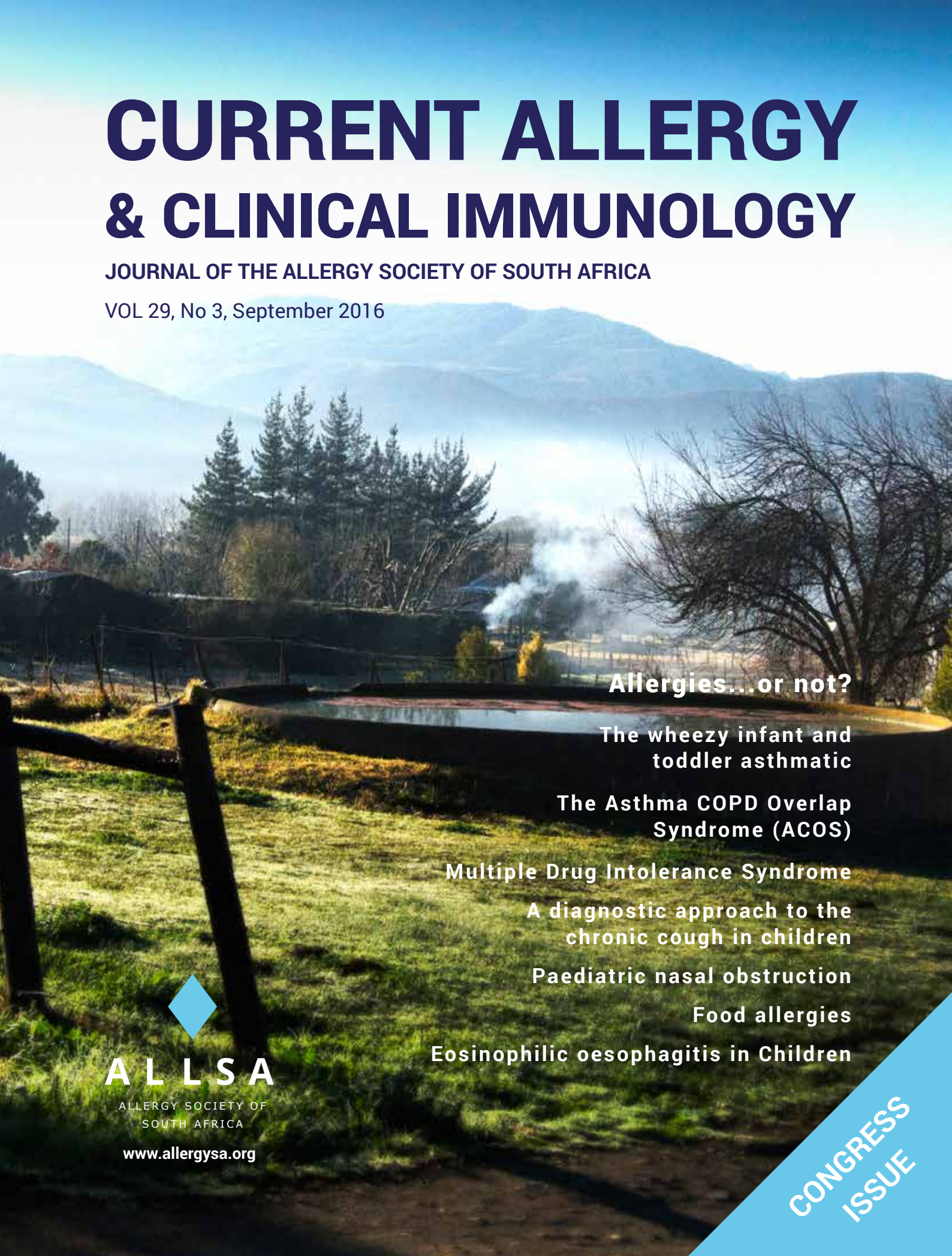
# CURRENT ALLERGY & CLINICAL IMMUNOLOGY

JOURNAL OF THE ALLERGY SOCIETY OF SOUTH AFRICA

VOL 29, No 3, September 2016



Allergies...or not?

The wheezy infant and toddler asthmatic

The Asthma COPD Overlap Syndrome (ACOS)

Multiple Drug Intolerance Syndrome

A diagnostic approach to the chronic cough in children

Paediatric nasal obstruction

Food allergies

Eosinophilic oesophagitis in Children

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CONGRESS ISSUE

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

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# GUEST EDITORIAL

It has been my pleasure and a privilege to edit this edition of *Current Allergy and Immunology*, to be published during the 2016 annual ALLSA congress.

This edition includes Professor Robin Green's overview of management of the wheezy infant, an always relevant topic that both perplexes and provokes debate. Professor Green is a paediatric pulmonologist and head of the Department of Paediatrics and Paediatric Pulmonology at the University of Pretoria. He is a past chairman of ALLSA and a regular contributor to our journal.

Professor Gillian Ainslie from the Department of Pulmonology at the University of Cape Town has contributed a wonderful review of the Asthma COPD overlap syndrome (ACOS), a topic that is receiving much recent attention.

Multiple drug intolerance syndrome is another 'hot topic', one that is covered by Dr Jonny Peter from the Department of Medicine at the University of Cape Town.

This edition also introduces two new contributors to our journal. Dr Fiona Kritzinger is a paediatric pulmonologist at the Children's Chest and Allergy Centre in Cape Town. Fiona trained at Toronto's Sick Kids hospital after completing her paediatric training at Stellenbosch University. Her review of chronic cough in children is both practical and clinically relevant. Dr Oliver Raynham, an otolaryngologist in Cape Town with a special interest in children, has contributed a systematic approach to the everyday problem of paediatric nasal obstruction.

Our international contributors for this edition include Dr George du Toit, a consultant in paediatric allergy at Guy's and St Thomas' Hospital London & Evelina Children's Hospital. He has also provided a short opinion piece for this issue of the journal and will be speaking on his breakthrough research on peanut allergy prevention at the congress.

Dr Mark Furman is the lead paediatric gastroenterologist from the Royal Free Hospital, London. He contributed to the recently published, latest UK/BSPGHAN guideline on coeliac disease. His areas of interest include IBD, food allergy, coeliac disease and eosinophilic oesophagitis, and he has kindly provided us with a review of eosinophilic oesophagitis.

As always, we have our regular features, including an interesting case report, an ethics topic as well as the abstracts submitted for presentation at the ALLSA congress. The next article in the wonderful 'ABC' series is also included. Please don't forget to complete the CPD questionnaire.

The theme of this year's ALLSA congress is: 'Allergy … or not?'

Our focus will be on allergy and the mimickers of allergy, coupled with overviews of the latest trends in allergy and clinical immunology.

We hope to see you all there!
**Dr Sarah Karabus**

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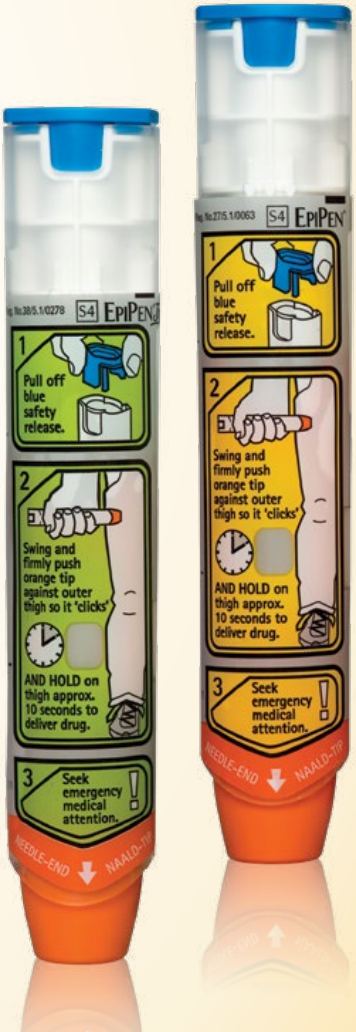


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**Reference: 1.** Simons FER, Ardusso LRF, Biló MB, El-Gamal YM, Ledford DK, Ring J, *et al.* World Allergy Organization Guidelines for the Assessment and Management of Anaphylaxis. *WAOJ* 2011;**4**:13-37.

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# Hello AFSA

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**Dear Members**

We are proud to launch the Allergy Foundation of South Africa (AFSA) at the ALLSA Conference 2016. AFSA is a recently established non-profit company (NPC) closely allied to the Allergy Society of South Africa. AFSA strives to save lives, enhance the quality of life and reduce the cost of healthcare for South Africans suffering from allergic disorders and primary immune deficiencies.

AFSA was officially established in 2015 by the Allergy Society of South Africa and registered as an NPC under the name 'The South African Allergy & Clinical Immunology Foundation'. It was established to fill a gap in advocacy and service provision that is beyond the scope or legal ambit within which ALLSA, as an official society for healthcare professionals, operates. We believe that AFSA will serve the broader needs of allergy and clinical immunology patients.

We aim to create awareness, advise and educate patients, promote responsible care, assist with advocacy and raise funds for professional development.

**The current activities of AFSA are:**

- Establishing our website, www.allergyfoundation.co.za.
- Establishing a membership base of people with an interest in allergies and primary immune deficiency (PID).
- Establishing a vital patient resource – a list of professionals with expertise and interest in allergy on the website.
- Compiling patient information brochures in four official languages (English/Afrikaans/isiXhosa/Sesotho).
- Drawing up a list of suppliers of house-dust protective linen.
- Co-ordinating and compiling the 'Allergy in schools' consensus statement of AFSA, ALLSA, Allergy Alive and Equal Education Law Centre. Advocating for the statement's adoption by school governing bodies, private-school policy organisations and the Department of Basic Education.
- Producing two educational modules on food allergy in schools, one aimed at laypeople and people without food allergies, and the second a training module for patients with food allergy, their parents, carers and school staff.
- A video on 'faces of anaphylaxis' to highlight that anaphylaxis is not only a First-World problem, highlighting true life stories of ordinary South Africans with severe allergies and anaphylaxis.
- Commenting on labelling legislation and engaging with the Department of Health about it.
- Liaising with South African Airways regarding allergy safety during air travel.

**Forthcoming projects will include:**

- Publishing regular newsletters.
- Developing closer relationships with organisations with overlapping interests.
- Holding workshops and events.
- Establishing an online allergy training academy for health professionals.
- Fundraising for the training of healthcare professionals and new research.
- Undertaking other projects that our members, advisors, sponsors and ALLSA Excom may propose.

As the organisation develops and becomes financially self-sufficient, we envisage changing the NPC's directors to include predominantly laypeople with an interest in allergy and PID. In the new team, we envisage including the head of the patient advocacy subcommittee, legal advisors, members of the business community, educationalists, along with the chairperson and vice-chairperson of ALLSA.

AFSA is currently co-ordinated by Mike Levin, who is serving as the CEO. The financial director is Dr Sarah Karabus and

the directors are André van Niekerk, Di Hawarden, Sharon Kling, Ahmed Manjra and Claudia Gray. Hayley Katz runs our patient advocacy subcommittee and is extremely active within AFSA as well as through her facebook page at www.facebook.com/allergyalive. Chandre Stuurman serves as our legal expert. A medical advisory panel scrutinises all AFSA materials, website content and endorsements.

We hope to see you all at the congress
**Mike Levin**


*Lynn Kämpf has joined us as business manager and can be contacted at info@allergyfoundation.co.za.*

Lynn says:
Our Mission Statement:
'AFSA will strive to save lives, to enhance the quality of life and to reduce the cost of healthcare in South Africans suffering from allergic disorders and primary immune deficiencies' speaks to my heart.

We are facing the reality of an allergy epidemic in South Africa – an issue that affects us all. AFSA's mission should therefore be embraced by all of us – parents, teachers, businesses and medical professionals.

As the newly appointed business manager to our NPC, I am excited about the technological advancements available to us, and I intend to take full advantage of them to disseminate AFSA's vital messages across devices – into homes, businesses, educational institutions and medical facilities.

I aim to ensure that members of the public will be able to access the key information and research regarding allergies and primary immune deficiencies via mobile applications. I also aim to make digital training solutions available to medical professionals, schools and other relevant institutions.

We need to educate, advocate and raise funds for a pressing cause. Collaboration with organisations, businesses and individuals who share our passion will be encouraged and pursued in order to ensure the long-term sustainability of our NPC.

If only I had had the information AFSA seeks to deliver, I believe that a devastating personal tragedy I experienced could have been avoided. It is therefore my passion to ensure that lives are saved and that suffering is alleviated.

With outstretched arms, I invite each and every one of you to embrace and partner with AFSA.
*Together, we will save lives!*

Thank you
Lynn

The Cas Motala Memorial Lecture

# THE WHEEZY INFANT AND TODDLER ASTHMATIC – A PRIMARY CARE APPROACH

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## ABSTRACT

Wheeze is common in infants and young children. Asthma is but one cause and it is obviously important to exclude or include as it is amenable to specific therapy. It is also obvious that the pre-school or young child is not just a smaller variety of the older child or adult and this is especially true of asthma, where special situations exist with regard to diagnosis and treatment. Although there is a differential diagnosis for the major symptoms that constitute asthma in this age group, no child should be left to wheeze or cough without the possibility of asthma being considered and excluded. New guidelines and reports suggest that differentiation of virally induced wheeze from multi-trigger wheeze (or toddler asthma) is less important than making an attempt to manage the child. If an infant, or young child, has a chronic wheeze and is atopic or responds to a bronchodilator, asthma is more likely and therapy should be tried. If, however, there is no response to the therapy, investigate for other causes. Remember that in South Africa wheeze may also be produced by chronic infections, gastro-oesophageal reflux, cardiac failure, cystic fibrosis and a host of other sinister conditions. Therapeutically, for mild and intermittent wheeze the choice of inhaled corticosteroid (ICS) or a leukotriene antagonist may be valuable options. Therapy is intermittent and should be started pre-emptively. However, for more severe and frequent symptoms regular use of ICS (moderate dose) is clearly the best therapeutic option.

*This article has been peer reviewed.*

## INTRODUCTION

One-third of all children have had a wheezy illness by their third birthday. Most are caused by viral triggers.[1] However, in patients diagnosed with asthma, symptoms start in the pre-school years in 80% of cases.[1] And this is the basis for both the under-treatment of pre-school/toddler asthma and the over-treatment of pre-school wheeze.

## WHAT IS A WHEEZE?

A wheeze is a high-pitched musical sound usually on expiration and it is associated with increased work of breathing.[2] Wheeze is produced by a narrowing of intra-thoracic airways and usually small airways.

However, the term 'wheeze' is often mis-classified and mis-identified by parents. Control of asthma symptoms is correlated best with composite scores of symptoms rather than wheeze only. Audible wheeze occurs late in airway obstruction and there is no data on the sensitivity or specificity of the term 'wheeze'. Cough correlates with lung function and atopy in pre-schoolers similar to and independent of wheeze.[3] Therefore it may be more important in children to use the term 'recurrent troublesome lung symptoms' to describe important chest events.

## EPIDEMIOLOGICAL DESCRIPTIONS OF RECURRENT WHEEZE

Wheeze, as a symptom, is common in children of all ages and is often the reason for presentation of a child to a doctor. In the mid-1990s Martinez et al published an epidemiological audit of the outcome of wheezing in childhood.[4] They classified wheezing into three distinct categories based on outcome:

- transient early wheezing was wheezing in the first three years of life which resolved;
- late-onset wheezing was no wheezing during the first three years of life, but onset during the fourth year;
- persistent wheezing was wheezing continuing from early onset beyond five years of life.

This epidemiological study has documented that, the main wheeze in young children is often not due to asthma, whereas a wheezy older child may well have asthma. Transient (limited to a few months or years) wheezing in infancy is more likely to be a function of small airways,[4] and wheezing in the first year of life does not persist as asthma in two-thirds of those afflicted.[4] Recent experimental evidence has shown that it may be possible to predict asthma from lung-function testing of wheezers at three years of age but clearly this is not a

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tool routinely available in clinical practice.[2] Unfortunately, this classification is not helpful in managing wheeze in the clinical setting and in the individual child.

Another publication by a European Respiratory Society (ERS) Task Force in 2008 suggested that the differential diagnosis of recurrent wheeze in pre-schoolers should include two phenotypes:[1]

- viral-induced wheeze, and
- multi-trigger wheeze (MTW).

The differences between these two groups are illustrated in Tables I and II.

**TABLE I: VIRAL-INDUCED WHEEZE[1]**

- Wheezing during discrete episodes;
- Usually associated with a viral trigger;
- No symptoms in between;
- Outcome:
  - declines by the age of six;
  - continues into childhood;
  - becomes MTW.

**TABLE II: MULTI-TRIGGER WHEEZE[1]**

- Wheeze during discrete episodes;
- Also symptoms in between episodes;
- URTI usually the trigger;
- But wheeze in response to other triggers:
  - exercise;
  - inhaled allergens;
  - environmental tobacco smoke;
- Possible evolution to asthma but poor evidence to support this.

The major problems with that report were twofold. Firstly, the broad classifications failed to classify correctly many children who wheezed (as wheezing in pre-schoolers may exist on a spectrum of disease as opposed to two distinct clinical entities). Secondly, the majority of the Task Force agreed not to use the term 'asthma' to describe pre-school wheezing illness since there is insufficient evidence showing that the patho-physiology of pre-school wheezing illness is similar to that of asthma in older children and adults. This created much confusion in deciding on treatment principles for individual children.

The symptom of wheeze causes a significant diagnostic dilemma in the very young child because as a recurrent or persistent problem there are a number of important causes, not all of which are amenable to specific therapy (see Table III).

**TABLE III: CAUSES OF CHRONIC WHEEZING IN INFANCY**

- Small airways;
- Asthma;
- Post-bronchiolitis;
- Cystic fibrosis;
- Chronic infections;
- Gastro-oesophageal reflux;
- Immune deficiency;
- Foreign body;
- Cardiac pathology;
- Lymphadenopathy due to TB, HIV.

## CAUSES OF WHEEZING IN INFANCY

The first episode of wheezing in the first year of life is likely to be labelled 'bronchiolitis', a specific acute inflammatory disease of the bronchi caused by the respiratory syncitial virus (RSV), rhinovirus (RV) and, less commonly, other viruses.[5] This condition is short-lived, associated with a mild upper respiratory tract infection, low-grade fever and hyperinflation of the chest and may be quite profound. Many studies have investigated the treatment of acute viral bronchiolitis and the only therapy that is recommended is oxygen for hypoxic infants.[6] No medical therapies are of any value.[6]

The close relationship between atopy and viruses is such that atopy probably predisposes to a sensitivity of the airway to viruses, which are the most important triggers of acute exacerbations of asthma in younger children and infants.[7] RSV infection can predispose to asthma, but this may be due to a pre-existing immune disorder predisposing to allergy and infection.[8] Alternatively, it may be possible that RSV bronchiolitis damages the airway epithelium to the degree that other aero-allergens gain easier access to inflammatory cells, thereby setting in motion the immune model for asthma (through the $TH_2$ pathway).[8] Certainly, it has been shown that RSV bronchiolitis severe enough to cause hospitalisation is a risk factor for allergic asthma in early adolescence.[9]

In South Africa the concept of 'wheezy phenotypes' is not applicable to a large percentage of the population who wheeze in response to other significant diseases (see Table III). Here a clue to many is the failure to thrive or poor weight gain. Other history and examination clues are found in the markers of specific diseases, such as stigmata of AIDS, tuberculosis, congenital cardiac disease, cystic fibrosis and gastro-oesophageal reflux. A careful examination is mandatory on an infant who is wheezing. Most of these significant diseases are marked by associated signs. They should not be missed. A chronic cough (CC) in a young child will create the same diagnostic dilemma, and again a differential diagnosis is important, especially in the child who is failing to thrive, has a cardiac murmur or vomits regularly, when HIV-associated infections, a congenital cardiac abnormality or gastro-oesophageal reflux are likely.

## WHEN IS PRE-SCHOOL WHEEZE ASTHMA?

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation causes an associated increase in airway hyper-responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment.[10] More simply, 'Asthma should be diagnosed in a child with a CC or wheeze who responds to a bronchodilator (asthma therapy)'.[11]

| TABLE IV: FEATURES SUGGESTIVE OF ASTHMA IN CHILDREN <5 YEARS |
|---|
| EVIDENCE A |
| Exercise-induced cough or wheeze;<br>Cough at night;<br>Symptoms persisting after the age of 3 years. |
| EVIDENCE B |
| Absence of seasonal variation;<br>Symptoms worsening with certain exposures;<br>Colds repeatedly going to the chest;<br>Response to a bronchodilator;<br>Response to a course of steroids;<br>Concomitant rhinitis, eczema or food allergies;<br>Family history of allergy or asthma. |
| EVIDENCE C |
| Wheezing more than 1 month. |
| EVIDENCE D |
| Modified bronchodilator response test. |

Despite the epidemiological classification of wheezy youngsters, the diagnostic approach to these children is poorly described. In view of the uncertainty of diagnosis and heterogeneity of wheezing phenotypes in young children, when deciding about appropriate management of recurrent wheezing in children under the age of five years it is useful to check the following clinical points (see Table IV). These clinical points indicate a diagnosis of 'asthma' rather than other causes of wheezing.[12]

Publication of the 'Asthma Prediction Index',[13] which makes use of features of atopy to diagnose asthma, has helped and suggests that asthmatic versus viral wheezers are more likely to be atopic. Another useful diagnostic tool for diagnosing asthma is the 'Modified Bronchodilator Response Test' (MBRT). In this test a patient suspected of having asthma (often a young child with persistent or recurrent wheezing) is given a bronchodilator by nebuliser or MDI with spacer and the symptoms/signs are evaluated 10–15 minutes later. Only asthmatics have sufficient bronchial hyper-responsiveness to respond to a bronchodilator. Most other causes of wheezing in young children will not respond. In these children further testing (such as a chest X-ray) may be useful.

In an older child the diagnosis of asthma must be made based on a typical history and examination, followed by a demonstration of reversibility:

- $FEV_1$ increase > 12% with bronchodilator;
- $FEV_1$ decline > 15% during an exercise challenge;
- positive metacholine challenge test;
- role of exhaled nitric oxide (FeNO) is controversial.

| TABLE V: CRITERIA FOR DIAGNOSING ASTHMA IN THE PRE-SCHOOL CHILD |
|---|
| • Wheeze on exercise or illness in between viral illness;<br>• History of other allergic disorders – allergic rhinitis or eczema;<br>• Familiy history of asthma;<br>• Response to controller therapy and worsening on cessation. |

The GINA Guideline of 2015[14] made the point that there is agreement that asthma in the pre-school child is a difficult diagnosis to make and that differentiation into phenotype should not be the aim – as the clinical significance of this is uncertain. Asthma is more likely if the criteria in Table V are met.

## TREATMENT OF PRE-SCHOOL WHEEZE AND ASTHMA

The literature is full of algorithms for the management of both chronic and acute asthma in children,[12,14,15] but treatment of the pre-school or young child remains a problem. However, the principles of treatment remain the same, and it is as important to treat inflammation in the persistent chronic young asthmatic as it is in the older child and adult.

The key to treatment decisions in the local context depends on the therapeutic tools that are available for treating asthma and non-asthmatic wheeze in very young children. Unfortunately, until recently, our therapeutic armamentarium was severely limited. Most available anti-asthma therapies have been disappointing in their effect on pre-school wheeze. This is true for both bronchodilators and anti-inflammatory drugs.

Four recent meta-analyses have informed opinion that use of inhaled corticosteroids is better than montelukast in pre-school children.[16–19] There are, however, clear guidelines here (see Table VI).

If the infant has a clear MTW and the criteria in Table VI are met, then first-line therapy should be regular ICS use: daily medium-dose ICS use is best.[19] In the case of clear virally induced wheeze, either ICS (high-dose)[19] or montelukast should be tried and titrated to clinical response. In this latter scenario, intermittent use (less than ten days) would be the first option. In addition, pre-emptive use (at the first sign of a 'cold') would be the best time to start.

The value of long-acting $B_2$ agonists in older children is controversial because they have not shown the same efficacy as in adults, and yet this is the group of patients where an alternative to ICS is particularly appealing. In the case of young children there is little information about these agents and their use is extrapolated from data for school-aged children and even adults. Recently, a retrospective study of young asthmatics demonstrated that the outcomes for young children with asthma are markedly

| TABLE VI: WHEN TO TREAT PRE-SCHOOL CHILDREN WITH REGULAR INHALED CORTICOSTEROIDS[20] |
|---|
| • Attacks are severe – requiring hospital admission;<br>• Attacks are frequent;<br>• Interval symptoms are being under-reported;<br>• Any controller therapy should be viewed as a trial of treatment and discontinued if there is no response;<br>• Taper down to lowest possible dose. |

improved with a combination of fluticasone and salmeterol, but prospective studies are still required.[21] Anecdotal clinical experience suggests that there is a place for their use but only once the dose of inhaled steroid is significant, the diagnosis of asthma is established and symptoms persist.

## THE IMPORTANCE OF MANAGING INFANT WHEEZE CORRECTLY

Although quality of life and socio-economic factors are difficult to quantify in young children, this is an age group when recurrent illness and decreased activity will have a profound impact on the development and socialisation of the child. In a study conducted in Scandinavia, children less than two years of age accounted for 44% of annual inpatient asthma costs and children two to five years old for 31% of such costs, even though the former group made up only 1% of the asthma population and the latter group 27%.[22]

Patients are often told that asthma in childhood is usually outgrown. This is not, however, the case and on average only about one-third of patients have some symptom relief, and then usually only at the time of puberty.[23] Many of these children, however, develop symptoms again in later life.[24,25] For this reason it may be possible and even essential to reduce or stop therapy in adolescence but the patient and their parents should be alerted to the possibility of recurring symptoms.

Whatever therapy is ultimately chosen for managing asthma in the young child, it is important to meet the 'Goals of treatment' as set out in guidelines and ensure that quality of life is restored.

*Professor Cas Motala was a scientist who kept the latest publications in mind when treating patients. However, more importantly, Cas was interested in people. He would always make sure children were treated as individuals and that therapy for infants and pre-school children who wheeze should be individualised and used only where it worked.*

## CONCLUSION

Wheeze is common in infants, young children and even older children. Asthma is but one cause and obviously important to exclude or include as it is amenable to specific therapy. It is also obvious that the pre-school or young child is not just a smaller variety of the older child or adult and this is especially true of asthma therapy, where special situations exist with regard to diagnosis and treatment. Although there is a differential diagnosis for the major symptoms that constitute asthma in this age group, no child should be left to wheeze or cough without the possibility of asthma being considered and excluded. This age group reveals many issues with regard to standard inhaled therapy, and for mild and intermittent wheeze the choice of ICS or a leukotriene antagonist may be valuable options. Consider intermittent use. However, for more severe and frequent symptoms regular use of ICS is clearly the best therapeutic option. The message seems simple: if an infant or a young child has a chronic wheeze and responds to a bronchodilator, asthma therapy should be tried. If there is no response to the MBRT, investigate for other causes.

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

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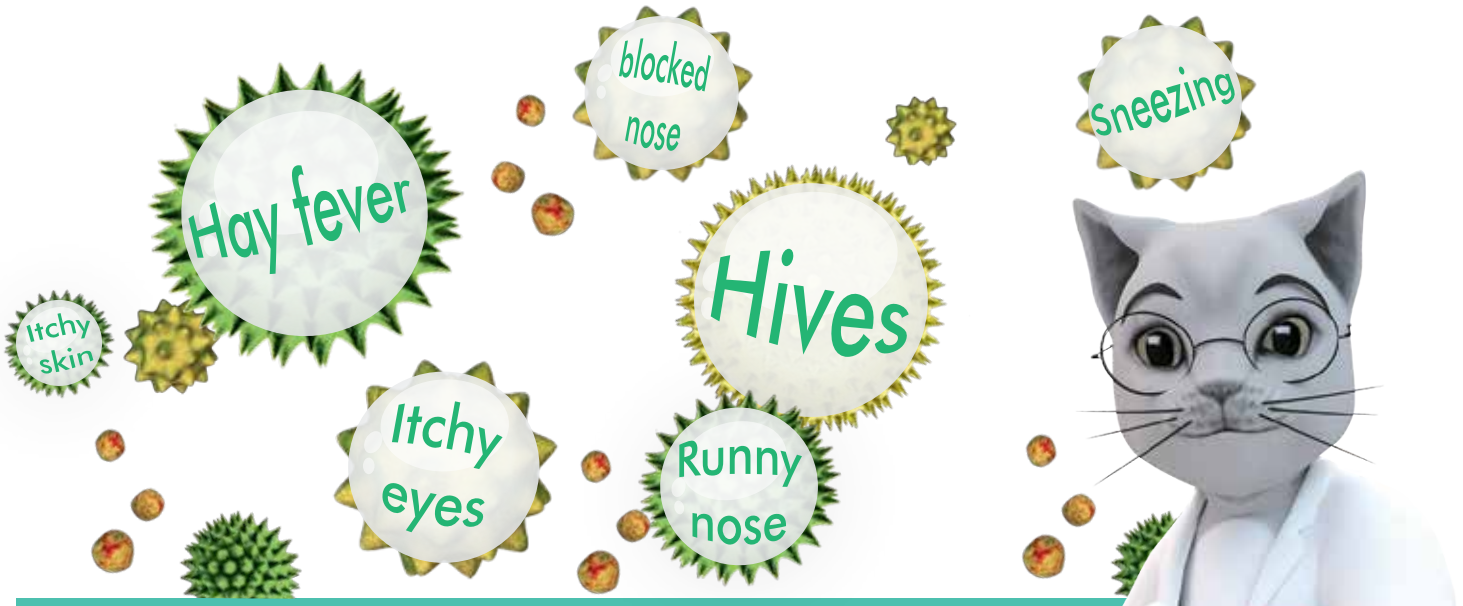


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ZA/05/2015/Allerway/001

Guest Review

# THE ASTHMA–COPD OVERLAP SYNDROME: WHAT IS IT AND HOW SHOULD WE TREAT IT?

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## ABSTRACT

Asthma and COPD are two distinct diseases but may overlap, especially in older patients. Typically, asthma patients have marked variability in their airflow obstruction with significant reversibility in response to both bronchodilator and corticosteroid therapy. However, it has become increasingly clear that many patients with asthma may develop fixed airflow obstruction, whereas many patients with COPD exhibit some bronchodilator reversibility. The term 'Asthma–COPD Overlap Syndrome' (ACOS) has been coined to describe patients who have features of both but, as yet, there is no validated definition for the combination of features. Patients with ACOS have worse outcomes than those with asthma or COPD alone: more frequent exacerbations, poorer quality of life, more rapid decline in lung function, higher mortality and greater healthcare use. The Global Initiative for Asthma (GINA) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) have recently published guidelines for the diagnosis and treatment of patients with asthma, COPD or ACOS.

*This article has been peer reviewed.*

## INTRODUCTION

Asthma and chronic obstructive pulmonary disease (COPD) represent two distinct diseases with differing pathogenesis, histology and risk factors. They do share certain clinical characteristics and these may overlap.[1] Several population studies have shown that a significant number of adult patients with obstructive lung disease are diagnosed with more than one condition.[2–4] This can be shown graphically in a non-proportional Venn diagram (see Figure 1). Typically, COPD has an onset from the fifth decade, has constant symptoms of dyspnoea and cough and is marked by slow progression. A history of significant smoking (greater than ten pack-years) or some other exposure (occupational or biomass fuel exposure) is usually a factor.[5] On the other hand, asthma usually but not always starts at a young age, is often associated with other atopic disease, has classically episodic symptoms with diurnal or day-to-day variability and has a good response to therapy.[6] Asthma and COPD can coexist in the same patient: many asthmatics smoke – not all develop COPD but most have an accelerated fall in lung function. In addition, poorly treated asthmatics may develop fixed disease, so-called 'remodelling'. The diagnosis of asthma rests on characteristic symptoms combined with tests showing variable airflow obstruction, airway hyper-responsiveness and bronchodilator reversibility.

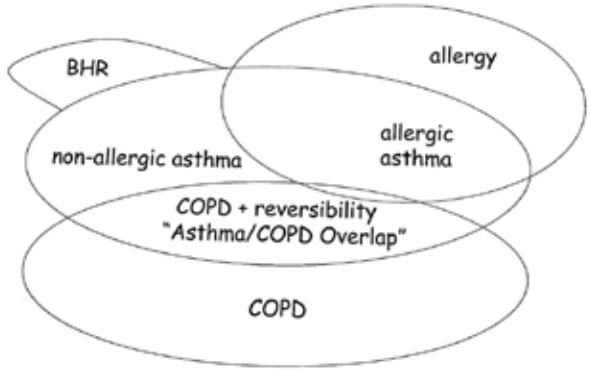


*Figure 1: Non-proportional Venn diagram of obstructive lung disease*
*Abbreviations: BHR = bronchial hyper-responsiveness, COPD = chronic obstructive pulmonary disease*

## BRONCHODILATOR REVERSIBILITY

Bronchodilator (BD) reversibility response remains the hallmark of the diagnosis of asthma. It has been used historically as a tool for distinguishing reversible from irreversible airway obstruction, although this distinction has become somewhat blurred. In the SATS and GINA Guidelines, the definition of bronchodilator reversibility is stated as an increase from baseline in the $FEV_1$ of both >12% and 200 ml, 10–30 min following the inhalation of 200–400 µg of salbutamol, or a 20% improvement in PEF (peak expiratory flow) from baseline.[6,7] In 2015, the GINA Guidelines added that a >15% and >400 ml increase in the $FEV_1$ gives greater confidence in asthma diagnosis.[7] However, most asthmatics will not exhibit reversibility at each assessment, particularly those on treatment, and the


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test therefore lacks sensitivity. Repeated testing at different visits is advised. This frequent absence of BD reversibility in patients with physician-diagnosed asthma has been shown in several studies in different countries,[8–10] including South Africa,[11] where almost half of young non-smoking asthmatics did not have a significant BD response at their first assessment at a tertiary referral centre. Possible reasons for this low incidence of reversibility include a temporary phenomenon due to severe viral or allergic airway inflammation (which may change after a course of oral or inhaled corticosteroids), recent BD use, inadequate BD dose, permanent airway remodelling and an incorrect asthma diagnosis.

Not only do many asthmatics not always show BD reversibility but it is not uncommon for COPD patients to have significant reversibility. In the UPLIFT study, >50% of the COPD patients enrolled had significant reversibility.[12] Using the GOLD severity stages, reversibility generally decreases as COPD severity increases.[13] However, a lack of acute BD reversibility does not predict a lack of response to long-term treatment with BDs (although acute responders usually show greater long-term improvements in PFTs).[13]

## ASTHMA–COPD OVERLAP SYNDROME (ACOS)

As discussed by Gibson and Simpson in their 2009 article, data from large population studies show that 17–19% of patients had more than one condition.[14] This is more common in older people, in whom epidemiological studies show that >50% with obstructive airway disease may have overlapping diagnoses of asthma and COPD. At a physiological level, patients with ACOS have evidence of incompletely reversible airflow obstruction that can be detected by a decreased post-BD $FEV_1$ but, in addition, have increased variability of airflow. This may be determined by enhanced BD responsiveness.

Overlap groups include:

- Subjects with asthma who develop fixed airflow obstruction (remodelling).
- Subjects with either asymptomatic bronchial hyper-responsiveness (BHR) or asthma who smoke or have other COPD risk factors (biomass fuel, occupational, previous chest infections, especially tuberculosis).

### ASTHMA WITH FIXED AIRFLOW OBSTRUCTION (REMODELLING)

Longitudinal studies show that at the start of adulthood, lung function is lower in asthmatics.[14] Moreover, a longitudinal study has shown that 16% of asthmatics develop incomplete airflow reversibility after 20–30 years of follow-up.[15] They also are at increased risk of death from airway disease.[14] This fixed airflow obstruction that develops is thought to be due to structural remodelling of the airways due to inflammation, subepithelial fibrosis and increased smooth muscle thickness.[16] This results in bronchial wall thickening and luminal narrowing, which can be seen on high-resolution computer tomography (HRCT).[17]

### BRONCHIAL HYPER-RESPONSIVENESS OR ASTHMA AND EXPOSURE TO COPD RISK FACTORS

Bronchial hyper-responsiveness (BHR) is defined by a drop in PEF or $FEV_1$ after challenge (exercise or chemical).[7] BHR is present in 10–20% of the population and is usually associated with clinical asthma but up to 50% may be asymptomatic. However, even asymptomatic BHR is associated with an increased risk of developing asthma or COPD after more than ten years' follow-up.[18] BHR is also associated with an increased decline in lung function. There is significant interaction with smoking, with a mean additional decline in $FEV_1$ of 12 ml/yr in smokers versus 4 ml/yr in non-smokers.[18] Therefore active smokers with BHR or asthma are at particular risk for the development of COPD and patients with ACOS are commonly ex-smokers.

## ACOS PATIENTS

Several papers have looked at the profile of patients with Asthma–COPD Overlap. In the COPD Gene study, 13% of 915 COPD patients reported a previous doctor diagnosis of asthma. The COPD and Asthma subgroup had a 41% ATS-defined positive BD response versus 36% in those with COPD alone. They also had a worse quality of life with more frequent and severe exacerbations despite younger age and a lower smoking history.[19]

In the Finnish NIHW Registry, the health records of the entire population (5.3 million) were studied and those of >34 years with a principal and secondary diagnosis asthma and COPD from 2000–2009 were focused on. It was found that 16% of this population had Asthma–COPD Overlap. These patients were of a similar age to those with COPD alone but had had more treatment periods (6 versus 2 in asthma and 3 in COPD) and more hospitalisations.[20]

**TABLE I: DOES THE PATIENT HAVE CHRONIC AIRWAYS DISEASE?**

| |
|---|
| HISTORY: |
| • chronic or recurrent cough, sputum, dyspnoea or wheezing, or repeated lower respiratory tract infections;<br>• previous doctor diagnosis of asthma and/or COPD;<br>• previous treatment with inhaled medications;<br>• history of smoking tobacco and/or other substances;<br>• exposure to environmental hazards, for example airborne pollutants. |
| PHYSICAL EXAMINATION: |
| • may be normal;<br>• evidence of hyperinflation or respiratory insufficiency;<br>• wheeze and/or crackles. |
| RADIOLOGY (CXR OR HRCT SCAN PERFORMED FOR OTHER REASONS): |
| • may be normal, especially in early stages;<br>• may show hyperinflation, airway wall thickening, bullae;<br>• may identify or suggest an alternative or additional diagnosis, for example bronchiectasis, tuberculosis, interstitial lung disease, cardiac failure. |

In the PLATINO multi-centre population-based study in five Latin American cities with 5 044 subjects >50 years, 594 (12%) of the total population were classified as COPD (defined as post-BD $FEV_1$/FVC <70%), 84 (1.7%) as Asthma (defined as positive ATS BD response) and 89 (1.8%) as Asthma–COPD Overlap. Of those with obstructive lung disease, 12% had Asthma COPD–Overlap. Overlap patients were more likely to have greater symptoms, more exacerbations (PR 2.1), more hospitalisations (PR 4.1), worse quality of life and lower lung function.[21]

In the EPI-SCAN study, a multi-centre population-based study in Spain, involving 3 885 subjects between 40 and 80 years of age, 385 (10%) were diagnosed with COPD (post-BD $FEV_1$/FVC <70%) and 67 of these (17%) were classified with Asthma–COPD Overlap. ACOS patients were more likely to be female and were again more likely to have worse dyspnoea and wheeze, more exacerbations, worse health-related quality of life and lower physical activity.[22]

ACOS has been specifically looked at in a special chapter in the 2015 GINA Global Strategy for Asthma Management and Prevention Guideline.[7] An important point is made that ACOS is not a single disease and that it is likely that a range of different underlying mechanisms and origins will be identified.

The reported prevalence of ACOS varies between 15% and 55% of patients with chronic airways disease, depending on the population studied (as it varies with age and gender) and also the definitions used for 'asthma' and 'COPD'.

Asthma is defined as a heterogeneous disease, usually characterised by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.[7]

COPD is defined as a common preventable and treatable disease, characterised by persistent airflow limitation that is usually progressive and associated with enhanced chronic inflammatory responses in the airways and the lungs to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients.[23]

Asthma–COPD Overlap Syndrome (ACOS) is characterised by *persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD*. ACOS is therefore identified by the features that it shares with both asthma and COPD. However, a specific definition for ACOS cannot be developed until more evidence is available about its clinical phenotypes and underlying mechanisms.[7]

## DIAGNOSTIC AND THERAPEUTIC APPROACH

It is suggested that when an adult presents with respiratory symptoms, the healthcare provider should ask if the patient has chronic airways disease (see Table I).[7] If so, they should make a provisional syndromic diagnosis of asthma, COPD or ACOS (see Table II). They should assemble the features that most favour a diagnosis of typical asthma or COPD and compare the number of features on each side. If the patient has ≥3 features of either asthma or COPD, there is a strong likelihood that this is the correct diagnosis. They should also consider the level

**TABLE II: SYNDROMIC DIAGNOSIS OF ASTHMA, COPD OR ACOS**

Several positive features (≥3) for either asthma or COPD suggest that diagnosis. If there are a similar number for both asthma and COPD, consider diagnosis of ACOS.

| FEATURES (IF PRESENT) | ASTHMA | COPD |
|---|---|---|
| Age of onset | Before 20 years. | After 40 years. |
| Symptom pattern | Variation over minutes, hours or days. | Persistent despite treatment. |
| | Worse at night or early morning. | Good and bad days but always daily symptoms and dyspnoea. |
| | Triggered by exercise, emotions, fumes, allergens, etc. | Chronic cough/sputum preceded onset of dyspnoea, unrelated to triggers. |
| PFTs during symptoms | Record of variable obstruction (spirometry or peak flow rate). | Record of persistent obstruction ($FEV_1$/FVC <70%). |
| PFTs between symptoms | May be normal. | Always shows obstruction. |
| Past history or family history | Previous doctor diagnosis of asthma, hay fever or eczema. | Previous doctor diagnosis of COPD, emphysema or chronic bronchitis. |
| | Family history of asthma, hay fever or eczema. | Heavy exposure to risk factor: tobacco, smoke, biomass fuels, occupation or PTB. |
| Time course | No worsening of symptoms over time. Variation in symptoms either seasonally or from year to year. | Symptoms slowly worsening over time (progressive course over years). |
| | May improve spontaneously or have an immediate response to BDs, ICS or oral steroids over weeks. | Short-acting BDs provide only limited relief. |
| CXR | Normal. | Hyperinflated (normal in early stages). |

of certainty surrounding the diagnosis as diagnoses are made on the weight of evidence, and the absence of any of these features does not rule out either diagnosis (e.g. the absence of atopy does not rule out asthma). When a patient has a similar number of features of both asthma and COPD, the diagnosis of ACOS should be considered. Spirometry should be performed. It shows whether chronic airflow limitation is present but is of more limited value in distinguishing between asthma with fixed airflow limitation, COPD and ACOS (especially if medications are taken before testing). Spirometry should be done at the initial visit and subsequent visits and, if possible, before and after a trial of therapy. Peak expiratory flow (PEF) testing is not a substitute for spirometry and a normal PEF does not rule out asthma or COPD, but repeated PEF measurement may confirm excessive variability, found in asthma or in most ACOS patients.

If the syndromic assessment suggests asthma, therapy should be started with twice-daily low-dose inhaled corticosteroids (ICS) and short-acting beta-agonists (SABA) when required. If there is poor control despite good adherence and correct inhaler technique, long-acting beta-agonists (LABA) and/or long-acting anti-muscarinics (LAMA) should be added. Do not give LABA alone without ICS.

If syndromic assessment suggests COPD, start with bronchodilators (BDs) or combination therapy and do not give ICS alone without LABA and/or LAMA.

If the differential diagnosis is equally balanced between asthma and COPD, diagnose ACOS and start treatment as for asthma, pending further tests. This is because if there is an asthmatic component, the underlying inflammation needs regular inhaled corticosteroid treatment; this avoids the reported danger of giving only BDs to these patients.

For all patients with chronic airflow limitation, manage the modifiable risk factors (including advice about smoking cessation and avoiding biomass fuel), treat comorbidities, advise about non-pharmacological strategies (including physical activity, pulmonary rehabilitation and vaccinations), provide appropriate self-management strategies and arrange regular follow-up.

Refer for specialised investigations (e.g. diffusing capacity for carbon monoxide, skin-prick tests, IgE levels, blood or sputum eosinophilia, exhaled nitric oxide, sputum bacteriology, HRCT) if there is diagnostic uncertainty, atypical or additional symptoms or signs (e.g. haemoptysis, weight loss, night sweats, fever, chronic purulent sputum), comorbidities that may interfere with management or the patient has persistent symptoms and/or exacerbations despite your therapy.

## CONCLUSIONS

The Asthma–COPD Overlap Syndrome (ACOS) is a work in progress and there is no clear-cut or validated definition. It is not a single disease but more likely represents a range of different underlying conditions. As shown by several studies, patients with ACOS have worse outcomes than those with asthma or COPD alone: more frequent exacerbations, poorer quality of life, more rapid decline in lung function, higher mortality and greater healthcare use. The above diagnostic and therapeutic strategy is an interim practical approach. It should be stressed that whether a patient has asthma, COPD or ACOS may often not be clear at the first or even the second assessment, and that there is great value in reassessment after therapy and over time.

DECLARATION OF CONFLICT OF INTERESTS

Cipla – Member of Inhalant Delivery Device Advisory Board in June 2015; Astra Zeneca: Sponsored speaker (on IPF) at Respiratory Symposium in March 2014.

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Guest Review

# MULTIPLE-DRUG INTOLERANCE SYNDROME

*Case records from the multi-disciplinary drug hypersensitivity clinic*

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## ABSTRACT

Multiple-drug intolerance syndrome (MDIS) is a condition where patients experience adverse drug reactions to three or more unrelated drugs. The immunological mechanism is unknown, hence the preferred labelling as 'intolerance' as opposed to 'allergy'. MDIS prevalence in South Africa is unknown, but may be as high as 2.1% according to international electronic medical record data. The majority of specialist physicians have encountered these complicated, sometimes frustrating, but always challenging patients.

MDIS patients have high rates of healthcare and medication use, and are highly prone to developing new adverse drug reactions. Risk factors include female gender and multiple non-life-threatening co-morbidities, but not atopy. Antibiotics, particularly cephalosporins and quinolones, together with NSAIDs are the common offending drug classes. The severity of reactions is often overestimated, but life-threatening anaphylaxis or severe cutaneous drug reactions are reported. Optimal management involves the judicious use of drug provocation testing in a safe environment to provide patients and treating physicians with safe drugs as and when medically indicated. Multiple costly *in vitro* and *in vivo* drug allergy testing should be limited.

This brief review first presents an illustrative case from our newly established multi-disciplinary drug hypersensitivity clinic and then provides a literature review on the risk factors, proposed mechanisms and optimal management of MDIS.

*This article has been peer reviewed.*

## ILLUSTRATIVE CASE

A 38-year-old architect from a coastal town in South Africa was referred to our multi-disciplinary drug hypersensitivity clinic with the problem of multiple allergy reactions to different antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs). The severity and diversity of adverse drug reactions (ADRs) had made her, her husband and her treating doctors very anxious: she felt that she no longer had any safe drug options to deal with her intermittent back pain or occasional antibiotic-requiring infection.

She has no chronic medical co-morbidities or history of atopy. She had a history of large local reactions to bee venom, and a delayed hypersensitivity reaction to Elastoplast®. She does not use chronic medication and last required analgesia (Adcadol® – paracetamol, codeine, caffeine and doxylamine; and Cataflam® – diclofenac) after a ligamentous injury to her right foot in 2015. Interestingly, both her mother and her maternal grandmother were intolerant to a number of drugs. During early childhood she tolerated intermittent antibiotic therapy for the occasional upper respiratory tract infection without problems, although she could not recall the specific drugs prescribed. She had her first ADR at age 15; she was given an antibiotic and seconds later began to experience swelling of her feet and hands, with associated chest tightness. She was rushed to the general practitioner (GP) and treated successfully. She had a similar reaction at age 18 years, also requiring hospital treatment. She was uncertain of the precipitating drugs, but from that point on avoided antibiotics if at all possible. In 1998 she had her worst episode, after the family dog was prescribed an unknown antibiotic; very soon after handling it to give it to the dog, she started with tongue, hand and face swelling. She required emergency room admission and treatment. The most recent and severe reaction occurred during a general anaesthetic for maxillofacial surgery for a mandibular cyst last year. She was given an antibiotic and Cataflam® (diclofenac), together with the general anaesthetic, and developed a reaction 30 minutes into the procedure. She required treatment with adrenaline and antihistamines, and recovered quickly. On systematic enquiry, she described episodes of spontaneous urticarial-like 'heat rash', which would last about 15 minutes and respond to antihistamine cream; she has never had spontaneous angioedema. There were no dietary triggers of reactions. The only relevant finding on physical examination was dermatographism. A great deal of *in vitro* drug-allergy testing had been done prior to her being

**TABLE I: ILLUSTRATIVE CASE ALLERGY DIAGNOSTIC TESTING**

| FLOW CAST TEST POSITIVE | FLOW CAST TEST NEGATIVE |
|---|---|
| Penicillin MDM 37.9% | PPL |
| Amoxicillin 42.9% | Clindamycin |
| Cefuroxime 48.8% | Diclofenac |
| Clarithromycin 57.1% | Indomethacin |
| Co-amoxiclav 17.7% | Aspirin |
| Moxifloxacin 47.4% | Naproxen |
| Doxycycline 41.0% | |
| Ibruprofen 47.9% | |
| **DIVERSE FLOW CAST** | **DIVERSE FLOW CAST** |
| Telithromycin 80.0% | Tigecycline 2.19% |
| | Meropenem 1.4% |
| | Amikacin 1.12% |
| | Metronidazole 0.43% |
| **SKIN/INTRADERMAL TEST POSITIVE** | **SKIN/INTRADERMAL TEST NEGATIVE** |
| Metronidazole SPT 1:10 – 3/6 mm wheal/flare; IDT 1:100 no reaction, IDT 1:10 not done | Meropenem |
| Linezolid dilutions 1:100 – 2/4 mm wheal/flare | Ceftriaxone IDT 1:100 |

*Abbreviations: CAST: Cellular antigen stimulation test; MDM: Minor determinant mix; PPL: Major determinant benzylpenicilloyl poly-L-lysine; SPT: skin-prick test; IDT: Intradermal test.*

reviewed in our clinic, including multiple cellular antigen stimulation tests (CAST) and skin-prick and intradermal testing (see Table I). In addition, she had two normal baseline tryptase measurements, a normal full blood count and thyroid function, negative thyroid autoantibodies, and a negative stool antigen for *Helicobacter pylori*.

The history and test results were consistent with a diagnosis of multiple-drug intolerance syndrome. CAST testing suggested she was not sensitised to the beta-lactam ring, but rather to specific side-chains, although reactivity to many chemically distinct agents is hard to explain. CAST can be performed using the flow cytometry (see Table I) or ELISA methods; flow CAST measures that upregulation of basophil activation markers on patients' cells, whereas ELISA CAST measures leukotriene levels in cell supernatants, both following stimulation with a drug. Our management plan involved hospital admission for drug provocation testing with a focus on ensuring that she has safe oral and intravenous antibiotics that cover a wide microbiological spectrum, as well as a safe NSAID. During her four-day hospital admission she was successfully challenged to Cefexime (oral second-generation cephalosporin), Ceftriaxone (intravenous third-generation cephalosporin), metronidazole and aspirin. I stressed to her the limitations of *in vitro* drug-allergy testing, noting that, in the future, should she require a specific antibiotic for a resistant organism – for example, linezolid – graded drug challenge is highly recommended irrespective of her CAST results.

## INTRODUCTION AND NOMENCLATURE

Drug-hypersensitivity reactions (DHR) affect approximately 7% of some populations, and therefore represent an important public health problem.[1] Up to one-third of patients presenting to drug allergy units report 'multiple-drug allergies', most of which are not validated.[2] The majority involve overuse of the term 'allergy'. Over-diagnosis of drug allergies can have a negative impact on the quality of medical care – for example, due to the use of non-preferred antibiotic therapy and resulting prolonged hospital stay.[3] However, there are patients who react to multiple different drugs and these patients need to be identified, appropriately worked up and an optimal management plan developed for them.

In 1989, Sullivan et al[4] first described the 'multiple-drug allergy syndrome' as drug allergies to two or more chemically different drugs (mainly antibiotics). The reactions were distinct from (i) cross-reactivity – due to structural similarities, common metabolic pathways or pharmacologic mechanisms; and (ii) flare-up reactions – exacerbations of existing drug-hypersensitivity reaction by the early switch of therapy to another drug.[5]

The name was revised to 'multiple-drug hypersensitivity syndrome' (MDH), but because the pathophysiological mechanisms remain poorly understood, the term has been used to describe a heterogeneous group of patients in the literature. Consequently, the term 'multiple-drug intolerance syndrome' was introduced to indicate that in many instances drug reactions might not be allergic.[6] Undoubtedly, there is a group of patients that have multiple immunological reactions to chemically distinct drugs, confirmed with *in vivo* testing. Sullivan et al estimated that 1% of 437 penicillin-allergic patients reacted to non-betalactam antibiotics[4] and Barbaud et al, in a large prospective study of severe cutaneous adverse reactions (SCAR), found that 18% of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) cases reacted to multiple drugs;[7] these patients may be best labelled as experiencing MDH. In contrast, there is also a group of patients who report adverse drug reactions to three or more chemically, pharmacologically and immunogenically unrelated drugs, but who have negative skin (specifically IgE) testing and, in most instances, challenge testing. This patient group has labelled as experiencing 'multiple drug intolerance syndrome' (MDIS) and is the largest group of patients with multiple-drug reactions presenting to allergists, with an *estimated prevalence of 2.1%* in a large electronic health record study in the United States.[6]

## RISK FACTORS AND USUAL OFFENDING DRUG CLASSES

History-taking is the cornerstone of diagnosis in MDIS because there is neither a biomarker nor a straightforward *in vitro* allergy test for confirmation. History-taking should

focus on identifying risk factors and ascertaining as detailed a description of each adverse drug reaction as possible in order to identify the list of possible offending drugs. Figure 1 provides a list of risk factors and the relevant frequencies of offending drugs as defined by the two largest studies of MDIS.[6,8] The diagnosis is one of exclusion, where better-known conditions such as cross-intolerance to NSAIDs in patients with underlying spontaneous urticaria or cross-reactivity to structurally similar drugs – for example, beta-lactams – need to be excluded. Across the available literature, female gender is the most consistent risk factor.[2,6,8] MDIS patients also tend to have multiple co-morbidities and use more medications and healthcare services; however, the prevalent diagnoses are frequently non-morbid conditions such as gastro-oesophageal reflux, dermatitis, hypertension and various forms of pain.[6] An association with psychiatric disease, including depression and anxiety, has been suggested and should be enquired after, but is not consistent across studies.[6,8,9] Proven anaphylaxis or a severe cutaneous drug reaction will increase the likelihood of positive allergy testing and the reproducibility of challenge (if indicated).

Omer et al examined the odds ratios (OR) for particular drugs being implicated in a large UK cohort of MDIS. Cephalosporin and quinolone ADRs were the most significant predictors of MDIS (OR of 11.3 and 11.1, respectively). In contrast, penicillin allergy was not associated with MDIS, while the likelihood of MDIS was lowest in those allergic to peanuts (OR 2.3), shellfish (OR 2.3), and aspirin (OR 2.6) compared to other NSAIDs (OR 5.4) and other non-beta-lactam antibiotics (OR >5).[8]

## POSSIBLE MECHANISMS

The pathogenesis of neither MDIS nor MDH is clear, and it is likely that different mechanisms are involved across the heterogeneous patient group. First, in a number of instances the ADRs in MDIS may be non-allergic, possibly even known off-target actions of the drug (side-effects). Secondly, the reactions may be pseudoallergic – reactions with clinical features suggestive of mast-cell mediator release – for example, urticaria – but not antibody- (IgE) or T-cell-mediated. Recently, a novel mast-cell G-protein coupled receptor, Mrgprx, has been characterised and demonstrated to cause mast-cell degranulation in response to chemically distinct cationic drugs containing a common structural motif.[10] Unpublished data suggest that this receptor is highly polymorphic with impacts on thresholds of activation; therefore it is reasonable to hypothesise that different individuals may have lower thresholds for activation. Further research into the reactions is required. Thirdly, other unidentified receptors or alternative non-IgE mechanisms may be associated with these ADRs. Lastly, there are patients with proven IgE-mediated or T-cell-mediated reactivity to multiple different drugs. Abnormalities of T-regulatory functions or increased frequency of certain effector T-cell populations has been implicated.[2]

## MANAGEMENT

MDIS patients are a particularly challenging and often frustrating group of patients. They have frequently seen many doctors and have long lists of co-morbid conditions and ADRs. They consume disproportionate healthcare resources and present with complications arising from the inability of treating doctors to use preferred first-line medications. A clear step-wise strategy to allergy assessment and management is therefore advised and outlined in Box 1 below. Allergy management can be performed by all doctors trained to perform drug-provocation testing and in a hospital environment in which testing can be performed safely.

Box 1: Step-wise management approach for MDIS patients

1. History and examination.
2. Detailed documentation of each ADR with list of possible offending agents.
3. Specific enquiry about risk factors, tolerance to NSAIDs, and atopic disease.
4. Examination for dermatographism.
5. Identification of main healthcare providers and a decision, together with the patient, on priority drug requirements – this should dictate plans for testing and drug provocation.
6. Limited *in vivo* and *in vitro* diagnostic testing guided by severity of reaction and known diagnostic accuracy of testing to the particular offending agent.
7. Arrange for oral-provocation challenge in safe environment.
8. Detailed letter for patient (and to future doctors) to summarise allergy findings and encourage graded challenge or even desensitisation rather than exclusion of preferred medications where clinically indicated.

*Abbreviations: MDIS: multiple-drug intolerance syndrome; ADR: adverse drug reaction; NSAIDS: non-steroidal anti-inflammatory drugs*

A detailed history of ADRs, potential offending drugs and risk factors is the starting point, as highlighted above. Where possible, hospital records of previous ADRs, prescriptions from the pharmacies to identify exact drug preparation used and direct discussions with the treating clinician are optimal. The aim is to clarify the clinical symptoms and severity, the timing of onset and whether any confirmatory testing – for example, serial tryptase measurements – was performed. Once the list of offending drugs is available, possible unifying explanatory models/diagnosis should be considered – for example, NSAID cross-intolerance with underlying spontaneous urticaria – or cross-reactivity – for example, beta-lactam hypersensitivity. In addition, it is important to consider any hypersensitivity reactions to a common drug excipient; this may necessitate contacting the medicines information centre to make direct enquiries with pharmaceutical companies for a detailed list of ingredients, which is often not found in the package insert.

The most important question to ask in the work-up and management of MDIS patients is which drug therapy they require to optimally manage their co-morbidities, and what the impact is likely to be of

- avoidance of the possible offending drug class, and
- using an alternative agent.

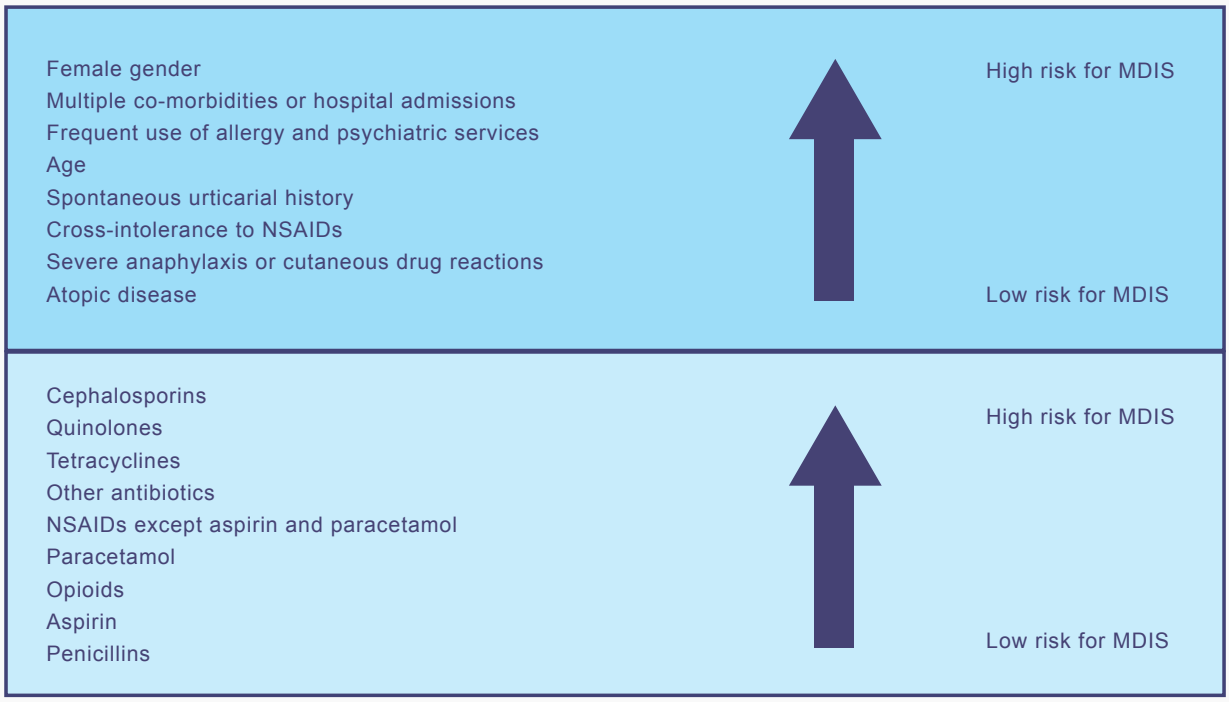


*Figure 1: Factors and offending drugs to identify the MDIS patient*
*Abbreviations: MDIS: Multiple-drug intolerance syndrome; NSAIDS: non-steroidal anti-inflammatory drugs*

The challenge in many instances, such as the illustrative case, is that patients appear allergic to 'all antibiotics'. In these situations, it is important to decide on a few essential medications that the patient/doctors wish to use in the near to medium future – for instance, an oral antibiotic for uncomplicated upper respiratory tract infection. *In vitro* testing should be tailored to the list of offending drugs and alternatives to be used as part of drug challenge. It is inappropriate and costly to perform *in vitro* testing on multiple drugs that the patient may or may not require in the future. The reason for this is that the diagnostic accuracy and predictive value of *in vitro* drug allergy testing when compared to gold standard drug provocation testing is highly variable, and in many instances unknown, for individual drugs. Where necessary, the clinician should discuss testing with a drug-allergy specialist or laboratory.

Judicious use of drug-provocation testing is the optimal management strategy for patients with MDIS if avoidance is neither safe nor convenient. The reasons for this approach include:

- the unknown aetiology of ADRs in MDIS;
- the limited utility of *in vitro* and *in vivo* drug-allergy testing for many offending drugs;
- the context-specific factors associated with a particular ADR that led to allergy labelling.

Schiavino et al performed 1 808 challenges in 480 patients – 84.4% female, mostly ages 40–60, with histories of ADRs to at least three unrelated medications. Only 224 (12.4%) challenges where positive, and in almost all those patients either the offending medication or an alternative was safely tolerated.[11] Raman et al performed 350 challenges in 23 MDIS patients, with only three positive challenges, all to NSAIDs.[12] Despite the infrequency of reactions, drug challenges should always be performed in settings where full resuscitation equipment is available and staff are trained in anaphylaxis management.

In all instances, following allergy work-up and testing, a detailed letter and tailored bracelet should be organised for the patient. Importantly, allergy labelling should be as focused as possible so as not to unnecessarily exclude the future use of potentially life-saving medications. Patients should be told, and letters should detail, that in hospital a challenge or desensitisation may be possible should the patient require life-saving medications, especially certain antibiotics, in the future.

## CONCLUSION

Patients with intolerance to multiple drugs are a challenge to both the attending physician and the allergist. They are a heterogeneous patient group, and undoubtedly certain patients do have proven immune-mediated hypersensitivity to multiple structurally unrelated drugs. However, in many instances allergic reactions are not validated, yet cause considerable distress to both patient and provider, increase healthcare use and jeopardise their optimal medical care. In these patients with MDIS, detailed and step-wise allergy work-up and, where appropriate, drug-provocation testing,

are invaluable in ensuring that patients safely access the therapies they need.

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

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Guest Review

# A DIAGNOSTIC APPROACH TO CHRONIC COUGH IN CHILDREN

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## ABSTRACT

Chronic cough, defined by the majority of studies and guidelines as a cough that lasts longer than four weeks, is common in the paediatric population, but the true prevalence and burden of disease remains difficult to define. It is now understood that the aetiology of chronic cough in children differs from that in adults. Children with chronic cough should be managed with paediatric-specific algorithms because those who are treated in this manner have improved clinical outcomes. Recent studies have focused on protracted bacterial bronchitis as a major cause of chronic cough in pre-school children and its role as a possible precursor of bronchiectasis. Recognising those children with possibly serious underlying diseases is critical to preventing delayed diagnosis and poor outcomes. However, it is equally important not to over-investigate those children who have an isolated non-specific cough. Clinicians should be familiar with the vast list of important causes of a chronic cough as well as the history-taking and clinical skill to define patients at risk of having a potentially serious disease in order to manage them timeously and appropriately.

*This article has been peer reviewed.*

## INTRODUCTION

Cough is a very common presenting complaint in paediatric practice. Even healthy children may cough daily;[1] but a chronic cough (CC) is associated with poor quality of life and may also be the presenting symptom of a serious underlying disease.[2]

The majority of recent clinical studies as well as the guidelines of the American College of Chest Physicians and those of the Thoracic Society of Australia and New Zealand have defined a CC as one that lasts for more than four weeks, because most acute uncomplicated respiratory infections in children resolve within this interval.[2–6]

In 2006 the prospective study of Marchant et al presented new insights into the etiology of CC in young children.[7] They found that the most common diagnosis was protracted bacterial bronchitis (PBB) and that the three most common CC-related diagnoses in adults (asthma, upper airway cough syndrome and gastro-oesophageal reflux) were found in only 9% of young children.[8] Following this and similar findings, specific management protocols (algorithms) for children with CC have been published.[5] In addition, it has been shown that children managed with these paediatric specific algorithms have better clinical outcomes.[5,6] Therefore, pending new data, CC in children should be evaluated systematically and treatment targeted to the underlying aetiology, irrespective of the cough severity.[6] This approach to the diagnosis and management of CC in children is presented in this article.

## DIAGNOSTIC APPROACH

All children with a CC should be evaluated with a detailed history, physical examination, chest X-ray (CXR) and spirometry, where possible.[3,9] This initial evaluation usually provides enough information to narrow down the long list of possible causes (see Table I) and categorise the CC as *specific* (i.e. caused by an underlying disease) or *non-specific* (i.e. no evidence of an underlying disease). Certain symptoms and signs are so predictive of a specific cough that it narrows the diagnostic possibilities (see Table II) and supports specific testing and/or referral (see Figure 1).

The causes of specific CC can be categorised in the following groups: asthma and allergies, airway abnormalities, aspiration, infections (chronic or less common), protracted bacterial bronchitis, chronic suppurative lung disease and bronchiectasis, interstitial lung disease, airway irritants (chemical or physical) and extrapulmonary causes (see Table I).

In the absence of any specific cough pointers (see Table II), a presumptive diagnosis of non-specific cough can be made (see Figure 2).

| TABLE I: CAUSES OF CC IN CHILDREN |
|---|
| ASTHMA AND ALLERGY |
| Asthma and cough-dominant asthma;<br>Allergic rhinitis and post-nasal drip. |
| AIRWAY ANOMALIES OR NARROWING |
| Laryngeal cleft;<br>Tracheoesophageal fistula;<br>Laryngotracheomalacia – primary or secondary to vascular or other compression. |
| ASPIRATION |
| Swallow dysfunction with aspiration;<br>Gastro-oesophageal reflux;<br>Tracheobronchial foreign body aspiration. |
| INFECTION |
| Recurrent viral infection (infants and toddlers);<br>Protracted bacterial bronchitis;<br>Pertussis-like syndrome *(Bordetella pertussis, Chlamydia, Mycoplasma);*<br>Granulomatous infections (mycobacterial, fungal);<br>Suppurative lung disease (bronchiectasis and lung abscess);<br>Impaired mucociliary clearance (cystic fibrosis, primary ciliary dyskinesia);<br>Immunodeficiency;<br>Chronic rhinosinusitis. |
| INTERSTITIAL LUNG DISEASE |
| Bronchiolitis obliterans;<br>Surfactant deficiencies;<br>Developmental disorders;<br>Secondary to cardiac disease, autoimmune disease or immune deficiency. |
| IRRITATION |
| Active and passive smoke exposure;<br>Pollution and dust;<br>Volatile chemicals. |
| IATROGENIC |
| Angiotensin-converting enzyme inhibitors;<br>Radiation or cytotoxic agents. |
| EXTRA-PULMONARY |
| Ear pathology;<br>Cardiac pathology. |
| HABIT COUGH |

HISTORY

A detailed history is the most important aspect of the child's evaluation. The history should focus in detail on the cough specifics: age and circumstances of onset, nature of the cough, timing and triggers, and associated symptoms. Table III explains how these questions can aid in determining the diagnosis. In addition, the past medical history should include the birth history, prematurity, atopy/allergy and past episodes of pneumonia, and provides important clues in the diagnosis. Focal recurrent or non-resolving pneumonia is suggestive of a foreign body or airway abnormality, whereas multifocal pneumonia suggests immune deficiency, aspiration, autoimmune disease or abnormal mucociliary clearance (e.g. cystic fibrosis (CF) and primary ciliary dyskinesia (PCD)). A family history of atopy, chronic lung disease or infectious contacts should be documented. Environmental exposures to pets/animals, indoor mould/damp, environmental tobacco smoke, indoor air pollution, recent travel and daycare are important and should be explored. The previous use of and response to antibiotics, antihistamines and bronchodilators should be noted and may provide a clue to the underlying condition such as allergic rhinitis, asthma and PBB. Lastly, exposure to specific medications such as angiotensin-converting enzyme inhibitors, radiation and cytotoxic drugs should be explored.

## PHYSICAL EXAMINATION

In the general physical examination close attention should be paid to signs of possible underlying chronic disease. A complete respiratory examination is mandatory and all chest signs noted, in particular, the presence of wheezing and whether it is polyphonic or monophonic in nature. Polyphonic wheezing is a sign of small and medium-sized airway diseases as seen in asthma, bronchiolitis, bronchiectasis, bronchopulmonary dysplasia and aspiration syndromes. Monophonic wheezing, on the other hand, is indicative of large airway pathology such as tracheomalacia, tracheal stenosis and extrinsic airway compression secondary to tumours, vascular rings or mediastinal lymphadenopathy. Coarse crepitations (previously referred to as ronchi) are often audible in infective conditions such as PBB, bronchiectasis and bronchiolitis obliterans, while fine crepitations are more common in interstitial lung diseases and pulmonary oedema. Focal areas of decreased air entry or bronchial breathing are also significant clinical findings.

## CHEST RADIOGRAPHY

All children with a CC should have a CXR. A definitive diagnosis is seldom made on CXR alone, but certain findings (e.g. focal parenchymal disease, airway narrowing, abnormal mediastinum or pleural pathology) can assist in making a diagnosis or directing further investigations. A normal CXR is mandatory to diagnosing a habit cough, but children with asthma, early bronchiectasis and even an inhaled foreign body may have a normal CXR. In interpreting the CXR findings, one should distinguish between alveolar, interstitial and airway disease, define focal versus diffuse involvement and exclude mediastinal, pleural and cardiac abnormalities.

## PULMONARY FUNCTION TESTING

Spirometry should be attempted in all children with a CC older than five years. Most of them will be able to perform reliable flow-volume loops. Spirometry can help to distinguish between obstructive and restrictive lung disease. Furthermore, pre- and post-bronchodilator spirometry can confirm whether there is a reversible airflow limitation indicative of airway reactivity. This finding is suggestive of asthma, but can also be seen in children with a recent bout of acute bronchitis, PBB, CF or PCD. An abnormal inspiratory loop is indicative of extrathoracic large airway narrowing.

## OTHER TESTS

Additional tests can be considered in cases where the

**TABLE II: SPECIFIC COUGH POINTERS[3,4,17]**

| PULMONARY | SYSTEMIC |
|---|---|
| **History** | **History** |
| • Abnormal cough characteristics (brassy, paroxysmal, staccato, present since birth)<br>• Daily wet cough<br>• Dyspnoea at rest/exertion or tachypnoea<br>• Chest pain<br>• Hemoptysis<br>• Hypoxia/cyanosis<br>• Recurrent pneumonia<br>• Previous lung disease or predisposing causes (e.g. foreign body aspiration) | • Infectious contacts (tuberculosis)<br>• Fever<br>• Feeding difficulties<br>• Immune deficiency (primary of secondary)<br>• Medications associated with chronic cough (e.g. ACE inhibitors)<br>• Neurodevelopmental abnormality<br>• Failure to thrive |
| **Examination** | **Examination** |
| • Chest wall deformity<br>• Abnormal auscultation (stridor, wheeze, crepitations) | Chronic suppurative otitis media<br>Cardiac abnormalities<br>Digital clubbing<br>Atopy (atopic dermatitis, allergic rhinitis) |
| **Investigations** | |
| • Abnormal CXR (other than perihilar changes)<br>• Pulmonary function test abnormalities | |

specific pointers to the cause of CC are present in their initial assessment. These tests should be carefully considered and used appropriately. The indiscriminate use of these tests in well children with an isolated non-specific cough should be strongly discouraged as it leads to parental/patient anxiety and unnecessary medical expenses.

### Allergy testing

Skin-prick testing or allergen-specific testing to aeroallergens and other specific allergens based on a suggestive history can be considered in children with features of atopy and asthma.

### Bronchoscopy and bronchoalveolar lavage

Children with suspected foreign-body inhalation should urgently be referred for bronchoscopy. The majority of foreign bodies can be removed with a flexible bronchoscope, but this depends on the skill and preference of the bronchoscopist. Bronchoscopy is also indicated in children with suspected airway abnormalities or persistent focal disease on CXR. A bronchoalveolar lavage is indicated in children with suspected chronic/unusual infections, interstitial lung disease or aspiration. Cilia biopsies can be collected nasally or from bronchial mucosa in suspected PCD patients.

### Oesophageal pH and impedance monitoring

Gastro-oesophageal reflux disease (GORD) is an uncommon case of CC in children, except in children with

**TABLE III: SUGGESTIVE FEATURES OF CC TO AID DIAGNOSIS**

| | *Causes* | *Differential diagnosis* |
|---|---|---|
| COUGH ONSET | | |
| • Neonatal<br>• Sudden<br>• Following severe preumonia<br>• Following URTI | • Congenital malformation<br>• Aspiration<br>• Genetic<br>• Inhalation<br>• Injury | • Tracheobronchomalacia<br>• Tracheosophageal fistula, laryngeal cleft and neurological disorders<br>• Cystic fibrosis, primary ciliary dyskinesia<br>• Foreign body<br>• Bronchiectasis, bronchiolitis obliterans<br>• Post-infectious, habit cough |
| NATURE OF THE COUGH | | |
| • Paroxysmal and triggered by exercise, cold air, sleep or allergen exposure<br>• Acute paroxysmal<br>• Barking or brassy<br>• Chronic productive | • Airway reactivity<br>• Infection<br>• Trachea and large airway pathology<br>• Chronic bronchitis<br>• Bronchiectasis | • Asthma<br>• Post-infectious<br>• Pertussis and parapertussis syndromes<br>• Airway malacia, extrinsic compression, foreign body, spasmodic croup<br>• Protracted bacterial bronchitis<br>• Cystic fibrosis, primary ciliary dyskinesia, immune deficiency, aspiration |
| TIMING AND TRIGGERS | | |
| • Worse in morning and more productive<br>• With swallowing<br>• First hour after a meal<br>• Worse when supine<br>• Disappears when asleep or distracted | | • Bronchiectasis<br>• Aspiration<br>• GORD<br>• Nasal pathology<br>• Habit cough |
| ASSOCIATED SYMPTOMS | | |
| • Failure to thrive<br>• Fever and weight loss<br>• Neurological impairment | • Suppurative lung disease<br>• Chronic infections<br>• Immune deficiency<br>• Aspiration | • Cystic fibrosis<br>• Mycobacterial |

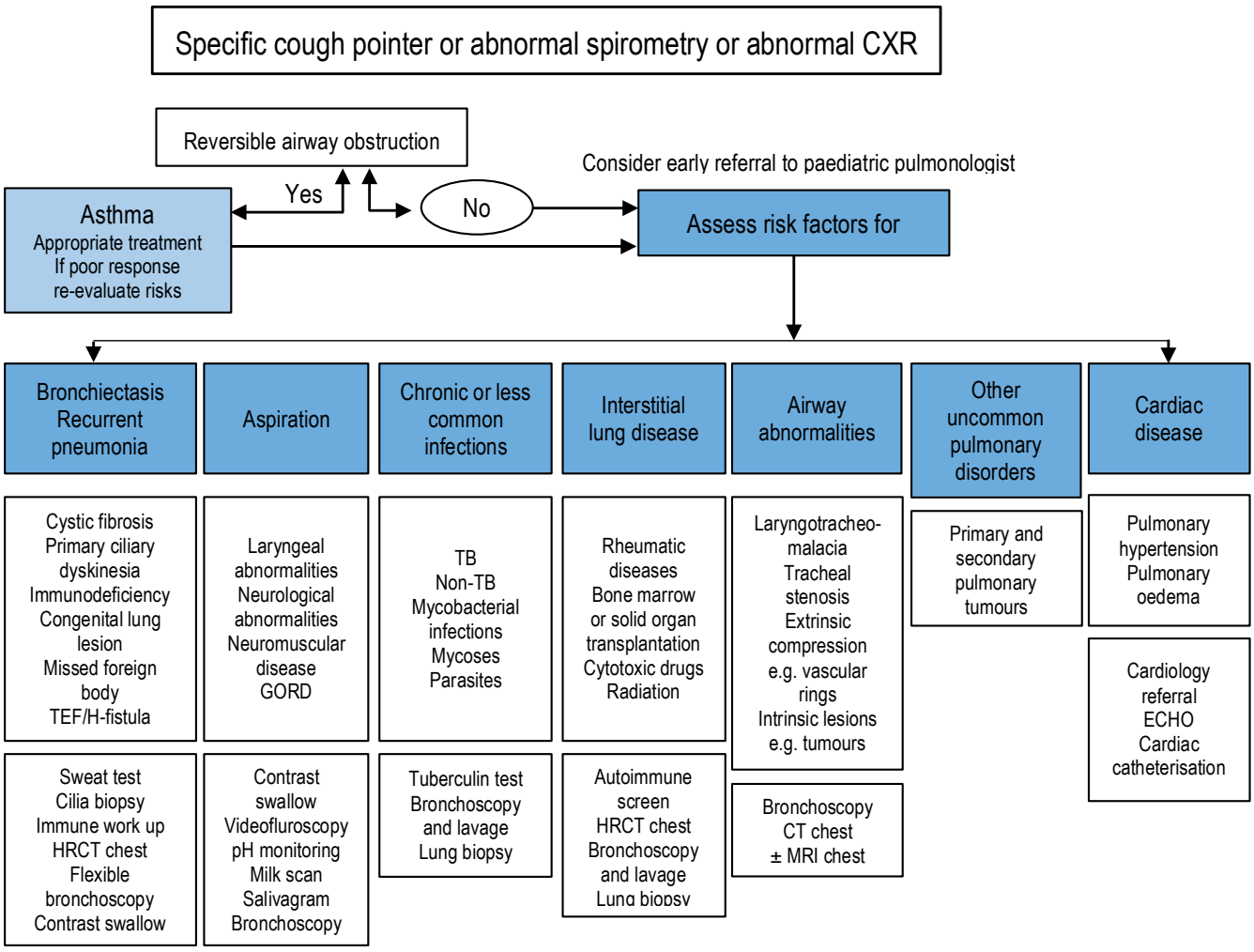


*Figure 1: Adapted management algorithm for specific CC in children <14 years of age*[3,5,9]
*Abbreviations: TOF – Tracheoesophageal fistula; GORD – Gastro-oesophageal reflux disease; HRCT – High-resolution chest tomography; TB – Tuberculosis; MRI – Magnetic resonance imaging, ECHO – Echocardiography*

anatomical or neurological abnormalities that predisposes to incoordination with swallowing and aspiration. However, if GORD is strongly suspected, oesophageal pH monitoring and/or a trial of GORD treatment may be offered.

## MANAGEMENT OF CC

Once the detailed history, physical examination, CXR and PFT have been evaluated, it should be clear whether the child has a specific or a non-specific cough. Those children with specific cough pointers in the history, examination or baseline investigations (see Table II) should be investigated and treated or referred as appropriate. Figure 1 illustrates the algorithm that was first proposed in 2006[3] and has been shown to lead to improved clinical outcomes.[5]

### CHRONIC WET/PRODUCTIVE COUGH

Chronic wet cough is a common presentation in children. Up to 64% of children newly referred for CC had a wet or productive cough. The two conditions most commonly associated with the wet cough were PBB (41%) and CT scan-proven bronchiectasis (9%).[2] Awareness of PBB has increased significantly during the ten years since the first description,[7] especially due to the observation that, left untreated, PBB can be a forerunner of bronchiectasis.[10,11] Recent modified diagnostic criteria have been proposed to simplify the diagnosis of PBB (see Table IV).[12]

A recent systematic review found high-quality evidence that the use of appropriate antibiotics in PBB improves cough resolution.[13] The choice of antibiotic depends on the drug susceptibility of local microbiota but usually includes amoxycyllin-clavulanate or cefuroxime. A two-week course of antibiotics is adequate in the majority of cases, but some cases may require a longer course. However, it is strongly advised to refer such cases to a referral centre as the indiscriminate/prolonged use of antibiotics should be avoided wherever possible and the likelihood of an underlying explanation increases.[13–16] More importantly, if specific cough pointers (e.g. digital clubbing) are present at diagnosis, further investigations (e.g. flexible bronchoscopy, immune work-up and CT chest) are indicated and children should be referred to specialist centres/pulmonologists without delay.

| TABLE IV: PROPOSED DIAGNOSTIC CRITERIA FOR PBB[12] |
|---|
| Original microbiologic-based case definition (termed PBB-micro). |
| Presence of chronic wet cough (>4 weeks);<br>Lower airway infection (recognised respiratory bacterial pathogens growing in sputum or at BAL at density of a single bacterial specifies (104 colony-forming units/ml));<br>Cough resolved following a two-week course of an appropriate oral antibiotic. |
| Modified clinical-based case definition (termed PBB-clinical) |
| Presence of chronic wet cough (>4 weeks);<br>Absence of symptoms or signs of other causes of wet or productive cough (see Table II);<br>Cough resolved following a two-week course of an appropriate oral antibiotic. |
| PBB-extended. |
| PBB-clinical or PBB-micro, but cough resolves only after four weeks of antibiotics. |
| Recurrent PBB. |
| More than three episodes per year. |

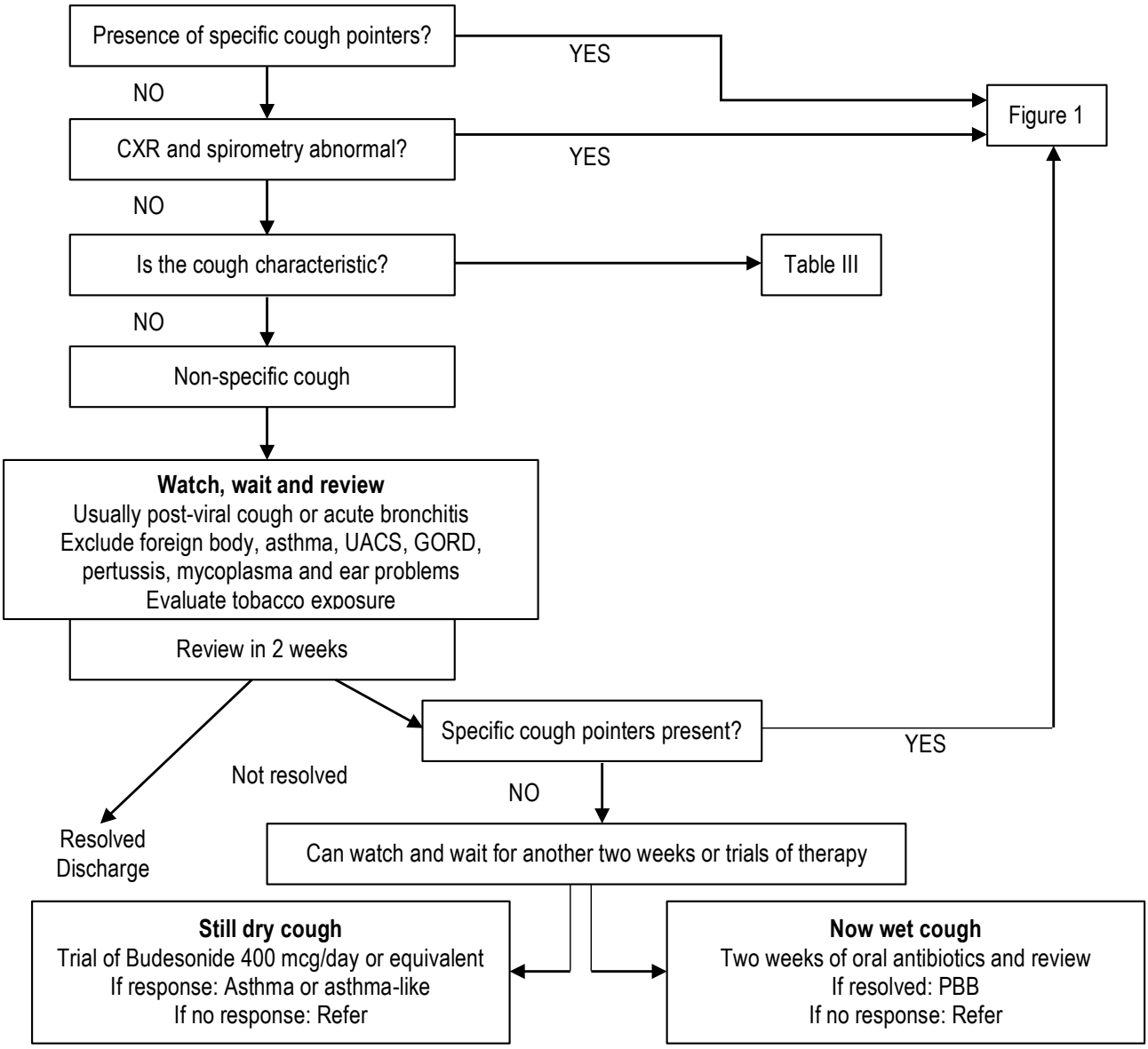


*Figure 2: Adapted management algorithm for non-specific CC in children <14 years[3,9] Abbreviations: CXR – Chest radiograph; UACS – Upper airway cough syndrome; GORD – Gastro-oesophageal reflux disease*

NON-SPECIFIC NON-PRODUCTIVE COUGH

Figure 2 illustrates the proposed algorithm for managing children with a non-specific cough.[3] Although it is pertinent to consider contributing factors such as asthma, missed foreign bodies, pertussis, mycoplasma pneumonia, upper airway cough syndrome (UACS)/post-nasal drip and GORD in these patients, it is also important to not subject these children to excessive and inappropriate testing that creates anxiety and stress, especially in those children who have specific pointers indicating a habit cough.

Treating children with a non-specific cough remains a challenge and treatment modalities are limited. An empirical trial of bronchodilators or inhaled corticosteroids can be considered in those with a troublesome non-productive cough, but if there is no clear response to the medication after two to four weeks, it should be stopped. Patients who present with symptoms or special investigations (e.g. pH manometry) strongly suggestive of GORD can be offered a trial of anti-GORD treatment for two weeks. The indiscriminate and/or prolonged use of proton pump inhibitors (PPI's) without treatment response must be avoided, because GORD as a cause for an isolated chronic cough in children is very uncommon to start with and the overuse of PPI is concerning.

For those who develop a wet, productive cough, a trial of antibiotics for two weeks can be offered. These families and children require support and very careful follow-up. Those who respond poorly are best managed in experienced referral centres early in the course of their illness.

## CONCLUSION

The causes for CC in children are vast and differ from those in adults. The diagnostic approach to children with a CC is paediatric-specific and includes a detailed history, physical examination, CXR and spirometry where possible. Symptoms and signs that are predictive of a specific cough are listed (see Table II) and should be identified correctly. These symptoms and signs indicate the need for specific testing and referral, where appropriate (see Figure 1). Protracted bacterial bronchitis has emerged as the leading cause of chronic wet cough in children and can possibly lead to bronchiectasis if left untreated. Children who present with a chronic wet cough as well as specific cough pointers such as digital clubbing should be referred immediately. The management of a chronic, non-specific cough in children remains a challenge as it requires careful consideration and long-term follow-up and the treatment options remain limited.

DECLARATION OF CONFLICT OF INTEREST

The author declares no conflict of interest.

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Guest Review

# PAEDIATRIC NASAL OBSTRUCTION – A PRACTICAL APPROACH

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## INTRODUCTION

Nasal obstruction and subsequent partial upper-airway obstruction can result in troublesome morbidity for the child. It is one of the most common reasons for the presentation of children to the doctor, whether allergologist, paediatrician, general practitioner or ear, nose and throat (ENT) surgeon.[1] This article offers a straightforward and practical approach to managing the most common causes of nasal obstruction in the paediatric population.

*This article has been peer reviewed.*

## NASAL OBSTRUCTION

In the majority of cases, nasal obstruction is mild with habitual snoring, mouth breathing and rhinorrhoea being the main problems. Chronic mouth breathing, especially during critical growth periods, is also associated with the development of craniofacial abnormalities.[2] Habitual snoring was thought to be innocuous but it has been shown that snoring children have a higher incidence of neurocognitive disorders.[3] Daytime sleepiness, behavioural hyperactivity, learning problems and restless sleep are all significantly more common in habitual snorers.[3]

Severe nasal obstruction, however, is associated with feeding difficulties, nocturnal enuresis, obstructive sleep apnoea (OSA), emotional problems, hyperactivity and impaired social functioning.[3,4,5] Upper-airway obstructive events causing apnoeas occur mainly during rapid eye movement (REM) sleep and several hundred of these events might occur each night. These obstructive events are terminated by subcortical arousals which greatly disturb the child's sleep pattern. Despite being relatively sleep deprived, these children often display hyperactivity and irritability during the day.[6]

## ANATOMY AND PHYSIOLOGY

The human airway – including the nose – is an extremely sensitive environment prone to a robust inflammatory response to a variety of stimuli. In children, airborne allergens and viral infections are the main offenders. The nose and paranasal sinuses are lined with respiratory epithelium. Characteristic of this epithelium is a vast number of goblet cells and ciliated epithelial cells whose cilia transport the mucus blanket towards the pharynx where it is swallowed. Seromucinous glands are found in the submucosa of the nasal epithelium and, together with the goblet cells, these glands produce most of the nasal mucus. In addition to the mucus is fluid from the lacrimal glands, fluid leaked or transported across epithelial layers, and condensed water.[7] Up-regulation of mucous glands through inflammation and infection as well as ciliary dysfunction, whether temporary or long term, results in mucus build-up and obstruction within the nasal cavity.

Unique to the nasal cavity is venous erectile tissue which underlies the mucosa of the inferior and middle turbinates and nasal septum. Engorgement of the capacitance vessels underlying the mucosa in these areas results in swelling of the mucosal lining and a marked increase in nasal resistance. The control of nasal resistance is mediated mainly by the sympathetic nervous system which determines the state of engorgement of the nasal mucosa. Increased sympathetic tone, for example during exercise, will result in a reduction of nasal resistance.

The nose accounts for 50 per cent of the total resistance of the upper airways.[7,8] The nasal valve region which occurs at the level of the anterior aspect of the inferior turbinate contributes approximately two-thirds of total nasal airway resistance.[7] Oedema and swelling of the mucosa overlying the anterior aspect of the inferior turbinate and corresponding nasal septum has a profound effect on nasal airflow.[7] A complex interrelationship therefore exists between anatomical factors, engorgement of nasal mucosa and the amount and viscosity of secretions which determine the degree of obstruction within the nasal cavity itself.

The nasopharynx (post-nasal space) is the space posterior to the nasal cavities. It begins at the choanae (posterior openings of the nasal cavities). The floor is the superior surface of the soft palate. The roof and posterior wall are formed by mucoperiosteum overlying the basisphenoid and basiocciput. The adenoid arises from this mucosa. Laterally

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is mucosa overlying the eustachian tube cushions and, posterior to this, lining the lateral pharyngeal recesses.

The adenoid can also cause nasal obstruction, although it is not situated within the nasal cavity. It arises from the posterior pharyngeal wall within the nasopharynx. Along with the palatine and lingual tonsils, it forms part of Waldeyer's ring of lymphoid tissue and is one of the first sites of immunological contact in early childhood. The function of lymphoid tissue in Waldeyer's ring is to produce antibodies. In this way, the adenoid plays a 'gatekeeping' function for the upper airway. The adenoid can be identified in all children by five months of age. It grows rapidly during infancy and reaches its maximum size at around six years of age.[8] Enlarging in an anteroinferior direction it encroaches on the choanae and the soft palate and causes nasal obstruction. The degree of obstruction does not depend directly on the size of the adenoid but rather on its size relative to the volume of the nasopharynx. Indeed, adenoid-induced nasal obstruction is more common in younger children due to the relatively small volume within the nasopharynx. In addition to physical obstruction of the airway, the presence of hypertrophic adenoid tissue can also impinge on the eustachian tube orifices in the nasopharynx. The adenoid can also serve as a reservoir of infection contributing to both chronic rhinitis as well as to eustachian tube dysfunction and resultant otitis media with effusion (OME). Moreover, severe adenoidal hypertrophy contributes to rhinorrhoea by sustaining both intranasal inflammation and impeding the passage of nasal secretions into the pharynx where they are swallowed.

Other nasopharyngeal masses that can cause obstruction of the nasal airways include branchial cysts, dermoid cysts, meningoencephaloceles, gliomas and Rathke's pouch cysts. Congenital narrowing of the nasopharynx is more common; this is usually associated with Down's, Treacher Collins, Apert and Crouzon syndromes. These syndromes are all associated with varying degrees of narrowing of the nasopharynx, usually as a result of mid-face hypoplasia.

## THE NEONATE

As the neonate is an obligate nasal breather, severe nasal obstruction can result in significant respiratory distress. Fortunately, this is rare with bilateral choanal atresia being the most common cause. Unilateral choanal atresia presents in older children with unilateral nasal obstruction and rhinorrhoea since birth. Choanal atresia can be diagnosed clinically by failure to pass a suction catheter or feeding tube through the nose. The obstruction is relieved with an oral airway until the definitive diagnosis is made, usually by CT scan. CT scanning will also identify other causes of nasal obstruction in neonates, including septal deviation, piriform aperture stenosis, nasal encephaloceles and teratomas.

Babies can suffer from idiopathic rhinitis which is characterised in the afebrile child with mucoid rhinorrhoea and nasal mucosal oedema that results in stertor and feeding difficulties.[9] Treatment should begin with saline drops and aspiration.[10] A short course of intranasal steroid drops usually brings relief within a week.[9] Systemic absorption of steroids poses a risk to the child, however, the risk can be minimised by use of topical steroids with minimal absorption (fluticasone and mometasone) and by using short courses.

## OLDER CHILDREN

The development of nasal obstruction in previously unobstructed children commonly occurs with exposure to aeroallergens and viral infections. The effects of viral infections have a major impact on the upper respiratory tract from the age of 12 months.[4] At about two years of age, as the immune system matures, allergic processes start to predominate in the child. Skin-prick tests are more reliably positive and can confirm the diagnosis of allergic rhinitis (AR). Long-term allergen exposure can lead to a state of chronic inflammation within the nasal cavity. This is responsible for the symptoms of nasal congestion, mucus hypersecretion and nasal hyper-responsiveness to allergens, viruses and other irritants.[4] In parallel with the period of the *atopic march*, and with exposure to viruses and allergens, the lymphoid tissue of the adenoids and tonsils may become hypertrophic and cause obstructive symptoms. Several studies confirm a link between AR and adenoidal hypertrophy by virtue of allergic inflammation in the nasal mucosa which is in close proximity to the adenoids.[8,11] The development of severe nasal obstruction in a previously healthy child raises the suspicion of a malignancy and should be appropriately investigated.

## HISTORY

Mouth breathing and stertor are both hallmark symptoms of the obstructed nose. Neonates are more likely to present with a history of 'snuffles'. Mouth breathing and cyclical grunting or cyanosis are features that suggest severe obstruction in neonates and warrant detailed investigation. Snoring, mouth breathing and recurrent apnoeas are more likely to arise in toddlers and older children.

It is also important to enquire about cough, wheezing and hearing loss as these commonly coexist in the nasally blocked child, particularly where AR features.[4] With the advent of high-quality video and audio recorders on mobile phones, video and/or audio recordings of the sleeping child made by the parent or caregiver can provide clear evidence as to the nature and degree of snoring and presence or absence of apnoeas. These are particularly useful at follow-up and may even be emailed to the physician as an aid to treatment efficacy.

## EXAMINATION

Examination of the child starts with observation. Mouth breathing, nasal discharge and the facial signs of allergy

*Figure 1: Modified stethoscope to allow auscultation of individual nasal airways*

(Dennie-Morgan lines, horizontal nasal crease, periorbital hyper-pigmentation) are often evident while the history is being taken. At this stage behavioural observations are also made and hyperactivity and inattention can be evident. The presence of non-resolving OME, particularly in older children without prior OME, may be caused by a nasopharyngeal mass which should be excluded.

In a nasally obstructed child, simple anterior rhinoscopy by elevation of the tip of the child's nose is a remarkably useful exercise and it is often possible to see the nature the obstruction using this manoeuvre. In a healthy child, the airway between these structures should be visible as a dark vertical slit. Effacement of the nasal valve region due to septal deviation, septal haematoma, inferior turbinate hypertrophy, foreign body or secretions is usually evident on simple anterior rhinoscopy. A good headlight is an invaluable tool and enhances the clinician's quality of view greatly. The degree of rhinorrhoea is noted as well as the nature of the secretions. If a suction aspirator is available, secretions may be cleared with a fine suction tip to improve visualisation of the anterior 2–3 cm of the nasal cavity. Particular attention is paid to the nasal valve area, where inferior turbinate hypertrophy or nasal septal deviation exerts the greatest effect on the airway. A visibly patent nasal valve area in a child with persistent nasal obstruction suggests that the obstruction lies posteriorly and is usually as a result of adenoidal hypertrophy. Other nasal tumours which are not visible with anterior rhinoscopy include juvenile nasopharyngeal angiofibromas, lymphomas and sarcomas.

A metallic tongue depressor placed under the child's nose in exhalation has traditionally been used as an office-based examination to quantify the degree of nasal airflow by noting the degree of misting produced on the depressor. A more effective and informative tool is the use of a modified stethoscope where the bell has been removed (see Figure 1). The open end of the stethoscope tubing is held half a centimetre away from the child's individual nostrils. The degree and quality of airflow is clearly heard and the variation between the two nostrils can be appreciated. Transmitted breath sounds from the upper airways can also be heard. Complete cessation of airflow through one or both nostrils is rare. In neonates, this usually suggests choanal atresia. In older children, it is usually due to nasal polyposis. These children should be routinely screened for cystic fibrosis.[12]

Fibreoptic nasendoscopy is routinely used as an office investigation in ENT consultations, particularly in adults. Its usefulness in the paediatric population should not go unrecognised. With a gentle technique it can be performed on children of any age depending on the cooperation of the child and the dimensions of the child's nasal cavity. Topical decongestion and anaesthesia are obtained by nasal spray or the placement of a soaked cotton wool pledget between the anterior aspect of the middle turbinate and nasal septum. A combination of 5% lignocaine HCl and 0.5% phenylephrine HCl is typically used. In the cooperative child, the nasal cavity and nasopharynx may be assessed. The endoscopist is able to 'tour' the nasal cavity and visualise the presence of polyps, foreign bodies and also the presence or absence of mucopus draining from the anterior or posterior sinus drainage pathways. In the nasopharynx the adenoidal pad is clearly visualised and the degree of obstruction assessed.[13] This obviates the need for a post-nasal space X-ray in these patients.

## INVESTIGATIONS

Skin-prick testing remains the most important investigation for the child with the obstructed nose in whom allergy is suspected. If adenoidal hypertrophy is suspected then a post-nasal space X-ray is indicated (see Figure 2). Both these tests are reliable and cost-effective and are therefore helpful in guiding treatment.[4,13,14] CT scanning is seldom required in children. Usual indications for this are the evaluation of masses within the nasal cavities, nasal polyposis and recalcitrant infective rhinosinusitis where endoscopic sinus surgery is being considered. Endoscopic sinus surgery is, however, rarely indicated in children.

## MEDICAL TREATMENT

Nasal saline irrigation is surprisingly well tolerated in the majority of children, irrespective of age.[10,15,16,17] Nasal

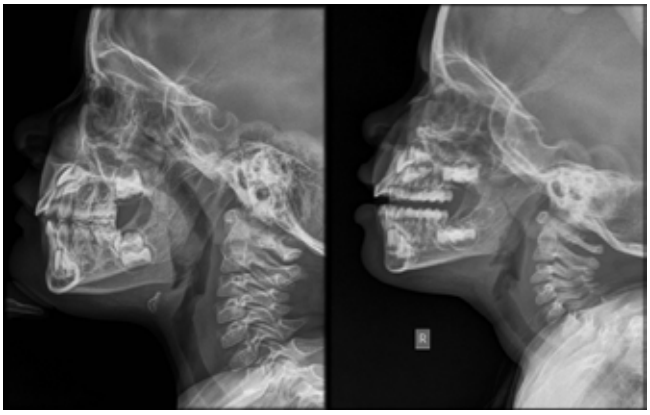

*Figure 2: Comparative X-rays of the post-nasal space demonstrating obstruction of the nasopharyngeal airway due to adenoidal hypertrophy in the image on the right*

saline lavage may be sufficient on its own in neonatal rhinitis and viral upper respiratory tract infections.[9] Nasal saline irrigation has also been shown to significantly reduce nasal symptoms in children with AR or acute sinusitis.[15] Marked rhinorrhoea may result in the dilution of the active ingredient of intranasal steroid (INS) sprays and failure of the drug to be deployed at a mucosal level. Therefore, saline nasal irrigation may be a useful adjunct in nasal obstruction with associated rhinorrhoea. It is beneficial in patients with AR where it maintains the effectiveness of INS sprays at lower dosages.[15,17]

Children with nasal obstruction and rhinorrhoea due to AR – with or without adenoidal hypertrophy – should be placed on an INS spray.[8] The benefits of INS sprays are well documented in patients with AR with or without asthma.[18] INS sprays have also been shown to be effective in reducing adenoidal hypertrophy.[19,20,21,22] In addition, INS sprays have been effective in reducing the severity of OSA.[20,23,24] Lastly, in patients following adenoidectomy, INS sprays have been shown to reduce adenoidal regrowth and nasal obstruction scores at least until one year post-operatively.[25] The safety of long-term INS spray use is a concern, especially in patients with asthma who also receive treatment with inhalational steroids (IHS). Studies have confirmed that with INS and IHS there is a small, transient reduction in growth velocity in that resolves with continued time on treatment.[26] Moreover, this effect does not occur in all children and, in the case of asthma, growth can be suppressed by poor control of the disease itself. The aim of treatment with INS is to start with a high dose in order to control the inflammation and then to reduce to the minimum effective dose to maintain control. At the same time steroid-sparing strategies should be employed where possible such as allergen avoidance and use of add-on therapies such as antihistamines and leukotriene inhibitors. [26]

## SURGICAL TREATMENT

In patients in whom INS sprays fail to reduce obstructive adenoidal tissue, adenoidectomy appears to be a safe and reliable procedure to undertake. In addition to the improvement of the nasal airway, adenoidectomy is shown to have positive effects on the resolution of OME and an improvement in polysomnographic scores in patients treated for OSA.[27] In patients with OSA, current recommendations suggest additional tonsillectomy irrespective of tonsil size.[6] Besides relief of nasal obstruction caused by adenoidal hypertrophy, adenotonsillectomy also improves several asthma outcomes.[28,29]

Gross inferior turbinate hypertrophy prevents the delivery of INS sprays to much of the nasal mucosa posterior to the nasal valve area. In these refractory cases where medical treatment has failed, inferior turbinoplasty is extremely useful. The aim is to reduce and effectively normalise the size of the turbinate without impairing the warming and humidifying function of the nose. Surgery is focused on the anterior third of the inferior turbinate in the nasal valve area. This allows improved nasal airflow without compromising the physiological function of the nose. A variety of techniques are employed in an effort to reduce the bulk of the inferior turbinate. Patients experience improvement in nasal patency irrespective of the technique used, however, patients with AR experience the greatest improvement of nasal patency.[30] Medial-flap turbinoplasty, a mucosa-preserving technique, where both turbinate bone and mucosa are judiciously excised from the critical nasal valve area, appears to be the most effective method in order to ensure long-term relief of symptoms.[31,32] Turbinoplasty is, however, not commonly indicated in the paediatric population.

Septal deviation seldom causes severe nasal obstruction as there is usually sparing of a functional nasal airway on one side. Symptoms tend to be worse if there is coexistent AR. Corrective septal surgery is controversial in children due to concerns that disruption of nasal growth centres can lead to changes in midfacial growth and final midfacial contour. Although surgery is deemed safe, most authors suggest deferring surgery until at least the early teenage years in cases where symptoms are not severe.[33]

## CONCLUSION

Nasal obstruction in the child is often multifactorial with links between AR and adenoidal hypertrophy. It is essential to attempt to extinguish local inflammation within the nasal cavity with anti-allergic medication in order to maximise the nasal airway and reduce rhinorrhoea. INS sprays have the added benefit of a reduction in adenoid size and reducing regrowth of adenoidal tissue following adenoidectomy. If medical treatment fails in patients with proven adenoidal hypertrophy, surgery to reduce bulky adenotonsillar tissue will improve upper-airway patency. In cases of refractory inferior turbinate hypertrophy, inferior turbinoplasty will improve both the nasal airway and the delivery of intranasal steroids to the greater nasal cavity.

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

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Opinion Paper

# FOOD ALLERGIES

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Food allergies are common and on the increase, therefore representing a public health concern in many countries. Indeed, mounting evidence shows that few communities are spared this modern-day epidemic.

As a result, effective prevention strategies are required, particularly in geographic locations where the epidemic is of recent onset. The fact that the food-allergy epidemic has occurred over a short time period gives hope to those who seek to prevent it, as its triggers or driving factors may be modifiable. There is precedence for the reduction of specific allergies; for example, the rise in latex allergy was minimised by restricting the widespread use of powdered latex gloves. Similarly, the rise in peri-anaesthetic allergic reactions induced by the neuro-muscular blocking agent (NMBA) was prevented in select countries by restricting the widespread access to the sensitising agent, pholcodine, which was previously available over the counter.

Sensitisation to foods, and food allergy, can occur in infancy. Increasing evidence suggests that prevention strategies should ideally be targeted at these early-life periods of 'immunologic vulnerability', even before the milestone of independent sitting at six months of age and certainly before walking at approximately 12 months of age.

Dietary interventions have long represented an attractive modality for the prevention of food allergy. However, the evidence supporting the use of dietary interventions in high-risk pregnant and/or lactating women for the prevention of atopic eczema in their offspring remains weak and findings are inconsistent. More importantly, such interventions may compromise maternal and foetal nutrition. While breastfeeding holds many benefits for both mother and infant, it remains equivocal as to whether exclusive breastfeeding for any length of time offers protection against the development of food allergies. Similarly, a recent meta-analysis demonstrated that for high-risk, non-exclusively breastfed infants the use of hydrolysed formula offers no protection against the development of allergic disease.

Studies investigating the use of dietary interventions such as fatty acids, antioxidants, pre- and probiotics, and vitamin supplementation are also unconvincing, inconsistent or not adequately tested. It is important to note that there are safety concerns surrounding some of these interventions.

It is clear that the paradigm has shifted from avoidance of common food allergens to early consumption in an attempt to induce tolerance. Previous cross-sectional studies aimed at the prevention of food allergy have now been superseded by interventional studies which herald a significant advance in our quest to contain this modern-day epidemic. Indeed, the learning early about peanut (LEAP) study findings have already influenced dietary recommendations across many allergy societies regarding the introduction of peanut in at-risk populations, with the recent enquiring about tolerance (EAT) study results further adding to the findings and strengthening the argument for a wider revision of infant-feeding recommendations. However, numerous questions still remain, such as what to do about the at-risk infants who have large skin tests to peanut and were not included in the LEAP study, with few such children also being captured in the general EAT study population. Furthermore, it needs to be determined how best to implement prevention strategies, as the uptake of food allergens in the EAT study was variable and efficacy was significant only for egg white and peanut among those children in the per-protocol analysis sample.

In light of all this information and the difficulties posed, it is reassuring that the LEAP and EAT interventions proved safe, nutritionally favourable and acceptable to most participants and their families. In addition, the allergenic foods are accessible and relatively affordable in many regions of the world. Therefore the adoption of early-life dietary allergen inclusion as a strategy for the prevention of food allergy lends itself to practice in a variety of settings.

*The author has received research support from the ITN/NIAID for his involvement in the LEAP and LEAP-On Studies. The National Peanut Board sponsored previous research, and currently part sponsors running costs of the KCL Clinical Trials Unit at St Thomas' Hospital. George is a voluntary scientific adviser for the Anaphylaxis Campaign; he has received lecture fees from the following commercial companies; Meda, Nestle-Nutrition, and Stallergenes.*

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Guest Review

# EOSINOPHILIC OESOPHAGITIS IN CHILDREN: MANAGEMENT OPTIONS FOR INDUCING AND MAINTAINING DISEASE CONTROL

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## ABSTRACT

Over the past decade the incidence of eosinophilic oesophagitis (EoE) has risen significantly and has become a common condition seen in paediatric gastroenterology centres around the world. The association with atopic disease is well known, and treatment options remain concentrated on acid suppression, dietary eliminations and topical corticosteroids. One of the greatest challenges is planning long-term disease management. Currently there is little published data on maintenance treatment for EoE in children. Many children remain on long-term elimination diets or topical steroids and undergo multiple repeat endoscopies. Large multicentre studies are required to gain a better understanding of this challenging condition, to standardise maintenance treatment and to find better methods for reliable disease surveillance.

*This article has been peer reviewed.*

## INTRODUCTION

EoE is an emerging chronic immune-mediated condition, defined by the histological finding of greater than 15 eosinophils per high power field in oesophageal biopsies (see Figure 1). In this condition, the eosinophilia is not a feature in other areas of the gastrointestinal tract[1] and is associated with symptoms relating to oesophageal dysfunction. The inflammation can be patchy and, while it is typically considered to be a clinico-pathologic disease, at follow-up surveillance endoscopies the symptoms frequently do not correlate with the microscopic findings.[2,3] Therefore follow-up and surveillance of this condition currently rely heavily on repeated endoscopic examination of the oesophagus, with biopsies. Treatments focus on a combination of proton pump inhibitors (PPI), dietary exclusions and corticosteroids. The incidence is rising alongside the increase in other atopic disease as well as inflammatory bowel diseases (IBD), such as Crohn's Disease. In the United States the prevalence in children is estimated to be around 40–50/100 000.[4,5]

## DIAGNOSIS

Symptoms may vary depending on age of presentation. Infants and toddlers are more likely to present with gastro-oesophageal reflux (GOR)-type symptoms and feeding issues, whereas older children and adolescents are more likely to experience symptoms related to oesophageal dysfunction, such as dysphagia, heartburn, regurgitation or, in more extreme cases, food bolus impaction from oesophageal muscle spasm or strictures.[6] The majority of patients with EoE have an associated atopic condition, such as asthma, eczema, food allergy or allergic rhinitis (the last being associated with some seasonal variation in the EoE in some patients).[7,8]

## ENDOSCOPY

Oesophago-gastroduodenal endoscopy (OGD) is the current essential gold standard investigation for diagnosing EoE. Endoscopic features are important, but much more important is obtaining the biopsies for histological analysis. Multiple biopsies are recommended from the lower, middle and upper areas. Endoscopic findings range from endoscopically normal mucosa to severely strictured oesophagus with minimal luminal patency. Other typical findings include the more subtle, milder so-called 'crepe-paper features' (small eosinophilic abscesses), more marked erythema, similar to gastro-oesophageal reflux disease (GORD), longitudinal linear streaking (see Figure 2), concentric rings ('trachealisation') and friable, ulcerated and damaged mucosa with bleeding.[6] Oesophageal strictures or spasms with food bolus impaction is one of the most severe findings, requiring urgent therapeutic intervention.[9] In the worst affected cases, mucosal laceration (sometimes with associated haematemesis) may occur. The ESPGHAN EoE Working Group has established a database called Paediatric European EoE Registry (pEEr) to achieve a better understanding of the disease incidence, management and outcomes across European centres. The patient entries include well-defined endoscopic classification. Standardisation of endoscopic

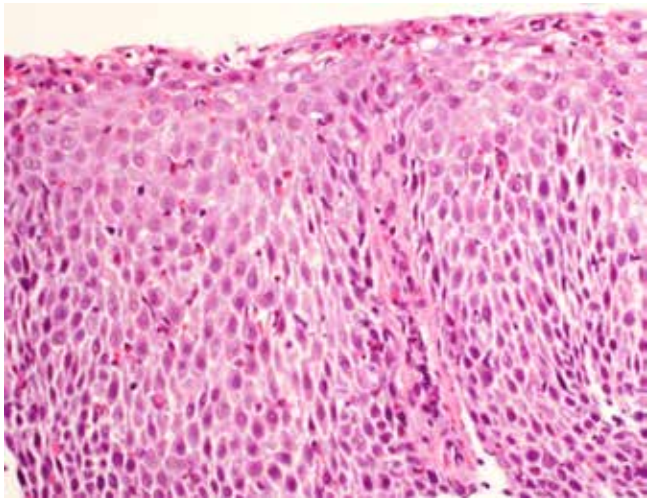

*Figure 1: Dense eosinophilic infiltrate in oesophageal biopsy*

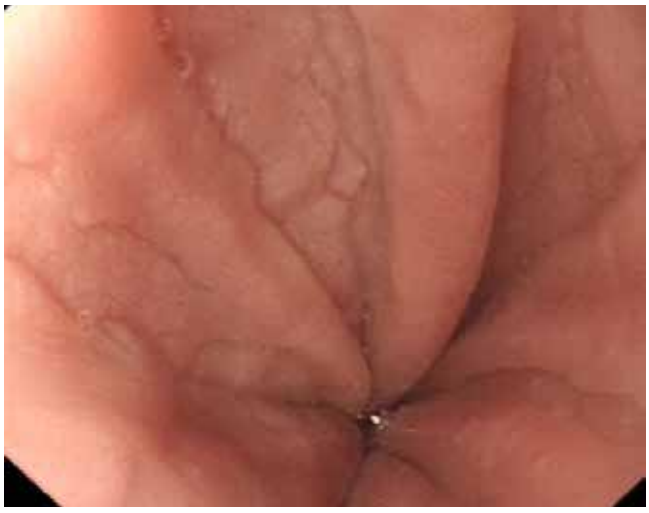

*Figure 2: Deep linear furrowing in mid-oesophagus in paediatric patient with EoE*

reporting is helpful in comparisons of cases on a much wider scale. In those patients with severe symptoms of dysphagia, it is advisable to perform a low-dose fluoroscopic swallow to assess for the presence of a stricture.[10]

## TREATMENT STRATEGY

Initial treatment with high-dose proton pump inhibitors (PPI) for 8–12 weeks will identify the 20–30% of patients whose disease responds to PPI therapy alone.[3,11] Omeprazole at up to double the usual age-dependent dosing has been shown to be effective, at a dose of 1 mg/kg twice daily.[22] Repeat endoscopy after this initial treatment identifies those patients as having PPI-responsive oesophageal eosinophilia (PPI-REE). There is some debate whether patients with PPI-REE represent a separate disease entity, or whether they are actually on the spectrum of EoE, with a disease phenotype which and therefore may actually be PPI-responsive EoE (PPI-REoE) rather than PPI-REE.[12] In those whose disease does not enter histological remission, an alternative strategy is indicated. The option then is a choice between food-elimination diets (FED), steroids or a combination of the two.

FED are indicated in those who do not respond adequately to initial PPI monotherapy. Targeted eliminations, guided by specific IgE testing, do not appear to be as effective as combination elimination or exclusive elemental nutrition (EEN) with an elemental dietary formula. Empiric 4 FED, which exclude cow's milk, soya, egg and wheat, and 6 FED, which in addition also exclude peanut and shellfish, are effective in the dietary management of EoE. Kagalwalla et al found that on food reintroduction after 6 FED, cow's milk was the commonest precipitating food.[13] Where FED has been ineffective and, particularly, where symptoms remain significant, further treatment escalation is indicated. A choice between exclusive enteral feeds with an amino-acid formula or swallowed topical steroids needs to be made. Multiple FED can be very difficult to maintain, often resulting in poor dietary compliance and social challenges, particularly in school-age children. Options and choices may depend on patient and parent choice. Unfortunately, after the reintroduction of food after a period of EEN, the relapse rate is very high, and EEN is not a practical maintenance strategy.[14]

Topical corticosteroids are effective in inducing remission in EoE. Studies have demonstrated the efficacy of both swallowed fluticasone[15] and oral viscous budesonide (OVB).[16] The OVB dose is dependent on height, 1 mg/day being given to those children <152 cm tall, and 2 mg/day to those >152 cm tall.[23] Both of these have excellent first-pass metabolism, minimising systemic steroid effects. It is critical to deliver these within a thickening agent to improve application and contact with the oesophageal mucosa for as long as possible. Solutions that have been used as suspending agents include Sucralose and even honey.[17] The author has experience with Ora-Blend® as an effective suspending agent within his centre. In one study with Fluticasone, 65% patients had complete remission.[15] In a paediatric study OVB was demonstrated to be effective with two different delivery vehicles after ten weeks of therapy.[16] Currently, no corticosteroid viscous solution is commercially available, so patients and carers have to mix the doses each day. Budesonide is dispensed as nebules – for nebulisers – and mixed with the suspending agent immediately prior to ingestion. Where possible, ingesting in the left or right lateral position slows down passage through the oesophagus, with the aim of increasing the contact time with the mucosa. No eating or drinking should occur for at least 30 minutes after each dose.

Systemic steroids, such as prednisolone, have also been reported to be effective, and may be indicated in cases where there is a lack of response to other treatments, or poor adherence to dietary exclusions.[6] A recent publication by Harel et al reported findings of adrenal suppression, even in topical steroid use.[18] No patient in the series had any clinical Addisonian features. The author highlighted a

particular issue with those patients using topical steroids for concomitant treatment of another atopic disease, including inhaled and dermatological applications. Although the steroids used for topical EoE treatments have extensive first-pass metabolism, caution is advised when starting treatment. Furthermore, weaning rather than sudden cessation of treatment is something that may need to be considered, even though this is not currently part of any published guidance on EoE.

Candida infection has been reported as a result of prolonged topical oesophageal steroid use. If this is noticed on follow-up endoscopy, brushings should be taken and sent for analysis.

## DISEASE MONITORING

Follow-up endoscopies after treatment interventions are part of most current recommendations, and as paediatric endoscopy is usually performed under general anaesthesia, this will result in multiple anaesthetics. Although symptoms may improve on treatment, the histological activity of the disease may still be significant, rendering symptom assessments relatively unreliable in many patients. The patients who feel well despite ongoing significant histological inflammation present a particular challenge in both convincing them of the need to continue on the treatments and also with disease surveillance. There is currently no commercially available test, other than endoscopy, that is reliable for disease activity assessment.

## MAINTENANCE

Whether the patient has PPI-REE, responds to a FED or requires a course of steroids, entering a state of remission or disease control is usually achievable. The greatest challenge for many will be that of disease-free maintenance. For those who are PPI responsive, and for those who are on a single FED, remaining disease-free is more easily achievable than for those who have required steroids, 6 FED or EEN. There is excellent evidence of effective steroid dosing for the initial treatment phase, but not much is published on the maintenance choices and doses.[15]

Where FEDs have been continued, a food challenge should be planned at some time. This may be influenced by the season for those who develop allergic rhinitis, and aiming for a winter challenge may be preferable in those cases. After each challenge, a clinical review should be conducted, and an endoscopic reassessment should be considered. Doing so should take into account the number of endoscopies already completed in that patient and the likelihood of needing further procedures. In those patients whose symptoms relapse, eliminating the food again would be a reasonable plan, without the need for endoscopic evidence of relapse.

The maintenance dose with topical steroids is less clear. Some discussion about half of the induction dose has been published.[13] Andreae et al reported good long-term results with two puffs a day of swallowed fluticasone from a metered dose inhaler (MDI), with a mean follow-up of 20.4 months. Improvement in endoscopic and histological features, including fibrosis, was observed on annual endoscopies, along with symptom improvement. No effect on growth was noted.[24]

The risks of possible adrenal suppression imply that adrenal function tests should be considered in those on longer-term treatment with steroids.[18] Other complications of chronic steroid use include potential growth effects and also the risk of developing oesophageal candidiasis.

Not much experience has been published on the use of immunomodulators in EoE, but a publication by Netzer et al found that the use of azathioprine and 6-mercaptopurine in EoE in three patients was successful in maintaining remission for several years.[19] One of the benefits of thiopurine use in EoE maintenance is the hope that this would have a steroid-sparing effect, but larger studies are needed over a longer period before this can be recommended in disease guidelines.

Modalities other than endoscopies are also being developed, with the intention of avoiding repeated endoscopies. Methods to assess for oesophageal eosinophilia could facilitate better clinico-pathological correlation, without the need for endoscopically obtained biopsies.

As some patients may have a strong influence of aeroallergens in their disease pathogenesis, treatment holidays during the winter months may be something to consider. In those who have severe aeroallergen reactions, immunotherapy may be considered as an option. There have been reports of SLIT improving EoE,[20] and aeroallergens have been implicated in seasonal exacerbations of EoE. SCIT has also been suggested as a possible treatment in managing EoE in combination with allergic rhinitis;[21] however, the author has experience of a patient with significant worsening, requiring systemic steroids, after use of both SLIT and SCIT for aeroallergen sensitisation.

## LOOKING AHEAD

Interleuken-5 antagonists have been studied in both adult and paediatric age groups and have been demonstrated to reduce eosinophil concentration within the oesophageal mucosa. The greatest effect was in those with higher eosinophil counts, but, disappointingly, there was an absence of significant clinical response to this.[25,26] Further research is required in the hope that a targeted approach to EoE will be identified. But at the moment the approach remains broad, with a combination of acid suppression, dietary intervention and corticosteroids being the main option currently. Immunomodulators

appear to have a potential role, but understanding the natural disease progression and the different phenotypes is important in assessing the risk of starting long-term immunosuppression in these patients. Understanding the aetiology and developing effective, safe and tolerable maintenance treatment which retains remission and prevents complications remains the big challenge in EoE.

DECLARATION OF CONFLICT OF INTEREST
Sponsorship from Thermo Fisher Scientific to attend the ALLSA Congress 2016 in Cape Town.

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Ethics

# CLINICIAN INTEGRITY, PATIENT AUTONOMY AND THE PATIENT'S BEST INTERESTS

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*'I wish my life and decisions to depend on myself, not on external forces of whatever kind. I wish to be the instrument of my own, not of other men's acts or will. I wish to be a subject, not an object: to be moved by reasons, by conscious purposes, which are my own, not causes which affect me, as it were, from outside. I wish to be somebody, not nobody: a doer – deciding, not being decided for, self-directed and not acted upon by external nature or by other men as if I were a thing, or an animal, or a slave … I wish, above all, to be conscious of myself as a thinking, willing, active being, bearing responsibility for my choices and able to explain them by references to my own ideas and purposes.'* Isaiah Berlin, 1969[1]

## INTRODUCTION

Respect for autonomy as described by Berlin[1] has become the dominant ethical principle in guiding any decision-making involving competent adults in contemporary medicine. Respect for individual autonomy and the individual's rights supersede the other ethical principles. When I was a medical student, the doctors practised medical paternalism. They made a decision regarding the patient's treatment, truly believing that this was in the patient's best interests, and the patient had very little say in the treatment plan. Subsequently, the patient became a partner in the decision-making process: the doctor explained the treatment options and made a recommendation as to which option was the preferred one; the patient then made the final decision. Is there a limit to the patient's autonomy in modern medical practice? What ought the doctor do if s/he believes the patient has made the wrong decision?

In clinical practice two types of situation may arise that could lead to conflict for the clinician when having to respect the patient's autonomy. The first situation encompasses the patient's requesting treatment that the clinician believes is inappropriate or futile; the second arises where the patient refuses treatment that the clinician believes is in the patient's best interests.

Consider the following case scenarios.

1. *Keith Smith, aged 12 years, had a local reaction after being stung on his right arm by a bee. He was referred by the family's general practitioner, Dr Jones, to the allergy clinic at the academic hospital. The referral letter requested specific IgE testing to bee venom and a course of bee venom immunotherapy, as the Smith family live on a farm 20 km from the city, and Dr Jones is concerned about a potentially life-threatening systemic reaction should Keith be stung again. Dr Cooper, the allergologist at the referral hospital, explains to Keith and his mom that immunotherapy is not indicated for local reactions and that the immunotherapy is not without risk. Mrs Smith is extremely unhappy and insists on the immunotherapy.*
2. *Mrs Denise Botha had a severe systemic reaction to a bee sting and was treated for anaphylaxis at the local hospital. She too consults Dr Cooper after being referred from the Emergency Department. She steadfastly refuses allergy testing and immunotherapy. She says she is prepared to carry antihistamine tablets and injectable adrenaline with her when walking outdoors. Despite extensive counselling by Dr Cooper, she will not accept immunotherapy, as she likens it to vaccination and she believes that vaccination is an assault on the immune system. Neither of her two children has been vaccinated, as Mrs Botha knows of a case of autism in a child who was vaccinated.*

## A HISTORICAL PERSPECTIVE: FROM PATERNALISM TO AUTONOMY

During the 1970s doctors made decisions for their patients, 'usually made with beneficent intention but without open discussion, much less the full participation of the patient.'[2] The advantages of this approach were that the patient and family could be protected from difficult decision-making and the doctor could ensure that employing new technology in medicine did not cause harm to the patient. The disadvantages of paternalism are that it is difficult to be certain what is in an individual's best interests and that patients are not given the opportunity to truly be involved

in making decisions for themselves.

Towards the end of the last century the individual patient's autonomy became the most important consideration in medical decision-making. Quill and Brody believe that the swing of the pendulum from paternalism across to autonomy is potentially detrimental to patients in that a great deal of information is presented to the patient without any recommendation from the doctor. This means that the patient has to make decisions without any medical guidance. One of the reasons postulated for the doctor's remaining neutral is that it may prevent the doctor from being sued in the event that the decision proves to be incorrect.[2]

## MODELS OF AUTONOMY IN MEDICAL DECISION-MAKING

Quill and Brody contrast the 'independent choice' and the 'enhanced autonomy' models in medical decision-making.[2] The former is 'patient centred' and requires the doctor only to provide the information, the options and the likely outcomes and for the patient to decide on the course of action. The idea is that the patient is able to make a decision without in any way being influenced by the doctor. Once the patient has authorised a course of action, the doctor has to carry it out, even if s/he disagrees with the proposed treatment plan.[2]

The 'enhanced autonomy' model promotes patient autonomy by providing not only the pertinent medical information but also the opinion and recommendation of the doctor, therefore enabling the patient to make a truly informed decision. It has been termed 'relationship centred' as it includes the medical team, the patient and the family. This model not only provides the medical information and treatment options with likely outcomes, but also takes into account the values of the doctor and the patient.[2]

The principle of autonomy has as its central tenet the concept of respect for the patient as a person. We have to be sensitive to the views of patients from different cultures. As an example, in the traditional African context, individual autonomy is less important than communitarian decision-making, and although it would seem that involving the family or community in medical decision-making violates the principle of autonomy, it in fact shows a higher level of respect because one is showing respect for the traditions and culture of the patient's community.[3]

Young children are not regarded as autonomous and so medical decisions are made for them by their parents or caregivers. Older children may well be able to participate in decision-making regarding their own healthcare, and South African legislation has made it possible for children older than 12 years to make healthcare decisions for themselves, provided that they have the capacity and maturity to do so.[4]

## THE DUTY OF DOCTORS

Numerous codes of ethics and professional guidelines emphasise the doctor's responsibility in respecting the autonomy of the patient, and always to act in the patient's best interests. The Health Professions Council of South Africa's (HPCSA) 'Guidelines for Good Practice in the Health Professions'[5] state the following:

The core ethical values and standards required of healthcare practitioners include the following:

1.1.1 Respect for persons: Healthcare practitioners should respect patients as persons, and acknowledge their intrinsic worth, dignity and sense of value.

1.1.2 Best interests or well-being: Beneficence: Healthcare practitioners should act in the best interests of patients even when the interests of the latter conflict with their own personal self-interest.

1.1.3 Autonomy: Healthcare practitioners should honour the right of patients to self-determination or to make their own informed choices, and to live their lives by their own beliefs, values and preferences.

The point is made that some of these values and standards may be in conflict, and that the doctor has to employ 'ethical reasoning' to resolve such conflicts.[5]

## ARE THERE LIMITS TO A PATIENT'S AUTONOMY?

What happens if the patient's request for treatment conflicts with the doctor's opinion because the doctor believes it to be inappropriate? In such a case respect for the patient's autonomy may conflict with the doctor's professional integrity and values.[6] Frequently, these conflicts arise in the context of end-of-life decision-making – for example, disagreements about do not resuscitate (DNR) orders or futile treatment. Clinicians are not obligated to provide treatment that they deem inappropriate and, therefore, they may place a limit on the patient's autonomy in such a situation. Lantos et al explain that 'patient autonomy has boundaries and limits' in that treatment choices are provided within a range of options. If this were not the case, then chaos could result, with resultant inefficiency and increased costs.[6] They also make the point that

> '[the] patient's right to forgo treatment is stronger than the right to receive a particular treatment. Competent patients can refuse most treatments, no matter how potentially beneficial they might be. Patients do not have the same authority to demand treatments, in part, because treatment usually requires the participation of a clinician. Thus, the clinician's own moral agency is engaged.'[6]

Clinicians may refuse patients' requests for treatment that the doctor does not feel qualified to provide or requests for treatment in an environment that is inappropriate to the patients' needs.

## THE CONCEPT OF 'BEST INTERESTS'

The concept of 'best interests' is usually interpreted to mean the 'highest net benefit among the available options'

that apply to any situation in which a decision has to be made regarding the health of the patient:[7]

> 'The best interests standard protects another's well-being by assessing the risks and benefits of various treatments and alternatives to treatment, by considering pain and suffering, and by evaluating restoration or loss of functioning.'[7]

In cases where medical treatment carries low risk and offers substantial benefit to the patient, it is generally thought to be in that person's interests. The 'best interests' standard is the one employed in making healthcare decisions involving children. The difficulty with the best interests standard, however, is that it is not always obvious in any given situation what the best interests of the patient are. Some of the criticisms levelled at the 'best interests' standard are that it is unrealistic, too restrictive, and too focused on the interests of the incompetent or incapacitated person.[8,9]

## DO DOCTORS ALWAYS HAVE TO ACT IN A PATIENT'S BEST INTERESTS?

Although most guidelines and even legislation tend to emphasise the importance of the patient's best interests in medical decision-making, an individual patient's best interests cannot always be considered paramount. In truth, there are many circumstances under which the interests of other patients would outweigh those of the present patient.[10] Wendler lists 27 exceptions to the traditional view of the obligations of the doctor in promoting the best interests of the individual patient.[10] A few examples of these are:

- not transfusing a Jehovah's Witness patient who needs blood;
- leaving a patient's bedside to go and resuscitate another patient;
- vaccinating children to promote herd immunity;
- cost containment by prescribing cheaper, less-effective drugs;
- notification of infectious diseases, and
- incarceration of patients with multi-drug resistant tuberculosis.[10]

We are required to respond to the claims of other parties, but this does not imply that we do not care about the individual patient: 'Instead, this fact helps to define the nature of our relationships by clarifying the extent of our obligations to significant others.' However, Wendler also emphasises that good medical care depends on relationships with patients and that doctors cannot be required to further the interests of all individuals. The essence of a clinical relationship revolves around an individual patient. He suggests that the requirement to act in the individual's best interests while at the same time realising that others may also have a claim on the doctor can be addressed by seeing the present patient's best interests as a 'pro tanto' obligation[10] (i.e. for so much or to a certain extent)[11] rather than as a strict obligation that cannot be overridden. This permits the doctor to weigh up the present patient's interests against those of others.[10]

## DISCUSSION OF CASE SCENARIOS

In the case of Keith Smith, his mother, Mrs Smith, insists on unnecessary and inappropriate therapy. Dr Cooper is not obligated to provide this therapy, but she should explore the reasons for Mrs Smith's insistence on the treatment. She should also take the time to explain the indications for specific IgE testing and bee-venom immunotherapy, as well as the fact that the immunotherapy is not without risk. Given Keith's age, he should also be involved in the counselling and decision-making process and be given full information regarding the indications for testing and immunotherapy.

The case of Mrs Botha is more difficult, as she is a competent adult refusing treatment, and her refusal should be respected if it constitutes a fully informed decision. However, given the scenario and the fact that she had a life-threatening bee sting, she should also receive extensive counselling regarding the risks of being stung. She must be given an anaphylaxis treatment plan and be carefully instructed on the use of the injectable adrenaline, as well as advice regarding precautions to be taken to avoid being stung. She should be counselled about anti-vaccine propaganda, the fact that vaccination is not 'an assault on the immune system', and the difference between vaccination and allergen immunotherapy. Many allergic reactions to vaccines originate in the additives, and the differences between these additives and the adjuvants present in allergen immunotherapy have to be explained.[12] To this end, Dr Cooper should have all the necessary knowledge to inform Mrs Botha fully about immunotherapy.

The issue of Mrs Botha's children not being vaccinated because of the fears of autism should also be addressed, but this is not the responsibility of Dr Cooper. Dr Cooper should suggest that Mrs Botha speak to her family doctor about this issue, and possibly suggest some resources for further reading.

## CONCLUSION

Individual competent adult patients have the right to make choices regarding their healthcare in accordance with the principle of respect for autonomy. If disagreement arises about the course of action to be taken, careful discussion of the issues and options should take place, with attention to what is in the patient's best interests. However, if the disagreement cannot be resolved, the patient's final decision should be respected. Should the doctor feel that the decision is inappropriate or is against his/her values, s/he has the right to refuse to be involved. In that case the patient should be informed, and the offer made to refer the patient to another doctor, if possible.

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

*References available on page 189.*

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# ALLERGIES AND OTHER OCCUPATIONAL DISEASES IN THE HAIRDRESSING INDUSTRY

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**ABSTRACT**

The demand for cosmetic and hairdressing services is high. The hairdressing industry has grown to become an important source of wealth and income internationally, with informal salons and hairdressing being more common in low-income settings. The daily exposure to a wide variety of repetitive practices, substances and chemicals puts hairdressers at an increased health risk for some conditions – particularly on the skin and respiratory and musculoskeletal systems – as the workers are exposed to a diverse range of chemicals (irritants and allergens) and ergonomic risk factors. By means of a case study we illustrate the challenges a medical practitioner faces in trying to identify the causal agent responsible for a health condition at work in a trade where products contain numerous changing chemicals, yet the same chemicals may be ingredients in personal hygiene products, food and medicines to which the worker is non-occupationally exposed. It indicates the necessity of identifying the potentially hazardous chemicals through good detective work, including a detailed workplace visit and report, an exposure and task-directed history of work, hobbies and activities of daily living together with relevant special investigations in order to achieve the best management of the clinical condition.

*This article has been peer reviewed.*

## ILLUSTRATIVE CASE

A 26-year-old qualified hairdresser presented with a one-year history of an itchy rash on both hands. She experienced recurrent exacerbations of the rash, associated with erythema and vesicles. The rash involved the hands, wrists and forearms but did not involve her palms, face or the rest of her body.

She had been working as a hairdresser in the same formal suburban salon for the past six years. She related the onset of her rash to a colour-master's course she attended, during which she was bleaching (using bleaching pastes) and colouring hair more often than performing tasks such as cutting and styling hair. Although she used latex-black professional hairdresser gloves for tasks such as dyeing and bleaching hair, she did not wear them for mixing the chemicals used for these processes. Furthermore, she could not wear them for cutting and shampooing hair. These gloves were re-usable between clients and their surfaces could easily become contaminated. After the rash started, she changed from latex to nitrile gloves, which she disposed of between clients without any improvement in symptoms. The brands of products used in the workplace or at home before the onset of the rash remained the same. She responded initially to Diprogenta® (betamethasone dipropionate and gentamycin) crème and emollients, but the rash recurred as soon as she stopped the steroid crème.

On examination of the hands, acute (erythema, vesicles and crusts) and chronic (lichenification, and fissuring) eczematous changes with secondary excoriations were evident over the metacarpal joints extending onto the proximal phalynx of the second and third fingers (see Figure 1A and B). Similar changes were evident over the left medial forearm and left dorsal metacarpal region of the left thumb (see Figure 1C and D). The palms, however, were spared. The rest of her skin was uninvolved and there were no concomitant illnesses.

A patch test with 45 commercially available common allergens (including fragrances, rubber additives, some dyes, formaldehyde and formaldehyde-releasing preservatives and resins) was performed, read and interpreted according to the Contact Dermatitis International Research Group Guidelines.[1] After 72 hours, a 1+ reaction (erythema and induration) to Balsam of Peru and potassium dichromate was noted. All other allergens were non-reactive, including fragrance mix 1 and 2, rubber additives, preservatives and nickel and cobalt. Her workplace was visited and multiple possible causative agents, both irritant and allergic, were identified (see Table I).

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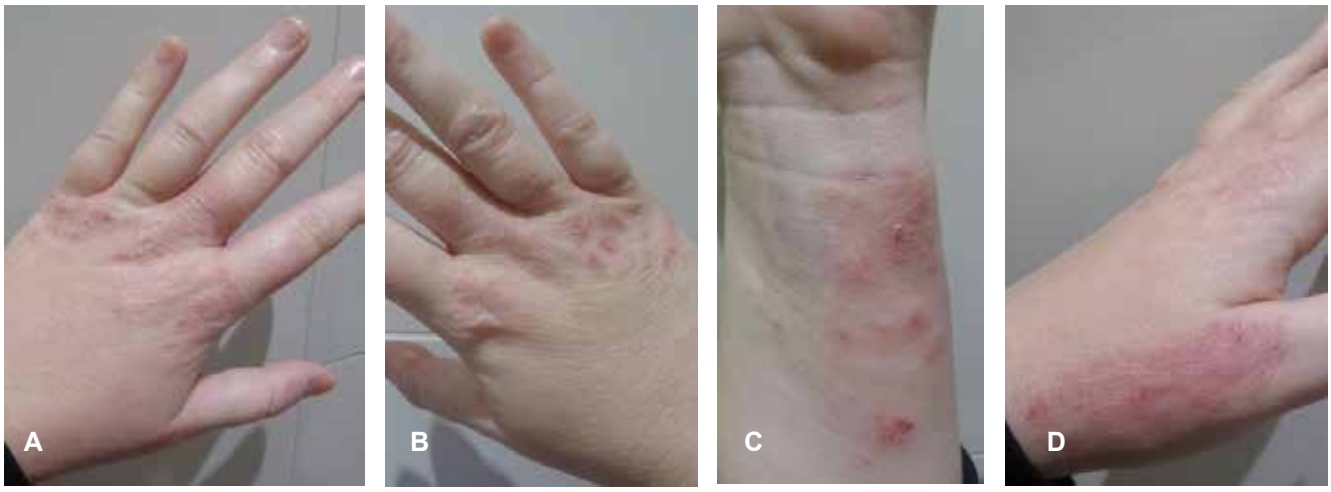


*Figure 1: The distribution and morphology of the patient's dermatitis. A and B - Patient's hands, showing erythema, red vesico-papules, crusts, excoriations and prominent skin markings predominantly over the knuckles of both hands extending onto the proximal phalanx of the second and third fingers. C and D - The left medial forearm and dorsal metacarpal region of the left thumb showing similar changes.*

## EPIDEMIOLOGY OF OCCUPATIONAL DISEASE IN HAIRDRESSERS

The hairdressing industry is an important source of income worldwide. According to the European Agency for Safety and Health at Work, more than a million people in Europe work in this industry.[2] In the United States approximately 400 000 people are employed in the hairdressing industry but this number includes only those in the formal sector.[3] Statistics are not available for Africa, but we can assume that the informal hairdressing sector, where backyard and ambulant hairdressers are common, is at least as large as the formal sector. In Ghana, the informal sector encompasses more than 70% of the total workforce and plays an important role in the country's strategy to reduce poverty.[4]

Hairdressers and other workers in the informal sector are routinely exposed to a range of recognised and unrecognised hazards, including physical, chemical, ergonomic and psychological, that can cause or aggravate several diseases.[5] Diepgen et al[5] state that in many countries in Europe and North America data on occupational diseases are scarce and it is recognised worldwide that occupational diseases are usually undiagnosed and under-reported. This under-reporting is even more likely in countries with weak health systems and where informal employment is high, such as in developing countries in Africa.

Dermatological, respiratory and musculoskeletal diseases are regularly reported among hairdressers and hair stylists. Hair products and hairdressing equipment contain numerous chemicals known to cause both irritant and allergic diseases, mostly in hairdressers and, less commonly, in consumers. The concentration of chemicals contained in hairdressing products is regulated to minimise the risk for consumers but not specifically workers in the field. The repeated, often daily exposure of hairdressers

**TABLE I: COMMON HAIRDRESSER ALLERGENS IDENTIFIED IN THE PATIENT'S WORKPLACE**

| HAIR PRODUCT | ALLERGENS |
|---|---|
| Colour activators | Acrylates, tetrasodium ethylenediaminetetraacetic acid (EDTA), oxyquinoline sulfate, etidronic acid |
| Bleaching paste and powder | Potassium persulphate, ammonium persulphate, cyamopsis tetragonolobus gum, sodium persulfate, tetrasodium EDTA |
| Colour (pigment) | Paraphenylenediamines (PPD) |
| Colour – cream base | Ethanolamine, polyquaternium-6, castor seed oil, glyceryl dihibenate, tribehenin |
| Conditioner | **Fragrance**, phenoxyethanol, sodium benzoate, behentrimoniom chloride, **linalool, limonene**, hydrogenated sweet almond oil, prunus domestica fruit extract, disodium EDTA, **hexyl cinnamal,** propylene glycol, dicaprylate |
| Nourishing vegetarian conditioner | **Fragrance**, hydrolysed wheat protein, Simmondsia chinensis (jojoba) seed oil, hydrogenated sweet almond oil, Vitis vinifera (grape) leaf extract, behentrimonium methosulfate, **hexyl cinnamal, linalool, limonene** |
| Hair spray | **Fragrance**, methylisothiazolinone, acrylates, propylene glycol, **linalool, limonene** |
| Mask colours | N,n-bis-p-phenylenediamine sulphate, **fragrance**, propylene glycol, toluene-2,5-diamine sulfate, hydrolysed milk protein, sodium sulfite, methylparaben, propylparaben, 2-amino-4-hydroxyethylaminoanisole sulphate |
| Shampoo | **Fragrance**, cocamidopropyl betaine, sodium lauroyl methylisethionate, **sodium benzoate**, coco-glucoside polyquaternium-7, trisodiumethylenediamine, **limonene, linallol** |

*Note: the bold chemicals are fragrances and may be related to balsam of Peru.*

puts them at high risk of diseases.[6] In addition, hairdressing tools can be contaminated by infective agents such as dermatophytes, posing as a source of infection for both consumers and hairdressers.[7]

Increased risk of cancer and reproductive health issues have been variously linked to hairdressing. Formaldehyde (present in hair dyeing and straightening products) is classified by the International Agency for Research in Cancer as a group 1 carcinogen, meaning it has proved to be carcinogenic to human beings. The World Health Organisation has presented evidence of human *in vitro* carcinogenic and mutagenic effects and *in vivo* carcinogenic properties for nitrosamine (present in hair-dye formulations). Cancer and harmful reproductive effects as a result of exposure to such chemicals daily pose additional, rarer occupational health concerns for hairdressers.[8]

Occupational diseases may have negative social and economic consequences for the individual because of temporary or permanent impairment and job loss.[9] A considerable proportion of hairdressers leave the profession due to occupational diseases. In Denmark, the time from starting training to leaving the profession has been documented as 8.4 years.[10] In a subsequent study of apprentices, 34.5% (49/142) had left the trade after six to seven years and 10.6% (15/141) never completed their training. Unfavourable working hours (37.5%, 18/48), back and joint pain (42%, 20/48) and hand and arm dermatitis (12.5%, 6/48) were the reasons given for leaving the profession.[11] A prospective Finnish study evaluated the reasons for leaving the profession over a 15-year period among 3 484 female hairdressers and 3 357 controls selected by proportionate sampling. This study showed that the hairdressers were more likely to leave the industry due to health concerns compared to the controls (RR: 1.33, 95% CI: 1.16–1.52). The same study reported that asthma, hand eczema, and strain injuries of the elbow and wrist (RR: 3.5, 95% CI: 1.8–6.8, RR: 3.5, 95% CI: 2.1–5.7, RR: 2.7, 95% CI: 1.1–6.3, respectively) topped the list of health reasons for leaving the trade. In addition, they reported that hairdressers had a 20% increased risk of leaving the trade if they had had a history of an atopic disease.[12]

## SKIN DISEASES

A 1999 review of the epidemiology of occupational contact dermatitis (OCD) from around the world reported that OCD ranked highest as a cause of work-related disability worldwide.[5] A German study of a labour force of approximately 2.6 million people in different professions over three years (1990 to 1993) reported that the one-year incidence rate for OCD in hairdressers (194 cases of OCD per 10 000 employees per year) was higher than for all other occupations, health-service workers included.[13] A Danish population-based study in Copenhagen reported a life-time prevalence of 44% (404/1063) for hand eczema in hairdressers, including hairdresser apprentices.[14] An Australian retrospective review of clinical assessments showed that 96% (157/164) of hairdressers and hairdressers apprentices who attended a dermatology clinic over 17 years (1993–2010) were diagnosed with OCD.[15] In Nigeria, a prevalence of 34% (34/108) for occupational hand dermatitis was reported in hairdressers.[16]

A survey of hand dermatitis from five randomly selected salons in the Netherlands showed that 26% of hairdressers (12/45) reported hand dermatitis. In addition, the authors reported that hand dermatitis as a cause of hairdresser absenteeism increased from 21 050 days in 1986 to 54 293 days in 1991.[17] A study of hairdressers in Copenhagen found that 37.6% (1 097/2 918) of those who were still active in the profession at the time of the study gave a history of ever having had hand eczema compared to 48.4% (1 123/2 321) among ex-hairdressers. In addition, the same study evaluated reasons why hairdressers left the profession. Among 2 321 ex-hairdressers, 41.9% left because of musculoskeletal pain and 23.15% because of hand eczema.[10]

In a retrospective cohort study from Taiwan, dermatitis was reported in 72% of all hairdressers studied (77/107 43 hairstylists and 64 apprentices). Tasks differed between hairstylists and apprentices. Hairstylists cut, blow-dried and waved hair, whereas apprentices shampooed and waved hair. Evidence of trauma presented as wounds or scars between the index and middle fingers of the non-dominant hand that would hold and guide hair during cutting, dyeing or styling. Scissors-induced trauma prevalence was 37.4% (40/107) for all hairdressers but 81% (39/43) for hairstylists alone.[18]

In a cross-sectional survey in Mali, West Africa, to assess anthrophophilic dermatophyte (*Trichophyton soudanese* and *Microsporum audouinii*) contamination, 41 samples were collected from hairdressing tools taken from five randomly selected suburban salons in Bamako. Diverse fomite samples, namely, cream pot, braiding needles, hair brushes, cloths, scissors, hair extension, combs, razors, table surfaces, hair clippers and shea-butter were collected and analysed. Contamination was demonstrated in 73.2% (30/41) of the samples, ranging from 43% to 100% dependent on salon and type of fomite sampled.[7]

## RESPIRATORY DISEASES

Respiratory symptoms are not rare in hairdressers. A French national survey (1996 to 1999) conducted to assess the incidence of occupational asthma among the working population, showed that hairdressers had the third-highest annual occupational asthma incidence rate, 308 per million (95% CI: 256–359, 138/112 000) following 683 per million for pastry makers and 326 per million for car painters.[19] These results are comparable to those of a Finnish study (330 and 370 per million for men and

women, respectively) but higher than those from Sweden and England (1982 to 1997) (129 per million and 24 per million, respectively).[19,20] A population-based study from Spain reported that hairdressers are at increased risk of developing asthma (OR: 1.94, 95% CI: 0.86–4.39) compared to a non-hairdresser population.[20] Data from a Danish population study among hairdressers, revealed that 7.8% (181/2 321) of them developed adult onset asthma after starting working in the trade and half of them changed profession because of asthma.[21]

In Ghana, 19.5% (23/120) of the participants (beauticians, mechanics, drivers and porters) in a cross-sectional survey reported occupational exposures as trigger events for asthma and 15.6% (18/120) for chronic upper-airways symptoms such as rhinitis and sinusitis.[4] A South African study reported that hairdressers who work in their own homes were at increased risk of developing asthma (OR: 2.89, 95% CI: 1.46–5.73) compared to the risk in the general population.[22] This characteristic of working within their own houses is common in low-resource settings.

### MUSCULOSKELETAL DISEASES

The physical and postural demands of the work, and non-ergonomic equipment, are common characteristics of the hairdressing industry and responsible for the high number of hairdressers reporting work-related musculoskeletal disorders. A cross-sectional study in Brazil in which ergonomic analyses were performed, reported a prevalence of 71% of work-related musculoskeletal diseases among 222 hairdressers, with the shoulder, back and neck being the most frequently affected body areas.[23] In a Danish study investigating fragrance-related chemical intolerance symptoms in hairdressers compared to the general population, work-related reasons for leaving the trade were also evaluated. Among those who developed symptoms by inhaling perfume or fragrance, 53% (49/89) left the trade due to musculoskeletal pain compared to 14.2% (317/1 232) without symptoms who left the trade for the same reason. This supported previous reports claiming that musculoskeletal symptoms are features of chemical intolerance.[24]

### CANCER

Epidemiologic studies have reported an increased risk for multiple myeloma and leukaemia in cosmetologists, hairdressers included, exposed to hair-dyeing products.[25] A 2009 meta-analysis reported that hairdressers and allied occupations carry higher risk of cancer compared to the risk to the general population. The commonest cancers among these professionals were lung cancer (random effects pooled RR: 1.29, 95% CI: 1.04–1.60), larynx cancer (random effects pooled RR: 1.52, 95% CI: 1.11–2.08), bladder cancer (random effects pooled RR: 1.06, 95% CI: 1.02–1.10) and multiple myeloma (random effects pooled RR: 1.12 95% CI: 1.03–1.23).[26]

A pooled analysis of ten studies from the InterLymph Consortium assessed the association between occupation and non-Hodgkin lymphoma and its subtypes among 10 046 cases and 12 025 controls. Being a women's hairdresser increased the risk of developing non-Hodgkin lymphoma (OR = 1.34; 95% CI: 1.02–1.74). The subtypes associated with hairdressers were diffuse large B-cell lymphoma (OR = 1.47; 95% CI: 1.08–2.00; 58 cases, 158 controls) and chronic lymphocytic leukaemia, also called 'small lymphocytic lymphoma' (OR = 1.79; 95% CI: 1.06–3.03; 18 cases, 130 controls), whereas no association was found for follicular lymphoma.[27]

### REPRODUCTIVE HEALTH

A Spanish study assessing the relationship between hairdressing and reproductive health compared 310 qualified hairdressers and assistants with 310 office workers. Menstrual disorders in the 12 months preceding the study were higher in hairdressers (prevalence of 9.7%; adjusted OR: 1.87, 95% CI: 0.99–3.91) when compared to office workers (3.9% prevalence). In addition, hairdressers were 2.17 (95% CI: 0.91–5.17) times as likely not to fall pregnant after 12 months of normal unprotected active sexual activity compared to the controls.[28] A meta-analysis of reproductive disorder among hairdressers and cosmetologists revealed an increased risk of infertility (OR1.15, 95 % CI: 1.03–1.28), foetal death (OR 1.14, 95% CI: 1.04–1.24), and preterm delivery (OR 1.04, 95 % CI: 1.00–1.07) compared to the general population.[29]

An earlier meta-analysis of 19 studies reported on the risk for five reproductive outcomes (time to pregnancy, preterm birth, small for gestational age, low birth weight and embryonic and foetal loss) among female hairdressers and cosmetologists. The combined risk ratios (RRc) were calculated for the outcomes time to pregnancy RRc 1.11 (95% CI: 1.03–1.19), premature birth RRc 1.05 (95% CI: 0.99–1.11), small for gestational age RRc 1.24 (95% CI: 1.10–1.41), low birth weight RRc 1.21 (95% CI: 1.06–1.39) and embryonic and foetal loss RRc 1.19 (95% CI: 1.03–1.39). Apart from premature birth, the other four outcomes reflected statistically significant, but weak increased risk for reproductive disorders among hairdressers and cosmetologist. The analysis failed to establish a definitive occupational causality because the evidence was weak and aspects such as alcohol consumption, current medication, dietary habits and other non-occupational exposures were not accounted for.[30] Regardless of the lack of robustness in some reports, possible reproductive health disorders should be recognised among these professionals and efforts should be made to reduce harmful chemical exposures.

## ALLERGENS IN THE HAIRDRESSING INDUSTRY

Among hairdressers, sensitisation to substances used in the hairdressing industry is increasing.[9,12,31–33] Although

allergic contact dermatitis (ACD) is the most common occupational allergic disease occurring in hairdressers with a prevalence of 58%,[32] asthma also poses a health problem.[21] Immediate IgE-mediated reactions may also occur. A recent case report described a hairdresser sensitised to persulphates in the workplace who developed an anaphylactic reaction when exposed to dental cement containing persulphates during a dental procedure.[34]

Specific substances and chemicals are clearly identified as occupationally relevant allergens among hairdressers as summarised in Table II. Diverse studies globally reported patch-test results which vary from country to country.[35] The North Bavarian study of 662 hairdressers showed sensitisation for glyceryl monothioglycolate (GMT) (54% sensitive, 50% relevant), paraphenylene diamine (PPD) (31% sensitive, 29% relevant), ammonium persulphate (24% sensitive, 23% relevant), toluylenediamine sulfate (21% sensitive, 19% relevant), o-nitro p-pheylenediamine (9% sensitive, 8% relevant), pyrogallol (6% sensitive, 4% relevant) and fragrances (5% sensitive, 2% relevant).[5] A retrospective study from 1980 to 1993 of hairdressers from Madrid found 48.8% had ACD, although 58.8% had positive patch tests. Positive patch-test reactions were seen in more than 10% of the 379 hairdressers tested for paraphenyldiamine (58.8%), nickle (41.4%), disperse orange 3 (32.2%), 4 aminobenzene (31.9%) and thioglycolate (15.3%). The nickel sensitisation rate was higher than in the general population (18.3%) and considered relevant for the hairdressers.[35] In a British retrospective review of 725 hairdressers patch-tested over a 26-year period from 1980 to 1993, the allergens giving positive reaction in >10% of the tested group were nickel (32,1%), followed by PPD (19%), GMT (21.4%) and ammonium persulphate (10.6%).[36] Guo et al, in a 1994 study among 98 hairdressers selected randomly from hairdressing shops in Taiwan, found that the most common allergens were nickel (22%), Captan (6%), methyl- and chloromethylisothisazolinone (Kathon CG) (5%) and fragrance mix (5%), whereas the sensitivity to hair dyes and permanent-wave components was low (<5%).[37]

Common sources of allergens are shampoo preservatives, hair dyes and straightening, permanent-waving and

**TABLE II: COMMON ALLERGENS IN THE HAIRDRESSING INDUSTRY, (modified from Kanerva)[38]**

| HAIR PRODUCTS OR TOOLS | ALLERGENS | ALLERGY REACTION |
|---|---|---|
| Reducing/blonding agents or hair bleaching | Glyceryl thioglycolate<br>Ammonium thioglycolate<br>Cysteamine<br>Thiolactic acid<br>Potassium persulfate | Type IV |
| | Ammonium persulfate | Types I and IV |
| Hair dyes | Para phenylene diamine<br>2,5-diaminotoluene sulfate<br>2-nitro-4-phenylene diamine<br>5-aminophenol<br>4-aminophenol<br>4-aminodiphenylamine<br>Resorcinol | Type IV |
| | Henna | Types I and IV |
| Preservatives (antibacterial, antifungal)<br>(*formaldehyde releasers) | Paraben mix<br>Methyldibromoglutaronitrile<br>2-bromo-2-nitropropane-1,3-diol<br>2,5-diazolidinyl urea*<br>Imidazolidinyl urea*<br>Methylchloroisothiazolinone<br>Mercaptobenzothiazole<br>Quaternium 15*<br>Formaldehyde | Type IV |
| Surfactants | Cocamidopropyl betaine | Type IV |
| Conditioners | Sodium coco hydrolysed animal protein | Types I and IV |
| Shampoo<br>Hair dyes | 3-dimethylaminopropylamine | Type IV |
| Hair straighteners<br>Hair dyes | Formaldehyde | Type IV |
| Gloves | Thiuram mix<br>Carba mix<br>Mercaptobenzothiazole | Type IV |
| | Latex | Types I and IV |
| Metallic tools/equipment (scissors, pins, clips, hair plates, etc) | Nickel S<br>Cobalt | Type IV |
| Can be in all products | Fragrance mix | Type IV |

bleaching agents.[37] However, conditioners, tools and a wide variety of other hair products may also contain allergens.

Table II lists the most common allergens used for patch tests in the hairdressing industry and the type of hypersensitivity reactions they evoke. The majority of the substances cause Type IV delayed hypersensitivity reactions. Prior sensitisation must take place, often at higher exposure concentrations of the substance than are necessary to evoke the subsequent eczematous allergic reaction.[38]

Valks et al[33] compared sensitisation trends to hairdressing products among 300 Spanish hairdressers from 1994 to 2003 with those found in 379 hairdressers from 1980 to 1993. They report an increased frequency in positive patch-test reactions (73.8% compared to 58.8%) and occupational ACD (58% compared to 48.8%). A significant increase in sensitisation for the majority of the known hairdressing allergens was observed, in particular p-phenylenediamine (45.9% to 54%), 4-aminobenzene (31.9% to 40.7%), ammonium thioglycolate (2.7% to 12.3%), ammonium persulfate (7.9% to 14.3%), p-toluenediamine sulfate (6.8% to 15.3%), p-aminodiphenylamine (2.9% to 7.7%), o-nitro-4-phenylenediamine (2.1% to 7.3%), and aminophenols (0% to 9%). A decrease in reactions and sensitisation was reported for disperse orange (32.7% to 17%) and thioglycolic acid (15.3% to 3%).[33]

Some food ingredients such as hydrolysed wheat protein (HWP), castor oil and grape seed oil can cause hairdressers to develop rhinitis, contact urticaria and asthma. These ingredients are used in a diversity of hairdressing products. A hairdresser may become sensitised to these products as a consumer and then, on re-exposure to them at the workplace, develop occupational rhinitis, urticaria or asthma. They are an important group of substances to consider as etiologic agents for occupational health problems in hairdressers.[39]

Metals such as nickel, cobalt and chromium are known to cause sensitisation and a high prevalence of ACD in the general public. Hairdressers are permanently in contact with tools made of metal alloys which may release these metals such as combs, scissors and hair clips.[40] Occupational metal sensitisation relevance among hairdressers appears low. Among 662 hairdressers from North Bavaria metal sensitisation was poorly correlated with occupational relevance; nickel (52% sensitive, 6% relevant), cobalt (17% sensitive, 2% relevant) and chromate (5% sensitive, 0% relevant).[13] Chrome's oxidative proprieties are relevant to the cosmetic industry as it may be mixed into hair-dyeing products to achieve better colour results.[41] Chrome may cross-react with cobalt and nickel, which are frequently present in hairdressing tools/equipment (scissors, clips, combs, etc.) and dyes. Although the North Bavarian hairdressers study showed possibly delayed-type hypersensitivity for potassium chromate, it also suggested no occupational relevance.[5]

Turčić et al reported that, following nickel, fragrances are the most frequent agents implicated in causing allergic contact dermatitis.[42] Balsam of Peru, otherwise known as *Myroxylon pereirae,* is a natural complex resin, and only 60–70% of its components have been identified precisely. Owing to the common use of *M pereirae* in the perfume (used as an aromatic and fixative delaying evaporation), food (flavourant), medicine (antiseptic, antifungal and antiparasitic) and cosmetic industry, it is accepted as a marker of fragrance allergy and is included in all standard patch-test series.[43] Also, positive patch-test reactions to fragrance (5%, 31/662) suggesting sensitisation and possibly delayed type hypersensitivity have been recorded among North Bavarian hairdressers, but occupational relevance was demonstrated in only 2% (13/662).[5]

## CONCLUSION

This hairdresser has been exposed to many chemicals over the past six years. The pattern of improvement of the symptoms when away from work for long periods and recurrence when back at work clearly suggests work-relatedness. However, it does not exclude the possibility of exposure to substances outside the workplace environment, either for initial sensitisation or for triggering ongoing symptoms.

Our patient has been classified as having OCD. She continues to work and remains exposed and her dermatitis persists despite varied and intermittent use of a variety of topical agents and the ongoing use of gloves for specific tasks. It is becoming urgent that the etiologic agent(s) are identified and her skin condition is controlled. With ongoing eczema and a damaged barrier function, she is at daily risk of increased sensitisation to additional chemicals, both at work and elsewhere. This could lead to worsening eczema, which could result in her having to leave her vocation. The active eczema and open skin lesions are also putting her and her clients at risk of infections. In addition, as she is now pregnant, she needs to be advised to limit exposure to potentially dangerous substances in her environment. The scheduled patch-testing with the hairdresser series and substances identified from her workplace has been delayed at her request because of her pregnancy, further delaying definitive treatment.

The clinical distribution of the eczema initially suggested a glove allergy. Changing gloves from latex to nitrile did not improve her skin. This is understandable as similar rubber chemicals may be found in both glove types. The initial gloves used were professional reusable black rubber ones. Glove re-use has its own problems: material degradation, physical damage and gradual contamination with the substances used in the profession and for cleaning. Her current use of nitrile gloves excludes contamination as the

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gloves are disposed of between clients. Overall it seems unlikely that gloves were the cause as the rubber glove allergens were negative on patch testing and sources of contamination and glove penetration have been minimised or eliminated. The distribution is more compatible with contact with treated, contaminated hair during styling and cutting.

The positive patch-test reaction to chromium is weak and does not seem to be occupationally relevant. Importantly, none of the products she used listed chrome as an ingredient (see Table I). Contamination of the raw materials used in their manufacture could still explain her exposure. The patient did not react to any of the other metals patch-tested, namely, nickel and cobalt, to explain a cross-reaction. Finally, the occupational relevance of chrome sensitisation has been shown to be low.[5]

The weak reaction to Balsam of Peru is difficult to link to occupational exposure, considering how widely it is encountered in day-to-day living in the modern world. None of the products she uses list it as an ingredient (see Table I). It is noteworthy that both fragrance mixes tested, which share many similar fragrance chemicals, were negative. This does not exclude an etiologic role for fragrances as several specific ones have been identified from the ingredients list (see Table I) that could be implicated.

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

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## CLINICIAN INTEGRITY, PATIENT AUTONOMY AND THE PATIENT'S BEST INTERESTS

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Ethics CPD Questionnaire

# CLINICIAN INTEGRITY, PATIENT AUTONOMY AND THE PATIENT'S BEST INTERESTS

Ethics articles are accredited for ethics CPD points. Log in to the ALLSA website (www.allergysa.org) and click on "My CPD" to submit your answers. Kindly send submissions or suggestions for topics to the section editor, Prof Sharon Kling at sk@sun.ac.za.

### INDICATE TRUE OR FALSE

1. *True or false:* Respect for autonomy has replaced paternalism as the ethical principle in guiding decision making for patients.
2. *True or false:* Paternalism involves making decisions that the doctor believes is right for the patient.
3. *True or false:* Medical decision making without a recommendation from the doctor has the potential to deprive the patient of full decision making ability.
4. *True or false:* The "enhanced autonomy" model means that the patient is given full information to make a decision, but without a recommendation from the doctor.
5. *True or false:* In the traditional African point of view, the individual's autonomy ought to be respected above all else.
6. *True or false:* The HPCSA guidelines state that the doctor's personal self-interest should outweigh the best interests of the patient.
7. *True or false:* Clinicians are not obligated to provide treatment that they deem to be inappropriate.
8. *True or false:* Withholding a blood transfusion at the request of a Jehovah's Witness patient respects patient autonomy over his best interests.
9. *True or false:* The obligation of a doctor to always act in an individual patient's best interest is a strict obligation that cannot be overridden.
10. *True or false:* A patient who has had a life-threatening allergic reaction to a bee sting cannot refuse allergen immunotherapy.


# EGG ALLERGY

**Dr Do-a-Lot's student presents short notes on egg allergy:**
Egg is a common cause of allergic reactions in children. Egg allergy occurs in about 2% of infants and children and is often present in the first year of life, especially in children with eczema. Most egg-allergic children develop tolerance to egg proteins in early childhood, but in cases where levels of antibodies to ovomucoid are high it is less likely that the allergy will be outgrown.

*Most reactions to egg are caused by the proteins in egg white*

## Egg proteins

Most reactions to egg are caused by the proteins in egg white, which include ovomucoid, ovalbumin, ovotransferrin and lysozyme. The main allergenic protein found in egg yolk is called alpha-livetin.

## Symptoms of egg allergy

Hypersensitivity reactions to egg are typically immunoglobulin-E (IgE)-mediated and therefore occur within minutes of exposure. Sometimes, however, symptoms may take more than an hour to present. Mild symptoms include skin manifestations such as flushing or urticaria and a tingling or itchiness in the mouth. Severe symptoms are less common and include swelling of the face, tongue and throat, nausea, vomiting, abdominal pain, shortness of breath and wheezing. Cardiovascular collapse may occur due to widespread vasodilatation and a sudden decrease in blood pressure, resulting in anaphylactic shock.

Highly sensitised individuals may develop respiratory symptoms from the inhalation of protein particles in the fumes of cooked eggs. Patients with eczema may experience a worsening of their skin condition in a delayed reaction. Some patients may develop gastro-intestinal inflammation with symptoms that include reflux, difficulty swallowing, diarrhoea, constipation, abdominal pain and bloating as a result of delayed reactions.

*Patients with eczema may be sensitised to egg proteins*

## Testing for egg allergy

Following a detailed history and careful examination, the following tests and procedures may be helpful in the diagnosis of egg allergy:

1. *Skin-Prick Test (SPT):* An SPT may be performed, even on young babies, by placing a few drops of fresh egg or egg solution on the skin and pricking through the droplet.
2. *Specific IgE test:* This is a blood test that measures IgE which has been produced by a patient's plasma cells and which is specific to egg proteins. Tests available from commercial laboratories include those for egg white, egg yolk and ovomucoid.
3. *An elimination diet followed by re-introduction of egg:* This may be useful, for example, in a patient with

eczema or non-specific gastro-intestinal symptoms where it is uncertain whether or not symptom flares are caused by the ingestion of egg.

4. *Oral food challenge:* This test may be helpful in establishing a clinically significant allergy in some of the following situations: where tests are equivocal, where the history and the blood or skin-prick tests do not concur, or where known allergic patients require re-testing to assess whether or not they have developed tolerance to an important food allergen over time. It is also helpful in establishing whether or not patients can tolerate the baked or cooked forms of the foods to which they are sensitised.

The oral food-challenge test is performed by feeding the patient increasing quantities of egg (or other allergenic food) under controlled circumstances, usually in a hospital, with sufficient trained staff and immediately accessible resuscitation facilities available should they develop a severe reaction. The test is stopped if at any stage the patient develops signs of an allergic reaction.

## Management

The management of egg allergy revolves largely around the avoidance of the allergen. Egg is an affordable source of protein, and a ubiquitous food ingredient, which complicates the task, so it is ideal to work closely with a dietician who specialises in food allergy when managing a patient with egg allergy.

*Egg is a good source of protein and is found in many foods*

Foods that may contain egg include: cakes, biscuits, pastries, pasta, crumbed foods, soups, sauces, dressings, mayonnaise, meatloaf, meat pies, ice-cream, desserts, sweets, nougat, chocolates, custard and health drinks.

Education regarding the reading and understanding of labels is essential. Terms that imply that a product may contain egg include: albumin, globulin, lecithin (E322), livetin, lysozymes, vitellin, and words starting with 'ov' such as ovalbumin, ovomucin or ovoglobulin.

## Follow-up

It is important to assess children with food allergies regularly to evaluate their growth and nutrition. This also provides an opportunity for ongoing education about egg allergy and avoidance, as well as the management of allergy symptoms and anaphylaxis.


*Understanding food labelling is important*

Allergy testing is repeated annually to assess whether patients are outgrowing their allergy. This allows a decision to be made regarding the appropriate timing of an oral food challenge to establish whether or not tolerance has been achieved.

## Tolerance

A patient may be able to tolerate the egg that has been exposed to high temperatures for long periods in muffins and cookies, but may react to lightly cooked egg in scrambled eggs or pancakes or to raw egg in mayonnaise.

More than 70% of egg-allergic children will tolerate baked goods containing small amounts of extensively heated egg. These patients should be encouraged to consume baked egg regularly as they may develop tolerance to egg sooner with regular exposure to the baked form. At least 66% (two-thirds) of children with egg allergy will have developed tolerance to all forms of egg by the time they are 16 years of age.

Note that children who have outgrown their allergy to egg may well not willingly agree to include it in their diets as the taste is unfamiliar and the food may be tainted with negative associations.

*Raw, cooked and baked egg*

## Immunising individuals with egg allergy

Children with egg allergy should receive their scheduled childhood immunisations. This includes the measles and the measles-mumps and rubella (MMR) vaccines. Although they are generally grown on chick embryos, these vaccines have been shown to be safe, even in children who have had previous anaphylaxis to egg. The influenza, yellow fever and

rabies vaccines may contain traces of egg protein and should be given under the guidance of an allergist. The intranasal topical influenza vaccine should not be given to individuals known to have egg allergy.


*'MMR' vaccine*

## The management of egg-allergy symptoms

If an egg-allergic individual has been exposed to egg and the symptoms are mild, involving only the skin (e.g. itching, flushing or hives), it may be sufficient to treat the patient with antihistamines. Second generation non-sedating antihistamines are recommended.

If symptoms are moderate to severe and involve more than one system, it is essential that the patient carry injectable adrenaline (e.g. adrenaline auto-injector). Adrenaline is life-saving in anaphylaxis and must be available for use at all times. Empowering education that leaves patients, parents and caregivers prepared rather than scared must accompany a new script for an adrenaline auto-injector.

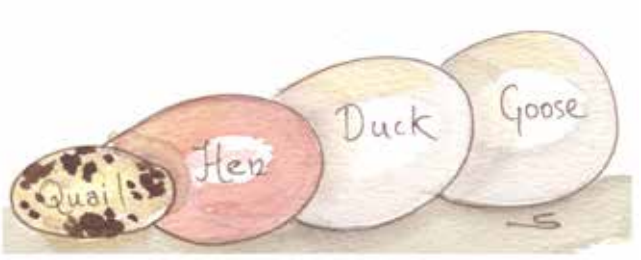
All patients should have a detailed written allergy action plan that differentiates between mild and severe reactions and provides clear instructions on management. Copies should be provided to schools and caregivers.

## Risk of other allergies

Research has shown that infants who have egg allergy have an increased risk for developing peanut allergy, and that it is probable that these children will develop allergies to inhalant allergens such as house dust mites and pollens, with the subsequent development of asthma and allergic rhinitis.

*Patients with adrenaline auto-injectors must carry them at all times.*

It is advisable for people who are allergic to hens' eggs to avoid eggs from ducks, geese, quails and other birds because of the risk of cross-reactivity. In very rare cases patients who suffer from egg allergy may also be sensitive to chicken meat.




*Cross-reactivity may occur between the eggs of different birds*

## Is there a cure?

Oral immunotherapy has shown some promise, but the treatment is still experimental and only carried out in specialist centres.

## Advice to patients with egg allergy

- It is essential to receive a definitive diagnosis and work out a treatment plan with a doctor, and preferably a dietitian, who specialises in allergy management.
- Learn to be vigilant regarding food and understand food labelling.
- Communicate clearly with others about your allergy when eating away from home.
- Carry allergy treatment everywhere.
- Patients who carry adrenaline auto-injectors must always have them available for use, and use them early in anaphylaxis.
- Patients with asthma must use their controller medications every day and always have their reliever medications with them.

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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.

## THE WHEEZY INFANT AND TODDLER ASTHMATIC – A PRIMARY CARE APPROACH

1. *True or false:* The first episode of wheeze in infancy is likely to be due to acute viral bronchiolitis and does not need antibiotic therapy.
2. *True or false:* Recurrent wheeze in early childhood requires a clear distinction of cause to start inhaled corticosteroid therapy.
3. *True or false:* When treating 'toddler asthma' it is important to ensure that the child remains well controlled.
4. *Choose the correct answer:* Preschool wheeze that is recurrent may be:
   a. Treated with prolonged courses of antibiotics;
   b. Treated with cough mixtures;
   c. Treated with intermittent short courses of high dose inhaled steroids;
   d. Treated early with long acting bronchodilators;
   e. Treated with nebuliser budesonide.

## THE ASTHMA COPD OVERLAP SYNDROME (ACOS)

5. *True or false:* In the SATS & GINA Guidelines, the definition of bronchodilator reversibility is stated as an increase from baseline in the $FEV_1$ of >12%, 10-30 mins following the inhalation of 200-400 μg of salbutamol.
6. *True or false:* Most asthmatics will not exhibit reversibility at each assessment.
7. *True or false:* Patients with Asthma COPD Overlap Syndrome (ACOS) have better outcomes (quality of life, decline in lung function, mortality and health care utilisation) than those with COPD alone.
8. *Choose the correct answer:* Which of the following is the most recommended therapy for patients with Asthma COPD Overlap Syndrome (ACOS)?
   a. Long-acting beta-agonists (LABA);
   b. Long-acting anti-muscarinics (LAMA);
   c. Twice-daily low-dose inhaled corticosteroids (ICS) plus long-acting beta-agonists (LABA);
   d. Long-acting beta-agonists (LABA) plus long-acting anti-muscarinics (LAMA).

## A DIAGNOSTIC APPROACH TO THE CHRONIC COUGH IN CHILDREN

9. *True or false:* The causes of chronic cough in children are similar to those in adults.
10. *True or false:* Children with chronic cough who are managed with published guidelines/algorithms have better outcomes.
11. *True or false:* All children with a very acute onset of cough that persists should be evaluated for possible foreign body inhalation.
12. *Choose the correct answer:* In young children who present with 4 weeks of a wet cough:
    a. The most common diagnosis is Protracted Bacterial Bronchitis;
    b. Recurrent episodes of prolonged wet cough should raise the suspicion of bronchiectasis;
    c. One should prescribe a minimum of 2-4 weeks of amoxicillin-clavulanic acid or cefuroxime orally;
    d. All of the above.

## PAEDIATRIC NASAL OBSTRUCTION – A PRACTICAL APPROACH

13. *True or false:* Allergic rhinitis has a limited association with obstructive sleep apnoea.
14. *True or false:* Intranasal steroid sprays have been shown to be effective in reducing adenoidal hypertrophy.
15. *True or false:* Children with nasal polyps should be tested for cystic fibrosis.
16. *Choose the correct answer:* Which of the following is not associated with severe nasal obstruction?
    a. Nocturnal enuresis;
    b. Obstructive sleep apnoea;
    c. Cystic fibrosis;
    d. Nasal foreign body;
    e. Adenoidal hypertrophy.

## EOSINOPHILIC OESOPHAGITIS (EOE) IN CHILDREN

17. *True or false:* Symptom control is the best way to confirm disease remission.
18. *True or false:* Measurement of specific IgE tests is a reliable method to plan targeted food elimination diet.
19. *True or false:* High dose PPI may be effective as a monotherapy in EoE.
20. *Choose the correct answer:*
    a. Sublingual immunotherapy is always effective in EoE associated with allergic rhinitis;
    b. High dose PPI treatment should be tried only after dietary elimination has failed;
    c. Eosinophils >15/HPF in the oesophageal biopsy is diagnostic of EoE;
    d. Seasonal variation is not a feature of EoE;
    e. There is no long term risk of fibrotic strictures in EoE.

Case Report

# ALLERGY TO APPLE SEEDS IN A PEANUT-ALLERGIC CHILD

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## INTRODUCTION

Allergic reactions to fruits are commonly described, resulting most frequently in symptoms of the oral allergy syndrome (pollen fruit syndrome), and less often in more severe reactions and anaphylaxis. The flesh or pulp of the fruit is most commonly the cause of such reactions. Less commonly described are allergic reactions to the seeds ('pips') of fruits, reported in only a handful of case reports, but probably under-recognised. This case report describes a young boy, with a known allergy to peanuts, who experiences an allergic reaction when biting into seeds of both apples and watermelons, but is tolerant of the fruit pulp. It is one of very few cases in the literature that describe an allergy to a non-citrus fruit seed.

## CASE

An eight-year-old boy, TO, attending the Red Cross Children's Hospital Allergy Clinic, had a history of an acute reaction to peanut (immediate-onset facial hives after consumption of a trace amount of peanut) at the age of two years. He had avoided peanuts as well as all tree nuts from that time onwards. He tolerated legumes and sesame seed. More recently, he had accidentally ingested a piece of cake containing nuts (he was not sure of which nuts exactly), resulting in an itchy mouth and hives on the neck. There was no respiratory distress on either occasion of a reaction and he responded well to oral antihistamines. He had signs of allergic rhinitis (and had previously been found to be sensitised to house dust mite and grass) but no asthma. Incidentally, he had a rare genetic bone dysplasia, sclerosteosis, which had caused skeletal overgrowth in the facial nerve canals, leading to bilateral facial nerve palsies requiring surgical decompression.

During one of the consultations, his mother mentioned that, on several occasions, he had reacted with facial urticaria after biting into apple seeds. He definitely did not react to the pulp/flesh of the apple, and continued to eat apples though carefully avoiding the pips. The same reaction occurred with watermelon seed but not the flesh. The results of the investigations are shown in Table I.

A diagnosis of ongoing peanut allergy was made, as well as allergy to apple seed (but not pulp) and probably watermelon seed (though watermelon was not tested as it was out of season at the time of testing). A challenge to mixed tree nuts (hazelnut, almond and cashew nut) was performed and passed.

**TABLE I**

| FOOD | SKIN-PRICK TEST RESULT | SPECIFIC IgE RESULT |
|---|---|---|
| Peanut | 10 mm | 3.91 kU/ℓ (Ara h 2 0.40 kU/ℓ) |
| Almond | Not performed | 0.92 kU/ℓ |
| Brazil nut | Not performed | 0.34 kU/ℓ |
| Hazelnut | Not performed | 1.73 kU/ℓ |
| Apple pulp | 1 mm (prick to prick test) | |
| Apple seed | 4 mm (prick to prick test) | |
| Negative control | 0 mm | |
| Positive control (histamine) | 3 mm | |

## DISCUSSION

Seeds come in a wide variety of forms, including those which are commonly added to foods (such as sesame or sunflower seeds), the seeds within fruits and vegetables, and other foods less commonly thought of as seeds such as the coffee bean and coconut! This case describes the unusual situation of a reaction to a fruit seed but not the pulp.

The majority of the case reports on fruit-seed allergy describe a citrus-seed allergy in patients with a concomitant nut allergy, most commonly cashew nut but in some cases peanut. The Rutaceae family (e.g. lemon, tangerine, orange) is botanically closely related to the Anacardiaceae family to which cashew belongs, both belonging to the Sapindales order.[1] This goes some way in explaining the frequently observed co-reactivity. In some cases it appears that the fruit seeds need to be cut or crushed before causing symptoms.

## PREVIOUS CASE REPORTS ON FRUIT-SEED ALLERGY

Brandstrom et al described a case series of four children with known cashew nut allergy, who reacted to citrus seeds in the form of lemon juice, lemon seeds, tangerine seeds

and lemon dressing, respectively.[2] One of these patients had an anaphylactic reaction. 11S globulin, 7S globulin and 2S albumin storage proteins were isolated from lemon seeds and described as allergens for the first time. The serologic cross-reactions between homologous proteins from cashew and citrus seeds were established.

A further case report described a patient with co-reactivity to peanut and citrus seed, who had an anaphylactic reaction to lemon soap.[3] Immunoblotting demonstrated complete IgE cross-reactivity among different citrus seed extracts, and partial cross-reactivity between the peanut and orange seed extracts.

A further case report described a six-year-old boy with cashew allergy who chewed and swallowed the seeds while eating a mandarin.[4] He developed a systemic reaction within one hour of ingestion, including periorbital oedema, widespread pruritus, abdominal pain and nausea. The SPT result was positive to mandarin seed and cashew but negative to mandarin juice.

Turner et al described two cases of citrus-seed allergy in children with a known peanut allergy, and also with sensitisation to cashew and pistachio nut.[5] A six-year-old girl experienced a generalised non-anaphylactic reaction to an unknown constituent of a fruit salad and had a positive skin-prick test (SPT) response to orange seed but negative to orange pulp. At a formal in-hospital open food challenge (OFC), she had anaphylaxis (abdominal pain, urticaria, and shortness of breath with oxygen desaturation) after ingestion of a single orange seed. The second child, a five-year-old girl, had anaphylaxis after ingestion of a cut slice of orange but had a negative SPT response to orange pulp and tolerated a full seedless orange at a subsequent OFC. The SPT response was positive to fresh orange seed and mandarin and grapefruit seeds, and she was therefore given a diagnosis of citrus-seed allergy.

Turner also described what appeared to be the first reported case of a reaction to a non-citrus seed.[5] The case was of a 15-month-old child, known to be sensitised to peanut, who presented with anaphylaxis on first exposure to commercially produced apple and oatmeal baby food (containing apple puree, apple juice, oats and cinnamon extract). Within minutes of ingesting two teaspoons, he vomited, became lethargic and had cyanosis with drooling, requiring multiple doses of intramuscular adrenaline. He had previously tolerated home-made apple puree and oats. SPT responses were positive to the ingested baby food (5 mm), apple seed (4 mm), and orange seed (4 mm) and negative to fresh apple, cinnamon and oats. The manufacturer confirmed that the baby food implicated was produced in a factory which did not handle other potential allergens, including nuts, but that apples were not routinely cored during production of apple puree, hence the puree was likely contaminated with crushed apple seed.

A more recent case report by Murad et al described the case of a child who developed two separate episodes of anaphylaxis after eating apple seed (found in apple puree made with whole apples) and grapes, respectively.[6] Evidence from analysis of an ISAC 112 test (Immuno Solid-phase Allergen Chip test, Phadia) suggested that non-specific Lipid Transfer Proteins (LTPs) may have been responsible for these reactions.

## CLINICAL IMPLICATIONS OF FRUIT-SEED ALLERGY

Allergy to fruit seeds is probably under-recognised and should be considered in the work up of fruit allergy, especially if the flesh of the fruit has been previously tolerated. Clinicians should be aware of the possible association between allergy to fruit seeds and nuts, particularly to peanut, cashew and pistachio nut. Fruit seeds should be considered as a potential cause of unexplained anaphylaxis in patients with nut allergy.

The prevalence of co-sensitisation between nuts and fruit seeds and the identification of cross-reactive allergens have both not been fully elucidated, and require further research. However, it seems reasonable to counsel nut-allergic patients to avoid chewing fruit seeds (especially citrus seeds in cashew-allergic patients) and to take care with freshly squeezed juices which may contain crushed seeds.

Certainly the clinician should consider fruit seeds as a possible cause of severe allergic reactions to fruits.

*This article has been peer reviewed.*

DECLARATION OF CONFLICT OF INTEREST
The authors declare no conflict of interests in relation to this publication.

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PID123

Primary Immunodeficiency

# CHRONIC GRANULOMATOUS DISEASE (CGD)

In this article in our series on primary immunodeficiency, Dr Goodheart, a paediatrician, is consulted regarding an interesting referral from the surgeons in her hospital. Brendan, a four-year-old boy, is admitted to the surgical ward presenting with fever and abdominal pain. He has pain and abdominal palpation with guarding and decreased air entry is heard over the right lower lobe of his lungs. He also complains of headaches and is mildly jaundiced but, strangely, he does not appear to be acutely ill.

The surgeon, Dr De Bruin, requests an abdominal ultrasound. Loculated fluid is seen in the right hepatic lobe and in the right lower lung region, with communication through the diaphragm. On laparotomy and thoracotomy, purulent material is drained. The surgeon takes a liver biopsy and requests the histology unit to look for granulomas and acid-fast bacilli, as he suspects tuberculosis (TB). He also sends aspirated material to the microbiology laboratory for culture.

The microbiologist plates the purulent sample and first results indicate a gram-positive organism but no acid-fast bacilli. On the liver biopsy, the pathologists sent a provisional report of evidence for granulomas.

In the meantime, Dr De Bruin also has a chance to review Brendan's history in more detail. Brendan is the only child of a South African-born family living close to the provincial hospital where Dr Goodheart works, but the nearest referral hospital is 50 km away. The family's social circumstances are adequate but they have limited financial resources. Their home has running water, flush-toilet facilities and electricity. The family also has a dog – Stoffel.

Dr De Bruin finds out that the boy had been admitted to the same surgical ward the previous year. At that time, he presented with an abscess of his right foot. *Staphylococcus aureus* had been confirmed on culture. There were also multiple scars from healed abscesses on the skin.

Apart from a history of failing to thrive, Brendan had frequent abscesses and delayed healing of skin sores during early childhood. He was breastfed until six months of age and tolerated all childhood vaccinations well (standard immunisations). He had uncomplicated chickenpox at the age of two years. No excess respiratory infections were reported. Brendan's parents are healthy.

*Brendan with Stoffel before his illness*

The surgeon who treated Brendan the year before thought that this was an unlucky course and instructed the parents on preventing future skin sores and boils with hygiene measures and to have the family's dog checked for sores.

De Bruin is alerted by the history of recurrent abscesses. This prompts him to contact his colleague, paediatrician Dr Goodheart, who has an interest in Immunology. She agrees to take over the patient for investigation.

During the course of the next week, the laboratory confirms a sensitive organism on culture of the liver aspirate *(Streptococcus melleri)*. The microbiologist alerts to the possibility of the spread of *S. melleri* to the brain, but fortunately on CT scan the brain appears normal.

In the meantime, Dr Goodheart finds out more about Brendan's family. One of the maternal uncles died in his teens from recurrent infections. With repeat abscesses confirmed, one of which was deep-seated, and based on the suggestive family history, she suspects a possible X-linked immunodeficiency, likely a neutrophil defect.

She prescribes broad-spectrum anti-bacterial treatment (co-trimoxazole) and antifungal prophylaxis for Brendan, even though the cultures so far are negative for fungi.

Dr Goodheart also initiates a basic immunology screen:

- A full blood count shows an elevated white blood cell count with neutrophilia. An HIV ELISA test is negative. A chest X-ray shows no evidence of tuberculosis or other infiltrates.
- Serum IgG, IgM, IgA, and IgE, as well as total complement, are normal.

Dr Goodheart now consults her friend, Dr Bala, an immunology specialist at the neighbouring tertiary hospital. Dr Bala is worried about chronic granulomatous disease (CGD) and requests a sample to test for neutrophil function/oxidative burst. This test can be performed only in specialised immunology laboratories either by the nitroblue tetrazolium reduction test (NBT) or by the more modern flow-cytometry burst test. The following day, a severely reduced neutrophil burst result is indeed confirmed by flow cytometry. This test needs to be repeated once Brendan has recovered from his acute infection.

*Blood samples are sent to Dr Bala's laboratory*

Dr Bala explains to Dr Goodheart that phagocytic cells of patients with CGD fail to produce hydrogen peroxide (oxidative burst!), but otherwise retain many other types of antimicrobial activity. CGD can be X-linked (via the carrier mother) but there are also forms with autosomal recessive inheritance. Dr Bala advises Dr Goodheart that a diagnosis of CGD seems now most likely.

Brendan recovers from his liver abscess and is discharged, but he will require antibiotic and antifungal prophylaxis for life. His family is educated regarding their child's compliance, that is, taking his medication regularly. They are again reminded about implementing general hygiene measures for Brendan: separate face cloths and towels for family members, washing with antiseptics, hot washing for clothes and bedding, short nails, hair washing with povidone/iodine if there are sores on the scalp. They are also asked to keep an eye on Stoffel for possible skin lesions. Brendan is at high risk for contracting TB and he may not show the typical signs of infection for TB or other illnesses. Therefore he will need to stay under surveillance for this.

Brendan will be evaluated by genetic diagnosis and for bone-marrow transplantation as soon as he has recovered from his acute illness because, unfortunately, with suspected X-linked CGD his long-term prognosis for adult survival is not good.


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PID Article

# MACROPHAGE ACTIVATION SYNDROME

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## SUMMARY

Macrophage activation syndrome (MAS) is an uncommon condition in which hyperinflammation and excessive cytokine release lead to excessive stimulation of T-lymphocytes and macrophages and result in a characteristic clinical picture of haematological dysfunction and multiple organ failure. This condition occurs most commonly in the context of inflammatory conditions such as systemic juvenile idiopathic arthritis (sJIA). MAS is currently classified as one of the forms of secondary haemophagocytic lymphohistiocytosis (HLH).[1] The diagnosis of MAS is clinically important as specific therapy may be required and a missed diagnosis may lead to high mortality. Unfortunately, the diagnosis is often not easily made due to the broad range of presenting features and their overlap with other potential complications of sJIA, such as severe infection. Also, no single clinical or laboratory test is able to diagnose MAS conclusively. In this review we highlight some of the most important clinical and laboratory features, diagnostic criteria, outcomes and management of MAS.

*This article has been peer reviewed.*

## CASE VIGNETTE

### CASE 1

A five-year-old boy with known sJIA since the age of four based on polyarthritis, evanescent rash, splenomegaly, lymphadenopathy and daily fevers. Malignancy, HIV and tuberculosis were excluded at diagnosis. The patient responded well to initial therapy with corticosteroids and non-steroidal anti-inflammatory drugs and methotrexate. The patient returned to a rural area to live with his grandparents and had not been to the clinic for six months. He now presents with continuous fever, bruising, jaundice and encephalopathy as well as hepatosplenomegaly. He still has active arthritis, but his parents report that since the fevers had become more of a feature his arthritis had improved somewhat. His initial laboratory results reveal anaemia (haemoglobin 4.6 g/dl), thrombocytopaenia (platelet count 50 000/ml) and leucopaenia (white cell count 2.4 × $10^3$/ml). Liver function derangement and renal failure are also present. His C-reactive protein (CRP) is 198 mg/L, but his erythrocyte sedimentation rate (ESR) is only 15 mm/hr. International normalised ratio (INR) is 3 and fibrinogen is very low. Because of a suspicion of MAS, a ferritin level of 16 400 ng/ml is detected and serum triglycerides are high. An urgent bone-marrow aspirate reveals abundant haemophagocytic macrophages, confirming the diagnosis of MAS.

## EPIDEMIOLOGY

MAS is seen most frequently in children with sJIA but it is well described in other rheumatic conditions such as SLE, Kawasaki syndrome, juvenile dermatomyositis and antiphospholipid syndrome.[2,3] It has also been described in Adult Onset Still Disease. Episodes of MAS can complicate the course of these diseases during states of high disease activity – for example, flares or at presentation – or may be triggered by viral infections especially CMV and EBV,[4] which are known causes of secondary HLH even in the absence of rheumatic diseases. Tuberculosis has been recognised as a trigger for MAS in countries where this disease is prevalent.[5,6] Infections are the trigger in approximately 39 per cent of cases.[7] Numerous medications, including sulphasalazine, gold and, more recently, some biologic agents, have in the past been implicated as triggers for MAS. It is possible that these therapies, which are now known to have no or limited value in the management of sJIA, have been implicated as bystanders in children with very severe sJIA who develop MAS as part of their sJIA.

## PATHOGENESIS

The principal feature of MAS is an over-expansion and increased activity of macrophages and cytotoxic CD8+ T-cells. These cells infiltrate the bone marrow and other tissues and cause disturbance in their functioning. The normal immune response to an infection involves the recognition by dentritic cells of pathogen-associated molecular patterns (PAMPS) by toll-like receptors (TLRs). This results in an expansion of cytotoxic T-cells and macrophages by the release of pro-inflammatory cytokines such as IL-1, IL-6, IL-18 and TNFalpha. These cytokines stimulate NK cells and cytotoxic CD8+ T-cells to produce INFγ, which in turn drives the activation of more macrophages and sets up a 'cytokine storm' and a vicious cycle of cytokine release and macrophage and T-cell proliferation. The role of the activated cytotoxic cells is to clear infectious cells and to dampen the immune response

by removing dentritic cells and activated macrophages.[8,9] This secondary self-regulatory step is crucial in titrating the activity of the immune system to the right level. Mutations in genes related to Perforin and MUNC13, which are important in mediating the granule-dependent cytotoxic effect of lymphocytes, result in familial HLH, the prototype disease for MAS. This phenomenon demonstrates the importance of this pathway in the pathogenesis of MAS.[10,11] In active rheumatic diseases such as sJIA there is a significant increase of these cytokines as a result of the disease activity of the underlying condition.

## CLINICAL FEATURES

MAS should be suspected in any child with a known rheumatic disease or features of a new diagnosis of a rheumatic disease who presents with cytopenia, liver function abnormalities and coagulopathy. It may complicate sJIA late in the clinical course or be part of the initial presentation. In younger children this makes the diagnosis more complex because HLH and other infectious and haematological causes need to be duly considered. In SJIA the pattern of fever can be an early sign of the development of MAS. In sJIA the fever pattern is very characteristically 'quotidien' – occurring daily. When this fever changes and becomes more persistently elevated, features such as infection or MAS should be considered. Additional features may include persistent rash or signs of CNS involvement such as behavioural changes or drowsiness. Ironically, joint involvement may actually lessen during MAS.

The most comprehensive study evaluating the clinical phenotype of patients with MAS secondary to sJIA described the clinical characteristics of 362 patients from 95 different investigators (which included paediatric rheumatologists and haemato-oncologists) and from 33 countries.[12] The most important clinical features and frequency of occurrence are given in Table I. In this study there were differences in presentation between patients in Europe, North America and other continents, with European patients having fewer CNS manifestations and patients from other continents having lower haemoglobin; but the overall clinical picture was remarkably similar.

## LABORATORY FEATURES

MAS relies on a number of laboratory tests for its diagnosis.

**TABLE I**

| CLINICAL FEATURES OF MAS (%) | |
|---|---|
| Fever | 96% |
| Hepatomegaly | 70% |
| Arthritis | 64% |
| Splenomegaly | 55% |
| Lymphadenopathy | 51% |
| CNS involvement | 34% |
| Haemorrhagic manifestations | 20% |
| Heart, lung or kidney failure | 10% |

Whereas absolute values are used in diagnostic criteria for secondary HLH and MAS, trends in the values of white cell count and platelets are essential when considering a clinical diagnosis of MAS. In a child with longstanding, active sJIA, for instance, platelet and white cell count and ESR can be markedly elevated before the onset of MAS; furthermore, a sudden drop in these values, even if not reaching the values set by diagnostic criteria, can alert the clinician to the onset of MAS and allow for timely intervention.

The relevant laboratory tests and their significance are given in Table II. In general terms, decreasing haemoglobin, leukocytes, platelets, fibrinogen and ESR as well as rising liver enzymes, INR, PTT, Ferritin, D-dimers and triglycerides herald the onset of MAS.[4] A dramatically elevated ferritin – into the thousands (nanograms per litre) – is considered highly suggestive of MAS. This is especially so in the context of sJIA, but it is important to note that a number of other conditions can cause extremely elevated ferritin, including malignancies and chronic blood transfusions.[13] It is also important to note that profound MAS can be present despite the absence of haemophagocytosis on bone marrow.

## DIAGNOSIS AND DIAGNOSTIC CRITERIA

Much has been written about the diagnostic criteria for MAS, especially as it compares to the diagnostic criteria for secondary HLH. It is recognised that the highly inflammatory starting background disease of sJIA, with characteristically very high white cell counts and platelets, as well as relatively elevated ferritin, renders the HLH diagnostic criteria insensitive in this context. New diagnostic guidelines based on international expert consensus of paediatric rheumatologists and haematologists and on real patient data have recently been published. These are compared to the 2004 HLH criteria in Table III. In young children who present with MAS in the absence of a known rheumatic disease, differentiating from secondary HLH can be very challenging, and known HLH mutations have been described in some patients with sJIA. Protein-based and degranulation screening essays may be important in diagnosing children with primary HLH who may need more intensive therapy, including haematopoetic stem-cell transplantation.[10]

## COMPLICATIONS AND OUTCOMES

MAS is associated with serious outcomes. The failure of multiple organ systems leads to death in approximately 8 per cent of patients and to ICU admission in approximately 35 per cent of patients.[12] Hepatomegaly, haemorrhagic manifestations, CNS dysfunction and heart, lung or kidney failure as well as lower levels of ESR, albumin and fibrinogen, and higher levels of AST, lactate dehydrogenase, triglycerides and D-dimer are associated with a more severe course.[4]

**TABLE II**

| LABORATORY TESTS | CHANGES IN MAS |
|---|---|
| Full blood count:<br>• Haemoglobin<br>• White cell count<br>• Platelets | <br>Decreased MAS (anaemia is also a feature of sJIA)<br>Decreased (usually high in sJIA)<br>Decreased (usually very high in active sJIA) |
| Erythrocyte Sedimentation rate (ESR) | Decreases (usually elevated in active sJIA) |
| Liver function tests<br>• Liver enzymes<br>• LDH | <br>Elevated<br>Elevated |
| Clotting<br>• INR and PTT<br>• Fibrinogen<br>• D-dimer | <br>Prolonged<br>Decreased<br>Elevated |
| Ferritin | Elevated (usually extremely elevated in MAS; also high in sJIA) |
| Triglycerides | Elevated |
| Bone marrow | Shows haemophagocytic macrophages, with increased CD163 staining |
| sCD25 and sCD163 | Elevated (not routinely available in most laboratories) |

## TREATMENT

### SUPPORTIVE THERAPY

MAS requires urgent management. Patients may experience the failure of multiple organ systems and these complications have to be managed concurrently with specific therapy for MAS. This may include seizure control, ventilatory support, renal replacement therapy or the provision of blood products. In conditions where MAS has been triggered by infections, these have to be managed appropriately in order for the MAS to be successfully managed and immunosuppressive or immunomodulatory agents to be safely administered.

### SPECIFIC THERAPY

The evidence base for therapy in MAS in rheumatic diseases consists mostly of small case series, and the challenge of building a robust evidence base for therapy remains.[16]

#### Steroids

First-line therapy consists of high doses of corticosteroids. Methylprednisolone and dexamethasone are frequently and effectively used for this indication, usually followed by prolonged weaning using oral corticosteroids. The response to steroids is usually prompt, but steroids are seldom able to be used as monotherapy in the longer term, because their side-effect profile is unacceptable.[12]

#### Cyclosporin A

Usually used in combination therapy with corticosteroids, particularly in MAS, which is not steroid responsive. Cyclosporin inhibits T-cell function and is frequently used early in the course of this condition in order to allow for earlier steroid weaning.[17,18]

**TABLE III**

| 2016 MAS DIAGNOSTIC CRITERIA (RAVELLI ET AL)[14] | 2004 HLH DIAGNOSTIC CRITERIA (HENTER ET AL)[15] |
|---|---|
| A febrile patient with known or suspected sJIA is classified as having MAS if the following criteria are met:<br>• Ferritin >684 ng/ml<br><br>AND any *two* of the following:<br><br>• Platelet count ≤181 × $10^9$/ℓ<br>• AST >48 units/ℓ<br>• Triglycerides >156 mg/dl<br>• Fibrinogen ≤360 mg/dl | The diagnosis HLH can be established if one of either 1 or 2 below is fulfilled:<br>1. A molecular diagnosis consistent with HLH<br>2. Diagnostic criteria for HLH fulfilled (five out of the eight criteria below)<br>A. Initial diagnostic criteria (to be evaluated in all HLH patients)<br>• Fever<br>• Splenomegaly<br>• Cytopenias (affecting 2 of 3 lineages in the peripheral blood):<br>- Hemoglobin <90 g/ℓ (in infants <4 weeks: hemoglobin <100 g/ℓ) Platelets <100 109/ℓ Neutrophils <1.0 109/ℓ<br>• Hypertriglyceridemia and/or hypofibrinogenemia:<br>- Fasting triglycerides 3.0 mmol/ℓ (i.e., 265 mg/dl) Fibrinogen 1.5 g/ℓ<br>- Hemophagocytosis in bone marrow or spleen or lymph nodes<br>- No evidence of malignancy<br>B. New diagnostic criteria<br>• Low or absent NK-cell activity (according to local laboratory reference)<br>• Ferritin 500 µg/ℓ<br>• Soluble CD25 (i.e. soluble IL-2 receptor) 2,400 U/mℓ |

Comments:
MAS criteria:
1. *Laboratory abnormalities should not be otherwise explained by the patient's condition, such as concomitant immune-mediated thrombocytopenia, infectious hepatitis, visceral leishmaniasis or familial hyperlipidaemia.*

HLH criteria:
2. If hemophagocytic activity is not proven at the time of presentation, further search for hemophagocytic activity is encouraged. If the bone marrow specimen is not conclusive, material may be obtained from other organs. Serial marrow aspirates over time may also be helpful.
3. The following findings may provide strong supportive evidence for the diagnosis:
   - spinal fluid pleocytosis (mononuclear cells) and/or elevated spinal fluid protein;
   - histological picture in the liver resembling chronic persistent hepatitis (biopsy).
4. Other abnormal clinical and laboratory findings consistent with the diagnosis are: cerebromeningeal symptoms, lymph node enlargement, jaundice, oedema, and skin rash. Hepatic enzyme abnormalities, hypoproteinaemia, hyponatraemia, VLDL↑, HDL ↓.

### Etoposide

Etoposide is frequently used in primary and secondary forms of HLH and has also been successfully used in refractory cases of MAS. It forms part of the 2004 HLH treatment guidelines from the international histiocyte society.[15] Etoposide is a potent bone-marrow supressing agent and its use may be complicated by severe infection. In addition, it is metabolised by the liver and kidney and caution is required in MAS patients with hepatic or renal impairment.

### IL-1 inhibition

There is growing evidence for the use of Anakinra (IL-1 inhibitor) in the treatment of MAS complicating sJIA.[19] IL-1 (or the activated form, IL-1β) plays a central role in the pathogenesis of sJIA and a majority of patients with this condition respond to treatment with Anakinra. The mechanism by which Anakinra works in MAS is not clear, as IL-1 levels are not high in MAS.

## OTHER THERAPIES

Intravenous immunoglobulin (IVIG) is not infrequently used. In fact, a recent review by Ravelli showed that it was used in nearly one-third of patients with MAS.[12]

Anakinra and IVIG are both considered relatively safe in the face of infection and as such have an advantage over other more immunosuppressive agents.

Many other biological agents, including Tumour Necrosis Factor inhibitors, Interleukin 6 inhibitors and cytotoxic T-cell-associated protein 4 (CTLA4) antagonists have been used anecdotally to treat MAS. But there is not a strong body of evidence to support their routine use. It may be that their primary role is to treat the underlying rheumatic disease and so interrupt the cycle of inflammation.[16]

## CONCLUSION

MAS is a relatively uncommon but life-threatening condition which occurs in children with rheumatic conditions, especially sJIA. There is some overlap between the sJIA, MAS and HLH, and genetic insights are continually increasing our understanding of the differences and similarities in these conditions. Early diagnosis and management of MAS is crucial to improving mortality. Clinicians who look after children and adolescents, especially those patients with rheumatic diseases, should be aware of MAS and the principles of diagnosis and management.

DECLARATION OF CONFLICT OF INTEREST
The authors declare no conflict of interests in relation to this publication.

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# ASCARIS INFECTION AND SENSITISATION IN RURAL AND URBAN XHOSA CHILDREN WITH AND WITHOUT ATOPIC DERMATITIS

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## INTRODUCTION

Helminth infestation has been associated with a reduced risk of allergic disease with hypotheses suggesting that decreasing parasitic infections associated with rising affluence contributes to the increase in immune-mediated diseases including allergies.[1] Moving from association to causality has been difficult, though, as interactions between parasite and host immunology are more complex than previously thought.[2] Interim results from the South African food sensitisation and food allergy (SAFFA)[3] study shows significant differences in allergy prevalence between rural and urban children with atopic dermatitis (AD) (24.4% and 2%, respectively) and challenge-proven food allergy (2.7% vs 0.5%). Rural participants were more likely to be dewormed regularly (74.8% vs 46%). We report on a nested case-control study (SOSALL) in participants with and without AD. The aim is to compare the prevalence of Ascaris infestation and sensitisation in children with and without AD in urban and rural settings.

## METHODS

In this case-control study, 12- to 36-month-old Xhosa case participants were recruited from dermatology clinics of the Red Cross War Memorial Children's Hospital in Cape Town and the Nelson Mandela Academic Hospital in Mthatha. The diagnosis of AD was made using the United Kingdom working-party criteria and the severity of disease assessed using scoring atopic dermatitis (SCORAD). Age-matched control participants were recruited from the urban and rural cohorts of the SAFFA study. These participants had negative skin prick test to seven food allergens and four aeroallergens with no evidence of atopy on history or examination. Stool samples were analysed for presence of worm ova and burden of infestation (Kato Katz examination kit, Vestergaard-Frandsen). Ascaris sensitisation was determined measuring Ascaris-specific IgE (ImmunoCAP, ThermoFisher). Anti-Ascaris IgE levels of >0.35 kU/ℓ were considered positive.

## RESULTS

Two hundred and twenty participants were recruited. Stool and serum samples were available from 158 and 129 participants, respectively – 6.7% urban and 10.5% rural non-atopic controls had KatoKatz positive stools with 5.1% and 9.7%, respectively, positive anti-Ascaris IgE. No urban or rural case participants had Ascaris in their stools – 21.4% urban and 9.7% rural cases had positive anti-Ascaris IgE.

## CONCLUSION

Markedly different Ascaris infestation rates between children with AD and their non-atopic controls were found across the urban-rural divide. Despite no evidence of infestation, both urban and rural case participants with AD had high levels of Ascaris sensitisation. One possibility is that children with AD have an upregulated Th2 response, clearing parasites effectively, whereas low-grade infestation may continue asymptomatically in non-atopic controls. The modulating effects of helminth exposure are complex and these results will direct further investigation including IgG4 and cytokine responses in this cohort.

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# CASE REPORT: ALLERGY TO APPLE SEEDS IN A PEANUT-ALLERGIC CHILD

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## INTRODUCTION

Allergic reactions to fruits are commonly described. The flesh or pulp of the fruit is most commonly the cause of such

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reactions. Less commonly described are allergic reactions to the seeds of fruits. They are reported in a handful of case reports only, but probably under-recognised. This case study describes the unusual situation of a reaction to a fruit seed but not the pulp. Such a reaction to fruit seed may be of broader relevance to children with nut allergy.

## CASE STUDY

We report the case of an eight-year-old boy with a known allergy to peanuts (urticarial and oral itching in response to peanut butter), who experiences an allergic reaction when biting into seeds of both apples and watermelons, but is tolerant of the fruit pulp. The history is that, on several occasions, he had reacted with facial urticaria after biting into apple seeds and watermelon seeds. There was no respiratory difficulty. He definitely did not react to the pulp or flesh of the apple and continued to eat apples though carefully avoiding the pips. The same reaction occurred with watermelon seeds but not with the flesh. Results of a skin-prick test (SPT) were 1 mm to apple's pulp and 4 mm to apple's seed. A diagnosis of allergy to apple seed was made (but not pulp) and probably watermelon seed. He was told to carefully avoid such seeds and to continue with peanut avoidance. A tree-nut challenge with cashew, almond and hazelnut was passed. An allergy to fruit seeds has been described in only a few case reports thus far. The majority of the case reports on fruit-seed allergy describe a citrus-seed allergy in patients with a concomitant nut allergy, most commonly cashew nut but in some cases peanut. Cross-reactivity between citrus seed and cashew nut has been demonstrated, but the prevalence of co-sensitisation between nuts and fruit seeds and the identification of cross-reactive allergens have both not been fully elucidated. Allergy to fruit seeds is probably under-recognised and should be considered in the work up of fruit allergy, especially if the flesh of the fruit has been previously tolerated. Clinicians should be aware of the possible association between allergy to fruit seeds and nuts, particularly to peanut, cashew and pistachio nut. Fruit seeds should also be considered as a potential cause of unexplained anaphylaxis in patients with nut allergy. It seems reasonable to counsel nut-allergic patients to avoid chewing fruit seeds (especially citrus seeds in cashew-allergic patients) and to take care with freshly squeezed juices and some commercial baby food which may contain crushed seeds.

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# URTICARIA MYSTERY CASES – NOT JUST SCRATCHING ON THE SURFACE


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## BACKGROUND

Chronic spontaneous urticaria (CSU) is incompletely understood and challenging to manage.[1,3,7] The cases below illustrate the heterogeneity of associated conditions and highlights the need to look more than just skin deep.

## CASES

Ms XA, a 27-year-old student, presented with severe urticaria and angioedema unresponsive to older antihistamines. There was partial response to prednisone and slow-release ketotifen. Food-allergy tests were negative and *Helicobacter pylori* eradication not helpful. She was successfully managed with fexofenadine and ranitidine, later switched to cetirizine and slowly weaned off other medications. Emotional stress may have been a contributing factor, as the symptoms resolved after graduation.

Mr SM is 59 years old with prolonged history of urticaria and severe facial angioedema. He suspected association with non-steroidal anti-inflammatory drugs, processed meats and sauces. Cellular antigen stimulation (CAST) tests were strongly reactive to sodium nitrate and moderately reactive to sodium benzoate and diclofenac, but negative for aspirin and sulphites. Full blood count (FBC) and erythrocyte sedimentation rate (ESR) was normal. He responded to avoidance advice and second-generation H1 receptor blockers.

Mrs SW, a 34-year-old female with a history of atopy, allergic rhinitis and asthma, presented with urticaria for six weeks. She was thin with increased heart rate, insomnia and prominent thyroid. SPT were negative for foods but positive for inhalant allergens. A clinical diagnosis of hyperthyroidism was confirmed with elevated blood T4 levels, undetectable thyroid stimulating hormone and elevated thyroid antibodies. Carbimazole was prescribed and a scintigraphic nuclear medicine thyroid scan confirmed Graves' disease.

Ms DF is a 42-year-old female with a three-month history of urticaria and angioedema responding partially to fexofenadine and prednisone. She suspected caffeinated beverages and stress to be the triggers. Her personal history included childhood AD and Hodgkin's lymphoma 12 years previously. There was a family history of scleroderma and asthma. On examination she was well with dermatographism, mild eczema and features of allergic rhinitis. SPT was positive for house-dust mites. Haematological, inflammatory, auto-immune and thyroid investigations were requested. Based on her history and markedly elevated ESR and CRP, she was advised to follow up with oncology. Imaging revealed a mass adjacent to the liver, which on laparoscopic biopsy was confirmed to be a recurrence of Hodgkin's lymphoma. She successfully received chemotherapy.

## DISCUSSION

The majority of CSU cases require little investigation and are managed symptomatically.[1,3,7] Thorough clinical evaluation may alert the physician to instances where urticaria is presenting as a symptom of a more serious underlying disorder or an avoidable trigger. Physical factors, emotional stress, food additives[10] and medications are potentially modifiable. Associations exist with thyroid[4,6,9] and auto-immune pathology and, occasionally, with malignancy or haematological conditions.[2,5,8] Food allergy tests are seldom indicated.

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# A CASE OF PARADOXICAL BRONCHOCONSTRICTION DUE TO BENZALKONIUM CHLORIDE


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## INTRODUCTION

Benzalkonium chloride (BAC) is a preservative commonly found in different medications and disinfectants used in clinical practice. Allergic and pseudo-allergic adverse reactions have been reported in both patients and healthcare workers and are supported by data in various studies.

## CASE REPORT

We present a case of a 15-year-old female with well-controlled asthma admitted with a severe asthma exacerbation and treated with 40 mg oral prednisone and three doses of nebulised salbutamol 10 mg and ipratropium bromide 250 mcgs during the first hour of admission. A single dose of 50% magnesium sulphate was administered intravenously as she did not appear to respond to initial treatment and an intensive care unit (ICU) bed was sought for continued management. On arrival in ICU she was commenced on intravenous salbutamol infusion and high-flow oxygen in addition to the continuous salbutamol nebulisation. Despite this she developed confusion and decreased level of consciousness necessitating intubation and mechanical ventilation. While on the ventilator she developed two discrete and severe episodes of worsening bronchospasm lasting about 20 minutes. During the second episode of bronchospasm it was noted that the deterioration occurred during nebulisation with salbutamol and improved once this was stopped. Further investigation revealed that the salbutamol used since admission came from a multidose vial that contained benzalkonium chloride (BAC) as a preservative. A presumptive diagnosis of BAC sensitivity was made. Preservative-free salbutamol (IV solution) was used for subsequent nebulisation resulting in improvement in her bronchoconstriction and she was successfully weaned of the ventilator. Plans for a basophil activation test (BAT) and possible drug provocation challenge have been made to confirm the diagnosis of BAC hypersensitivity.

## DISCUSSION

BAC or N-Alkyl-N-benzyl-N N-dimethyl ammonium chloride is a mixture of quaternary benzyl dimethyl alkyl ammonium chlorides. It is one of many quaternary ammonium chloride compounds (QACs) used as preservatives.[1] Though BAC has been deemed safe since its introduction as a preservative in 1935, it has been implicated in a wide array of hypersensitivity reactions including paradoxical bronchoconstriction, allergic and irritant contact

dermatitis, ciliostasis with reduced transport and, last but not least, anaphylaxis with BAC-containing eye and nasal medications.[2,3,4] The prevalence of paradoxical bronchoconstriction with inhalation of nebulizer solutions is unknown but case reports have been documented and are supported by clinical studies in stable asthmatic patients.[1,5,6,7] A high index of suspicion is required to make an accurate diagnosis and this can be confirmed by skin-prick, basophil-activation tests and drug-provocation challenges.

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# CORRELATION BETWEEN PRO-INFLAMMATORY ALLELES AND CLINICAL AND LABORATORY MARKERS OF ALLERGY IN XHOSA SOUTH AFRICANS


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## INTRODUCTION

Asthma and allergic disease are the result of a complex interaction between genetic predisposition and environmental exposure, although the precise nature of the genetic basis for allergic disease remains to be elucidated. The developed world has yielded several promising candidate polymorphisms involved in the development of asthma and allergies, however, there is a paucity of literature from the developing world, and for people of African origin in particular. It is possible that evolutionary adaptation of inflammatory immune responses may increase the genetic predisposition to allergic disease among people of black African origin. This study aims to provide prevalence data for 27 proposed pro-inflammatory alleles in a group of isiXhosa-speaking adolescents, and to correlate this data with clinical and laboratory markers of allergy.

## METHODS

A convenience sample of 300 Xhosa school children provided phenotypic data via a symptom questionnaire, blood samples for total IgE and IgE to *Ascaris lumbricoides*, SPT to food and aeroallergens, and a methacholine challenge to assess for bronchial hyper-reactivity (BHR). Twenty-seven single nucleotide polymorphisms (SNPs) were genotyped. The results of association modelling between genotypes and clinical and laboratory markers of allergy are presented, along with effect sizes from the best-fitting inheritance model. All results have been corrected for known and suspected confounders.

## RESULTS

From the genes that influence immune tolerance, IL10 592A>C was associated with eczema, as well as positive house-dust mite (HDM) SPTs. IL10 1082A>G was associated with wheeze, rhinitis, BHR, positive HDM SPT, and any positive aeroallergen SPT. The '$T_H2$' polymorphism IL-4 SNP 589C>T was associated with wheeze, eczema, having any positive SPT, having any positive aeroallergen SPT, and having a positive cockroach SPT. In addition, IL-13 SNP 130A>G was associated with rhinitis, eczema, and having any positive food-allergen SPT. The IL4RA polymorphisms 478T>C and 551A>G were associated with wheeze. The STAT6 polymorphism 2964A>G was associated with eczema. Of the 'TH1' polymorphisms, the IL-12 polymorphism 6408delCTCTAAinsGC was associated with wheeze, eczema, and having any positive food-allergen SPT. IFNGR 156T>C was associated with serum IgE levels, and having any positive SPT.

## CONCLUSION

This is the first trial of its kind among the Xhosa population and, indeed, in South Africa. Despite some limitations, we report several associations between SNPs and allergy phenotypes across several different gene classes including those related to the formation of immune tolerance, as well as traditional $T_H1$ and $T_H2$ genes. We would encourage further research in this population to duplicate or refute our findings.

# CASE STUDY: CAN SHELLFISH ALLERGY CAUSE ANAPHYLAXIS IN IODINATED CONTRAST MEDIA?

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## CASE

A 36-year-old lady was referred to the Groote Schuur Hospital (GSH) Allergy clinic following an allergic reaction to iodinated contrast media during attempted coronary angiography. She was atopic with a history of asthma and allergic rhinitis. She suffered with hypertension, type 2 diabetes and dyslipidaemia, with resultant ischaemic cardiomyopathy. Angiography was performed as part of her transplant work-up. Heart disease resulting in significant structural damage to her heart, needing heart replacement. She is obese and has multiple psychosocial stressors. She gave a history of a mild allergic reaction to molluscs but specific IgE were negative. She is due to have a rapid intravenous desensitisation with iomeron given the absolute indication for angiography.

Subsequent to the above patient's case, the allergy service at GSH has received calls concerning patients reporting shellfish allergy receiving iodinated contrast media.

## DISCUSSION

There are misconceptions both regarding the role of iodine in seafood allergy a specific link between shellfish allergy and hypersensitivity reactions to iodinated contrast media. Despite current evidence, many medical doctors still believe that shellfish allergy specifically increases risk of contrast reactions; this alters how patients are treated, ranging from the use of prophylactic corticosteroids or antihistamines to unnecessary avoidance. The majority of shellfish allergy is an IgE-mediated type 1 hypersensitivity to tropomyosin protein and not to iodine. Adverse reactions to contrast media are non-IgE-mediated. Screening for seafood allergy is not indicated for patients undergoing radiocontrast media.

# CLINICAL AUDIT OF SUSPECTED SODIUM BENZOATE-ASSOCIATED ANGIOEDEMA AND/OR URTICARIA

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## INTRODUCTION

Sodium benzoate is a preservative used widely to prevent yeast spoilage of acidic foods. It is ubiquitous across South Africa, found in bottled soft drinks, fruit juices, jams, pickles, condiments and baked goods. The causative link and benefit of benzoate elimination diets for idiopathic angioedema and urticaria remains controversial.

## AIM

An audit elimination diet was evaluated as an effective therapeutic tool in treating angioedema caused by the preservative sodium benzoate.

## METHODOLOGY

A clinical review was conducted of 100 patients with angioedema and/or urticaria in whom a preservative association was suspected and CAST testing to sodium benzoate (and other preservatives) was performed as part of the diagnostic work-up. Pseudo-allergy-causing angioedema and treated with an elimination diet. A sample size of 100 patients was reviewed using an extraction data form which included:

i. demographics;
ii. angioedema history and associated clinical features;
iii. atopy background and other chronic conditions associated with angioedema;
iv. chronic medical history;
v. relevant blood tests and treatment provided.

A questionnaire was administered telephonically, within a year to follow up on the efficacy of elimination diet.

## RESULTS

A total of 100 folders from the years 2013 to 2015 were reviewed: 70% of female and 30% male. The age range was:

- 10% between 11 and 20 years;
- 18% between 21 and 30years;
- 25% between 31 and 40 years;
- 24% between 41 and50 years;
- 13% between 51 and 60 years, and
- 10% above 60 years.

Fifty percent of the patients had associated urticaria, 30% had other associated allergies (asthma, allergic

rhinitis, eczema, food and drug allergies) and 20% had angioedema without other symptoms. All the patients had angioedema at two or more sites, 76% had periorbital and oral and 24% in other body parts. Eighteen percent of patients had associated chronic medical conditions. Forty-six percent of the patients gave a history of diet that consisted of canned food, sauces or drinks. Seventy-four percent of the patients tested positive to sodium benzoate. Seventy-one percent the patients were managed with elimination diets, and follow-up appointments at between two and six months.

## CONCLUSION

Angioedema due to preservatives is increasing in South Africa. Patients with unknown angioedema aetiology need to be investigated for preservatives, especially sodium benzoate for effective management. Antihistamines are prescribed but an elimination diet is the most essential and effective therapy tool.

# DESENSITISATION TO L-ASPARAGINASE FOR CHILDHOOD LEUKAEMIA

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## INTRODUCTION

The prevalence of childhood leukaemia is increasing worldwide and in resource-poor areas of sub-Saharan Africa. L-asparaginase is an important chemotherapeutic agent in the treatment of childhood leukaemia. Allergic hypersensitivity reactions include wheals, angioedema, wheezing, chest tightness, hypotension and anaphylaxis following the administration of L-asparaginase. Although there are newer formulations of asparaginase associated with less adverse reactions, these are not readily affordable and accessible in many resource-poor countries.

## METHODS

Two children with prior severe allergic reactions (anaphylaxis) to L-asparginase were referred to the Allergy Division, Department of Paediatrics and Child Health of Red Cross War Memorial Children's Hospital. They were pre-medicated with H1 and H2 antihistamines, and received L-asparaginase administered using a desensitisation protocol devised by the authors based on modifying a generic drug desensitisation protocol comprising 13 steps of dose increments comprising 1/1 000 000, 3/1 000 000, 1/100 000, 3/100 000, 1/10 000, 3/10 000, 1/1 000, 3/1 000, 1/100, 3/100, 1/10, 3/10 and ½ of the total dose administered. Because these do not add up to exactly 100% of the total dose, modification was made using an Excel spreadsheet to calculate individual doses of 1/1 000 000, 4/1 000 000, 11/1 000 000, 36/1 000 000, 109/1 000 000, 363/1 000 000, 1 080/1 000 000, 3 600/1 000 000, 10 800/1 000 000, 35 000/1 000 000, 104 000/1 000 000, 340 000/1 000 000 and 505 000/1 000 000 of the total cumulative dose.

The protocols were commenced in individual patients with each step lasting 30 minutes for a total duration of 6.5 hours, but with subsequent successful infusions on a single subject, subjects were tried on sequentially faster protocols by increasing the infusion rates of steps to reach a lower duration of time and/or omitting the first 3 to 6 steps of this protocol. This was particularly successful in children on the lower-dose (6 000 U/m$^2$) infusions and for those with short delays between subsequent infusions. Where subjects received 3 × 6 000 U/m$^2$ doses in one week, these were done preferably on subsequent days to allow immunological memory to persist and allow more rapid infusion protocols.

## RESULTS

We performed 34 desensitisation procedures over a seven-month period (from 30 December 2015 to 18 July 2016). One subject had no adverse reactions, the other had five adverse reactions comprising non-allergic side-effects (three), one minor reaction (urticaria) and one major reaction (urticaria, stridor and behaviour change) requiring a single dose of IM adrenaline. The major reaction occurred when the higher dose of asparaginase (15 000/m$^2$) was given via a shorter duration of administration after a two-week period intervening period since the last prior infusion.

## CONCLUSION

With premedication and desensitisation, L-asparaginase can be successfully administered to children with prior severe allergic reactions.

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# REACTIONS TO FOOD ADDITIVES


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## INTRODUCTION

Food additives are substances that are added to food to enhance preservation, palatability and appearance or to alter and stabilise form.[1] Although reactions to food additives are thought to be relatively uncommon, their ubiquitous use and ability to cause a wide spectrum of clinical reactions necessitates their consideration when managing reactions to food.

## CASE

Twelve-year-old TD first developed angioedema, urticaria and a cough two hours after ingesting processed watermelon. During the same month she experienced similar symptoms following the ingestion of tinned tuna mixed with mayonnaise. She recovered spontaneously in both episodes within an hour. TD continued to experience episodes of urticaria and angioedema without systemic symptoms and consulted paediatric outpatients. She was referred to the Red Cross Allergy Clinic where a detailed history revealed that these reactions closely followed the ingestion of certain fruit juices, condiments and cooldrinks. She had previously eaten watermelon and tuna without a reaction. An assessment of a severe hypersensitivity to sodium benzoate was made and the following investigations were performed:

- Specific IgE to watermelon and tuna both <0.1 kU/ℓ.
- CAST for sodium benzoate 23 pg/ml.

She followed a benzoate-free diet and at her review appointment two months later she had had no further reactions, including no further urticaria. TD was provided with an adrenalin auto-injector and action plan, and an application for a Medic Alert bracelet was made.

## DISCUSSION

Interest in adverse reactions to food additives remains an area of public concern. Current literature estimates the prevalence to be between 0.01–2%,[2,3] but may be up to 7% in children with allergies.[4]

The clinical manifestations of a food-additive hypersensitivity range from mild to severe.[5] Natural food additives are more commonly implicated in anaphylactic reactions (annatto, carmine, guar gum and psyllium).[6] Synthetic additives reported to cause anaphylaxis include sulphites and sodium benzoates.[7,8]

Identifying a reaction to a food additive can be difficult and relies on comprehensive history. Explicit questioning enables the revelation of 'hidden ingredients'. A physical examination is required to exclude an underlying medical condition.

No definitive diagnostic test is available and the relevance of skin or specific IgE testing in these patients is to exclude an allergy to the main food components. A cellular activation stimulation test can be useful if positive but lacks specificity to fully exclude clinical reactions if negative.[9] Elimination diets may be useful to strengthen the diagnosis. Oral-food challenge with the additive in question is confirmatory.[10]

Treatment comprises avoidance. Patients require education regarding the common foods where the additive may be found and the nomenclature used in food labelling. In those whom severe reactions are anticipated, a Medic-Alert disc should be provided and an adrenalin auto-injector supplied.

## CONCLUSION

Although uncommon, reactions to food additives incorporate

a wide spectrum of clinical manifestations, which may include anaphylaxis. Awareness of their relevance enables accurate diagnosis through meticulous history taking and the provision of appropriate management, without unnecessary dietary restrictions.

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# HYPER IgE SYNDROME: DECODING NOVEL MUTATIONS IN BLACK AFRICANS


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## BACKGROUND

Hyper IgE Syndrome (HIES) is a rare primary immunodeficiency first described in 1966 as 'Job's syndrome' and characterised by the triad of eosinophilia, eczematous dermatitis, and recurrent skin and pulmonary infections. In 1972, Buckley et al identified elevations in IgE.[1] Autosomal dominant HIES is now recognised as a multi-system disorder including abnormal healing of pneumonias leading to pneumatoceles and bronchiectasis, scoliosis, retained primary teeth, minimal trauma fractures, hyperextensibility, and characteristic facies with high palate and broad nose. Dominant-negative mutations in the signal transducer and activator of transcription 3 (STAT3) gene account for the vast majority of HIES cases and have been found in diverse ethnic groups. However, the pathogenesis of many of the varied clinical features of HIES remains poorly understood. The role of genetic involvement in the pathophysiology of HIES is historical. However, the emergence of patients from different ethnic backgrounds not displaying the classical mutations has become more prevalent in recent times.

## INTRODUCTION

We present the case of a nine-year-old girl with convincing objective features of the syndrome, despite negative yield on genetic studies to commonly described mutations. Miss LN is a well-known patient at the Division of Allergy at the Red Cross War Memorial Children's Hospital in Cape Town. She is of black ethnic origin and presents with no significant family history.

Our patient tested negative to the commonly associated STAT3, DOCK (dedicator of factor 8) and TYK2 (tyrosine kinase 2) mutations, which are identified as major culprits in the white Caucasian population.

Many European studies have demonstrated different variants in the STAT3 gene. The fascination in this case is the fact that we have an overlap of clinical symptoms, between the AR (autosomal recessive) and AD (autosomal dominant) groups. Studies in Asia have demonstrated similar results, suggesting ethnic differences in the HIES genotype.[2] One study conducted in Europe, investigating recurrent and novel mutations among a cross-ethnic cohort found novel mutations in the STAT3 gene.[3] There are no studies looking at this disease in children of black ethnic origin in Africa. Currently, we have two patients within the South African Allergy Service presenting with this phenotype.

We performed genetic sequencing on her to identify the anatomical defect in her genetic make-up in order to lead the way in diagnosing this syndrome in our own population. The results are still pending.

Early diagnosis is imperative to initiate appropriate therapy, which would invariably improve outcomes by aiding in sourcing curative modalities such as stem-cell transplants in a particular population.

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# SOCIO-ECONOMIC STATUS AND THE PREVALENCE OF FOOD SENSITISATION AND FOOD ALLERGY IN URBAN CAPE TOWN CHILDREN

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## INTRODUCTION

Health outcomes are known to be influenced by socio-economic status (SES); however, data to explore the relationship between SES and food sensitisation (FS) or food allergy (FA) in children is limited. The objective was to describe the prevalence and explore the associations of FS and FA to SES – measured using household size, parental education, household income and employment status – in urban Cape Town children.

## METHODS

The prevalence of FS and FA was assessed in the South African Food Sensitisation and Food Allergy study 2012 in 739 of 764 eligible one- to three-year-old children (96.7% participation rate) attending randomly selected crèches in the Cape Town metropole. Skin-prick tests (SPT) were used to examine seven commonly allergenic foods (egg, milk, peanut, wheat, soy, fish and hazelnut) and food allergy was confirmed by an open food challenge. Associations between SES and FS/FA were assessed using the Z-test, Chi-square/Fisher's exact and Wilcoxon Ranksum tests.

## RESULTS

In a group of 739 participants, 91 were sensitised at any degree of reactivity to one or more foods and 648 were sensitised negative for all foods (87.7%). FS prevalence at SPT≥1 mm to any food was 12.3%, at SPT≥3 mm 9.6% and at SPT≥7 mm 4.5%. Challenge-proven IgE-mediated FA was 2.4%.

A statistically significantly higher prevalence of FS was seen in children with employed (or student) parents rather than unemployed parents (none unemployed 13.5%, one unemployed 8.2%, both unemployed 0%; p = 0.03). Parents of children with sensitisation had a significantly higher total monthly household income. The disparity in household income in those with and without sensitisation increased, with increasing cut-off levels of sensitisation from R2 000/month at SPT≥1 mm to any food (p = 0.06), to R3 500/month at SPT≥3 mm (p = 0.02) and R6 000/month at SPT≥7 mm (p = 0.02).

A higher prevalence of sensitisation was apparent in children with parents who attained tertiary education compared to those whose parents had attained primary/secondary education; however, these results did not achieve statistical significance.

Total cumulative skin tests did not show any significant associations with any SES measure. Differences in FA patterns were evident but low numbers preclude meaningful assessment of significance. Household size showed no association with FS and FA. No significant differences in sensitisation patterns were noted between ethnic groups.

## CONCLUSION

Certain markers of SES are associated with food sensitisation in young children in Cape Town. Enlargement of the cohort may allow the effect of SES on food allergy to be assessed.

# FACTORS HAVING AN IMPACT ON ASTHMA CONTROL IN CHILDREN IN A LOW- TO MEDIUM INCOME COUNTRY STUDY: A RETROSPECTIVE STUDY

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## BACKGROUND

Asthma is a well-known and well-researched condition, but few studies of the factors that have an impact on asthma are done in low- and middle-income countries (LMIC).

## OBJECTIVES

First, to assess asthma control and the evolution of asthma control over time in asthmatic children in an LMIC setting. Secondly, to explore whether demographics, type of asthma medication, co-morbidities or exacerbations had an impact on asthma control.

## METHODS

A retrospective study of asthmatic children of 6 to 18 years of age was undertaken between 2005 and 2010. We collected clinical and demographic data and used the Global Initiative for Asthma (GINA) criteria to assess the level of asthma control. The proportions of children with well-controlled, partially controlled and uncontrolled asthma were calculated. Associations between different time points for lung functions were investigated using Pearson correlation coefficients. Mixed-effect regression analysis was used to investigate the effect of demographics, medication, co-morbidity and exacerbations on lung functions.

## RESULTS

A total of 189 children with a mean age of 7.9 years (62% males) were enrolled. Using GINA criteria, well-controlled asthma was achieved in 44.9% of the children. The choice of add-on therapy with doubling dose ICS, long-acting beta agonist or leukotriene receptor antagonists did not affect the lung function tests, all $p>0.05$. On mixed-model analysis, there was a correlation between the duration of asthma treatment and FEV1% predicted; $p<0.05$. Exacerbations and uncontrolled asthma had a negative impact on $FEV_1$% predicted; $p<0.05$. Spirometry guided therapeutic decisions in only 21% of cases.

## CONCLUSION

Asthma control was not achieved in the majority of children. The choice of step-up therapy did not influence the levels of asthma control or lung functions.

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# SENSITISATION PROFILES OF WORKERS TESTED WITH BAKERY FLOUR ALLERGENS


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## INTRODUCTION

Allergic respiratory disease has been reported in workers exposed to flour allergens.[1] Common flour exposures found in bakeries and milling companies include soya bean, wheat, rye, rice, maize (corn) and oats. The aim of this study was to determine the sensitisation profiles of workers tested with the six bakery flours and ten common inhalant allergens using a skin-prick test (SPT) at the National Institute for Occupational Health (NIOH).

## METHODS

Sensitisation profiles to commercial flours and common inhalant allergens were determined among 129 bakery and milling workers seen at the NIOH clinic with respiratory tract symptoms between 2002 and June 2016 using SPT. Atopy was defined as three or more positive common inhalants. Statistical analysis was performed using Stata 11 computer software (StataCorp, Tx, United States). Frequencies were calculated for sensitisation to different allergens. Pearson chi2 was used to compare sensitisation to flour allergens between atopic and non-atopic workers.

## RESULTS

Among this population, two-thirds (67.7%) were males with an average age of 39.9 (±9) years and one-third (34.8%) of them were atopic. The common determinants for atopy was house-dust mite (*D. pteronyssinus*) at 37.8%, Bermuda grass (29.9%), corn pollen (25.5%) and grass mix (24.1%). Forty-two (42.5%) of the workers tested were sensitised to one or more bakery flour allergens. The flour allergens that most workers were sensitised to were rye (44.1%), followed by wheat (28.1%), corn pollen (24.7%) and rice (24.1%). Sixteen (16.5%) of the workers were sensitised to oats and 14.0% to soya bean flours. Sensitisation was significantly associated with atopic status for all the allergens tested ($p<0.05$).

## CONCLUSION

Approximately 42% of workers in the bakery and milling companies demonstrated sensitisation to flour allergens. It is therefore important to control exposure in the workplace to reduce the prevalence of sensitisation.[2] More atopic workers were sensitised to flour allergens compared to non-atopic individuals.

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## COMPONENT RESOLVED DIAGNOSTICS AND PEANUT ALLERGY

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### INTRODUCTION

Genuine peanut allergy has the potential to cause life threatening anaphylaxis in patients following ingestion. It is important to determine whether a patient with IgE antibodies to peanut extract is allergic or sensitised but tolerant. This ongoing pilot study used component resolved diagnostics (CRD) to determine:

- true peanut allergy;
- potential severity of the reaction;
- cross reactivity.

### METHODS

The ImmunoCAP 250 (ThermoFisher Scientific, Uppsala, Sweden) was used to identify patients with IgE antibodies to the peanut extract. Results were expressed in kU/ℓ of antigen-specific IgE antibodies. The measuring range is 0.10 to 100 kU/ℓ. Results >0.35 kU/ℓ were considered positive. Twenty-four patients sensitised to peanut were further tested against various peanut components. These components included the storage proteins Ara h1, Ara h2 and Ara h3 which indicate primary peanut allergy are associated with increased risk for systemic and more severe reaction; Ara h8, a marker of cross-reactivity in patients with combined birch pollen and peanut allergy; the stable lipid-transfer protein Ara h9 associated with systemic and more severe reactions, as well as Oral Allergy Syndrome; and the cross-reactive carbohydrate determinant (CCD), o214.

### RESULTS

The mean age of patients was 7.65 years and the majority were male (67%). The level of IgE antibodies to peanut extract ranged from 0.60 to ≥100 kU/ℓ with a mean of 33.21 kU/ℓ. Eighty-eight percent of patients were positive for Ara h2. Three patients were negative for antibodies to Ara h2, two of whom are clearly sensitised to peanut extract but tolerant. Seventy-one percent of patients were positive to Ara h2 and at least one or more of the other storage proteins. Four patients were positive to Ara h8, but these levels were low. In addition, these patients were positive to three or more storage proteins. Reactions in these Ara h8 positive patients may vary from mild to severe. In ten patients, antibodies to CCD were detected, however, levels were low. One patient is clearly cross reactive; however, eight of these patients had antibodies to storage proteins which indicates primary peanut allergy.

### CONCLUSION

From these results, patients at risk of anaphylaxis can be identified. While oral food challenge (OFC) is considered the gold standard for determination of peanut allergy, it is clear from the data that some patients are extremely allergic and the OFC would be too dangerous to perform. Our laboratory routinely performs a test for antibodies to the storage protein Ara h2 on all patients sensitised to peanut extract. In some patients potentially at risk for anaphylaxis, it may be useful to measure antibodies to additional components so that a more informed decision can be made prior to OFC.

## DE-LABELLING PENICILLIN ALLERGIC PATIENTS: A TOOL FOR ANTIBIOTIC STEWARDSHIP

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### BACKGROUND

Allergic reactions to beta-lactam antibiotics are the most common reported antibiotic allergies, with up to 20% of patients admitted to hospital carrying a penicillin allergy label. However, diagnosis is often based on a vague recollection of childhood reactions; in fact, only 1 out of 20 patients reporting penicillin allergy have proven IgE-mediated hypersensitivity necessitating penicillin avoidance. The public and individual health impacts of using alternative non-beta lactam antibiotics are significant and include: cost, prolonged hospital stay, recurrent infections and other adverse drug reactions.

### AIM

To raise awareness among allergists of the impact of incorrect penicillin allergy labelling and to provide simple and effective strategies for de-labelling patients with possible penicillin allergy.

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## METHODS

Two case studies previously diagnosed and labelled with penicillin allergy recently seen at the ADCRU UCT Lung Institute are presented. These patients were re-evaluated using different strategies from international and local guidelines for de-labelling of penicillin. Patients were administered skin-prick and intradermal tests and test dosing or challenge in conjunction with history taking. Patients underwent skin-prick and intradermal testing (1:10) with Benzylpenicilloyl (PPL) and minor determinant mix (MDM) preparations. If negative, patients were given a drug challenge with either 500 mg Moxypen or Amoxycilin.

## RESULTS

SPT and intradermal tests were negative in both cases with no reactions observed with the challenge. In one case specific IgE and CAST ELISA were also negative. Other international guidelines are now available to advise on empiric antibiotic decisions with preferred beta-lactam antibiotics in situations where allergy testing is not routinely available.

## CONCLUSION

There is a critical need for simple and effective strategies for de-labelling of penicillin allergic patients to avoid the significant impact of costly alternative medications and/or subsequent hospitalisation.

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# THE UTILISATION OF COMPONENT-RESOLVED DIAGNOSTICS IN EGG AND MILK ALLERGY

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## INTRODUCTION

The gold standard for egg and milk allergy is the oral food challenge (OFC). The dominant allergen in egg is the component ovomucoid (Gal d1). This component is highly allergenic in minute amounts and very stable to heat. High levels of IgE antibodies to ovomucoid are associated with persistent egg allergy. In contrast, the lower the antibodies to ovomucoid, the greater the probability of tolerance to cooked egg. The crucial component of cow's milk is casein (Bos d8), which is heat stable and a major milk allergen. Antibodies to casein are associated with reactions to all forms of milk. In addition, high IgE antibody levels to casein may be associated with persistent milk allergy. The aim of this study was to determine how many patients allergic to egg white and/or cow's milk extract were also allergic to the components ovomucoid and casein, respectively. In addition, the level of these component antibodies could be used to determine whether baked egg or milk could be tolerated. High levels of casein antibody would indicate a risk to all forms of milk.

## METHODS

This was a retrospective study on serum samples submitted to the Clinical Immunology Laboratory and positive for milk and/or egg white antibodies. Patients ≤ 12 years of age were considered as children. The ImmunoCAP 250 analyser (ThermoFisher Scientific, Uppsala, Sweden) was used to identify patients with relevant antibodies, as discussed above. Results were expressed in kU/ℓ of antigen-specific IgE and results >0.35 kU/ℓ were considered positive. The measuring range for this assay is 0.10 to ≥100 kU/ℓ. Patients positive to egg white (extract) were tested for sensitisation to the component ovomucoid. Patients positive to milk (extract) were further tested against the component casein.

## RESULTS

Seventy-five percent of children tested were sensitised to egg white; 85% of whom demonstrated antibodies to ovomucoid. Fifty-seven percent of children investigated, displayed antibodies to cow's milk; 79% of these patients were also positive for casein antibodies. The majority of children evaluated for allergy to egg-white extract, also showed sensitivity to ovomucoid. This contrasts with adults, where only 19% were sensitive to both egg white and ovomucoid. A similar trend was noted for milk sensitivity in children and adults; where 35% of adults tested displayed antibodies to milk.

## CONCLUSION

It is prudent to test children for both extracts and components, when assessing allergy to egg and milk, as clinicians are better able to make informed decisions regarding complete dietary avoidance of milk and egg or whether baked products may be tolerated. In addition, these results would indicate whether OFC could be undertaken, as OFC is associated with a risk of anaphylaxis.

# ANALYSIS OF PATTERNS AND COSTS OF ALLERGY TESTING AFTER IMPLEMENTATION OF A CONSENSUS APPROACH FOR AEROALLERGEN TESTING

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## BACKGROUND

Allergic conditions may range in severity and frequency and are common reasons for patients presenting to health care providers. Careful history taking is essential for the diagnosis of allergy to identify specific triggers in the patients' environment or diet. Laboratory tests measure sensitisation and are useful for screening out allergic conditions, if there is uncertainty about the allergens involved and to assess the potential severity of an allergic reaction. A rational approach to allergy testing was adopted after a consultative process with clinicians and laboratories in 2014. This study assesses the costs and patterns of allergy testing at a large private laboratory after the implementation of this consensus approach.

## METHODS

The diagnostic algorithm change to the consensus occurred at Lancet laboratories on 20 January 2015. Data regarding allergy tests (specific IgE screens Phadiatop and FX5, specific allergens and components) from 1 April 2015 to 30 April 2016 were examined. Trends according to which tests were ordered, health practitioner, breakdowns, component and SA tree testing were analysed.

## RESULTS

Over this period 101 125 allergy tests were submitted to Lancet, 23.9% were total IgE requests 23.1% Phadiatop, 24.1% FX5 and 28.9% the ALLSA/NPG/SAARWG (ANS) panel. Testing was mainly from general practitioners (41.6%) and paediatricians (33.1%) with ear, nose and throat (ENT) specialists contributing to 6.4% of the requests and allied medical practitioners only 0.3%. Most pooled FX5 testing was done in >20 year olds (41%) compared to 16 and 18% in the 0–1 and 1–4 years groups respectively. 1.4% were tested for the SA tree mix, of which 16% were positive. Grass cross-reactions were common and identified in 7.2% of individuals who had FX5 and Phadiatop breakdowns.

## CONCLUSION

The ANS panel has been implemented successfully and provides a logical and streamlined approach to allergy testing. Pooled screening tests are useful if there is a low chance that a patient has allergies but may deplete funding to allow further investigation. FX5 is not an appropriate screen for food allergies in adults but is used for this reason. Recommendations are needed for adult food testing and the use of risk indicators such as component testing. Cross-reactive reactions of grass-allergic individuals to wheat/soya/peanut are relatively common.

# THREE CASE REPORTS OF OCCUPATIONAL CONTACT URTICARIA

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## INTRODUCTION

In occupational contact urticaria (OCU), continued contact with the offending allergen can result in anaphylactic reactions or even death. It is important to establish whether the urticaria is caused by an allergen in the workplace.[1] A total of 524 cases were referred to the National Institute of Occupational Health (NIOH) dermatology clinic from September 2005 to June 2016. Twenty six cases (7.7%, 26/339) of OCU, either generalised or localised to the site of contact were diagnosed.

Three cases of OCU with a delayed response are presented. The investigations and management of each case are described.

## CASE I

A maintenance fitter, who had worked with cooling oils for 10 years, developed generalised urticaria. He was patch tested with diluted samples of cooling oil from the workplace. After six hours he developed wheals at the site of contact.

## CASE II

A line supervisor working at an international cosmetic company developed urticaria at the site of contact with spilt cream and developed bronchospasms, requiring hospital admission. Skin-prick tests with the individual components of the cream were conducted in a hospital setting. Although no response was noted at the site of the skin-prick tests, she became distressed and breathless with rhonchi and a hoarse voice. After four hours she developed a large wheal at the site of the perfume component.

## CASE III

A student baker at a biscuit factory developed urticarial wheals on her hands and arms. Skin-prick testing was done using a wheat allergen and three dilutions of a raising agent used in the factory. There was no reaction within one hour of skin-prick testing, however she developed wheal-like reactions at the site of the rising agent pricks five hours later.

## DISCUSSION

The diagnosis of OCU was proven in all three cases by testing with the suspected allergen from the workplace. All three cases demonstrated delayed reactions to the causative allergen. Although delayed reactions are well documented in the literature, its significance is questioned as it may be considered non-specific.[2,3] The reactions experienced by the above cases are indicative of workplace exposure. In all cases the urticaria resolved once they were removed from their respective sites of workplace exposure. Occupational practitioners should be aware of the possibility of delayed reactions in cases of urticaria and not dismiss tests as negative if there is no reaction within the recognised time limit of 60 minutes.

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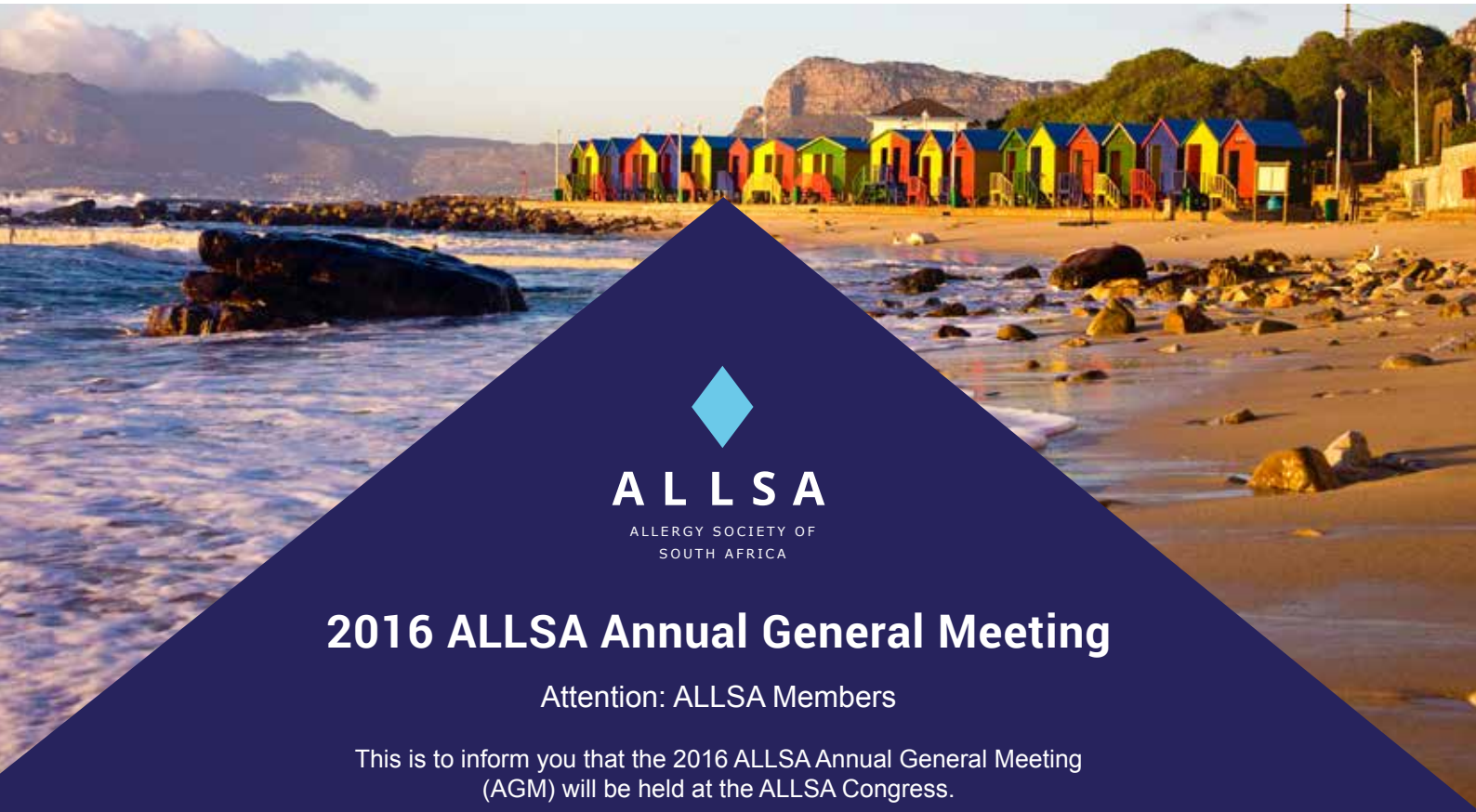

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# 2016 ALLSA Annual General Meeting

Attention: ALLSA Members

This is to inform you that the 2016 ALLSA Annual General Meeting (AGM) will be held at the ALLSA Congress.

**DETAILS OF THE AGM ARE INCLUDED BELOW:**

**DATE |** Saturday, 17 September 2016
**TIME |** 13:30-14:30
**VENUE |** Hall C, Century City Convention Centre, Cape Town

1. Welcome | Dr Di Hawarden
2. Minutes of previous meeting
3. Chairman's report | Dr Di Hawarden
4. Treasurer's report | Dr Sarah Karabus
5. Portfolio reports
6. General

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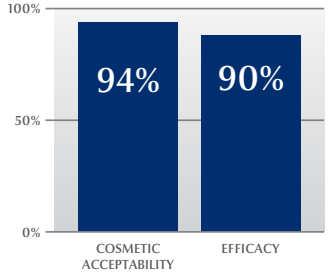


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