build-up dosing; however, 3 (33%) were treated with epinephrine during the final peanut DBPCFC.
Vickery 2013[71] n = 24; age 1–16 years Subjects were treated for up to 5 years with peanut OIT, and then stopped treatment for 1 month to test for sustained unresponsiveness. Goal maintenance dose: The protocol was modified over time to permit dose increases to a maximum of 4 000 mg peanut protein daily.	Of the 39 subjects originally enrolled, 24 (62%) completed the protocol and had evaluable outcomes. All subjects completing the study successfully ingested 5 000 mg of peanut protein without symptoms during a desensitisation challenge. Only 12 out of 24 (50%) successfully ingested 5 000 mg of peanut protein 1 month after stopping OIT and achieved sustained unresponsiveness. Of those who failed the 5 000 mg challenge, the median amount of peanut protein ingested cumulatively before the development of symptoms was 3 750 mg (range, 1 500–5 000 mg).	In those who achieved sustained unresponsiveness, subjects had smaller skin test results, lower IgE levels specific for peanut, Ara h 1, and Ara h 2, and lower ratios of peanut-specific IgE/ total IgE compared to those who did not achieve sustained unresponsiveness. There were no differences in peanut IgG4 levels or forkhead box protein 3 CD4+ CD25+ T cells between these groups.	This study is the first to demonstrate sustained unresponsiveness after peanut OIT.

STUDY/SUBJECTS	SUCCESS RATE	IMMUNOLOGIC CHANGES	SIDE-EFFECTS/COMMENTS
Anagnostou, 2014[18] n = 99; age 7–16 years Phase 1: Subjects were randomised 1:1 to OIT or control (standard of care food avoidance) for 26 weeks. Phase 2: Cross over from the control group into OIT for 26 weeks. Goal maintenance dose: 800 mg peanut protein daily.	84% of subjects receiving OIT were able to ingest 800 mg of daily peanut for 26 weeks in the first phase, and 91% of subjects from the cross over control group were able to ingest 800 mg of daily peanut for 26 weeks during the second phase. Twenty-four of 39 subjects (62%) receiving OIT tolerated 1 400 mg of peanut at the end of the first phase of the study, as compared to 0 of 46 control subjects (P < 0.001).	After OIT, there was a small reduction in peanut SPT wheal diameter. After 24 weeks of OIT there was an increase in peanut-specific IgE. No significant within-patient differences were identified after treatment for basophil activation (although there was a reduction in MFI and proportion of CD63 at lower peanut concentrations after OIT).	During the first phase of the study, one subject discontinued and 5 withdrew from the OIT arm. Four subjects could not achieve target maintenance dose at 6 months in the OIT arm. In the control group, 4 subjects withdrew and one discontinued. The number and nature of adverse events was similar in both groups after treatment, and most events were mild. The most common adverse event was oral itching, which occurred after 6.3% of all doses.
EGG OIT			
Burks,2012[17] n = 55; age 5–11 years Subjects were part of a multicentre double-blind placebo controlled clinical trial. Goal maintenance dose: 2 000 mg egg white powder daily.	At the 10-month challenge, 22 of 40 subjects (55%) receiving OIT tolerated 5 g of egg-white powder, and 0 of 15 subjects of the placebo group passed (P < 0.001). At the 22 month challenge, 30 of 40 subjects (75%) receiving OIT tolerated 10 g of egg-white powder (were considered desensitised). At the 24 month challenge (6–8 weeks off OIT), 11 of 29 subjects (28%) tolerated 10 g of egg-white powder plus whole egg (were considered to have sustained unresponsiveness). According to the intention-to-treat analysis, 11 of the 40 subjects (28%) in the oral-immunotherapy group passed the oral food challenge at 24 months (P = 0.03, as compared with placebo).	Compared to subjects who received placebo, those who received OIT had a decreased wheal size on SPT, reduced egg-induced basophil activation, and increased egg-specific IgG4 antibody levels over time, whereas no change in egg-specific IgE antibody levels was noted.	All 55 subjects completed the initial-day dose escalation, but 7 subjects withdrew before the maintenance phase (5 in the OIT group and 2 in the placebo group). There were no severe adverse events, and rates of adverse events were highest during the first 10 months of OIT. Adverse events were associated with 25 % of 11 860 doses of OIT and 3.9% of 4 018 doses of placebo. The results of this clinical trial raise concerns about the long term protection (sustained unresponsiveness) afforded by OIT. It remains to be determined whether a higher maintenance dose and longer duration of OIT might improve the rates of sustained unresponsiveness.
MILK OIT			
Staden, 2007[28] n = 45; age <1–12 years Subjects were randomised to OIT or elimination diet. Oral tolerance for all subjects was evaluated after a median 21 months (range 11–59 months). Goal maintenance dose: Doses were increased (according to individual tolerance) to a maximum dose of 8 250 mg cow's milk protein or 2 800 mg hen's egg protein. The maintenance phase mandated a minimum daily maintenance dose of 3 300 mg cow's milk protein and 1 600 mg hen's egg protein.	Twenty-five subjects were randomised into milk or egg OIT, and 14 underwent milk OIT. 20 subjects were randomised into an elimination diet, 10 of which were avoiding milk. In the OIT group, 16 of 25 subjects (64%) were able to integrate the food allergen into their diet. Nine of 25 subjects (36%) showed sustained tolerance after a secondary elimination diet, 3 of 25 (12%) showed tolerance with regular intake, and 4 of 25 (16%) were partial responders who never met planned full maintenance dose. In contrast, only 7 of 20 subjects (35%) showed tolerance (P = 0.05).	Allergen-specific IgE levels decreased. Significantly, both in subjects who developed natural tolerance during the elimination diet (P < 0.05) and in those treated with OIT (P < 0.001).	All subjects in the OIT group had adverse events to some extent; 21 had mild symptoms and 4 had moderate symptoms. In the control group, 5 subjects had mild to moderate adverse events due to inadvertent ingestion of food allergens.

STUDY/SUBJECTS	SUCCESS RATE	IMMUNOLOGIC CHANGES	SIDE-EFFECTS/COMMENTS
Skripak, 2008[26] n = 20; age 6–17 years Subjects were randomised 2:1 to OIT or placebo for 13 weeks. Goal maintenance dose: 500 mg cow's milk protein daily.	Nineteen subjects completed treatment (12 receiving OIT and 7 receiving placebo). After OIT, the median cumulative dose of milk inducing a reaction in the active group increased from 40 mg to 5 140 mg, but there was no change in the placebo group (P = 0.0003).	Milk-specific IgE levels did not change in either group. Milk IgG levels increased significantly in the OIT group, with a predominant milk-IgG_4 increase. End-point titration milk SPT wheal decreased over time (P = 0.0091 from baseline).	Among 2 437 active OIT doses, there were 1 107 reactions (45.4%). Among 1 193 placebo doses, there were 134 reactions (11.2%). Local symptoms were most common.
Narisety, 2009[25] n = 15; age 6–16 years Open label follow up to Skripak study, which occurred over 13–75 weeks (median 17 weeks). Fourteen subjects were able to escalate daily doses, with maximum doses ranging from 1 000 to 16 000 mg (median, 7 000 mg).	After 13–75 weeks of open label dosing, challenges were conducted on 13 subjects. Six tolerated 16 000 mg with no reaction, and 7 reacted at 3 000 to 16 000 mg.	Milk-specific IgE levels decreased and IgG_4 levels increased in over the follow up period from 3 to 17 months.	Challenges were not performed in 2 subjects because of ongoing reactions with home dose escalations. Adverse reactions were common and unpredictable, but overall rates of reaction decreased over time. In the 2 465 home doses recorded, there were 419 local reactions (17% of doses). Epinephrine was required for 6 (0.2%) of doses in 4 subjects. Of note, one subject developed symptoms consistent with eosinophilic esophagitis.
Pajno, 2013[79] n = 32; age 4–13 years Subjects who were successfully desensitised with oral immunotherapy were randomised to two maintenance regimens for 1 year: Group A had to ingest 150–200 ml milk daily, and Group B had to ingest 150–200 ml milk twice weekly.	Twenty-nine subjects completed the 12 month study, 15 randomised to daily milk and 14 randomised to twice weekly milk. No subjects permanently discontinued their maintenance diet based on adverse events.	There were no significant differences in milk-specific IgE, IgG_4, and SPT reactivity between Group A and B.	Three subjects and their families withdrew during maintenance because of personal problems, not related to the study procedures. Adverse events included asthma, oral itching, urticaria, rhinitis and abdominal pain, usually associated with concomitant illness or exercise. There were 8 events in Group A, and 9 events in Group B (no difference between the groups, P = 0.08).
MULTIPLE FOOD OIT			
Begin, 2014[97] n = 40; age 4–46 years Pilot phase I study for multi-food OIT (15 subjects on peanut OIT, 25 subjects on multi-food OIT). Goal maintenance dose: 4 000 mg of food protein per allergen daily.	Rates of reaction per dose did not differ significantly between the two groups (median of 3.3% and 3.7% in multi and single OIT group, respectively; P = 0.31). In both groups, most reactions were mild but two severe reactions requiring epinephrine occurred in each group. Those on multiple food OIT took longer to reach equivalent doses per food (median +4 mo.; P < 0.0001).	In the multi-food group, there was an increase in peanut-specific IgG4 similar to the monotherapy group. Peanut-specific IgE levels were stable after one year.	This was a proof of concept phase I safety study, and the primary endpoint of the study was occurrence of allergic reactions. Over the study period, there were 5 dropouts for reasons which included non-compliance with study medication and change of residence. One subject in the multi-OIT group was unable to increase doses due to eczema flares and was categorised a treatment failure.

Abbreviations: OIT, oral immunotherapy; SPT, skin-prick test; OFC, oral food challenge.

placebo-controlled trial of omalizumab in combination with food OIT, significant improvements in safety were evident but not in efficacy (desensitisation and sustained unresponsiveness). The optimal duration of co-treatment with omalizumab and OIT needs to be established due to the concerns about the high cost of anti-IgE treatment.

OIT WITH MULTIPLE FOODS

A safety trial of a multi-food OIT was conducted in parallel to peanut OIT in subjects with peanut allergy.[97] Forty subjects reacted at the baseline DBPCFC to a maximum cumulative dose of 182 mg of peanut protein; of those, 25 had additional food allergies (eg walnut, cashew, pecan, almond, hazelnut, cow's milk, egg and sesame). OIT with two foods was done in 24% of the participants, three foods in 32%, four foods in 20% and five foods in 24%. The protocol had three phases: the initial dose escalation day, home dosing with up-dosing every two weeks, and the maintenance phase. The daily maintenance dose was 4 000 mg protein of each allergen, with up to 20 000 mg as a cumulative dose for five-food OIT. Rates of reaction per OIT dose were (median) 3.3% in multi-food OIT and 3.7% in the single OIT group. Most reactions were mild, but two severe reactions requiring epinephrine occurred in each group.

Pre-treatment with omalizumab may also be applicable to multiple-food OIT.[98] In a pilot study, 25 participants, median

age seven years, had failed an initial double-blind placebo-controlled food challenge at a protein dose of 100 mg or less to each food included in OIT. After 16 weeks of pre-treatment with omalizumab, 19 participants tolerated all six steps of the initial escalation day (up to 1 250 mg of combined food proteins), requiring minimal or no rescue therapy. The remaining six were started on their highest tolerated dose as their initial daily home doses. The participants reported 401 reactions per 7 530 home doses (5.3%) with a median of 3.2 reactions per 100 doses. Ninety-four per cent (94%) of reactions were mild; one reaction was severe. The maintenance dose of 4 000 mg protein per allergen was reached at a median of 18 weeks. These results suggest that multi-food OIT combined with omalizumab pre-treatment may be a practical and safe option for patients with multiple-food allergy, pending validation by large and rigorous clinical trials.

ORAL IMMUNOTHERAPY – RECOMMENDATIONS FOR CLINICAL PRACTICE

The studies of food OIT give hope that an effective interventional treatment for food allergy is within reach. Preliminary data suggest a beneficial treatment effect; however, there cannot be a definitive statement yet regarding efficacy as no study has carried both a treatment and a placebo arm to identical end points. In most published studies to date, the placebo group has been treated differently from the active group (ie followed over time, but not systematically challenged). In addition, significant adverse reactions to OIT are common. Meta-analyses on immunotherapy for milk, egg and peanut allergy pointed out significant limitations of the published studies.[35-37,99] The most recent analyses included all randomised controlled, quasi-randomised controlled, and case-controlled trials of peanut and milk OIT published from 1990 through to January 2012.[37,99] In the meta-analysis of peanut OIT papers, one study only out of 746 fulfilled the Cochrane inclusion criteria.[71] Authors of the *Cochrane Report* concluded that, based on the findings of one small trial, peanut OIT cannot be recommended as a routine treatment for patients with peanut allergy. In the meta-analysis of milk OIT papers, slightly less rigorous criteria were used and 16 records representing five clinical trials were reviewed.[99] The authors concluded that the quality of these trials was low; because no standardised protocols were used, milk OIT could not be recommended as a routine treatment for patients with milk allergy. However, it is clear that some allergists provide oral immunotherapy for different foods in their practices.[82] Nevertheless, at this time, expert consensus and formal guidelines recommend that food OIT should remain limited to the research setting until properly evaluated for its long-term efficacy, safety and cost-effectiveness.[4,10,12,13,83,84]

CONCLUSIONS

In the past two decades, food allergy has emerged as an important public health issue on a global scale. The current management of food allergy is restricted to dietary avoidance and no treatment reliably restores permanent oral tolerance to food.[4] Diets containing extensively heated (baked) milk and egg may represent a safer approach to oral immunomodulation applicable to the majority of children with milder phenotype of milk and egg allergy.[57]

OIT alone or in combination with anti-IgE antibody is likely to advance into clinical practice in the more immediate future. However, OIT protocols require further validation in large clinical trials before their incorporation into clinical practice. There is a need to harmonise the protocols for the clinical trials for food immunotherapy to maximise the data quality and allow for better comparison of the outcomes from different studies.[38] OIT with multiple foods, OIT with cross-reactive foods and OIT starting at younger ages (e.g. infants with peanut allergy) are potential future options. In addition to OIT, sublingual and epicutaneous immunotherapy are being evaluated in clinical trials. Modified hypoallergenic peanut molecules are being evaluated regarding their feasibility for clinical trials.[100] Nanoparticles targeting dendritic cells to induce T regulatory cells and to provide slow release of the antigen, as well as oligomannose-coated liposomes (OML) that induce MHC class I-restricted CD8+ T-cell responses, show promise in mouse models of food allergy.[101,102] Immunotherapy with specific peptides represents yet another approach to food antigen-specific immunomodulation.[103,104] These advances in the field of novel therapies for food allergy bring hope for allergy patients that effective therapy is within reach.

DECLARATION OF CONFLICT OF INTERESTS

The authors have no conflicts of interests to declare.

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Press Release

PHARMA DYNAMICS APPOINTS NEW CEO

29 March 2016

Pharma Dynamics' founder, Paul Anley, has resigned as Chief Executive Officer and has named industry-veteran Erik Roos as the company's new CEO.

Anley, who started Pharma Dynamics in 2001, has driven the company's meteoric rise to national recognition and prominence. Pharma Dynamics is now SA's biggest distributor of cardiovascular medicine and ranks as the third largest generic pharmaceutical company in the country.

Following the full purchase of Pharma Dynamics in April 2015 by the Lupin Group, India's third largest pharmaceutical company by total sales, Anley will step down as CEO at the end of March 2016, but will remain a non-executive Director.

Erik Roos, former CEO of Mylan South Africa, will take over the reigns as CEO of Pharma Dynamics with effect from 1 April 2016.

Commenting on the announcement, Anley says Pharma Dynamics is ideally positioned to continue the sales momentum into the next phase of its growth.

"The company has an experienced management team, an extensive and strong sales force, and an enviable brand image and corporate reputation. This, combined with what could be the largest product pipeline in the industry, will ensure its continued success," says Anley.

Roos' vision for Pharma Dynamics is to sustain success and remain the fastest growing generic pharmaceutical company in SA by identifying unique future product portfolios to bolster established lines, tightening distribution and logistics in the face of exchange rate challenges and investigating the feasibility of establishing local manufacturing and packaging facilities.

He aims to break into additional therapeutic areas, such as oncology and biosimilars to boost Pharma Dynamics' already strong position in the cardiovascular, central nervous system and over-the-counter categories.

The company is also well established in Namibia and has successfully registered various dossiers in the Southern African region.

"I am looking forward to shaping the future of our company together with an excellent local and global team. We have strong brands and technologies, leading positions in many healthcare classes in SA and with Lupin around the world. Building on this foundation, together, we will successfully lead Pharma Dynamics into the future," concludes Roos.

Erik Roos (new CEO of Pharma Dynamics

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Guest Review

'MIDNIGHT ANAPHYLAXIS' TO RED MEAT IN PATIENTS WITH ALPHA-GAL SENSITISATION: A RECENT DISCOVERY IN THE FOOD ALLERGY WORLD AND A CASE REPORT FROM SOUTH AFRICA

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INTRODUCTION

A syndrome of delayed anaphylaxis to red meat, occurring in geographical 'clusters' initially identified in the United States, was first described in 2009. A few years later, this enigmatic anaphylactic reaction was ascribed to IgE antibodies to galactose-alpha-1,3-galactose (alpha-gal), an oligosaccharide, which is a major blood group substance in non-primate mammals. It appears that the predominant source of sensitisation to alpha-gal is bites from certain ticks.[1–4] Since 2009, several hundreds to thousands of cases of delayed red-meat allergy have been described worldwide, but very few reports have come out of Africa. This case series describes 2 cases of an acquired form of delayed anaphylaxis to beef and mutton in patients who were subsequently found to be highly sensitised to alpha-gal, residing in the same region.

CASE 1

Mr HS is a 63-year-old male from George, South Africa, who is generally fit and well, apart from psoriasis, for which he is on topical treatment. He grew up on a cattle farm and has in the past spent a significant amount of time in the 'veld' (open country). He also currently resides on a golf estate adjacent to a cattle farm. He has no past history of food allergy apart from an episode suggestive of MSG-syndrome after a Chinese meal 15 years ago. Around one year ago HS ate out for dinner and, unexpectedly, experienced an urticarial rash three hours after the dinner with, at that stage, no clear trigger. The rash occurred mainly at active psoriasis sites. Subsequently, similar symptoms started occurring repeatedly, especially after he had eaten out, always about three hours later. On a different occasion after eating steak and chips, he experienced a severe attack with diffuse urticaria and tightening of the throat three hours after eating, for which he was hospitalised and given intravenous antihistamines (please note that intramuscular adrenaline would have been preferable to antihistamines for these symptoms). Over the course of this past year, he has experienced about ten episodes of an allergic reaction, always three or more hours after eating, two of which required hospitalisation for severe symptoms.

After a few episodes, HS started recognising that he had always eaten red meat before such symptoms occurred. The main cause was beef; lamb caused milder symptoms, which could usually be minimised by taking an antihistamine before eating the lamb.

HS discussed the symptoms with his family practitioner, and after discussion with an allergist the diagnosis of delayed-type allergy to red meat as a result of alpha-gal sensitisation (so called 'midnight anaphylaxis', as symptoms often occur several hours after the evening meal) was entertained. Blood tests showed results as follows:

- Specific IgE to beef: 1.26 kU/ℓ
- Specific IgE to mutton: 0.34 kU/ℓ
- Specific IgE to alpha-gal: 29.6 kU/ℓ.

The diagnosis of alpha-gal allergy was confirmed, and HS was advised to avoid meat of mammalian origin, especially beef, which caused more severe symptoms in his case. He was also given an emergency treatment plan in case of reactions.

CASE 2

Shortly after diagnosing HS with alpha-gal syndrome, another similar case in the same region became apparent. CD is a 71-year-old male who happens to reside in the same golfing estate as HS – adjacent to the same cattle farm. About three years ago CD first started experiencing

unexplained urticarial rashes in the late evenings and early hours of the morning. He had no respiratory symptoms. He recalls being bitten by a tick four years ago. For a long time he could not link specific foods to the development of the rashes, despite many visits to doctors, numerous allergy tests and using topical and systemic corticosteroids to try and control the symptoms. For years he pursued a varied exclusion diet to no avail. CD's sister-in-law, a nursing sister from England, then suggested a possible link to meat allergy and, on the advice of a local laboratory, she arranged an IgE test for alpha-gal which came back positive at 19.3 kU/ℓ. Once this link had been established, CD realised that he reacted consistently to red meat (lamb more so than beef; minimally to pork) approximately six hours after ingestion. Elimination of lamb and beef was advised, and a fast-acting antihistamine such as cetirizine was prescribed in case accidental red-meat ingestion led to urticaria.

DISCUSSION

Relatively recent research in the past decade has identified a novel IgE-mediated antibody response which can lead to two distinct forms of anaphylactic reaction: the first is a delayed onset reaction after the ingestion of food products of mammalian origin. The second is immediate-onset anaphylaxis during the first exposure to the intravenous chemotherapeutic agent, cetuximab.[1,3] In both cases, tick bites are the significant cause of the initial IgE-response. These reactions can occur at all ages and do not appear to have a predilection for otherwise atopic individuals.

ALPHA-GAL SENSITISATION AND REACTIONS TO RED MEAT

The syndrome of 'midnight anaphylaxis' to red meat describes a delayed-onset allergic reaction three to six hours after eating mammalian food products. Patients typically react to beef, mutton or pork, but have no trouble with chicken or fish. The responsible IgE antibody for this type of reaction is not to a major protein allergen specific to the meat; rather it is to the oligosaccharide galactose-alpha-1,3-galactose (alpha-gal). Alpha-gal is found in all mammalian cells, but not in the tissues of humans and Old World monkeys.[1,3] The kidneys appear to be particularly rich in alpha-gal.[5]

Most reports of delayed meat allergy due to alpha-gal cross-reactivity have been described in adults, who classically present with an acute onset of delayed anaphylaxis and urticaria. However, a few recent cases have been described in the paediatric population.[3] Unlike their adult counterparts, it appears that the majority of children with alpha-gal syndrome present with urticaria rather than anaphylaxis.

Sensitisation to alpha-gal may occur through tick bites, possibly via parasitic infection[6] or through exposure to cetuximab,[1] a chimeric IgG1 monoclonal antibody against the epidermal growth factor receptor, used in treating colon and squamous carcinomas. Skin-prick tests with commercial extracts to meat are often equivocal, and specific antibodies to red meat extracts often show low positive results only despite a severe reaction, as seen in this case. Specific IgE to alpha-gal, however, is clearly positive in this type of allergy. Moreover, patients with this syndrome also classically test positive to cat on SPT and specific IgE, as cat IgA has an alpha-gal epitope. However, IgE to alpha-gal does not create a risk for asthma.[7]

Bites from certain types of ticks have been described as the initial causes of sensitisation to alpha-gal (see Figure 1). Ticks (Ixodida) are obligate bloodsucking parasites, an order within the class Arachnida.[4] Several ticks are known to feed on non-primate mammals as their primary host. In the United States, bites from the lone star tick *Amlyomma americanum* are causative (see Figure 2); this was established by correlating the IgE antibodies to alpha gal, the IgE antibodies to this tick and from the known distribution of this tick.[8] In Australia, *Ixodes holocyclus* and in France *Ixodes ricinus* appear to be responsible.[4,8] Studies in Sweden have reported clear evidence that the alpha-gal epitope is present in the gut of the tick *Ixodes ricinus* and can be transmitted via saliva during a tick bite.[9]

In Africa, alpha-gal-positivity has been described in Harare[6] and Kenya[10] with possible causative candidates including helminths, scabies and ticks; however, associated cases of delayed reaction to meat have seemingly not been published previously in Africa. It is interesting that the two cases from South Africa described above lived in the same golfing estate and adjacent to a cattle farm. This raises the possibility that a particular local tick species was responsible for the initial sensitisation. Since discussing these case reports, other South African allergologists have described further unpublished cases in Cape Town (personal communication, Paul Potter) and possible (strong history but not confirmed by blood tests) cases in the rural Eastern Cape (personal communication, Michael Levin).

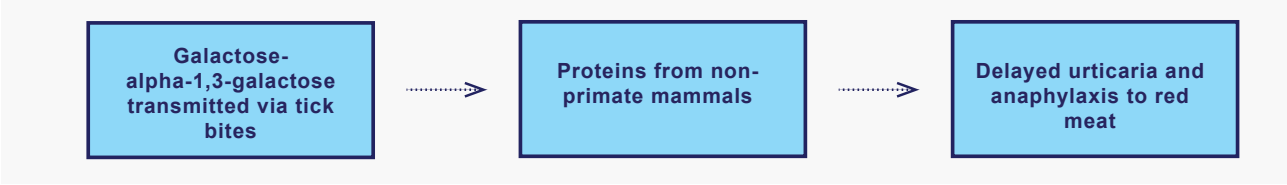

Figure 1: Pathogenesis of delayed reaction to meat

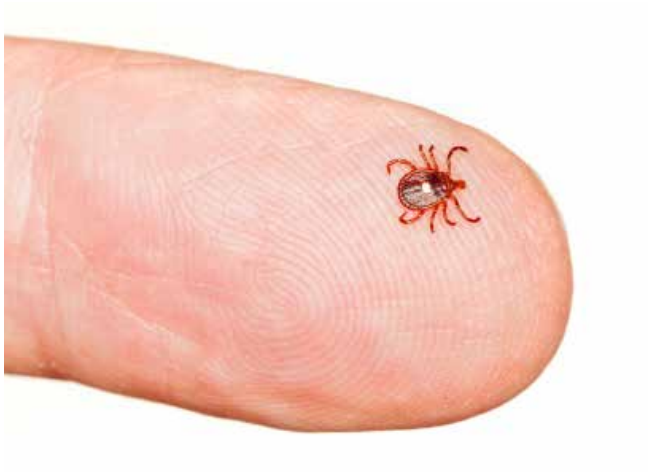

Figure 2: The lone star tick (Ixodes ricinus)

Patients with anaphylaxis to red meat due to alpha-gal sensitisation typically present three to six hours after ingestion, which is a far longer interval than classical IgE-mediated reactions. Because of this delay in symptoms, the allergy often goes undiagnosed for some time or is ascribed to idiopathic anaphylaxis before the pattern is recognised. Other nuances of this type of reaction are that dose, temporal relation to tick bites and fatty content of the meat appear to influence the allergic reaction.[2,3] Frequently, a small amount of mammalian meat is tolerated, but larger amounts lead to a reaction; the more meat that is consumed, the more severe the reaction tends to be. Reactions to red meat and even dairy are more easily elicited if the patient has recently had a tick bite (in the preceding one to four weeks). The IgE to alpha-gal can decrease over time but the trend can be reversed by recent tick bites. It also seems that fattier meats provoke episodes more consistently and more severely.

The reason for the characteristic delay in the presentation is poorly understood. Given the fact that the lipid content of the meat influences the reaction, it may be that lipid absorption is a rate-limiting step in the delay.[3] Chylomicrons may be involved in transporting alpha-gal antigens from the gut via mesenteric lymph nodes to the circulation, and fats ultimately enter the bloodstream three to four hours after a meal. This is a possible explanation for the delay of three hours before symptoms tend to occur.

The delayed anaphylaxis syndrome to mammalian meat caused by alpha-gal sensitisation differs from the 'pork-cat syndrome', in which patients develop an IgE to cat serum albumin (Fel d 2) that cross-reacts with porcine albumin. In the pork-cat syndrome patients can develop a severe allergic reaction on consuming pork, but usually within 45 minutes to an hour after consumption.[11,12]

ALPHA-GAL SENSITISATION AND ANAPHYLAXIS TO CETUXIMAB

The concept of the antibody to alpha-gal came to light because of a regional clustering of reactions to cetuximab in the United States.[13] Cetuximab is a monoclonal antibody produced in a mouse cell line. Unlike the cross-reactivity syndrome with mammalian meats, the reaction to cetuximab tends to be immediate and often on first exposure. Such hypersensitivity reactions were reported in up to 20 per cent of people using cetuximab in Tennessee or North Carolina,[13] and research has shown that the reactions were caused by pre-existing antibodies to the alpha-gal oligosaccharide on the Fab portion of cetuximab.[14] The distribution of the pre-existing antibodies was noted to correlate with areas with the highest prevalence of Rocky Mountain Spotted Fever, which led to more detailed research into tick bites as an associated factor. A rise in IgE to alpha-gal was demonstrated after tick bites,[8] which led to the finding that tick bites were the original source of sensitisation to alpha-gal.

ALPHA-GAL SENSITISATION AND REACTIONS TO MILK

Apart from being found in meat, alpha-gal is also found in mammalian milk, including cow's milk and goat's milk.[3] It is possible to have an allergy to the alpha-gal component of milk rather than the classical protein component. This entity should be considered in late-onset milk allergy in subjects over the age of five years as an alternative to cow's milk protein allergy. However, this has, to date, been poorly described and the prevalence of this type of milk allergy is unknown.

CONCLUSION

Allergy to mammalian meat secondary to alpha-gal sensitisation is a newly understood food allergy with increasing case reports worldwide. Although there is evidence of alpha-gal sensitisation in Africa, previous reports of meat allergy have been rare there. This case report demonstrates typical features of 'midnight anaphylaxis' with strongly positive allergy tests to alpha-gal. Increased awareness of the characteristic features of this type of allergy will lead to more astute diagnosis and more precise management of cases that may previously have been ascribed to idiopathic anaphylaxis.

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CPD QUESTIONNAIRE

Earn 3 CPD points after you have read the journal by completing the following questionnaire online on the ALLSA website at www.allergysa.org. To earn points you need to log in to the member section to access the questionnaire (contact ALLSA office if you do not know your user name and password). There is only one correct answer and you will have only two opportunities to submit the questionnaire, so please check answers carefully. A pass of 70% or higher is required to gain 3 points.

ADVANCES IN THE LABORATORY DIAGNOSIS OF FOOD ALLERGY

1. *True or False:* Pollen-food syndrome is usually caused by IgE antibodies to cross-reactive components.
2. *True or False:* Sensitisation to the peanut allergen component Ara h 8 is most commonly associated with anaphylaxis.
3. *True or False:* The wheat allergen component omega-5-gliadin is rarely associated with symptomatic wheat allergy.
4. *Choose the correct answer:* IgE sensitisation to the following allergen component may be associated with seafood allergy:
   a. PR-10;
   b. Parvalbumin;
   c. Apha-gal;
   d. Lysozyme.

ADVANCES IN THE DIETARY MANAGEMENT OF FOOD ALLERGY

5. *True or False:* A 2 week elimination diet always leads to symptom improvement in children with non-IgE-mediated gut allergies.
6. *True or False:* A maternal elimination diet is not usually required for FPIES.
7. *True or False:* A four food elimination diet (milk, egg, wheat and soya) leads to better symptom improvement in children with EoE.
8. *Choose the correct answer:* Challenges dose for food protein for FPIES are the following?
   i. 0.5 g and 1 g/kg;
   j. 3 g as total dose;
   k. 0.15-0.3 g/kg;
   l. Depends on the dose the child reacted to.

ORAL IMMUNOTHERAPY FOR FOOD ALLERGY

5. *True or False:* Oral immunotherapy has superior safety profile compared to sublingual and epicutaneous immunotherapy?
6. *True or False:* Optimal maintenance dose, frequency of dosing and duration of treatment have not been determined for oral immunotherapy.
7. *True or False:* Baked milk and egg diets induce humoral and cellular changes similar to food OIT.
8. *Choose the correct answer:* Which statement describes OIT most accurately?
   a. OIT has been shown to induce permanent oral tolerance;
   b. The outcomes of OIT are not influenced by baseline food-specific IgE antibody levels;
   c. Desensitisation during OIT is temporary and depends on the continued, regular intake of food;
   d. OIT is not associated with systemic adverse reactions;
   e. EoE is not a known complication of OIT.

"MIDNIGHT ANAPHYLAXIS" TO RED MEAT IN PATIENTS WITH ALPHA-GAL SENSITISATION: A RECENT DISCOVERY IN THE FOOD ALLERGY WORLD AND A CASE REPORT FROM SOUTH AFRICA

9. *True or False:* Alpha-gal allergy is a reaction to a meat protein in mammalian meat.
10. *True or False:* The most common source of sensitisation to alpha-gal is via tick bites.
11. *True or False:* Because of alpha-gal sensitisation, patients can have an immediate type IgE-mediated reaction (within minutes to hours) to cetuximab.
12. *True or False:* Alpha-gal allergy can lead to reactions to milk of non-primate mammals.
13. *Choose the correct answer:* The mechanism of alpha-gal allergy to mammalian meat is:
    a. Delayed type cell-mediated reaction with symptoms 3-6 hours after meat ingestion;
    b. Delayed type IgE-mediated reaction with symptoms 3-6 hours after meat ingestion;
    c. Immediate type IgE-mediated reaction with symptoms within minutes to 2 hours after meat ingestion;
    d. Mixed IgE and non IgE reaction.

Ethics

FOOD ALLERGY: A HUMAN RIGHTS ISSUE?

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INTRODUCTION: WHAT ARE HUMAN RIGHTS?

'Human rights are entitlements people can claim relating to their basic needs because they are human.'[1] The original conception of human rights was to protect individuals from abuse by the state, and so they were referred to as 'first-generation' rights. These rights included civil and political rights, such as freedom of speech, freedom to vote and choose political associations, and freedom of movement. Socio-economic rights were referred to as 'second-generation' rights. However, nowadays all types of rights are seen as equally important and so these classifications have fallen away. Human rights are considered to be universal, even though cultural differences exist in society.[1]

A *positive* right refers to a right 'to receive a particular good or service from others', whereas a *negative* right is 'a right to be free from some action by others'.[2] A positive right implies that someone has an obligation to do something for the person receiving the right, whereas a negative right means that a person has to desist from doing something.

The responsibility to ensure that human rights are upheld, rests with the state. According to London,[1] the onus rests on the state to meet its obligations in the following ways:

- It must *respect* the rights of its citizens;
- It must *protect* people's rights;
- It must *fulfil* rights by taking action.
- It must *promote* people's rights and enable their access to rights.

CAN THERE BE A RIGHT TO HEALTH?

The World Health Organisation (WHO) defines health as follows: 'Health is a state of complete physical, mental and social wellbeing and not merely the absence of disease or infirmity.'[3] In order to realise the right to health of its citizens, the state has to ensure that public healthcare facilities are available and functioning properly and that other services are available and accessible, obviously within its available resources. The right to health does not equate to the right to be healthy, as this is determined by other factors, such as genetics.[1]

The South African Constitution (1996) defines certain health-related rights, such as the right to have access to healthcare services, including reproductive rights, and the right to have access to emergency healthcare. It also outlines the provision of the social determinants of health, such as adequate housing, sufficient food and water, and social security. Children have the right to basic nutrition, shelter, basic healthcare services and social services.[4]

The Patients' Rights Charter lists the rights of patients accessing healthcare in South Africa. The Charter states that these rights entail certain responsibilities, such as respecting the rights of others.[5]

CAN RIGHTS BE ABSOLUTE?

Beauchamp and Childress argue that some rights, such as the right to choose one's religion, may be seen as absolute, but, generally speaking, rights have *prima facie* claims only.[2] This means that the right should be fulfilled unless there is another right that weighs more heavily at that specific time. In other words, rights can never be so powerful that they cannot be superseded by other rights or another's rights. A distinction is made between *violating* and *infringing* a person's right: 'Violation refers to an unjustified action *against* a right, whereas infringement refers to a justified action *overriding* a right.'[2]

Individuals' rights may be limited in the public interest during pandemics or outbreaks of highly infectious diseases. Beauchamp and Childress cite the example of a severe outbreak of disease where the state may override an individual's right to refuse vaccination to prevent the spread of that disease. However, they also make the point that careful consideration must be given to the individual's rights, which must not summarily be overridden in the community's interests.[2] Examples of limitations of individuals' rights in the public interest include the Severe Acute Respiratory Syndrome (SARS) outbreak in 2002–2003 that started in southern China and spread to other countries in Asia and then to Canada and North America, and the more recent outbreak of Ebola in West Africa. In South Africa, patients with extensive drug-resistant (XDR) tuberculosis were confined to a hospital against their wishes by a court order, after the two judges hearing the case ruled that it could be justified in the public interest.[6] Section 26 of the Bill of Rights permits the limitation of individual rights, provided the limitations are 'reasonable and justifiable in an open and democratic society'.[6,7]

THE FOOD-ALLERGIC INDIVIDUAL'S RIGHTS: AIR TRAVELLERS

Can a person at risk of severe food allergy demand that his or her rights override those of other, non-allergic, people, in order to reduce exposure to the offending allergen? Scenarios that come to mind are exposure to the airborne peanut allergen on aeroplanes, and exposure to peanuts,

dairy and egg in a school environment.

To what rights are airline passengers with severe food allergies entitled? In other words, if a passenger has a severe peanut allergy, can the airline be compelled to refrain from serving peanuts to other passengers? According to the Allergy Law Project (ALP) in the United States, there are no federal regulations that force airlines to make special arrangements for peanut-allergic patients.[8] The law in the United States that makes provision for people with disabilities, the Americans with Disabilities Act (ADA), does not apply to airline passengers, nor do the provisions under section 504 of the Rehabilitation Act of 1973, although both do apply to airports. Airlines therefore determine their own policies regarding nut-allergic passengers. The Federal Aviation Administration (FAA) has a circular providing advice to passengers and airlines as to how to prevent and manage severe allergic reactions, of which peanuts pose the greatest risk.

The ALP cites the case of Alisa Gleason, who flew on a United Airlines flight from Florida to Chicago in 2011. As Ms Gleason suffers from life-threatening peanut allergy, she asked airline employees to request that other passengers on the flight refrain from eating peanuts, which they agreed to do. However, the air crew refused to make the announcement, and Ms Gleason suffered an anaphylactic reaction as a result of another passenger eating peanuts a few rows behind her. There was a poor response to her medication and the aeroplane had to make an emergency landing in Missouri. Ms Gleason required intensive care for two days and subsequently sued United Airlines for negligence, emotional distress and breach of contract, but was unsuccessful under legislation protecting airlines from being sued in the United States.[8]

South African Airways has a section on medical clearance and treatment on its website. Regarding patients with peanut and other nut allergies, the following is stated: 'If you have any allergies, please bring it to the attention of our reservations department. In the event that you suffer from a severe allergy, you are required to bring your own emergency medication, e.g. Epipen.'[9]

British Airways has extensive guidance for travellers with severe allergies and will not serve nut-containing snacks on an aircraft if it has been informed that a passenger has a severe peanut allergy.[10]

Should the food-allergic air traveller be able to claim the right to travel in an allergen-free aircraft? The risk of allergic reactions on airlines is not known, but a 2008 survey of food-allergic air travellers reported that nine per cent of 471 people had experienced allergic reactions during a flight, the majority of which were due to peanuts.[11] Most of these reactions were not severe and were self-managed with antihistamines, but six passengers required emergency department treatment after landing. This suggests that it would be difficult to demand a complete ban on peanuts during flights, and that severe food-allergic individuals should carry an adrenaline auto-injector together with a doctor's letter and a written anaphylaxis plan.

THE FOOD-ALLERGIC CHILD'S RIGHTS IN CHILDCARE, PRESCHOOL AND SCHOOL

Severe food allergy affects children predominantly. The prevalence of allergic reactions to different foods varies according to the child's age. Children younger than four years may have allergic reactions to dairy and eggs in addition to peanuts and tree nuts, and these food allergens are particularly difficult to avoid.[12] It has been estimated that more than 60 per cent of first-onset allergic reactions in children occur at school, making potentially life-threatening allergic reactions at school a significant public health risk.[12] Behrmann cited a 2001 survey of elementary schools in the United States in which more than half of the schools reported having ten or more learners who were known to have allergic problems.[13] There are no data regarding the incidence of severe food allergic reactions in South Africa, although the prevalence of food allergy appears to be on the increase[14] and one would therefore expect the same to apply to severe allergic food reactions.

What are the rights of allergic children in a preschool or school environment? The 'Act to Protect Anaphylactic Pupils' or 'Sabrina's Law' in Canada (eventually signed into law in 2006 after a fatal anaphylactic reaction at a school in 2003) and similar legislation in other countries address the availability of adrenaline auto-injectors at school and mandate the training of teachers or other school personnel in the management of allergic emergencies.[15,16]

In Canada in 2014, the mother of a six-year-old girl who is severely allergic to dairy and eggs accused the school where she enrolled her daughter of violating her child's human rights because they were not prepared to create a dairy- and egg-free environment for her. The daughter had previously had nine acute anaphylactic reactions after exposure to eggs and dairy.[17] The school subsequently instituted measures to ban eggs and dairy from the child's classroom, and created an allergy management plan for the school. The following question was posed to the public via an online forum: 'Should allergy protection in schools be a human right?'[18] Of a total of 1 714 votes, 72.9% voted No, 20.48% voted Yes and 7.23% were uncertain.

What is the situation regarding learners with severe food allergy in South Africa? In a recently published online commentary, two attorneys with the Equal Education Law Centre cite the cases of Tariq and Jesmine, who both suffer from severe food allergies.[19] Tariq, a Grade R learner, suffers from a potentially life-threatening peanut allergy. Tariq's mother requested that his school implement measures to minimise the risk of Tariq being exposed to

peanuts and to keep injectable adrenaline at the school for use in the event of an anaphylactic reaction, but the school refused both requests. Jesmine also has a potentially life-threatening peanut allergy, and her school took steps to accommodate her. However, a fellow-learner discovered that Jesmine is peanut-allergic, and began teasing her and bullying her, even throwing peanuts at her. Instead of being understanding, this learner's parents were hostile when approached by Jesmine's parents, and demanded that her parents remove Jesmine from the school.[19]

The learner suffering from severe food allergy has the right to be educated in a safe learning environment, but this must be balanced against the rights of non-food-allergic children.[13] The food-allergic child also has the right to learn in a setting free from bullying, discrimination and harassment.[13] Experts advise that care should be exercised to prevent the isolation of the food-allergic child from other children.

Food allergy policies in schools need to deal with two issues:

- the management of an emergency situation (anaphylaxis), and
- the prevention of exposure to and/or accidental ingestion of a food allergen.[12,13]

Regarding the prevention of exposure to food allergens, the solution does not lie in completely banning food allergens such as peanuts, eggs and dairy from schools or childcare facilities. Although this may well reduce allergen exposure, it infringes other (non-food-allergic) children's rights, and may result in stigmatisation of the food-allergic child. Prevention of exposure to food allergens may be achieved by strict policies that forbid any sharing of food or food containers between children, and the creation of 'allergen-free' areas in canteens or classes.[12,13]

CONCLUSION

Severe food allergies are potentially life-threatening and food allergy sufferers have the right to a safe environment, whether this be at school or in other environments such as aeroplanes. They also have the right to emergency treatment, and this implies that schools and airlines should provide access to injectable adrenaline.

How does one balance the food allergy sufferer's right to a safe environment with the rights of others who do not suffer from food allergies, and who may be inconvenienced or put to excessive expense by not being able to eat certain foods in an environment that has been proclaimed allergy-free? This situation frequently creates conflict between families, and we wish to avoid confrontational and adversarial relationships between these groups. We need to create awareness about severe food allergies. We also need to establish guidelines for childcare and school environments, and advocate for South African legislative framework that deals with these problems.

The Allergy Society of South Africa should engage with the Equal Education Law Centre and patient advocacy groups to promote discussion about developing national policies to deal with the prevention and management of severe allergic disorders, particularly in schools. This would also be an ideal project for the newly formed Allergy Foundation of South Africa (AFSA) to take forward as an important advocacy task.

DECLARATION OF CONFLICT OF INTEREST

The author declares no conflict of interest with respect to the contents of this article.

This article has been reviewed.

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WORK-RELATED ASTHMA AMONG WORKERS IN THE WOOD-PROCESSING INDUSTRY: A REVIEW

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ABSTRACT

Various studies, including some in Africa, have reported an association between occupational exposure to wood dust and known probable asthma. Globally, the prevalence of asthma in woodworkers is between 5.6% and 18%; in Africa it is between 3% and 7%. This review focuses on epidemiological evidence from studies performed around the world to interrogate the evidence for the association between the exposure to wood dust and asthma. The review confirms a positive association between occupational exposure to wood dust and asthma. However, it has identified some limitations in the literature that relate to variable diagnostic criteria and epidemiological definitions for asthma: a lack of objective markers of asthma such as non-specific challenge tests and other inflammatory markers as well as markers for allergic sensitisation; understanding the pathophysiological mechanisms involved in the causation of asthma; limited number of studies of other agents present in wood dust such as endotoxins, glucans, terpenes and wood dust allergens; and the limited number of epidemiological studies investigating the dose–response relationships for allergens and other agents causing rhinitis and asthma among workers exposed to wood dust. These issues need to be addressed in future studies contemplating further investigation in this field.

This article has been peer reviewed.

INTRODUCTION

Wood is among the most important natural resources in the world and annually at least 1 700 million cubic metres are collated for industrial use.[1] Worldwide 12 000 tree species exist, and more than 1 000 of these are used for commercial purposes.[2] More than 52 types of wood species are grown in Mozambique.[3] The National Institute of Statistics (INE) (2011) estimated that at least 5 500 people are employed in 506 companies in the formal sector in Mozambique. The number of workers and companies in the informal sector is not captured by the INE estimates and is unknown, but is likely to be higher than that in the formal sector. This review was undertaken to better understand the respiratory health risks associated with exposure to wood dust in order to develop preventive strategies to reduce these risks.

WOOD PROCESSING AND HIGH-RISK WORK PROCESSES

The major wood-working processes are debarking, sawing, sanding, milling, lathing, drilling, veneer cutting, chipping and mechanical defibrating (Figure 1-4). From the tree-felling stage onwards through the various stages of woodworking and manufacturing processes, workers are exposed to airborne dust of different particle sizes, concentrations and compositions. Sawing and sanding both shatter lignified wood cells and break out whole cells and groups of cells (chips).[4] With increased cell shattering finer dust particles are produced. Sawing and milling are mixed cell shattering and chip-forming processes, whereas sanding is almost exclusively cell shattering. In hardwoods, the cells are tightly bound, resulting in more shattering and more dust. Similarly, dry wood leads to more dust formation. Softwood particles are more fibrous and usually larger and as a result less capable of becoming airborne.[4] Owing to their damp consistency, fungal or bacterial contamination occurs on a large scale when green or fresh wood is processed.

Considerably high heat generation during sawing, machining and sanding may change the chemical composition of wood dust. It has been reported that hardwoods give rise to finer airborne dust at a lower rate during sanding than softwoods, but that the total amount of airborne dust produced depends only on the total mass of wood removed, and not on the type of wood.[4]

Besides exposure to wood dust itself, wood workers are potentially exposed to various chemicals used in the different stages of the production process in the furniture industry, including glues (during assembling), dyes, solvents, dryers (in the finishing stage for painting), varnishes (in the finishing stage for polishing) and hardeners.

Figure 1: Carving and sawing wood

Figure 2: Drilling operations

Figure 3: Planing wood

Figure 4: Machine cleaning

CONSTITUENTS OF WOOD AND WOOD DUST

Wood is the hard fibrous substance composed mostly of the stem and branches of a tree or shrub, and covered by the bark. The inner core of the wood is referred to as 'heartwood' and the outer layer is called 'sapwood'. For industrial purposes, wood is classified into two types: hardwoods and softwoods. Softwoods are derived from coniferous trees (botanically named as *Gymnospermae* with exposed seeds), whereas hardwoods are derived from deciduous trees (botanically named as *Angiospermae* with encapsulated seeds).[4]

The major component (about 95% by weight) of wood is cellulose, hemicellulose and lignin.[2] Cellulose, which is built up exclusively of D Glucose units joined by β (1–>4) glycosidic linkages, is the major component (40–50%) of both hardwood and softwood. The remaining 5% comprises numerous other high and low molecular weight organic and inorganic compounds, including proteins, which can be extracted ('wood extractives'). These low molecular compounds include terpenes, terpene derivatives such as abietic acid, phenolic compounds, tannins, stilbenes, flavonoids and glycosides, many with known sensitising and irritative properties.[2]

Dust generated from wood processing is a heterogeneous mixture of inorganic and organic particles – wood fragments, viable and non-viable microorganisms, endotoxins, glucans, allergens, or mycotoxins – which are all potentially hazardous upon inhalation.[1]

EXPOSURE AND CAUSATIVE AGENTS

Furniture workers are exposed to several sensitisers or irritants including wood dust, 'wood extracts' (terpenes, terpene derivatives such as abietic acid and plicatic acid), endotoxins, glucans, isocyanate vapours and other chemicals (including glues, dyes, varnishes, paints, solvents and hardeners).[5,6]

Exposure assessment studies have demonstrated that workers in the wood-processing industry are exposed to variable concentrations of hazardous agents (microorganisms, endotoxins, glucans and terpenes) associated with wood dust. The exposure summary estimates reported in these studies have wide ranges, namely, wood dust particulate (0.05–12.0 mg/m^3, microorganisms (1.696–2,000 cfu/m^3 × 10^3), endotoxins (0.4–6.93 ng/m^3), glucans (3.5–18.9 ng/m^3) and terpenes (0.23–158 mg m^3).

As expected, dry mills had higher dust particulate levels than wet mills. In six of the 11 exposure studies evaluated[1,7,8,9,10,11] the threshold limit values for wood dust particulate recommended by ACGIH (2013) of 0.5 mg/m^3 for Western red cedar and 1 mg/m^3 for all other species was exceeded. There are currently no international exposure

standards for other agents such as the glucans, endotoxins, terpenes and wood allergens found in wood dust.

AIRWAY DISEASE AND PATHOPHYSIOLOGICAL MECHANISMS

Exposure to wood dust and other causative agents associated with wood dust has long been associated with a variety of adverse health effects of the upper and lower airways. Health effects associated with exposure to wood dust and associated agents present in the upper airways include rhinitis, whereas in the lower airways it results in occupational asthma and general lung function deficits.[12]

The mechanisms for wood dust-causing asthma are far from fully understood.[13] For Western red cedar, a unique constituent, plicatic acid, has been shown to be a causal factor, and both immunological and non-immunological mechanisms are involved. For other types of wood no clear causal agent has consistently been found. Specific IgE sensitisation has been reported to be responsible for asthma in woodworkers; however, Type 1 allergy is not suspected to be a major cause of wood dust-induced asthma. Apart from IgE-mediated sensitisation, several other mechanisms, including irritative mechanisms, have been reported.

Animal studies have shown that wood components, such as the major constituent in pine resin – abietic acid – causes direct toxicity via lytic damage to alveolar, tracheal and bronchial epithelial cells. Wood-dust extracts from both hard and soft woods are able to induce the release of pro-inflammatory mediators from macrophages, express and induce the release of inflammatory mediators in human epithelial cell line, and modulate the expression of cytokines and chemokines.[13,24]

The oxidative products of monoterpenes or abietic acid can also cause airway inflammation through immune reactions. This was supported in an experimental study, which showed increased alveolar cell concentration, mainly macrophages in bronchoalveolar lavage (BAL) after exposure to concentrations of 450 ng/m^3.[13] Pylkkänen et al[14] studied the capacity of wood dusts to induce the production of reactive oxygen species (ROS) and caspase-3 activity in human bronchial epithelial cells. Dust from three wood species – pine, birch and oak – induced (ROS production. The study concluded that exposure to external particles may induce cellular apoptosis and necrosis of epithelial cells, which again may lead to shedding of the bronchial mucosa, to bronchial hyper-reactivity, and the exacerbation of asthma.

EPIDEMIOLOGY OF ALLERGIC SENSITISATION AND ASTHMA ASSOCIATED WITH WOOD DUST

The association between exposure to wood dust and asthmatic symptoms has been documented previously.[15]

A meta-analysis of wood-dust exposure and risk of asthma showed that the pooled relative risk (RR) of asthma among workers exposed to wood dust was 1.53 (95% CI 1.25–1.87). When the analysis was restricted to studies carried out on Caucasian populations, the pooled RR was 1.59 (95% CI 1.26–2.00), whereas the pooled RR of studies on Asian populations was 1.15 (95% CI 0.92–1.44).[16]

Table I reports on various epidemiological studies of asthma and other respiratory symptoms and the definitions used in these studies. While the prevalence of asthma in woodworkers globally based on various different definitions is between 5.6% and 18%, the prevalence in Africa appears to be lower: between 3% and 7%.[4,17,18,19] The prevalence of rhinitis appears to be much higher ranging, at between 16% and 33%.

The prevalence of asthma appears to be higher in dry sawmills (11.8%) compared to green sawmills (7.5%); however, the prevalence of symptoms appears to be higher in the green sawmills.[17] Woods species such as pine, mahogany, African teak, red cedar and imbuia are associated with a higher prevalence of asthma and rhinitis. Furthermore, fibre- and chipboards and mansonia are also associated with a high prevalence of rhinitis.

HOST RISK FACTORS

A. GENETICS

A meta-analysis of wood-dust exposure and risk of asthma conducted by Perez-Rios[16] demonstrated a higher risk of asthma among European and American studies than among Asian studies, indicating possible genetic factors in the development of asthma. This suggests the existence of interactions between genetic susceptibility to asthma and environmental factors. Several genetic factors are probably responsible for allergen sensitisation, which is determined by HLA genotype, including sensitisation to occupational agents.[27]

B. ATOPY

Schlünssen at al,[15] in their Danish study, demonstrated that asthma was associated with atopy, using clinical endpoints such asthma symptoms; OR = 4.2 (95% CI = 2.4–7.7) as well as asymptomatic bronchial hyper-responsiveness; OR = 7.4 (95% CI = 2.8–19.7).

C. UPPER AIRWAY SYMPTOMS

Occupational rhino-conjunctivitis often precedes the onset of IgE-mediated occupational asthma and it should be considered an important risk factor for the future development of occupational asthma, especially when high molecular weight agents are involved.[27] Occupational rhinitis is associated with an increased risk of asthma, although the proportion of subjects with occupational rhinitis who will develop occupational asthma remains uncertain.[28]

TABLE I: EPIDEMIOLOGICAL STUDIES OF WOOD WORKERS

TYPE OF WORKFORCE (AUTHOR, COUNTRY)	DEPARTMENTS	N	OUTCOME MEASURE	WOODS IMPLICATED	PREVALENCE	DEFINITION OF ASTHMA AND RHINITIS
Sawmill plants (Ugheoke, Nigeria)[19]	Not stated	228	Respiratory symptoms	NR	Symptoms: Cough 35.1% Breathlessness 8.3% Wheezing 3.1%	NR
Furniture industry (Publio, Brazil)[20]	Furniture, painting and finishing	499	Respiratory symptoms	NR	Asthma 5.6% Rhinitis 16%	Asthma: Wheeze and attack of shortness of breath. Rhinitis: Nasal congestion, rhinorrhoea and sneezing.
Carpentry, sawmill plant (Aguwa et al, Nigeria)[21]	Carpentry, sawmill, carving and timber marketing	591	Occupational asthma and rhinitis	Mahogany, iroko, cedar and mansonia	Asthma 6.3% Rhinitis 78%	Asthma: Wheezing and breathlessness. Rhinitis: One or more of the following – sneezing, rhinorrhoea and/or nasal/pharyngeal itching.
Sawmill (Fox, South Africa)[8]	Dry mill – stress grading Wet mill – green chain, stacking and kilns	392	Asthma	Pine	Asthma: Definite 0.5% Probable 2.6% Possible 10.2%	Definite: Positive questionnaire and ≥15% improvement in FEV_1 post-salbutamol or on return from leave. Probable: Positive questionnaire and >10% and <15% improvement in FEV_1 post-salbutamol or on return from leave or doctor diagnosis of asthma. Possible: Positive questionnaire (except doctor-diagnosed asthma).
Furniture plant (Arbak et al, Turkey)[22]	Furniture decoration	64	Respiratory symptoms and peak expiratory flow rate	Fir tree (*Aberia mulleriana*)	Symptoms: Nasal 34.4% Cough 23.4 % Shortness of breath 18.8 % Chest tightness 15.6% Wheezing 14.1%	NR
Plywood and wood-working plant (Borm et al, Indonesia)[23]	Veneer preparation, veneer peeling, veneer drying, assembly, grading, composer and finishing	982	Respiratory symptoms, lung function, and nasal cellularity	Meranti	Symptoms: Cough 23.5 % Shortness of breath 4.1% Wheezing 1.6%	NR
Furniture factory (Milanowski et al, Poland)[6]	Sawing, trimming, sanding, plaining, and varnishing workshop	48	Work-related symptoms	Fibre- and chipboards	Symptoms: Cough 52.1% Shortness of breath 12.5% Asthma 6.2% Rhinitis 33.3%	Asthma: Specific inhalation challenge test. Rhinitis: Rhinorrhoea and nasal congestion.
Furniture factory (Schlünssen et al, Denmark)[25]	Sanding, cutting, assembling and packing	2507	Respiratory symptoms and lung function	Pinewood, particle board, hardwood, beech medium-density fibreboard, and mixed.	Asthma 6.3% Rhinitis 19.2%	'Yes' to: • At least one group A question (Have you been told by a doctor that you have asthma? Do you have asthma? Have you ever had asthma? Do you ever had wheeze?) **AND** • Two or more group B questions (Do you ever have chest tightness? Do you wake in the night with chest tightness? Do you wake in the night wheezing?).

TYPE OF WORKFORCE (AUTHOR, COUNTRY)	DEPARTMENTS	N	OUTCOME MEASURE	WOODS IMPLICATED	PREVALENCE	DEFINITION OF ASTHMA AND RHINITIS
Small-scale wood industries (Rongo et al, Tanzania)[9]	Planing, sawing, carving, and drilling	546	Respiratory symptoms and dust exposure	African teak, mahogany, bloodwood, East African camphor, East African afzelia.	Asthma 5–7%	Asthma: Asthmatic symptoms of shortness of breath with wheezing.
Sawmill (Douwes et al, New Zealand)[18]	Administration, green mill, planer mill, remanufacturing and moulding	772	Asthma and other respiratory symptoms	Pine	Symptoms: Wheezing 29.6% Asthma: 18%	Asthma: Awoken by shortness of breath in past 12 months or asthma attack in past 12 months or current asthma medication.
Sawmill (Mandryk et al, Australia)[17]	Three green mills and two dry mills	87	Work-related symptoms	Eucalyptus	Symptoms in dry mill: Asthma 11.8% Cough 29.4% Breathlessness 8.8% Wheezing 8.8% Chest tightness 11.8% Symptoms in green mill: Asthma 7.5 % Cough 50.9% Breathlessness 24.5 % Wheezing 24.5% Chest tightness 28.3%	Asthma-like symptoms.
Furniture industry (Talini et al, Italy)[5]	Furniture manufacturing, spray painting and assembling	296	Asthma-like symptoms, bronchial hyper-responsiveness	Pine and beech	Asthma 7.7%	Asthma: Symptoms such as chronic cough, wheeze, attack of shortness of breath; Non-specific bronchial hyper-reactivity: PD20 <0.8 mg/ml.
Wood-processing factories (Alwis, Australia)[4]	Two logging sites, four sawmills, one major wood-chipping operation and five joineries	195	Symptoms	Eucalyptus, Pinus radiate, meranti (Shorea spp), Western red cedar (Thuja plicata), brushbox (Tristania conferata)	Symptoms: Breathlessness 17.4% Wheezing 22.6% Chest tightness 27.2% Asthma 10.8%	NR
Furniture plant (Shamssain, South Africa)[26]	Not stated	145	Pulmonary function and symptoms	Pine and medium-density board fibre wood	Symptoms: Nasal 49% Cough 43% Phlegm 15%	NR

*NR: Not reported.

D. SMOKING

The relationship between smoking and occupational asthma is complex and contradictory. However, various studies have shown that smokers are at increased risk of developing sensitisation, although not necessarily asthma, due to agents that cause asthma through an IgE-mediated mechanism. Schlünssen,[15] in her study of asthma among atopic and non-atopic woodworkers, found that smokers were more often asthmatic, with OR = 3.6 (95% CI = 1.7–7.6) for work-related asthma symptoms and OR = 2.3 (95% CI = 1.0–5.4) for symptomatic bronchial hyper-responsiveness compared to non-smokers.

ENVIRONMENTAL RISK FACTORS

A. JOB DURATION

Aguwa et al,[21] in their study among woodworkers in south-eastern Nigeria, reported that the prevalence of occupational rhinitis and asthma among woodworkers increased with the duration of exposure. Among workers with less than two years' exposure, the prevalence of rhinitis was 8.7% and of asthma was 1.9%, whereas in workers with more than 10 years of exposure the prevalence of the rhinitis was 36.5% and that of asthma 6.5%.

Meo's[29] study among workers in small-scale wood industries found that the peak expiratory flow (PEF) in exposed workers was negatively associated with years of exposure. In workers with less than four years' exposure the PEF was 312.28 ± 23.62 ℓ/min compared to those with more than eight years, having a PEF of 177.00 ± 22.29 ℓ/min.

Shamssain et al[26] found that the prevalence of respiratory symptoms increases with the increase in the number of years of employment. Cough and nasal symptoms showed a pronounced increase with years of employment. The prevalence of cough in workers with 1–4 years of employment was 35%, whereas in workers with 9–12 years this was 66%. The prevalence of nasal symptoms in workers with 1–4 years of employment was 49% compared to workers with 9–12 years employment was 55%. The study also found that the proportion of subjects with an FEV_1/FVC ratio below 70% in the exposed group employed for 10–19 years was 56.2% compared to the 26.7% in the exposed group with less than 10 years of employment.

B. EXPOSURE LEVELS

Schlünssen and Schaumburg[15] found that symptomatic bronchial hyper-responsiveness was related to dust in a dose-dependent manner, with OR = 18.3 (2.0–170.8) when comparing the group with the highest (4.10 mg/m^3) to the lowest (0.17 mg/m^3) exposure level. The same tendency was seen for work-related asthma symptoms with OR = 6.4 (95% CI = 1.6-26.4).

Schlünssen and Schaumburg,[25] in their earlier study, reported that the prevalence of asthma and rhinitis increased with increasing of level of exposure. The prevalence of asthma in male workers exposed to wood-dust levels ranging between 0.0 mg/m^3 and 0.74 mg/m^3 was 3.9% compared to workers exposed to dust ranging between 0.74 mg/m^3 and 1.42 mg/m^3 which was 7.8%. Similarly, the prevalence of rhinitis in workers exposed to wood dust ranging between 0.0 mg/m^3 and 0.74 mg/m^3 was 19.1% compared to workers exposed to wood dust ranging between 0.74 mg/m^3 and 1.42 mg/m^3, which was 22.3%.

Mandryk et al[17] demonstrated a relationship between exposure to endotoxins and glucans and work-related symptoms in workers at three green mills and two dry mills. The mean (GM) personal inhalable endotoxins (6.61 ng/m^3) and inhalable glucans (2.63 ng/m^3) exposures were high for the green mills (1.58 ± 1.52 ng/m^3) compared with those of dry mills (0.38 ± 1.73 ng/m^3), respectively. Green-mill workers showed a strong association between personal exposure and work-related symptoms. Significant relationships were found between glucan exposure and nasal congestion (OR = 62; 95% CI: 30.79–124.85), endotoxins and nasal congestion (OR = 49; 95% CI: 24.29–98.67), when the same logistic model was adjusted for endotoxins and glucans, respectively. Similarly, glucan exposure was associated with chronic bronchitis (OR 163; 95% CI: 71.52–368.71), as were endotoxins associated with chronic bronchitis (OR = 17; 95% CI: 7.92–36.23).

In a study of respiratory symptoms and dust exposure among male workers in small-scale wood industries in Tanzania, allergic symptoms were reported more commonly in the low-exposure group with OR = 2.4 (95% CI = 1.8–3.1) and the high-exposure group with OR = 2.7 (95% CI = 1.8–4.0), compared to control groups.[9]

A study of asthma and other respiratory symptoms in workers at a New Zealand pine-processing sawmill showed that working in sawmilling was associated with an increased prevalence of asthma and cough symptoms. Asthma symptoms in the exposed workers (18%) were more common than in the general population (12.1%), with adjusted OR = 1.6 (95% CI = 1.1–2.3). Asthma was also more common in the low-exposure group (15.6%) and high-exposure groups (high exposure to 'green dust' = 20.4% and 'dry dust' = 18.8%) than in non-exposed workers (9.2%). The respective adjusted odds ratios were OR = 1.9 (95% CI = 0.7–4.9), 2.7 (95% CI = 0.9–7.6), and 2.1 (95% CI = 0.8–5.7), respectively, but these were not significant. Adjusted odds ratios for symptoms of cough were OR = 2.7 (95% CI = 1.2–6.5) for the low, OR = 5.2 (95% CI = 2.1–13.0) for the high 'green dust' and OR = 3.3 (95% CI = 1.4–7.9) for the high 'dry dust' exposure groups compared to the non-exposed group.[18]

In an investigation into the increased incidence of respiratory symptoms among female woodworkers exposed to dry wood, the cumulative incidence proportion of daily coughing and chronic bronchitis was found to be associated with baseline wood-dust exposure in a dose-dependent manner. The risk estimates for daily coughing (with reference to the lowest exposure quartile) was OR = 1.6 (95% CI = 0.6–4.3), OR = 3.2 (95% CI = 0.9–6.8) and OR = 3.8 (95% CI = 1.5–9.7), respectively, in the second and third lowest and the highest quartile. The figures for chronic bronchitis were, accordingly, OR = 2.3 (95% CI = 0.4–14.5), OR = 3.0 (95% CI = 0.5–18.7) and OR = 6.0 (95% CI = 1.2–28.8).[30]

Kespohl et al found that obeche wood from Cameroon (called *ayous*) had less allergen content compared to obeche wood from Ghana (called *wawa*).[31] Further analysis showed that the reduced allergen content in *ayous* wood could be ascribed to a reduced amount of major obeche wood allergen Trip s 1. This emphasises the importance of using the content of wood dust allergens, and not only the concentration of airborne wood dust, in estimating dose–response relationships.[2]

PREVENTION STRATEGIES

Primary prevention of occupational asthma includes reducing exposure in order to prevent the development of respiratory disease in susceptible workers. Several studies support the view that reduction is likely to be followed by a concomitant reduction in disease burden and that use of personal protective equipment is the less effective measure in the hierarchy of controls against health hazards.[32] Control of exposure can be achieved by different control measures and the hierarchical strategy commonly applied is elimination, reduction, isolation, ventilation, avoidance of exposure and personal protection.[32] The preferred measure is substitution of an agent in the work process, for instance, the substitution of woods with strong sensitising potential with less strong sensitising woods. When substitution is not possible, exposure reduction, which is achieved in practice through a combination of different interventions, is the next best approach. It is important to define a desirable reduction in exposure and exposure standards can play an important role in this process.

Several organisations and countries have set standards or drawn up recommendations for limiting wood-dust exposure. The ACGIH has proposed a level of 0.5 mg/m^3 for Western red cedar and 1 mg/m^3 for all species [American Conference of Governmental Industrial Hygienists (ACGIH), 2013]. The Swedish exposure limit is 2 mg/m^3 for all types of wood.[33] In South Africa the occupational exposure limit for wood dust is 5 mg/m^3 (http://www.labour.gov.za/DOL/legislation/regulations/occupational-health-and-safety/regulation-ohs-hazardous-chemical-substances).

The intervention study conducted in Minnesota, United States, which included a combination of engineering, administrative, and behavioural components, has demonstrated that a combination of these measures can contribute to a reduction in the level of exposure. The median dust concentration at baseline in the original study was 5.87 mg/m^3 among intervention businesses and 6.23 mg/m^3 among comparison businesses. One year later, the median dust concentrations were reduced to 4.71 mg/m^3 (a reduction of 19.8%) and 5.58 mg/m^3 (a reduction of 10.4%) from baseline in the intervention and comparison businesses, respectively.[34]

Hasle et al[35] have suggested that small enterprises have special problems that need to be considered when designing interventions for the work environment. The risk is higher and the ability to control lower due to limited human and financial resources. Tools and methods aimed at small enterprises may include different types of checklist (including both risk assessment and more action-oriented types), comprehensive health and safety management systems, and accident prevention. The most successful methods appear to be action-oriented, combining health and safety with other management goals, and based on trust and dialogue.[35]

RESEARCH GAPS

While this review confirms a positive association between occupational exposure to wood dust and asthma, it has identified some deficiencies in the literature that relate to methodological issues, including a lack of

- power due to small sample sizes, variable diagnostic criteria and epidemiological definitions for asthma;
- objective markers of asthma, including non-specific challenge tests and inflammatory markers;
- information on the actual wood species used in the production processes;
- detailed information about the concentrations of other agents present in wood dust such as endotoxins, glucans, terpenes and wood dust allergens, and
- epidemiological studies investigating the dose–response relationships for rhinitis and asthma among workers exposed to wood dust.

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DECLARATION OF CONFLICT OF INTEREST

The authors declare no conflict of interests.

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ABC of Allergy

HYPERSENSITIVITY TO SEAFOOD AND FISH

Shaunagh Emanuel & Di Hawarden

Dr Do-a-Lot's student presents his notes on seafood and fish allergy

Epidemiology

Seafood allergy occurs in about one per cent of the population and is more common in adults than in children. It tends to be a lifelong problem in most patients. It is more common in areas where there is a high consumption of fish and seafood such as Scandinavia and Australasia. Seafood allergy is an important cause of anaphylaxis.

Signs and symptoms

Signs and symptoms usually occur within minutes of contact or ingestion. They may occur in the gastrointestinal tract with nausea, abdominal cramps, bloating and diarrhoea, in the skin with flushing, urticaria and angioedema, and in the respiratory system with wheezing, cough and rhinitis. Symptoms may be mild and confined to one body system, but in severe reactions anaphylaxis may occur with multisystem involvement and cardiovascular collapse.

The allergenic proteins

We can loosely divide seafood into three main groups: fish, crustaceans and molluscs.

Fish include tuna, mackerel, salmon, yellowtail, sardines, cod, herring, anchovies, trout, haddock, eels and rays.

Crustaceans include prawns, shrimps, lobster, crayfish and crab.

Molluscs include mussels, oysters, clams, octopus and squid.

The distinction is important because the groups have distinct allergenic proteins. This means that if a patient is allergic to tuna fish, they may be able to tolerate mussels or crayfish. Within the same group the allergens are similar, so patients who are allergic to crayfish are likely to be allergic to shrimp and should avoid all crustaceans.

A seafood platter containing examples of molluscs and crustaceans

Cross-reactivity between groups may occur, but often individuals are allergic to more than one seafood group. Seafood allergenic proteins tend to be heat stable. Cooking does not typically improve tolerance. Some individuals may tolerate tinned fish but this is unpredictable. Steamed

or braaied fish may release vapours that contain minute allergenic amine particles that can cause symptoms in highly sensitive individuals. Even handling fish can cause symptoms in some sensitised individuals. This can be an occupational hazard for food handlers and chefs.

Cape Yellowtail (Seriola lalandi)

Diagnosis

A careful history is important in order to distinguish true seafood allergy from food poisoning (toxicity), sensitivity to parasites, or a reaction to preservatives consumed as part of a seafood meal.

Skin-prick tests or serum-specific immunoglobulin E (IgE) tests are helpful in diagnosis.

In some cases a food challenge test under controlled conditions (with resuscitation facilities) is indicated.

Note: a positive test for an allergen means that an individual is sensitised to that specific protein. They may, however, not be 'allergic' to it. That is: they may not express their sensitivity through clinically discernible physical symptoms or signs. This can be a confounding factor when making a diagnosis.

Management

Avoidance of the offending allergen is the only available treatment for seafood allergy.

Restaurants that serve fish and seafood are best avoided as there is a high chance of contamination in the kitchen through the use of shared cutting boards and utensils.

Special attention must be paid to products that may contain fish such as oils, sauces, dips, supplements and dog food.

Accidental exposure may result in anaphylaxis so it is important that all individuals that are allergic to seafood carry adrenaline auto-injectors. Empowering education regarding anaphylaxis recognition and treatment must be given, and patients should receive a written anaphylaxis action plan.

An adrenaline auto-injector

When patients are admitted with anaphylaxis, it is important that, on discharge, they receive: a new adrenaline auto-injector, a written anaphylaxis action plan, a referral to an allergy doctor, and an identification bracelet that states clearly: 'Seafood allergy: give adrenaline'.

Medical identification bracelet

Seafood and iodine

Seafood allergy is not related to iodine allergy, or to sensitivity to radio-contrast media.

Other causes of hypersensitivity reactions following the consumption of fish and seafood

Scromboid fish poisoning

Bacteria in the flesh of fish that has not been adequately refrigerated multiply and break down the fish protein, ultimately releasing histamine. Histamine is a powerful mediator of inflammation. When the histamine-rich fish is ingested, the patient experiences symptoms very similar to those experienced in an allergic reaction, with flushing, urticaria, nausea, palpitations, headache, vomiting and abdominal cramps. In severe cases dizziness and a drop in blood pressure may occur. This is not an IgE-mediated reaction, although it looks very much like one clinically. Game fish such as yellowtail and tuna that contain a high content of red meat that turns brown when cooked are often implicated. Affected fish has a metallic or peppery taste, and symptoms typically commence within 30 minutes of ingestion. Treatment is with antihistamines, although in severe cases that require admission to hospital for supportive care adrenaline may be administered. Testing for fish allergy will usually yield a negative result.

Anisakis simplex

This nematode is a parasitic worm that lives in the flesh of fish. It is found in most parts of the world. If fish is freshly cooked at a temperature of more than 60°C, or freshly frozen and properly cooked directly after defrosting, the parasite is destroyed. Infection occurs when fish is eaten raw, pickled or undercooked. Symptoms are typically gastrointestinal due to inflammation of the gut wall, with

nausea, vomiting and abdominal cramps. Sensitisation results in an IgE-mediated reaction. The history may be confusing as the patient will report intermittent reactions to fish ingestion, depending on the *Anisakis* content of the fish in question. The diagnosis can be made by testing serum for specific IgE to *Anisakis*.

Ciguatera poisoning

This condition is caused by eating fish that has been contaminated by toxins that are produced by algae present in the sea in the tropics. We see this condition on our African east coast, where the sea is warm and there is an abundance of large reef fish.

Paralytic shellfish poisoning and diarrhoetic shellfish poisoning

Toxins in algae that contaminate shellfish, in particular mussels and oysters, cause neurological symptoms when ingested.

The toxins in both the fish and shellfish in the above two conditions affect nerve endings causing tingling of the lips, tongue and throat. This may be followed by nausea, vomiting, headache, fever and muscle aches.

In severe cases cardiovascular symptoms, numbness, confusion and loss of consciousness have been described. Recovery is usually spontaneous within days or weeks with supportive treatment.

Preservatives and additives

Preservatives such as metabisulphites are sometimes used to prevent discolouration of shellfish such as prawns and crayfish. They are also found in beverages such as beer and wine, and prepared sauces that may be served with seafood. Reactions to food additives may include wheezing, gastrointestinal upset and skin rashes. It is therefore important to consider additives in the food, or the sauce or beverage accompanying it, when taking a history in a patient describing a hypersensitivity reaction following eating a seafood meal.

Preservatives and additives must be considered when seeking a cause for a hypersensitivity reaction

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Case Study

SHERBET! TWO CASES OF FOOD-ADDITIVE REACTIONS

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INTRODUCTION

Food additives are used extensively in the food industry and include thousands of natural and synthetic substances used as flavourants, colourants, preservatives, sweeteners, antioxidants and thickeners.[1]

Many patients blame food additives as the cause of a wide variety of symptoms. Early literature (pre-1990s) overestimated the prevalence of food-additive reactions as a result of poorly designed trials. Many of the cases of adverse reactions to food additives in the medical literature are anecdotal or characterised by poorly controlled challenge procedures.[2] More recent evidence suggests that additive-associated reactions are relatively rare, with a prevalence of 0.23% in a population-based study.[3,4] Relatively few food additives have been convincingly demonstrated to cause urticaria, angioedema, asthmatic reactions or anaphylaxis. Some groups, such as asthmatics with sulphite sensitivity, appear to be at higher risk of food-additive reactions.

The mechanism of reaction to several food additives is not completely understood. In very few cases, symptoms are typical of IgE-mediated reactions; several other immunological or non-immunological mechanisms may play a role, leading to a variety of presentations. This case report describes two different reactions to food additives in two different children, both occurring while eating 'sherbet'!

CASE 1

A nine-year-old girl was seen in the allergy clinic at the Red Cross War Memorial Children's Hospital for asthma, allergic rhinitis and eczema. She described an episode of hives about 20 to 30 minutes after eating yellow-coloured sherbet. She also described similar hives on two occasions within 30 minutes of eating yellow-coloured potato crisps. A panel of cellular antigen stimulation tests (CAST) to food additives showed a highly positive result to tartrazine (232 pg/ml, positive is >100 pg/ml), and a 'weakly reactive' grading to red food colourant mix (19 pg/ml, positive is >100 pg/ml). CAST tests were negative to sodium benzoate and sodium glutamate. She regularly ate red sweets/icing without a reaction, hence the weak reaction to red food colouring was not deemed to be clinically relevant. On the basis of recurrent reactions to 'yellow-coloured' foods coupled with a highly positive CAST test, a diagnosis of tartrazine sensitivity was made and she was advised to go on a tartrazine-free diet, under dietetic guidance. Interestingly, she more recently tolerated the yellow potato crisps to which she had initially reacted and, subsequently, found that these particular crisps had been reformulated to become tartrazine-free.

CASE 2

A seven-year-old girl with no previous atopic history presented at a school fair with a dramatic and unusual constellation of symptoms within minutes of eating a sachet of sherbet. The sherbet was manufactured in China but the sachet did not state the exact ingredients. The girl experienced a sudden severe pounding headache, dizziness, a feeling as if her face was going to 'burst' with pressure, and a burning sensation in her legs. Her mother noted that she also had tachycardia and immediately took her to an emergency department. By the time she was seen at the ER approximately one hour after the incident, her symptoms had almost completely abated and she was discharged without further intervention. She presented to a private practice for an allergy consultation and to rule out a food allergy to commonly allergenic food, fearing contamination of the sherbet with nuts.

A skin-prick panel to peanut, cashew, hazelnut, walnut and almond was negative. CAST tests to sodium benzoate, sodium glutamate and red and blue food colourant mixes were negative.

On the basis of the very suggestive history, a diagnosis of 'MSG-complex syndrome' was made ('Chinese restaurant syndrome') and she was counselled that normal amounts of dietary MSG would be insufficient to trigger a reaction, but that large amounts of MSG such as those found in some Chinese food may cause a symptom complex similar to the one she experienced, and were best avoided.

DISCUSSION

Only a small fraction of the thousands of agents added to our food have been associated with cutaneous or anaphylactic reactions. The above two cases demonstrate different reactions to the confectionery 'sherbet'. In South Africa, sherbet is a powder made from bicarbonate of soda,

sugar and a variety of flavourants/colourants, designed to provide a 'popping' sensation on the tongue. It is not to be confused with the American 'sherbet', which is a food of frozen fruit juice with a dairy product such as milk added. In the first of the two cases, the tartrazine added as a colourant was assessed to have been responsible for the hives associated with the sherbet, and in the second case an 'MSG-complex syndrome' was deemed to have been responsible.

REACTIONS TO TARTRAZINE

Tartrazine is a synthetic lemon-yellow azo dye derived from coal tar that is primarily used as a food colourant, also known as Yellow 5 (E102).[5,6,7] It is widely used in the making of potato crisps, jams, confectionery, drinks, and even some vitamins, medications and shampoos/cosmetics. Tartrazine is banned in Austria and Norway, but still widely available in most other areas of the world, including the United States and South Africa.[5]

The prevalence of tartrazine-induced adverse reactions is unknown, but it is thought to be less than 0.12% of the general population.[8]

Tartrazine-induced urticarial reactions have been described in various case series, though they are thought to be rare.[6,7] Other rare side-effects described with tartrazine have been bronchospasm/asthma, persistent rhinitis symptoms and an exacerbation of eczema.[9] There is insufficient evidence to support the exclusion of tartrazine from the diet of asthmatics.[10] Hyperkinesis and learning disorders in children have been attributed to the ingestion of tartrazine, but this is controversial, with no scientific backing, hence a definite conclusion cannot be drawn.[5]

REACTIONS TO MONOSODIUM GLUTAMATE (MSG)

Glutamic acid is a non-essential amino acid that is a normal constituent of food protein, constituting about 20% of dietary proteins.[1,2] When added to food in the form of a sodium, potassium or calcium salt, glutamic acid provides a unique taste and flavour-enhancing properties which enhance palatability. Glutamate is recognised by the taste receptors as a distinctive taste dubbed 'umami', a brothy, mouth-watering savoury sensation. MSG is rapidly and effectively metabolised by the intestinal mucosa and liver.

Glutamate salts are widely used in the food manufacturing and restaurant industries and flavour a variety of foods, including crackers, potato crisps, soups, frozen dinners, salad dressings, and Chinese and other Asian food. Glutamate and its salts carry the additive labels E620-625, and can be labelled as per the list in Table I.

The normal dietary intake of glutamates in the United States is around 1 g/day from naturally occurring forms, and an additional 0.5 g from added MSG. Naturally occurring high levels of glutamates are found particularly in tomato and Parmesan cheese. Normal dietary levels of MSG are deemed to be safe and MSG is generally recognised as safe by the Food and Drug Administration in the United States. However, certain people may be sensitive to MSG consumed at high levels.

TABLE I: FOOD LABELLING OF THE GLUTAMATES

FORM OF GLUTAMATE	E-NUMBER
Glutamic acid	E620
Monosodium glutamate (MSG)	E621
Monopotassium glutamate	E622
Calcium diglutamate	E623
Monoammonium glutamate	E624
Magnesium diglutamate	E625

MSG has anecdotally been associated with headaches and even some psychiatric symptoms; however, extensive research has failed to substantiate this relationship.[11–12] Associations with urticaria and asthma have been described, but these are deemed to be rare.[11–12] Large doses of MSG in excess of 3 g, especially if ingested on an empty stomach without concomitant food, may initiate the so-called 'MSG-symptom complex'.[2]

THE MSG-SYMPTOM COMPLEX ('CHINESE RESTAURANT SYNDROME')

In 1968 the first case of so-called 'Chinese restaurant syndrome' was published describing numbness at the back of the neck, general weakness and palpitations after dining in a Chinese restaurant.[13,14] The prevalence of the MSG-symptom complex is unknown; however, in 1979 Kerr et al used a National Consumer Panel to select a population-representative group and found the prevalence of MSG-symptom complex after the ingestion of high doses of MSG to be 2%.[15] Although MSG is strongly believed to be the causative factor in the so-called Chinese restaurant syndrome, an association has never been demonstrated under rigorously controlled conditions. Symptoms of the MSG-complex syndrome are described in Table II.[2,13,14]

The symptoms are self-limiting and usually abate within hours (as soon as the MSG has been metabolised), without specific intervention. Simple measures such as paracetamol may ease some of the symptoms.

TABLE II: SYMPTOMS DESCRIBED IN THE MSG-COMPLEX SYNDROME

- Flushing
- Headache
- Sweating
- Chest pain
- Sensation of facial pressure or burning
- Numbness or burning around the mouth, throat or other parts of the body
- Back pain
- Nausea
- Fatigue
- Uncommonly arrhythmias or difficulty in breathing

The pathophysiology of MSG-symptom complex remains elusive. It is definitely not an allergic reaction but, rather, it seems to be a 'chemical' reaction. The mechanism of these reactions has been proposed to involve an exaggerated sensitivity to the MSG, which is metabolised after ingestion to glutamate, a major excitatory amino acid neurotransmitter. Glutamate is also a precursor to acetylcholine, which could be responsible for some symptoms.[16] Nitric oxide production and consequent vasodilatory action has also been proposed as an associated mechanism of symptoms.[17] What is clear is that it is not a classic 'allergic reaction', therefore positive allergy tests are not required to diagnose the syndrome.

CONCLUSION

Confirmed reactions to food additives and preservatives are rare and probably overdiagnosed. The mechanism of reaction is frequently poorly understood and this has led to a lack of standardised tests to diagnose such reactions. However, food-additive reactions should be considered in cases when there are recurrent symptoms after consumption of certain processed/packaged foods, but no classical reaction to the pure or fresh form of the foods. Patients should beware of foods such as 'sherbet,' which may be loaded with food additives and are often poorly labelled.

This article has been peer reviewed.

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PID123

Primary Immunodeficiency

HYPER IgE SYNDROME

In this article in our series on primary immunodeficiency, Dr Goodheart is referred a patient for whom she initially did not consider the diagnosis of an immune deficiency. The case shares one of the hallmarks of allergic conditions, that of elevated Immunoglobulin E (IgE), and may easily be mistaken for an atopic condition.

Fezeka, a six-year-old girl, lives with her aunt, who is trying her best to look after the girl's health problems since her mother died from cardiac problems. Fezeka has an older brother who was diagnosed with foetal alcohol syndrome (FAS). Fezeka's facial features are also suggestive of FAS.

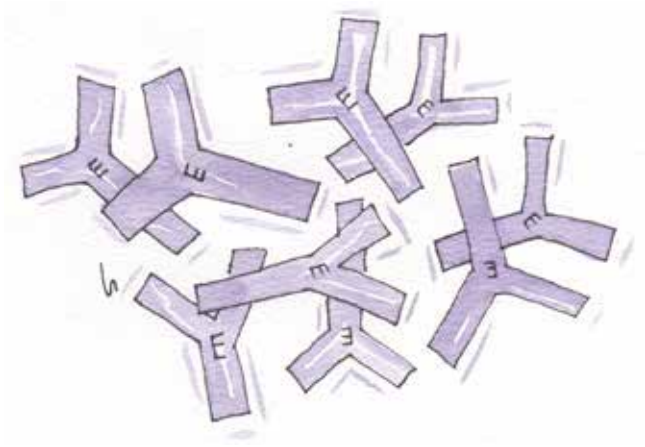
Fezeka was breastfed during infancy and had all the routine childhood vaccinations. From approximately two years of age, she suffered from multiple respiratory infections, including pulmonary tuberculosis, which was treated successfully. At five years of age, she was diagnosed with chronic lung disease and pulmonary hypertension and it was also documented that she had developed bronchiectasis. Home-based oxygen care became necessary. Fezeka had also developed severe eczema and suffered from recurrent *Staphylococcus aureus* skin abscesses. She tested negative for HIV infection.

Dr Goodheart is consulted for a review of the causes of the chronic cough, recurrent pneumonia, severe eczema and skin abscesses. At this stage, she considers a number of possible diagnoses, which initially focus on atopic conditions such as atopic dermatitis and severe asthma.

Initial laboratory tests reveal strongly elevated IgE levels (>3 000 IU/ml) but no specific responses to known allergens. Her family history is also negative for atopy. Dr Goodheart is now alerted to the fact that Fezeka may not be suffering from an allergic condition. She requests further testing. Two subsequent sweat tests prove negative, excluding a diagnosis of cystic fibrosis. Sputum testing for tuberculosis is negative. A very basic screen for the immune deficit is ordered. The full blood count shows moderate white blood cell elevation, above normal neutrophil and lymphocyte numbers, and eosinophilia. Complement (C3 and C4) is within normal limits. Immunoglobulin levels (IgG, A, M) are elevated, possibly indicating frequent infections. Vaccine antibody results are in the protective range.

Fezeka has unusual facial features and severe eczema

Dr Goodheart contacts her colleague, the paediatric immunology specialist, Dr Bala. She points out the severity of the respiratory infections, the documented presence of lung damage (bronchiectasis) in combination with very elevated IgE levels, the eosinophilia, and the skin abscesses despite the good care of the eczema. Dr Bala agrees that Hyper IgE Syndrome (HIES) and not allergy should be considered in the differential diagnosis.



Strongly elevated IgE levels were present in the serum

Dr Bala requests a clinical scoring test to be completed based on the features of the clinical phenotype of Hyper IgE Syndrome (see Table I). Fezeka scores above the cut-off of 40, which is suggestive of Hyper IgE Syndrome caused by a mutation in the STAT3 gene.

Anatomical features that support the diagnosis include clubbing, pectus carinatum ('pigeon chest'), and a cathedral (high-arched) palate. Fezeka's coarse facial features, initially interpreted as part of foetal alcohol spectrum disorder, also fit the HIES physiognomy. However, there is no record of a newborn rash, though she is showing early signs of scoliosis. Her bone strength appears normal, although there is evidence of a forearm fracture that she suffered in a recent motor vehicle accident.

Dr Bala has blood samples extracted for DNA and referred to a genetic testing laboratory. This confirms the diagnosis of autosomal dominant (AD) STAT3 Hyper IgE syndrome. Fezeka is started on antibiotic prophylaxis in the form of daily azithromycin and her aunt is taught chest physiotherapy to be given at home. She can eventually stop her spironolactone given for pulmonary hypertension and requires oxygen only occasionally at night. Her skin is improving, too, with regular use of emollients.

TABLE I: HYPER IgE SYNDROME (HIES)

HIES is also known as 'Job Syndrome' after a character in the Old Testament of the Bible whom the Lord 'smote … with sore boils from the sloe of his foot until his crown'.

HIES not only affects the immune system, but also the skin and the respiratory system with pathological susceptibility to infections, the cardiovascular system, the skeleton and the central nervous system.

There are two better-known forms of HIES: an autosomal dominant (AD) and an autosomal recessive (AR) form. HIES (AD) is due to a mutation in STAT3, whereas HIES (AR) is due to mutations in Tyk2 or Dock 8. The clinical presentations differ slightly. For example, HIES (AR) presents with viral infections and neurological symptoms which do not fit the case described here.

Diagnosis of HIES

Elevated IgE levels of 2 000 IU/ml (or >10 times the norm for age) are the hallmark of HIES; however, high IgE levels are also observed in several other conditions, including allergies, infections and primary immunodeficiency disorders other than HIES. Note that patients younger than six months of age may have very low IgE levels and adult levels are reached only by five to seven years of age. There should be no evidence of T-cell or B-cell deficiency.

The diagnosis of HIES is facilitated by a clinical-scoring system devised by the National Institute of Health (NIH) (Grimbacher et al 1999). STAT3 deficiency is differentiated from atopic dermatitis by factors such as the presence of skin abscesses, pneumonia, pneumatoceles and anatomical abnormalities, in particular coarse facial features.

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PID Article

CHRONIC GRANULOMATOUS DISEASE AND THE CHALLENGES OF DIAGNOSIS AND MANAGEMENT IN SOUTH AFRICA

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SUMMARY

Chronic granulomatous disease (CGD) is a rare genetic primary immunodeficiency disorder (PID) of phagocytes which manifests with severe bacterial and fungal infections but also granuloma formation that may be mistaken for Tuberculosis. CGD is caused by gene mutations or deletions of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (phox) complex which result in defective phagocytic respiratory burst function required for killing microbes. Patients with X-linked CGD and delay in diagnosis have a worse prognosis, as this is usually fatal in the first decade of life without prophylactic antibiotics and antifungals. Haematopoietic stem-cell transplantation and future gene-replacement therapy hold the only hope for a cure.

On the South African PID Registry, ten cases have been reported, of whom two have died prematurely. This article summarises the history, clinical presentation and laboratory investigations of two brothers with CGD, illustrating also the importance of family history and compliance.

This article has been peer reviewed.

INTRODUCTION

The reported incidence of CGD in Europe is 1/250 000,[1] and in the United Kingdom and Ireland approximately 1/120,000.[2] Seven cases of CGD have been described in the South African literature since 1983, and four patients could be genetically confirmed to date.[3,4]

Despite an increasing awareness of genetic susceptibility to infections and the realisation that PID is more common than previously thought,[5,6] there is still a delay in diagnosis globally and especially in Africa. Even with the use of prophylactic antimicrobials and antifungals survival past the age of 30 years was until recently estimated to be approximately 50%, with an annual mortality rate of 2–5% and a worse outcome for those with a complete absence of phagocytic respiratory burst.[7]

CGD is due to the defective killing of phagocytosed microbes. It is caused by an inherited defect in the NADPH-oxidase enzyme complex present in neutrophils, eosinophils, monocytes and macrophages.

NADPH oxidase is required for the 'respiratory burst'. This enzyme decreases molecular oxygen to superoxide, which subsequently reacts to form reactive oxygen species (ROS).

The NADPH oxidase enzyme complex comprises two membrane-spanning subunits, gp91phox and p22phox, as well as three cytosolic components, p47phox, p67phox and p40phox.[8] Approximately 66% of all CGD cases are from mutations in the X-linked gp91phox gene (CYBB) and 30% are from the autosomal recessive forms of CGD, with defects in the gene coding for p47phox (NCF-1). The remaining 5% of the cases are due to mutations in CYBA, NCF-2 or NCF-4 that encode for p22phox, p67phox and p40phox, respectively.[9,10]

The impairment in the function of the complex results in the defective intracellular and extracellular killing of especially catalase-positive bacteria, for example *Staphylococcus aureus*, and of fungi (aspergillus species) and actinomyces species. Chronic inflammation is a feature of CGD, especially in the second decade of life, because NADPH oxidase deficiency also impairs the regulation of pro-inflammatory cytokine signals.

CASE REPORT

The index patient GD who is now 16 years old first presented in 2005 (at five years of age) with a liver abscess which cultured *Staphylococcus aureus*. He was also treated for Salmonella septicaemia and Tuberculosis (TB) in 2008 and had further episodes of liver abscesses (*Staphylococcus aureus* cultured on pus from an abscess)

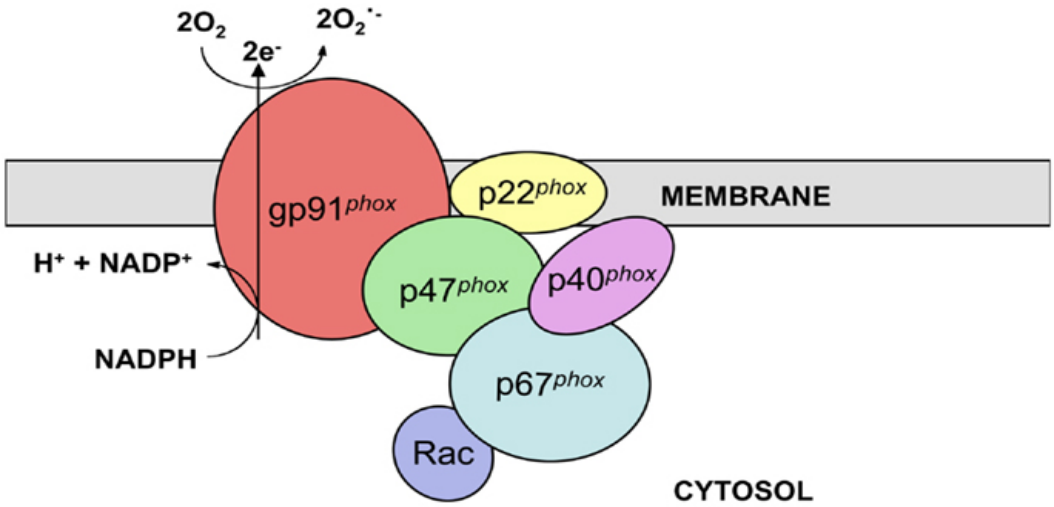

Figure 1: NADPH oxidase structure. NADPH oxidase is a multi-subunit enzyme complex present in the vesicular and plasma membranes of leukocytes. Two transmembrane subunits, gp91phox and p22phox, make up flavocytochrome b558, the catalytic core of the complex. This heterodimer catalyzes the transfer of electrons from cytosolic NADPH to molecular oxygen, thus generating superoxide. Flavocytochrome b558 is regulated by association with the subunits p47phox, p67phox and p40phox along with the small GTPase Rac. These regulatory subunits are present in the cytosol of resting cells and translocate to the catalytic core following stimulation. (Front Immunol, 23 September 2013. Available at http://dx.doi.org/10.3389/fimmu.2013.00295)

in 2008 and 2009. In 2010, he presented again with a liver abscess. Chronic granulomatous disease was suspected and his neutrophil burst test was reduced but not absent, indicating possible autosomal recessive inheritance. Antimicrobial and antifungal prophylaxis was instituted but with variable patient compliance. GD then presented again in 2012 with a two-week history of fatigue, fever and significant weight loss. There was a TB contact in the home but investigations for TB were negative. An ultrasound of the abdomen revealed multiple liver abscesses; again, *Staphylococcus aureus* was cultured. He was treated with appropriate antibiotics and a prolonged course of corticosteroids, two pigtail drainage procedures, and surgery for near-fatal gut perforation followed by prolonged hospitalisation.

His younger brother BD was seen for CGD screening in the clinic in 2010 after GD was diagnosed with CGD. He also had an abnormal neutrophil burst response similar to his older brother's with a reduced but not absent burst response. In both brothers the burst responses improved markedly in times of good health. The mother's neutrophil burst response was normal; however, it showed two populations of neutrophils, indicating an X-linked, more severe mode of inheritance. At the time of screening BD was almost four years old and already had a prior history of acute gastroenteritis requiring hospital admission at seven months of age and tuberculous meningitis with multiple tuberculomas on CT scan in 2008. After completion of his TB treatment, he had a focal seizure which became generalised. In 2010, he had also suffered from measles complicated by bronchopneumonia and he had an abscess of the left thigh which was incised and drained. After his abnormal neutrophil burst findings he was started on antimicrobial prophylaxis with subsequent variable compliance.

However, in 2014 BD then presented with a liver abscess and *Staphylococcus aureus* septicaemia complicated by bilateral pleural and pericardial effusions. As he was previously identified with a neutrophil function defect due to his brother's history, and hence with a high suspicion of liver abscess formation, his treatment was prompt and recovery uneventful.

DISCUSSION

With a lack of awareness for the clinical manifestations and without access to specialised laboratories, including facilities for molecular diagnosis, the recognition and correct management of CGD can be very delayed and result in unnecessary morbidity and early death. Both brothers described in this article were diagnosed and treated for TB. As there is such a high prevalence of TB in the Western Cape, this did not raise suspicion for PID initially. Furthermore, CGD patients are known to be more susceptible to disease manifestation of TB as part of their immune defect. However, our patients also presented with unusual infections such as *Salmonella* (patient GD) and multiple and severe infections: measles, tuberculous meningitis and a deep-tissue abscess of the thigh (patient BD). They did however not present with infections due to *Burkholderia cepacia, Serratia marcesens* or *Listeria, Aspergillus* or *Nocardia* species which are other all indicator organisms associated with CGD.

The diagnosis of any PID can be suspected by using the '**SPUR**' warning signs for PID: **S**evere, **P**ersistent, **U**nusual or **R**ecurrent infections or autoimmune/auto-inflammatory symptoms and the clinical phenotype. An example is the

TABLE I: BASIC IMMUNE SCREENING AND NEUTROPHIL BURST TEST

TEST	PT GD	PT BD
Full blood count and differential count	WCC = 6.05 (4.0–10.0) Neutrophils normal Haemoglobin = 10.7 (13.0–17.0) Platelets = 201 (137–333)	WCC = 9.06 (3.9–10.2) Neutrophils = 5.11 (1.7–5.0) Haemoglobin = 11.1 (11.8–14.6) Platelets = 332 (180–440)
HIV Elisa	Negative	Negative
IgG, IgA ,IgM IgE	Normal 381 IU/ℓ (raised but not hyper IgE level)	Normal Normal
Neutrophil burst test	Decreased response to PMA stimulant with almost normal response to physiological stimulation with E coli during good health.	Below normal PMA stimulant response. Burst response to physiological stimulation with E coli almost normal during good health.

typical liver abscesses of CGD, as in our two patients. A basic screening for immune function should be prompted by these warning signs.

The specific diagnosis of CGD should be pursued with the 'gold standard' nitroblue tetrazolium assay, which is available only in specialised laboratories.[11] A flow cytometric-based assay[12] also suggests the diagnosis of CGD. This assay, referred to as a 'neutrophil burst test', is based on the reduction of dihydrorhodamine-123 (DHR) by phorbol myristate acetate (PMA) stimulated phagocytic cells. It is particularly useful as it can demonstrate two populations of cells in carriers. Patients who are systemically ill from other causes may have a transient reduction in burst activity that will normalise as they improve.[13]

Both BD and GD had neutrophil burst responses which were partially reduced but never normalised completely after recovery from their acute illnesses.

As the neutrophil burst tests with near-normal E coli stimulant response were atypical for CGD presenting with typical hallmark infections, genetic testing was requested at the Division of Molecular Biology and Human Genetics, Faculty of Medicine and Health Sciences, Stellenbosch University for confirmation of the diagnosis.

Both brothers were found to have a mutation in the CYBB gene. This protein change has previously been shown to be pathogenic for CGD.

Molecular testing finally confirmed the diagnosis of X-linked CGD and enabled the clinicians to offer the family genetic counselling and instructions on appropriate management. A third sibling (male) with failure to thrive and mild recurrent infections has subsequently tested negative for the CYBB mutation.

TREATMENT MODALITIES

Previously reported mortality from CGD was high, but with antibiotic and antifungal prophylaxis as well as haematopoietic stem-cell transplantation (HSCT) outcomes have improved and reported mortality is currently less than 5%.[14]

Both patients were started on prophylactic co-trimoxazole and isoniazid as well as itraconazole for GD. Patient GD also required a prolonged course of prednisone in 2012. This has been shown to be effective in controlling multiple liver abscesses that are not amenable to surgery.[15] The use of interferon-gamma for CGD remains controversial and its cost is a major issue in South Africa. Both boys are now confirmed with X-linked CGD and would benefit from HSCT, but this is not a routine option in South Africa at this time. A study in the United Kingdom showed 90% survival at 15 years with and without HSCT; however, children who did not undergo HSCT had more frequent infections, hospital admissions and surgery, and had poorer growth.[16] Currently, both boys are being looked after by their grandmother and are taking prophylaxis and attending clinic. At their last visit they were both healthy, gaining weight and attending school regularly.

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DECLARATION OF CONFLICT OF INTEREST

The authors declare no conflict of interest.

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INDICATE TRUE OR FALSE

1. *True or False:* Civil and political rights are known as first-generation rights.
2. *True or False:* The right to health is the same as the right to be healthy.
3. *True or False:* The Patients' Rights Charter includes both rights and responsibilities.
4. *True or False:* The individual's right to health is absolute.
5. *True or False:* In pandemics the state may infringe on an individual's rights in the public interest.
6. *True or False:* The South Africa Bill of Rights permits the limitation of individual rights, as long as the limitations are reasonable and justifiable in a democratic society.
7. *True or False:* Airlines permit the carrying of an adrenaline auto-injector by travellers who are at risk of a severe allergic reaction.
8. *True or False:* Sabrina's Law mandates that schools in Canada must have policies in place to manage severe allergic reactions in school children.
9. *True or False:* The food allergic child's rights outweigh those of non-food allergic children in that food allergens should be completely banned in the school environment if one of the learners suffers from a severe food allergy.
10. *True or False:* The Allergy Society has no responsibility in ensuring the safety of learners with severe food allergy in South African schools.

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