

Allergies and the skin

It is common in primary care to see people presenting with symptoms secondary to allergy, which could range from minor rashes or rhinitis to life-threatening anaphylaxis. The skin is the largest human organ, and it is involved in allergy; through both direct exposure to the allergens and manifestations of the allergic reaction. The aim of this article is to improve understanding of skin allergy and provide an outline on how to investigate and manage allergic skin conditions.

The GP curriculum and allergies and the skin

Clinical example 3.21: Care of people with skin problems requires GPs to:

- Recognise emergency skin conditions, e.g. anaphylaxis, and act appropriately
- Understand the different indications for patch and prick testing, and when these are appropriate
- Understand the effect of a patient's environment/occupation on skin conditions

Hypersensitivity is an immune-mediated release of chemicals that produces undesirable effects in response to a stimulus. There are four types of hypersensitivity reactions (Table 1) with types I and IV forming the bulk of suspected allergies in primary care; these reactions are the focus of this article.

A type I hypersensitivity reaction is also known as an immediate hypersensitivity or an allergic reaction. It is mediated by immunoglobulin E (IgE), in response to exposure to allergens via inhalation, ingestion or direct skin contact. Type II and type III reactions are immune-mediated and usually have other systemic effects along with skin involvement. Type IV reactions tend to be delayed and are cell-mediated.

Allergy

In immediate-type reactions, exposure to allergens produces effects secondary to IgE-mediated mast cell degranulation. (Thomas, 2001). Chemicals released from these mast cells and basophils cause itching, redness and swelling of the skin and sometimes mucosal surfaces in addition. See Box 1 for the phases of an allergic reaction and their clinical significance. Figure 1 and Box 1 illustrate the way an antigen is presented to the immune system, leading to specific IgE production, cross linkage and chemical release.

Box 1. The three phases of an allergic reaction.

Sensitisation

Allergens are taken up by antigen-presenting cells, and go through the process outlined in Figure 1 to induce allergen-specific IgE production. These IgEs attach to the mast cells and basophils to complete the sensitisation process.

Mast cell degranulation

This happens following re-exposure to the pre-sensitised allergen. This time, when the allergen presents, it causes IgEs on the mast cells to cross-link with each other. Cross-linking causes mast cell degranulation that results in the release of inflammatory mediators such as histamine, tryptase, heparin and other enzymes. The National Institute for Health and Care Excellence (NICE) advises serum tryptase measurement soon after emergency treatment of anaphylaxis, with repeat sample within 4 hours of symptom onset. A positive test for tryptase indicates mast cell degranulation (NICE, 2011).

Late response

Finally, other inflammatory cells (neutrophils, basophils, etc.) are recruited, leading to a vicious cycle of chemical production and damage. This is responsible for the biphasic reaction where signs and symptoms recur/ worsen after 4–10 hours.

Table 1. Types of hypersensitivity reactions.

Type	Mediation	Examples	Investigation	Management
I (Allergic/ immediate)	IgE-mediated	Urticaria Anaphylaxis Food allergies	1. History 2. Specific IgE test 3. Skin prick testing 4. Challenge testing	Avoidance Antihistamines A steroid Adrenaline Admission
II	Antibody-mediated	Pemphigoid Dermatitis herpetiformis	Antibody levels	Steroids Treatment aimed at the specific disease
III	Immune complex- mediated	Vasculitis Purpura Erythema nodosum	Blood tests guided by the presentation	Treat underlying cause, e.g. sepsis Steroids
IV (Delayed)	Cell-mediated (T-lymphocytes)	Contact dermatitis Morbilliform reactions	1. History 2. Patch testing	Avoidance Steroids Incremental exposure

Assessment in primary care

History

A detailed skin history can provide enough information to enable a diagnosis and subsequent guided management. Symptoms of skin allergy can include itching, burning or soreness. It is important to note the location of the symptoms (and rash if there is one), and particularly whether the rash is symmetric and/or associated with contact of a suspected allergen. If a cause is suspected, it is useful to know the time elapsed between contact with the potential allergen and onset of symptoms. It is also important to record the duration of the rash and whether it is episodic, and to establish whether there are any relevant associated symptoms such as wheeze or breathing difficulty. An occupational history is important, particularly if a trigger related to the patient's work is suspected.

Examination

Examination of the skin should determine whether there is any persistent rash. If there are clinical findings you should determine what level of the skin structure is affected. Scale or lichenification would suggest epidermal involvement. Weals may suggest dermal histamine infiltration.

Investigation

Most skin conditions discussed in the latter part of this article do not require tests and are a clinical diagnosis. Depending on clinical presentation, occasionally blood tests (e.g. specific Ig-E or tryptase) may be done.

Management

Patients with mild symptoms can be assessed and managed within primary care. Where there is diagnostic doubt, or potential multiple food allergies, patients should be routinely referred to a dermatologist or allergy clinic depending on local protocols. Patients with severe symptoms, particularly those suggestive of anaphylaxis, should be managed within a hospital setting. If the patient has symptoms, then immediate referral to the emergency department may be needed; if there is a history of an anaphylactic-type reaction that has now resolved, an urgent allergy clinic referral is indicated with appropriate safety netting to ensure that the patient (and/or carers) know what to do should symptoms return before the patient has been seen.

Clinical conditions

Urticaria

Urticaria is common, affecting one in six people at some point in their life and accounting for 50% of the total skin manifestations of allergic reactions. Therefore, it is important that GPs are familiar with it. Urticaria can be associated with other signs of allergy, for example, one study, which was based in an out-patients department, found one-third of cases have some degree of angio-oedema associated with urticaria (Nettis et al., 2003).

The 'weal' is the characteristic lesion of urticaria. Weals are raised and swollen; they are associated with profound itchiness, and each individual weal usually lasts less than 24 hours. Patients are increasingly using digital photography to record rashes that evolve and resolve before their encounter with their doctor. This can provide helpful information.

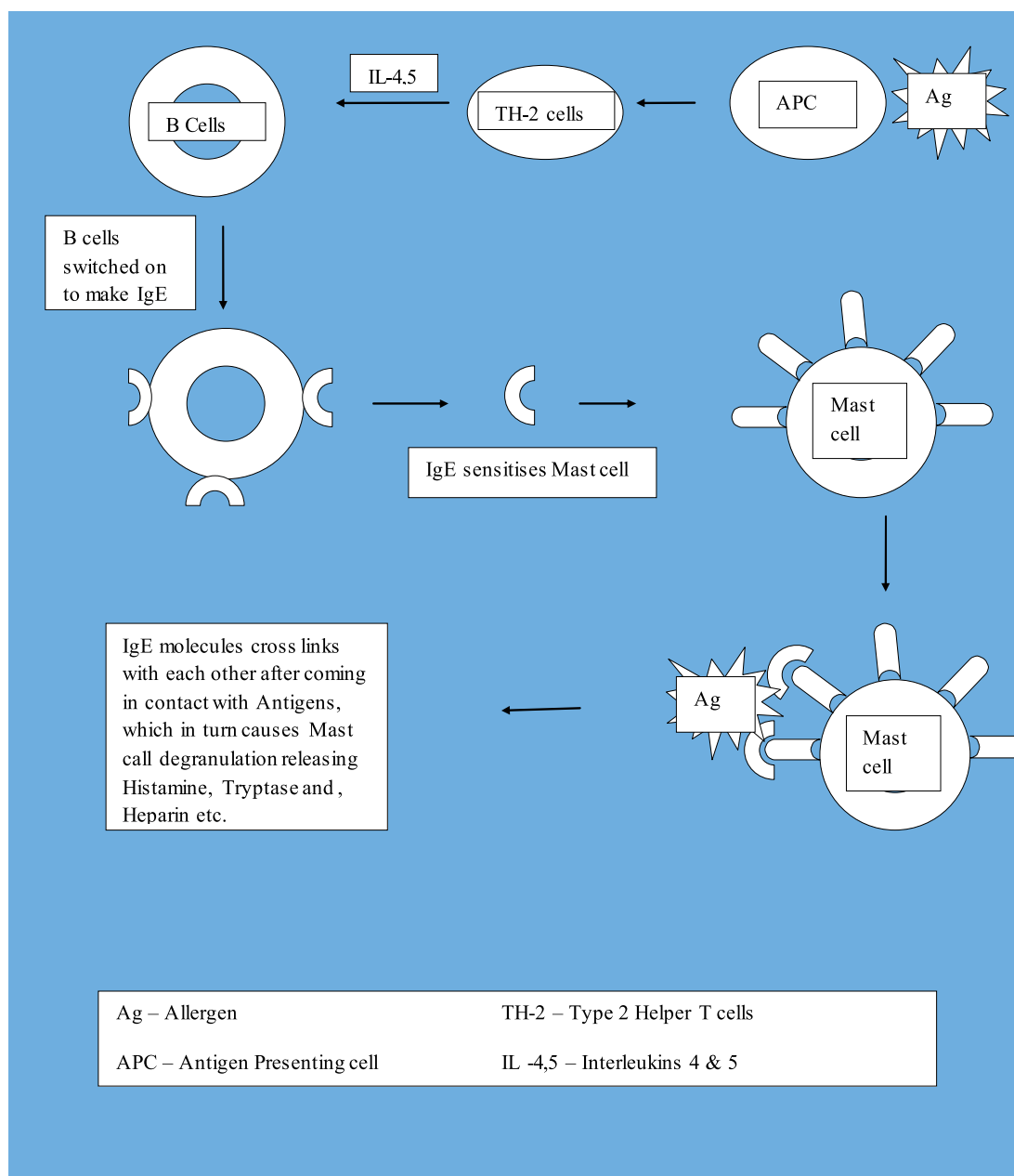


Figure 1. Mechanism of IgE-mediated hypersensitivity.

The weal, once cleared, leaves normal skin behind. Thus, any lesion lasting for longer than 24 hours, or any abnormal or flaky skin after the rash has cleared, should raise the possibility of some other diagnosis. Urticarial vasculitis and deep physical urticaria, for example, can last for more than 48 hours and are usually associated with other systemic features.

There are numerous causes of urticaria with allergy being only one of them. Causes are usually classified as follows (Grattan & Humphreys, 2007):

1. Ordinary urticaria: This is further divided into acute (of less than 6 weeks duration), chronic (continuously present for more than 6 weeks) and episodic urticaria

2. Physical urticaria: Reproduced by the same stimuli, e.g. secondary to thermal or mechanical stimuli
3. Angio-oedema without weals, e.g. drug-induced angio-oedema or C1 esterase inhibitor deficiency
4. Contact urticaria secondary to allergens/chemicals
5. Urticarial vasculitis
6. Auto-inflammatory syndromes

Diagnosis of urticaria is mainly clinical. Most urticarias are mild, self-limiting and do not need to be investigated. Severe reactions involving mouth, throat or airways should be investigated. Careful history taking is most important and in some cases helps to establish the allergen. Specific IgE tests and skin prick testing can be used

to confirm an allergic reaction. Tests should be guided by the history and interpreted in clinical context.

Management initially includes general measures, as outlined in Box 2, and medical management, in Box 3. In the case of chronic and difficult to control skin conditions, it is important to look into the psychological burden of the disease and provide adequate support.

Box 2. General measures for an allergy.

- Avoidance of allergen, if identified. For non-allergic urticarias, recognition and avoidance of triggers (stress, caffeine, alcohol, spices, etc.) is important
- A diet diary may help link a particular food to the reaction
- Patient education (information leaflets) and reassurance that their condition is manageable can go a long way to helping the patient
- Cooling lotions, such as menthol in aqueous cream or calamine lotion, can be soothing and reduce itching. They are freely available over the counter

Box 3. Medical management of urticaria.

Antihistamines

Non-sedating antihistamines remain the cornerstone of treatment of mild urticaria in primary care. Regular doses of antihistamines may be needed if having continuous urticaria. It is helpful to use antihistamine prophylactically if a patient has an identified trigger. It is important to know that if symptoms are not controlled with licensed doses, then sometimes specialists may use doses of antihistamines that are much above licensed doses. For example, specialists may prescribe cetirizine 10 mg twice a day for urticaria not responding to the British National Formulary dose of 10 mg once a day. Among the seven antihistamines licensed in the UK for urticaria, cetirizine takes the shortest time to attain maximum concentration, making it more suitable to be used in an acute setting. Occasionally, sedating antihistamines such as chlorphenamine or hydroxyzine can be added, especially if symptoms are affecting sleep. Adding an H₂ receptor blocker (e.g. ranitidine 150 mg twice daily) is an option for urticaria not responding to the previous two steps (Grattan and Humphreys, 2007) though it is an off label indication. However, a referral to a specialist would be worth considering by this point.

Steroids

Rescue steroids (prednisolone 40 mg daily for 3 days) can be used in severe cases of allergy or in specific situations, for example, wedding or an exam. It is not encouraged and should be limited to severe cases or difficult to control urticaria.

Angio-oedema

Angio-oedema is a deeper swelling that can last up to 72 hours and can affect mucosal surfaces such as lips, mouth, tongue and genitalia. Occasionally, it may affect the gastrointestinal tract (causing abdominal pain, diarrhoea, and vomiting) or, the respiratory tract (causing breathlessness, wheeze, and stridor). As it involves the dermis and subcutis, the oedema can be deeper and more extensive. Angio-oedema can present with or without urticaria. In the event of airway compromise or circulatory collapse, treat it like anaphylaxis (see the next section). Otherwise, angio-oedema should be treated with anti-histamines, steroids and admission for observation (NICE, 2012).

Anaphylaxis

Anaphylaxis is a severe allergic reaction that is characterised by rapid development of life-threatening breathing and circulatory compromise. It is a medical emergency, so time is of the essence in treating anaphylaxis. Skin symptoms (urticaria, angio-oedema) are common but might be absent or very subtle (one in five cases). See Box 4 along with Table 2 for management of anaphylaxis and Box 5 for guidelines for referral to an allergy clinic.

Box 4. Management of anaphylaxis in primary care.

- ABCDE approach (**A**irway, **B**reathing, **C**irculation, **D**rugs including looking for hypoglycaemia, **E**xposure). Ask for help including getting someone to call for an ambulance
- Adrenaline : Intramuscular (IM) injection on antero-lateral aspect of the thigh. The dose can be repeated after 5 minutes if needed. See Table 2 for age-appropriate doses
- Comfortable positioning and monitoring (pulse oximetry, blood pressure) / high flow oxygen
- Intravenous (IV) access and if systolic blood pressure less than 90 mmHg, then fluid challenge with normal saline or Hartmann's solution. In adults, with 500 ml – 1 L or 20 mg/ Kg in paediatric cases. This is a step that can get delayed or is always available in primary care
- IM/IV hydrocortisone (especially in asthmatics)
- IM/IV chlorphenamine
- Consider nebulised salbutamol in patients with a wheeze or past history of chronic respiratory disease

NICE advises that every patient should be observed for 6–12 hours from the onset of symptoms and so most patients need to be referred to hospital.

Source: NICE (2012).

Table 2. Age-appropriate doses of medicine used in anaphylaxis management.

Age	Adrenaline	Hydrocortisone	Chlorphenamine
Younger than 6 months	150 microgram (0.15 ml of 1:1000)	25 mg	250 microgram/kg
6 months–6 years	150 microgram (0.15 ml of 1:1000)	50 mg	2.5 mg
6–12 years	300 microgram (0.3 ml of 1:1000)	100 mg	5 mg
Older than 12 years	500 microgram (0.5 ml of 1:1000)	200 mg	10 mg

Source: British National Formulary (2014).

Box 5. Who should be referred to an allergy clinic?

- Anyone with anaphylaxis
- Angio-oedema without identifiable cause or if it persists/ recurs 3 months after stopping the offending drug (e.g. angiotensin-converting enzyme inhibitors)
- Proven IgE-mediated food allergy and concurrent asthma
- Suspicion of multiple food allergy
- Diagnostic uncertainty
- Strong clinical suspicion of food allergy with negative allergy test results

Source: NICE (2012), British Society for Allergy and Clinical Immunology (2007), Muraro et al. (2007).

Who should be prescribed an adrenaline auto-injector device?

An adrenaline auto-injector device should be prescribed to anyone who has experienced an anaphylactic reaction on the advice of an immunologist or an allergist. A specialist may also consider prescribing for those who are at high risk of complications, for example, a child with severe food allergy and co-existent uncontrolled asthma. Patients should have enough auto-injectors to accommodate their lifestyle. In children this would include having a suitable supply of devices both at school and at home. Many patients need a repeat dose of adrenaline within 5 to 15 minutes of the initial dose or later due to delayed reaction. Therefore, it is good practice to prescribe two devices to be kept in each location that the patient usually frequents (e.g. two for home, two for work and two in the car). It is important to note that auto-injectors have a limited shelf-life and should be replaced before their expiry date regardless of whether they have been used.

Injection technique is device-specific and patient training can be undertaken in primary care, in the allergy clinic, or sometimes by school nurses. All those who are likely to be required to administer adrenaline to the patient should have training. This may involve patients, carers,



Figure 2. Morbilliform rash.

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other family members, school teachers and/or work colleagues as appropriate.

Mimics of allergic reactions

Morbilliform drug rash

A morbilliform rash is a measles-like rash (see Fig. 2) and it is the most common drug rash referred to secondary care. It is a type of delayed hypersensitivity reaction, mediated by type 2 T-helper cells, and is classified as a IV b hypersensitivity reaction. The rash is treated by stopping the offending drug and recording the response. Reassurance and watchful waiting is all that is usually required, however, in severe cases a 3 to 5 day course of oral steroids may be needed. Of note, giving antihistamines is not effective as mast cells (and thus histamine) are not involved in the causation of this type of rash.

It is always important to record drug reactions on a patient's notes to ensure that the drug is not prescribed again to the same patient. Drug reactions are classified into:

- Type A reactions: These are common and relate to the pharmacology of the drug (e.g. constipation with opioids), and
- Type B reactions: Rare, idiosyncratic and unpredictable reactions that are often serious

Type A accounts for almost 80% of drug reactions presenting to the health professional. These can in many instances be incorrectly recorded as an allergy, but should be labelled as intolerance rather than allergies, unless they caused angio-oedema or anaphylaxis.

Pseudo-allergic reaction

Conditions that can cause direct mast cell activation (without involvement of IgE) are called 'pseudo-allergies'. Their clinical presentation is similar to allergic reactions, as they too release the same inflammatory chemicals after mast cell degranulation. Presentation can vary from mild urticarial symptoms to anaphylaxis. Common examples are urticaria pigmentosa (cutaneous mastocytosis) and drug-induced urticaria (e.g. codeine).

The clinical significance of understanding pseudo-allergies lies in the fact that blood tests for IgE and skin prick testing will yield a negative reaction. Also, unlike allergic reactions they do not need sensitisation and can occur even after first exposure. If the reaction is severe enough to cause anaphylaxis it is termed an 'anaphylactoid reaction'. Management depends on the clinical presentation, with cutaneous involvement responding well to antihistamines. Mast cell stabilisers, e.g. sodium chromoglycate can be helpful in cutaneous mastocytosis. Steroids are not as effective, due to the lack of Ig-E involvement in the pathogenesis. Adrenaline is the main stay of treatment of anaphylactoid reactions and they should be treated in the hospital setting.

Atopic eczema

Sometimes, a parent may bring a child to the GP with worsening eczema, wondering if it is due to an allergy. 'Atopy' indicates a genetic susceptibility to the development of allergic diseases (one or more of the triad of asthma, allergic rhinitis, and eczema) in response to environmental factors such as irritants or allergens.

Atopic eczema has shown to symptomatically worsen due to food allergy in 10% children, but less so in adults. Some people with atopic dermatitis have been found to have excessive levels of IgE and eosinophils. That along with a reduced barrier function of skin, which makes it easier for the allergens to penetrate skin, makes them more prone to allergy.

Investigation is usually not needed. Frequent and liberal use of emollients to restore skin barrier function is the most important part of management. Patient education regarding the condition, use of soap substitutes and at least twice daily use of a moisturising cream (cosmetically more acceptable), or ointment (greasy but more effective) helps with compliance and better management. Patient.co.uk and British Association of Dermatologists have good web-based patient information leaflets.

Allergic contact dermatitis

Allergic contact dermatitis is the most common presentation of delayed hypersensitivity that we see in general practice (Thomas, 2001). Sometimes it can be confused with allergies rather than hypersensitivity and given some of the treatments, especially antihistamines, which are not effective. Its most important differential is irritant contact dermatitis and Table 3 explains the main differences between allergic and irritant dermatitis. However in practice these two entities may co-exist. Common allergens

Table 3. Differences between allergic and irritant dermatitis.

	Allergic contact dermatitis	Irritant contact dermatitis
Who is at risk?	Genetic predisposition	Everyone who is exposed to an irritant
Mechanism	Delayed cell-mediated	Breakdown of barrier function of the skin
Substances involved	Haptens (low-molecular-weight substances) e.g. metals	Soaps, solvents
Borders	Can be very clear and distinct	Usually indistinct
Investigation	History Trial of avoidance Patch testing	History Trial of avoidance
Management	Complete avoidance of exposure	Restoration of skin barrier function Try to avoid/reduce exposure

Table 4. Patch and skin prick testing.

	Patch testing	Prick testing
Used for	Type IV (delayed sensitivity)	Type I (immediate type)
Possible indications	Allergic contact dermatitis	Food allergies
How is it done	Application of pre-selected patches, usually on the back, is guided by history.	Skin is pricked through a suspected allergen (in a solution) with a lancet
Usual site	Back	Forearm
Time to read	At 2 and 4 days	15–20 minutes

responsible for contact dermatitis include nickel, balsam of Peru (found in many fragrances), rubber (due to either latex or accelerator chemicals), cobalt and chromium, with treatment-resistant hand dermatitis being the most common presentation in primary care. Health care, pharmaceutical, construction and metal workers, hair-dressers and cosmetics industry workers are at increased risk of developing allergic contact dermatitis.

Allergic contact dermatitis is a type IV delayed hypersensitivity reaction. The allergen is taken up by the skin macrophages (Langerhans cells) and processed into smaller peptides, which in turn are presented to lymphocytes. Interleukins are released, which activate antigen-specific memory T-cells. These memory T-cells are multiplied and release cytotoxic chemicals when re-exposed to the allergens.

Contact dermatitis needs sensitisation by prior exposure before a response with dermatitis can be seen. It typically presents as redness, itching, swelling, scaling and sometimes weeping lesions.

Think of contact dermatitis in patients presenting with the following symptoms and signs (Burge and Wallis, 2012):

- Hand dermatitis (though up to 70–80% of cases are caused by irritant contact dermatitis)
- Chronic leg ulcers not responding to usual treatment
- Treatment-resistant facial dermatitis
- Pruritis ani (especially when a few creams have already been used).

A thorough history, including occupation as well as hobbies, should be taken. Simple strategies such as allergen avoidance, emollient use and careful use of topical steroids may enable the patient to be managed in primary care. If a trigger has not been identified or there is diagnostic doubt consider patch testing. A dermatology referral may be required to do this if this not available in the community. There are different batteries of patch testing available that are used based on patient history and clinical context. See Table 4 for the difference between patch and skin prick testing and Box 6 for management of allergic contact dermatitis.

Box 6. Management of allergic contact dermatitis.

- Avoidance: Once a diagnosis of allergic contact dermatitis is made, the patient should be clearly informed about complete avoidance of the allergen
- Potent topical steroids: Potency will depend on the body area and the total surface area involved, with reduced potency if widespread or if the face is involved
- Change in occupation/hobby may need to be considered if severe contact dermatitis
- Incremental exposure: not suitable for primary care

Key points

- Skin-related problems due to allergy are common in primary care
- History is the most important step in ascertaining allergy
- Think IgE or skin prick testing for food allergy and patch testing for contact dermatitis
- Avoidance of the allergen once identified is vital
- Reduced skin barrier function in atopic dermatitis may make people prone to allergy
- Be aware of anaphylaxis and its management algorithm

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Acknowledgement

The author would like to thank Dr Joy Wright for her help with the writing of this article under the *InnovAiT* 'buddy' scheme and Dr Janis Tait and Dr Peter Kelly for proof reading this paper.

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