## Allergy Today

Allergy UK's publication for healthcare professionals

Spring/Summer 2019

AllergyUK

Allergy News • Allergic Rhinitis • The Walk to School • Perioperative Anaphylaxis Drug Allergy • Allergic Eye Disease • Allergy Testing

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Allergy UK is the operational name of the British Allergy Foundation. We are the leading national charity for people living with allergic disease, providing advice and support on all types of allergy. Allergy UK acts as the 'voice' of the millions of people who live with allergic disease, representing the views and healthcare needs of those affected by this multi-organ disease.

Our vision is for everyone affected by allergy to receive the best possible care and support and we work with healthcare professionals, health organisations and government towards our mission to raise the profile of allergy at all levels. 05

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Allergy UK is the leading national charity providing support, advice and information for those living with allergic disease. www.allergyuk.org

## Foreword





#### Welcome to this edition of Allergy Today. I hope you will find it interesting and useful.

In the last edition of this magazine I talked about food allergy as probably the most high profile allergic condition. Since then this condition has hit the headlines for the most tragic of reasons – the deaths of young people who lost their lives because they unknowingly ate something to which they were seriously allergic. These tragic events have put allergic disease higher up the news agenda than it has ever been and government and service industries have taken notice, in a way they have never done before.

Now DEFRA, with the FSA, is working on ways to improve the allergen information on PPDS (foods that are packed for direct sale), restaurant chains are reviewing how they serve and support people living with food allergy and the Civil Aviation Authority is exploring ways in which UK airlines can provide improved support and better consistency in their protocols for food allergic passengers. At the same time, the FSA is a key stakeholder in the Codex international initiative to improve allergen management from farm to fork. All of this will hopefully be good news for people living with food allergy and the healthcare professionals who treat them, but there is no doubt that the way forward will be complex and challenging. We are already seeing food outlets discouraging food allergic customers because they do not feel confident to provide the advice and information they need and, understandably, are reluctant to take a risk on their, or their customers' behalf. This does not feel like progress.

Patient charities such as Allergy UK are in a unique position to engage with these important initiatives to represent those people who live with anxiety and fear because of their food allergy, never sure if, or when, a serious reaction might occur. We know that people with food allergies are careful about the foods they eat and take responsibility to read labels carefully, ask questions and check and double check. What they ask for is clearly presented and accurate labelling information, clarity around statements such as 'may contain', clear menu information so that they can make safe, accurately informed, choices and better recognition and understanding of their condition.

Food allergy is a major public health issue in developing countries and there is a clear need for change in the way allergen information is disseminated to the people who need it. Let us make every effort to ensure, through our active engagement, that we make the most out of the current initiatives in government and in the service industries, to instigate the changes and innovations that people with food allergies, and their families, need to help improve their lives.

# Welcome

This latest edition of Allergy Today coincides with our 2019 Spring Allergy Awareness Week. Our focus this Week is outdoor air quality – a topic which is on the government agenda, with the Draft Clean Air Quality consultation published last year. With air quality the fourth greatest threat to public health after cancer, heart disease and obesity this is a vital issue for human health. Poor air quality can have a significant impact on allergic conditions and during this Allergy Awareness Week we will be providing information on our website and through on and offline media on how people living with allergic disease can help reduce their exposure to air pollutants and allergens. We have added a new free Factsheet to our website called Outdoor Air Quality – why it matters. This is one more in our series of downloadable Factsheets on a wide range of allergic conditions and practical advice.

With air quality a campaign focus for us this year, we will continue our work with experts and influencers to support initiatives to improve the quality of the air we breathe, on behalf of our allergic community. Later this year we will move the focus onto the impact of poor indoor air quality on people with allergy.

In this Allergy Today we cover a broad range of topics, including allergic eye disease which can be a painful and serious condition. There are also topical features on pollen, pollution and paediatric health and on allergic rhinitis. The results of a national audit by the Royal College of Anaesthetists on perioperative anaphylaxis are explored, with the outcomes and the lessons learnt from these life threatening reactions, and the presentation of drug allergy in primary care is also featured. All Allergy Today articles are written by experts in their fields, providing information and guidance which we hope will be useful in your day to day practice.

We do hope you enjoy reading this issue.



Carla Jones, CEO

Amena Warner, Head of Clinical Services

## Allergy News

#### Food for Thought

In February, staff from food outlets in Bexley, Kent attended an allergen training course developed by Allergy UK and delivered by the borough's food safety team. This session was part of a pilot scheme in which Allergy UK is working with local councils to ensure that all food businesses within their local authority understand the importance of food allergen management. The training also provides a platform to introduce the Allergy Awareness Scheme, a scheme developed by Allergy UK for food outlets which recognises food businesses which have gone above and beyond the basic requirements of the law to train their staff to safely and competently cater for people affected by food allergy.

#### SAAG

This spring will see the launch of SAAG (the School Allergy Action Group) programme as a user-friendly free downloadable toolkit accessible through the Allergy UK website. This seven stage programme takes secondary schools through a process to develop their own Whole School Allergy Awareness and Practical Management Policy, involving representatives from all aspects of a school's operations.



The toolkit and supporting resources reflect EAACI (European Academy of Allergy and Clinical Immunology) guidance on managing patients with food allergies, UK Department for Education guidance on supporting pupils with medical conditions at school and EU legislation for food labelling.

#### Aviation 2050

At the end of 2018 the Department for Transport published Aviation 2050, a consultation paper for a new aviation strategy. The consultation paper recognises the additional stress and anxiety allergy sufferers may experience when travelling by air and it includes a proposal to provide consistent standards for people living with allergy to make sure that they know what to expect when they fly. Stakeholders including patient organisations, allergy specialists, airlines and passengers attended a roundtable in February to discuss the issues and exchange views around the needs of food allergic passengers and ways in which to instil confidence from booking to disembarking.

EFA

The European Federation of Allergy and Airways Diseases Patients' Association has re-appointed Allergy UK CEO Carla Jones as Secretary of the Board for 2019. 30% of the population of Europe has allergies, asthma or COPD and EFA's mission is to be the voice of people in Europe who live with these conditions, to help them access the best quality care, participate in their own care and live in a safe environment.

#### **RHINA 2019**

The inaugural of the 1st European Rhinallergy Meeting (RHINA) took place in Eastbourne from 21-23 March 2019.

RHINA is an interactive interdisciplinary EAACI Focused Meeting and the programme was designed to facilitate clinical, scientific and bench-to-bedside discussions by clinicians, scientists and industry colleagues. This focus meeting is aimed at encouraging scientific collaborations and facilitating the translation of emerging discoveries in Ear, Nose and Throat (ENT), Allergen Immunotherapy (AIT) and biologicals in upper respiratory disciplines into clinical practice to benefit patients.

RHINA 2019 brought together clinicians and scientists (faculty and industry-based), with a broad range of experience from junior scientists/medical doctors to

key opinion leaders, at a focused meeting dedicated to all aspects of upper, lower airway and ocular diseases. Speakers and participants from all over the world attended the meeting to share their knowledge and expertise and take part in an interactive interdisciplinary dialogue. Amena Warner, Head of Clinical Services at Allergy UK, attended this inaugural meeting acknowledging "this wonderful opportunity to learn about the latest research and findings around the topic of rhinitis".

## **FEATURE:**

#### THE WALK TO SCHOOL: Pollen, Pollution and Paediatric Health

Jackie Herald MA is an award winning garden designer specialising in children's and family gardens. She is also a freelance writer on landscape design and ecology. Shenagh Hume RN specialises in asthma and allergy, latterly at Guy's Hospital. She has spent many years treating and desensitising patients with severe allergy to tree and grass pollens. Now Shenagh works as a garden designer specialising in low pollen planting designs.

Collaborating as Herald & Hume, Jackie and Shenagh offer consultancy and design services to individuals and institutions, with a particular focus on preventative approaches to health by choosing the right plants for the right person in the right place.

One of the first signs of spring: pretty catkins trembling in the trees above, ready to cast pollen into the warming air. Walking to school, on the pavement children notice fallen catkins and yellow smudges of pollen. What tree has it come from? Is the pollen cast onto their clothes and hair too? Perhaps a sniffle develops when they get back home – and their parents' first thoughts: not that winter cold again!

Which types of allergenic tree pollen are particularly problematic for sensitised individuals? What is the link between pollen, allergic rhinitis (AR) and asthma? Who is most vulnerable to air borne pollen and other particulates in the highly polluted air of our towns and cities? How can we stem the trend of increased instances of AR and asthma?



Evidence to answer these questions – and more – was presented in Allergy UK's poster entitled **THE WALK TO SCHOOL: tree planting, air quality, global warming and their exponential impact on allergic rhinitis (AR) and asthma**, presented in the paediatric health category at BSACI's conference in September 2017. The poster is downloadable from **www.allergyuk.org**, HCP zone.

The poster's objective has been to raise awareness of how and why planting allergenic species of trees in urban areas may increase allergy and asthma in children by exposure to higher levels of allergenic pollen. The focus is on birch – a so-called "Tree of Life"



- as it is one of the most popular, and allergenic, trees currently planted in streets, school playgrounds and urban gardens around the UK.

#### The Walk to School – background

Allergy clinics across the NHS spend millions every year desensitising patients with severe allergies to tree and grass pollen. The UK has the third highest rate of AR, and the highest rate of asthma in the world<sup>(1)</sup>. The pollen of birch (Betula spp), alder (Alnus spp), and hazel (Corylus spp) trees is used in combination pollen immunotherapy (IT) treatments because they are considered to be the most allergenic triggers of late winter and springtime AR. Co-authors of the poster Amena Warner RN, Head of Clinical Services at Allergy UK and Shenagh Hume RN, know this from many years'



professional experience managing IT clinics at Epsom & St Helier University NHS Trust and Guys' and at St Thomas's Hospital NHS Foundation Trust respectively. In a lightbulb moment it struck Shenagh that mass planting silver birch in order to mitigate air pollution, especially in areas of heavy traffic, may actually increase current levels of particulate matter in the urban air, and thus escalate the instances of birch pollen allergy. A few years ago there was no research available to confirm this theory, although clinical experience and the anecdotal evidence of people with pollen allergies and asthma would suggest that a field study might yield significant results. And so Shenagh embarked on a detailed international literature search for clinical and environmental data and was soon collaborating with Jackie Herald MA, garden and landscape designer, on

healthy planting schemes and associated publications. Along the way, Shenagh and Jackie were in close dialogue with Amena and her colleagues at Allergy UK. They co-wrote a new edition of the **Pollens and Moulds in the Garden** fact sheet **(see www.allergyuk.org)** and the article 'Pollen: Friend or Foe?' <sup>(2)</sup>.

#### Know your trees

Ignorance is not bliss! When discussing the pollen problem with clinical and horticultural colleagues, tree suppliers and clean air campaigners, the poster authors regularly faced a barrier of scepticism and requests for more solid evidence. When Shenagh and Jackie gave a presentation at Palmstead Nurseries' soft landscaping workshop on plants and health, they launched a survey of delegates' perceptions of pollen, AR and associated factors. There were two key findings from the sample. First, many people working in the landscape industry suffer from AR. Second, they all sought more information about which plants are allergenic and how to manage AR and asthma<sup>(3)</sup>.

Extensive media coverage of air quality, allergies and asthma – especially in children – has made the general public receptive to understanding more, as it impacts on their personal health and prospects in life. Yet many organisations do not recognise the detrimental impact of AR. For example, local authority planning departments commonly specify in their treeworks policies that allergy to pollen is not a reason for felling a tree. The effects of the pollen are dismissed as a mere nuisance and ephemeral, like the seasons or the weather <sup>(4)</sup>.

The lack of knowledge is understandable when encyclopaedias of plants are focused on aesthetics, and selecting Right Plant for Right Place. In other words, people's health is not brought into the equation. However, pollen calendars and charts indicating the cross-linkage between allergenic pollen and certain foods are easily accessible online.<sup>(5)</sup>

#### Pollen facts

For people working with, or affected by pollen allergies, **The Walk to School** poster clarifies some botanical basics. One common misconception: birch is dioecious (i.e. the genus is made up of separately sexed plants). It is in fact monoecious, with male (pollen producing) and female flowers appearing on the same plant. **Anemophilous** (airborne, dispersed by wind) pollen of birch, alder and hazel is particularly light and fine. By

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POLLEN TYPE	January	February	March	April	May	June	July
HAZEL (Corylus)		_	_				
YEW (Taxus)	_	_	_				
ALDER (Alnus)		_		_			
ELM (Ulmus)		_	_	_			
WILLOW (Salix)		_	_	-	_		
POPLAR (Populus)			_	_	•		
BIRCH (Betula)						-	
ASH (Fraxinus)				_	_		
PLANE (Platanus)			_		_		
OAK (Quercus)						_	
PINE (Pinus)					_	_	_
LIME (Tilia)							_

The main periods of pollen release

contrast, **entomophilous** pollen (dispersed by insects) is usually heavier and stickier, thus less likely to become airborne and cause respiratory allergy.

A common assumption is that tree pollen occurs for a brief period in the spring. Not so. The National Pollen and Aerobiology Research Unit (NPARU) data indicates that the season for airborne allergenic tree pollen lasts 6 months<sup>(6)</sup>. Its effect can be extended by 2 months by taking pollen indoors between home and school on clothing<sup>(7)</sup>. What is more, pollen can stay around long after the shedding season has passed due its tough coating that only releases the allergens when in contact with warmth and increased humidity, such as inside the nostrils or eyes.

One reason why tree pollen is not often mentioned in the discussion of particulate matter (PM) in air quality studies is its relative size. Pollen grains measure PM10 and larger, dependent on species. PM10 particles may enter the nostrils. On contact with humidity and warmth, pollen grains rupture into much smaller particles<sup>(8)</sup>. Clinically PM2.5 particles raise severe public health concerns as they easily penetrate the pulmonary alveoli<sup>(9)</sup>.



These interim findings suggest that field research is urgently needed, in order to analyse the potentially potent connections between noxious emissions, especially of Nitrous Dioxide (NO2), and the aerosol effect of allergenic pollens fragmented into PM2.5 particles.

#### The impact of pollen allergy on daily life

Children, especially babies in buggies and young children whose lungs are at a sensitive stage of development, are in the front line of exposure to vehicle emissions and dust on pavements. HM Government's document 'Moving More, Living More'<sup>(10)</sup>, and the Department of education (DFE) statutory guidance on sustainable travel<sup>(11)</sup> promote walking to school to increase physical activity in children, and more broadly to improve public health. Higher levels of both noxious traffic pollution and airborne pollen coincide with the beginning and end of the school day.

Statistics serve to emphasise how vulnerable children are. For example: allergies trigger asthma exacerbations in up to up to 90% of children with asthma<sup>(12)</sup>. 7% children vs. 2% adults are susceptible to food allergies; birch pollen is a common trigger of Pollen Food Syndrome. Neo-natal exposure increases the risk of allergy<sup>(13)</sup>, and the symptoms of AR can have a profound impact on children's life chances, as this graphic shows.

#### Proximity pollinosis

The greater the quantity of trees of one species emitting allergenic pollen within a space, the higher and more intensive the exposure will be, and commensurately the worse will be the AR symptoms. The closer a sensitive individual is to the allergen's source, the more susceptible they will be. Thus living with pollen allergy near a busy road is more likely to exacerbate asthma. Similarly, if allergenic trees are in the garden or park frequented by that individual. Or even, as Shenagh herself experienced, the trees planted outside her local GP's surgery might offer welcome shade and a calming scene, but inadvertently cause more harm than good. Bordering the footpath was a hazel; beside the entrance to the GP's reception, overhanging the pram park, was a silver birch that showered pollen onto children who - in many cases - were attending for respiratory conditions. This case is cited in past tense as, since publication of The Walk to School poster and consultation with the practice, the offending trees have been removed.

#### Practical considerations to prevent exposure

Based on the first principle of avoidance, it seems plain common sense to stop planting allergenic trees on highways and wherever young children are especially vulnerable. Only a handful of allergenic trees cause a problem and create a huge burden on the NHS. In fact, there are many non-allergenic alternatives to these species. Of the 2951 vascular plants listed in **The New Atlas of British Flora**, only a few that trigger respiratory allergy in the UK are regularly found in NPARU's pollen traps, where birch, alder and hazel predominate <sup>(14)</sup>. That leaves many non-allergenic trees with foliage suitable to capture PM2.5.

The poster cites several worldwide examples of preventative solutions to tree pollen related respiratory health in the public realm <sup>(15)</sup>.

#### Poster power!

The poster is proving to be an effective visual, evidencebased stimulus for raising awareness of allergenic pollen. It has been the opening gambit for many conversations with tree nurserymen, tree officers, policy makers, clinicians, landscape architects and contractors, and individuals with AR and asthma. The poster, and associated articles in, for example, Allergy UK's magazine, RHS's The Garden, Pro Landscaper and the Garden Design Journal, is influencing further research into tree species suitable for mitigating air pollution, but which will not trigger pollen allergies.

For example: Lancaster University's field studies demonstrated how the planting of birch trees, to create a biofilter of foliage in the street outside people's homes, could reduce the particulates indoors<sup>(16)</sup>. Widely publicised through the media, including BBC TV's **Trust Me I'm a Doctor** programme, this gave birch the green light as a beneficial street tree. Moreover, the beautiful bark and dappled light are a popular choice of landscapers, local authorities and architects. Birch trees are inexpensive to buy; light leaf fall generates little street litter – another reason for being favoured by cash-strapped local authorities. Notably, birch has been planted in NHS initiatives for a healthy greener environment, for example the densely birch-lined street outside the Royal National Orthopaedic Outpatients Hospital in central London<sup>(17)</sup>. More recently, Professor Barbara Maher, speaking on Radio 4's **Inside Science**, has acknowledged that allergenic pollen from species such as birch can cause health problems<sup>(18)</sup>. The Lancaster Environment Centre is one of several academic institutions now testing the effectiveness of different tree species in filtering the air. And now, the Trees and Design Action Group (TDAG)'s online Tree Species Selection Guide, published in 2018, includes information on the allergenicity of trees, and which species are appropriate biofilters in roadside situations <sup>(19)</sup>.

#### What next? - Recommendations

We are not advocating that all birch and other allergenic trees be felled – but that the mass planting of them, especially in urban areas with expanses of hardstanding, should be avoided. This is particularly critical for new housing developments and in locations serving vulnerable people, such as hospitals, hospices and schools.

For existing trees, pollen production could be reduced by tip pruning. This involves removing the catkins before they come into flower. However this is a timeconsuming process for which both access and funding may not be factored into the tree maintenance programme.

And last but not least, greater knowledge of pollen allergens, AR and asthma, among general practitioners, carers for children and educators, would benefit public health as a whole. The poster is evidence of and recommends a cross-professional MDT approach. Good communication at the least, and collaboration as an ideal between clinicians, urban planners, horticulturalists, designers, environmental scientists, engineers and economists is needed to boost research, and to generate substantive statistics and financial data that would support the case for preventative planting policies in the public realm.

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## **FEATURE:**

#### **Allergic Rhinitis**

Amena Warner is Head of Clinical Services at Allergy UK. She took up this appointment after working as a Clinical Nurse Specialist in Immunology and Allergy at an NHS Hospital Trust. She trained at University College Hospital, followed by paediatric training at Great Ormond Street Hospital in London. She also holds a Public Health and Specialist Practice in School Nursing qualification gained in 1994. Visiting



schools and carrying out health assessments made Amena very aware of the rising incidence of allergy in the UK and was instrumental in developing her interest in the field.

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#### What is Allergic rhinitis?

Allergic rhinitis (AR) is an IgE-mediated inflammatory disorder of the nose which occurs when the nasal mucosa becomes exposed and sensitized to allergens.

This triggers the release of histamine and other inflammatory mediators, which act on nerve endings and blood vessels <sup>(1).</sup>

Allergic rhinitis is common and affects 10–15% of children and 26% of adults in the UK, it affects quality of life, school and work attendance, and is a risk factor for development of asthma.

#### How does it present?

Typical symptoms include: sneezing, itchy nose, runny nose/ nasal discharge/ rhinorrhea (that is most commonly clear fluid), nasal blockage/ congestion, feeling of mucous running down the back of nose/ throat (post nasal drip).

#### How is it diagnosed?

Allergic rhinitis is diagnosed by history and examination, supported by specific allergy tests. (See article on diagnostic testing in this Allergy Today magazine).

#### What can be the triggers?

This can sometimes be difficult to identify so indepth clinical history taking (either from the patient themselves if old enough or parent) is key. Take time to find out about the symptoms, how long they have had them for, are there times when symptoms completely resolve (important for seasonal allergy, such as hay fever, where specific pollens can be the cause, such as grass, trees or weed pollen). Some patients may have their AR triggered by multiple pollens, so their symptoms may last from late winter/ early spring until autumn, adding to their hay fever misery. Grass pollen is the most common cause and tends to affect people every year from around May to July. The Royal College of General Practitioners' Research and Surveillance Centre (RSC) revealed there were 45,355 cases of hay fever, or allergic rhinitis, presented to GP practices between 4 June-10 June 2018 (76.7 presentations per 100,000 population); up from 19.8/100,000 the previous week (11,708 cases).

This was significantly above the five-year average for cases in general practice, in fact, more than 45,000

people visited their GP with hay fever symptoms in that week in England.<sup>(5)</sup>

Tree pollens tend to affect people from March to May and weed pollens from summer to early autumn. Find out about pets as this can be a trigger. There are indoor allergens such as house dust mite (HDM) that can also trigger AR. This tiny animal is the cause of a major global health burden. It is 0.3 of a millimetre in size but house dust mite allergy affects 1-2% of the world's population and is associated with asthma. (See AUK factsheet on HDM). There is evidence of HDM reduction that can be achieved with heat (washing bedcovers above 60 degrees) and steam, with emerging HDM therapies for those who remain symptomatic.



Mould can also be a trigger for AR and is also associated with difficult to treat asthma.

So history taking is key and diagnostic testing can help confirm suspect allergens.

#### How AR is treated to minimise the effects

There are nasal allergen barrier balms, saline nasal irrigation/ douching for mild symptoms and long acting non- sedating antihistamine may relieve nasal itching and rhinorrhoea. All these are available over the chemist counter for short term use, especially if patients only get these symptoms for a month or two in the year. Many patients happily self-medicate like this if their symptoms are mild. However, for others, symptoms can interfere with activities of daily living and impair quality of life. These are often the patients that seek medical advice and present to primary care. It may be likely that these patients have chronic disease and need prescribed active management. Topical nasal corticosteroids are the treatment of choice for moderate to severe disease. Combination therapy with intranasal corticosteroid plus intranasal antihistamine is more effective than either alone and provides second

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line treatment for those with rhinitis poorly controlled on monotherapy. <sup>(2)</sup> What is not recommended is treatment by steroid injection (Kenalog) for AR. If a patient has historically required this then the current guidance is to refer for consideration of immunotherapy, which provides a longer term relief rather than a short term one that has a high side effect profile. (ie osteoporosis, injection site atrophy)

#### What happens if these don't work?

Referral to an allergy service helps not only to identify triggers but also access to advanced management strategies of therapeutic benefit such as use of immunotherapy/ desensitisation. Immunotherapy is highly effective when the specific allergen is the responsible driver for the symptoms and is available usually for monosenstised individuals, such as those who have severe allergic rhinitis driven by allergy to grass or some tree pollens. Also for those whose work is affected by allergy to animals, such as vets. There is strict criteria for its use. (www.BSACI.org)

Additional monoclonal antibody therapy may be helpful for those with clinically important polysensitization. <sup>(3)</sup> These are newer types of therapies and appear efficacious.

#### Considerations for differential diagnosis:

Rhinitis mayalso be eosinophilic and steroid-responsive or neurogenic and non- inflammatory. Non-allergic rhinitis may be a presenting complaint for systemic disorders such as granulomatous or eosinophilic polyangiitis, and sarcoidoisis. Infective rhinitis can be caused by viruses, and less commonly by bacteria, fungi and protozoa.<sup>(2)</sup>

#### Why it is important to treat rhinitis

As well as reduction in the nasal symptoms and trying to improve QOL, allergic rhinitis is a risk factor in the development of asthma and treatment of rhinitis is associated with benefits for asthma. Non-allergic rhinitis also is a risk factor for the development of asthma. (2) There is a 'one airway one disease' concept where it is acknowledged that the nasal airways have a direct correlation to the respiratory airways.

Asthma is a common disease in childhood with a minority of affected children having severe therapy-resistant asthma (STRA). Children with STRA can be

differentiated from those with mild-moderate disease by greater allergic sensitization, increased eosinophilic airway inflammation, increased airway remodelling and reduced corticosteroid responsiveness. The aetiology of STRA in children is multifactorial but allergy seems to play a key role<sup>(3)</sup>. Many children with asthma have coexisting allergic disease, and severe rhinitis seems to be an important driver of STRA in children. Allergies to foods, moulds, pollen and pets have also been associated with severe asthma exacerbations. Identifying allergens that are driving asthma symptoms in children with STRA may provide additional strategies for improving their disease control. Avoidance strategies may be possible. <sup>(3)</sup> (More information about avoidance strategies and allergen reduction measures can be found within our factsheets).

Exposure to pollen can contribute to increased hospital admissions for asthma exacerbation. One study applied an ecological time series analysis to examine associations between atmospheric concentrations of different pollen types and the risk of hospitalization for asthma in London from 2005 to 2011. The analysis examined short-term associations between daily pollen counts and hospital admissions in the presence of seasonal and long-term patterns, and allowed for time lags between exposure and admission. Models were adjusted for temperature, precipitation, humidity, day of week, and air pollutants. Analyses revealed an association between daily count (continuous) of grass pollen and adult hospital admissions for asthma in London, with a 4–5-day lag. When grass pollen concentrations were categorized into Met Office pollen 'alert' levels, 'very high' days (vs. 'low') were associated with increased admissions 2–5 days later, peaking at an incidence rate ratio of 1.46 (95%, Cl 1.20–1.78) at 3 days.(4)

#### What guidelines exist for use in the U.K.?

The national institute of clinical excellence (NICE) has produced a clinical knowledge summary (CKS) on allergic rhinitis that was last revised in September 2018. This covers the management and referral of children and adults with allergic rhinitis in primary care.

There are also the Royal College of Paediatrics and Child Health (RCPCH) care pathway for asthma and/ or rhinitis and is presented in two parts: an algorithm with the stages of ideal care and a set of competences required to diagnose, treat and optimally manage asthma and/or rhinitis.<sup>(6)</sup> Guidelines also exist for the management of patients with allergic and non-allergic rhinitis<sup>(2)</sup> that has been prepared by the Standards of Care Committee (SOCC) of the British Society for Allergy and Clinical Immunology (BSACI). The guideline is based on evidence as well as on expert opinion and is for use by both adult physicians and paediatricians practicing in allergy. The recommendations are evidence graded. See www. BSACI.org/rhinitis guidelines for more information.

#### Additional support is available for patients -How they can get more information

Allergy UK is a patient support and information

organisation which has a wide range of factsheets on many areas of allergy including allergic rhinitis. Patients can visit the website www.allergyuk.org and freely access all the information. As a clinician, you may find it helpful to print factsheets off to give to your patient as they are all free to download. They are written by experts and then peer reviewed. They then go for 'user testing', to make sure it is understandable to the majority of people as we hold the information accreditation standard. There is a healthcare professional part of the website where clinicians can find important information and resources that may help in their clinical practice.

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## **FEATURE:**

Life Threatening allergic reactions during surgery: results of NAP 6

Nigel Harper is MAHSC Honorary Professor of Anaesthesia and Perioperative Medicine in Manchester. He has a longstanding interest in adverse drug reactions, especially those occurring during anaesthesia and surgery. He started the first UK anaesthesia/ clinical immunology joint clinic for the investigation of these reactions. He chaired the Association of Anaesthetists of Great Britain and Ireland Safety Guidelines on anaphylaxis during anaesthesia. Professor Harper represented the Royal College of Anaesthetists on the Royal College of Physicians Working Group following the House of Lords report on the provision of allergy services. He has served on NICE clinical guideline development groups and has lectured and published widely on the subject. Nigel was Clinical Lead for NAP6, the recent Royal College of Anaesthetists multidisciplinary UK-wide clinical audit and service evaluation: Anaesthesia, Surgery and Life-Threatening Allergic Reactions which is the subject of this article.

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#### Allergy**Today**

#### NAP6

The Royal College of Anaesthetists regularly performs major audit projects on serious adverse events that can occur during anaesthesia and surgery. These are the National Audit Projects, or NAPs for short. The broad aim is to quantify the problem, to learn from these events and to make recommendations about how patients' safety and care can be improved. Cases reported by anaesthetists to NAPs are entirely anonymised; patients, hospitals and clinicians cannot be identified. The 'buy-in' to NAPs is impressive: NAP6 was endorsed by all four Chief Medical Officers and every NHS hospital in the UK engaged with the project, so we can be confident that our results are truly representative. I hope this article will provide an interesting summary of our findings.

NAP6, which reported in May 2018, was the largest ever prospective study of life-threatening anaphylactic reactions occurring at the time of anaesthesia and surgery. Perioperative anaphylaxis is characterised by dangerously low blood pressure often with severe wheeze, swelling and rash. In extreme cases there is cardiac arrest and even death.

I was privileged to be the Clinical Lead anaesthetist for NAP6, working with a dedicated multidisciplinary team, including several experts from the world of allergy. NAPs also investigate how health services are provided to patients and in NAP6 we looked at the provision of specialist allergy services across the UK, including allergy investigations and advice given to patients and clinicians.

NAP6 was subdivided into several phases. Our first task was to discover how many anaesthetics of various types are administered each year as well as the types of surgery and the characteristics of surgical patients, using up-to-date data submitted by anaesthetists in 342 hospitals. Many people might be surprised to know that 3.1 million anaesthetics are administered each year in NHS hospitals: almost 90% are administered by a consultant or equivalent grade. Around a quarter are local or regional anaesthetics rather than general. One in five patients has a co-existing illness that affects their daily life and potentially increases the risks of anaesthesia. The most common age to require an anaesthetic is 26-35yrs, and there is a second peak between 66 and 75 yrs. Almost 60% of patients are female. The busiest surgical specialties

are orthopaedics/trauma, followed by general surgery. There are over 200,000 obstetric anaesthetics each year, approximately one third of all deliveries, and the majority are epidural or spinal (regional) rather than general anaesthetic.



#### Exposure to allergens during anaesthesia and surgery

Unlike food allergy and venom allergy, it is often unclear what has caused the reaction until comprehensive tests have been performed. An average of eight drugs are administered during a general anaesthetic but the number may be as high as twenty. Most of these are given directly into an intravenous drip. With the exception of anaesthetics that are breathed-in, almost all the drugs administered during general anaesthesia are potentially allergenic. Allergic reactions tend to be more rapid and more severe when drugs are administered intravenously. During a general anaesthetic, in addition to drugs that cause unconsciousness, almost 90% of patients also receive at least one painkiller and almost half at least one drug to relax the muscles. Intravenous antibiotics are used prophylactically to prevent surgical infection in almost 60% of all cases, a surprisingly high figure equating to over 1.7 million administrations each year.

In addition to drugs, patients may be exposed to other potential allergens during surgery and anaesthesia. The majority of surgical patients are exposed to chlorhexidine, an antiseptic commonly used to clean

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the skin prior to surgery, and many patients receive an injection of dye for X-Ray or other imaging. Latex surgical gloves are still used: four in five anaesthetics are given in hospital areas that contain latex.

#### Case reports of perioperative anaphylaxis

We asked anaesthetists to report anonymised cases of life-threatening perioperative anaphylaxis to NAP6 over a 1-year period using a detailed on-line pro forma. Minor allergic reactions such as isolated rash or swelling or a minor fall in blood pressure were excluded. Cases were reviewed in detail by the NAP6 panel which included anaesthetists, critical care consultants, allergists, clinical immunologists and allergy nurses as well as a representative from hospital pharmacy, Medicines and Healthcare products Regulatory Agency and clinical governance. Allergy UK was represented by Amena Warner.

We received 541 reports of life-threatening perioperative anaphylaxis. We reviewed cases only if the patient had subsequently attended an allergy clinic and details of the clinic investigations, diagnosis and advice given were known. After all protocol exclusions, the NAP6 panel reviewed 266 cases. The calculated incidence was 1 in 11,752 anaesthetics.

#### Resuscitation

NAP6 found that resuscitation by anaesthetists was generally good, although there were occasional delays in starting specific treatment, possibly because several more common problems during anaesthesia and surgery can mimic anaphylaxis. All patients in cardiac arrest received CPR: 40 patients for an average of 14 minutes duration. Adrenaline (epinephrine) is the most effective treatment for anaphylaxis and during anaesthesia this is usually given intravenously for the most rapid effect. Some patients received adrenaline in smaller than recommended doses, possibly because the blood pressure had started to respond to other drugs. The second requirement is for large volumes of intravenous fluids to be given as rapidly as possible and NAP6 found that inadequate volumes of fluids were given in some cases. Most patients required additional drugs to support the blood pressure or to treat severe wheeze and, in addition, intravenous steroids and antihistamines were commonly administered.

#### **Clinical features**

Clinical features of anaphylaxis occurred within 10 minutes of exposure to the trigger agent in over 80% of cases. A severe fall in blood pressure occurred in all cases. Fifteen per cent of the patients experienced cardiac arrest. Severe wheeze occurred in half the cases and was more common in asthmatic patients. Patients taking beta-blocking drugs or ACE-Inhibitor drugs (usually for high blood pressure) were more likely to have a very severe reaction. Rash was often absent in the most severe cases. The surgical procedure was abandoned or postponed in two thirds of cases; urgent surgery was delayed in 10% of all cases. More than half of patients required transfer to Critical Care. Ten patients died. A third of patients who survived experienced one or more ongoing adverse effects such as anxiety, change in mood and symptoms of PTSD as well as impaired memory, co-ordination and mobility.

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#### Causes

We were surprised to find that antibiotics given during surgeryarenowthemostcommoncauseofperioperative anaphylaxisintheUK, being responsible for 48% of cases. Previously, it had been generally reported that muscle relaxant drugs were the commonest culprit. The penicillins are the most frequent problem although a different antibiotic, teicoplanin, has a higher numerical risk of anaphylactic reaction. Teicoplanin is a frequently-used alternative when patients give a history of penicillin allergy but is an allergen in its own right. Approximately 90% of people who have a 'label' of penicillin allergy are not in fact allergic to penicillin. It is probable that some life-threatening teicoplanin reactions could be avoided in the future if pre-surgical patients who have possible penicillin allergy are tested and 'de-labelled' if appropriate before having their surgery so they could safely receive a penicillin. There would clearly be work load consequences for over-stretched allergy services. It is also probable that antibiotics in general are over-used for surgical prophylaxis and the number of anaphylactic reactions could be reduced if guidelines were improved as well as being followed more closely.

Patent Blue Dye and chlorhexidine are two prominent non-drug allergens causing anaphylaxis during surgery. Patent blue dye is injected into the tissues by the surgeon during some types of cancer surgery to show-up lymph nodes.

#### There were 61,768 exposures each year and 9 anaphylactic reactions.

The NAP6 panel felt that this risk should be discussed with patients during the surgeon's pre-operative visit.

Chlorhexidine has been described as a 'hidden allergen'. This antiseptic is found widely in everyday life, including in many household products. Chlorhexidine is used to clean the skin before siting an intravenous drip and prior to surgical incision. It is also a constituent of some medical lubricants and intravenous catheters. The vast majority of patients undergoing surgery are exposed to chlorhexidine, which can enter the circulation. There were 18 life-threatening allergic reactions to this antiseptic.

Perioperative allergic reactions to latex appear to be exceedingly rare: there were no reactions reported during the audit.

#### Investigating to find the cause

Unless the exact cause of the anaphylactic event is found, there is a considerable risk that patients could be re-exposed during future anaesthesia. Allergy Clinic waiting times were often excessive: only 16% of patients were seen within the ideal 6 weeks and 23% waited longer than 18 weeks for their appointment. There was marked geographical variation across the UK. Investigation of suspected perioperative anaphylaxis is very specialised and includes comprehensive skin tests and blood tests. Published guidelines were not always followed. In particular, it is important that no potential culprit is left out of the panel of tests and potential cross-sensitivity between muscle relaxant drugs should be fully explored by the clinic. Patients should receive clear communication, including a list of safe alternative drugs and a hazard-warning form, and this was not always the case in practice.

#### NAP6 conclusions and recommendations

The NAP6 report contains important recommendations for hospitals and clinicians, centred on improvements in clinical management, investigation by allergy clinics and communication with patients and between healthcare professionals. It is clear that provision for UK allergy services should be increased so that investigation and follow-up of these life-threatening events can be improved.

The full NAP6 report and recommendations can be found on the Royal College of Anaesthetists website: https://www.nationalauditprojects.org.uk/NAP6home

Information for patients on the risks of perioperative anaphylaxis is also available: https://www.rcoa.ac.uk/ system/files/09-Anaphylaxis2018.pdf

## FEATURE:

#### Allergic Eye Disease

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Many people suffer from allergic conjunctivitis, either seasonally (seasonal allergic conjunctivitis) or all year round (perennial allergic conjunctivitis). The main symptoms are itching, burning, watering and redness of the eye, and puffiness of the eyelids. The cause is exposure to a substance to which a person has become allergic, known as an allergen. Being allergic means that the body has become sensitised to a particular allergen and has generated an immune protein (IgE) to that allergen which coats the surface of mast cells in the tissues. When challenged again by the same allergen, granules in the mast cells break open and release noxious substances, including histamine, into the tissues. It is these substances that produce the symptoms of allergy. Many allergic people are sensitised to more than one allergen.

#### Seasonal allergic conjunctivitis

For most of those with seasonal allergic conjunctivitis, and this means around a fifth of the adult population of the United Kingdom, their symptoms are part of their hay fever, and the cause is the same. The allergens responsible are often grass pollens (or other pollens from trees, weeds or shrubs; also mould spores) which land on the eye surface and trigger the release of histamine and other inflammatory substances. The part of the eye that is visible in the face is not the area mainly affected. The cornea (the transparent window of the eye overlying the coloured iris) is not affected at all, and the surrounding 'white of the eye' only slightly.



The part that is not seen directly, a relatively large area of the white of the eye and the underside of the eyelids, is where the reaction mainly takes place.

What the clinician sees in allergic conjunctivitis, under the upper eyelid in particular, is slight redness (hyperaemia), slight swelling (oedema) of the tissues, and sometimes a little bumpiness (papillary hyperplasia). These are quite mild findings, and the lack of major signs, coupled with the typical seasonal history and symptoms, is what helps to distinguish allergic conjunctivitis from other forms of inflammation, including infection.

**Perennial allergic conjunctivitis** is caused in the same way, but is usually a reaction to house dust mite or pets in the indoor environment, rather than to seasonal pollens. In other countries, where other environmental allergens are more common, the same condition can be caused by these different allergens.

The allergy tests normally used to identify the causes of an allergic reaction (skin prick tests and blood tests) are sometimes unhelpful in finding the triggers for allergic conjunctivitis. The correlation between the allergic antibody (IgE) levels in the tears and those in the blood or skin is limited because most of the IgE found in tears does not come only from the blood, but also from the tear (lacrimal) gland. The equivalent, in the eye, of the

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skin prick test is the conjunctival provocation test, in which extremely small amounts of allergen are introduced into the tear film, and the effects observed. This is only undertaken in specialist clinics, but it may be helpful in diagnosing some cases of allergic eye disease when the cause is not obvious from the patient's history.

In addition to seasonal and perennial allergic conjunctivitis, other much rarer but more serious allergic eye diseases are recognised. These are vernal keratoconjunctivitis (VKC), which occurs in some severely allergic children, and the adult equivalent, atopic keratoconjunctivitis (AKC). In both conditions the cornea is usually involved, affecting and even threatening the sight of the eye, and only the eye specialist (ophthalmologist) is fully equipped to manage them. Some contact lens wearers suffer from a condition, giant papillary conjunctivitis (GPC), which is similar to VKC and AKC, but does not involve the cornea.

#### Vernal Keratoconjunctivitis (VKC)

Vernal keratoconjunctivitis is so named because it affects the cornea as well as the conjunctiva, and tends to occur in the spring; however, it can occur at any time of the year and sometimes persists all year round. It affects young children, especially boys, and tends to resolve around puberty, though this does not always happen. The disease differs from allergic conjunctivitis in that many more immune processes are involved, including the production of substances (such as eosinophilic major basic protein) that damage the eye surface. Symptoms can be severe, with eye pain in addition to itching, and blurred vision. Reduction in the vision of one or both eyes can interrupt the normal development of adult vision, which is still taking place up to the age of 10 or even later. The signs of VKC are characteristic, especially the giant papillae (larger than 1mm in diameter) that are present under the upper lid. These do not themselves cause symptoms but they are evidence of the long-lasting nature of the inflammation.

Effective treatment of this childhood condition is essential. The mainstay of treatment for many years has been steroid eye drops, and it is often a challenge to steer the patient through their unwanted effects, but more precise treatment is now available in the form of suitable formulations of immune suppressants, such as ciclosporin (see below).

#### Atopic Keratoconjunctivitis (AKC)

Like VKC, AKC involves the cornea as well as the conjunctiva and can threaten sight. It occurs in some severely allergic adults, who often have facial and eyelid eczema also. They usually complain of eye irritation, which may be constant, and their vision is usually impaired when the cornea is inflamed.

The signs of AKC are similar to but more diffuse than those of VKC, and eyelid inflammation is often a major feature.

Treatment follows the same lines as for VKC, and the eyelids are very likely to need medication also.

#### Management of allergic eye disease

Allergen avoidance is the first strategy, but before allergens can be avoided they must be identified. In many cases the likely triggers can be identified by taking a careful history from the patient. Many allergic people react to common allergens, which are, by definition, difficult to avoid. Allergy UK publishes factsheets on Avoiding Pollen and Avoiding Indoor Allergens.

Anti-histamine eye drops can be helpful. For drugs that are currently available, a prescription is needed, but an eye drop combination of an antihistamine and a decongestant is available from pharmacies. Oral antihistamines suit many patients whose eye symptoms

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coincide with other symptoms of hay fever. Some of these can be bought over-the-counter while others require a prescription.

Mast cell stabilisers have been used in eye drop form for many years. The first of these was sodium cromoglicate, the effectiveness and excellent safety record of which have earned it 'gold standard' status in the management of allergic eye disease. A number of manufacturers produce their own versions of this preparation, some of which can be bought without prescription. Other mast cell stabilisers, and compounds that have both mast cell stabilising and anti-histaminic properties (e.g. olopatadine), require prescriptions.

**Steroid eye preparations** are very effective in allergic eye disease but their actions are broad and some of them are unwanted: these can be severe and even sight-threatening. The medical literature includes reports from other countries of children with VKC who have been blinded by steroid eye drops. They should therefore be prescribed only by ophthalmologists, or by optometrists registered as Independent Prescribers, as these are the only two professional groups properly trained and equipped to diagnose and manage these complications.

Non-steroidal anti-inflammatory drugs (NSAIDs) are available in eye drop form, but their place in the overall management of allergic eye disease is not fully determined.

**Immunosuppressive agents** are not needed in simple allergic eye disease, but they may be used in the management of VKC and AKC under the guidance of an ophthalmologist. Ciclosporin is one of these, and its beneficial effects have been known for some years, but the lack of a suitable commercial preparation has limited its use. The introduction in October 2018 of a ciclosporin eye drop, was particularly welcome. It is licensed for use in VKC in children from the age of four years to adolescence. We can anticipate that the

availability of this drug will reduce the need for steroid eye drops, with their potentially severe side effects.

**Immunotherapy** may help a small minority of people whose allergic eye disease is caused by a single allergen rather than a number of allergens. By giving very small doses of the allergen at regular intervals for three years or more, either by injection into the skin or by tablets held under the tongue, the body can be desensitized.

Supportive measures: in addition to all these active treatments, supportive measures can be very helpful in controlling the symptoms of allergic eye disease. These include cold compresses to reduce inflammation, and artificial tear preparations, some of which are available at pharmacies without prescription.

The management of the contact lens-related disease Giant Papillary Conjunctivitis (GPC) is a specialist area which is best left to optometrists and ophthalmologists.

A note on the use of eye drops: Eye drops are best instilled with the head well back, or when lying down. The forefinger of one hand is used to gently pull down on the lower eyelid, creating a small recess into which a drop can be made to fall from the bottle held in the other hand. (The ophthalmologist may sometimes recommend the instilling of drops under the upper lid.)

Though the instructions provided with the drops may state that one or two drops should be used, only one is necessary. Indeed, the use of more than one drop may be counterproductive. It is important that the top of the bottle (or dropper) should not touch the eye, or the lashes, lids, face or fingers. The hands should be washed before and after use of eye drops. Once opened, the drops should be kept in a cool place (such as in the door of the fridge) and thrown away when they expire (usually one month later). It is not safe to use eye drops that have been open for longer than the recommended interval. Some eye drops come in single dose units; they should never be re-used. Eye drops should never be shared with another person.

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## FEATURE:

**Drug Allergy in Primary Care** 



Rubaiyat Haque is a Consultant Allergist at Guy's Hospital in London. He studied medicine at Cambridge University followed by St Bartholomew's and The Royal London Hospitals. He undertook specialist training in Allergy at Addenbrooke's Hospital in Cambridge before returning to London for his current consultant post at Guy's Hospital. In addition to working in the Adult Allergy Department at Guy's Hospital, he also works in the Children's Allergy Service at St Thomas' Hospital and in the Department of Oral Medicine at Guy's. His main clinical interests are drug allergy, cutaneous allergy and telemedicine.

In your day-to-day practice, you will frequently come across patients labelled as being allergic to one or more drugs. Approximately 10% of the population are labelled as being allergic to penicillin, for example. However, when such patients are referred to a specialist allergy centre for objective testing, over 90% will not be allergic.

Why is are so many people wrongly labelled as being allergic to drugs? When it comes to antibiotic allergy, the symptoms of infection can sometimes mimic those of allergy. A childhood fever with an infection can often produce an exanthematous rash. If the child happens to be on an antibiotic, there is no easy way of knowing whether the rash is a viral exanthem or a delayed hypersensitivity to the drug. The child is labelled as being allergic to the antibiotic and avoids it for the long term, potentially compromising future treatment.

Additionally, even if the child is correctly labelled with a drug allergy, the passage of time often leads to the loss of their allergic sensitisation, meaning that lifelong avoidance may not be required. It may take decades for the loss of the allergy, but if the drug is potentially useful to the patient, allergy testing can be helpful to assess whether the allergy has resolved.

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Many incorrect drug allergy labels arise due to misinterpretation of drug side-effects as being allergy. Most antibiotics will cause some degree of gastrointestinal upset often due to a temporary disruption of commensal gut bacteria ('good bacteria'). A bout of loose stools or diarrhoea after a course of erythromycin does not constitute an allergic reaction, but the patient suffering these symptoms might interpret it in such a way and report to medical practitioners that they are allergic.

I am often referred patients who have suffered vasovagal episodes after an injection of local anaesthetic into their gums prior to a dental procedure. This is not allergy. (Incidentally, genuine allergy to local anaesthesia is fabulously rare). Recently a patient in my clinic reported that she was allergic to GTN that she had previously used to treat angina. Her symptoms? A headache!

In primary care, one can easily remove such spurious allergy labels without recourse to a drug allergy specialist. One would need to have some familiarity with common drug allergy side-effects. The BNF is always a good friend in these circumstances, but even better is the patient information leaflets that come

with these drugs (easily accessible via medicines.org. uk). Keep in mind that side-effects can be significant enough to warrant drug avoidance, but this is a decision between patient and prescriber, not requiring the input of an allergist.

#### Presentation of drug allergy

To make a meaningful distinction between predictable side-effects and genuine drug allergy, one has to have some understanding of the nature of drug allergy symptoms. The mechanisms of drug allergy are complex, spanning a range of different immunological mechanisms. To keep this simple, I classify drug allergy into three broad categories:

- 1. Immediate hypersensitivity
- 2. Delayed hypersensitivity (mild)
- 3. Delayed hypersensitivity (severe)

Immediate hypersensitivity reactions occur quickly (usually within an hour for oral medication and quicker via parenteral routes) after a single dose of the drug in question. The symptoms include urticaria (hives, welts, weals), angioedema and, in more severe cases, difficulty in breathing (either bronchoconstriction or laryngeal oedema) and collapse / loss of consciousness (due to hypotension). The latter severe symptoms are classed as anaphylactic and can be life-threatening.



A mild delayed hypersensitivity is more common and usually occurs a few days into a course of a medication – penicillin is the classic example. The main symptom is a skin rash but not an urticarial one as is the case in immediate reactions. In a mild delayed reaction, the patient experiences a maculopapular, exanthematous or morbilliform ('measles-like') rash. The lesions of such a rash a relatively fixed, compared to the flitting nature of individual urticarial weals. The rash can last from as little as a few days to as long as several weeks. Like urticaria, the rash is often itchy.

Severe delayed hypersensitivity reactions are potentially life-threatening and encompass the following conditions (also known as Severe Cutaneous Adverse Reactions or SCAR):

- 1. Stevens-Johnson Syndrome (SJS)
- 2. Toxic Epidermal Necrolysis (TEN)
- 3. DRESS (Drug Reaction, Eosinophilia, Systemic Symptoms) Syndrome
- 4. Acute Generalised Exanthematous Pustulosis (AGEP)

Detailed explanations of these conditions are beyond the scope of this article, but briefly: SJS and TEN are the same condition but differing in severity. They involve extensive skin detachment (>30% surface area in TEN and <10% in SJS), mucosal membrane involvement, flu-like illness and multiple organ failure. Mortality rates are high (up to 30% in TEN).

DRESS syndrome involves milder skin eruptions (usually morbilliform) but with peripheral eosinophilia and multiple organ involvement, particularly liver, kidneys and lungs. The condition is associated with a mortality rate in the region of 10%. AGEP involves a characteristic pustular skin eruption and is the least severe of the SCAR conditions. Mortality rates are less than 5%.

#### Acute management of drug allergic reactions

It is unlikely that you will be faced with the acute management of immediate or severe delayed reactions – such patients will often end up in hospital. Nevertheless, it is worth having some knowledge of how these things are treated. In all suspected drug allergic reactions, the culprit drug should be discontinued. For immediate reactions involving the skin alone (urticaria and angioedema) the patient need only receive antihistamines and oral steroids. If the reaction involves anaphylactic symptoms (difficulty in breathing, lightheadedness, collapse, loss of consciousness) then intramuscular adrenaline is the treatment of choice, after which the patient should be sent to hospital for further observation.

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A mild delayed hypersensitivity can be treated with courses of non-sedating oral antihistamines (such as cetirizine or loratadine) and steroids (oral, topical or a combination of the two).

Severe delayed reactions need treatment in hospital. Treatments include intravenous immunoglobulins, steroids, antibiotics, fluids, antihistamines and analgesics. Specialist burns units are the best place to treat SJS / TEN due to extensive skin loss.

#### Whom to refer and what investigations we will do

Not all allergy services will have the facilities to investigate drug allergy reactions. You may be aware of appropriate centres local to you, but if further information is required, please consult the British Society of Allergy and Clinical Immunology (bsaci.org. uk) website for a comprehensive list. Allergy UK can also help in this regard. Most centres will shy away from any investigations of Severe Cutaneous Adverse Reactions (SCAR). If you have such a patient, then my drug allergy clinic at Guy's Hospital in London is the only comprehensive option at the moment.

In deciding whom to refer, firstly exclude those cases which are almost certainly side-effects of the drug rather than allergy. If you decide that the patient's history is possibly consistent with allergy, then please gather as much information from you GP notes and prescriptions about the nature of the reaction:

- Which drug was involved (be specific co-amoxiclav or flucloxacillin rather than 'penicillin')?
- Dosage and duration of course
- Timing of reaction relative to when the drug was given

- Nature and duration of symptoms
- Treatment required
- Has the patient received the same drug again?

Such information will not be immediately available to us in secondary care but is invaluable in appropriately investigating the reaction. If the patient has suffered an allergic reaction during general anaesthesia, the referral must be made by the anaesthetist involved (see article on 'Perioperative anaphylaxis' elsewhere in this issue).

The investigations that we perform depend on the nature of the allergic reaction. Immediate reactions are the most straightforward. We would start with skin prick tests and intradermal tests. If these are negative, then we would proceed to a challenge test (or drug provocation test) performed in a graded manner in a closely supervised environment (either a day care unit or a ward). The procedure usually takes half a day.

A mild delayed reaction would initially be investigated by delayed intradermal tests – the reading of the tests is carried out after 48 hours rather than 15 minutes as is the case of immediate reading intradermal tests. Patch tests are another option. This involves application of the drug as an intravenous solution or as crushed tablets in petrolatum onto the patients back where it remains beneath a 'patch' for 48 hours. Again, if negative, we would proceed with a challenge test with dose timing modifications appropriate for delayed reactions.

Investigations for SCAR patients involve similar skin tests (delayed intradermal tests and patch tests) but due to the risk of reactivating severe reactions, we judge this on a case-by-case basis. We can also request in vitro tests that are without risk. Challenge tests are contra-indicated in SCAR except in very special circumstances.

In summary, we are happy to accept referral of any patient with a history of drug allergy to a drug that might be useful to them either now or in the future. This includes patient with recent reactions that are unconfirmed or those with historical reactions that have likely resolved.

# FEATURE:

#### Allergy testing in Primary Care

Amena Warner is a member of the Immunology and Allergy Nurses Group and was the first nurse to sit on the British Society of Allergy and Clinical Immunology (BSACI) council where she started the National Nurses Allergy Group, now known as the Allied Health Professionals Group.

### The Why, When and How We Should Do Allergy Tests in Primary Care

Allergic disorders are now the most common chronic condition in children and young people. Allergic disorders encompass asthma, eczema, food allergy, allergic rhinitis (hay fever) and drug allergy.

- 150 million Europeans live daily with allergy
- 100 million Europeans live with allergic rhinitis. In the UK we have the third highest rates
- 17 million people have food allergy
- 45% have never received an accurate diagnosis
- Allergy has a more severe impact on quality of life than diabetes or heart disease

Source: European Academy of Allergy & Clinical Immunology, 2016

#### It has been estimated that 'allergic conditions' account for 8% of all general practice consultations in the UK<sup>1</sup>.

Only 29% of GPs and 9% of nurses receive allergy training, highlighting a clear need for further education in allergy at primary care level<sup>2</sup>.

Allergy is defined as a 'hypersensitivity reaction mediated by immunological mechanisms'. Atopy is defined as 'a personal or familial tendency to produce IgE antibodies in response to low doses of allergen, usually proteins, and to develop symptoms such as asthma, eczema or rhinoconjunctivitis.'

#### We can divide allergic reactions into:

- a) Those that happen immediately within an hour of exposure to the allergen (and up to a maximum of two hours). These are referred to as Type 1 IgE mediated reactions. They directly involve the immune system and it is these types of reactions that can be 'lifethreatening'.
- b) Those that happen after two hours, which are referred to as delayed reactions. When these types of reactions happen with food they are often referred to as Non IgE mediated reactions (these reactions are very different to intolerance, which does not involve an immune response that causes the symptoms).
- c) There are also delayed reactions from contact of an allergen, on the skin, which are called Type 4 hypersensitivity skin reactions (contact reactions of this type are not due to foods but usually to ingredients in skin care lotions/creams, chemicals in cleaning agents or metals such as nickel, or allergens such as latex in rubber gloves.

Allergy can affect people differently. To the 'non' allergist/immunologist, it can be very difficult to link symptoms together. However, it is important to have

an understanding of the immune response and its underpinning role in 'defending' the human body. Historically, we were exposed to parasitic infections and some 'developing' countries still have high levels of parasitic infections within their populations. Research tells us that in these populations there is very little symptomatic allergy. Immunoglobulin E (IgE) fights parasitic infection. In the absence of our bodies having to defend itself against parasites, IgE is rather redundant in this role, so can try to 'defend' against harmless everyday things, such as foods or pollens. These then become perceived as the 'enemy' it needs to defend against, giving symptoms and then making them, in some extreme cases 'harmful' to that individual (in the case of anaphylaxis).

Below are some common 'allergic triggers'. A person can have symptomatic allergy to one or a few of these. There are some who have allergic reactions to many foods as well as having pollen and house dust mite allergy. This can highlight the complexity of allergy.

- Food
- Venom
- Drugs/medicine
- Pollens
- Pets/animal hair/dander/skin
- Moulds
- House dust mite

#### How should allergy be investigated?

1. An allergy-focused clinical history should be taken

- 2. Physical examination (nose, skin)
- 3. Diagnostic test

#### What things need to be considered when taking an allergy-focused clinical history?

Some questions to ask are:

#### What are the patient's symptoms?

**Symptoms** are a key feature. They may or may not be present all the time (intermittent or persistent) and they may only arise on acute exposure to the allergen (such as when the culprit food is eaten). Symptoms can include itchy mouth/throat, nausea, vomiting, diarrhoea, and clear runny nasal discharge. Ask about nasal blockage; this can be unilateral or bilateral (but note that allergy rarely gives unilateral symptoms). Symptoms also include post nasal drip, sneezing, itching, rubbing nose in upward direction (allergic salute), asthma, angioedema, urticaria and eczema.

Is it one food or many foods that cause symptoms?

**Does the severity** of symptoms indicate anaphylaxis (respiratory/cardiovascular) (Refer to NICE guidelines for management pathway).

How long have symptoms been present?

Are they **persistent** or **intermittent** symptoms? Such as worsening at a particular time of year i.e. seasonal, or all year round/perennial or episodic.

What is the **history of atopic conditions**? i.e. asthma, hay fever, eczema or family history of asthma, eczema, hay fever, food allergy.

Are there **environmental factors** to consider such as the setting at work, home, school etc?

Do symptoms improve when on holiday? Or when away from work or home?

Are they worse in morning or at night?

Are they worse indoors or outdoors?

Do they have any pets or animal contact?

What is their occupation and hobbies?

#### Validated allergy tests

1) Immediate allergy (IgE mediated) is tested by:

A) Total and serum specific IgE. This is a 'blood sample' test and can be taken and used in primary, secondary and tertiary settings.



B) Skin Prick Testing (SPT). This is usually done in secondary and tertiary settings due to remote risk of anaphylaxis. NICE have produced guidance around this.

The rest of these tests are carried out in specialist **allergy/immunology** services:

C) Prick to prick testing (e.g. useful for fresh fruit testing, as the prepared commercially available allergens biodegrade quickly, so may give inaccurate results).

D) Intradermal testing. This is a very important test often used in drug testing clinics.

E) Basophil Activation Test (BAT)

F) Component resolved diagnostics (CRD). These are advanced allergy tests, where the allergen is broken down into the various protein components. We now have a greater idea of which one of these components give rise to greater probability of serious allergic reactions. This is a useful tool to 'risk assess' further as to who may be at risk of anaphylactic reactions and would therefore be required to carry adrenaline and who would not be, so would have no need to carry adrenaline. These are very complex tests that need a high level of understanding to interpret the results accurately, so are being done regularly in **specialist immunology and allergy services** right across the UK.

G) Challenge test (done in controlled hospital settings, to confirm or refute an allergy diagnosis, when the allergy tests are unclear). This is often seen as the 'gold standard' for confirmation.

Drug testing: requires skin prick testing, intradermal tests and often a challenge test. It is a highly specialised and complex procedure.

During an acute episode of anaphylaxis evidence of mast cell degranulation can be tested for by taking serum mast cell tryptase levels. These are usually done in Accident & Emergency departments, perioperatively or at a hospital ward level, when requested.

2) Type 4 hypersensitivity reactions are tested for by patch testing for contact allergy of the skin (this is often referred to as for type 4 IgE mediated and usually done in **dermatology clinics** for delayed hypersensitivity reactions). The type of conditions often referred for

patch testing are eczema in older children and adults, occupational contact allergy, hand eczema etc.

Delayed food allergy (Non IgE), where there are no immediate symptoms and usually this is done for things like Non IgE cow's milk allergy, where the symptoms are colic, prolonged crying and discomfort, eczema, constipation or diarrhoea etc. and requires elimination then reintroduction (under the supervision of an allergy dietitian or paediatrician).

Total and Specific IgE (formally known as RAST testing) Specific IgE blood tests are standardised and highly quality controlled. [Both internal, in the laboratory they are measured in and externally, where samples are sent to a reference laboratory (NEQUAS is the accreditation standard required)]

#### Sensitivity as well as specificity is important.

Reliability without procedure variation are another one of the strengths of this test along with the standardised results.

Sensitivity and specificity values of 90% can be obtained with Immunocap technology. This means the test is very sensitive to pick up the majority of people with allergy and specific enough for it to be allergen measured.

There is no relation between specific IgE result and severity of allergic reactions (although some allergens have a higher positive predicative value than others <sup>(5)</sup>). So it is very important these tests are interpreted correctly.<sup>(6)</sup>

A 4-7ml blood sample is required, in a tube with no anticoagulant, although a minimum of 1ml blood can be used in exceptional circumstances. A 1ml blood sample is sufficient to test up to eight allergens, which is important to note for paediatric patients, as this could be obtained from a finger prick, although it is usually serum and plasma (EDTA or Heparin)

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samples from venous blood that is used. Phone your local immunology laboratory for more guidance on paediatric specific IgE samples.

## There are over 650 different allergens available.

Selection from clinical history is vital to request the most relevant allergens as it can become very expensive when requesting multiple allergens. This is especially the case if it is not driven by logical rationale of thought, for the most likely culprit allergen from taking the allergy-focused clinical history, as blind screening for allergens is both misleading (as you may miss the culprit allergen) and expensive.

Some labs will use panels, the most common being aeroallergen or food mixes (but this is dependent on the lab and their protocols). Allergy clinics are not testing centres (in the same way you would go for an ECG or lung function test), as much of this testing can be done in primary care. They are there to provide specialist tests, advice, management and treatments.

For example, if an individual feels they have an allergic reaction every time they are near a cat a specific IgE test can be carried out in primary care to see if the person is allergic to cats. If the test returns positive then you can advise them to avoid cats and not to get one as a pet. However, if the individual's job brings them into daily contact with cats, such as a vet, then they cannot avoid them so can be referred to a specialist allergy service for consideration of a desensitisation treatment called immunotherapy.

So to recap, the relevant allergens are selected from clinical history, blood sample and a test request form sent to your local lab. The results usually take one to two weeks to be returned. This may be a good opportunity to recall the patient to discuss the results and assess the efficacy of any treatment you may have commenced, as well as influencing decision-making of further referral to a specialist allergy service. Please note many immunology services around the country also specialise in the treatment and management of patients with allergy. Allergy and also immunology services also provide specialist advanced treatments such as immunotherapy and biological treatments (using monoclonal antibodies for severe asthma and chronic spontaneous urticaria). Many of these types of therapies have been shown to improve the quality of life of those with these conditions, so it is important to have knowledge of their existence and the benefits to patients from referral to these services.

- A positive result indicates sensitisation to that allergen, it does not measure how severe the reaction can be.
- Specific IgE can be measured for all ages.
- It is not dependant on a person's skin condition, medications, symptoms, disease severity or activity.
- It can also be performed in pregnancy and breast feeding.

Many patients with eczema may have high total IgE as well as many positive specific IgE, so expert interpretation of these tests are needed before removing lots of food from the diet based on the test. It is in these types of cases when a referral to an allergy clinic is very beneficial.

#### Interpreting the test

ImmunoCAP detects IgE antibodies in the range of 0-100kUA/L (where A represents the allergen specific antibody). As a general rule, the higher the specific IgE antibodies, the higher the risk of symptomatic allergy (but beware, as serious allergic reactions can happen at low levels as well, as specific IgE testing cannot predict severity of reaction).

A raised total IgE is seen in allergic disease, some parasitic infections, with immunodeficiencies and patients on immunosuppressant.

#### Indications for specific IgE testing

There are many advantages to using a test such as Specific IgE and they can be used in:

- People who can't stop anti-histamines or TCAD
- Patients with dermatographism or extensive eczema
- Those with a history of anaphylaxis
- Those with persistent severe or unstable asthma
- Pregnancy
- Patients on β blockers or ACEI

#### Important caveats:

- A negative specific IgE test does not necessarily exclude clinically significant allergy.
- A positive specific IgE test indicates sensitisation which can occur without the clinical expression of allergy.

#### Importance of doing a diagnostic test

- Identify allergic people through allergy history taken to help select the allergen(s) that may be causing the symptoms
- Helps identify allergen, and so, potential allergic triggers
- Correct allergen avoidance/reduction advice can be given
- Doing a diagnostic test directs correct and adequate prescribing of anti-allergy medication and treatment
- Appropriate medical intervention can be implemented
- Supports decision-making as to whether it is allergy or not, for referral pathways
- Can also rule out allergy
- Newer tests can help to risk assess patients i.e. (Component Resolved Diagnostics/molecular testing).

When discussing allergy testing with your patient it is important to note there are some tests not recommended by NICE for diagnosing allergy, these are:

- a) Applied kinesiology (a process based on muscle testing)
- b) Vega test (which involves measuring electromagnetic conductivity in the body)
- c) Hair analysis
- d) Serum specific IgG tests

These tests are often available from the internet or on the high street. The NICE guidelines advise there is little evidence that these tests work, some can leave children at risk of malnutrition from restricted diets.

#### Allergy: clinical implications

- Can be Life threatening
- Multi-system
- Progressive
- Life changing
- Psychological morbidity

#### Impact of allergy

- Strict dietary restrictions large variety of foods with a 'may contain' discretionary labelling
- Lower quality of life than those diagnosed with type-1 diabetes
- Impact on psychological well-being, living with fear of an allergic reaction
- Prescription of adrenaline auto-injectors for life is routine practice (economic burden to the health system).



#### **Key messages**

A diagnostic allergy test should only be selected after a thorough clinical allergy history is taken to identify allergic individuals and the suspected allergen(s) that maybe either causing or exacerbating the symptoms.<sup>(6)</sup>



It supports decision-making as to whether it is allergy or not for appropriate referral pathways. (6)



Doing a diagnostic test helps direct correct and adequate prescribing of treatment and management of allergic disease.

4

Blind screening for allergens using Specific IgE or skin prick tests is misleading. Never just do blanket screening as there is a remarkable high levels of positive results, as not all sensitised individuals will have symptoms on exposure. Always take an allergy focused history and then do focused tests.

Only use validated allergy tests as per NICE guidelines.

If there is a history of anaphylaxis to food, venom (bee or wasp) or a drug (i.e. Antibiotic, NSAID, aspirin etc) then follow the MRHA guidance and prescribe two adrenaline auto injectors. Refer to an allergy/immunology service for further decision-making and risk assessment (they can do this by very advanced testing called 'component resolved diagnostics').

Patient support groups such as Allergy UK provide extensive information on their website and also a helpline.

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