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Advances in peanut allergy

Development of peanut allergy and the role of environmental exposure

Peanut introduction and the prevention of peanut allergy: evidence and practical implications

The ABC of dietary management of peanut and nut allergy

Food allergies - should we be going peanut-free in South African schools?

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SUBMISSIONS
The editors encourage articles, letters, news and photographs relating to the field of allergy and clinical immunology. Please send submissions to Robyn Marais, at robyn@jesser-point.co.za

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GUEST EDITORIAL

ADVANCES IN PEANUT ALLERGY

The peanut – a legume that comprises multiple protein components with the designated prefix *Ara* – has traditionally been an affordable, nutritious and protein-packed snack. Of late it has become (in)famous for acting as the 'covergirl' of the food allergy epidemic, with studies in certain areas of the world showing two- to three-fold increases in peanut allergy (PA) over the past few decades,[1,2] an increase that has now plateaued in certain areas but may still be on the rise in others.

PA tends to be persistent in all but approximately 20 per cent of cases. Peanut is a ubiquitous and 'sticky' allergen, and PA now affects 1 : 50 to 1 : 100 of our children. It can be severe – it is the most common cause of food-induced anaphylaxis in children. All these factors make PA a hot topic and have led to major policy shifts on airlines and in schools in an attempt to reduce exposure to and risk in those with a PA. Moreover, with there being no 'cure' per se for PA at present, the recent focus has shifted to prevention strategies. These strategies have been aided by several excellent studies which have helped to clarify the pathogenesis of PA and the possible windows of opportunity for introducing peanut during which tolerance is more likely to occur.[3] In those who already have an established PA, peanut desensitisation (specific oral tolerance induction) is becoming more common place in clinical practice, the main aim of desensitisation being to increase the threshold at which patients react and therefore to afford a better quality of life (QoL). In some cases, even long-term tolerance has been established.

Given the current 'epidemic' of interest in PA, and the fact that the current volume is dedicated to the topic, I am honoured to have guest-edited this volume of *Current Allergy and Clinical Immunology* entitled 'Advances in peanut allergy'. This edition focuses on the pathogenesis, prevention and policies related to PA. Information on component-resolved diagnosis and specific oral-tolerance induction has been provided in a recent issue of *Current Allergy and Clinical Immunology* entitled 'Advances in food allergy'. I commend that issue to you if you wish to read up on those particular aspects of PA.

We have had some wonderfully knowledgeable colleagues contribute to this parade of pertinent articles on peanuts. Dr Helen Brough, a prestigious paediatric allergist and researcher from the St Thomas' Hospital in London, has done significant research on environmental peanut exposure and epicutaneous sensitisation, and has partnered with her colleague, Morium Akthar, to delight us with a state-of-the-art article on the role of environmental exposure in the development of PA.[4] I have been honoured to co-author an article on PA prevention with top international food allergy gurus Carina Venter and David Fleischer from the Children's Hospital in Colorado.[5] Both Carina, a paediatric dietician and researcher, and David, a paediatric allergologist, have been involved in international consensus documents on early peanut introduction and peanut prevention.[6] Shaunagh Emanuel, our talented Cape Town-based general practitioner with an interest in allergy, has also contributed towards this article with her practical mind and brilliant illustrations.

Lauri-Ann van der Poel was a colleague of mine at the UCT Medical School, and is now practising as a paediatric allergist at St Thomas' Hospital in London. She has been at the forefront of developing a helpful app for food-allergic patients, 'Food Maestro'. Lauri-Ann, together with experienced allergy research nurse Helen Fisher, has contributed a wonderful article on the dietary management of nut allergy, including the debate on avoidance versus exposure to related allergens in peanut and tree-nut allergy.[7]

Lastly, I have teamed up with Michael Levin, head of the Division of Paediatric Allergy at the Red Cross War Memorial Children's Hospital in Cape Town, to write a piece on school policies regarding PA, promoting peanut awareness and including some suggestions for creating safer school environments for food-allergy sufferers.[8]

In addition, we have our regular pieces on occupational health, ethics and immunology to complete this first volume of 2018. We hope that our readers can be enlightened by this volume and subsequently better equipped to deal with several aspects of PA.

Professor Claudia Gray
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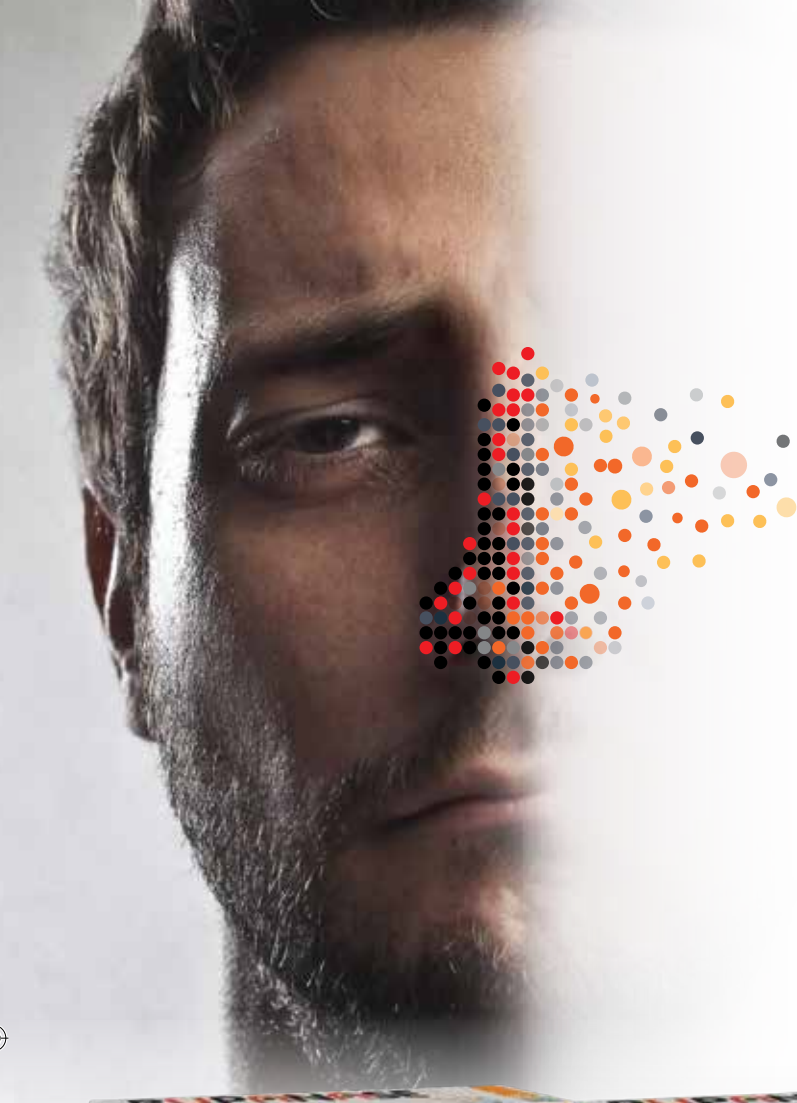

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*Platelet Activating Factor (PAF) is one of the most important mediators for induction of oedema/nasal obstruction, as well as increasing vascular permeability and causing rhinorrhoea, whereas histamine is responsible for itching and sneezing[6]

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ERRATUM:
The cover of the Vol 30 No 4 December (2017) issue of the *Current Allergy and Clinical Immunology Journal* erroneously stated Vol 30 No 3 September (2017). It should have been Vol 30 No 4 December 2017. We apologise for this error.

Review Article

THE DEVELOPMENT OF PEANUT ALLERGY AND THE ROLE OF ENVIRONMENTAL EXPOSURE

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BACKGROUND

The prevalence of peanut allergy (PA) in children has gradually increased over the years and is now believed to affect 1–2% of all children in Western countries.[1–3] This is in conjunction with an overall increase in the prevalence of all food allergies in children in the past two decades.[4] In addition, PA remains one of the leading causes of food-induced anaphylaxis[5] and has also been shown to be the leading cause of death related to food allergy in a number of countries.[6–10] However, it should be noted that death from food allergy still remains uncommon and is, in fact, relatively rare in children.[11] Yet the impact of having PA can be enormously burdensome, leading to increased anxiety, the limitation of social activities and an overall reduction in the quality of life for children and their families.[12–13]

As with all food allergies, avoiding the allergen and treating allergic reactions appropriately continue to be the mainstay of managing PA. Work has been done on inducing peanut tolerance by oral immunotherapy (OIT), but its role is limited to increasing the threshold of reactivity to peanut and has not been shown to induce long-term sustained oral tolerance. Anagnostou et al (2014) demonstrated that peanut OIT raised the reactive threshold so that up to 91% of participants could tolerate a daily ingestion of approximately five peanuts.[14] However, Vickery et al (2014) showed that only 50% of those who underwent five years of peanut OIT had sustained unresponsiveness (SU) one month after discontinuing OIT.[15]

This leads us to look at ways of preventing PA as this is likely to be the most effective way of reducing its incidence and prevalence. Prevention can be tackled only when there is a thorough understanding of the mechanisms underlying the development of PA. In recent years, a number of studies have brought to the forefront the importance of the role of environmental peanut exposure and the disrupted skin barrier in the development of PA.

THE NATURAL HISTORY OF PA

The median age at which PA presents is 14 months,[16] and PA commonly persists into adulthood. Peters et al (2015) demonstrated that only 22% of patients who had a food-challenge of PA confirmed at one year of age had resolution of PA by four years of age, also confirmed by a food challenge.[17] However, there is evidence that the incidence of resolution of PA may be greater if it were to include those patients who have never had a reaction to peanut but have been shown to be sensitised or have allergy as diagnosed by SPT or specific IgE only.[18] It should also be noted that those patients who have experienced anaphylaxis in response to peanut are unlikely to have their allergy resolved.[19] A number of studies have also highlighted that peanut sensitisation (PS) and PA can recur following a negative food challenge if patients do not ingest peanut frequently or do so in significant amounts after that.[18,20-21]

THE IMMUNOLOGICAL MECHANISM OF PA

The body's immune system can be exposed to allergens via a number of routes; these include the gastrointestinal tract, the respiratory tract and the skin. The pathophysiology of food allergy involves the initial exposure of the allergen (eg peanut) to the immune system. Once the allergen has been introduced into the body, antigen presenting cells (APC) engulf the allergen and interact with naive CD4+ T-helper lymphocytes. These T-helper cells then activate

B cells, triggering them to mature into plasma cells and produce antigen-specific antibodies (IgE) to peanut. The plasma cells continue to produce and secrete specific IgE to various peptides of peanut protein. The IgE bind to the surface receptors of mast cells in a number of sites around the body, including the GI tract, the respiratory tract and the skin. They also bind to basophils circulating in the peripheral blood. After the immune system has been primed (sensitisation), repeat exposure to the allergen leads to peanut peptide binding to specific IgE bound to mast cells and basophils causing these cells to degranulate and release a number of inflammatory mediators such as histamine, leukotrienes and cytokines, which leads to the signs and symptoms of an allergic reaction. Symptoms may involve the cutaneous organ systems (rash, hives and angioedema), respiratory tract (wheeze, stridor), gastrointestinal tract (vomiting, diarrhoea) and/or cardiovascular system (low blood pressure, pallor and collapse).

FACTORS ASSOCIATED WITH DEVELOPMENT OF PA

There are a number of factors that contribute to the development of PA. There are those factors relating to exposure and others relating to individual susceptibility, such as genetics and ethnicity.

GENETICS AND ETHNICITY

Twin studies have shown that there is a 64% concordance rate in the development of PA in monozygotic twins.[22] Hourihane et al (1996) assessed 622 adults and children and their families with suspected PA in the United Kingdom (UK) and showed that grandparents reported PA in 0.1% of cases, aunts and uncles in 0.6%, parents in 1.6%, and siblings in 6.9%; therefore, only sibling history of PA increased the risk. Further evaluation by SPT and diagnostic OFC revealed a 7% prevalence of PA in siblings of peanut-allergic individuals.[23]

A number of reports have also highlighted that children of non-white ethnicity are more susceptible to the development of PA.[24–26] Fox et al (2015) found that the rate of increase in PA was greater in non-white children than white children;[26] they conducted an ethnicity-based study of children given a diagnosis of PA at a UK tertiary allergy clinic over a 14-year period between 1990 and 2004, with children with egg allergy as control subjects. Among the patients with PA there was a 23.5% increase (from 26.82% to 50.31%, p = 0.001) in the proportion of non-white subjects given a diagnosis of PA over time. As a comparison, among non-white children there was a <1% change in egg allergy over the same timespan.

EXPOSURE

A number of routes for peanut sensitisation have been proposed and there are varying amounts of evidence to support these.

a. *In-utero*

The available evidence thus far suggests that the in-utero development of sensitisation to peanut is unlikely. The Avon Longitudinal Study of Parents and Children (ALSPAC) was a birth cohort study comprising almost 14 000 pregnant women. Cord blood was assessed retrospectively from the mothers of children who developed challenge-positive PA. The group found no detectable peanut-specific IgE (level >0.35 kUA/L) in cord blood.[27] Another study demonstrated that any detectable peanut-specific IgE in cord blood is likely to be maternal in origin, because peanut-specific IgE was no longer detectable once the infant had reached six months of age.[28]

b. *Breastmilk*

Vadas et al (2001) demonstrated that peanut protein, including major peanut allergen proteins Ara h1 and h2, can be detected in maternal breastmilk.[29] Their study looked at peanut protein levels in breastmilk in hourly intervals after mothers had consumed 50 g of dry-roasted peanuts and showed these were detectable within three hours of ingestion. Other studies have also reported detectable peanut protein in breastmilk in a proportion of women studied after maternal consumption of peanut.[30–31] However, presence of peanut protein in breastmilk does not necessarily correlate with the development of PA via exposure to peanut protein in breastmilk. The ALSPAC study and another large UK cohort study, the Isle of Wight study, did not find any correlation between maternal peanut consumption during pregnancy and breastfeeding with PS or PA in children.[27,32]

The CoFAR2 study, an observational study of infants at high risk of developing PA (due to eczema or egg and/or milk allergy), found that maternal peanut consumption during breastfeeding was not linked to the development of PA.[33] However, they did show that maternal peanut consumption during pregnancy in infants who were formula fed were more likely to have PS than those babies who were breastfed.[33] Among 71 infants who were formula fed only, the frequent maternal consumption of peanut during pregnancy was strongly associated with peanut IgE >5 kUA/L (OR 4.99, 95% CI, 1.69–14.74; p <0.004). This suggested a protective effect of peanut consumption during breastfeeding. More recently, a Canadian study showed that it was the combination of peanut consumption during breastfeeding and introduction into the child's diet before 12 months that conferred the lowest rate of PS in the children at seven years of age, whereas either of these exposures in isolation increased the risk of PS.[34]

c. *The environment*

The skin and the respiratory tract are two possible major routes for peanut sensitisation via exposure from peanut protein in the environment and there is a varying amount of evidence to support this, detailed below.

i. Airborne peanut protein

The evidence for PS occurring through the respiratory tract is weak as there is little evidence to support peanut protein being airborne.[35,36] In the study by Perry et al (2004) participants wore air-sampling monitors and ate and stamped on peanuts in an enclosed room. The monitors did not detect any significant airborne peanut-protein allergens.[36] Brough et al (2013a) evaluated airborne peanut using sensitive polyclonal ELISA directed against peanut protein. They also used personalised air-sampling monitors in a number of situations – 1 cm above peanut butter and a dry-roasted peanuts packet, while eating peanuts and simmering satay sauce on a stove. They found that peanut protein was not detectable in these situations. Peanut protein was detectable during active peanut shelling but disappeared immediately after shelling was discontinued.[35]

It should be noted that airborne peanut in planes with recirculated air may provide different findings. It has been reported that peanut protein has been detected in the ventilation system filters of commercial airliners after 5 000 flight hours using an inhibition assay with peanut extract; however, this abstract was never published.[37] In addition, a survey of peanut-allergic individuals reported allergic reactions to peanut on planes, presumed to be due to environmental exposure; however, this could have been from either peanut on surfaces rather than airborne peanut, given that peanut has been detected on aeroplane tray-tables (both when staff served peanut and when they did not, albeit at much lower levels).[38,39]

ii. Peanut protein in environmental surfaces and dust

There is an increasing body of evidence suggesting sensitisation via the skin as a route for developing PA.[40–43] In order for sensitisation to occur via the skin it follows that there must be peanut allergen in the environment. Fox et al (2009) carried out a study which used household peanut consumption as an indirect marker for environmental peanut exposure.[44] The group demonstrated that household peanut consumption during infancy was associated with an increased risk of PA in these children. They compared peanut-allergic children with atopic controls (non-peanut allergic but egg allergic) and non-atopic controls. They showed that household peanut consumption was significantly higher in peanut-allergic children (18.8 g/week) than in egg-allergic children without PA (1.9 g/week) and three times higher than in households with non-atopic children with no PA. There are several studies that have demonstrated the presence of peanut proteins in the environment at home,[35,45] in schools and in preschools.[46–47]

Brough et al (2013) demonstrated that household consumption of peanut correlated highly with peanut protein levels in dust from bedrooms, living rooms and kitchens.[45] They also found a positive correlation between household peanut consumption and peanut protein found on surfaces such as the infant's bed, cot sides and play area, even when the infants did not consume peanut themselves. In addition, the group looked at potential routes of peanut protein transfer into the environment after the consumption of peanut.[35] They found that peanut protein was still present on hands and saliva for up to three hours after consumption. In addition, even after cleaning household surfaces with detergent, the surfaces were still found to contain detectable levels of peanut protein. Furthermore, peanut protein in dust has been shown to be biologically active, as basophils from peanut-allergic children were activated in a dose-dependent manner on exposure to dust extracts containing peanut protein.[45] The above studies support the hypothesis that household peanut consumption leads to increased exposure to peanut protein in the environment during infancy.

THE SKIN, PS AND PA

There is increasing evidence that a disrupted skin barrier is linked to the development of food sensitisation and food allergy. The disrupted skin barrier may take the form of clinical diagnosis of eczema, filaggrin loss-of-function mutation or demonstration of dry skin as measured by transepidermal water loss (TEWL).[40]

a. *Eczema*

The association between a disrupted skin barrier, in the form of eczema, and the development of food sensitisation or allergy has been established in a number of studies, such as the Melbourne Atopy Cohort (MAC) study[48–49] and the HealthNuts study.[50] In the MAC study, infants with a history of mild eczema had a three-fold increased risk of developing IgE food sensitisation compared with those with no history of eczema (36% vs 11%). Furthermore, infants with a history of severe eczema had a six-fold increased risk of developing food sensitisation compared with those infants without eczema (65% vs 11%). In the same cohort eczema before *six* months was associated with an increased risk of having a new food sensitisation as measured by SPT at *one* year (Hazard Ratio = 2.26, 95% CI = 1.34–3.82, 29.4% vs 13.8%).[49]

The HealthNuts study, a large population-based cohort study of infants, found that infants with eczema were six times more likely to have egg allergy and 11 times more likely to have PA by 12 months than infants without eczema. The study also found that 50% of infants with early onset severe eczema (<3 months of age and requiring doctor-prescribed topical corticosteroid treatment) developed a challenge-proven food allergy.[50] Data from the ALSPAC study also demonstrated that infants who were exposed to topical peanut oil (in the form of Arachis oil) were at an increased risk of PA, but only if they also had eczema.[27] In addition, a history of eczema modified the impact of environmental peanut exposure on PS and PA in infants in the CoFAR2 study;[42] in children with a history of eczema, each log2 increase in peanut-dust levels increased the odds of PA by 2.34 (95% CI; 1.31–4.18 $p < 0.01$).

b. *Filaggrin loss-of-function mutation*

Filaggrin (*FLG*) is a filament aggregation protein that plays an important role in maintaining the integrity of the skin. Mutations in the *FLG* gene lead to the abrogation of the normal flattening of keratinocytes in the stratum corner and a reduction in natural moisturising factor (breakdown product of filaggrin).[51] *FLG* loss-of-function mutations have been associated with eczema and skin barrier dysfunction, as demonstrated by raised TEWL. Brown et al (2011) demonstrated there was a positive association between children with *FLG* loss-of-function mutations and challenge-proven PA.[52] An association with *FLG* loss of mutation and food allergy and food sensitisation has also been demonstrated in a number of other studies.[53–54]

Brough et al (2014) demonstrated that children with *FLG* loss-of-function mutations not only had an increased risk of PS but also challenge-proven PA.[43] As part of the Manchester Asthma and Allergy Study (MAAS) it was shown that there was a dose-responsive relationship between early environmental peanut protein exposure in the home and PS and PA in children with *FLG* loss-of-function mutations. It was shown that for every natural log (*ln*) unit increase in peanut-protein exposure via house dust during infancy, these children had a five-fold increased odds of PS (OR 5.2 95% CI: 2.1–13.1, p <0.001) and a three-fold increased odds of developing challenge-proven PA (OR 3.2 95% CI: 1.1–9.8, p = 0.04). Therefore the more concentrated the exposure to peanut levels in dust during early life the higher the risk of subsequent PS and PA.[43]

c. *Skin-barrier impairment as measured by TEWL*

A study by Flohr et al (2014) found that a functional assessment of the integrity of the epidermis using TEWL was associated with food sensitisation even after adjusting for atopic eczema and *FLG* mutation status.[55] Kelleher et al (2015) measured TEWL at day 2 of life and again at two months and six months and they found that TEWL levels in the upper quartile preceded the onset of clinical eczema at one year of life.[56] Impairment of the skin barrier at day 2 of life was also predictive of food sensitisation and food allergy at two years of age.[57] Even in those without eczema, infants with upper-quartile TEWL levels on day 2 were 3.5 times more likely to have food allergy at two years than infants in the lowest quartile. To date, no study has assessed whether there is an interaction between peanut-dust exposure and high TEWL.

In summary, these studies support the outside-in hypothesis for the pathogenesis of eczema,[58] in that skin-barrier disruption occurs before the onset of Th2 inflammation. They also suggest that children with a disrupted skin barrier are at increased risk of PS and PA from environmental peanut exposure.

DUAL-ALLERGEN EXPOSURE HYPOTHESIS

The dual-allergen exposure hypothesis proposes that early oral exposure to food protein induces tolerance, whereas early cutaneous exposure to environmental food allergen results in food sensitisation and allergy development. Randomised controlled trials such as the Learning Early About Peanut (LEAP) and Enquiring About Tolerance (EAT) studies both support the concept of inducing tolerance by early oral exposure.[59–60] It is thought that the balance and timing of the two different routes of exposure, particularly in atopic individuals, determines this outcome and that early gut exposure to food allergen primes the immune system to develop tolerance, but that early exposure to food allergens via the skin leads to sensitisation and allergy.[41,61] This hypothesis is supported by evidence in a study by Fox et al[44] that high levels of early oral exposure to peanut in infants abrogated the risk from high peanut consumption in households. To date the impact of oral peanut consumption on exposure to high peanut-dust levels has not yet been evaluated.

CONCLUSION

In summary, the collective data demonstrate that there is a reduced risk of PA if exposure to peanut protein is early and via the oral route. There is also evidence that environmental exposure, in the form of peanut protein found in dust, is associated with an increased risk of PS and/or PA in children with a disrupted skin barrier or the carriage of an *FLG* loss-of-function mutation, although causation has not been proven. The studies detailed above support the Dual Allergen Exposure hypothesis and could therefore provide a strategy for trying to prevent the onset of PA. Guidelines regarding the early peanut introduction for the prevention of PA in high-risk infants have been drafted in association with numerous international allergy societies.[62] Studies to prevent the development of eczema through repairing the skin barrier are also showing promise,[63–64] although these small studies did not show a reduction in food sensitisation. More recently, the PEBBLES (Prevention of Eczema by a Barrier Lipid Equilibrium Strategy) pilot study showed a trend in early emollient therapy to reduce the risk of food sensitisation.[65]

DECLARATION OF CONFLICT OF INTEREST

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Review Article

PEANUT INTRODUCTION AND THE PREVENTION OF PEANUT ALLERGY: EVIDENCE AND PRACTICAL IMPLICATIONS

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ABSTRACT

Peanut allergy, a major public-health concern, is persistent in the majority of cases, with no current long-term cure, therefore the prevention of peanut allergy presents an attractive option. The Learning Early about Peanut Allergy (LEAP) study, published in 2015, found significantly lower rates of peanut allergy in infants at high risk of peanut allergy if peanut was introduced early (between four and 11 months) and given regularly. These findings led to an international effort to develop practical clinical recommendations on peanut-allergy prevention. Such recommendations are discussed in this article, which aims to summarise the practical implications of recent research outcomes in peanut-allergy prevention.

INTRODUCTION

Peanut allergy (PA) is a major public-health concern estimated to affect between 0.5–2% of children.[1–3] PA can be severe or life-threatening and is one of the most common causes of food-related anaphylaxis in the United States.[4] Moreover, PA begins early in life for the majority of patients and is persistent in the vast majority of cases.[5] Therefore, preventing PA would have a significant impact on the individual and potentially also at a public-health level.

EVIDENCE FOR EARLY PEANUT INTRODUCTION IN HIGH-RISK INFANTS: THE LEAP STUDY IN A NUTSHELL

The Learning Early about Peanut Allergy (LEAP) study was published in 2015, a landmark trial in the realm of PA prevention.[6] This study enrolled 640 children at high risk of PA, which was defined for this study as infants between four and 11 months of age with severe eczema and/or egg allergy. At study entry, LEAP participants were stratified according to skin-prick test (SPT) results to peanut into those with a negative SPT response (n = 530) – a primary prevention group – and those with a measurable SPT response (1–4 mm, n = 98) – a secondary prevention group – as the latter group were considered sensitised but not allergic to peanut at study entry. Participants with an SPT of greater than or equal to 5 mm were excluded because of their study-defined high risk of established PA, although these patients did not undergo oral food challenges (OFC) to determine whether they were truly peanut-allergic. Patients were randomised to consume at least 2 g of peanut protein thrice weekly or to avoid peanut-containing food until five years of age, at which stage a peanut OFC was performed. Infants randomised to consume peanut ingested a median of 7.7 g peanut protein per week during the first two years of the trial.

In the group with negative SPT at baseline, the prevalence of PA in the avoidance group was 13.7% at five years age versus 1.9% in the consumption group. This represented a 12.6% absolute risk reduction and an 86.1% relative reduction in PA (p <0.001), with a number needed to treat (NNT) of 8.5 (number of infants needed to have early peanut introduction to prevent peanut allergy in one child). In the subgroup with a measurable SPT to peanut of 1–4 mm the prevalence of PA was 35.3% in the avoidance group and 10.6% in the consumption group. This represented a 24.7% absolute risk reduction and a 70% relative reduction

in PA (p = 0.004), and resulted in an NNT of 4. The results of the LEAP study are summarised in Figure 1.

Regarding trial safety, seven of the 319 children (2.2%) randomised to the consumption group reacted to peanut at the baseline OFC. This suggests that peanut OFCs are safe and feasible even in those children with minimally positive SPT. However, six children in the consumption group developed signs of PA during the study, therefore PA can still occur despite primary and secondary prevention strategies.

The LEAP-ON study[7] demonstrated the long-term persistence of oral tolerance to peanut achieved in the LEAP trial when peanut consumers subsequently avoided peanut for one year from 60–72 months of age. A further analysis of nutrition in the LEAP cohort[8] showed that the introduction of peanut did not affect the frequency or duration of breastfeeding and did not influence growth or nutrition.

TABLE I: RECOMMENDATIONS FOR PEANUT INTRODUCTION IN INFANTS ACCORDING TO RISK STRATIFICATION

INFANT CRITERIA	RECOMMENDATIONS	EARLIEST AGE OF PEANUT INTRODUCTION
No eczema and no other food allergies	Introduce peanut-containing foods	In accordance with family preferences and cultural practices, but no need to delay beyond six months
Mild to moderate eczema	Introduce peanut-containing foods	Around six months
Severe eczema,* egg allergy or both	Evaluation by sIgE measurement and/or SPT and, if necessary, an OFC. Based on test results, introduce peanut-containing foods (see Figure 2 and Table II)	Around 4–6 months

** Severe eczema defined as persistent or frequently recurring eczema with typical morphology and distribution assessed by a healthcare provider, requiring frequent need for prescription-strength topical corticosteroids or calcineurin inhibitors despite appropriate use of emollients.*

IMPLICATIONS OF THE LEAP STUDY

The significant reduction in PA in the early consumption group led to an international effort to develop practical clinical recommendations on PA prevention. Although many existing infant-feeding guidelines prior to 2015 had already suggested the introduction of allergenic foods from 4–6 months onwards, these did not specifically emphasise that avoidance may be harmful. However, a population programme aiming to identify and screen all infants at risk of PA would pose major logistic and economic challenges, hence a more pragmatic approach needs to be taken for patients.[9] A consensus statement about the implementation of the LEAP findings was published after the LEAP findings in 2015 on behalf of nine international professional societies.[10] In addition, the National Institute of Allergy and Infectious Diseases (NIAID) published addendum guidelines for the prevention of PA in the United States in 2017.[11] This is an addendum to the 2010 'Guidelines for the diagnosis and management of food allergy in the United States'.

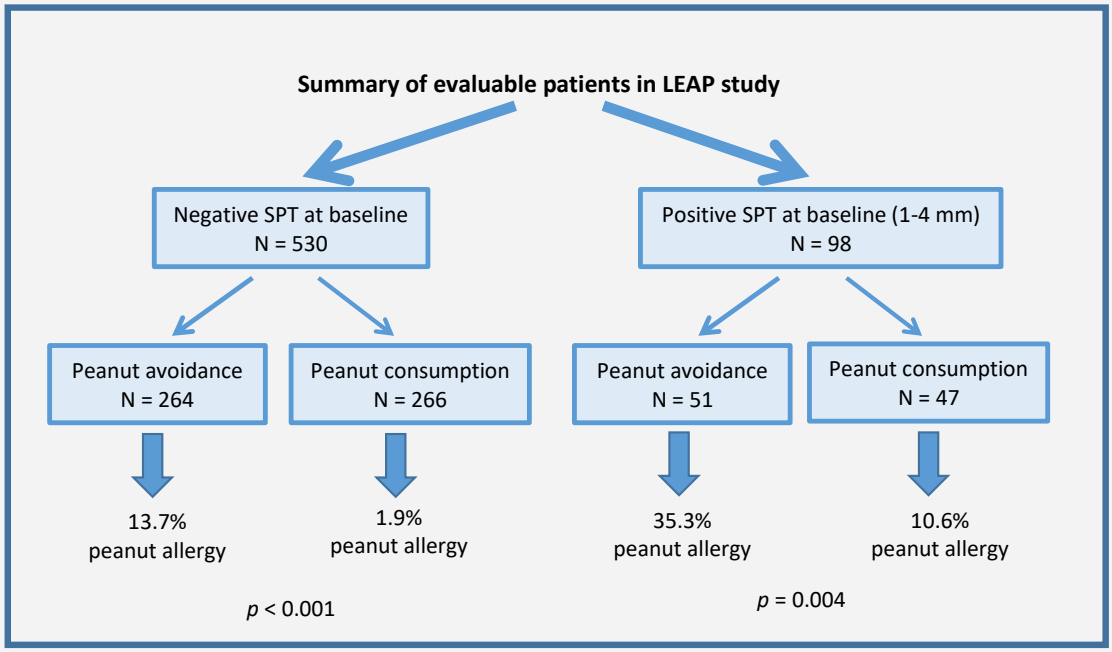


Figure 1: Summary of LEAP Study Outcome

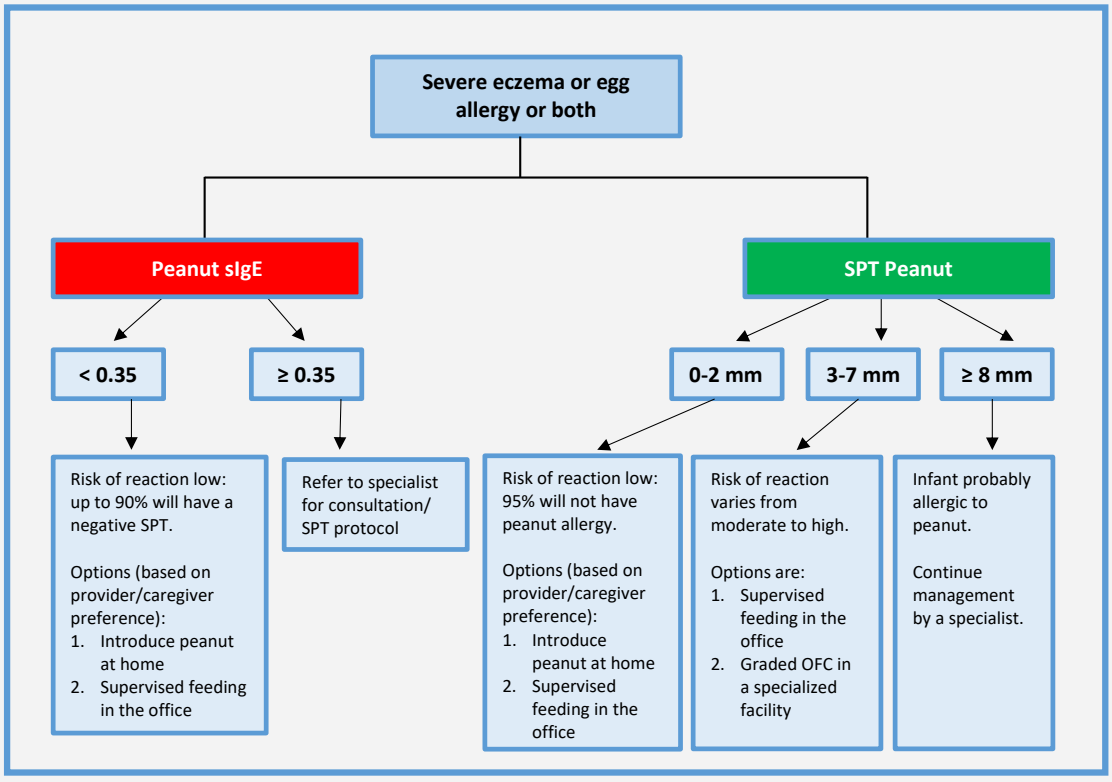


Figure 2: Peanut protein introduction in infants at high risk of PA (adapted from reference 11)

The latter two sources of recommendations for the introduction of peanut were used as a basis for this summary below.

RECOMMENDATIONS FOR PEANUT INTRODUCTION IN INFANTS

Table I summarises the general recommendations for peanut introduction in infants according to risk level for PA.[11]

INFANTS AT LOW RISK OF PA

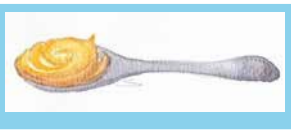
- There is no evidence for restricting allergenic foods in infants without known risk for food allergy.
- There is no evidence to suggest that mechanisms of oral tolerance induction differ in infants at low risk of PA from mechanisms that are protective in infants at higher risk of PA.
- Therefore, infants without eczema or any food allergy should have age-appropriate peanut-containing foods introduced freely into the diet after the initial introduction of other age-appropriate solid foods.
- Introduction should be in accordance with cultural practices and family preference.
- This low-risk category was not studied in the LEAP study. However, in the EAT study (Enquiring about Tolerance), in which infants from the general population were introduced to six allergenic foods from the time of enrolment at three months, the per protocol group who had early peanut introduction showed a significant reduction in peanut sensitisation and allergy at three years.[12]

INFANTS AT 'MEDIUM' RISK OF PA

The NIAID addendum guidelines suggest that infants with mild to moderate eczema should be introduced to age-appropriate peanut-containing foods around six months of age to reduce the risk of PA.[11]

- The exact timing and method of peanut introduction should be in accordance with family preference and cultural practice.
- Other solid foods should be introduced before peanut-containing foods to show that the infant is developmentally ready.
- Infants in this category may have peanut introduced at home without further evaluation.
- However, some caregivers or healthcare providers may prefer in-office evaluation, supervised feeding or both.
- This risk category was not targeted by the LEAP study, therefore data to support recommendations have been extrapolated from the LEAP and EAT studies.[6,12]

TABLE II: TYPICAL PEANUT-CONTAINING FOODS AND PORTION SIZES[11]

FOOD	TYPICAL SERVING CONTAINING 2 G OF PEANUT PROTEIN		FEEDING TIPS
PEANUT BUTTER	8–10 g (2 teaspoons)		Mix with warm water, breast milk or formula milk for a smoother texture. In older children, mix with pureed fruit or vegetables.
PEANUTS	8 g peanuts = approximately ten whole peanuts or 2½ teaspoons of ground peanuts (whole peanuts are a choking hazard in young children under the age of three years)		Add ground peanuts to a portion of yoghurt or pureed fruit.
PEANUT FLOUR (50% PEANUT PROTEIN)	4 g Approximately two teaspoons		Mix with yoghurt, apple sauce or apple juice.
BAMBA SNACK	17 g (2/3 of a 28 g packet or 21 sticks)		For a smooth texture, mix with warm water/ infant milk and mash well.

INFANTS AT HIGH RISK OF PA

In infants with severe eczema, egg allergy or both, early introduction of peanut-containing foods (ideally 4–6 months but up to 11 months may be beneficial) has been shown to reduce the risk of PA.

- Other solid foods should be introduced before peanut to show that the infant is developmentally ready.
- Evaluation of SPT to peanut, peanut-specific IgE or both should be strongly considered before the introduction of peanut.
- If SPTs are not immediately available, testing for specific IgE may be the preferred approach to minimise delay in peanut introduction.
- The results of the specific IgE or SPT will determine the feasibility of peanut introduction and the details around it, as outlined in Figure 2.

HOW MUCH PEANUT PROTEIN SHOULD BE GIVEN?

The first dose of peanut protein should be a cumulative dose of around 2 g of peanut protein (see Table II). After that, the total minimum amount of peanut protein should be 6–7 g per week, consumed over three or more feedings per week.[6,11] However, this is a suggested amount based on the LEAP study, which was the only amount and frequency studied. Therefore, it is not known if other amounts and frequencies of ingesting peanut would have the same results.

ILLUSTRATIVE CASES: PATIENTS AT HIGH RISK OF PA

CASE 1

Background: Patient MB, seven months old, severe relapsing eczema and rash around the mouth after egg introduction, breastfed with selected solids, mainly fruits and vegetables. Never eaten peanut before, no cow's milk products, soya, wheat, fish in diet yet.

SPT: Egg white 4 mm, fresh raw egg white 7 mm, peanut 2 mm. Cow's milk, soya, hake fish, wheat: 0 mm.

Risk assessment: Confirmed egg allergy. Risk of PA relatively low, based on SPT result of 2 mm.

TABLE III: PRACTICAL TIPS FOR WEANING

GENERAL WEANING	PEANUT INTRODUCTION	OTHER ALLERGENS
The weaning period is the ideal time to set the foundations for healthy eating habits. Tastes and flavours that infants are exposed to affect their food preferences for life. The more an infant is exposed to certain flavours, the more likely they are to eat those; this highlights the importance of regular vegetable and fruit intake.[13]	Whole peanuts can cause choking in children under five years of age. Whole, shelled peanuts and lumps of peanut butter should not be given to children under five years of age due to the risk of choking. The NIAID guidelines recommend that you give your baby peanut puffs (e.g. Bamba), smooth peanut butter mixed with hot water and then cooled down, peanut flour or peanut powder.[11]	There are currently no guidelines about the introduction of other allergens – suggestions for the introduction of other allergens are adapted from the EAT study and listed below.[12] Also take into consideration infant readiness and the recommendation of your physician.
Textures are important. Start with purees or soft finger foods but step up timely to mashed, dissolvable and finger foods – the aim should be for infants to eat family-type meals by 12 months. Infants who have not eaten lumpy foods by ten months of age are more likely to develop picky eating behaviour.[14]	Infants often refused to eat or may eat less than usual. The median intake of peanut protein in the LEAP study was above the recommended guidance for the study – this was despite the fact that some of the infants did refuse peanut from time to time.[6] Just keep feeding when the infant is ready and well.	Milk – infant formula, if not totally breastfeeding. If breastfeeding: milk in baked foods or yoghurt (cheese can be given from around 6–7 months due to high salt content).
Importance of variety. The more varied the foods introduced during the first few months, the more likely children will have a varied diet later. A diet that includes a large variety of foods, with regular intake of these, may prevent the development of allergic diseases.[15–17]	Some infants have really good appetites and love peanut. There is no need to adhere strictly to just 2 g of peanut protein; allow the infant to eat more if they prefer – toddlers in particular may want to eat the whole bag of Bamba as opposed to just 2/3 of the bag.	Egg – give baked cooked/fully cooked egg to start with (such as low sugar cookies, muffins or pancakes) rather than soft-boiled egg/poached egg/ raw egg powder/pasteurised egg. Raw/undercooked egg is also not recommended for children under one year of age in most countries.
Food preparation. Commercial foods contain less natural bacteria than homemade foods; the anti-oxidant content and variety may be less as well.[18] There is no need to avoid commercial food, but do cook as often as possible.	Some infants are picky eaters and will not eat any of the options suggested in the NIAID guidelines. Any peanut-containing foods providing about 2 g of peanut protein is acceptable – a dietitian may be very helpful in finding local and culturally acceptable options that the infant will eat. Any dietitian (irrespective of their knowledge of food allergy) can advise parents about the peanut content of food by calculating it from the label (if peanut is the only ingredient) or from information obtained from the manufacturer.	Soy – soy milk, soy yogurt or tofu (there is not much protein left in soy sauce and the salt content is very high – best to avoid these).
	Do not medicalise the weaning process. Infants are ready for solid foods at different ages; look out for developmental cues – there is no need to start weaning at an exact age – all infants are different.	Sesame – hummus and tahini.
	Is it safe to eat peanut around an older peanut-allergic sibling? This should be dealt with individually within each family.	Fish – the fish species that the family eats; continue with regular intake (check the local guidance on fatty fish intake in toddlers).
		Wheat – softly cooked pasta, bread fingers (check ingredients for other allergens that have not been tried).

Action: Office-based short peanut challenge in two stages: 0.5 g peanut and 2 g peanut with observation for one hour.

Outcome: Peanut challenge passed. Patient advised to include peanut in diet, around 2 g three times a week. Eczema management discussed. Egg avoidance discussed. Counselled to include other allergenic foods in diet. Reassessed for eczema two weeks later and again six months later: peanut being consumed with no reactions.
Learning point: In patients at high risk of PA, after initial assessment, PA can be successfully introduced into the diet in many cases and a potential PA avoided.

CASE 2
Background: Patient KD, five months old, severe relapsing, difficult-to-control eczema from three months of age,

exclusively breastfed and not yet on any solids.

SPT: Egg 3 mm, fresh raw egg white 10 mm, cow's milk 3 mm, fresh cow's milk 7 mm. Peanut, soya, hake fish, wheat 0 mm.

Risk assessment: Highly probable egg and cow's milk allergy. Risk of PA low (<5%), based on negative SPT result.

Action: Eczema management discussed. Egg and cow's milk avoidance discussed. Simple solid purees including fruits and vegetables introduced. Two weeks later, office-based short peanut challenge in two stages: 0.5 g peanut and 2 g peanut with observation for one hour.

Outcome: Peanut challenge passed. Patient advised to include peanut in diet, around 2 g three times a week. Reassessed for eczema one month later: peanut being consumed with no reactions.

Further course: At six months, patient unexpectedly reacted to cashew nut. Thereafter, refused regular peanut butter and did not consume peanut products for two months. At eight months, peanut reintroduced and led to urticarial rash around mouth and vomiting. SPT peanut repeated two weeks later: 5 mm.

Learning point: The LEAP study protocol involved the consumption of peanut at a minimum of 6–7 g per week for the first five years of life. While it is not known whether shorter periods or different amounts of ingestion would prevent allergy, the cessation of consumption of peanut after initiation may result in the development of PA in some patients. Therefore, in patients at high risk of PA, if peanut consumption has been initiated, it should be encouraged regularly.

CASE 3

Background: Patient AM, six months old, moderate to severe relapsing eczema from three months of age, breastfed and on some pureed vegetables. Mother worried that the baby has macular rashes when the mother herself consumes egg and dairy.

SPT: Egg 3 mm, fresh raw egg white 5.5 mm, cow's milk 5 mm, fresh cow's milk 8 mm. Peanut 3.5 mm. Soya, hake fish, wheat 0 mm.

Risk assessment: Highly probable egg and cow's milk allergy. Risk of PA moderate to high based on 3.5 mm positive SPT result.

Action: Eczema management discussed. Egg and cow's milk avoidance discussed. Formal peanut challenge performed with incremental doses, cumulative dose 3.5 g peanut protein. Observed for two hours after last dose.

Outcome: Peanut challenge passed. Patient advised to include peanut in diet, around 2 g three times a week.

Further course: Three days later, when mother gave the first home instalment of peanut butter, patient reacted within 15 minutes with urticaria around the mouth, followed one hour later by profuse vomiting and a loose stool. Settled with oral fluids and quick-acting antihistamines.

Learning point: Even in the LEAP study, some patients in the consumption group became allergic during the course of the study. Unfortunately, after the promising initial peanut challenge (which may possibly have represented a rapid desensitisation in this case), the patient presented with symptoms of a true PA, and avoidance with regular follow-up was advised.

PRACTICAL POINTERS FOR WEANING AND INTRODUCTION OF PEANUT AND OTHER ALLERGENS

Table III contains practical advice for weaning, including the introduction of peanut and other allergens.

CONCLUSION

The LEAP study provides level 1 evidence that healthcare providers should recommend introducing peanut-containing products into the diet of 'high-risk' infants (those with severe eczema and/or egg allergy) early on in life, between four and 11 months of age.

Infants at risk of food allergy with early-onset eczema, difficult to control moderate–severe eczema, or an existing IgE-mediated food allergy may benefit from evaluation by an allergist to evaluate the appropriateness of early peanut introduction and help implement it practically. Those with a positive peanut SPT (3–7 mm) may benefit from an observed incremental peanut challenge.

A practical consideration for applying this guideline at 4–6 months of age is that infants visit their healthcare provider for routine healthcare visits during this time. This provides a fortuitous opportunity for the evaluation of risk factors such as eczema and/or reported milk or egg allergy, and a prompt referral to a specialist for PA evaluation and introduction advice.

The LEAP study included a high-risk population and cannot make recommendations on the benefit of early peanut introduction in the general or low-risk populations. In general, the guidelines do not recommend delaying any major allergen's introduction into the diet, even in the low-risk population. In addition, areas of uncertainty include the value of lower doses of peanut protein than those used in the LEAP study, minimal length of treatment to induce tolerogenic effect, effect of sporadic feeding of peanut, and potential disadvantages of premature discontinuation of regular peanut feeding.

What is certain is that healthcare providers will need to be a major source of education and support for patients in order to implement the early introduction of allergenic foods such as peanut. This strategy goes against a parent's intuition that peanut is a risky food and may cause or exacerbate eczema. Furthermore, the longstanding notion that the delayed introduction of certain foods may help reduce allergies will have to be 'undone' as we learn now that avoidance may in fact be harmful. Allergists and healthcare providers taking care of young infants and children need to take this evidence-based approach and 'leap' into action.

DECLARATION OF CONFLICT OF INTEREST

C Gray and S Emanuel have no conflicts of interest to declare. C Venter has received honoraria for consultation work/lectures for Danone, Mead Johnson, Nestlé, ThermoFisher. D Fleischer is a member of the scientific advisory council for the National Peanut Board, represented the American Academy of Allergy, Asthma and Immunology in the formation of the Consensus Communication on Early Peanut Introduction and the Prevention of Peanut Allergy in High-Risk Infants; was a Coordinating Committee and Expert Panel member of the NIAID-sponsored Guidelines for Peanut Allergy Prevention; is a member of physician/medical advisory boards for Aimmune Therapeutics, DBV Technologies, INSYS Therapeutics, Intrommune Therapeutics, Kaleo Pharmaceutical, and Nestlé; receives royalties from UpToDate; and received grant support from DBV Technologies and Aimmune Therapeutics.

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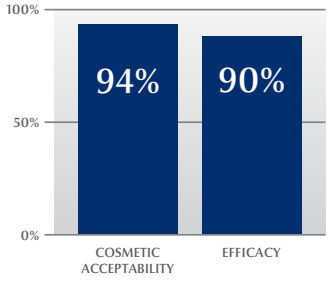

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*Angelova-Fischer, I. et al JEADV 2014, 28 (Suppl. 3), 9-15. **Acceptability study: In-use test under paediatric control, BDF data on file.

Review Article

THE ABC OF DIETARY MANAGEMENT OF PEANUT AND NUT ALLERGY

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ABSTRACT

The global rise in food allergy, including peanut and nut allergies, is well-documented. Nut allergies are the most common cause of life-threatening food-allergic reactions and safe dietary management has classically meant complete nut avoidance. However, recent studies on the primary prevention of allergy and on the facilitation of oral tolerance demonstrate that, on a tailored and informed basis, more active dietary management of nut allergy is recommended. Many specialist allergy centres are already advising safe selective nut eating. A multidisciplinary approach including education regarding food ingredients and regulatory aspects of food labelling is essential to minimise risks and optimise quality of life in this active dietary management of nut allergy. This article examines the practical aspects of supporting patients through this approach, signposting recent and new relevant literature. A brief look at digital tools available to facilitate the safety and variety of a patient's food choices highlights new options for a more patient-specific and tailored approach for potentially improved self-care in food allergy. We await further published evidence due shortly on the potential benefits of safe selective nut eating and on threshold levels for better risk assessments.

BACKGROUND

Food allergy, especially peanut and nut allergies in Westernised countries, is rising and the reasons are multifactorial. UK and US figures approximate that 3–4% of adults and 6–8% of children are affected by diagnosed food allergy and even greater numbers are affected by self-reported food allergy.[1] The South African Food Sensitisation and Food Allergy (SAFFA) study[2] found that 2.5% of one to three-year-old children in Cape Town had a challenge-confirmed food allergy, most commonly to egg (1.9%), with a peanut allergy (PA) prevalence of (0.8%) and lower of hazelnut. While this is below the PA prevalence rates of up to 5% quoted in Western countries such as Australia, the United Kingdom and the United States, as well as the one in five children with eczema, who will develop PA by the age of five years quoted in the Learning Early About Peanut Allergy (LEAP) study,[3] allergy prevalence literature in the developing world confirms that food allergy is on the increase,[4,5] as access to food is more global and homogeneous than in the past.

Due to the potential for severe or life-threatening reactions in nut allergy, logically, the most straightforward and overtly safe approach to prevent children from developing food allergy is to avoid consuming allergenic foods. A diagnosis of peanut or nut allergy classically meant complete nut avoidance, however, practice is now changing following interesting evidence from primary food-allergy prevention studies. The faciliatation of oral tolerance is being further investigated with respect to the assessment of safety, feasibility and the impact on quality of life (QoL) of eating certain 'safe' nuts for children with a known nut allergy.

This article examines the practical aspects of supporting patients through this approach, signposting recent and new relevant literature. We also present digital tools available to facilitate the safety and variety of a patient's food choices through a more personalised approach. Not all allergy practices enjoy the benefit of a specialist dietitian or tertiary allergist, hence some knowledge of current considerations in nut and PA management will benefit patients and professionals and therefore improve the quality of care and QoL.

TABLE I: THE POTENTIAL BENEFITS AND CHALLENGES OF SELECTIVE NUT EATING		
	POTENTIAL BENEFITS OF SELECTIVE NUT EATING	CHALLENGES OF SELECTIVE NUT EATING
For the patient and family	Improved QoL through reassurance in presence of safe nuts and more dietary options.	Precautionary allergen labelling (PAL) can be difficult to risk assess. Individuals vary with regard to anxiety or overconfident behaviours. Eating nuts from shells is safest to reduce the risk of cross-contamination, where possible. Eating out of the home or specific controlled environments remains higher rrisk and is to be discouraged.
	Nutritional benefit especially in cases of multiple food allergy or in vegetarian families.	Other family member/s may have contrasting food exclusions. More expensive than exclusion and certain nuts may be a luxury item or not easily available for regular intake.
	Maintenance of tolerance of relevant nut.	Should only be considered if the child and family commit to at least weekly consumption of the selected nut/s.
For the healthcare professional	Potential to prevent other nut allergies or to promote cross-tolerance between related nuts, for example cashew and pistachio, walnut and pecan.	Selective nut eating is not advocated for fussy eaters or ambivalent carers.
	Ability to offer some options for improved QoL and nutrition for selected families.	Impact on service or increased demand for hospital-supervised food challenges needs to be assessed and managed.

A: AVOIDANCE (COMPLETE OR SELECTIVE?) AND APPLICABILITY OF ADVICE

Children who have an allergy to one type of nut or peanuts are more likely to be allergic, or to become allergic to other nuts. Thirty per cent (1 in 3) of nut-allergic people will react to more than one type of nut.[6] Given these cross-reactivities between groups of allergenic food, particularly tree nuts and peanuts, and the potential for contamination during the food-manufacturing process, complete peanut and tree nut avoidance is an understandable option.

The dual-allergen exposure hypothesis challenges this. It suggests that early environmental exposure to food protein through a disrupted skin barrier leads to allergic sensitisation, whereas early oral exposure to food allergen induces tolerance.[7] This hypothesis has now been tested under stringent randomised controlled trial (RCT) conditions and the findings have led to changes in practice. Recent evidence for PA prevention from the LEAP data[7] and the Enquiring About Tolerance[8] study has resulted in a shift in the approach to weaning onto solids, and it is now accepted that there is a 'window of opportunity' for oral tolerance induction. These studies have resulted in changes to public-health policy globally: rather than avoiding peanuts, early introduction of peanut protein in infants at high risk of PA (those with severe atopic dermatitis and/or egg allergy) is now actively recommended by the World Allergy Organisation (WAO), the Australasian Society of Allergy and Clinical Immunology (ASCIA) and the US National Institutes for Health (NIH) for the prevention of PA.

There is also a growing body of evidence on the safety and benefits of selective nut eating. Brough et al in 2015 stated:

> 'In peanut or tree nut allergic children, introduction of specific nuts to which the child is not allergic may improve quality of life and should be considered in patients with multiple food allergies, vegan or ethnic-specific diets, in whom nuts are an important source of protein.'[9]

This approach may also promote improved nutrition in areas of the world afflicted by malnutrition and obesity. When adopting such an approach it is important to consider safety. Allergy testing by skin-prick test (SPT) and/or spIgE, should be conducted prior to introducing any new nuts. Consideration should also be given to conducting oral food challenges under medical supervision where low-level sensitisation indicates this. Unless and until a patient has been tested for specific nuts and assessed by an expert clinician, it is still safest to advocate complete nut avoidance. It is also useful to be aware of common cross-reactivities, such as between cashew and pistachio, walnut and pecan. These associations can also help the clinician guide appropriate nut avoidance.

While selective nut eating is gaining momentum and has potential for significant benefit, it is important to note that there are associated risks and challenges. Table I summarises many of these.

B: BETTER LABELLING AND INFORMATION

FOOD LABELLING

Understanding food labels is key to making safe choices. For example, peanut may also be known or listed as: *Arachis hypogaea*, beer nuts, cacahuete, chinese nuts, earth nuts, groundnuts, goober nut/pea, mandelonas or monkey nuts. Food-allergic individuals should be given written information regarding the specific foods they are allergic to, with all the possible names they could be referred to by.

Many nut-allergic patients are concerned by foods which are not related to peanuts or tree nuts but which, nevertheless contain the word 'nut': chestnut, water chestnut, coconut,

palm nuts, nutmeg (mace) and butternut squash need not be avoided unless they are known to cause a clinical reaction.

REGULATION

Common food allergens must be listed in the ingredients list of manufactured foods although the list of common allergens varies between countries: 14 allergens in the United Kingodm and eight in the United States. South African regulations relating to the labelling and advertising of foodstuffs were updated to mandate that allergens (gluten, milk, eggs, soya, peanuts and tree nuts, shellfish or crustaceans) or significant cereals (wheat, rye, barley, oats and triticale – a cross between wheat and rye) must be indicated on food labels. Additives such as Tartrazine (E 102 or Yellow No 5), monosodiumglutamate (MSG), sulphur dioxide and related compounds (sodium sulphite, sodium bisulphite, hydrogen sulphites and metabisulphites) must also be declared on labels. Uncommon allergens, namely those not classified in the common allergen category, must be disclosed by manufacturers upon request by a consumer, inspector or the Department of Health.[10]

European Union (EU) food-labelling laws, which continue to cover UK policy to date, also require that labels must state clearly whether tree nuts, peanuts, lupin (a legume which may cross-react with peanut used for flour, especially in French baking) and sesame, as well as other common allergens, are ingredients in a food product.[11] This mandatory disclosure has applied to all pre-packaged food since December 2014. The laws also stipulate that any products that contain peanut (even if an alternative name for peanut is used) should use the term 'peanut' on the ingredient label and those containing tree nuts should list each type of nut (e.g. cashew, walnut, almond). The regulations also apply to foods sold in restaurants and takeaways and 'loose' (without packaging), such as from a bakery, delicatessen, butcher or café, as well as foods packed for direct sale (e.g. sandwich bars, market stalls and some catering products). Since the implementation of these laws, there has been an acknowledged improvement in better visibility of declared allergenic ingredients.

PRECAUTIONARY ALLERGEN LABELLING (PAL)

These warnings, represented in excessively variable wordings, are used by food manufacturers to highlight a possible risk of an otherwise nut-free product being accidentally contaminated by nuts during manufacturing. There is currently no law to say how or when this type of labelling should be used but it appears on a wide variety of products. This is a complex area and the subject of ongoing work in which dialogue between the food industry, regulatory bodies, patient and consumer organisations, and healthcare providers is required so that clear consistent and reliable labelling may be developed.

It is important to note that PAL is not compulsory and therefore one cannot assume the product is free from the relevant ingredient. Cross-contamination remains a risk, and this risk is magnified when eating out.[10] While the advice remains: always check the precautionary allergen labelling, Brough and Turner et al, in their 2015 paper, 'Dietary management of peanut and tree nut allergy: What exactly should patients avoid?', note that although the published rate of peanut contamination in 'snack' foods with PAL ranges from 0.9–32.4%, peanut contamination in non-snack items with PAL is far less common. They propose that in some peanut-allergic patients (depending on history of reactivity to trace levels of peanut, reaction severity, other medical conditions, willingness to always carry adrenaline, etc), consideration may be given to allow the consumption of non-snack foods containing PAL following discussion with the patient's (and their family's) specialist.[9]

REACTION THRESHOLDS

Several studies are underway to establish reaction thresholds for clinical guidance, allergen testing and regulatory standards. The Integrated Approaches to Food Allergen and Allergy Management (iFAAM) study[12] is the follow-on study to the EuroPrevall[13] birth cohort study (within EuroPrevall, the development of food allergies in the first two years of life was assessed and clues were identified as to why some children develop food allergies and others do not). This EU-funded academic/clinical/industry collaboration also aims to develop a clinically validated tiered risk assessment and evidence-based risk-management approach for food allergens for allergens in the food chain.

Studies such as iFAAM and the TRACE study[14] have assessed the eliciting (reaction) dose for peanut-allergic patients, using food challenges where peanut-allergic individuals eat incremental doses of peanut under strict medical supervision. While eliciting doses provide useful information, this is complicated by key factors which may impact an allergic individual's reaction threshold at a given allergen exposure. These include exercise, illness, alcohol consumption, menstruation, seasonal pollens, the food matrix or method of cooking or processing.

In 2014, the Voluntary Incidental Trace Allergen Labelling (VITAL) project proposed a risk-based labelling system with allergen reference doses for precautionary labelling.[15] This work and that of the International Life Sciences Institute;[16] and the TRACE studies are providing ongoing insight into the way forward for a single-dose challenge for individual threshold information. The TRACE study is due for publication this year.

Eating out presents particular challenges for food-allergic individuals related to variable allergen management, education and communication along the chain. Up to one-third of accidental ingestions occur when eating in

restaurants and another 13–23% occur in other eating-out environments, such as school canteens.[17] Legislators and food-providers need guidance to provide clear allergen information via trained and pro-active allergen-aware staff to improve confidence in eating-out choices.[18]

Key messages for patients, however, remain the same:
- always be vigilant when food is around;
- check food labels;
- be proactive when eating out;
- carry prescribed medication everywhere;
- learn how and when to use your adrenaline auto-injector (with a view to earlier recognition of symptoms);
- ensure that asthma is well managed.

For selective nut eating, it is strongly recommended to do so at home to better control any risk of cross-contamination. Eating nuts from the shells avoids the risk of cross-contamination from other nuts. Patients and their carers will need guidance to recognise foods where the risk of cross-contamination is particularly high. These include African and Asian dishes, baked goods (e.g. pastries, cookies, crackers, bread) and confectionary. It is also important to inform families that the selected nuts should be eaten regularly; long periods of avoidance of a select nut may result in new onset allergy, particularly if children showed low-level sensitisation before introducing specific nuts.

The food-allergic patient should have an individualised Allergy Action Plan. Most UK centres use the British Society of Allergy and Clinical Immunology's plans, available online in several versions tailored to the relevant adrenalin device prescribed (see http://www.bsaci.org/about/download-paediatric-allergy-action-plans). In South Africa, an action plan is freely available via the Allergy Foundation of South Africa website.

EDUCATING HEALTHCARE PROFESSIONALS

For healthcare professionals operating in the rapidly changing allergy landscape, continuing medical education is essential. Standard IgE tests or SPTs may be positive to more than one nut due to cross-reactivity (allergens common to several nuts), or co-sensitivity (frequently associated positive test results without true cross-reactivity) and evidence of clinical reactivity is advisable before advocating sustained avoidance. Component testing facilitates decision-making to differentiate between the likelihood of direct allergy vs pollen cross-sensitisation.[19]

C: CONSIDER CHALLENGE, CLINICAL CONTEXT AND CURRENT PRACTICAL ADVICE

The decision whether to consider nut avoidance or selective nut eating is often best undertaken through medical supervision through an oral food challenge. Sensitisation to peanut alone is insufficient for a diagnosis of PA in most, and conducting an oral food challenge in these children is advisable, providing the family are willing to introduce peanut protein to their diet regularly (2–3 times a week) after the challenge.

Once peanut or tree nut allergy is confirmed, the patient and family should receive a dietary review and preferably a referral to a dietitian for nutritional assessment and advice on the appropriate avoidance and substitution. Patients receive a burden of new information, and best practice is to provide written information for reference and to signpost additional appropriate information. This may come via local hospital trusts, national and international allergy or dietetic societies, health departments and patient-support organisations.

SELECTIVE NUT EATING

The Pronuts study based at King's College London University, led by Dr Helen Brough with Prof G Lack, evaluated whether in children who already have one nut allergy, the introduction of nuts and seeds to which they are not allergic may prevent the development of new nut allergies. The feasibility of performing challenges to several nuts and seeds, and the introduction of the safe nuts and seeds into the diet on a regular basis was assessed. The definitive results of the randomised controlled trial await publication. The existing Pronuts study work has helped to inform the dietary advice on eating certain 'safe' nuts for children with a known nut-allergy.[20] Selective nut consumption should only be considered if the child and family are committed to a regular intake of the relevant nut/s 2-3 times a week. The LEAP study used 2g peanut protein 3 times a week,[3] but no amounts have been validated for the tree nuts as yet. The main points are summarised as:
- Ensure that your child's emergency medicine is in date and easily accessible.
- Only offer your child the nut(s) that they tolerate when in your own home.
- When out of the house (at school, visiting family, in a restaurant or at a party), it is advisable that your child avoids all nuts due to risk of cross-contamination and possible confusion about identifying different nuts.
- Offer the tolerated nuts in pure form only, for example cracked from the shell or from a single nut pack (whole nuts rather than ground). Avoid if in processed foods, such as bread, cakes, biscuits, cereal bars or chocolate, due to the increased risk of cross-contamination with other nuts to which the child may be allergic.
- Nut oils: neutralised, bleached, deodorised (NBD) peanut oil will not cause allergic reactions for the majority of peanut-allergic individuals due to the negligible protein content but this is not the case with cold-pressed or unrefined oils, which should be avoided.
- Discuss your approach to 'May Contain Nut' products with your dietitian or your allergy team for specific advice for your child.

Detailed advice on precautionary allergen labelling and education on how to read the label, with practical tips is given in an additional resource available to members of the British Dietetics Association, written by the Food Allergy and Intolerance Group (FAIG) called 'Peanut and Tree Nut Allergy: Dietary Advice for Adults, Young People, Parents and Carers'.[21]

CHOOSING SAFE FOODS

It is known that food-allergic consumers take longer to shop due to reading labels and that this has a significant impact on QoL.[22] New tools to assist safe food choices are available or are being developed and this offers the patient options for food choices, improves self-care and allows specialist dietitians' time to focus on more on personalised information.

DIGITAL ALLERGEN INFORMATION TOOLS

Food ingredient platforms or digital applications to aid buying safe foods are increasing in number and improving in quality. Allergy consumers are enabled to set up their own allergy profile and dietary requirements and, when the pre-packaged food's barcode is scanned, a symbol indicates instantly if the food is likely to be a safe choice, based on the labelling supplied by the manufacturer, and with extra product or recall notes if available. These systems vary and patients should be advised to choose a system that is regularly and automatically updated when there is a change in the recipe. Those systems with clinical backing are to be favoured, and in the United Kingdom there are leading apps supported by dietetic and allergy clinicians, as well as patient support groups. Validation work looking at these is in process and major allergy bodies will be reviewing apps over time to offer the best recommendations for patients and their families.

Most recently and controversially, patient-held food-allergen detection systems are being developed and publicised. The commercial sensor uses the chemistry used to make all allergen detection possible, equivalent to those used by many allergen test-kit companies, namely, a special immunoassay called a 'Lateral Flow Device'. The concern with these kits is that they can only, even if appropriately used and accurate, test the small area of food inserted into the device at the table. As most food is not a homogenous mixture of allergens and ingredients, especially with nut-containing foods, the pitfalls are self-explanatory. Concerns include permitting a false sense of security with a negative test which could result in the individual experiencing a severe allergic reaction, and false positives or unvalidated thresholds leading to confusion. For now these systems cannot be safely recommended to allergy patients at risk of immediate reactions.

Finally, depending on the tastes, priorities, resources, baseline level of experience of allergic reactions and anxiety related to the potential risks of the patient and family in question, managing the practical aspects of selective nut eating may not represent an improvement in QoL, even when counterbalanced with the hope of maintained tolerance to the specific nut. Decision regarding selective nut eating should be reviewed regularly and patients are advised to avoid a nut if not eaten for more than six months, due to the risk of having developed that nut allergy, unless specifically reassessed.

It remains to be proven whether selective nut eating reduces the rate of other nut allergies or promotes cross-tolerance or if clearer advice on reaction thresholds of specific foods and improved food-ingredient awareness through better labelling will lead to a better patient experience and fewer reactions. We eagerly await the results of the studies mentioned that are due to be published soon.

CONCLUSION

The impact of the diagnosis of food allergy permeates many aspects of the life of a patient, their family and society. Depending on the age, when nut allergy is diagnosed, safe nuts can be introduced into the diet if there are clear guidelines given for safe eating and management of accidental reactions. While evidence for best practice is growing, it is the allergy clinician's duty to best assess the safety, feasibility and factors likely to influence QoL in each patient's case.

This necessitates a multidisciplinary approach and specific education around food ingredients and labelling, involving specialised medical and dietetic personnel, as well as parents and schools. Optimising QoL through the promotion of better food labelling and an active approach to safer, broader food choices makes the active management of allergy, aiming at maintenance of tolerance, an area of growing interest for patients and allergy-aware clinicians.

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DECLARATION OF CONFLICT OF INTERESTS

Lauri-Ann Van der Poel co-developed Foodmaestro, a digital ingredients platform with an app of the same name, and is a currently a shareholder.

Helen Fisher has no conflict of interest to declare.

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Review Article

FOOD ALLERGIES – SHOULD WE BE GOING PEANUT-FREE IN SOUTH AFRICAN SCHOOLS?

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INTRODUCTION

Peanut allergies (PAs) have increased tremendously in some countries in the past few years, with the United Kingdom showing a doubling in PA prevalence over the past few decades.[1] Data in South Africa suggest a PA prevalence of 1–2% of the childhood population,[2] which means that up to 1 in 50 children has a PA. In reality, in most average-sized schools, with three–four classes per grade, this equates to 1–2 children per grade.

There are many other causes of food allergy, including cow's milk, egg, seafood and wheat, but PA in particular has caught the public's attention because of the reported severity of reactions.

There are several reasons why PA is of particular concern:

- PA has increased at a rate which has been difficult to explain.
- There is a spectrum of severity of PA but peanut is the most common food causing serious adverse effects and anaphylaxis in children.[3]
- Although a small percentage of children outgrow their PA, the allergy is usually lifelong.
- Peanut is a commonly consumed and nutritious snack that is frequently used as a sandwich filler.
- Peanut is a 'sticky' allergen: it can stick to surfaces, toys and computer keyboards for a long time.[4]

ALLERGIES IN SCHOOLS

Going to school is an extremely stressful time for food-allergic children and their families, as they move from a controlled to a relatively uncontrolled environment. Understandably, many parents tend to be over-anxious or overprotective during this transition.

More and more schools are starting to understand the severity of allergies, yet there are frequently instances of pushback from staff and other parents when it comes to allergen safety: this is an international problem, not one confined only to South Africa. Essentially, it can become a battle between the right to eat peanut butter, a nutritious and convenient snack, and the right to stay safe or even alive for those with severe allergies. While the majority recognise that parents want to keep their children safe, the minority sometimes make a real fuss. Unfortunately, the minority view can lead to ostracism or even the bullying of children with allergies.

It is a child's right to stay safe during eating time and to be socially included. With this in mind, what is the best approach to nut allergy in schools?

IS A TOTAL BAN OF NUTS IN SCHOOLS THE ANSWER?

A total ban of nuts is an option, but not necessarily the answer for all schools. Further research is needed regarding the pros and cons of a total nut ban in schools. Potential disadvantages of a total nut ban include:[5,6]

- A false sense of security. In reality, an allergic child and their teachers should always be prepared for a reaction and should not let their guard down.
- A total nut ban is not representative of the 'real' world and the child may not be equipped to deal with the reality of allergens outside the school environment, on outings, at birthday parties, etc.
- It may make the school lax about other protective measures – for example, hand-washing – which may become an issue if there is a 'lapse' in the nut-free status or a child is given a nut-containing sandwich by a caregiver in error, and no further nut-reduction techniques may be in place if the school is 'nut free'.
- A nut-free school may discount other food allergies – for example, egg and milk allergies – that may be just as severe, but this may not be recognised if the school is considered to be 'allergen free'.

A recently published study from the United States provided the first large dataset (over 2 000 schools over a five-year period) exploring the effects of school peanut-free policies on clinical outcomes. Interestingly, this study identified higher rates of adrenaline usage in schools with peanut-free policies compared to schools without such policies.[7]

TABLE I: RESPONDING TO ALLERGIC REACTIONS[8]

1. Assess whether the reaction is either mild or moderate/severe.
2. If any uncertainty exists, treat it as a severe reaction.
3. Severe reactions (involvement of breathing, throat, cardiac or abdominal systems):
   a. Administer adrenaline via auto-injector (Epipen®):
      Remove the blue safety cap.
      Hold the pen in the fist with the orange end pointing towards the child's outer thigh.
      Holding the leg firmly, place the orange end of the pen on the mid-outer thigh and push firmly until a click is heard.
      Maintain the pressure for five seconds to ensure the medication is released. Remove the pen and massage the injection area for ten seconds.
   b. If wheezing or chest tightness is present, administer reliever medication (via an asthma pump):
      Administer one puff at a time using a spacer device and allowing ten breaths to breathe it in.
      Repeat this ten times over ten minutes.
   c. Give antihistamine as per the emergency action plan.
   d. Transfer to hospital even if symptoms resolve promptly. Do not allow the child to stand suddenly as this can lower their blood pressure.
4. Mild reactions (involvement of the skin only, without any other systems involved)
   a. Administer antihistamine as per the emergency treatment plan.
   b. Locate the adrenaline auto-injector and assess the child for any escalation to severe reaction. If their reaction is uncertain, treat as a severe reaction.
   c. Children with mild reactions may not need to be sent home, but parents must be notified of events. Review the avoidance and preparedness measures.

SO WHAT ARE OUR OTHER OPTIONS?

Both the Allergy Society of South Africa and the Allergy Foundation of South Africa advocate that schools should be 'allergen aware' and 'allergen safe' rather than necessarily being totally allergen-free.[8] Going nut-free is a major, and commendable, step that some schools have chosen to take, and they deserve kudos for doing this. Alternative options do exist, however, and these include:

- Nut-free classrooms or zones for those children in a class with a nut allergy, particularly if it is a severe allergy.
- A nut-free table or protected eating area, which is cleaned regularly.
- An integrated eating area, but a strict policy of no lunchbox sharing.
- Close supervision of eating times if there is an allergic child in the class.
- Strict handwashing after meal times to minimise the transmission of allergens to work surfaces.

The school should decide on which allergy-aware options they will adopt and make specific plans accordingly.

WHAT OTHER MEASURES NEED TO BE TAKEN?

Under all circumstances, whether allergen free or allergen safe, the following steps need to be taken if there are food-allergic children in a school:

- Make a point of becoming aware of children's allergies. Each school should have a form for capturing details of medical conditions, including allergies and chronic medications, to be completed by parents/guardians at the beginning of each year. This information should be verified by a doctor in the form of an official chronic-care plan. The form should clearly indicate confirmed food allergies and their severity. Details of the food allergy should be recorded in the learner's profile.
- Elicit the support of co-learners, their families and school staff to limit the presence of specified food allergens on the school premises, in tuckshops, and at after-class activities, parties, trips and school events. In the case of a severely allergic child, a letter written by the child's doctor/allergologist to the parents/caregivers in the class explaining the need for allergen awareness will go a long way towards educating learners and parents, and towards gaining their support.
- Avoid the use of common food allergens in classroom projects or activities, as rewards or incentives, if there is a food-allergic child in the class. Suitable 'safe treat' alternatives can be identified, discussed with the child's parents or doctor and kept at hand for allergic children.
- Be vigilant around meal times and introduce a designated routine for them.
- Do not allow any lunchbox sharing with an allergic child.
- Instil a general habit that children wash their hands before and after meal times to reduce the carriage of allergen.
- Put in place an official emergency treatment plan for allergic children in case of accidental ingestion of allergens; this includes identifying a reaction and knowing what the appropriate response should be. The emergency treatment plan should document which medications the school personnel are mandated to administer and when they should be administered, and should be signed by the child's doctor as well as the parents/legal guardians. This action plan be kept in the child's classroom as well as in the school secretary's office; it should include a photograph of the child and should state where the child's emergency kit is kept.
- Ensure that emergency medications available, accessible and up to date. The child should have an emergency kit which includes the action plan, to be kept in a safe place (either in the child's bag or accessible in the secretary's office, or both).
- Ensure that staff are well trained in recognising a reaction and using emergency medication. Schools must maintain a record of all the medications used in an emergency, notify parents immediately and document the circumstances of the incident.
- Reassure staff that no legal action will be taken if they give the emergency medications, if deemed necessary.
- Consider keeping a generic 'emergency box' with allergy medications such as antihistamines and an adrenaline auto-injector (Epipen®) for use with children

with previously undiagnosed allergies, or for those who, for whatever reason, do not have an emergency kit at hand. Recent legislation in the United Kingdom allows schools to obtain an adrenaline auto-injector (Epipen®), without a named prescription, to be kept on campus for emergencies.[9]

- Each child with a suspected food allergy should be seen by an allergologist to confirm the diagnosis and to grade the severity of their reactions. This can help to put the risk into perspective. For example, the school strategy for someone with mild oral itching in response to nuts may be very different from that for someone with a severe life-threatening reaction.
- Treat allergy-related teasing or bullying seriously and, if necessary, implement the school's anti-bullying policies.

ALLERGY TRAINING IN SCHOOLS

Schools should form a small body of teachers who comprise the 'allergy action committee', ideally incorporated into the school-based support team. These particular teachers need up-to-date training on allergy-avoidance measures, recognition of reactions and administration of emergency treatment. This committee should be aware of all the food-allergic children in the school, should know exactly where the emergency medications are kept, and should be the 'go-to' people in the case of an allergy emergency. They should all undergo online training such as that provided by the Allergy Foundation of South Africa, at www.allergyfoundation.co.za.

In addition:

- All teachers, sports coaches, secretaries, cafeteria staff and other staff should be trained in allergy

TABLE II: EXAMPLE OF A PARENTS'/DOCTOR'S APPROVAL FORM FOR ADMINISTERING MEDICATION BY SCHOOL TEACHER(S)[8]

Parents/guardians/caregivers please note: The school can refuse to administer medication to your child if the form below is not completed by both you and your medical doctor and the requirements below are not met. Medication must be supplied in the original container. Ask the pharmacist to supply medication in two fully labelled containers, one for home use and one for school use. Only medication authorised by a medical practitioner may be administered by school personnel. It is the parents' responsibility to notify the school when there is a change in medication. It is the parents' responsibility to provide all supplies, medication and/or equipment necessary for administering any medication(s), and to collect from the school any medication not used during the specified period.

Learner's name: …… Grade: ……..

Condition for which medication is required: ……

MEDICAL PRACTITIONER

Name of medical practitioner: ……..

Contact number: ……

Name of dispensing pharmacist: ……..

Contact number: ……

Brand name of medication: ……

Method of administering: ……..

Frequency and time of administration: ……..

For how long will your child be taking this medication? ……

Special precautions/instructions (eg storage): ……

Possible side-effects: ……

Is the medication to be self-administered?

Signed: …….. Date: ……..

PARENT/GUARDIAN

Name: ……

Contact number (in event of emergency): ……

Relationship to learner: ……

I hereby request …… (Name of school) to administer the abovementioned medication(s) to my child as detailed above. I agree to the requirements of this guideline document. I understand that the school has the right to refuse to administer the medication if these requirements are not met. I understand that this request is valid for only one year, and will need to be renewed annually.

awareness. All members of staff should know their roles in the case of emergencies. They should all know where emergency medication is kept.
- Teachers and cafeteria staff should be trained in basic food-handling and cleaning procedures to prevent cross-contamination from hands, surfaces and utensils if foods containing the known allergen are prepared and/or served in the classroom of a food-allergic child.
- Education for learners regarding allergies can be built into school curricula, for example Health, Science or Life Skills programmes.

CONCLUSION

In conclusion, providing a safe school environment for students with life-threatening food allergies is essential to allowing children to achieve their full potential in a healthy and safe learning environment. Going 'allergen-free' – for example, nut-free – may be an option for some schools, but is not the only approach and it is not without its potential disadvantages. We strongly advocate taking the steps outlined in this document to create 'allergy awareness' and an 'allergen-safe' learning environment.

DECLARATION OF CONFLICT OF INTEREST
The authors declare no conflict of interest.

This article has been peer reviewed.

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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. This CPD activity is for ALLSA members only.

DEVELOPMENT OF PEANUT ALLERGY AND THE ROLE OF ENVIRONMENTAL EXPOSURE

1. *True or false:* Filaggrin loss of function mutations have been shown to increase eczema but not food allergies.
2. *True or false:* Eczema itself is a significant risk factor for developing peanut allergy, especially if severe and of early onset.
3. *Choose the correct answer:* If a child has a peanut allergy, the risk of peanut allergy in a sibling is around:
   a. < 1 %
   b. 2-3%
   c. 6-7%
   d. 20-25%

PEANUT INTRODUCTION AND THE PREVENTION OF PEANUT ALLERGY: EVIDENCE AND PRACTICAL IMPLICATIONS

4. *True or false:* Peanuts are amongst the most common food allergens causing food-induced anaphylaxis in children.
5. *True or false:* The LEAP study studied patients at low as well as high risk for peanut allergy.
6. *True or false:* The LEAP study showed that in patients at high risk of peanut allergy, early introduction of peanut protein may be advantageous for allergy prevention.
7. *True or false:* In advising caregivers on early peanut introduction in infants, a total of one gram peanut protein weekly seems sufficient for sustained effect in reducing peanut allergy.
8. *True or false:* In an infant, never knowingly exposed to peanut before, with eczema and a skin prick test to peanut protein of 5 mm, a careful home challenge to peanut should be advised.

CPD Questionnaire continued on page 38.

Allergies in the workplace

OCCUPATIONAL HEALTH PROBLEMS ASSOCIATED WITH THE FIBREGLASS-REINFORCED PLASTIC INDUSTRY

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ABSTRACT

The demand for fibreglass-reinforced plastic (FRP) has increased progressively and in many fields its use has replaced asbestos. FRP is a composite material comprising glass fibres embedded in a resin. Because of its strength, light weight and durability, it has many uses, among others, the production of textiles, aircraft, automobiles, bath tubs, enclosures, boats and ships. FRP manufacturing requires embedding of the glass fibres in a resin which may contain organic solvents such as methyl ethyl ketone peroxide (MEK) and styrene, known neurotoxins which contribute to several health problems.

Commonly observed health conditions among workers in the FRP industry include cancers, and skin, respiratory and neurobehavioural symptoms, as the employees are exposed to a wide variety of hazards (chemical, physical and ergonomic). This case report highlights the causal agents associated with contact dermatitis in a FRP laminator. Clinical evaluation and a careful history were supplemented by a workplace visit and patch testing. Although exposed to many hazardous substances, this worker was allergic to the components used in manufacturing the rubber gloves given as personal protective equipment (PPE). This emphasises the important contribution of PPE to occupational dermatoses.

CASE REPORT

A 38-year-old female laminator in the FRP boat building industry presented to the workplace occupational health clinic with a two-year history of an itchy rash on both hands. There was no past medical history of allergies and no history of atopy, in particular, no eczema or asthma. She had a background history of hypertension controlled by one hydrochlorothiazide daily. She is a single parent supporting one child.

She had worked as a laminator for the past 12 years. The laminating process involves the gradual build-up of layers of woven glass-fibre material impregnated with resin matrix in a mould. The resin is worked into each layer of glass fibre with a roller. Because of hazardous chemicals in the resin (styrene active diluent) and the hardener, MEK peroxide, laminators wear natural-rubber latex gloves for most of the working day. A laminator uses up to three pairs of gloves per day, because when working with a resin and fibreglass, these substances adhere to the gloves and damage them by making them hard. If small particles adhere to gloves, these are removed with acetone and the gloves are re-used. However, this shortens the life of gloves which means the gloves must be replaced more often. The patient related the onset of her rash to the use of latex gloves. Two years after the start of her skin rash, she was seen by the occupational health nurse at her work with itch, swelling of her face and neck, and red eyes. She was referred to a local hospital and diagnosed with 'latex' allergy. The work arranged for her to get nitrile gloves with cotton inners (see Figure 1), and for some time she had no skin rash.

However, nitrile gloves were sometimes not available in the factory, and when she returned to wearing latex gloves, her skin rash would flare up again.

When we saw the patient at the occupational skin clinic, she had used latex gloves for three days and the rash on her hands had flared. Scaly erythematous plaques, lichenification and excoriations were evident on the dorsum of the hands (see Figure 2). The palms were spared. There were no acute lesions at the time of examination, but these had been present previously. The rest of her skin was normal. The pattern of dermatitis noted in this laminator is classic for a glove-allergic contact dermatitis which typically involves the dorsum of the hands (see Figure 2).

Advantan® disrupts the Itch-Scratch cycle by relieving the itch in eczema[1]

Advantan®
methylprednisolone aceponate

Reference: 1. Garcia Ponte L, Ebert U., Frontiers of Rapid Itch Relief: A review of methylprednisolone aceponate. JEADV 2012, 26, (suppl. 6), 9-13

ideal for use in aerospace, wind-generator, marine and automotive industry constructions.

The UP resin matrix used by the patient, includes a base resin (UP), styrene and auxiliary chemicals. Styrene is an essential reactive diluent which thins the resin making it easier to incorporate into the fibreglass during the laminating process. As a reactive diluent it is chemically incorporated into the final plastic as a polymer cross-linking agent and thus does not need removal from the final composite.[3] Auxiliary ingredients include accelerators, inhibitors, hardeners, catalysts and a variety of pigments. Most of the industry uses MEK peroxide as a hardener and cobalt naphthenate or diethylaniline as an accelerator. Furthermore, acetone is used for cleaning purposes.[4] Workers in the FRP industry are heavily exposed to fibreglass particles, styrene, uncured resin and MEK peroxide.

SKIN DISEASES

One of the commonest health effects in the FRP industry is occupational skin disease. Irritant contact dermatitis (ICD) is more common than allergic contact dermatitis (ACD).[5] Epidemiological studies conducted in various factories manufacturing FRP have reported the prevalence of occupational dermatoses in the industry as 62.45% in wind-turbine industries followed by 58.85% in factories making boats and tanks.[6]

A 1993 survey of 100 workers (86 from the FRP industry, 11 from the polystyrene production industry and three from polyester resin-coating manufacture) reported that 26% (22/86) of the FRP workers had occupational dermatoses. Most were mild with only three workers requiring sick leave. ICD accounted for 12 cases, four were due to accidental injuries and six had ACD. The ACD was due to natural rubber in gloves (*n* = 4), phenol-formaldehyde resin (*n* = 1) and cobalt naphthenate (*n* = 1). ICD was caused by the dust and mechanical friction of clothes (*n* = 7). Irritant hand dermatitis was caused by the combined hazards of unsaturated polyester or vinyl ester resins, fibreglass, organic solvents and dust from finishing work (*n* = 5).[7]

A Japanese survey examined skin problems in 148 workers from 11 small to medium-sized FRP industries exposed to unsaturated polyester resins and a variety of auxiliary agents including styrene. Skin problems (itch and dermatitis) were reported by 58.8% (87/148) of workers, 17% (25/148) of whom had consulted their doctor. One worker had severe dermatitis and took sick leave.[4] An interesting finding was the seasonal occurrence of skin problems identified by examination of 67 workers, 23.3% were documented with skin problems in summer and 13.4% in winter.

A Spanish study reported on ten workers with suspected dermatitis attending an occupational health clinic, who were employed in the wind-energy industry. Materials used in the construction of the wind-turbine blades include epoxy resin (bisphenol) and curing agents strengthened by glass fibre. Five workers (5/10) were diagnosed with ACD to epoxy resin. The diagnosis of the remaining five workers (5/10) was ICD.[4]

Figure 1: Nitrile glove used to replace natural rubber later ones.

These studies were significant in demonstrating that multiple exposures can cause skin diseases.

RESPIRATORY DISEASES

Another important health effect in FRP industries is respiratory disease. A National Institute for Occupational Safety and Health (NIOSH) cohort study conducted in Washington State between 1959 and 1978 among styrene-exposed workers in the FRP boat-building industry reported an overall mortality of 598 deaths (standardised mortality ratio (SMR) = 0.96, CI 0.89–1.04), including non-significant excess mortality from lung cancer (SMR = 1.23, CI 0.95–1.56) and chronic obstructive pulmonary disease (COPD) (SMR = 1.15, CI 0.81–1.58). COPD mortality increased two-fold (SMR = 2.02, CI 1.08–3.46) among 580 workers with potential high-styrene exposure.[8]

She responded well to highly potent topical steroids and emollients, but the rash recurred as soon as she started using latex gloves.

A walk through of the laminating, painting, moulding, assembly and joinery areas was undertaken. The moulding and lamination took place in a large open, well-ventilated shed. Laminators applied fibreglass sheets and resin manually to preformed gel-coated moulds in a bending or kneeling position for most of the day, often positioned on top of the structure under construction. Exposure to uncured resin and additives was thus unavoidable. The workers were provided with PEP including respirators, disposable overalls and gloves which were variably used. Some workers wear their own clothes which are presumably washed at home, a potential hazard for family. The laminators wore natural-rubber latex gloves for most of the working day and needed to change them regularly due to damage and contamination. Several hazardous substances (see Table I) and exposures were identified.

In accordance with the International Contact Dermatitis Research Group Guidelines (ICDRG),[1] a patch test was performed using a standard battery of 45 commercially available common allergens applied in Finn chambers. The allergens included rubber additives, fragrances, formaldehyde, formaldehyde-releasing preservatives and some dyes and resins. Because of the classic pattern of the dermatitis – supported by her dermatitis history – a glove-allergic contact dermatitis seemed the most likely diagnosis and none of the hazardous substances identified during the work visit were incorporated in the initial patch testing. The patch tests were removed after 48 hours occlusion and the results were read 24 hours later. A strong (2+) positive reaction was noted for thiuram mix and carba mix (both rubber allergens supporting glove dermatitis), nickel sulphate and paraben mix. A weak positive reaction was noted for cobalt chloride (1+). The remaining allergens, including epoxy, tested negative.

EPIDEMIOLOGY OF OCCUPATIONAL DISEASE IN THE FRP INDUSTRY

Global demand for FRP has grown rapidly in the past 30 years and is expected to continue to grow in the future.[2] Production capacity has increased significantly at an annual growth rate of 33% between 2002 and 2006. Worldwide production of FRP was approximately 4.2 million tons in 2007, whereas demand was 4.5 million tons. In China alone, the production of FRP was 38.1% of the global FRP production.[2] Unfortunately, there is little information about the South African FRP industry.

TABLE I: THE MAIN ALLERGENS AND IRRTANTS IDENTIFIED IN THE PATIENT'S WORKPLACE

SUBSTANCE	MODE OF ACTION
Glass fibre (reinforcing fibre)	Irritant
Styrene (active solvent diluent and cross-linking agent)	Irritant and type I and IV Allergen
Methyl ethyl ketone (MEK) peroxide	Irritant and type IV allergen
Cobalt naphthenate (auxiliary agent)	Irritant and type IV allergen
Acetone (solvent used for cleaning)	Irritant
Unsaturated polyester resin (UP)	Potent type I and IV allergen
Natural rubber latex (PPE gloves)	Type I and IV allergen

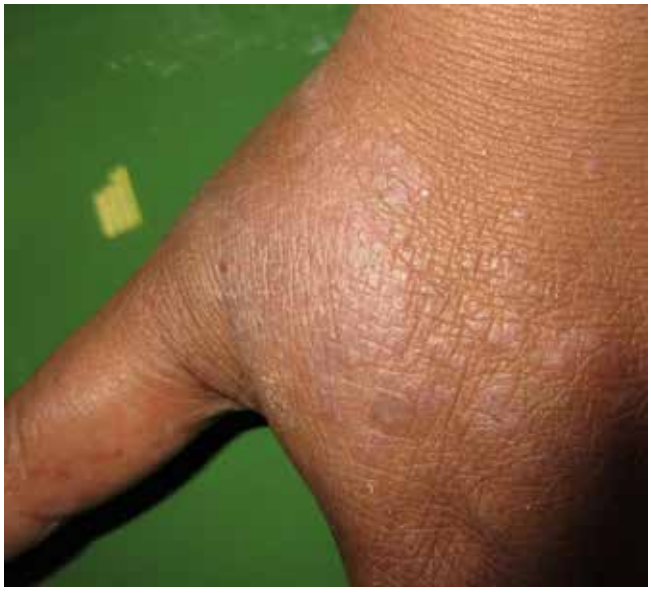

Figure 2: Scaly erythematous plaques, lichenification, and excoriations of the dorsum of the left hand with excoriated vesicopapules on the thumb border and 1st webspace.

FRP is a composite material made of a polymer matrix reinforced with fibres. The fibres are usually glass ('fibreglass'), carbon, aramid (aromatic polyamide) or basalt. Fibres such as paper, wood or asbestos are rarely used. The polymer is usually an epoxy, vinyl ester, unsaturated polyester or rarely phenol formaldehyde resin derivative. When combined with agents to enhance or alter the material properties of the polymer, the polymer is known as a 'plastic'. Composite plastics refer to plastics that result from bonding two or more materials with different material properties to achieve a final product with specific characteristics. Fibre-reinforced plastics are a category of composite plastics that specifically use fibre materials to mechanically enhance the strength and elasticity of the plastic. The extent that strength and elasticity are enhanced in a fibre-reinforced plastic depends on the mechanical properties of both the fibre and matrix, their volume relative to one another, and the fibre length and orientation within the matrix. Reinforcement of the matrix occurs when the FRP material exhibits increased strength or elasticity relative to the strength and elasticity of the matrix alone. The fibrous material is bonded with the matrix during moulding. FRP moulding begins by placing the fibre on, or in, a mould. Dry fibres are 'wet' with resin and then cured, leaving the matrix and fibres in the shape created by the mould.

The composite materials are stable, strong, light and imperious to sound, solvents and water making them

A literature review, analysing 55 articles from industries using styrene, identified ten case reports of obliterative bronchiolitis, eight of occupational asthma and four of chronic dyspnoea. Thirteen (87%) of 15 cross-sectional studies of workers provided evidence of an association between styrene exposure and airflow limitation. Furthermore, six out of nine mortality studies found excess COPD-related mortality.[9]

CANCERS

According to the International Agency for Research on Cancer (IARC), styrene is classified as possibly carcinogenic in humans and experimental animals.[10]

Various cancers have been associated with exposure to FRP. One Danish study followed 36 610 workers of FRP industries, mostly involving boat-building and hand-lamination techniques, and 14 293 workers not exposed to styrene between 1970 and 1990. A standardised incidence ratio (SIR) of 3.16 (95% CI 1.03–7.39) for cancer of the salivary glands was reported for employees exposed to styrene from the 1960s. Compared to workers not exposed to styrene, workers in the FRP industry with the highest exposure probability had a statistically significant two-fold increased incidence of pancreatic cancer.[11]

Among the 598 deaths recorded for styrene-exposed workers in the FRP boat-building industry reported in the National Institute for Occupational Safety and Health (NIOSH) mortality cohort study, excess lung (SMR = 1.23, CI 0.95–1.56) and ovarian cancer (SMR = 3.08, CI 1.00–7.19) were recorded.[4]

A retrospective cohort study extended the study period of the NIOSH mortality cohort of workers at two FRP boat-building plants between 1959 and 1978. Overall, 860 deaths occurred among 5 204 employees (SMR = 1.09, CI 1.02–1.17) with excess mortality for oesophageal cancer (SMR = 2.30, CI 1.19–4.02, *n* = 12) and prostate cancer (SMR = 1.71, CI 1.09–2.54, *n* = 24). They also showed a higher incidence of urinary tract cancer (SMR = 3.44, CI 1.26–7.50, *n* = 6) among 2 062 highly exposed workers, which increased with duration of employment.[12]

NEUROBEHAVIORAL EFFECTS

Exposure to substances in FRP industries can result in several neurobehavioural effects.

A study done in the boat-building industry in Finland demonstrated that the laminators who were exposed to high levels of styrene had worse postural stability than non-laminators and the impairment was witnessed at a younger age (less than 50 years).[13]

In 1989, a Belgium cross-sectional study of workers was performed three years after the closure of a FRP polyester boat-building plant. The study found that most complaints disappeared after the end of exposure, although abnormal equilibrium and reduced sense of smell persisted in previously exposed workers ($p \leq 0.05$). These results suggest that at an average concentration of 155 mg/m^3 of exposure to atmospheric styrene for less than ten years may result in persistent neurotoxic effects.[14]

ALLERGENS IN THE FRP INDUSTRY

Sensitisation prevalence to substances used in the FRP industry is increasing among workers.[5–7] Specific substances and chemicals are recognised as allergens in the FRP industry as described in Table II. The most common causes of ACD are epoxy resin compounds. Polyurethanes which are well-known causes of asthma, rhinitis and conjunctivitis are also implicated in ACD. Carboxylic acid anhydrides may cause IgE-mediated rhinitis and asthma.[6]

Occupational skin dermatoses among plastic composite industry workers was described in 2% (43/2 178) of workers diagnosed with occupational skin disease attending a tertiary Finnish Occupational Health Service from 1974 to 1993. ACD accounted for 32% (18/43) of those with occupational dermatitis in the FRP industry and was second only to ICD at 49% (21/43). Immunologic contact urticaria accounted for 9% (4/43) of skin diseases. Epoxy accounted for most ACD. Asthma (2 cases) and allergic rhinitis (1 case) caused by exposure to epoxy resin or its hardeners was also reported.[5]

A retrospective Finnish study screened the patch-test results of 4 445 workers from 1991 to 2014 for allergic reactions to various epoxy resins, epoxy hardeners and reactive diluents in their baseline, epoxy compound, and plastic and glues allergen patch-test series. A positive reaction to diglycidyl ether of bisphenol A resin (DGEBA-R) was found in 4.1% (181/4 445) workers. No testing was done in 17 workers with known contact allergy to DGEBA-R. The total number with DGEBA-R was 4.5% (198/4 445). The total number of patients with sensitivity to the epoxy resin system was 5.4% (240/4 445). Thirty-one (13%) of the 240 patients gave no history of exposure to epoxy resin systems leaving 209 (87%) of tested workers diagnosed as occupational contact allergy to epoxy resin products.[15]

Most of the chemicals used by employees in FRP product manufacturing, including UP resin, styrene and hardeners have been reported to cause both ACD and ICD.[4] A case report described a worker in the boat-building industry with occupational hand dermatitis. Patch testing showed one weakly positive (1+) reaction to cobalt-2-ethylhexanoate (used as an accelerator in UP resin). The diagnosis was not clear initially, but after the patient's pruritic rash improved on holiday an occupational dermatoses was strongly suggested. The patch test was repeated with commercial allergens, a selection of his own diluted samples, plus two

TABLE II: COMMON ALLERGENS FROM THE FIBREGLASS INDUSTRY (MODIFIED FROM TARVAINEN AND KANERVA)[4]

INDUSTRIES	ALLERGENS	ALLERGY REACTION
Aircraft-building	DGEBA ER ER amine hardener Non-DGEBA epoxy resin UP resin Chromium (VI) Cyclohexanol peroxide Glass fibre Mold releasers	Type IV Type IV Type IV Type IV Type IV Type IV Types I Types I
Boat-building	ER UP resin Cobalt Phenol formaldehyde resin Natural rubber latex Glass fibre Styrene	Type IV Type IV and Type I Type IV Type IV Type I as CU Types I Types I
Ski and ski poles-building	DGEBA ER ER amine hardener MTHPA Polyester resin Cobalt Glass fibre dust	Type IV and Type I Type IV and Type I Types I Type IV Type IV Types I
Wind-turbine building	DGEBF	Type IV

ER = epoxy resin, DGEBA = diglycidylether of bisphenol-A, DGEBF = diglycidylether of bisphenol-F, UP = unsaturated polyester, MTHPA = methylte-trahydrophthalic anhydride, CU = contact urticaria

cobalt salts. The tests showed strong allergic reactions to the cobalt salts and a weaker reaction to nickel sulfate.[16]

In another case report from the fibreglass-reinforced plastic industry, the worker had positive patch-test reactions to MEK peroxide, benzoyl peroxide, rubber chemicals and cobalt chloride, but not to the polyester resin itself.[17]

In Madrid, Spain, a recent descriptive observational study was done between 2009 and 2011 at companies that produced aerogenerators (wind turbines). Ten patients were referred to the dermatology clinic of the National School of Occupational Medicine. Five of ten workers had ACD. Using the standard patch-test series of the Spanish Contact Dermatitis and Skin Allergy Research Group, a positive reaction to epoxy resin (bisphenol A) was reported in four patients, one of them was also sensitised to triethylenete-tramine and diethylenetetramine which are curing agents. One patient was sensitised to bisphenol F (epoxy resin).[18]

Two field surveys were conducted in 1997 and 1998 in Japan in 11 small to medium-sized FRP factories. Questionnaires and dermatology examinations were completed for 148 workers. Only 20% (29/148) of these workers from two of the original 11 factories were available for a follow-up patch-testing study for various reasons. Patch-test allergens included commercial plastic and glue-series allergens and many in-house preparations of products identified and collected from the two participating factory workplaces. Sensitisation to at least one of the substances tested was found in 62.1% (18/29) workers, two of whom reported no skin problem. The patch-test results revealed two positive reactions to UP resin, six to cobalt chloride, five to benzoyl peroxide, four to methyl ethyl ketone peroxide, two to para-tertiary butyl catechol, one to styrene, one to formaldehyde and one to glass-fibre dust. Of the 22 workers who experienced skin problems 16 showed a positive reaction to at least one substance tested. After accounting for exposures and dermatitis history, 32% (7/22) workers were diagnosed with pure ACD and 41% (9/22) with ACD and/or mechanical irritation. Irritant dermatitis was diagnosed in 27% (6/22) 3 cases of chemical irritation and three of mechanical irritation.[19]

CONCLUSION

The patient discussed in this case report has worked as a FRP laminator for the same company and has been exposed to hazardous substances for more than 12 years. These substances include fibreglass, UP resin, styrene, MEK peroxide and the chemicals used in the manufacture or released during degradation of protective personal equipment. The onset of the hand dermatitis related to glove use and the distribution and pattern of eczema suggested a glove reaction. She demonstrated improvement in symptoms when she changed from latex to nitrile gloves. Despite her obvious exposure to the hazardous substances used in the FRP manual open-moulding lamination process, it was a type-IV delayed hypersensitivity reaction to rubber chemicals present in the PPE issued for her protection that caused her allergy.

The appropriate choice of gloves in any occupational setting is fraught with problems. There is no single glove material that is suitable for all chemical exposures. At best gloves should be worn as 'splash protection' only and changed as soon as they are contaminated or damaged. Natural-rubber latex gloves were chosen for the laminators. While these are readily available and relatively cheap they are not effective barriers to styrene, acetone, UP resin and related compounds. Nitrile, neoprene and butyl gloves offer more effective barriers but have distinct disadvantages especially manual dexterity, availability and cost. Irrespective of the glove material, resin and fibre adheres to the gloves which, with time, hardens and damages the gloves requiring frequent replacement with new ones.

With the increase in demand for FRP in many fields, the occupational health effects are expected to increase. Sensitisation to substances used in the FRP industry is increasing among workers as demonstrated by research described in this case report. Most cases of ACD have been due to UP resin contact in lamination work. Prevention by elimination or minimising the exposure using engineering is the key to controlling the rising prevalence.

DECLARATION OF CONFLICT OF INTEREST
The author declares no conflict of interest.

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CPD QUESTIONNAIRE CONTINUED:

9. *Choose the correct answer:* Peanut allergy resolves over time in approximately:
   a. 10% of children
   b. 20% of children
   c. 50% of children
   d. 80% of children
10. *Choose the correct answer:* A typical weekly serving of peanut protein should be 6-7 g per week in infants as a peanut allergy reduction strategy. Two grams of peanut protein is equivalent to:
    a. About 2 teaspoons of peanut butter or peanut flour, or 8-10 peanuts
    b. About 4 teaspoons of peanut butter or 20 peanuts
    c. About 1 teaspoon of peanut butter or 4 peanuts
    d. Half a teaspoon of peanut butter, or 2 peanuts

THE ABC OF DIETARY MANAGEMENT OF PEANUT AND NUT ALLERGY

11. *True or False:* It is a regulation in South Africa that peanuts and tree nuts need to be indicated on labels of packaged foods.
12. *True or False:* Selective consumption of tree nuts which the patient has been proven to tolerate is not an option for tree nut allergy sufferers.

FOOD ALLERGIES - SHOULD WE BE GOING PEANUT-FREE IN SOUTH AFRICAN SCHOOLS?

13. *True or false:* A peanut-free policy in schools has substantially reduced the incidence of anaphylaxis requiring Epipen® use.
14. *True or false:* Schools should be allergen-aware, ideally with a small committee of staff members standing as the "allergy committee".
15. *True or false:* Every child with a food allergy should have an emergency action plan in place, accessible to teachers and staff.

ETHICS: IS IT ETHICAL TO PUBLISH CHILDREN'S MEDICAL INFORMATION AND PHOTOGRAPHS?

16. *True or false:* Ownership of photographs taken for medical purposes lies with the patient.
17. *True or false:* The International Committee of Medical Journal Editors (ICMJE) recommendation regarding a publication in which a patient is identifiable is that the manuscript has to be shown to the patient, and written informed consent obtained.
18. *True or false:* The ICMJE recommendations state that masking the eye region in photographs of patients is adequate protection of anonymity.
19. *True or false:* The use of children's photographs for advocacy of an organisation or fundraising effort can never be justified.
20. *True or false:* Unequal power relationships that exist between doctors and their patients make it difficult for patients to refuse consent to be photographed.

THE EOSINOPHIL

Shaunagh Emanuel & Di Hawarden

Ethel the eosinophil

Introducing Ethel

Ethel, the eosinophil, is a white blood cell; a granulocyte like Phred, the neutrophil, and Basil, the basophil. Ethel, Phred and Basil do not, however, look alike under a microscope. Acid-loving Ethel stains brick red when exposed to an acidic dye called 'eosin' because all the granules (containing enzymes and proteins) in Ethel's cytoplasm have a very strong affinity for the acidic eosin dye. Also her nucleus, which stains purple, consists of two similar lobes, whereas the nucleus of the neutrophil is composed of several (about 3–5) irregularly shaped lobes. Basil, the basophil, has a particular affinity for basic dyes (such as haematoxylin), which turns his cytoplasm blue. The granules in the cytoplasm of the neutrophil stain only weakly so the cell appears pale pink and is referred to as 'neutral'.

Eosinophil *Neutrophil* *Basophil*

Staining and naming

When pathologists wish to study a histological section or blood smear they often use a stain made up of a combination of haematoxylin and eosin. This is commonly termed the 'H and E stain'. The reds, blues and violets that the stain produces makes it possible for the pathologist to see which structures have an affinity to acids (red-staining) and which structures are basophilic (blue-staining). Hence the names of the granulocytic white blood cells (eosinophils, neutrophils and basophils) in a blood smear.

Ethel's origins

The granulocytes stem from myeloblasts in the bone marrow. Eosinophils are relatively rare; they typically make up only approximately 1–3% of the white blood cells. They are released from the bone marrow into the blood stream but quickly (within hours) find their way to the tissues. They reside in the spleen, lymph nodes and thymus, as well as in the submucosal areas of the gastrointestinal, respiratory and genitourinary tracts. They are not typically found in the lung, skin and oesophagus under normal conditions. Elevated numbers of eosinophils found in these areas are associated with disease.

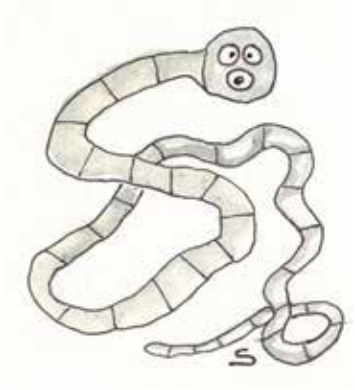
The role of the eosinophil

The full extent of the role of the eosinophil has yet to be uncovered, but some of its activities include fighting microbes, mediating allergic responses and asthma pathogenesis, and fighting helminthes and parasites. They are also implicated in post-pubertal mammary gland development, oestrus cycling, allograft rejection and neoplasia.

Eosinophilia

Eosinophilia is a raised eosinophil count. It may be measured in the serum or in the tissues. A count of more than 500 eosinophils in a microlitre of blood is considered a raised-serum eosinophil count.

Clinically, when we think of eosinophilia we tend to think of intestinal worm infestations, parasitic infections or allergic reactions; however, eosinophilia may be associated with several conditions including autoimmune illnesses, endocrine conditions, systemic inflammatory conditions and a variety of malignancies.



Tapeworm

Large numbers of eosinophils may be found in the nasal mucosa in patients suffering from allergic rhino-conjunctivitis.

Eosinophils are implicated in tissue damage and inflammation in several conditions including asthma. Interleukin 5 plays an important role in this process.

Eosinophils respond to the invasion of the body by an allergen or invader by moving to the area and producing a variety of toxins. This causes damage to the offending intruder as well as to the host tissues.

Large numbers of eosinophils may be found in the nasal mucosa in patients suffering from allergic rhino-conjunctivitis. In eosinophilic oesophagitis a biopsy of the oesophageal wall typically reveals a raised tissue eosinophil count. Other areas of the gastrointestinal tract may also be involved resulting in eosinophilic gastritis, enteritis or colitis. Hyper-eosinophilic syndrome occurs with simultaneously raised serum and tissue eosiniophils. More than 1 500 eosinophils per microlitre of blood that lasts for several months is referred to as 'hyper-eosinophilia'.

Eosinophilic disorders are often misdiagnosed as the symptoms may mimic other conditions. Treatment is challenging, often requiring a multidisciplinary team. Dietary management and glucocorticosteroid therapy are widely used.

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Ethics Article

IS PUBLISHING CHILDREN'S MEDICAL INFORMATION AND PHOTOGRAPHS ETHICAL?

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ABSTRACT

Children's medical stories are frequently used in the print and online media for teaching and research purposes to publicise medical conditions and treatments, and also to solicit donations for institutions and organisations. I contend that the latter use is wrong and exploits children.

INTRODUCTION

While browsing one of my social media platforms recently, I came across the following post from the Maboneng Heart and Lung Institute:

> 'A baby Ruben update: At his 6-week check-up with paediatric cardiologist, Dr KG, since leaving ICU, it was decided that he will go for catheterisation in August/September this year to inspect if any arteries or veins have narrowed. Overall, he is doing really well! Pictured is Ruben with his brave-heart scar and his dad.'

There is an accompanying photograph of a baby boy being held in the seawater by his dad, his sternotomy scar clearly visible. Ruben's story was also displayed on Maboneng's website.[1]

I wondered about this post: What purpose does it serve, other than to advertise the institute? Does the public have the right to know about Ruben's medical history and what the plan is for his future management? And does the fact that the Maboneng Heart Foundation offers cardiac surgery to children from elsewhere in Africa justify using Ruben and his story in this way?

A Google search of peanut allergy reveals numerous web sites with stories about people who suffer from food allergy and anaphylaxis, and one site lists the names and stories of people who died as a result of anaphylaxis.[2,3]

All over the world patients' stories are used to publicise details of diseases, established and new treatment options, and response to different treatments. Knowing that someone has the same condition you have and how they have dealt with it may promote positivity and healing, as well as providing access to information. Online and social media support groups are valuable resources for people with long-term or life-threatening health conditions.

An online search of local and international hospitals' web sites revealed many stories about young child patients with the major focus being advertising the institution and its expertise or soliciting funds. We had a long-term patient in our hospital who became the public face of many of our fundraising campaigns, of which only a few aimed to raise funds specifically for her. We will most certainly use patients' stories as part of awareness and funding campaigns for the Allergy Foundation of South Africa, and some of these stories will feature children. Adults and older children can provide informed consent to the publication of their information, but what of young children? What ethical issues arise from using paediatric patients' stories and photographs arise in case reports, congress presentations, and to publicise diseases and treatments, and how do we ensure that no harm results from such publication?

MEDICAL PHOTOGRAPHY IN RESEARCH AND JOURNAL PUBLICATIONS

Medical photography has long been a part of clinical teaching and research presentations and publications, but the advent of digital photography and its availability on smartphones have made it accessible to many more people. When I was training we would have to obtain consent, complete a request form and contact the medical photographer to come and photograph the patient. These days many photographs are taken with a cursory 'do you mind if I take a photo of you/your child?' and no explanation of what will be done with the photograph. Many of the social-media posts of child patients I have seen state: 'Posted with permission.' But can parents truly provide informed consent if their child's paediatrician or surgeon asks them

if it is okay for them to do so? There is a power imbalance between the patient and the doctor which may be increased when the patient is socio-economically disadvantaged, and where cultural and language differences exist.[4]

Devakumar, et al conducted focus group discussions with researchers and paediatricians around the ethical issues associated with the medical photography of children in low-resource settings.[4] Five categories of reasons for taking photographs were identified:

- teaching;
- research;
- environment – to show the setting of the research or service;
- personal reasons, differentiating 'tourist'-type photographs from clinical photographs, and
- advocacy.[4]

Medical photographs are useful in certain types of research, such as displaying data from communities in which genetic abnormalities are being investigated. They may also help to provide context and information in feedback sessions with communities.[4] However, one has to be sensitive when using photographs of subjects with conditions that may result in them being stigmatised, such as HIV/AIDS or chromosomal abnormalities.[4]

Patient photographs are often shared between clinicians when seeking advice regarding diagnosis and management. One of the popular social media platforms used for this purpose is WhatsApp; photographs, videos and special investigations are shared between doctors to obtain opinions and advice, and this makes a big difference to communication within and between teams, and to the management of patients. Fairly recently WhatsApp secured the platform with 'end-to-end encryption', which means that messages and images are secured and locked from outside access, and not stored on a server.[5] The Vula medical app also has data encryption, so that when patient information is shared between clinicians it is not available to anyone else.[6]

When may one use patients' photographs in congress presentations? I believe there must be good scientific or teaching value in using them, and then it must be done with consent and acknowledgement. The same applies to radiology and other imaging. Philip Snyman wrote an article in which he described the case of a baby with multiple congenital deformities whose digital photographs were sent to a specialist for an opinion, after verbal consent was obtained from the parents.[7] Subsequently, the specialist used the photographs in an international congress presentation without obtaining consent from the parent or the photographer.[7] Ownership of the photographs lies with the photographer, and permission should be obtained before they can be used by anyone else.[4,7]

Publication of photographs and personal information in journals requires the consent of the patient.[8] The *BMJ* policy on consent to the publication of patient information requires de-identification and anonymisation of such information, and photographs will be published without consent only if this is adhered to. There is no ethical objection to republish photographs that are in the public domain, although other considerations may need to be taken into account. The International Committee of Medical Journal Editors recommendations are as follows:[9]

> 'Patients have a right to privacy that should not be violated without informed consent. Identifying information, including names, initials, or hospital numbers, should not be published in written descriptions, photographs, or pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) gives written informed consent for publication. Informed consent for this purpose requires that an identifiable patient be shown the manuscript to be published. Authors should disclose to these patients whether any potential identifiable material might be available via the Internet as well as in print after publication. Patient consent should be written and archived with the journal, the authors, or both, as dictated by local regulations or laws. Applicable laws vary from locale to locale, and journals should establish their own policies with legal guidance. Since a journal that archives the consent will be aware of patient identity, some journals may decide that patient confidentiality is better guarded by having the author archive the consent and instead providing the journal with a written statement that attests that they have received and archived written patient consent.
>
> 'Nonessential identifying details should be omitted. Informed consent should be obtained if there is any doubt that anonymity can be maintained. For example, masking the eye region in photographs of patients is inadequate protection of anonymity. If identifying characteristics are de-identified, authors should provide assurance, and editors should so note, that such changes do not distort scientific meaning.'[9]

I will discuss some of the ethical issues associated with using children's medical information and photographs in publications, presentations and in social and other media in the sections below.

BEST INTERESTS AND THE RIGHT TO DIGNITY, PRIVACY AND CONFIDENTIALITY

Children's rights are protected by local and international frameworks and charters. The rights to dignity and privacy and confidentiality are protected by the United Nations Convention on the Rights of the Child (UNCRC), the

African Children's Charter and the Bill of Rights in the South African Constitution.[10,11,12,13] Publication of information and/or photographs of a child violates these rights, unless informed consent is obtained. In medical photographs taken for teaching purposes, only those details that are essential should be revealed. Similarly, using chest X-rays or CT scans in presentations or articles should have the patient identifiers removed. An example of a clear violation of a child's rights that offended readers of the *BMJ* involved the publication of a photograph of a young boy, together with his name, stating that he suffers from attention-deficit hyperactivity disorder, accompanying an article on the mechanism of action of methylphenidate.[14]

THE USE OF PHOTOGRAPHS FOR ADVOCACY: DOES THE GREATER GOOD OUTWEIGH INDIVIDUAL HARM?

As previously mentioned, children's photographs and stories are frequently used for fundraising or advocacy for organisations, hospitals and other causes. Can violating the privacy and confidentiality of an individual child be justified by the advantages to other individuals and families? I would argue that, using the example of food allergy, this may be justifiable, provided that the child is not stigmatised as a result. Consider, however, the example of baby Ruben: how is this conceivably justifiable?

In the study by Devakumar, et al, one participant stated that 'it's important to have a human face to things … [or] you wouldn't have an emotional response'.[4] The aims of an organisation or agency should not take precedence over a child's dignity, and one should exercise care to protect the child. The concern is, however, that, once a child's photograph is available on the internet, control is lost over its future use.

Sometimes parents approach the media with their child's story in the hope of obtaining public and financial support for rare or expensive treatment, with the newest method that of soliciting crowdfunding for this. One of the best known medical crowdfunding sites is GoFundMe; by 2014 it had raised US$150 million in 60 000 campaigns.[15] Ethical concerns associated with medical crowdfunding initiatives include potential fraud, loss of privacy and confidentiality, and distributive justice issues.[15]

CONSENT

The media, whether mainstream or social, can be a valuable tool in publicising health-related information. Food allergy is a potentially life-threatening condition, and patients' stories may alert others to the danger and pitfalls to which children may be exposed. Resources and strategies may be shared. The question is who should provide consent for the publication of children's photographs and medical information, and who should obtain the consent?

Parents are usually seen as the decision-makers for their children: they have common interests; they have the responsibility of raising and caring for their children; and they should share the same values. They should be able to decide whether publicising their child's story is in the child's interests, or whether it may be in other children's interests, and the potential harm to their own child is minimal. Older children are able to make decisions regarding their medical and even surgical treatment for themselves. If they consent to the publication of their information, this should be respected, provided they understand the implications of their decisions. In the context of medical decision making, if parents make decisions that are not in their child's best interests, they can be overruled by the courts. I am not aware of any cases where parents were taken to court because of publication of their child's medical information or photographs.

The participants in the focus group study found that several barriers to informed consent existed in low resource environments. One of these was the lack of understanding of the concept of informed consent, which some communities see as a Western concept. The setting influenced whether the informed consent was verbal or written, with some participants mistrusting the latter. Language barriers and a lack of comprehension as to the implications and uses of medical photography featured high on the list.[4]

In addition to obtaining parental consent or permission, assent should be obtained from young children.

POWER IMBALANCE BETWEEN HEALTH PROFESSIONAL AND PATIENT

Unequal power relations exist between doctors and patients, and between researchers and subjects. In the context of medical photography, the imbalance exists between the photographer and the photographed subject. Depending on the relationship, patients or research subjects may find it very difficult to say no to being photographed. If appropriate, a third party could approach the patient or subject to discuss the taking of photographs with them.[4]

LEGAL AND RIGHTS FRAMEWORKS

The legislative framework governing publication of children's stories and photographs reside in the Constitution of South Africa and the Bill of Rights. Section 28.2 of the Bill of Rights states: 'A child's best interests are of paramount importance in every matter concerning the child.'[13] This implies that publication of information or photographs that may cause harm to the child should be avoided.[16] Section 129 of the Children's Act stipulates that children over 12 years of age can consent to their own medical and surgical treatment, although in the latter case they must be assisted by a parent or legal guardian.[17] Extrapolating from this one would assume that children over 12 years of age could consent to medical photography, provided they

understood for what purpose it will be used and where it will be published. The United Nations Convention on the Rights of the Child (UNCRC) stipulates that children have the right to participate in decisions that affect them; they have the right to protection; and that their best interests are paramount.[11] These provisions would also apply to taking photographs of children.

CONCLUSION

The use of children's medical information and photographs in publications and online is open to the possibility of misuse and the subsequent violation of the patient's privacy and confidentiality. Informed consent must be sought before a child can be photographed, but this may not provide sufficient protection for the subject, especially in low-resource settings and where a significant power imbalance exists between subject and photographer. I contend that the use of children's photographs and information for fundraising purposes and to advertise organisations and services should be permitted only under exceptional circumstances. However, using children's stories to help others, as for example in peanut allergy, should be permitted in the interests of the greater good, provided all the necessary protections are in place.

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PID123

Primary Immunodeficiency

MENDELIAN SUSCEPTIBILITY TO MYCOBACTERIAL DISEASE (MSMD)

Zinhle in a wheelchair

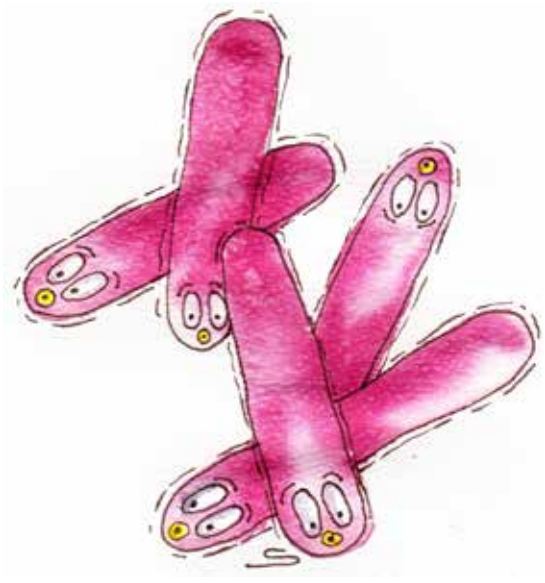
Dr Goodheart is called to see a little girl called, Zinhle, who, despite tuberculosis (TB) treatment, is failing to gain weight, has chronic anaemia, septic arthritis and a persistently raised CRP/ESR (a non-specific measure of inflammation). She is referred from a chronic-care facility where she was sent for rehabilitation of chronic septic arthritis of her ankle which was not responding adequately to treatment. She is wheelchair-bound and unable to walk. She has already received standard TB treatment for clinical suspicion of pulmonary infection, without initial sputum or culture confirmation. Because of failure of response to standard anti-tuberculous treatment she has just been started on treatment for suspected drug-resistant TB. An earlier Ziehl-Neelsen (ZN) stain was positive for acid-fast bacilli (AFB) in the sputum but no growth was obtained on culture. Three months later the stain is now negative, but has come back culture-positive for AFBs and also non-tuberculous mycobacteria. The presence of mycobacteria was confirmed by Polymerase Chain Reaction (PCR) from sputum and lymph-node samples, but not further speciated; *Mycobacterium avium intracellulare* is suspected (this belongs to the group of MOTTs – mycobacteria other than TB).

The doctor starts her evaluation with a thorough review of the history: Zinhle lives with her family in a nearby township. Both parents are employed. She has two half-siblings from another father. Nobody in the family has been ill with infections (specifically TB) and there is no known TB contact. At six months of age Zinhle had also been treated for suspected TB, while still living in the Eastern Cape. She has received full vaccinations including BCG at birth without any complications being recorded at the time.

On examination Dr Goodheart observes that Zinhle looks chronically ill and wasted. An extensive BCG scar is noted as well as active arthritis of the left ankle. The girl's lungs are clear but Dr Goodheart finds abnormally enlarged lymph nodes in the neck.

With this persistent history of TB, she initiates further investigations of sputum and the chronically swollen left ankle. A methicillin-sensitive *Staphylococcus aureus* (MSSA) is initially cultured from the ankle biopsy and aspiration. Dr Goodheart thinks this is an unusual course and in conjunction with an unusual TB organism this alerts her to a possible PID. She therefore consults the immunology specialist, Dr Bala, for review of the biopsy sample and for further advice. The samples sent to Dr Bala's reference laboratory show granulomatous inflammation, even after many months of treatment. A bone scan ordered subsequently at Dr Bala's hospital shows multiple 'hot spots' in Zinhle's vertebrae, pelvis, tibia and orbit.

Dr Bala also requests baseline immunological investigations, including lymphocyte subsets and immunoglobulin levels



MOTTs – mycobacteria other than TB

which both turn out to be normal. Lymphocyte stimulation tests with a number of mitogens (stimulants) show reduced lymphocyte proliferation implying reduced function to protein A and candida stimulation (implying reduced lymphocyte function), but are normal for other T-cell stimulants. The neutrophil burst test for phagocyte function is normal, excluding Chronic Granulomatous Disease (CGD). The IFN-γ release response to TB-specific antigen is impaired but not completely absent. Both doctors agree that an immunodeficiency disorder has to be considered in the presence of atypical bacteria, persistence of TB on treatment and abnormal lymphocyte function.

Zinhle is then admitted to a neighbouring Tuberculosis Children's Hospital where she continues extended MOTT treatment for another six months.

She improves slowly and visits Dr Goodheart regularly at her clinic. Meanwhile, Dr Bala has been talking to her colleagues at the molecular laboratory and they agree to investigate Zinhle for genetic susceptibility to TB. Although several PIDs can cause susceptibility to TB non-specifically, Dr Bala suspects a TB-specific genetic defect in Zinhle (see Box).

When the report from the molecular laboratory arrives, exome sequencing indeed shows a mutation in the interferon gamma receptor IFNR1, which has already been identified in other patients with MSMD and which is responsible for an impaired response to interferon gamma. This confirms Dr Bala's diagnosis of MSMD.

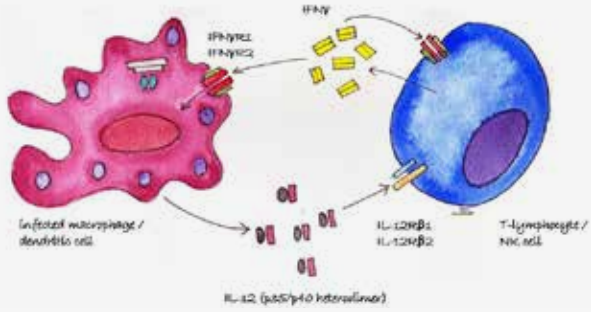
Zinhle recovers gradually but Dr Goodheart knows that her patient will be at risk for recurrent TB and MOTT infections and she will have to be followed-up closely. The doctor also refers the family for genetic testing to find out whether other family members are affected. Dr Bala points out to her colleague that special treatment with Interferon gamma might be an option but this is very expensive and has many side-effects. It will have to be considered for Zinhle if she does not recover from her unusual TB infection.

Zinhle is happy to be back at school and out of the hospital. She does not understand why the doctors are so concerned about her.

Box: PIDs resulting in increased risk of mycobacterial infection

Severe PIDs such as Severe Combined Immunodeficiency (SCID), Hyper-IgM (HIGM) syndrome, CGD and Hyper IgE Syndrome (HIES) are susceptible to a broad range of diverse infections, which can include mycobacterial infections.

In contrast, patients with an isolated inborn error of the IL-12/23-IFN-γ pathway are almost exclusively prone to infections with mycobacteria other than TB and non-typhoid salmonella infections, which are non-virulent in healthy individuals. This is known as 'Mendelian susceptibility to mycobacterial disease (MSMD)'.



The figure shows the **crosstalk between infected macrophages and T-lymphocytes/NK cells in mycobacterial immunity:** Infected macrophages (or dendritic cells) release IL-12, which binds to the IL-12 receptor (IL-12R) on natural killer (NK) cells or T-cells. Binding of IL-12 induces intracellular that result in the activation of genes. The secretion of IFN-γ by NK and T-cells by binding to the IFN-γ receptor (IFNR) on macrophages, elicits a cell-mediated immune response to intracellular pathogens within the infected macrophage. IFNR activation induces a wide range of IFN-γ-responsive genes. Several proteins in this signalling loop can be mutated and are associated with MSMD, e.g. IFN-γR1, IFN-γR2, TYK2, IL-12p40, IL-12R-β1, STAT-1, NEMO, CYBB, IRF8, among others.

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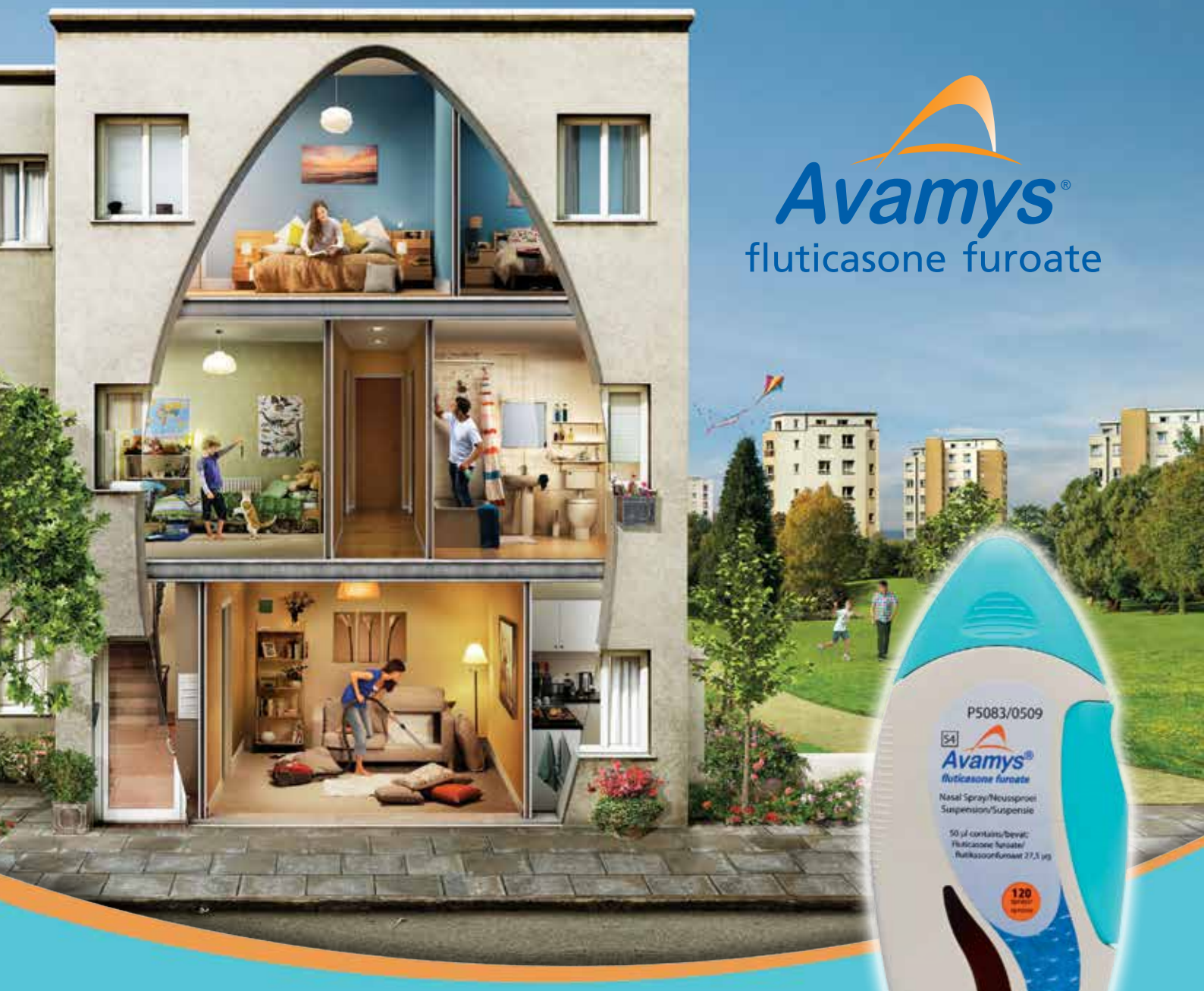

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