

# MORE ABOUT... PAEDIATRIC ALLERGY

## Anaphylaxis in children

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Professor Eugene Weinberg asked me to write a 'magic' article on anaphylaxis.

This edition being devoted to allergies in children, and stories having the magical quality of making things come alive, I decided to start with a story from a child, which highlights some important aspects of the management of anaphylaxis in children.

## Good teachers save lives

Anna Filax



My name is Anna. I am 13 years old.

I have to stay at school aftercare on Thursdays, because my mother works a '7-7' shift at the hospital once a week. She is a professional nurse in the emergency unit.

My father surfs on weekends. He is allergic to bees. Once he was stung by a bee on the beach, resulting in a bad reaction, and had to go to hospital. My mother held a family conference soon after that, using a pile of oranges, injection needles, syringes, and vials of expired adrenaline. She explained what might happen to dad if he got stung again, showed us how to give

an injection properly, and made us practise on the oranges. Even my little brother had to do it.



One Thursday at aftercare I heard a commotion in the kitchen. When I went to investigate, I found Mrs Love and Mr Cook, our caregivers, shouting and panicking. Lying half out of the broom cupboard was Lucy. She looked bad. Her breathing was loud and fast. Her lips were swollen and her face was red and patchy. It seemed as if she had fainted.



I know Lucy. She is a shy, skinny little kid who is always wiping her nose. She lives mostly with her dad. She is allergic to just about anything that tastes good: chocolates, cake, ice cream, milkshake, even peanuts. She wears a bracelet with a list as long as your arm of all the foods that can kill her.

Suddenly I remembered what mom had told me about allergies, and what could happen to dad if he got stung again.

I saw that there were some crumbs from the tea-time choc-chip muffins around her mouth and in the cupboard.

Poor Lucy must have had enough of not being allowed to have treats like the rest of us.

She had hidden in the broom cupboard so that she would not be seen eating the muffin. Luckily we had all made quite a mess around the tea table and Mrs Love had gone to fetch a broom to sweep it up. That was when she discovered Lucy.

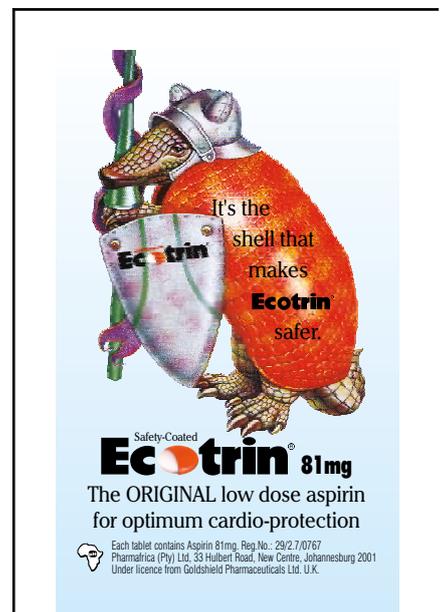
Suddenly I knew just what to do. Lucy needed an adrenaline injection, and fast! I asked Mrs Love if an injection was kept for Lucy at school.

She panicked a bit more, and then remembered that it was kept in the medicine cupboard in the office.

It was already 16h30 and the school secretary would have gone home.

I ran to the office. I tried the door. It was locked. I bashed on the door in frustration. To my surprise it opened, and Mrs Top, the principal, glared sternly at me.

I explained about Lucy, and she helped me to find the key to the medicine cupboard to get Lucy's adrenaline pack. We both rushed back to the aftercare room, where Mr Cook had laid Lucy on the couch and cleaned her mouth.



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## More about...

Mrs Love was in the next room, calling an ambulance.

The pack was a purple, plastic soap box with needles, syringes, small glass adrenaline ampoules and a paper towel.

Mrs Top was shaking. She could not remember what she had been told about the injection, and had never given one before.

I opened up the piece of paper towel on the side table, laid out the equipment, put the needle onto the syringe, broke open the glass vial (like I had done before), sucked up a bit less than half of the adrenaline (I reckoned Lucy would not need as much as my dad needed), and got rid of the bubbles.



Mrs Top glared sternly at me...



An ampoule of adrenaline

Mrs Top asked, 'Are you sure this is a good idea, Anna? What if the injection is dangerous?'

My mother had told me that I should give the injection even if I wasn't sure if it was right. It would do less harm to give it than not to do so.

I gave the injection into her big thigh muscle on the outside, right through her stockings. It felt pretty much the same as an orange.

I even remember-ed to draw back to check that no blood came back into the syringe.



Magic

Like magic, with-in minutes, Lucy started to look and breathe better.

By the time the ambulance arrived she was awake again, but still not in great shape. They put her on a stretcher, with her feet on a cushion, and into the back of the ambulance.

The paramedic asked us some questions.



The paramedic asked us a few questions...

In the meantime his partner attached an oxygen mask to Lucy's face, and put up a drip with a big bag of fluid hanging from a hook inside the roof of the ambulance.

They closed the doors and jumped into the vehicle, taking the soap box with them.

With a roar and a wail they were gone.

Mrs Love was crying. Mrs Top was trying to comfort her, and Mr Cook just said, 'Good girl Anna!'

My mother was a little late to fetch me because they had just had an unstable admission to ICU - a little girl who was allergic to milk, eggs and peanuts, who had eaten a whole choc-chip muffin with peanut sprinkles for afternoon tea.

'It's all right,' I said to my mom, 'you saved her life.'

'And how would you know that, Missie?' she asked, surprised.

'Because you took the time to teach me good,' I answered.

'Properly,' she said, looking puzzled, 'teach you properly!'

I acted cool, but I was way proud of my mother that day.



Proud of my mother

The end.

## Important aspects of anaphylaxis in children

This story highlights a few important aspects of anaphylaxis in children.

- Adrenaline is the drug of choice in anaphylaxis in children and adults, but the dose is smaller in children. Anna administered less than half an ampoule, which was a fair guess. Initial dosage: Infants and children - 0.01 mg/kg (1 mg/ml) injected into the anterolateral thigh. This treatment may be repeated at 5 - 15-minute intervals. If an auto-injector is used, children under 30 kg should receive the paediatric dose. Adults - 0.3 - 0.5 ml (1 mg/ml) intramuscularly into the anterolateral thigh. Treatment may be repeated at 5 - 15-minute intervals.<sup>1</sup>
- Adrenaline is life-saving in cases of anaphylaxis. Anna had been taught this without ambiguity, and was therefore

able to act decisively. Antihistamines, glucocorticosteroids and beta-agonists are useful adjunctive treatments, but it is important to remember that in anaphylaxis adrenaline is the life-saver.<sup>1,2</sup>

- In anaphylaxis the bronchi constrict, and the peripheral blood vessels dilate. Over 100 years ago a drug was discovered that relaxes the smooth muscle in the airways while simultaneously contracting the smooth muscle that lines the arterioles.<sup>1</sup> This drug was adrenaline. It is extremely useful in the treatment of the physiological effects of anaphylaxis. Lucy responded 'like magic' to the injection.
- If you do not have access to adrenaline you cannot use it. This may seem self-evident, but it has been repeatedly reported that children who have had past episodes of anaphylaxis infrequently have adrenaline self-administration devices available for use.<sup>2,3</sup> Lucy's adrenaline pack was kept too safely at school. If Mrs Top had not been working late, Lucy may not have survived. It is essential that there is quick and easy access to adrenaline for allergic patients at all times. Anaphylaxis strikes unpredictably and quickly.
- If you do not know how to administer adrenaline, it is of no use. This, too, may seem obvious; however, adrenaline is frequently not administered timeously to children with anaphylaxis. Caregivers and parents must not simply be taught to give an adrenaline injection, but be empowered to give one. They must feel confident that they would be able to perform the task if it were required. This necessitates an approach to education that is engaging and practical, and that is repeated often.<sup>1-8</sup> Mrs Top had been taught how to give the injection, but was not empowered to do so. She had no practical experience, and was therefore unable to perform the task under stress.
- There is no absolute contraindication to giving adrenaline in anaphylaxis, especially in children, in whom co-morbidities and potential drug interactions are unlikely to play a role.<sup>1</sup> Mrs Top asked: 'Are you sure this is a good idea Anna? What if the injection is dangerous?'
- The auto-injector adrenaline delivery system is very useful in anaphylaxis. The dose is preloaded and easy to administer. EpiPen is one of the commercially available adrenaline auto-injectors in South Africa. It is obtainable in doses for adults and children (but not for infants). It is, however, not always available at pharmacies as supply is variable. It is also costly, and the relatively rapid expiry rate, and the fact that most patients require more than one 'pen', make it unaffordable

for many families. A 1 ml vial of adrenaline with a needle and syringe, on the other hand, is a relatively affordable alternative, and many patients opt for this choice. It requires expertise to administer; therefore caregivers need skill and careful training.<sup>1,9</sup> Fortunately Anna had been well trained to perform the task.

- Other important first-line management procedures in anaphylaxis include keeping the patient supine with legs raised (if their bronchospasm allows it), giving oxygen at a high concentration, and ensuring rapid volume expansion.<sup>1</sup> The paramedics laid Lucy on a stretcher with her feet on a pillow, gave oxygen by face mask and immediately put up a drip with a large bag of fluid.
- The most common causes of anaphylaxis in children outside the hospital setting (where drugs and latex are most frequently implicated) are foods and insect venom.<sup>1,3,10</sup> Lucy was allergic to a variety of foods, many of which were present in a single muffin.
- Anaphylaxis can present in a myriad of ways; however, the initial signs of anaphylaxis in children are usually dermatological or respiratory in nature.<sup>1,3</sup> Lucy had urticaria, angioedema and bronchospasm with hypotension, resulting in her collapse. It is important for physicians, parents and caregivers to be familiar with the signs of anaphylaxis to be able to act quickly. The faster the treatment, the better the outcome.<sup>1,3</sup>
- Anaphylaxis and anaphylactic shock are different conditions. It is important to recognise the signs of anaphylaxis and treat the condition with adrenaline before the patient goes into shock. Lucy was found in a state of anaphylactic shock.<sup>1</sup>
- Anaphylaxis is a chronic condition and predominantly occurs in childhood.<sup>3,10</sup> The risk of a fatal reaction looms menacingly in the background at every meal, on every outing, at school, and at what should be the safest place – home. This puts extraordinary stress on families. Children are often psychologically affected by their condition. Lucy lives mostly with her dad because her parents are divorced. Her food allergies may not have been the cause of their separation, but the psychological distress of raising a child with anaphylaxis should not be underestimated. Health care providers must be aware of the psychological challenges that these families face and must know when to encourage families to seek psycho-educational advice.<sup>11,12</sup>
- Children in whom anaphylaxis occurs should have accurate medical

identification. A written anaphylaxis action plan must be part of the treatment strategy.<sup>1</sup> Lucy wore a MedicAlert bracelet. Anna's understanding of her condition made the diagnosis of anaphylaxis easier and expedited treatment, probably saving Lucy's life.

References available at [www.cmej.org.za](http://www.cmej.org.za)

## The oral allergy syndrome

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Individuals with pollen allergy often report adverse effects after the ingestion of a wide variety of foods from plants. Because of the increasing prevalence of pollen allergy, this association has in recent years gained greater recognition.<sup>1-3</sup> The clinical effects are usually restricted to the oral cavity and include oral pruritus, swelling of the lips, tongue and throat, hoarseness, pharyngitis, and laryngeal oedema. These localised symptoms, caused by fruit, vegetables and spices, have been termed oral allergy syndrome (OAS).<sup>4</sup> Immunoglobulin E antibodies (IgE) to the aeroallergen cross-react with the proteins in fresh fruit(s) and vegetable(s) to cause symptoms. Symptoms that patients experience are usually mild and do not require immediate medical attention. Rarely, some patients may experience severe and systemic reactions, such as severe laryngeal oedema, urticaria, asthma, or even food-induced anaphylaxis. This variation has resulted in a debate over whether such reactions may be considered a severe form of OAS or, as other authors contend, OAS includes only mild symptoms.

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Further, whereas the term OAS has been used by some authors to describe oral symptoms caused by any food allergen, and not necessarily related to pollen allergy, others have argued that the term pollen-food syndrome (PFS) should be used to highlight the association between pollen sensitisation and oral symptoms, since this is less ambiguous.<sup>4,6</sup>

Estimates of the percentage of patients with pollen allergy who also suffer from PFS vary from 47% to 70%, and this is thought to be the most common food allergy in adolescents and adults.<sup>7</sup>

Although most scientific evidence is related to co-sensitisation with birch pollen, a tree sparsely found in South Africa (where it is planted mainly as an ornamental), many other sources of pollen are likely to contain one or more of the cross-reactive panallergens, and therefore similar clinical effects may be seen locally.<sup>8</sup>

#### Associations

Although individuals may experience oral symptoms following ingestion of fruit and vegetables without underlying pollen allergy, in the majority of cases the initial event is sensitisation to pollen, and then there is subsequent development of cross-reactivity to food allergens, so that patients often develop pollen allergies before the development of oral symptoms.<sup>5</sup>

### Food-allergic patients may be sensitised to more than one allergen found in a specific food, complicating cross-reactivity.

The association of oral symptoms and pollen allergy results from cross-reactivity of pollen-specific IgE with homologous food allergens.<sup>5</sup> The pollens and foods involved usually are not botanically related but contain homologous proteins, as there are shared binding sites (epitopes) in the structures of pollen and food allergens.<sup>4</sup> Several clinical syndromes have been described<sup>9</sup> resulting from these associations depending on the particular cross-reactive allergens, e.g. between latex and fruit (latex-fruit syndrome).<sup>10,11</sup>

The plant proteins involved in OAS and PFS have been shown to belong to plant protein families, including those of profilins, pathogenesis-related proteins (PRs), and lipid transfer proteins. Other allergen families, e.g. calcium binding proteins (polcalins), are occasionally responsible

for FPS.<sup>4</sup> Appreciating the pattern of sensitisation to foods and to pollen may assist in the deduction of the responsible panallergen, and thereby assist with predicting the range of food that may affect an individual.

However, not all patients with cross-reactive antibodies will actually experience symptoms, i.e. the IgE cross-reactivity will be either clinically manifest or irrelevant. Cross-reactivity is influenced by the degree of ripeness of the fruit or vegetable, storage conditions and other factors, and may even vary even among cultivars.<sup>12</sup>

Food-allergic patients may be sensitised to more than one allergen found in a specific food, complicating cross-reactivity. For example, a high prevalence of OAS/FPS occurs to ingestion of apple in birch pollen-sensitised individuals as a result of the cross-reactivity between Mal d 1 from apple and Bet v 1 from birch pollen; however, apple-allergic individuals may be monosensitised or polysensitised to any number of apple allergens, e.g. to Mal d 1 (PR-10), Mal d 2 (PR-5), Mal d 3 (PR-14), Mal d 4 (profilin), etc.<sup>13</sup>

#### Diagnosis

The diagnosis is based almost entirely on the patient's history. A history of allergy to aeroallergens and then tingling or itching of the mouth after eating fresh fruits or vegetables is enough to make the diagnosis of OAS in almost all cases. The OAS reaction is usually immediate and can occur as soon as the fruit or vegetable is put into the mouth.

Commercial fruit and vegetable skin prick test extracts often lose their potency and sensitivity and may be unhelpful.<sup>4</sup> The prick-to-prick method involving pricking the fresh fruit with the lancing and then immediately using the same lancing for the skin prick, may be more useful.<sup>14</sup> Recently recombinant allergens, as used in component resolved diagnosis (CDR), may assist in the prediction and management of OAS/FPS.<sup>15</sup>

#### Treatment

Most patients with OAS will avoid the fruit(s) or vegetable(s) eliciting their symptoms. If the patient wishes to tolerate the localised symptoms and there is no suggestion of systemic symptoms, it is safe to continue eating the food.<sup>7</sup> Cooking alone may be sufficient to deactivate the responsible panallergen.<sup>16</sup> Taking an antihistamine prior to eating a culprit food may be acceptable, as long as this does not mask symptoms beyond the OAS.

References available at [www.cmej.org.za](http://www.cmej.org.za)

### Penicillin allergy

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Penicillin and penicillin-based antibiotics are the most frequently used agents for treating common infections but are also the antibiotics that most often cause allergic reactions.<sup>1,2</sup> Many patients are diagnosed as having penicillin allergy. However, on testing, it has been found that as many as 90% of individuals labelled as having penicillin allergy have no evidence of the condition.<sup>3,4</sup>

### Penicillin and penicillin-based antibiotics are the most frequently used agents for treating common infections but are also the antibiotics that most often cause allergic reactions.

The diagnosis of penicillin allergy is based on a comprehensive history which includes details of the symptoms and signs and their timing and duration in relation to exposure to and discontinuation of the drug. Reactions after penicillin administration may be classified as immediate (occurring within 2 hours), accelerated (from 2 to 72 hours) or delayed, developing more than 72 hours after exposure. Immediate reactions are likely to be IgE-mediated and clinically may include anaphylaxis, urticaria, bronchospasm or angio-oedema. Accelerated and delayed reactions are not IgE-mediated and those affected may develop a morbilliform rash, serum sickness, vasculitis, contact dermatitis, Stevens-Johnson syndrome or toxic epidermal necrolysis.

Penicillin is metabolised into major (penicilloyl) and minor (penicilloate and penilloate) antigenic determinants. It is essential to test for both determinants as testing for only the major determinants would miss at least 10% of penicillin-sensitive subjects.<sup>5</sup>

The investigations which should be performed include blood tests, skin tests and a drug provocation test. Blood is drawn for serum tryptase, CAP-RAST® and a CAST (cellular antigen stimulation test). Serum

tryptase, which is a marker of acute mast cell degranulation, should be done during an acute reaction. Anaphylaxis can be diagnosed with confidence if the tryptase level is found to be elevated within 1 - 2 hours of the reaction and subsequently falls to baseline after 6 hours. The CAP-RAST® measures IgE antibody levels and is sent for penicilloyl V, penicilloyl G, ampicilloyl and amoxicilloyl. These CAP-RASTs are 80 - 90% specific, with a lower sensitivity, but react only with the major antigenic determinants (allergy to minor determinants is tested by skin prick testing). The CAST is a newer test that measures the *in vitro* production of sulphidoleukotrienes by leucocytes on stimulation with the specific drug. It is approximately 46% sensitive and 85% specific for penicillin hypersensitivity.

Skin prick tests (SPTs) are done to diagnose immediate (IgE-mediated) reactions. They are not useful for non-IgE-mediated reactions. The SPT panel should include a positive and negative control, major and minor determinant mixture (PRE-PEN®), amoxicillin (20 - 25 mg/ml) and the specific implicated drug if it is something other than the above. If the SPT is negative it should be followed by an intradermal test (IDT) which is performed by injecting various dilutions into the skin. Intradermal testing is more sensitive than an SPT but carries more risk of producing false positives. IDT is a potentially dangerous procedure as it can induce anaphylaxis in susceptible individuals. It should be performed only by experienced personnel under controlled conditions with

resuscitation equipment available and after obtaining written informed consent.

If the above tests are negative or equivocal but the history is suggestive, a drug provocation test (DPT) is indicated. This is also useful to exclude hypersensitivity when the history is not suggestive or the symptoms are nonspecific. A DPT is not indicated if there is a suggestive history of allergy as well as a positive IgE or SPT as these are sufficient to diagnose allergy.<sup>5,6</sup> A DPT involves administering the drug at incremental doses and observing the patient for the symptoms and signs of a reaction. Safety precautions similar to those for IDT should be in place.

There are few tests available for non-IgE-mediated reactions. Atopy patch testing is increasingly being used, especially for contact dermatitis. A DPT, which would confirm the diagnosis in many cases, is contraindicated due to the severe and possibly life-threatening nature of some of the resultant reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis. In these cases, the implicated drug should be avoided indefinitely.

Management of confirmed penicillin allergy includes discontinuation of the drug and treatment of the symptoms of an acute reaction. Over the long term, patient education should be offered and a Medic-alert bracelet issued. If it is felt that the use of penicillin might be essential, the patient should be desensitised.

### Cross-reactivity with other antibiotics *Cephalosporins*

Up to 20% of proven penicillin-allergic patients will cross-react with first- and second-generation cephalosporins.<sup>7</sup> The cross-reaction is due to the presence of similar R-group side chains and not, as previously thought, because of the common  $\beta$ -lactam ring. The risk of reaction with the newer third- and fourth-generation cephalosporins is extremely low – in the order of 1 - 2%. Penicillin-allergic patients who require a cephalosporin should undergo SPT with the appropriate antibiotic. If the SPT is negative the cephalosporin can be administered with a less than 1% chance of a reaction occurring.<sup>3</sup> In a patient known to be allergic to a cephalosporin, substitution with a cephalosporin which has a different side chain is usually safe. If such a cephalosporin-allergic patient requires treatment with a penicillin, an SPT with penicillin should first be performed. Should the result be negative, penicillin may given.

### *Carbapenems*

Studies based on history and SPT alone have reported cross-reactivity of between 10% and 50% in penicillin-allergic patients who are tested with carbapenems.<sup>8,9</sup> Subsequent studies where drug provocation tests were also performed showed the risk to be less than 1%.<sup>10</sup>

References available at [www.cmej.org.za](http://www.cmej.org.za)

## SINGLE SUTURE

### *Miscarriage delay*

The World Health Organization suggests that women should wait for 6 months after a miscarriage before trying to conceive again. However, new research suggests that it might be better to try again as soon as possible.

The WHO guidance is based on a South American study that found more adverse outcomes in women who conceive early. Now Sohinee Bhattacharya at the University of Aberdeen, Scotland, and colleagues, have analysed the hospital records of 30 000 women who miscarried between 1981 and 2000. Those who became pregnant again within 6 months were less likely to experience another miscarriage or ectopic pregnancy than those who waited 6 months. The new study suggests that there is no physiological reason to delay pregnancy after miscarriage.

*New Scientist*, 14 August 2010, p. 14.