REVIEW ARTICLE

# Testing children for allergies: why, how, who and when

## An updated statement of the European Academy of Allergy and Clinical Immunology (EAACI) Section on Pediatrics and the EAACI-Clemens von Pirquet Foundation

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**Abstract**

Allergic diseases are common in childhood and can cause a significant morbidity and impaired quality-of-life of the children and their families. Adequate allergy testing is the prerequisite for optimal care, including allergen avoidance, pharmacotherapy and immunotherapy. Children with persisting or recurrent or severe symptoms suggestive for allergy should undergo an appropriate diagnostic work-up, irrespective of their age. Adequate allergy testing may also allow defining allergic trigger in common symptoms. We provide here evidence-based guidance on when and how to test for allergy in children based on common presenting symptoms suggestive of allergic diseases.

Allergy is defined as a hypersensitivity reaction to a specific immunological trigger initiated by immunological mechanisms (mostly IgE- or cell-mediated). Allergic diseases in childhood (in particular, atopic dermatitis, asthma, allergic rhinitis and conjunctivitis as well as food allergy) have reached a high prevalence in the last decades (Table 1), and accordingly the need for allergy testing has increased (1–3). An early diagnosis is a prerequisite for optimal care of allergy in children. Most commonly, children are evaluated first by their primary care physician, sometimes with symptoms highly suggestive of an allergic disease (e.g. seasonal rhinitis and conjunctivitis), or with symptoms where allergy is part of the differential diagnosis (e.g. recurrent vomiting in an infant). The challenge to the physician is then to determine in whom, when and how to use allergy diagnostic tests.

In 2003, the Section on Pediatrics of the European Academy of Allergy and Clinical Immunology (EAACI) published evidence-based recommendations on allergy testing in children (4). This was in the context of a close collaboration between primary care physicians and physicians specifically trained in paediatric allergy by the European Union of Medical Specialists (UEMS) criteria following the syllabus for European paediatric allergy training (thereafter referred as PA-trained physicians) (5). The current publication, a collaboration of the

**Table 1** Prevalence of common allergy-related symptoms and allergic diseases in childhood

| Symptom/disease | Age | Prevalence | References |
|---|---|---|---|
| Allergic asthma | At age 6–7 yrs | Up to 25%* | (1) |
| Allergic rhinitis & conjunctivitis | At age 6–7 yrs | Up to 20%* | (1) |
| Chronic diarrhoea | Infants | 3–5% | (95) |
| Food allergy | Childhood | 3–5% | (137) |
| Atopic eczema | At age 6–7 yrs | Up to 18%* | (1) |

*From a world-wide cross-sectional questionnaire survey. Prevalence may vary between countries and might be different in prospective cohort studies.

**Table 2** Levels of evidences and grades of recommendation

| | Level of evidences |
|---|---|
| Level I | Systematic reviews, meta-analyses, randomized controlled trials |
| Level II | Two groups, non-randomized studies (e.g. cohort, case-control) |
| Level III | One group, non-randomized (e.g. before and after, pre-test and post-test) |
| Level IV | Descriptive studies that include analysis of outcomes (single-subject design, case series) |
| Level V | Case reports and expert opinion that include narrative literature reviews and consensus statements |
| | **Grades of recommendation** |
| Grade A | Consistent level I studies |
| Grade B | Consistent level II or III studies *or* extrapolations from level I studies |
| Grade C | Level IV studies *or* extrapolations from level II or III studies |
| Grade D | Level V evidence *or* troublingly inconsistent or inconclusive studies of any level |

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EAACI-Clemens von Pirquet Foundation and the EAACI section on Paediatrics, revises this initial publication, by providing updated state-of-the-art, evidenced-based recommendations graded by level of evidence and marked in the text in brackets as [Grades of recommendation] (6) (Table 2). The recommendations were discussed and validated in a meeting by the authors, representing expert opinion from representative European academic paediatric allergy centres. Although the authors have reviewed the relevant literature published since the initial guidelines, the current recommendations are not based on a systematic review approach. To make these recommendations accessible also to primary care physicians, a large section, 'Who & How', is devoted to allergy diagnosis according to the symptoms. We strongly encourage these recommendations on allergy testing in children to be implemented across Europe and beyond, according to local needs, resource availability, local organization of professionals and the level of knowledge. It is also recommended to ensure and strengthen cooperation between primary care physicians and PA-trained physicians.

Principles of allergy diagnosis in children:

- Why: In children, many common symptoms can be allergy-related.
- Who & When: Allergy testing should be initiated according to presenting symptoms and signs.
- How: Allergy testing should only be undertaken with validated tests.

## Allergy testing: why?

Allergy testing is a very important diagnostic process regarding:

A. Specific allergen avoidance measures and disease monitoring.
B. Specific allergy treatment.
   Pharmacotherapy and timing of therapy.
   Specific allergy immunotherapy.
C. Early identification of infants at increased risk for later development of allergic diseases.

### Allergen avoidance

Correct identification of allergens that elicit symptoms (inhalant, food or drug) allows a logical, allergen-focused avoidance plan to be offered and prevents unwarranted allergen exclusion by negative allergy testing. Appropriate allergen avoidance can ameliorate the burden of allergic conditions, such as allergic asthma, with improved lung function and normalized markers of allergic inflammation and can reduce the need for pharmacotherapy (7). Food allergies in young children can resolve spontaneously; however, strongly positive skin prick test (SPT) or elevated specific IgE (spIgE) at diagnosis or during follow-up may predict disease persistence (8,9). Monitoring is essential, as for example milk and egg can often be safely reintroduced in milk- or egg-allergic children during a food challenge once the spIgE levels have fallen sufficiently.

### Specific allergy treatment

*Relevant pharmacotherapy*

Information provided by specific allergy diagnosis may be a prerequisite for advising the correct pharmacological anti-allergy treatment. For example, commencing therapy just before the onset of the local grass pollen season can maximize treatment effectiveness for grass pollen-driven allergic rhinitis (10).

*Specific allergy immunotherapy*

Allergy testing is also essential for a proper composition of allergen-specific immunotherapy (SIT). SIT has been demonstrated in many studies to be an effective treatment for patients with allergic rhino-conjunctivitis and asthma (11,12). Additionally, SIT in children with pure seasonal allergic rhinitis results in significantly fewer children subsequently developing asthma than in an untreated parallel control group, an effect that was maintained over 10 yrs of follow-up (13). SIT may also prevent the onset of new sensitizations (14). Oral immunotherapy is also now being developed for food allergies but is not yet ready for routine clinical use (15).

### Early identification of infants at increased risk for later development of allergic diseases

Children with early development of IgE sensitization to cow's milk or hen's egg proteins or early sensitization to inhalant allergens have an increased risk for later development of asthma (16). The early identification of these children may provide opportunities to prevent the development of asthma. Also children with an existing food allergy may be at higher risk for further food allergies. For example, infants with egg allergy are commonly (20–25%) sensitized to peanut (17). So these egg-allergic children should be offered peanut SPT or specific IgE testing [B]. A proportion of peanut allergic children will develop tree nut allergy (18); therefore, testing to tree nuts might be considered in countries where peanut and tree nut allergies co-exist [B]. However, co-sensitization may rather reflect increased exquisite immune responsiveness of a high risk individual, and serological cross-reactivity is not always necessarily clinically relevant.

## How – practical allergy testing

### History and physical examination

A thorough history and physical examination is paramount in allergy diagnosis. On many occasions, the description of symptoms and the temporal relationship of the reaction in relation to an eliciting factor may lead to specific confirmatory tests. Directly related to the symptoms, the history aims to:

- characterize the type and severity of the reaction,
- identify eliciting allergens and/or other factors,
- define the timing between exposure to those factors and the reaction, and
- identify related conditions.

In addition, the following factors might be important: the general environment (home, climate, school and exposure to pets), a family history of allergy, maternal smoking, the mode of delivery as well as the dietary history of the child.

### Skin prick test and serum IgE tests

The diagnosis of IgE-mediated allergies in childhood, suggested by a clinical history and the physical examination, should be based on validated allergy tests such as SPT and/or spIgE in the serum, when indicated.

*Skin prick test*

For practical performance, the guidelines for SPT should be followed (19) together with a proper training for the tester (20,21). The panel of allergens will depend on the age and the case history (see section on testing by symptoms) and varies according to regional allergen prevalence (Tables 3 and 4) [C]. Although there is no lower age limit for performing SPT (4,22,23) [C], SPT results should be interpreted with caution in children younger than 2 yrs of age (21) [C]. Intradermal testing may be indicated in specific indications (e.g. drug allergy). The extensive variability in devices, techniques, skin reactivity, interpretation and extract qualities makes SPT standardization difficult (24) [C]. In larger wheal reactions, the longest wheal diameter has been proposed as the optimal measurement (25). A mean wheal diameter $\geq 3$ mm larger than the negative control is widely accepted as a positive reaction (21,26), with exceptions for certain devices (27) [C]. Although the use of standardized extracts should be preferred, in selected cases the use of fresh fruits/vegetables (by the prick-to-prick method) can be considered to exclude false negativity caused by labile allergenic extracts (28) [C]. Contraindications for SPT are as follows: active eczema on the test site or use of antihistamines within $\leq 3$ days prior to SPT (4,19,21) [C]. Skin prick testing should be avoided on skin areas treated with topical steroids or immunomodulators; nevertheless, there is no convincing evidence that topical use of steroids suppresses skin tests. In general, the time interval between the occurrences of an acute allergic reaction and the performance of skin testing should be 4–6 wks [E].

*Total serum IgE measurements*

Total IgE has no indication in specifically diagnosing allergic diseases. Serum total IgE might be used in the following indications:

- as an inclusion, and dose determining parameter for omalizumab therapy [B]
- as a diagnostic and monitoring parameter in allergic bronchopulmonary aspergillosis (21) [B]
- as an assessment parameter in algorithms to predict reactivity in food challenge (29) [B]

### Allergen-specific IgE assays (spIgE assays)

Testing for allergen-specific IgE should be conducted with a validated method (30) [B] and can be performed at any age (4,23) [B]. The number and the list of allergens tested should be defined according to symptoms, age and local sensitization patterns (Tables 3 and 4). Most of the validated spIgE assays use an ELISA-type method and provide quantitative results [B]. These assays bind serum allergen-specific IgE antibodies in sera to the allergen extract bound to a solid (sometimes fluid) phase (23,30). SpIgE levels >0.1 kU/ml or >0.35 kU/ml are considered as positive but there are significant inter-assay variations, mostly

**Table 3** Foods most commonly involved in childhood atopic eczema (AE)

| | Switzerland [ref (143)] *(%) | USA [ref (55)] *(%) | Germany [ref (138)] *(%) | Australia [ref (139)] *(%) | Denmark [ref (140)]†(%) |
|---|---|---|---|---|---|
| Hen's egg | 21 | 29 | 70 | 82 | 62 |
| Cow's milk | 20 | 15 | 51 | 17 | 31 |
| Peanut | 18 | 33 | n.d. | 35 | 7 |
| Tree nuts | 5 | 0 | n.d. | n.a. | n.a. |
| Wheat | 7 | 6 | 44 | n.a. | n.a. |
| Fish | 12 | 0 | n.d. | n.a. | n.a. |
| Soy | 2 | 0 | 16 | n.a. | n.a. |

n.a., information not available; n.d., not tested for.

*AE exclusively.

†AE and other symptoms.

due to methodological differences (23,30) [C]. Multi-allergen IgE screening, often used with point-of-care devices, can measure IgE binding to a panel of common allergens in a single test. These tests have generally a high negative predictive value (NPV) for atopic disease (23,30) [C].

In general, SPT and most commercial spIgE assays display a good sensitivity, but a lower specificity (21,28,31) [C]. However, these depend largely on the antigen tested. SPT and spIgE tests are complementary and in certain circumstances only (e.g. when a test is negative despite a suggestive history), a combined use of both tests enhances their diagnostic accuracy. The high NPV of both tests is especially useful for ruling out IgE-mediated food allergies (31) [C]. Neither spIgE nor SPT levels can reflect the clinical severity of allergies in individual cases, but in quantitative studies [C], their absolute values appear proportional to the likelihood of clinical allergy. For different foods, predictive diagnostic cut-off values have been determined. However, cut-off values and the positive predictive value (PPV) may vary substantially between studies and populations and should be interpreted accordingly (31–34) [C]. In patients with a panel of very high spIgE test results, a high total IgE (>1000 kU/ml) will indicate that the results of the specific IgE testing needs to be interpreted with caution.

Crude allergen extracts might not be standardized. Thus, false-positive results can occur, caused, for example, by tree pollens in bee venom-sensitive patients due to cross-reactive carbohydrate-determinants. To overcome these limitations, novel diagnostic tests (component-resolved diagnosis (CRD), microarrays) have been developed. CRD utilizes highly purified or recombinant allergenic components instead of crude extracts. For example, Ara h 2, a major allergen of peanut has been successfully used to predict peanut allergy in children (35–37) [C].

### Other *in vitro* and *in vivo* tests

In recent years, several studies have indicated a role for the basophil activation tests in the diagnosis and follow-up of food allergies, drug allergies, as well as for monitoring anti-IgE treatments (38–41) [B]. Lymphocyte activation tests might also be used in selected cases of food or drug-related reactions (42,43) [B and C]. Their use is mostly limited to tertiary referral centres. Serum tryptase measurement is a helpful test to assist the clinical diagnosis of anaphylaxis presenting with atypical symptoms (44). The test has a high specificity, but the sensitivity is limited, in particular, for food-induced reactions. Atopy patch testing may be indicated in a limited number of patients with atopic eczema and with gastro-intestinal symptoms of food allergy, with positive tests often needing confirmation with food challenges (45) [B]. Finally, allergy diagnosis may also require the use of endoscopic procedures, mostly of the GI tract, as well as less specific evaluation of inflammation (e.g. exhaled nitric oxide measurement for diagnosis or follow-up of asthma).

### Food Challenges

Positive IgE test results indicate sensitivity to the food but do not prove food allergy unless ingestion of the food has been clearly linked to allergic symptoms. Clinical history has a limited positive predictive value for clinical allergy, the magnitude of the IgE test result may help to rule in or rule out clinical allergy as well as planning follow-up of food allergy; however, these levels are clearly population related and cannot be broadly used (33,46) [B]. In addition, algorithms might help to predict the outcome of food challenges, possibly leading to less resource to this time-consuming diagnostic procedure (47) [B]. Food challenges may be used in both IgE- and non-IgE-mediated food allergies. Double-blind, placebo-controlled food challenges remain the gold standard in research settings, and for investigating delayed, or non-specific symptoms (48) [B]. Open food challenge protocols are usually adequate; where only subjective symptoms develop, a blinded challenge should be undertaken to confirm the diagnosis. Food challenges need to be conducted by trained and experienced professionals, in compliance with current guidelines. It must be emphasized that safety is the prime concern, limiting food challenges to settings where appropriate surveillance and emergency care are available.

*Food challenges will allow*

- A clear diagnosis and decrease unnecessary elimination diets based only on positive IgE tests.
- A follow-up of food allergy assessing evolution and resolution of the condition.
- A patient experiencing an allergic reaction and seeing how to manage it, and determining the threshold of reaction.

### Drug challenges

Drug-related reactions will be explored following guidance provided in the section '*When & How… should a child with a drug-induced skin rash be diagnosed for allergies?*' Similarly to food challenges, drug challenges need to be conducted in a safe environment, by following protocols adapted to the history of the reaction. In many cases, drug allergy might be ruled out (e.g. in benign beta lactam-induced rashes in young children) by a negative challenge (49) [B].

### Inhalant challenges

Nasal or conjunctival challenges should be considered when IgE test results are not in concordance with the history, in particular, when immunotherapy is indicated. They will confirm the diagnosis and can indicate which allergens should be selected for immunotherapy (50). Bronchial allergen challenges are currently limited to research purposes. In addition, non-specific bronchial challenges (methacholine, mannitol, exercise) need to be considered for assessing airway hyper-reactivity in patients with asthma, but are not necessary in most cases of suspected allergy (51).

### Unproven and non-validated diagnostic tests

*Unproven tests* include serum IgG measurements. IgG4 testing is not recommended for diagnosis (52) but the possible role of IgG4 in tolerance/counteracting IgE is under current research (53). *Non-validated tests* include the Vega test (electromagnetic conductivity) applied kinesiology, hair analysis, iridology, facial thermography, gastric juice analysis (21,32) and are not recommended.

## When & How to test for skin symptoms

### When & How… should a child with atopic eczema be diagnosed with allergies?

Atopic eczema is a common skin condition in children, in particular, in infants and toddlers. The primary pathogenesis of eczema is related to dry skin, aggravated in a subset of patients by a barrier defect, mediated in part by mutations in the filaggrin gene (54). Allergens, in particular, foods in up to 30% of young children with moderate to severe atopic eczema, may act as triggers to the severity of the disease (55).

When: Allergy diagnosis will aim to identify potential allergic triggers for eczema flares in infants and children at high risk, for example, infants and children with moderate to severe, persistent eczema (55,56) [B].

How: Skin prick tests or spIgE should include at least tests to hen's egg white and cow's milk, as well as the most prevalent food allergens in a given population (Table 3) for identifying *eczema-associated food allergy* in infants and children <3 yrs with moderate to severe eczema (infants and children with constant lesions requiring frequent topical treatment with corticosteroids or calcineurin inhibitors) [B]. In children >3 yrs, the prevalence of food allergy diminishes, due to the favourable natural history; these children might be tested for *mite sensitivity*, mites being potential allergic triggers in eczema in older children and adults. In addition, to quantify the atopic risk, the panel of allergens should include the most prevalent allergens in a given population (e.g. pollens, dust mites, animal dander) (Table 4). The correlation of positive tests with clinical allergy (and not only sensitization) might be facilitated by predictive cut-off values, in particular, to foods (33,46). Nevertheless, standardized food challenges may be needed to provide a definite diagnosis and avoid unnecessary dietary avoidance (57) [B]. A negative test has a good negative predictive value (31,32) [B]. Older children with atopic eczema may develop contact dermatitis and may need patch testing (58) [B].

**Capsule summary**

- Eczema is the commonest chronic skin condition in infancy and may be linked to food allergies, responsible for exacerbations of the disease, mostly in children with moderate and severe atopic eczema.
- Infants with early onset severe eczema are at high risk for developing food allergies.
- Food challenges might be necessary to assess the clinical relevance of a positive IgE test, in particular, before introducing exclusion diets.

### When & How… should a child with acute urticaria/ angioedema be diagnosed with allergies?

Acute urticaria and angioedema are common presentations of IgE-mediated allergy (59) [B]. In childhood, these signs are often associated with other diseases. Other causes of acute urticaria include viral infections, drugs (e.g. NSAID), histamine (e.g. scromboid poisoning), physical urticarias (e.g. cold, pressure) and vasculitis (e.g. Henoch-Schonlein purpura) (60) [B]. Other causes of acute angioedema include drugs (e.g. ACE inhibitors) and hereditary angioedema (e.g. C1 esterase deficiency) where there is no co-existing urticaria (61) [B].

When: An allergic cause is possible when urticaria or angioedema occurs within 2 h of contact to a possible allergic triggering factor (62) [B]. Allergy-related urticaria and angioedema typically last up to 24 h, rarely longer if there is persisting exposure to the allergen. There may also be associated type 1 hypersensitivity symptoms and signs, for example, rhinitis, conjunctivitis or wheeze. Episodic urticaria or angioedema in association with one particular trigger also suggests an allergic cause. Lesions lasting more than 24 h suggest that the urticaria or angioedema is viral or drug associated; co-existing signs such as bruising or joint involvement suggests that there is an underlying vasculitis.

How: where the history and examination is suggestive of an allergic cause, SPT or specific IgE testing can be performed (62) [B]. The allergens used in testing should be directed by the history. Common causal allergens include egg, milk, peanut, tree nuts and other foods. Some aeroallergens may also give rise to urticaria with or without angioedema, including pollens, cat, dog and house dust mite. Where a trigger is not obvious, a diary of food, activities and environmental features in the few hours prior to episodes may be instructive. Screening with a panel of common allergens, not guided by a careful clinical history, may give false positive results. When the trigger is not clear, a provocation test can be used to exclude or confirm a particular trigger. When the diagnosis of urticaria or angioedema is unclear, photographs taken by the family are useful to confirm or refute the diagnosis. Where there are features of a non-allergic cause, others tests are required to investigate these (62,63) [B].

**Capsule summary**

- An allergic cause for acute urticaria or angioedema is likely when they occur within 2 h of a potential allergic trigger and the symptoms last for < 24 h.
- Where allergy is suspected, the allergens tested via skin prick or specific IgE testing should be directed by the history.

**When & How… should a child with chronic urticaria/ angioedema be diagnosed with allergies?**

Chronic urticaria is defined as recurrent lesions lasting for more than 6 wks. It is estimated that life-time prevalence of any type of urticaria is 20% (64). Chronic urticaria is less frequent than acute urticaria in children, and less frequent than chronic urticaria in adults. In addition, chronic urticaria is time limited in most children (62). The condition is due to spontaneous skin mast cell degranulation and might be facilitated by the presence of anti-FCε receptor auto-antibodies (65). Chronic urticaria is only exceptionally linked to a 'hidden' food or environmental allergy (66,67).

Who: Chronic urticaria is primarily a skin condition. Thus, allergy testing is not indicated in chronic urticaria.

How: If the history is suggestive of other co-existing pathologies, other investigations to exclude parasites, auto-immune diseases (thyroid), celiac disease, ongoing occult infection (sinus, UTI), reaction to drugs, mastocytosis and C1inh deficiency might be warranted (62) [C]. The primary care physician should refrain from a 'blind' allergy screening which has a higher potential of false-positive results than of finding a hidden trigger (55), and if necessary refer to a PA-trained physician for more extensive investigations. Skin prick testing should be avoided in these patients due to a high false-positive rate in relation to increased dermographism.

**Capsule summary**

- Chronic urticaria is primarily a skin disease caused by excessive sensitivity of the skin leading to spontaneous mast cell degranulation.
- Allergy testing is very rarely diagnostic and the high risk of false-positive results should refrain from screening testing in chronic urticaria.

**When & How… should a child with a drug-induced skin rash be diagnosed with allergies?**

According to definition, immediate reactions (mostly IgE-mediated) occur within the first hour and non-immediate reactions (mostly T cell-mediated) occur after more than 1 h. Immediate reactions are characterized by urticaria, angioedema, rhinitis, bronchospasm and anaphylaxis, whereas non-immediate reactions display maculopapular/morbiliform rashes and delayed-appearing urticaria/angioedema (68,69).

When: All children with a drug-related skin rash with/ without other symptoms suggestive of allergy should be assessed by a PA-trained physician.

How: The eliciting factor will be identified by the history (timing and suspected culprit drug), leading to appropriate *in vivo* and *in vitro* testing on the basis of the timing of the reaction (Table 5). Antibiotics (e.g. beta-lactams, macrolides, sulphonamides) and antipyretics/non-steroidal anti-inflammatory drugs (NSAIDs) are most frequently incriminated in drug-related skin rashes in children. Hypersensitivity reactions to NSAIDs may appear after a time interval of a few minutes to several hours (acute), or after 24 h (delayed). They can be induced by pharmacological mechanisms, with patients classified as cross-intolerant, or by specific immunological mechanisms (IgE or T cell) with patients classified as reactors to a specific drug (70). Allergy work-up for anaphylaxis during anaesthesia (immediate or non-immediate) will include neuromuscular blocking agents (NMBAs), latex, hypnotics, antibiotics, opioids and other agents (71,72). Hypersensitivity reactions to anticonvulsants and iodinated contrast media have also been reported in childhood (73).

**Capsule summary**

- The history of the reaction will provide most important information on the timing of the reaction in relation to the drug intake, as well as identification of the potential culprits.
- Allergy testing for drugs requires specific testing mostly available to PA-trained physicians in referral centres.

**Table 4** Clinically relevant sensitization rates (in%) to common inhalant allergens in various European countries

| | AU | BE | DK | DE | GR | FI | FR | HU | IT | NL | PL | PT | CH | UK | SP(*) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Outdoor | | | | | | | | | | | | | | | |
| Hazel | 13.3 | 13.5 | 37.8 | 32.4 | 6.5 | 22.9 | 7.4 | 15.9 | 7.2 | 24.4 | 13.3 | 3.9 | 24.8 | 10.3 | 0 |
| Alder | 12.4 | 14.3 | 36.2 | 31.7 | 6.5 | 24.6 | 4.8 | 12.3 | 2.3 | 24.2 | 13.6 | 4.4 | 22.8 | 11.1 | – |
| Birch | 9.5 | 13.9 | 49.1 | 34.1 | 5.1 | 30 | 4 | 16.2 | 7.7 | 26.5 | 19.6 | 4.4 | 43.4 | 11.9 | 0.5 |
| Olive/Ash | 5.9 | 3.4 | 9.1 | 4.9 | 29.9 | 1 | 8.9 | 12.1 | 23 | 11.9 | 2 | 17.9 | 32.4 | 12.7 | 26.9 |
| Grasses | 20.2 | 24.5 | 64 | 34.1 | 42.3 | 18.5 | 19.3 | 37.3 | 18.6 | 34.4 | 30.8 | 31.6 | 71 | 50.8 | 32.4 |
| Ragweed | 5.3 | 3 | 14.3 | 9.3 | 5.1 | 1.4 | 4.5 | 49.7 | 3.1 | 16.7 | 5.4 | 10.8 | 9.7 | 7.1 | – |
| Mugwort | 6.9 | 4.7 | 23.8 | 19.1 | 11.7 | 13 | 3.5 | 38.8 | 5.8 | 5.8 | 14.9 | 14.6 | 6.2 | 3.2 | 6.2 |
| Parietaria | 1 | 0.7 | 4.9 | 3.9 | 20.6 | 0.9 | 3.6 | 2 | 30.7 | 8.7 | 2.2 | 14.7 | 0.7 | 16.7 | 4.6 |
| Alternaria | 2.6 | 4.9 | 8.2 | 7.9 | 18.7 | 1.5 | 4.2 | 10.4 | 3 | 5.5 | 3.5 | 7.3 | 4.1 | 0 | 8.3 |
| Cladosporium | 0 | 0.4 | 7 | 4.4 | 5.1 | 0.5 | 0 | 8.5 | 0 | 3.9 | 0.4 | 7.4 | 0.7 | 5.6 | 1.4 |
| Indoor | | | | | | | | | | | | | | | |
| Cat | 11.5 | 18.1 | 32 | 23.6 | 15.4 | 26.2 | 14.8 | 22.6 | 17.6 | 18.5 | 16.3 | 15 | 24.8 | 27.8 | 15.3 |
| Dog | 8.8 | 15 | 29.4 | 18 | 10.8 | 24.6 | 14.2 | 20.8 | 13.4 | 28.3 | 12.3 | 7.7 | 13.1 | 15.9 | 13.7 |
| Aspergillus | 0.5 | 1.7 | 4.3 | 3.7 | 5.6 | 1.5 | 0.5 | 1.5 | 0 | 4.6 | 2.8 | 3.5 | 2.1 | 7.1 | 1.4 |
| Dermatophagoides pteronyssinus | 12.6 | 29.9 | 40.9 | 17 | 26.2 | 15.2 | 29.2 | 26.1 | 34.7 | 29 | 16.8 | 65.3 | 22.1 | 31.7 | 41.0 |
| Dermatophagoides farinae | 11.4 | 26.4 | 40.7 | 16.1 | 22.9 | 13.9 | 28.8 | 20.6 | 31.9 | 30.6 | 15.3 | 63.5 | 22.1 | 31 | 32.9 |
| Blatella | 2.2 | 1.4 | 10.7 | 6.8 | 7 | 3.6 | 8 | 0.6 | 3 | 8.8 | 6.8 | 21 | 0.9 | 0 | 0.6 |

[Adapted from (141)] and *(142).

## When & How to test for respiratory symptoms

**When & How… should a child with chronic or recurrent rhinitis and/or conjunctivitis be diagnosed with allergies?**

Among allergic diseases in childhood, the prevalence of allergic rhinitis and conjunctivitis has increased considerably in developed countries (5,6) in the last 20–30 yrs, and accordingly the need of allergy testing has increased. Rhinitis may present with rhinorrhea, snuffling, sneezing, nasal pruritus and congestion; conjunctivitis with red, itchy and watery eyes (74). Symptoms might have a seasonal pattern, or a perennial pattern, thus the history is important to provide guidance for further testing. Seasonal rhinitis/conjunctivitis with itch is almost always IgE-mediated (75) [B]. In typical seasonal rhinitis or conjunctivitis like in the spring or summer period without any other symptoms, symptomatic pharmacotherapy can be initiated before allergy testing.

When: Seasonal rhinitis/conjunctivitis should be tested in treatment-resistant cases (76) and in cases of associated pollen-induced asthma, or associated severe pollen-food syndrome. Perennial rhinitis/conjunctivitis cases should be tested in all cases as the causal allergen is not always immediately apparent [B].

How: Where allergy testing is indicated, skin prick or specific IgE testing should be performed in order to prove/disprove the cause of the disease and make possible specific allergy treatment, for example, avoidance measures or allergy vaccination. Testing for seasonal symptoms will focus mostly on pollens according to regional prevalence (Table 4). Diary cards might be helpful to identify the clinical relevance of positive tests to seasonal allergens. Allergy testing for perennial symptoms will include indoor allergens such as allergens from mite, cat and dog. Allergy to outdoor moulds is associated with symptoms during spring, summer and autumn and is never perennial. In addition to allergy testing in rhinitis and conjunctivitis, an asthma work-up should always be included.

**Capsule summary**

- Seasonal rhinitis/conjunctivitis should be tested in treatment-resistant cases, perennial rhinitis/conjunctivitis should be tested in all cases.
- Testing should include the most relevant allergens according to local exposure data.

**Table 5** Diagnostic tests of hypersensitivity reactions to drugs according to the timing of the reaction

| Type of reaction | | Type of tests |
|---|---|---|
| Immediate | *In vitro* | Specific IgE assays |
| | | Basophil activation tests |
| | *In vivo* | Skin tests |
| | | Drug challenge tests |
| Non-immediate | *In vitro* | Lymphocyte transformation tests |
| | *In vivo* | Intradermal tests with delayed-reading |
| | | Patch tests |
| | | Drug challenge tests |

**When & How… should a child with cough be diagnosed with allergies?**

Cough is the commonest cause for new visits in childhood ambulatory care, and the prevalence of persistent cough in the absence of wheeze ranges from 5% to 10% at any given time (77,78) and is even higher among preschool children (79). Cough in children can be associated with impaired quality-of-life and significant parental stress that both improve with symptom resolution (78). A significant proportion of children (up to 10%) receive over-the-counter cough and cold medications before seeing a health care provider (80–83). Cough can be the sole or the most overwhelming symptom of allergy in a child. An initial work-up will exclude other common causes of cough (Table 6) (84).

When: In cases of difficult to control, persistent (sub-acute: 3–8 wks; chronic: >8 wks) and/or recurrent cough (more than two episodes per year), dry/nocturnal cough, or exercise/allergen-exposure-induced cough. Testing is also warranted when the child has another allergic disease, a family history of allergy, a positive allergy screening test, or when cough improved with asthma controlling medication.

How: An allergy work-up for cough might follow the algorithm modified from (85) in Repository Fig. 1. The type of tests used and the panel of allergen included are similar to children with wheezing/asthma (Table 4).

**Capsule summary**

- Cough is a common symptom in childhood, and other causes need to be considered prior to allergy testing.
- Allergy testing will primarily address those children with a history of allergy-associated diseases.

**Table 6** Potentially serious disorders that are associated with chronic coughing in children

- Cystic fibrosis
- Immunodeficiency
- Primary ciliary disorders
- Persistent bacterial bronchitis
- Bronchiectasis
- Recurrent aspiration, gastro-oesophageal reflux, laryngeal cleft, H-type tracheoesophageal fistula, swallowing incoordination with or without neurodevelopmental or neuromuscular disorder
- Retained inhaled foreign body
- Tuberculosis
- Anatomical abnormality, tracheomalacia, bronchomalacia, congenital lung malformation
- Interstitial lung disease or obliterative bronchiolitis
- Cardiac disease

**When & How… should a child with chronic or recurrent wheezing/asthma be diagnosed with allergies?**

Wheezing is a very frequent symptom in children. Among children who recurrently wheeze early in life, a considerable proportion will overcome their disease until early school years. Furthermore, it should be kept in mind that wheeze can be the presentation of many respiratory conditions (7). However, asthma or asthma-like conditions (e.g. virus-induced wheezing) (86) are by far the most frequent cause of wheezing, start early in life and persist, particularly in children with IgE sensitizations (87,88). The proportion of asthma associated with atopy in childhood is very high, making its confirmation helpful in asthma diagnosis. In sensitized individuals, asthma symptoms can be triggered, at least in part, by the respective allergens; 'allergen-induced asthma' is a phenotype for which particular treatments, including allergen-specific immunotherapy or anti-IgE therapy, can be considered (51).

When: There are four clear indications for allergy testing in asthmatic children: (i) supporting the diagnosis of asthma (89), (ii) informing prognosis (88,90,91), (iii) phenotyping (51,92) and iv) indicating avoidable disease triggers (93). Consequently, all children with recurrent (>3 times) wheeze not triggered by upper airway infections, chronic wheeze or possible asthma diagnosis should be tested for IgE sensitizations [A]. Testing becomes increasingly desirable with increasing age, positive family history, as well as the presence of additional allergic symptoms.

How: Asthma diagnosis is based on history, lung function testing, evaluation of bronchial hyper-responsiveness and bronchial inflammation or, in cases where there is difficulty or doubt, a well-designed therapeutic trial (7). Trigger-based phenotyping should be attempted, as it may influence treatment decisions (7,51). Both *in vivo* (skin prick tests) and *in vitro* (specific IgE antibodies) methods can be used, considering the ease of performance, cost, accuracy and other parameters. The selection of allergens to test will depend upon age and regional importance. A short panel of the most frequent local allergens (Table 4) is enough to confirm allergy for diagnostic and prognostic purposes. Focused history should inform testing for phenotyping and confirming suspected allergen triggers. It is emphasized that, especially early in life, positive IgE tests do not necessarily imply disease triggering (7,88).

**Capsule summary**

- Allergy testing will primarily address children with recurrent symptoms, but also those with a history of concomitant allergic diseases.
- Testing should include a small panel with the most relevant allergens according to local allergen exposure (indoor and outdoor) and specific features of the history.

### When & How to test for gastro-intestinal symptoms

Gastrointestinal (GI) manifestation of allergic disease can be divided into IgE-mediated conditions, IgE-associated/cell-mediated pathologies, and cell-mediated pathologies. IgE-mediated GI symptoms are mostly associated with others symptoms, frequently within the context of an anaphylactic reaction. The commonest non-IgE-mediated GI symptoms of allergy include vomiting, diarrhoea, gastroesophageal reflux and symptoms of abdominal pain, poor weight gain, poor sleep and irritability. Most of these symptoms are associated with well-characterized syndromes such as the food protein-induced enterocolitis syndrome (FPIES), eosinophilic diseases of the GI tract (e.g. eosinophilic esophagitis) (94). Suggestive symptoms might also appear isolated and in the frame of the differential diagnosis, allergy testing will then be considered. Guidance to this is provided here.

**When & How… should a child with chronic or recurrent vomiting and/or diarrhoea be diagnosed with allergies?**

Vomiting and/or diarrhoea are common symptoms in infancy and early childhood. Whereas acute symptoms are most often of infectious origin (95), various allergy syndromes might present with these (94). Nevertheless, chronic or recurrent vomiting and/or diarrhoea as a primary symptom of allergy are most uncommon, and warrant a work-up including an extensive differential diagnosis. Associated allergic diseases or suggested symptoms might enhance the likelihood of an allergic origin of chronic or recurrent vomiting and/or diarrhoea, and support an allergy work-up in these patients (96).

When: A child with chronic or recurrent vomiting and/or diarrhoea should be investigated for allergies after excluding another common causes of vomiting and/or diarrhoea, or in the presence of other symptoms suggestive of allergy.

How: The clinical history is cardinal in the assessment of children with chronic or recurrent vomiting and/or diarrhoea, as the clinical picture might be suggestive of a given syndrome, and IgE testing is rarely helpful (50,51) [B].

The role of a definite food as a trigger can be identified by an exclusion/re-exposure diet with resolution and recurrence of the symptoms. However, this procedure needs to be well supervised, as unnecessary long-lasting diets might result. Finally, an endoscopy might contribute to the diagnosis (97). The coordination of these investigations often requires the help of a specialized physician.

**Capsule summary**

- Syndromes involving foods in the pathogenesis of the disease, such as celiac or eosinophilic diseases of the gastrointestinal tract should be considered in the differential diagnosis.
- Testing should include non-IgE tests, including food exclusion/challenges and endoscopy.

**When & How… should a child with colic be diagnosed with allergies?**

Colic is a common symptom in infancy. The cumulative incidence has been reported to vary between 5 and 19%. Colic is defined as excessive crying >3 h/day, >3 days/wk and lasting >3 wks. The natural course of crying in infancy is little crying between 0 and 2 wks, 2–3 h crying 2–6 wks, and at 12 wks <1 h crying per day (98). Evaluation of infants with excessive crying should include physical examination to exclude identifiable aetiology and a history regarding evaluation for hunger, air swallowing, gastroesophageal reflux and food allergy (99,100).

When: A child with excessive inconsolable crying should be investigated for food allergy in case of recurrent symptoms in relation to intake of a specific food particularly cow's milk or other human milk substitutes. The indication for allergy testing is emphasized in cases where colic is combined with allergic signs/symptoms from the skin, the gastrointestinal tract or the airways (99,101). In non-selected series of newborns with cow's milk protein allergy, colic has been confirmed by evaluation/challenge procedures in 30–46% of infants with CMA (101) [B].

How: In the absence of reliable diagnostic tests, dietary elimination and re-challenge are usually required to confirm food allergy in infants with colic. In formula-fed infants, elimination of cow's milk-based formula followed by controlled challenge with cow's milk-based formula should be considered to confirm the diagnosis of food allergy (100,102,103) [B].

In exclusively breast-fed infants, dietician-supervised elimination of maternal intake of cow's milk protein/other relevant food protein for at least 1 wk followed by controlled challenge might be considered to confirm the diagnosis of food allergy (104) [B]. This procedure will most often require involvement of a PA-trained physician.

**Capsule summary**

- Infants with excessive, inconsolable crying should be investigated for cow's milk allergy/other food allergy in case of excessive crying combined with atopic signs/symptoms from the skin, gastrointestinal tract or airways.
- The diagnosis of food allergy in infants with colic should be confirmed by controlled elimination/food challenge procedures.

## When & How to test for other potential allergy symptoms

### When & How… should a child with failure-to-thrive be diagnosed with allergies?

Failure-to-thrive (FTT) in the definition used here implies being underweight, loss of weight and/or insufficient weight and length gain during childhood (100), after exclusion of non-organic causes such as maternal-infant bonding issues. The clinical evaluation of FTT includes a thorough history and physical examination; observation of parent–child interactions; observation and documentation of the child's feeding patterns; and might include a home visit by an appropriately trained health-care professional [C] (105). Body weight, body length and weight-to-length ratio are objective parameters for establishing nutritional status, measurements must be assessed by comparing them with normal values for the child's age (106). In relation to allergic diseases, FTT can develop in children, mostly in infants and young children, with eosinophilic gastroenteropathies, food protein-induced enteropathy/enterocolitis (107,108). Also, FTT was described in severe atopic dermatitis with hypoalbuminaemia, oedema and anaemia (109).

When: An allergy work-up is warranted for FTT in atopic children with other allergic conditions, after excluding non-organic causes and optimizing nutritional input.

How: Tests should also be directed to consider celiac disease, cystic fibrosis and immunodeficiencies (97,110). When a specific food is suspected and in the presence of other gastrointestinal symptoms, a time limited elimination diet, under nutritional supervision, followed by a test reintroduction can be envisaged [D].

**Capsule summary**

- Allergy diagnosis should be considered in young atopic children with failure-to-thrive and other gastrointestinal symptoms after excluding non-organic causes and optimizing nutritional input.
- The diagnosis will mostly be based on exclusion/reintroduction of suspected foods.

### When & How… should a child with anaphylaxis be diagnosed with allergies?

Anaphylaxis is a serious generalized allergic reaction that may occur following exposure to food allergens, drugs or insect stings (111). Food allergy is the leading cause of anaphylaxis in children and almost all such episodes are IgE-mediated reactions (112).

When: Anaphylaxis in children and in infants might be difficult to recognize and need a high degree of suspicion. Sudden onset of urticaria or swelling of the oro-pharynx, rhinorrea, cough, breathing difficulties, vomiting and progressive abdominal pain, pallor, irritability, sleepiness or hypotension should be carefully evaluated in any allergic child. Investigations are mandatory if exposure to a likely allergen is reported (111,113) [B-C].

How: *During the acute episode at the Emergency*. A sample of serum should be properly stored for later testing of spIgE. According to the clinical history and age, foods, drugs, insect venoms and inhalant allergens may be considered as cuprites. Serum tryptase levels should be measured, ideally within the first 1–3 h after the anaphylactic episode. Tryptase levels can be normal in food-induced anaphylaxis (93) [B–C].

*At the PA-trained physician's office*. Specific allergy testing will be directed by a careful history. When prick testing, consider prick-by-prick for raw food to enhance sensitivity or when relevant allergens may be denatured during processing. *In vitro* spIgE tests to the suspected allergens might include recombinant allergens in order to improve the identification of a child at risk for recurrences (115,116) [C]. IgE tests may be falsely negative up to 4–6 wks after the event due to anergy [E]. Allergy diagnosis in anaphylaxis will lead to a personal management plan including avoidance and emergency medication [D]. Self-injectable adrenaline devices with pre-loaded dosages of adrenaline (at 0.15 and 0.3 mg according to weight) are recommended for self-management of the reactions in the community. Auto-injectors with 0.15 mg can be used from 7.5 kg (114). Allergen challenges should be considered when no correlation is found between exposure to a given allergen and results of allergy tests (refer to specific sections) (114).

**Capsule summary**

- Severe allergic symptoms suddenly occurring in an otherwise healthy child should be investigated with allergy tests.
- Appropriate specific IgE tests should be performed at the first episode of anaphylaxis to identify the patient's risk of relapse.

**When & How… should a child with insect sting reactions be diagnosed with allergies?**

Insect venom allergy can manifest as immediate local reactions up to severe, even fatal, anaphylaxis. In Central Europe, most anaphylactic reactions are caused by honeybees and common wasps. In other geographic areas, allergies to other insects may be more prevalent, for example, to paper wasps in Mediterranean countries, to various ant species in Central or South America, or to jack jumper in Australia (117). The severity of allergic reaction may depend upon the patient's age and initial symptoms. Systemic reactions are more often observed in adults than in children, children with severe initial reactions have the highest risk of recurrence, and children with symptoms limited to the skin (even if widespread) have a 10% risk of a future systemic reactions (118).

When: Children with a history of a systemic reaction have a significant risk for further severe reaction and will need allergy testing. In these patients only, SIT is a treatment option. Large local reactions are not an indication for allergy testing as SIT is not recommended in these patients (117–119) [B]. Venom skin testing is not indicated in an individual who has never experienced a sting event [D].

How: Diagnosis after an allergic reaction to insect venom initially relies on the history of the event (for grading the reactions and identifying the responsible insect). Allergy testing to the relevant insect will assess venom-specific IgE sensitization (by skin prick testing and/or *in vitro* spIgE testing) (120,121). For patients with positive venom skin tests, neither the size of the wheal and flare reaction, nor the concentration to which the patient reacts, reliably predicts the severity of future systemic reactions (122) [B]. Additional tests may be ordered by PA-trained physicians, for example, when test results are not in accordance with the history. Useful tests include the basophil activation test or spIgE tests to recombinant insect venom allergens (116) [B]. In addition, a basal serum tryptase will exclude an underlying mastocytosis (much less frequent in children than adults) which represent an increased risk of severe reaction or SIT treatment failure (123) [B].

**Capsule summary**

- Only children with a history of systemic reaction after an insect sting will need an allergy work-up.
- Allergy diagnosis in these patients will provide guidance for SIT and preventive measures in case of a repeated sting as prescribed by a PA-trained physician.

**When and How… should a child with a sibling with food allergies be diagnosed with allergies?**

Atopy is a heritable tendency to suffer from allergic diseases but the relative contribution of shared genetic influences and shared environmental exposures is not determined to date. The common allergic diseases frequently coexist, both within families and within individuals (124). For example, rhinitis is common in children with asthma and vice versa (125) and the majority of children with IgE-mediated food allergy have eczema (126). Peanut allergy is much more common in siblings of peanut allergic children than in families without a peanut allergic child (127–129), although it remains uncertain if this effect or finding is disease-specific for peanut allergy or rather is due to the broad atopic phenotype in children with peanut allergy (130). In this context, families often want siblings of their index child with allergies to be investigated for the same and other allergies. Allergy specific tests have very high negative predictive value, particularly in food allergy (131) so negative food allergen-specific IgE-based tests can give a high degree of confidence that the food can be safely consumed. False-positive results are, though, seen.

When: All siblings who have symptoms suggestive of allergic diseases should be treated as cases and be offered allergy testing as if they were presenting independently [A]. Siblings of food allergic children, especially those with significant lesions of eczema, might be considered for allergy testing.

How: Testing should only include the most common age-relevant major allergenic foods that have not already been demonstrated to be consumed without adverse (allergic) consequences [C]. Foods with negative IgE-based tests can be introduced at home [A–B]. Foods associated with positive IgE tests should be introduced in the context of either a formal food challenge or under less formal professional supervision, according to individualised patient assessment, clinical competencies and the estimated probability of an allergic reaction being elicited [A–B].

**Capsule summary**

- Siblings with moderate or severe eczema should be screened for sensitization to foods not already consumed clearly without symptoms.
- According to specific requests and needs, asymptomatic siblings of food allergic children, might be considered for allergy testing to foods.

## Conclusions and future perspectives

Allergy-related symptoms and allergies are widespread in children. They are usually first investigated and managed by primary care physicians. We emphasize the need for adequate primary and continuous education for allergic diseases in primary care, and a good collaboration between primary care physicians and PA-trained physicians. Practical organization on 'who does what' is variable by countries and can be implemented by following these guidelines.

Allergy tests need carefully to be interpreted by knowing their limitations. For example, IgE test results may be age- and total serum IgE-dependent (132,133). These may influence effector cell-mediator release and the induction of symptoms of allergies. Further studies are needed to investigate the exact relationship between IgE and disease activity (134). In this line, recent studies using CRD suggest that in future patterns of IgE sensitivity to recombinant allergens might be helpful to evaluate the potential efficacy of SIT (135,136), or effectively predict clinical cross-reactivity between different foods.

Allergy test results should always be interpreted in correlation with clinical relevance. Allergen challenges are a core activity in our specialty. In the hands of PA-trained physicians, they are safe and will provide a definite answer, thus reducing unnecessary avoidance of, for example, useful medications or common foods, and definitely improved the quality-of-life of our patients.

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