

ALLERGY UPDATE

Food allergy & anaphylaxis | Bites & stings | Rashes swellings |
Respiratory allergy | Drug allergy

Introduction

The last 29 years have seen a dramatic increase in the incidence of IgE-mediated/rapid onset food allergy and anaphylaxis and more recently, evidence of increases in non-IgE-mediated conditions such as infantile proctocolitis, FPIES/food protein induced enterocolitis and eosinophilic oesophagitis.

Some of these topics have been the subject of research studies undertaken in Canberra with colleagues here and abroad

(<https://scholar.google.com.au/citations?hl=en&pli=1&user=d9qoxaQAAAAJ>).

Between 1995 and 2008, we mailed out 10 clinical bulletins discussing a range of allergy related topics including allergic respiratory disease, food allergy, anaphylaxis and drug allergy.

A number of recent changes to therapeutic options have arisen, so it is time to revisit some topics of interest, but also to briefly review some **allergy mimics** that don't require allergy testing or allergy assessment. These are best considered in the differential diagnosis *before* a referral is made.

I hope you find this material useful, based on 29 years of practice in Canberra, assessing over 39,000 individual patients (including hay fever- 15,900 cases; urticaria- 6100; food allergy- 7800; anaphylaxis- 3870; drug allergy- 2200; eosinophilic oesophagitis- 560; and laryngospasm- 210).

Thank you for your support over the last 29 years.



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Food & anaphylaxis

Childhood food allergy risk factors

The major risk factors for development of food allergy in early life are those of atopic eczema and delayed introduction of allergenic food. There is also evidence that food allergy is more common in cities compared to rural areas in Australia and at higher rates are seen in those who live in higher socio-economic advantage areas of the country compared to less advantage areas. There is also conflicting evidence that vitamin D status/sun exposure may also be an influencing factor, with latitudinal gradients in food allergy incidence noted in Australia in the USA.



Contact urticaria to food – not always allergic

Some children get hives around the face from food contact yet are happy to consume the food; nothing else happens.

Contact urticaria is equivalent to a positive allergy skin test but that is not identical to actually being allergic. In those who have contact reactions alone, only around half are allergic to the food if they actually consume it, based on HealthNuts data.

In such a situation there is a potential risk of trying the food again if they are allergic which needs to be balanced with the risk of avoiding the food, since delayed introduction of allergenic food like dairy, egg and peanut has been shown to actually increase the risk of allergy development.

In *some cases*, if the child is happy to consume the food, it could be tried again in the morning during business hours, starting with small amounts in the mouth but not allowing the child to self-feed, and given regularly twice per week to maintain tolerance if tolerated.

Food & anaphylaxis

Early food introduction appears to reduce the risk of early childhood food allergy

A number of trials involving egg, peanut and dairy, have shown that early introduction of allergenic food dramatically reduces the risk of new food allergy development. Importantly, early introduction is not once – it requires twice-weekly to maintain tolerance. For example, one is not likely to be allergic on Friday if one has eaten that food on Monday, but one can be allergic in June if it has not been consumed since January! See the "Nip Allergies in the Bub" website for patient and medical information on this important topic – <https://preventallergies.org.au/> Current Australian guidelines recommend introduction of common allergenic food in the first year of life. The LEAP/EAT study group based in the UK are pushing that time line earlier to between 4 and 6 months of age if possible, based on their studies of early compared to delayed allergenic food introduction, as published in March 2023.

Blood testing for food allergy

At times, blood allergy testing for specific foods is important, but it is best to not try to save money by testing using food mixes which can provide misleading results. For example, a person allergic to cashew, will have a false negative nut mix test because there is no cashew in that blood test. The most common allergenic food in childhood are those of egg, peanut, dairy, sometimes seafood and fish and crustaceans like prawn, or tree nuts.

Every nut is different so if testing for nut allergy, one needs to test for every single nut – almond, Brazil nut, cashew, hazelnut, walnut, macadamia nut and pinenut. Pistachio and cashew almost always cross-react and walnut and pecan almost always cross-react, so, one only occasionally needs to test for both.



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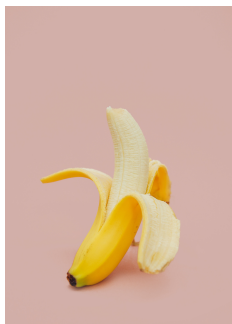


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Oral allergy syndrome

Some patients with seasonal hay fever develop itch and irritation of the tongue, mouth and throat after ingestion of some fresh fruits and vegetables, known as Oral Allergy Syndrome. Surprisingly, they can usually tolerate the same foods after cooking. Common triggers include kiwi fruit, mangoes, stone fruit, some nuts, salad and other vegetables. The majority of patients are allergic to cross-reactive proteins common to some pollens and foods.

These proteins are normally denatured by cooking, usually allowing cooked food to be safely consumed.

Less than 1% ever become serious and thus patients can be reassured about the nature of the symptoms, how to minimise symptoms but don't normally require allergy assessment or testing. Indeed, blood allergy testing is often negative.

A very rare patient can't tolerate any fruit or vegetables, in which case dietetic assessment and advice is appropriate.

Total IgE is of no use in someone with suspected food allergy. Since a person with egg or nut allergy has a roughly 30% chance of being allergic to another food, it is not unreasonable to screen for each of the above foods if they are not been consumed on a regular basis. It may save another trip to hospital.

Food is for eating, not for use as a moisturiser

Food should never be used as a moisturiser. I've seen many cases of goat and sheep cheese anaphylaxis in those who used topical goat milk products for treatment of eczema. Other cases of nut or allergy and reactions to oats, wheat and dairy have been described when these products have been used as a moisturiser. We are not a "number 10 chicken" – food is for eating, not for marinating in! Furthermore, goats milk soap is just that – soap. Which means it dries the skin.

Adrenaline prescribing guidelines

Australian adrenaline autoinjector (AAI) prescribing guidelines (see ASCIA website) recommend prescription of the EpiPen 0.15 mg device of those with a weight between 7.5 and 20 kg, and the higher 0.3 mg AAI devices for those greater than 20 kg in weight.

Those guidelines have not changed in the last 10 years but are slightly different from the drug prescribing guidelines you will see in MIMS. The adrenaline dose is based on weight, not age. More recently, the higher dose Anapen device has become available with doses up to 0.5 mg for those weighing more than 50 kg. Training is important as the administration instructions are completely different to the EpiPen device.

Importantly, a GP can prescribe an AAI on the PBS by ringing the authorities line, and quoting the name of an authorising specialist.



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Fatal anaphylaxis

When I and colleagues examined all death from anaphylaxis in the last 20 years in Australia, most insect sting fatalities occurred in middle-aged males with comorbidity who had not been offered immunotherapy and where adrenaline was not available.

Drug-related fatalities were generally unpredictable but tended to occur in older individuals. Food-related fatalities in younger individuals were usually triggered by nuts and in older patients, seafood.

The most common factors associated with fatal anaphylaxis were delayed or absent use of adrenaline, and an upright posture, for example, having a shower after having anaphylaxis or sitting upright being driven to hospital.

Early use of **adrenaline and lying flat** are thus recommended in management, and included in ASCIA anaphylaxis management plans.

Is it food allergy?

In attempting to determine whether the relationship between food and symptoms is causative or coincidence, one looks at the history, results of allergy testing at times, challenge. Since we eat all the time, symptoms will always follow food consumption such that the relationship between food and symptoms can be one or more of coincidence, food followed by acid reflux followed by painful tight throat, laryngospasm after eating or drinking, clear food allergy (generalised rash and vomiting soon after consumption of a likely allergenic food), so-called pseudo allergic reactions or panic attacks, or food intolerance like bloating after too much pasta or migraines after chocolate, cheese or red wine. If the history does not suggest allergy in the first place (eg, diarrhoea after lactose, bloating after pasta), then the results of allergy testing are not going to be helpful and often misleading. Note also that false positive food tests are **not** uncommon.

Non-IgE-mediated food allergy

As well as rapid onset IgE-mediated food allergy with vomiting and rash and sometimes more serious symptoms where allergy testing is positive, there are a number of delayed inflammatory reactions to food which are allergic but have a different mechanism but where allergy testing will be negative. Examples include **infantile proctocolitis**, with multiple sloppy poos and diarrhoea and mucus and blood in breastfed babies (most commonly triggered by soy and dairy), FPIES/food protein induced enterocolitis syndrome is characterised by delayed severe and repetitive vomiting and sometimes lethargy and diarrhoea (most commonly triggered by rice, dairy and soy).

FPIES in adults is rare but present in much the same way - severe repetitive delayed vomiting, with onset a couple of hours after food ingestion and lasting many hours. The major trigger in adults is seafood, but other triggers like nuts have been described. **Eosinophilic oesophagitis** in children can present with choking and gagging on food, very slow eating and abdominal pain. In adults, it tends to present with food getting stuck on the way down and hard to swallow food. There is no non-invasive test - if the diagnosis is suspected, then endoscopy and biopsy is the only way to confirm the diagnosis.

Food intolerance

An individual, for example, with migraine headaches or irritable bowel syndrome, aggravated by food, does not have food allergy and will not benefit from allergy assessment or testing.

They can be referred to a skilled dietician for a trial of dietary manipulation or neurologist or gastroenterologist depending on the symptoms of concern.

Influenza vaccination of the egg allergic individual

This is another myth that won't go away. Traditional influenza vaccines are grown in eggs or egg-derived fibroblast cultures. There is minimal allergenic protein present in current influenza vaccine.

A number of studies have demonstrated that the risk of having allergic reaction to the influenza vaccine is not only rare, but no different between those who are allergic to eggs and those who are not.

Therapeutic options are limited - some respond to trials of dietary manipulation, others respond to proton pump inhibitors alone and others require swallowed asthma steroids to cut the oesophagus, and reduce inflammation.

Children with sloppy poos

Common things occur commonly - lactose intolerance occurs in one in 30 people, and switching to lactose free dairy will normally sort the problem within a week. Fructose intolerance is the fruit equivalent and some young children who consume lots of apples, pears or grapes or watermelon have loose bowel motions. Switching to a low fructose diet will normally fix things within a week.

By contrast, coeliac disease occurs in roughly one in 100 people but an allergy test won't pick that up - different serological tests are available instead. Infantile proctocolitis in breastfed babies with a dozen watery bowel motions and blood and mucus, for example, occurs in one in 2000 children (usually very young babies, not toddlers) and may prompt either paediatric or allergy assessment. Even then, allergy testing is uniformly negative. Soy and dairy are the dominant triggers so if proctocolitis is suspected, cutting out these foods from mum's diet while breastfeeding will often fix the problem within 2 weeks.

So if sloppy poos or stomach upset is a concern in a child, many only need simple dietary advice; others may require paediatric or dietician review. Only some require allergy assessment.



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Bites and stings

Insect bite reactions - allergy assessment almost never needed

Many small insects like sandflies and mosquitoes bite, and some unlucky individuals will have large local swelling or even blistering. This is mainly a childhood issue and rarely persists into later adult life.

Covering up and using insect repellent when outside, removing breeding grounds, adding fly screens to the house and sometimes using insecticide in the bedroom to kill insect before people go to sleep, maybe assist.

Topical anti-itch cream like Zostrix and antihistamines might have *some* benefit. Vitamin supplements and wristbands are promoted without any convincing evidence of benefit. Immunotherapy to insect bites is not possible. The likelihood of progression to anaphylaxis is close to 0 - there are only case reports in the entire world literature on this. Those with bite reactions in the absence of anaphylaxis need simple reassurance, not testing.

Localised insect venom sting reactions - allergy assessment rarely indicated

Small localised reactions are common and can be treated with antihistamines, paracetamol and ice. Large local reactions where a person gets gigantic swelling, worsening over the first 24 hours and lasting days at a time are distressing, but are not dangerous. These local reactions are most common in childhood and often caused parental anxiety. Nonetheless, follow-up studies following such patients for many years show that less than 10% ever become dangerous. Therefore, if a person has not had a systemic allergic reaction with generalised rash, with or without dizziness and difficulty breathing, they do *not need* allergy testing or assessment, do not need an adrenaline autoinjector and do not need five years of immunotherapy injections, unless they worsen in the future.

Generalised /systemic allergic reactions to insect stings

A person with anaphylaxis or generalised urticaria response after an insect sting **should** be assessed for adrenaline provision and provision of immunotherapy. There are lots of online resources on management of insect sting reactions on the ASCIA website as well as GP Journal review articles on the topic.



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Tick bite reactions and mammalian meat allergy

The tick/red meat/alpha galactose syndrome is an interesting topic that has developed over the last 15 years.

This involved initial observations in Sydney by Dr Sheryl Van Nunen, showing a clinical relationship between tick bites and later having allergic reactions to red meat, later observations in the USA of some patients treated with a cancer drug containing alpha galactose would have allergic reactions to that medication in some parts of the USA and not others, and in the ACT, the relationship between living at the coast, being allergic to red meat and being allergic to gelatin as well.

Essentially, alpha galactose is a carbohydrate present in ticks saliva that is also present in mammalian meat other than humans and New World monkeys. Most of those exposed to tick bites will have local minor swelling. Some get gigantic local swellings and others will get anaphylaxis, typically when the tick is disturbed.

Some exposed to tick bites will develop allergic reactions to red meat as well, with onset typically delayed hours later. A substantial proportion (around a third) will react to gelatine as well (oral or IV gelatine colloid).

If this syndrome is suspected, blood allergy testing is available to alpha galactose, pork and lamb and beef, but gelatin allergy testing is generally negative, even in a patient who is allergic to it.

Affected patients need to be equipped with knowledge how best to remove ticks (freeze, not squeeze), how to reduce the risk of further ticks bites and how to manage dietary restrictions. The TIARA website has useful information on this syndrome and its management - <http://www.tiara.org.au>

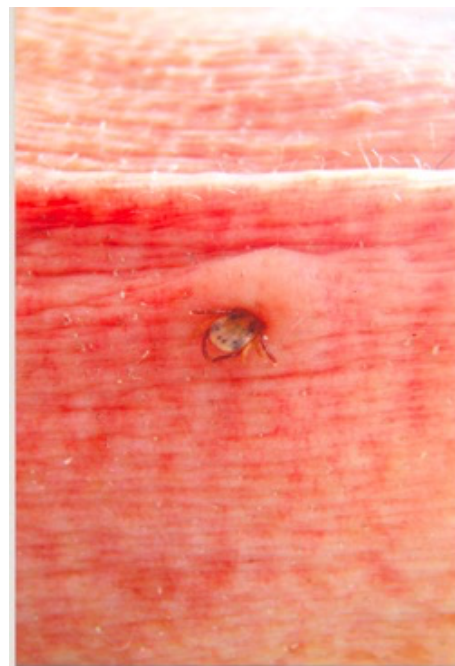


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Drug allergy

When evaluating patients with possible antibiotic sensitivity, one examines the circumstances surrounding the episode (and the likelihood that the symptoms experienced were due to side-effects, coincidence or drug hypersensitivity or underlying disease being treated with medication), the results of allergy testing (not always possible, accurate or available), and at times, deliberate challenge to prove or disprove hypersensitivity to medication.

When examining the history, the timing and characteristics of the reaction may help classify the event as possibly or probably representing an allergic reaction. Allergy testing can be done for some (eg. intravenous antibiotics, anaesthetic agents) but not all medications (eg. pain killers, antibiotics where only oral forms are available). Unfortunately, testing for antibiotic allergy is even more difficult, as tests are not 100% accurate, not just because of the passage of time, but also because many patients allergic to medications are allergic to the breakdown product of the drug, not the native drug itself. It is often difficult (and sometimes impossible) to obtain commercial extracts for this purpose. The situation can also be complicated by the fact that some patients with antibiotic allergy will grow out of their sensitivity with time, with their skin tests turning negative after a few months. There is at least some evidence, however, that re-exposure in some patients can then switch on the allergy again. In patients with a negative result, the interpretation can be that the patient is not allergic now and never was, that the patient was allergic and has grown out of their sensitivity, or that the test result itself is inaccurate. Finally, deliberate challenge is sometimes required to prove or disprove ongoing sensitivity, or the inability to re-sensitize patients.

If a drug reaction is suspected, it is important to document the circumstances - what condition was being treated, what specific drug was given, what was the time relationship between first dose and symptoms, what actually happened and their duration and severity. Both history and results of allergy testing are going to be more reliable if this is documented at the time and assessment performed close to the event, not 20 or 30 years later. Of course, vomiting after morphine is clearly a side effect, not allergy.

There has been a movement in recent years to try to remove unnecessary antibiotic allergy labels where possible, as around one in 10 of the population believe they are allergic to penicillin, for example, but only 1/1000 actually are. There is potentially a risk of antibiotic challenge at times but also a risk of **not** challenging. A number of studies have shown that those labelled as being allergic to penicillin needing hospital treatment end up being given more expensive and less effective antibiotics with more side-effects, have longer hospital stays and are at greater risk of developing antibiotic resistance from having to use more broad spectrum drugs. In a patient who develops a non-specific maculopapular rash, a few days after starting a drug lasting a few days, 94% will pass a challenge without a problem. Even if a person is allergic to a medication, there are protocols available to temporarily "desensitize" them to the drug to allow its use in important situations, but the allergy returns once the drug is stopped. But there are some situations where one would **not** consider a drug challenge: the sudden onset of likely anaphylaxis, Stevens Johnson Syndrome (target lesions, extensive rash, mouth and ocular ulceration) or DRESS syndrome, characterized by hepatitis, eosinophilia and all-over peeling rash.

Pain killer allergy

One can divide painkillers into three broad groups - narcotics (such as morphine or codeine or tramadol), Cox 1 inhibitors (such as paracetamol, ibuprofen, naproxen, indomethacin, diclofenac) and Cox 2 inhibitors (such as Celebrex or Mobic).

Most having allergic reactions to a **Cox 1 inhibitor** are allergic to one drug alone and can usually tolerate another drug from the same group. Paracetamol, however, a weak inhibitor of the Cox 1 enzyme, is usually tolerated. There are two exceptions to this rule of thumb:

- (A) **Asthma**: an estimated 10% will develop asthmatic symptoms to all drugs in this group.
- (B) **Sampter's triad** (aspirin triad) characterised by late-onset asthma, nasal polyps/sinusitis and allergy to anti-inflammatory drugs) where patients will be allergic to all Cox 1 inhibitors.

Cox 2 inhibitors suppress a different enzyme and are normally tolerated, although there is a higher risk of having allergic reaction to these if patients are allergic to paracetamol.

These reactions are not IgE-mediated, there is no blood or skin allergy test to prove or disprove tolerance or otherwise, other than deliberate challenge.

One might challenge, for example, to prove tolerance in a patient with arthritis that requires a painkiller or in someone who has heart disease and needs aspirin to thin the blood. Even then, desensitisation protocols exist to induce tolerance, although regular consumption is required to maintain tolerance, there is no test for side-effects.

Immunotherapy for Allergic respiratory disease

The aim of immunotherapy is to switch off allergy by exposing an individual to graded doses of commercial allergen extracts. The aim is to feel better with less medication, especially when medication is ineffective or trigger side-effects. The first case report of use was in 1911; injections have been in widespread use since the 1950's.

But there are more therapeutic options available these days. Grass pollen tablets ([Oralair](#), [Grazax](#)) have been available since 2013, and dust mite tablets ([Acarizax](#) and [Actair](#)) have been shown to be effective in reducing the allergic component of asthma as well as hay fever since 2017. Benefit is based on large international double blind placebo controlled trials. These tablets are fully registered and purchased on prescription.

Cat and Birch tree tablets are available as well (smaller pharmaceutical companies, smaller trials, lesser evidence of benefit).

Allergoid injections have been available for the last few years and they are more friendly - instead of a tedious weekly increase in dose over a few months, updating normally occurs over a couple of weeks and one reaches maintenance treatment within a month. These products appear to be safe and but it is not clear whether they are as effective as traditional extracts, where updosing occurs gradually on a weekly basis for a couple of months.

My experience is that the vast majority of individuals on grass and dust mite tablets do quite well, but that allergoid injections or immunotherapy directed against pets. can be hit and miss in terms of benefit.

Eyeball irritation

There are lots of causes of irritable eyeballs other than allergy including dryness, Sjogrens syndrome, rosacea keratitis and blepharitis, where one gets inflammation of the oil glands, resulting in red irritable eyeballs, dryness and grittiness and thick discharge.



Vernal conjunctivitis is an inflammatory allergic -like condition of the conjunctiva, most common in children and can cause red painful itchy and sticky eyes, worse when swimming. In the vast majority of these individuals, results of allergy testing are negative and there is not really convincing evidence that immunotherapy will help in the setting of negative allergy tests. The major differential diagnosis in vernal conjunctivitis is infective conjunctivitis.

Blood allergy testing in those with hay fever or asthma

If undertaking blood allergy testing for hay fever and asthma assessment, testing for dust mite, Alternaria mould, grass mix, and relevant pets covers the bases. **Total IgE** really does not add much to the assessment unless one is worried about allergic bronchopulmonary aspergillosis (ABPA).

IgE is elevated in 5% of healthy individuals, 30% of those with hay fever, 60% of those with asthma and a 90% of those with eczema. Total IgE almost never tells you anything that you do not already know, and does not correlate with severity. A high level (highest in eczema) simply unnecessarily worries patients. So, unless you are suspicious about allergic ABPA, it is essentially a useless test.

But one important thing to avoid - Food allergy testing in someone presenting with hay fever unless the *history clearly indicates* the likelihood of food allergy as well as allergic respiratory disease. Doing food allergy mix testing in someone with hay fever often gives false positive misleading results and can result in unnecessary dietary restrictions and impact on nutrition, especially in young children, generate unnecessary referrals and parental anxiety.

Furthermore, a stable tolerated food that is removed from a diet based on a test alone can result in new food allergy development after withdrawal in young children rather based on published studies.

And long-term unnecessary withdrawal of dairy products young children is associated with osteoporosis and poor growth.

“Sinus” pain

Once or twice per month, we see individuals who complain of so-called “sinus pain”, where there is nothing wrong with the sinuses at all.

They are often given antibiotics. But in the absence of green yellow mucus and bad breath and bad taste and blocked nose and facial pain, there may lurk another cause. It can worthwhile thinking laterally as to the many potential causes of facial pain.

Around half of those without sinus disease have migraines with atypical features. Other potential causes include tooth grinding and clenching, radiation of neck and shoulder pain to the face, dehydration, headaches and frontal tension headaches or non-specific headaches, with sometimes stress is a trigger.

The fact that antihistamines sometimes help headache, does not mean the problem is allergic – some antihistamines have a migraine preventer action. If a person has ongoing facial pain and headaches, it can sometimes be useful to undertake a CT sinuses to exclude or prove blocked sinuses as a cause or to experiment with antimigraine drugs like Imigran if the headache is suggestive of possible migraine.



Rashes and swellings

Red faced babies

We often receive referrals for babies with red faces after having strawberry, eggplant, tomato, citrus or Vegemite or soy sauce.

There are many causes of facial redness, including eczema, dribble, heat, a reflex phenomenon called auriculotemporal syndrome and acid food like tomato and citrus and berries often cause red faces as can very salty food like soy sauce and Vegemite. Reactions are even worse in those with underlying irritable skin (dry skin, eczema).

These foods simply irritates the skin. I've never seen a child with allergy to any of the above in over 29 years. Parents can be reassured to simply use a greasy barrier to the skin to reduce irritation or not give the child the food. They do not, however, need allergy testing or assessment.

Contact urticaria to allergenic food such as peanut or egg is a different story and may require assessment.

Facial swelling

There are a number of potential causes facial swelling, but when isolated swelling occurs, allergy to food or medication is not likely to be the cause. Common causes are those of **angioedema** (which is not necessarily itchy) and generally disappears within 24 hours or so of onset. It is most common in those aged over 50 years of age. Most of the time, a cause is not found, although ACE inhibitors and to a lesser extent ACE receptor blockers can be a trigger. Someone with facial swelling in the context of urticaria has mixed urticaria/angioedema and if ongoing, is not allergic in origin.

Contact allergic dermatitis occurs in around 1% population with the onset of itching and burning followed by redness and swelling and then either blistering or peeling over several days. Most of the time, the episode has gone within one or two weeks, whereas angioedema won't last that long. Most cases referred have had contact allergic dermatitis.



Much less common causes of facial swelling include subtle swelling from rosacea, hypothyroidism and much more rarely, superior vena cava obstruction or even non-specific fluid retention occurring overnight that improves during the day. If someone presents with a puffy face, it is worthwhile checking whether they have intercurrent urticaria, take photographs of the rash and sort out whether the rash lasts days at a time in one place and goes rough dry and scaly and maybe get them back a few days to check clinical progress. In someone who has a constant puffy face for weeks at a time, is not likely to be angioedema (which is episodic) and one needs to look for another cause like contact dermatitis or maybe other more obscure syndromes.

Since the diagnosis is often more evident a few days later, often the best approach with rashes and swellings is take photos and get the patient back for review the following week, and this may save unnecessary referrals.

Eye swelling

There are lots of potential causes of swelling around the eyes of which urticaria/angioedema and contact allergic dermatitis are the most common

Rosacea can also trigger non-specific facial puffiness and redness, as well as prominent nasal pores and people like lesions.

Less common triggers include blepharochalasis characterised by local lymphoedema which is often their most of the time, and sometimes trauma or proptosis triggered by Graves' disease, chronic sinusitis or orbital cellulitis (usually obvious), orbital pseudotumour (very rare). Very rare causes include localised skin amyloid associated with dark pigmentation and often bruising or dermatomyositis (puffy face, molar rash, muscle weakness)

It is worthwhile taking photos, looking at the frequency and duration of episodes and whether this is rough dry skin to suggest eczema/contact dermatitis.



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Lip swelling - common causes

Coldsores/Herpes simplex infection is very common, painful and is associated with vesicle formation in and around the mouth. A

Another common cause is *urticaria/angioedema* where swelling is transient, normally gone within 24 hours, is improved with antihistamines, may have lesions occurring elsewhere simultaneously and is not associated with dryness and crusting and symptoms lasting several days at a time. In patients on ACE inhibitors for example, one normally attributes swelling to the drug until proven otherwise and a trial of stopping the drug for a few months is appropriate.

Contact allergic dermatitis is another potential cause, occurring in around 1/100 patients with over 2000 potential triggers. Contact can be direct or indirect such as by the hand. Episodes start usually within a day or so of contact, it worse for the first 24 hours or so and then disappear within 5 to 10 days with blistering and eventual dryness and peeling of skin with resolution.

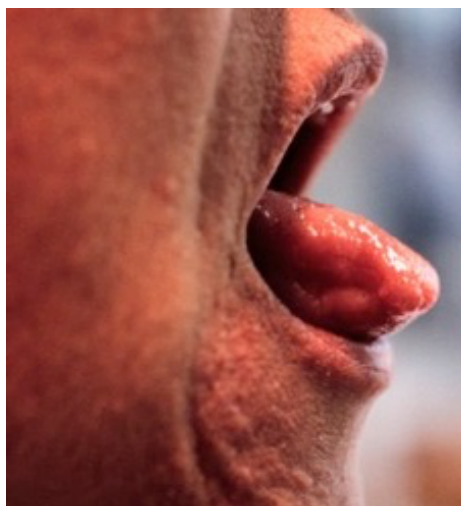
Lip swelling - uncommon causes

Orofacial granulomatosis (also known as granulomatous cheilitis, Melkersson Rosenthal syndrome) is less common, occurring on its own or associated with inflammatory bowel disease. It is relatively easy to diagnose in retrospect in patients present with permanent rubbery swollen lips, but is less easy to diagnose when patients present early on in life. Swelling often starts off lasting for a few hours at a time, and then over a period of months or years, starts to last four days at a time and then becomes permanent with intermittent fluctuation.

Other less common symptoms include facial paralysis, enlargement of regional lymph nodes, fissured tongue and gingivitis and mouth ulceration and sometimes blistering and dryness around the lips. The lips are not the only areas which can be involved; sometimes swelling of the tongue or cheeks can also occur, and there are also case reports of genital swelling. In patients who have gastrointestinal symptoms, investigation for possible inflammatory bowel disease is appropriate. Chest x-ray and measuring ACE level is also reasonable to help exclude sarcoid but the diagnostic test is that of a wedge biopsy of the lip. Unfortunately, characteristic granulomas are often missing a minor non-specific dilatation of blood vessels and lymphocytic inflammation can sometimes be seen in early disease.



Orofacial granulomatosis



Ascher's syndrome is another occasional cause of recurrent face and lip swelling, cause unknown. This condition is characterised by the appearance of a double upper lip which can look swollen, blepharochalasia with swelling around the upper and lower eyelids, and with thyroid enlargement (goitre) observed in between 10 and 50% of patients. This condition typically starts in adolescence and is associated with vascular dilatation and leakage of fluid into the tissues. Treatment of this condition is difficult. Surgery to correct the lip abnormality may assist and corticosteroids to reduce inflammation have been tried.

Urticaria - most cases are not allergic

Urticaria occurs in up to 25 % of the population some time in life. A cause is rarely found for chronic symptoms and some cases are recurrent. In the vast majority, it is associated with distressing symptoms but fortunately only rarely, with underlying disease.

Infection is the most common triggers for symptoms, particularly in young children. If a patient has urticaria lasting a few days or even weeks, they will not have an allergic cause unless they have recently completed a course of antibiotics.

The vast majority of patients with urticaria will settle after a few weeks, and high-dose antihistamines anywhere between one and four tablets per day will control the vast majority. Other drugs require a trial-and-error approach - famotidine as an H2 blocker or montelukast.

A typical person with food or drug allergy or develop symptoms within a couple of hours (usually within 15 minutes in young child), start with itchy hands and feet, generalised rash and often vomiting or more serious symptoms, all disappearing within 6 to 8 hours. I.e. akin to anaphylaxis, but not urticaria lesions moving around all day or for days. These episodes are rare, and are associated with one common trigger.

Unless the person is sick, most presenting with urticaria do not normally require extensive blood investigations nor do they need allergy testing for short lived episodes.



Instead, initial treatment followed by review the next week is often the best approach.

While there are some obscure syndromes where urticaria is a component (for example, **auto inflammatory conditions** presenting in very young infants with high fever and transient rash and swollen joints), most of the time blood investigations required are not required unless symptoms are ongoing for months.

Reasonable investigations in someone with chronic urticaria include thyroid function, Helicobacter serology and coeliac disease serology.

The risk of dangerous upper airway swelling in someone with **non-allergic urticaria and who is not on ace inhibitors** is close to zero.

In someone who woke up with urticaria on Saturday, went to hospital on Sunday with similar symptoms, and turns up to your surgery on Monday with ongoing rash, may have a terrible distressing condition, but unless they have recently completed a course of antibiotics, the diagnosis is rash, not allergy. It also means they do not need extensive blood investigations unless they are sick, have atypical urticaria or have ongoing symptoms unresponsive to medication.

When to worry more about urticaria

There are a couple of exceptions where allergy assessment is appropriate - cold induced urticaria/anaphylaxis. Triggered by skin cooling (cool air, contact with cold objects or cold water), severe cases can result in anaphylaxis when swimming when subjected to whole body immersion. Surgery in cold operating theatres also poses a risk. Most cases last for decades, medication is usually unhelpful, and a recent retrospective review of 99 cases found only two with evidence of lymphoproliferative disease as a cause (DOI: [10.1111/jdv.13841](https://doi.org/10.1111/jdv.13841)).

In rare and short-lived episodes of urticaria lasting 12 hours or less (especially if associated with symptoms involving more than 1 organ. Eg. Vomiting, rhinitis), allergy as cause can be considered. If so, one is looking for a common food or medication ingested in the previous couple of hours. A person getting hives a couple of times per fortnight for several times per month, however, is not likely to have allergy as a cause.



When exercise is followed by urticaria, the explanation may be coincidence, or cholinergic/sweating urticaria where symptoms occur often when a person sweats, and generally every time.

Less common is food and exercise urticaria/anaphylaxis. Episodes occur occasionally during or just after exercise, not with each bout of exercise. The variables that determine the reaction and its severity are those of the amount of food ingested, the vigour of the exercise and the time between. While many foods are associated with this syndrome, wheat/gluten containing cereals are the dominant trigger. If wheat is implicated historically, blood allergy testing to wheat, omega-5-gliadin wheat, rye and barley is appropriate.

Use of Xolair in chronic unresponsive urticaria

Xolair anti-IgE is available on PBS Authority prescription in patients who have had chronic symptoms lasting more than six weeks, with set high symptoms scores, and unresponsive to medication such as high-dose antihistamines, H2 blockers and montelukast. Dermatologists are eligible to prescribe Xolair and patients do not have to see an allergy/immunology specialist to get access.

Angioedema

Angioedema results from leakage of fluid into the deep dermal and subcutaneous tissue.

Most cases have a similar aetiology to urticaria.

When angioedema occurs on its own, hereditary angioedema, acquired C1 inhibitor deficiency or swelling triggered by ACE inhibitors should be considered.

Isolated angioedema, however, is almost never due to food allergy, but painkillers like ibuprofen certainly came within an hour or two.

The differential diagnosis of angioedema includes:

- Contact allergic dermatitis; Dermatomyositis;
- The diffuse redness and swelling of rosacea;
- Hypothyroidism;
- Superior vena caval obstruction (1 case seen ever);
- Subcutaneous emphysema;
- Orofacial granulomatosis;
- Systemic capillary leak syndrome;
- Premenstrual fluid retention involving the face and other parts of the body and occasionally;
- Cluster headache associated with periorbital oedema.

Unlike angio-oedema which tends to be episodic and relatively short lived, many of the mimicking conditions last much longer.



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Tight throat

There are a number of potential explanations for symptoms or throat swelling, but it is important to differentiate between throat swelling on the **inside** and a sensation of neck/skin swelling on the **outside**, something many patients don't clearly differentiate between.

If the issue is internal throat swelling, potential causes include angioedema, but also eosinophilic oesophagitis where food gets stuck on the way down and patients find it hard to swallow. If a person has symptoms of the latter, they need to see a gastroenterologist for endoscopy and biopsy.

Around once per month, I will see someone who has food followed by acid reflux followed by a painful sore throat that felt swollen for a day or so. The mechanism is reflux, not allergy.

Laryngospasm can be much more frightening (but not dangerous) and is most commonly triggered by food or acid reflux after eating or inhalation of irritants like dust. Onset is usually within minutes or seconds, with tight throat, husky voice, inspiratory stridor and off and difficulty getting air into the lungs for around 20 minutes. There is no itching or rash or anything else to suggest allergy or anaphylaxis with these mimicking conditions.

And of course, other mimicking conditions include anxiety attacks, hyperventilation syndrome and so-called "Globus".



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Rashes - most are not allergic

Most rashes do not have an allergic origin. The exceptions are **contact allergic dermatitis** (refer to dermatologist for patch testing) and acute rare short lived urticaria (which generally presents with **anaphylaxis-like** symptoms rather than rash alone). If the diagnosis is uncertain, a reasonable approach is:

- Take photos;
- Consider skin biopsy (some cases);
- Treat based on initial diagnosis;
- Review to determine the natural history over the next days/week.

Contact allergic dermatitis

Contact allergic dermatitis is a type of contact allergy present in 1% of the population.

If contact allergy is suspected, the patient can document what they have been doing in touching in the previous 24 hours and undertake provocation testing to a small area in an attempt to identify an avoidable trigger.

Such cases are best referred to a dermatologist for patch testing if this is suspected.



Nickel dermatitis (above);
Shoe leather dermatitis (below)



Eczema

Eczema is largely a genetic disorder, aggravated by a number of potential factors including soap, dry climate and irritants. A patient with eczema may be allergic to dust mite but any doctor can organise a blood allergy test and recommend avoidance measures if positive. There is no cure, but treatment is usually effective.

While there are immune mechanisms operative in eczema (providing the rationale for novel biological therapies like dupilumab), it is not really quite an "allergic disease". Eczema is associated with allergic diseases like asthma, food allergy or hay fever, but these don't cause eczema - they are just fellow travelling companions. So, you may find they have a positive allergy test to grasses or pets or dust mite or elevated IgE if testing is undertaken, but that does not mean that allergy is the cause of the eczema specifically.



Eczema and allergen immunotherapy

There is conflicting evidence from a number of small trials that immunotherapy can help eczema (as opposed to allergic respiratory disease).

A recent systematic review of multiple trials suggest that some may benefit (doi: 10.1016/j.jaci.2022.09.020) but at a cost of between \$600 per year (injections) or \$1200 per year (tablets) for the immunotherapy reagents, it is an expensive experiment.

Diet and eczema

Food allergy is not the cause of eczema and allergy testing to food is not required as a routine in a patient with eczema **unless** they specifically have rapid onset obvious food allergic reactions, such as generalised rapid onset rash and vomiting and difficulty breathing soon after consumption.

Importantly, attempts to control childhood eczema by cutting out a previously tolerated food in a child can result in 10% of those children developing allergy to the food that was removed, as described above.

BUT: *Food allergy can be considered in a very young child with severe difficult to control eczema. That does not mean that food is the causes, but rather intercurrent food allergy as well is more common in this group. The same issue may be relevant in a breastfed baby where transfer of food allergen in breastmilk may be an aggravating factor.*