Allergy Today 2014

Allergy UK's publication written by healthcare professionals, for healthcare professionals

In this issue:

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Allergy UK
leading the fight against allergy

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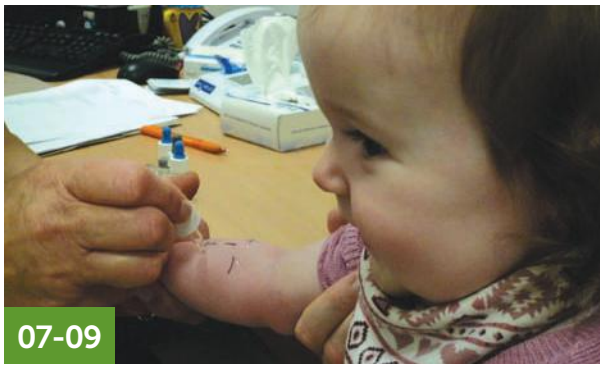
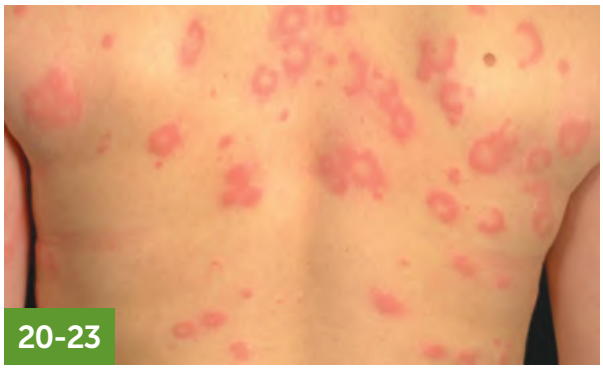




Allergy UK is the leading national medical charity providing advice, information and support to people with allergies and food intolerance.

Foreword

Welcome to the third edition of *Allergy Today*. The past year has been another exciting one in the world of allergy. Recent high profile news coverage of the excellent work around peanut desensitisation at Addenbrooke's Hospital gives us all hope that we can bring a whole new dimension of care to our patients. The media prominence of the news about such new advances on the front pages of both medical and lay publications also illustrates how much allergy has now penetrated into the mainstream of public consciousness. It is essential we build on this to ensure we secure better services for our patients. Whilst research continues to show an increasing burden of allergic disease in the UK, we have also seen positive steps in raising awareness with meetings held in Parliament, and new guidelines for milk allergy for both primary care and specialist care being published.

This issue of *Allergy Today* reflects the changing pattern of allergic disease in the UK with a particular focus on non-IgE-mediated presentations such as allergic gut disease and Food-Protein Induced Enterocolitis. These conditions can have an enormous impact on quality of life and a delay in diagnosis is all too common. Whilst the past few years have seen an enormous increase in awareness of the less subtle forms of food allergy, we must continue to ensure that the less obvious forms enter the minds of healthcare professionals in primary care when they are assessing small children.

I am delighted that Allergy UK continues to develop its role in supporting both patients and healthcare professionals as well as ensuring that patients have a strong, clear voice in the process of developing the services that they will rely on for the future. A firm commitment to education means that the Allergy UK bursary scheme continues to provide support to HCPs wishing to develop their knowledge in allergy – make sure you take advantage of this.

I hope you enjoy reading this edition of *Allergy Today*.

Dr Adam Fox, Chairman of Allergy UK Health Advisory Board; Consultant Paediatric Allergist (St Thomas' Hospital) and Reader in Paediatric Allergy (King's College London)

Welcome

Allergy UK plays a significant role in supporting people with allergies and food intolerances. As we receive a vast number of enquiries through our website (www.allergyuk.org), helpline and web chat, we able to act as their collective voice and advocate on their behalf.

Our first Annual Conference in April at St Thomas' Hospital was a resounding success and brought together patients and healthcare professionals working together to improve the experience of allergy sufferers through the different stages of their allergic journey. In coming years we will build on this success with conferences across the country. I would be very interested in hearing from you about the topics you would find compelling.

We are always looking for ways in which we can better support healthcare professionals. We currently have over 130 factsheets on allergic conditions and their management. They are free to download from our website.

Working with you we can make a significant difference to the lives of people with allergies or food intolerances.

D'Arcy Myers
Chief Executive, Allergy UK

Introduction: Director of Clinical Services

I have recently attended the European Academy of Allergy and Clinical Immunology (EAACI) meeting, the biggest annual allergy conference worldwide, this year attended by around 7,500 delegates. It is a unique opportunity to hear the latest worldwide research presented and to be able to question and discuss with experts in all allergy related disciplines. The evidence for the worrying growth of emerging allergies in paediatrics sends an overwhelming message of the need for clinicians to be constantly aware of symptoms that indicate atopic eczema and food allergy, in all its different forms.

In this edition of *Allergy Today*, we have articles on the different presentations of food allergy, an emerging science and a condition that can severely affect the child and their future development, as well as the awful impact on families. Misdiagnosed non-IgE food allergy may cause malnutrition leading to long-term growth and developmental problems. The articles on urticaria and angioedema are part of our ongoing activities to promote recognition and better management of these conditions in Parliament and in the press, as we have so many calls about this from sufferers.

Maureen Jenkins
Director of Clinical Services, Allergy UK

Allergy News

Vitamin D

Research from the Murdoch Children's Research Institute in Australia showed that low levels of serum 25-hydroxyvitamin D were related to food allergy in Australia but nowhere else. Levels differed in ethnic groups. There was a big difference in children whose parents were both born in Australia. Raised binding protein levels were associated with raised food allergy. Maternal supplementation with Vitamin D seemed to have a protective effect from food allergy in the child and lowered blood pressure levels.

The Southampton Lung Biology research group found symptom improvements in patients with severe asthma given huge weekly supplements of Vitamin D for a few months. The protection lasted for some time and can be given again if serum levels later drop.

Allergic Threats to Consumers

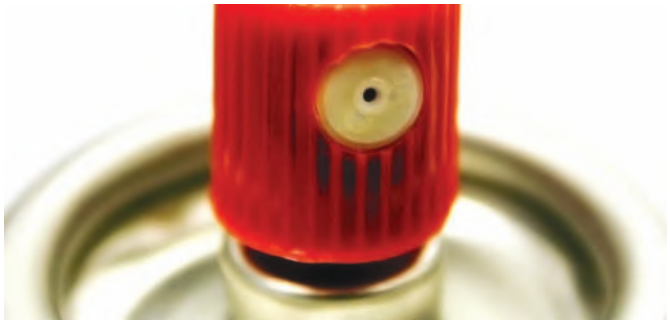
Fragrances in toiletries and cosmetics rarely cause sensitisation but often trigger symptoms in previously sensitised individuals. The fragrance as it is put in the bottle is not always the problem but once open and standing, it oxidises which can trigger reactions. Natural plant compounds, terpines, such as limolene and limolol may also trigger symptoms.

The accumulated dose may eventually lead to symptoms, particularly on the face and in the axilla.

Respiratory symptoms related to perfume – only high doses cause histamine release, although lower doses can aggravate inflamed airways or those with severe chemical sensitivity. Capsaicin may trigger a cough reflex.

Preservatives and Contact Allergy – all water-containing products need preservatives, i.e. cosmetics, medicines, paints and glues, and household products. For those without skin disease, this is rarely a problem. However, they can affect those with eczema or particularly sensitive skin.

Isothiazolinones (MI/MCI:KathonCG) are powerful biocides very commonly used in skin products and which have caused increasing levels of allergic reactions. In December 2013, EU advice to industry was not to use them at all in 'leave-on' products and use at <15ppm in 'rinse-off' products.



Dimethyl fumarate is an antifungal that was used to stop mould growth in leather products, such as sofas and shoes, and a cause of allergic contact dermatitis (in allergic individuals) or, in larger exposures, irritant contact dermatitis. It is now labelled as a 'Human Health Hazard', not allowed in manufacture but still allowed in pharmaceutical use, as a treatment for multiple sclerosis. The ban in 2009 is reassessed annually.

Parabens are preservatives commonly used causing less than 0.5% contact allergy. Methylparaben and butylparaben cause less than 0.19% of contact allergies and are approved for use.

Allergy News

Anaphylaxis – Important Information

The MHRA (Medicines and Healthcare Products Regulatory Agency) has issued new guidance on the use of adrenaline auto-injectors and, following their concerns about the safety and utility of adrenaline auto-injectors, the European Medicines Agency are conducting a review on all adrenaline auto-injectors. This was after the post-mortem of a teenager who died, despite using two adrenaline pens.

The MHRA Drug Safety Update (June 2014):
People who have been prescribed an adrenaline auto-injector because of the risk of anaphylaxis should carry two with them at all times for emergency, on-the-spot use. After every use of an adrenaline auto-injector, an ambulance should be called (even if symptoms are improving), the individual should lie down with their legs raised and, if at all possible, should not be left alone.

Prescribers should be mindful of the adequacy of the needle length and dose for the patient.

See further information: www.anaphylaxis.org.uk/userfiles/files/MHRA_AAI_Guidance_June2014.pdf

EAACI Annual Meeting 2014
Latest findings from the European Academy of Allergy and Clinical Immunology

Anaphylaxis

- A previous mild anaphylactic reaction is not a predictor of the severity of future reactions
- Anaphylaxis can be fatal after only one mild reaction or even at a first reaction
- A pharmacist can legally dispense an adrenaline auto-injector without prescription if someone is having an anaphylactic reaction
- Anybody may legally administer an adrenaline auto-injector if they believe that someone is having an anaphylactic reaction

Co-factors in anaphylaxis are exercise, alcohol, NSAIDs, stress. A low allergen dose plus a co-factor can exceed the threshold for anaphylaxis, particularly in **patient groups at increased risk:**

- Infants: cannot describe itch, dyspnoea, impending doom. They stop interacting, cling, cry inconsolably
- Teenagers: body changes; attitudes, more willing to take risks and not carry adrenaline
- Pregnant women: hormonal changes; cramps, back pain, pre-term labour; labour and delivery: betalactam aetiology, peri-operative agent, latex. Differential diagnosis may include amniotic fluid embolism
- Elderly: co-morbidities, e.g. CVD, COPD. Chest discomfort is hard to diagnose
- Increased in cardio-vascular disease: Mast cells in the myocardium are increased in cardio-vascular disease and play a key role in athero-sclerosis. Mediators from these cells cause coronary artery spasms

Delayed reactions:

- Red meat, cross-reactivity from tick bites
- Five to six hours later, after a very heavy meal

There are dif erent phenotypes; not all have a lowered blood pressure. Common reactions:

- Infants: skin and vomiting. Rarely have a lowered blood pressure
- Children: skin and respiratory
- Teens: skin, respiratory and cardio-vascular

IgE-mediated Allergy

Focus on Food Allergy in Children

Allergy Profile

Dr Jo Walsh

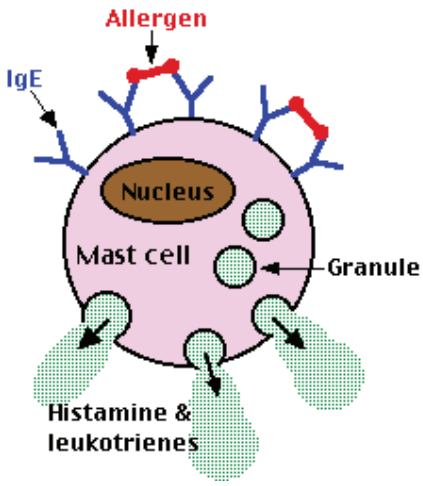
GP, with a specialist interest in allergy

Having qualified from the University of Manchester, with preclinical training in St Andrews, Jo worked in several paediatric posts in the North of England before commencing her GP training in East Anglia. She has always incorporated her interest in paediatrics into her daily practice and now combines this with her interest in allergy.

She was the GP member of the Guideline Development Group for the NICE Guideline on Diagnosis and Assessment of Food Allergy in Children in Primary Care and Community Settings and the GP on the Food and Gastrointestinal allergy stream of the RCPCH allergy pathway project.

The role of the immune system is to recognise and respond to any 'substances' which pose a threat to the body. It is important in the body's management of infections and in the promotion of healing. Immune 'reactions' are therefore a 'normal' functioning of the body. The immune system may however malfunction by recognising as a threat a substance, which by most of us would be accepted. What may in some prompt a minor and unrecognisable immune response, i.e. with no clinical symptoms, may in others produce a response which is considered abnormal. If this response to the allergen occurs within minutes of exposure it is likely that the mechanism of the immune response is predominantly IgE-mediated. We therefore term responses occurring within minutes as acute or IgE-mediated reactions or allergy.

If we look at the mechanism of this reaction:



The breaking down of the mast cells and the release of histamine gives the clinical symptoms. The symptoms of an IgE-mediated reaction may involve a specific organ system, or several, such as skin, airway and gut.

An IgE-mediated reaction may be localised within the skin if a sensitive individual has skin contact with a substance to which they are allergic. This may result in a localised area of pruritus, erythema or even urticaria. It may however be that the skin is involved in a more systemic reaction resulting in widespread urticaria and even angioedema. The gastrointestinal system may further be involved with sudden onset nausea, vomiting, abdominal pain or diarrhoea. The respiratory symptoms, seen more commonly with inhalant allergens than food allergens, may involve nasal itching, rhinorrhoea or congestion and sneezing.

"The breaking down of the mast cells and the release of histamine gives the clinical symptoms."

Eczema can be made worse by reaction to certain food proteins, most commonly milk, and there may be acute flares of eczema as a result of IgE-mediated reactions, but early onset eczema is also a risk factor for food allergies.

Systemic reactions may result in anaphylaxis where the features are of a life threatening generalised, or systemic, hypersensitivity affecting the whole body. The reaction affects the **airways** (oedema), **breathing** (bronchospasm with tachypnoea) and **circulation** (hypotension and/or tachycardia).

The NICE guidelines recommend that when presenting with suspected anaphylaxis:

- Children under 16 years should be admitted to hospital under the care of a paediatric medical team
- Over the age of 16 years, patients should be observed for 6–12 hours from the onset of symptoms
- With appropriate post-reaction care, those reactions that were controlled promptly and easily may be observed for a shorter period[1]

Patients presenting with severe allergic reactions should therefore not be managed in the community. As part of the secondary care management process, these patients should be referred to a specialist allergy service (age-appropriate where possible) and provided with an appropriate adrenaline injector.

Before discharge, these patients and their families should be offered:

- Information on the signs and symptoms of an anaphylactic reaction and what to do in an emergency
- Advice on the risk of a biphasic reaction
- Advice on how and when to use an adrenaline injector and carrying medication
- Advice on avoiding suspected triggers (if known)
- Information on the specialist allergy service to which they will be referred
- Relevant contact information for patient support groups[1]

"Eczema can be made worse by reaction to certain food proteins, most commonly milk, and there may be acute flares of eczema as a result of IgE-mediated reactions, but early onset eczema is also a risk factor for food allergies."

If the reactions are less severe, immediate referral may not be appropriate. NICE, with respect to children and food allergy, suggests referring before testing any child with a severe acute reaction, possible multiple food allergies, parental suspicion of food allergy but an unconvincing history, and significant atopic eczema with suspicion that more than one food is contributing to the symptoms[2].

If there is a good history of an IgE-mediated reaction to a substance, it is appropriate to consider testing. NICE recommends GPs doing this if, from the history, they consider that just one particular food may be causing a reaction[2].

IgE skin prick testing and serum specific IgE tests should be undertaken with caution. With regard to safety, NICE considered that anywhere where there is provision to treat anaphylaxis to be appropriate for skin prick tests to be performed. As there is a risk of anaphylaxis with vaccinations, the community, e.g. GP surgeries, where vaccinations are performed are considered appropriate. It is however important that the person(s) requesting, performing and interpreting the tests are competent to do so[2].

Serum Specific IgE and Skin Prick Tests

Serum specific IgE and skin prick tests tell you only if a patient is sensitised, i.e. that the immune system is capable of producing a response to the substance. Results do not indicate the severity of future reactions. Testing should not be used to 'screen' people with no allergy history. One study showed that 80% of people who are sensitised to peanut will not get symptoms on exposure[3]. A positive result and a positive history should confirm the relevance of the specific trigger to that patient. A positive result on its own is meaningless.

Following testing, NICE suggests referral for children with food allergy if there is:

- A proven IgE-mediated reaction and asthma (the biggest risk factor for severe reactions)
- Negative test results but a history giving strong clinical suspicion of IgE-mediated allergy[2]

For all IgE-mediated reactions, avoidance of the allergen is the most important factor. Those with IgE-mediated reactions may require antihistamines or adrenaline to manage their symptoms, although education on avoidance is most important.

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Eosinophilic Gastrointestinal Disorders (EGID)

Allergy Profile

Adriana Chebar Lozinsky

Clinical and Research Gastroenterology Fellow at Great Ormond Street Hospital, London

Adriana graduated in Medicine in 2008 and is a specialist in Paediatric Gastroenterology from the Federal University of São Paulo, Brazil.

Since 2011 she has been studying food allergies and is currently a Research and Clinical Fellow at Great Ormond Street Hospital under the supervision of Dr Neil Shah.

Eosinophils are white blood cells found in blood and in certain body tissues like the gut. They play an important function in the immune system to help fight certain types of infections, e.g. parasitic infections. Increased numbers of eosinophils are also associated with allergies. When there is an increase in the production of eosinophils that are then deposited in various parts of the body this can lead to chronic inflammation that results in tissue damage and symptoms. Eosinophilic gastrointestinal disorders (EGID) are a group of diseases characterised by an increased number of eosinophils in the gastrointestinal tract. The causes of EGID remain unclear and the diagnosis is a clinical diagnosis aligned with the biopsy findings. EGIDs are classified as:

- Eosinophilic Oesophagitis (EoE): Characterised by excess eosinophilic infiltration in the oesophagus
- Eosinophilic Gastroenteritis (EGE): Characterised by excess eosinophilic infiltration in the stomach and small bowel
- Eosinophilic Colitis (EC): Characterised by excess eosinophilic infiltration in the large bowel

EGID can affect patients of all ages and ethnicities, are more common in males and can run in families. Approximately 75 per cent of patients with EGID have an atopic background meaning they are likely to suffer from hay fever, asthma or eczema. There are several symptoms associated with EGID; however none is specific and the clinical presentation can be different from patient to patient. The most common symptoms are vomiting, dysphagia (difficulty in swallowing), poor appetite, abdominal pain, diarrhoea, blood/mucus in the stools, constipation, faltering growth or poor sleep patterns.

"EGID can affect patients of all ages, ethnicities, is more common in males and can run in families. Approximately 75 per cent of patients with EGID have an atopic background meaning they are likley to suffer from hay fever, asthma or eczema."

The diagnosis is usually based on clinical history married by performing an endocopy with biopsies, which show increased eosinophils. Depending on the symptoms, endoscopy may be performed on the upper part of the bowel, called gastroscopy, or the lower bowel, called colonoscopy. During the examination, biopsies are taken for microscopic evaluation. The presence of increased eosinophilic infiltration and signs of local inflammation confirm the diagnosis. EGID is a relatively uncommon disorder; the mixed presentation of symptoms and the lack of validated tests make the diagnosis of EGID a challenge. The number of eosinophils varies in the bowel depending on the site the biopsy is taken from, ranging from zero in the oesophagus to varying numbers in the rest of the bowel.

Once the EGID diagnosis is confirmed, treatment options will be discussed with the family. The treatment may vary according to the site where the disease has been diagnosed. Eosinophilic Oesophagitis is the most common disease among EGID and for this reason is the most studied and well known.

Eosinophilic Oesophagitis (EoE) is a chronic oesophageal disease characterised by elevated levels of eosinophils and inflammation in the oesophagus, and symptoms such as dysphagia, which is food getting stuck in the oesophagus. Other symptoms include abdominal pain, anorexia and vomiting unresponsive to therapy. The diagnosis is made by the presence of greater than 15 eosinophils per microscope high powered view in one or more biopsies after the exclusion of gastro-oesophageal reflux disease.

Treatments should be individualised and based on the clinical context of each patient. There are three main ways to treat:

1. Elimination diet: The elimination diet consists of excluding allergic foods from the patient's diet. This exclusion can be based on positive allergy tests (skin prick test and/or specific immunoglobulin E (IgE) testing) or empirically removing the most common known foods that cause allergies, e.g. cows' milk protein, egg, soy, wheat, peanut, tree nut, fish and shellfish.
2. Elemental diet: Elemental diets are diets where the entire nutrition given to the patient is made up of a liquid formula which is composed of amino acids (building blocks of proteins). It can be offered in conjunction with an elimination diet or as an exclusive food.
3. Medications: These can help control inflammation and the symptoms for EGID. Steroids applied locally to the oesophagus are the most commonly used in EoE (e.g. swallowed fluticasone or budesonide slurry), or medications such as cetirizine, ketotifen, sodium cromoglycate, montelukast, oral prednisolone and occasionally other medications called immunosuppressants have been used.

EGID requires long-term treatments, many life-long, with medications and dietary restrictions, which can be complex and require cooperation between parents, dietitians and physicians in order to maintain a quality of life for the patient and family.

Useful links:

http://apfed.org/drupal/drupal/index.php

http://www.fabed.co.uk/

http://www.cincinnatichildrens.org/service/c/eosinophilic-disorders/conditions/default/

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Food Protein-Induced Enterocolitis Syndrome (FPIES)

Allergy Profile

Dr Helen Brough
MSc MA (Hons)
MB BS FRCPH

Consultant Paediatric Allergist

Helen is a Consultant in Paediatric Allergy at Guy's and St Thomas' Hospital; she has set up integrated paediatric allergy services with community based clinics and education for Primary Care clinicians. Helen also runs Joint Allergy & Respiratory clinics and Joint Allergy & Gastroenterology clinics. Helen has written a book in Paediatrics (Rapid Paediatrics and Child Health) and was awarded 'Health Professional of the Year' runner up in 2010 by Coeliac UK. Helen's research interests are in food allergy prevention and diagnostics.

Food protein-induced enterocolitis syndrome (FPIES) is a delayed food allergy characterised by severe prolonged vomiting 1–4 hours after eating a recently introduced food. During an acute episode of FPIES, the majority of children become sleepy and pale and around one in four children experience diarrhoea (which can last for several days) and develop a low temperature (<36ºC); there are no features of immediate allergy such as hives, urticaria or angioedema. Blood tests during the acute episode often reveal an elevated white cell and platelet count which may be mistaken for infection. FPIES can lead to dehydration, a fall in blood pressure and shock and therefore may be misdiagnosed as sepsis. Usually it is only after the second time that the same food causes this type of reaction that FPIES is considered as a possible cause for the reaction.

FPIES is very rarely found in exclusively breastfed babies. The first episode of FPIES usually occurs between 4 and 6 months with the introduction of first complementary foods (solid foods and/or breast-milk alternatives); however, FPIES can occur earlier if breast-milk alternatives are used before. The most common foods which induce FPIES are cows' milk and soya; however, rice is the most common solid food to induce FPIES and is also one of the most common 'weaning' foods. Any food can induce FPIES but the main foods described are cereal grains (oat, barley, wheat, corn), poultry meats (chicken, turkey), legumes (green peas and beans, lentils), vegetables (sweet potato, squash), fruit (banana), seafood, egg and lamb.[1] Children with solid food-induced FPIES tend to have more severe reactions than children with cows' milk or soy-induced FPIES.[1] Around half of children have FPIES to more than one food, particularly if they have solid food- or soy-induced FPIES. Soya-induced FPIES was previously thought to be commonly associated with cows' milk-induced FPIES (in up to 50% of cases); however, more recently this was found to be much less commonly associated (in less than 12% of cases).

In a large study of 13,019 newborns assessed over two years in Israel,[2] 44 infants (0.43%) were proven to have cows' milk-induced FPIES. In another study over 16 years, only 35 children with FPIES were identified who presented to the Children's Hospital in Sydney.[3] Therefore FPIES is uncommon. About one in two children with FPIES also has eczema and one in ten has immediate food allergies.[3] Gender, gestational age, birth weight, maternal age, number of siblings, cows' milk consumption by the mother during pregnancy and age of introduction of cows' milk into the infant's diet do not increase the risk of cows' milk-induced FPIES; however, having a Caesarean section is associated with an increased risk of cows' milk-induced FPIES in the child.[2]

No skin prick tests or laboratory tests can confirm the diagnosis of FPIES; therefore, the diagnosis is usually based on the clinical history and is confirmed by an oral food challenge to the suspected food in hospital. Endoscopy is also usually not helpful.

Management of FPIES includes removal of the offending food from the child's diet; this should be performed under the supervision of a paediatric dietitian, in order to prevent accidental exposure to the offending food and to ensure that the child's diet is nutritionally complete. Infants who have FPIES reactions to cows' milk or soya formulas will usually be commenced on an extensively hydrolysed formula or an amino acid formula. A breastfeeding mother does not need to exclude cows' milk or soya from her own diet if her infant has cows' milk- or soya-induced FPIES respectively, as long as there are no chronic problems such as low weight gain in the infant.

A child who is suspected of having FPIES should be assessed by a paediatric allergy specialist and should be given a personalised FPIES emergency management plan. This management plan should list the foods that induce FPIES and explain what to do in case of accidental exposure to the FPIES inducing food(s), and can be presented to the emergency department. There is no place for the use of adrenaline autoinjectors in the management of FPIES. Management consists of close monitoring after the child has eaten the offending food and rehydration with either oral fluids or intravenous fluids in hospital. Intravenous corticosteroids may also be administered during an acute episode of FPIES; although there are no studies demonstrating the use of corticosteroids in FPIES, their administration is thought to counteract the effects of this delayed food allergic reaction.

In general FPIES is outgrown by three years of age; however, different studies have shown a wide variety of rates of FPIES resolution. Resolution of cows' milk-induced FPIES was demonstrated in 3 out of 4 children by 18 months, and in 90 per cent of children by 2.5 years of age in the large Israeli study;[2] however, resolution was only 60 per cent by three years of age in the US.[1] Resolution of soy-induced FPIES by three years of age ranges from 20 per cent (US)[1] to 100 per cent (Canada).[4] Resolution of rice-induced FPIES by three years of age ranges from 40 per cent (US)[1] to 80 per cent (Australia).[3] These differences relate in part to how children were referred into the service but also to how frequently the children undergo oral food challenges to see if they had outgrown FPIES. Oral food challenges to determine whether the child has outgrown FPIES should be performed every 18 to 24 months as long as there is no recent history of reaction.

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Non-IgE-mediated Food Allergy in Children

Allergy Profile

Dr Jo Walsh

GP, with a specialist interest in allergy

Having qualified from the University of Manchester, with preclinical training in St Andrews, Jo worked in several paediatric posts in the North of England before commencing her GP training in East Anglia. She has always incorporated her interest in paediatrics into her daily practice and now combines this with her interest in allergy.

She was the GP member of the Guideline Development Group for the NICE Guideline on Diagnosis and Assessment of Food Allergy in Children in Primary Care and Community Settings and the GP on the Food and Gastrointestinal allergy stream of the RCPCH allergy pathway project.

What does it mean?

In order to understand non IgE-mediated food allergy we need to look at some definitions. The terms food sensitivity or hypersensitivity are used to describe any symptoms produced by ingestion of a food. Food intolerance is a reaction to food, which is reproducible on repeat exposure. Food allergy is a form of intolerance, which involves the immune system[1].

In 2001, the European Academy of Allergy and Clinical Immunology classified Adverse Reactions to Foods.[2]

What are the symptoms?

Immune reactions to food, which should be termed "allergy", are subdivided into those which are immediate, occurring within minutes and are IgE-mediated, and those which are usually delayed or non-IgE-mediated. Non-IgE-mediated reactions usually present with one or more of gastrointestinal, respiratory or skin symptoms and occur 2–72 hours after ingestion. These reactions are often, confusingly, referred to as food intolerance. The term intolerance, however, should not be used when reactions involve the immune system. Intolerance refers to those adverse reactions that are due to enzyme deficiencies e.g. lactose intolerance, reactions to pharmacological agents in foods, e.g. salicylates, and substances such as benzoates which naturally occur in foods.[3]

"Milk allergy" and "lactose intolerance" are terms which cause confusion. Milk allergy is an IMMUNE RESPONSE to the PROTEIN in milk. Lactose intolerance is MALABSORPTION of lactose, the SUGAR in milk. Both cause different symptoms. Lactose intolerance produces symptoms only in the lower GI tract, where the sugar is not absorbed, e.g. bloating, abdominal pain and diarrhoea. The symptoms of milk allergy, however, can manifest in other organs such as the skin, resulting in eczema, or the respiratory system, as well as throughout the gastrointestinal tract, producing a variety of symptoms such as reflux or constipation[3].

"Non-IgE-mediated reactions usually present with one or more of gastrointestinal, respiratory or skin symptoms and occur 2–72 hours after ingestion. These reactions are often, confusingly, referred to as food intolerance."

How do we make a diagnosis?

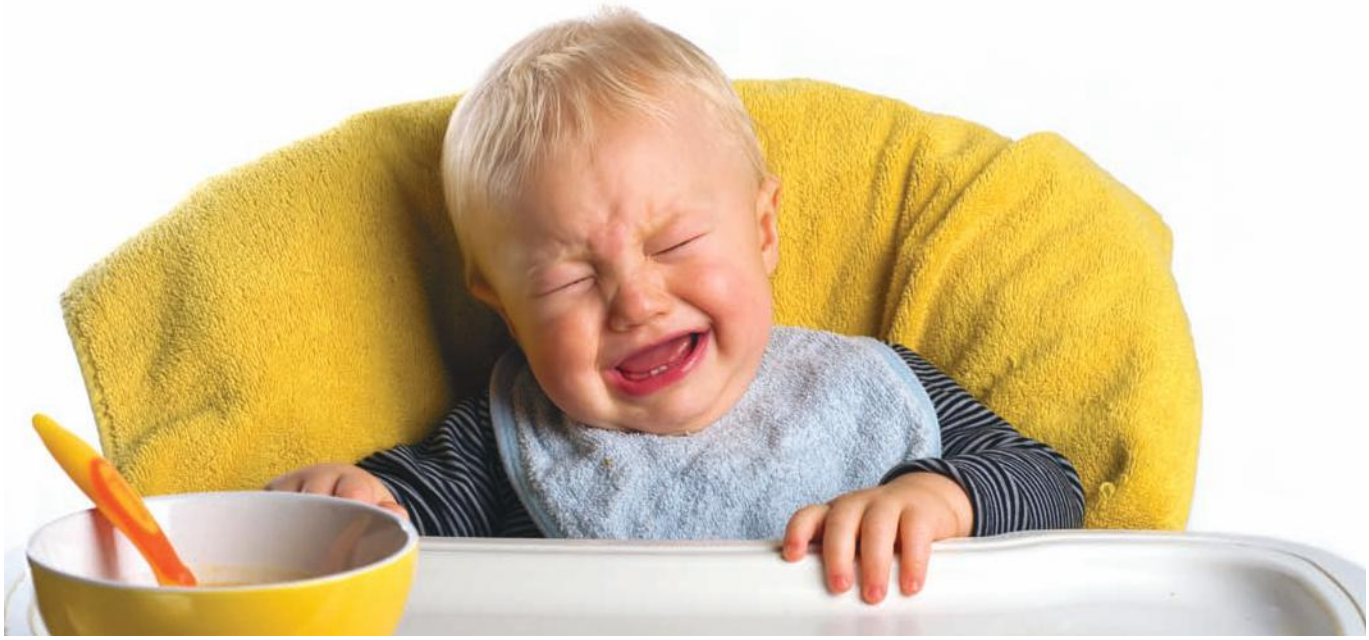
The only way of 'proving' a non-IgE-mediated reaction to food is to eliminate the suspected food(s) from the diet. If symptoms improve, but then return when the food is reintroduced to the diet, the diagnosis is confirmed. Traces of an allergenic protein may cause reactions and therefore in order to test whether a food is causing symptoms it must be totally removed from the diet. Sometimes there may be symptoms as a result of exposure to several foods. Cross reactions may also produce symptoms. 60 per cent of those with non-IgE-mediated reactions to milk show symptoms on ingestion of soya[4].

The exact mechanism of delayed reactions to food protein is unknown. It is an area of much research interest. Eosinophils have been implicated in the process and eosinophilic oesophagitis has become increasingly recognised, particularly by paediatric gastroenterologists. Eosinophilic disorders further down the gastrointestinal tract are also increasingly diagnosed. The general term for eosinophilic disorders of the bowel is eosinophilic gastrointestinal disorders (EGID).

How do we manage it?

Gastrointestinal motility problems and functional obstruction are increasingly linked to non-IgE-mediated food allergy[5,6]. A spectrum of disease is seen. The symptoms may be mild and respond to diet alone, or require medication, even immunosuppressants in severe cases, as well as the dietary changes.

"Milk allergy and lactose intolerance are terms, which cause confusion. Milk allergy is an IMMUNE RESPONSE to the PROTEIN in milk. Lactose intolerance is MALABSORPTION of lactose, the SUGAR in milk. Both cause different symptoms."



"The only way of 'proving' a non-IgE mediated reaction to food is to eliminate the suspected food(s) from the diet."

Immune reactions affecting the neuromuscular junctions have been implicated in the proposed mechanism. In cows' milk allergy, for example, "allergic constipation" may occur when high pressures have to be reached to relax the anal sphincter so there will be straining but with soft or normal stools and little, if any, response to stool softeners. Mast cells degranulating close to nerve endings have been implicated as a cause of the pain. Reflux associated with non-IgE-mediated food allergy has been found not to respond to proton pump inhibitors, as the mechanism is a dysmotility triggered by food, rather than a reflux of acid[7,8].

Gastrointestinal symptoms can occur throughout the length of the bowel. Symptoms such as rectal bleeding and diarrhoea may occur from inflammatory changes and mucosal damage, whilst immune reactions in deeper layers of the bowel are thought to produce symptoms of dysmotility.

NICE lists skin symptoms of non-IgE-mediated food allergy as pruritus, erythema and atopic eczema[3]. Symptoms of the upper and lower respiratory tract usually occur in combination with symptoms of the gastrointestinal tract and the skin[3].

Mild, isolated and non-troublesome 'symptoms' occur in many children and so not require any medical input BUT a combination of symptoms in different organ systems or persistent, isolated symptoms not responding to usual treatments should prompt consideration of non-IgE-mediated food allergy[3].

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Angioedema

Allergy Profile

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His special clinical interests include allergic disorders, food intolerance, skin prick testing, immunodeficiencies, systemic auto immune disorders including connective tissue diseases, auto inflammatory syndromes and paediatric immunology.

Definition

Angioedema is defined as short-lived and self-limiting swelling of the subcutaneous and submucosal tissue. Resulting from transient leakage of fluid into the interstitial space, it is usually asymmetrical, non-pitting and non-dependant. It is a consequence of increased vascular permeability, due to release of vasoactive mediators such as histamine, prostaglandins, leukotrienes and bradykinin[1].

Pathogenesis

Histamine is typically released following activation of mast cells, through either allergic or non-allergic pathways. The angioedema associated with NSAIDs is caused by altered metabolism of prostaglandins and leukotrienes, whilst the principal mediator of angioedema in C1 inhibitor (C1-INH) deficiency is bradykinin. C1-INH regulates activation of the complement pathway, but also regulates the kallikrein-kinin pathway through which it controls bradykinin levels.

Classification

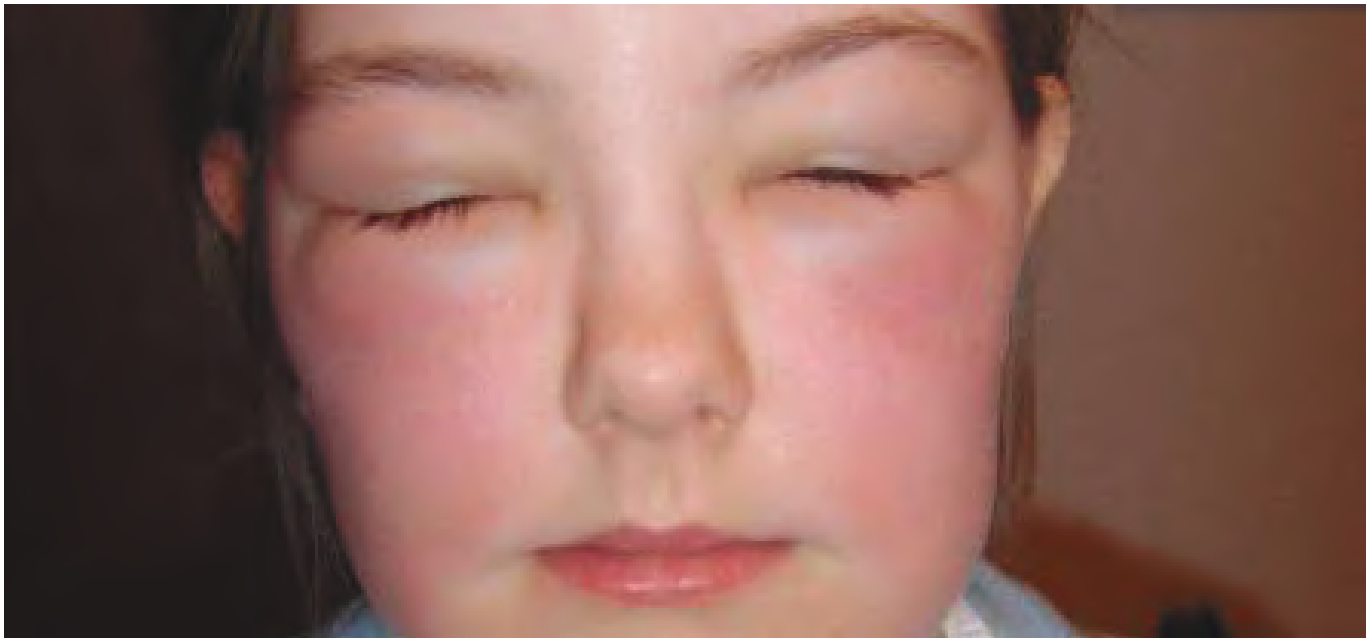
The classification and diagnosis of angioedema can be difficult. All angioedema looks grossly similar to the naked eye, irrespective of the underlying cause, and there are currently no tests to reliably measure all the vasoactive compounds implicated in its pathogenesis. However a thorough clinical history usually provides clues which help to classify the different forms of angioedema and thereby guide treatment.

The first step towards classification of angioedema is to distinguish between angioedema occurring together with urticaria, and angioedema occurring in isolation. Angioedema in combination with urticaria is usually histamine driven and can result from either IgE-mediated (allergic) or non-IgE (non-allergic) mediated release of histamine from mast cells.

Common causes of allergic angioedema include foods (peanut, tree nuts, shellfish), drugs (penicillins) and insect venoms. Histaminergic angioedema resulting from non-IgE dependent mast cell activation is frequently seen together with urticaria, both physical and spontaneous[2]. This is discussed in more detail elsewhere in this edition.

The classification of angioedema occurring in isolation has recently been updated by the Hereditary Angioedema International Working group (HAWK), and uses criteria such as response to anti-histamines, family history and C1 inhibitor levels[3]. Different types of angioedema based on these criteria include:

- Idiopathic histaminergic acquired angioedema (IH-AAE)
- Idiopathic non-histaminergic acquired angioedema (InH-AAE)
- Acquired angioedema related to angiotensin-converting enzyme (ACEI-AAE)
- Acquired angioedema with C1 inhibitor deficiency (C1-INH-AAE)
- Hereditary angioedema with C1 inhibitor deficiency (C1-INH-HAE)
- Hereditary angioedema with normal C1 inhibitor and factor XII mutation (FXII-HAE) and of unknown origin (U-HAE)



The main clinical features of the different types of angioedema are summarised below:

IH-AAE

This condition shares many of its clinical and pathological features with chronic spontaneous urticaria. Diagnosis is based on excluding other forms of angioedema, and establishing a response to anti-histamines. Typically, episodes of angioedema cannot be related to a specific allergen or trigger. Patients are usually systemically well. In a proportion of patients it is possible to establish a history of viral illness prior to the onset of angioedema. Regular non-sedating anti-histamines are the mainstay of treatment. It is important to reassure patients that no known deaths due to laryngeal angioedema have occurred as a consequence of IH-AAE[3].

InH-AAE

Patients who fall in this category are those IH-AAE patients who fail to respond to anti-histamines. Typically these patients respond extremely well to tranexamic acid[4]. It is presumed, although not proven, that angioedema in these patients is bradykinin-mediated.

ACEI-AAE

Angioedema associated with use of ACEI can occur at any time during treatment and affects around 1 in 200 patients[5]. It is thought to result from inhibition of the normal breakdown of bradykinin. Once angioedema has occurred, it is imperative to stop the medication since continued use is strongly associated with recurrent angioedema and consequent serious morbidity[3]. Interestingly in one series, up to 46 per cent of patients continued to experience angioedema despite stopping ACEI[6].

A novel bradykinin inhibitor, icatibant, which is licensed for the treatment of acute attacks of HAE has also shown efficacy in ACEI-AAE.

C1-INH-AAE

This is usually associated with autoimmune disorders or lymphoproliferative conditions. C1 deficiency in these cases results either from presence of autoantibodies that neutralise C1-INH function, or due to increased C1-INH consumption.

Management of these patients is focused on treating the underlying condition and managing acute episodes of angioedema.

Hereditary Angioedema

The best-characterised group here are patients with C1-INH-HAE. C1-INH deficiency results either from reduced circulating levels of C1-INH (type I), or dysfunctional C1-INH (type II). Trauma, dental surgery, infection and contraception are all known to trigger attacks; however there is often no specific trigger. The swelling associated with C1-INH deficiency is usually slow in onset, reaches maximum intensity over several hours, and can last up to 5 days. The most serious complication is laryngeal oedema which can be fatal if untreated[1].

"This condition shares many of its clinical and pathological features with chronic spontaneous urticaria."

Most of the patients with C1-INH-HAE in the UK are under the specialist care of clinical immunology. Patients (and GPs) will typically be provided with information about the condition and an individualised treatment plan. Acute attacks are treated with an infusion of C1-INH concentrate, or icatibant. Adrenaline, steroids and anti-histamines have no role in treatment of C1-INH deficiency.

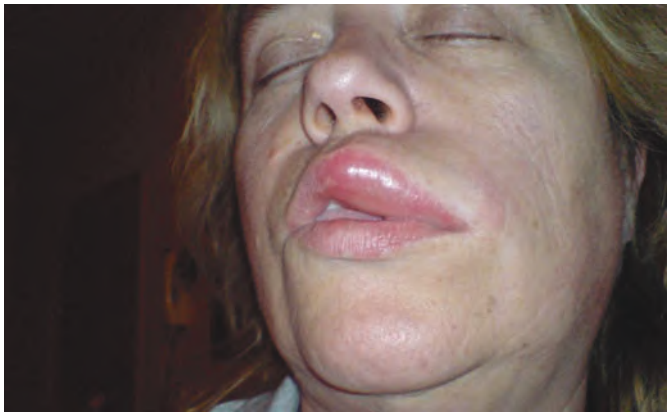
Other forms of hereditary angioedema are less well understood. Further information about these conditions can be found in the references provided with this article.

Practical Approach Towards Diagnosis and Management

The majority of patients in routine clinical practice will have an acquired form of angioedema. The most relevant fact to establish in this group is whether the angioedema is due to release of histamine or whether another vasoactive compound is responsible; in most cases this is bradykinin.

Distinguishing between histaminergic and bradykinin-mediated angioedema on clinical grounds alone is difficult. However, histamine mediated angioedema tends to develop more rapidly and is shorter lasting (hours versus days) than bradykinin induced episodes. Often, patients will have tried over the counter anti-histamines before seeking help and their response to these can provide a useful clue as to which vasoactive mediator is involved. Indeed a trial of regular anti-histamines (e.g. once daily non-sedating preparation) may be the only way to make a diagnosis.

For non-histaminergic forms of angioedema, further assessment includes looking for specific triggers, such as ACEI and NSAIDs. If no obvious trigger is identified it is essential to exclude a possibility of C1 deficiency. This is particularly relevant where there is a family history of angioedema. In patients aged over 40, acquired forms of C1 inhibitor deficiency are more likely than hereditary forms[7]. A simple screening test for suspected cases of C1-INH-HAE is serum C4, which is usually reduced even between attacks. However since normal levels of C4 do not always exclude C1-INH deficiency, all suspected cases should be referred to a specialist for further evaluation[8].



"Distinguishing between histaminergic and bradykinin mediated angioedema on clinical grounds alone is difficult. However, histamine mediated angioedema tends to develop more rapidly and its shorter lasting (hours versus days) than bradykinin induced episodes."

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Chronic Urticaria

Allergy Profile

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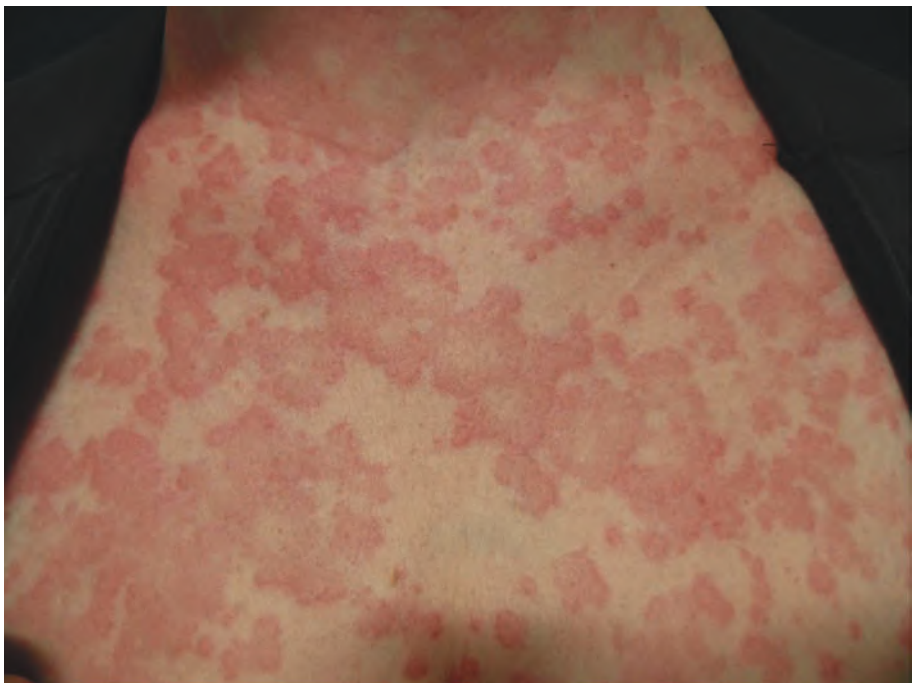
Since 1996 Dr Leslie has practised as a Consultant Adult and Paediatric Dermatologist in London. In 1990 she gained Membership of the Royal College of Physicians (MRCP) and was made Fellow of the Royal College of Physicians (London) in 2002. Dr Leslie provides NHS and private adult and paediatric treatment for all skin conditions.

For several years Dr Leslie has specialised in complex cases of urticaria (hives), cutaneous allergy and itch. This is now her special clinical and academic interest at the St John's Institute of Dermatology, St Thomas' Hospital.

Urticaria, derived from the latin *urtica*, meaning nettle, is also known as hives. It is a common disease affecting one per cent of the population, which is characterised by the development of itchy wheals, angioedema or both[1]. Acute urticaria lasts less than six weeks and can be associated with a precipitating cause that may be identified and treated, such as infections or drugs. Chronic urticaria is defined as lasting more than six weeks, where a cause is not usually identifiable. Causative mechanisms can include immunological and non-immunological stimuli. Aggravating factors should be considered, such as dietary pseudo-allergens. These include foods containing amines, food preservatives and dyes. These should be investigated and treated accordingly (see Table 1). Chronic urticaria resolves spontaneously in 50 per cent of patients within six months, although in up to 20 per cent of patients it can last for 10 years or more.

Table 1: Causes of Urticaria

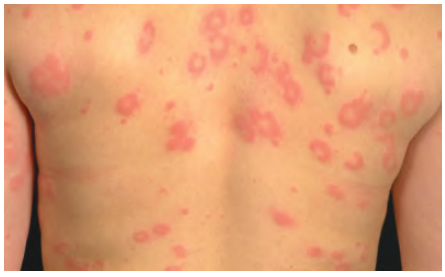
Endogenous causes	Exogenous causes
Infection	Drugs – topical and systemic
Connective tissue disorders	Foods and food additives
Hyperthyroidism	Bites
Diabetes	Inhalants
Pregnancy	Pollens
Intestinal parasites	Insect venoms
Cancer	Animal dander
Lymphomas	

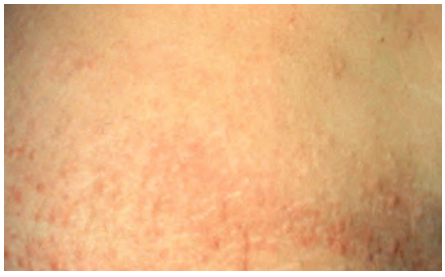


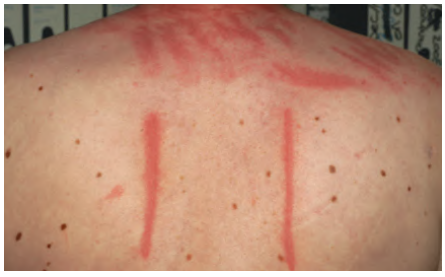
Chronic urticaria is classified as chronic spontaneous urticaria (with or without a cause) or chronic inducible urticaria (physical, contact, cholinergic, and aquagenic)[2,3], (see Table 2). The wheals of chronic spontaneous urticaria usually last around 4–24 hours, whereas in delayed pressure urticaria the wheals may take six hours to develop, and can last for 24 hours. In the chronic inducible urticarias the wheals may have a different morphology, onset and duration, such as cholinergic urticaria where small, extremely pruritic papules may appear 30 minutes after stimulus (sweat, heat or exercise) and reduce over an hour. Therefore, clinical history, examination and assessment of the patient are very important, as well as laboratory tests, as there may be no rash when the patient is seen. In symptomatic dermographism (skin writing), the wheals will appear at the sites of friction, as can be elicited by a calibrated dermographometer in clinic. Cold contact urticaria may need to be elicited using an ice cube test, or by using calibrated instruments that are available to determine temperature threshold[4].

Table 2: Classification of Urticaria Adapted from Leslie (2013)

4th International Consensus Classification of Chronic Urticaria (CU) 2012	
Chronic spontaneous urticaria (CSU)	CSU due to unknown causes
	CSU due to known causes
Chronic inducible urticaria (CINDU)	Physical urticarias Acquired cold urticaria Cold air, water, wind Delayed pressure urticaria Vertical pressure, wheals arising 3–8 hours later Heat urticaria Localised heat Solar urticaria Ultraviolet or visible light Dermographic urticaria, (urticaria factitia) Mechanical shearing forces, wheals arising after 1–5 minutes Vibratory angioedema Cholinergic urticaria Exercise-induced anaphylaxis, urticaria Contact urticaria Aquagenic urticarial







"...clinical history, examination and assessment of the patient is very important, as well as laboratory tests, as there may be no rash when the patient is seen."

It is important to exclude differential diagnoses, particularly diseases presenting with angioedema alone, which include the bradykinin-related hereditary angioedemas, as well as angiotensin-converting enzyme inhibitor induced angioedema. Autoinflammatory disorders (Schnitzler's syndrome, Muckle Well's syndrome) and urticarial vasculitis (due to infections, drugs or autoimmune disease – systemic lupus erythematosis) can also be confused with urticaria, but are IL-1 mediated. In these conditions, the wheals commonly last 48–72 hours and are usually not itchy.

Chronic urticaria can present with distressing unpleasant sensation of itch, redness and swellings which can severely impair quality of life, leading to lack of sleep, depression, and difficulty with relationships, work and sport, as well as restricted choice in clothing. It is important to determine disease activity, and frequently we use the Dermatology Life Quality Index (DLQI) and the Urticaria Assessment Score over seven days (UAS7). Other measures available include the chronic urticaria quality of life survey (CU-Q_2oL), Angioedema Assessment Score (AAS) and methods to determine threshold in inducible urticaria [ref JDDG].

In chronic spontaneous urticaria underlying disease should be excluded by looking at the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and blood differential. Drugs that potentially exacerbate the urticaria, such as non-steroidal anti-inflammatory drugs, should be avoided. Thyroid antibody and thyroid function tests should be performed, as 25 percent of patients with chronic spontaneous urticaria have thyroid antibodies. Further investigations should include detection of autoreactivity, infection and food intolerance. In chronic inducible urticaria, no cause is identified and diagnosis is limited to determining triggers and their threshold.

Management of urticaria is aimed at treating the symptoms and recognising any causes or aggravating factors (see Table 3).

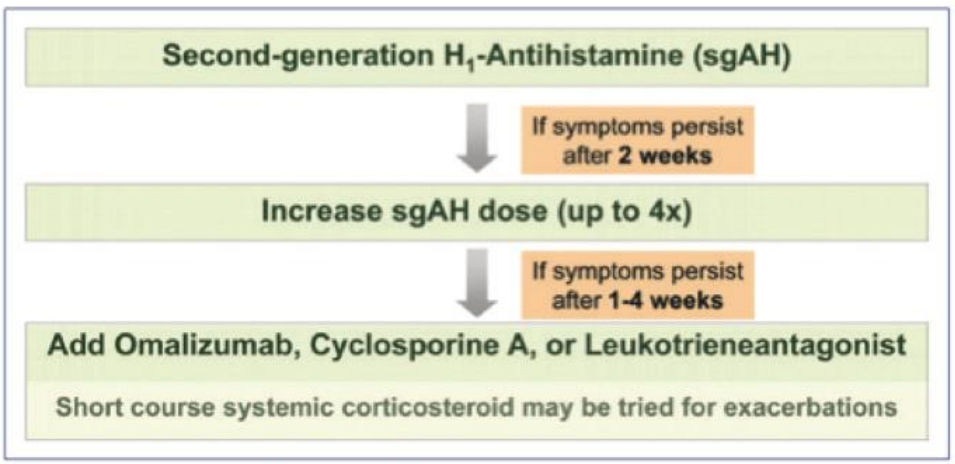
"Chronic urticaria can present with distressing unpleasant sensation of itch, redness and swellings which can severely impair quality of life, leading to lack of sleep and depression, difficulty with relationships, work and sport"

Table 3: Clinical Approach to Managing Urticaria

TREAT THE CAUSE Recognise and avoid aggravating factors	PHARMACOLOGICAL
Minimise overheating, stress, alcohol	First Line - Antihistamines *Symptomatic treatment*
Wear comfortable clothing and shoes	Second line - Targeted therapies *Symptomatic therapies*
Avoid NSAIDs	Third line - Immunomodulatory therapies *Disease modifying?*
Minimise dietary allergens	Fourth line - Biologics

The international consensus guidelines of 2012 (see Table 4) recommend the initial use of a second generation (non-sedating) H_1- antihistamine (loratadine, cetirizine, fexofenadine). It is recommended that the dosage of these be increased four-fold if symptoms do not resolve within a few weeks. Subsequently, leukotriene receptor antagonist (montelukast), cyclosporine[5] or omalizumab can be added[6]. During exacerbations short courses of systemic corticosteroids (25mg reducing over 10 days) have been recommended[7]. The use of H_2-antihistamines (ranitidine and dapsone) are no longer recommended in the latest guidelines, due to lack of sufficient evidence. However, anecdotally, many people feel these can be useful.

Table 4: Berlin 2012 Consensus Treatment Algorithm for Chronic Urticaria. Maurer (2013)



Other drugs not included in the latest guidelines have been found to be clinically effective in some patients, but did not have sufficient evidence to be included in the guidelines[8] (see Table 5).

Table 5: Targeted ('second line') Treatments

PHARMACOLOGICAL	
Corticosteroids	Severe urticaria exacerbations (short courses only)
Dapsone	Delayed pressure urticaria in aspirin-sensitive patients and urticarial vasculitis
Danazol	Cholinergic urticaria
Doxepin	Anxiety or depression
Montelukast	Aspirin-sensitive and pressure urticaria
Sulphasalazine	Delayed pressure urticaria
Tranexamic acid	Non-histaminergic angioedema
Hydroxychloroquine	Autoimmune urticaria
OTHERS:	Vitamin D, warfarin, heparin, thyroxine, phototherapy, psychotherapy, low pseudoallergen diet

The only treatments licensed for urticaria are the H_1-antihistamines, and most recently the biologic agent, omalizimab, which is now licensed in the use of urticaria refractory to antihistamines. Omalizumab is an anti-IgE monoclonal antibody, which has been shown to be effective in different types of urticaria[9]. The mechanism of action is not fully understood, but may be via reduction of free IgE in the blood with subsequent down-regulation of the high affinity IgE receptor on mast cells and basophil cell surfaces. It is licensed for use as a monthly subcutaneous injection at 300mg with close supervision of the patient on the day of administration in hospital, due to the rare possibility of anaphylaxis. The patients refractory to other treatments usually notice a substantial improvement within days of starting treatment. However, the drug does not modify the disease process in the long-term and therefore has to be administered until the urticaria resolves spontaneously[10].

In conclusion, patients in primary care can be treated with second-generation antihistamines, montelukast, and pulses of oral prednisolone. They should be referred to secondary care if they do not respond to treatment for further therapies, such as cyclosporine, omalizumab or other immunosuppressive/ immunomodulatory drugs.

This publication is kindly supported by an unrestricted grant from NOVARTIS

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