

POSITION PAPER

# Recommendations for the allergy management in the primary care

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## Abstract

The majority of patients seeking medical advice for allergic diseases are first seen in a primary care setting. Correct diagnosis with identification of all offending allergens is an absolute prerequisite for appropriate management of allergic disease by the general practitioner. Allergy diagnostic tests recommended for use in primary care are critically reviewed in accordance with the significant workload in a primary care setting. Simplified pathways for recognition and diagnosis of allergic diseases are proposed, that should be further adapted to local (national) conditions.

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In most of the European countries, the majority of patients who seek medical advice for allergic diseases are first seen in a primary care (PC) setting, partly because relative ease of access but also because of the paucity of trained allergists to meet the ever growing demand (1). Correct diagnosis with identification of all offending allergens is an absolute prerequisite for appropriate management of allergic disease by the general practitioner (GP). One of the aims of the EAACI Task Force for Allergy Management in Primary Care was to critically review the diagnostic tests and to provide management pathways for the most common allergic diseases seen and treated in PC.

## Skin prick testing

Skin prick tests (SPT) are the oldest and, to an extent, the most straightforward tests to confirm or reject the suspicion

of IgE-mediated allergic disease. SPTs reproduce the allergic response locally: a drop of allergen extract is placed on the skin and the skin barrier is disrupted with a lancet. If specific IgE against the allergen is present on local skin mast cells, a wheal and flare reaction is produced, recognized macroscopically and recorded.

## Indications

Skin prick tests are indicated whenever there is clinical suspicion of IgE-mediated allergy (2). In association with a suitable history, SPT results can help in the confirmation or rejection of specific allergen triggers in an individual with allergic rhinitis (AR), asthma, atopic dermatitis or food allergy. There are no absolute age limits, although skin reactivity is lower in infants and possibly the elderly. The number of tests should be guided by clinical and economic criteria

(3). The IgE sensitizations change over long periods of time, therefore tests should only be repeated infrequently (4).

### Contraindications

Systemic and respiratory infections may increase skin reactivity affecting the results and the possibility of systemic reactions (5). Following anaphylaxis, there can be a nonreactive period, therefore SPTs are preferably not performed until a few weeks later (6). The skin should be intact. In patients with severe eczema or dermatographism SPTs are difficult to interpret.

### Safety and precautions

Systemic reactions or severe anaphylaxis in association with SPTs are exceedingly rare and most are associated with testing to foods, often fish, but also nuts or milk (7). One study reported a higher frequency in infants, with six cases among 1152 tested over a period of 3 years, all associated with food testing (8), however, this proportion was questioned by another study during the same period that reported no systemic reactions among more than 10 000 children tested (9). All cases recovered promptly with appropriate treatment. In a series of surveys reporting deaths associated with skin testing or immunotherapy in the USA from 1945 up to 2001, two cases attributed to SPTs are included (10, 11, 12).

Intradermal testing, often used in the evaluation of drug or venom allergies, and less in respiratory allergies, carries a much higher risk for systemic reactions and is not detailed here as such tests are usually performed in the specialist environment.

To reduce the consequences of a serious adverse event, it is recommended that SPTs are performed in settings where emergency equipment, availability of adrenaline and personnel trained for its use are available so any systemic reaction can be readily treated. Food allergen testing and active/severe asthma should be considered as risk factors. On the contrary, SPTs with commercial aeroallergen extracts should be considered safe.

### Procedure

Parameters considered include drug interference, co-morbidities, location, extracts, controls, panel, prick device, duration, interpretation, cut-off values, recording and reporting (13). The details of various protocols are outside the scope of this article and will be described in a separate manuscript.

In short, several medications, most notably antihistamines, may affect the test results and should be queried and discontinued before the performance of SPTs (13). Contraindications mentioned above should also be excluded. The forearm and the back are the preferred sites. The drops should be placed at least 2 cm apart, as there might be interference in the case of highly positive tests. Manufacturers standardizes available extracts in different ways, therefore results are not directly comparable. Noncommercial extracts are of less value, however, they may be useful when standardized

extracts are not available, or in the case of foods, where fresh products can be more sensitive (14). The diluent (usually sodium chloride) should always be used as a negative control and histamine at 10 mg/ml, as positive control. The allergen panel should reflect the local sensitization map, however, GA<sup>2</sup>LEN has recently proposed a European panel that may improve harmonization of testing and provide comparative data (3). Several prick devices are available (15). A new lancet should be used for each allergen to avoid cross-contamination (16). The solution can be dried off as soon as the prick is performed, taking care to avoid spill-over to adjacent prick sites. Results can be read 15' later (10' for the histamine positive control). The negative control is expected not to produce any wheal, while the positive should produce a wheal of more than 3 mm in diameter. With such controls, an arbitrary cut-off of 3 mm is most frequently used in clinical practice for positivity; however, smaller wheals can still have clinical significance. Wheals are marked with a pen and transferred to paper with scotch-tape for archiving. The maximum wheal diameter is sufficient to report (17).

### Interpretation

When interpreting SPTs, the differences among allergic diseases and different allergen extracts should be kept in mind. As for other methods evaluating IgE sensitization, a positive test does not prove allergy. As a general rule, SPTs are more sensitive than specific (18); this may reflect the fact that a considerable proportion of the population, varying between countries, may have asymptomatic sensitization. In this respect, SPTs are stronger in rejecting a hypothesized association between an allergen and a patient's symptoms, rather than confirming it. Nevertheless, the latter can be most often achieved in combination with the clinical presentation.

In food allergy, cut-off values, frequently close to 7–8 mm, have been shown to have high predictive values in relation to positive challenges (19). Such cut-offs have not been established for respiratory allergy, although in general terms, the larger the SPT response, the stronger the possibility for a clinically significant test.

### Usefulness of SPTs in PC

There is no general consensus on the feasibility of GPs performing SPTs, taking into account the variability of access to training and regulations around Europe. GPs who are trained to perform and interpret SPTs and working in settings where any serious systemic adverse event can be treated, can facilitate the diagnosis and management of AR and mild-to-moderate asthma. Additional caution should be taken in respect to food allergy or severe/uncontrolled asthma, where GPs may wish to refer to secondary care for SPTs (13).

### *In vitro* allergy diagnosis

Allergen-specific IgE measurement in serum is an important tool aiding the diagnosis of allergy. Today, the *in vitro*

diagnostics market is quite diverse with a large number of available options. The task force evaluated which assays could be most useful in a given clinical situation and how to compare between different options.

### Indications

The indications for *in vitro* diagnostic tests are the same as for SPTs. *In vitro* diagnostic tests usually show higher sensitivity but lower specificity and therefore are performed whenever SPTs do not provide reliable results. In some European countries, health insurance companies demand *in vitro* IgE testing before allergen-specific immunotherapy is reimbursed.

### Interpretation

As for SPTs, the same considerations referring to asymptomatic sensitization are valid. The interpretation of allergen-specific IgE assays depends on the cut-off. A number of comparative studies (20, 21) show that, even if results obtained with different systems correlate and are expressed in the same or similar type of units, they are not interchangeable. Therefore, critical and clinically relevant cut-off levels should be defined and established for each allergen and system used.

### The choice of the test

Irrespective of which test is employed for IgE detection, the GP should expect that the assay be performed with sufficient accuracy. GPs have a choice of either analyzing samples at site or sending them to an external laboratory. If doctor's

office testing is available, it may be used as a first line evaluation. Of note is that the panels sometimes give the summarized picture of IgE against a number of allergens without any further discrimination. Doctor's office tests are not as well documented as the more conventional lab assays tested in auto analyzers. The general impression of is that they are less sensitive, and therefore exclusion of allergy needs further confirmation in a laboratory assay. Nevertheless, doctor's office tests allow feedback while the patient is still at the clinic, with the advantage that the decision on the subsequent action or treatment is not delayed. The results from these assays can be interpreted qualitatively or semi quantitatively without the aid of particular reading equipment.

Different tests from different manufacturers may provide inconsistent results. For biological reasons, the quantity of allergens used for the production of the tests significantly varies between sources and preparations, thus contributing to the variability between the test systems. Currently, no source material quality or quantity description is available for the major allergy tests, thus comparison of allergen content as a quality parameter between different providers is not feasible.

To provide reliable recommendations 15 European companies producing *in vitro* allergy tests were identified. Available websites were analyzed for assay methods, products and cited publications. Most tests (Table 1) use a reference curve calibrated against the WHO 75/502 reference IgE standard. The level of detected IgE antibodies is commonly given in IU/ml or KIU/l.

Several studies (22, 23, 24) comparing accuracy, correlation and precision of IgE tests indicate that there is variability in assessed IgE levels. The variation between assay systems is also allergen dependent (Table 2).

**Table 1** Comparison between specific IgE assays

| Company                        | Adaltis         | Dr. Fooke                         | Hitachi                     | Hycor Bio-medical | Phadia/Thermo Fisher Sci | R-Biopharm         | Siemens                     |
|--------------------------------|-----------------|-----------------------------------|-----------------------------|-------------------|--------------------------|--------------------|-----------------------------|
| Product                        | Allergen        | REAST                             | MAST Optigen                | HYTEC Turbo RAST  | Immuno-CAP               | Rida-screen        | Immulite 2000               |
| Measuring range                | 0.36–100        | 0.35–100                          | 0–243                       | 0.35–100          | 0.35–100                 | 0.35–50            | 0.1–100                     |
| Units                          | KIU/l           | IU/ml                             | LU                          | IU/ml             | kU/l                     | IU/ml              | kU/l                        |
| Clinical Sensitivity           | NA              | NA                                | Inhal 90% food 62% (ref. 4) | NA                | 93–98% (ref. 6)          | 84.3% (ref. 7)     | NA                          |
| Clinical Specificity           | NA              | NA                                | NA                          | NA                | 82–89% (ref. 6)          | 91.2% (ref. 7)     | NA                          |
| CV within                      | 4.7–6% (ref. 1) | 2–6.5 (ref. 2)                    | 5–31% (ref. 5)              | NA                | 7% (ref. 6)              | 3.9–12.7% (ref. 7) | NA                          |
| CV between                     | 9.50% (ref. 1)  | 3.8–6.7                           | 1–25% (ref. 5)              | NA                | 9% (ref. 6)              | 3.4–11.7% (ref. 7) | NA                          |
| Reference assay                | ImmunoCAP       | ImmunoCAP                         | NA                          | NA                | NA                       | SPTs               | ImmunoCAP                   |
| Agreement with reference assay | 92.6% (ref. 1)  | Inhal.: 90% food: 70–80% (ref. 3) | 83–98% (ref. 5)             | NA                | NA                       | 88.3–90.6 (ref. 7) | 85.7% (ref. 8) 90% (ref. 9) |
| WHO ref                        | Yes             | Yes                               | NA                          | Yes               | Yes                      | Yes                | Yes                         |
| DFU on line                    | x               | x                                 | NA                          | NA                | x                        | x                  | NA                          |

NA, Not available; CV, coefficient of variation; DFU, directions for use.

**Table 2** Performance of specific IgE assays with respect to symptoms

| Allergen source       | Ridascreen*<br>Sensitivity %<br>Specificity % | ImmunoCap<br>Sensitivity %<br>Specificity % | Rapid†<br>Sensitivity %<br>Specificity % | Intex‡<br>Sensitivity %<br>Specificity % |
|-----------------------|-----------------------------------------------|---------------------------------------------|------------------------------------------|------------------------------------------|
| Rhinitis and asthma   |                                               |                                             |                                          |                                          |
| Tree pollen           | 91.2<br>88.2                                  | 84–95<br>85–94                              | 86–96<br>86–100                          | 65<br>90                                 |
| Grasses               | 91.2<br>88.2                                  | 84–95<br>85–94                              | 86–96<br>86–100                          | 78<br>100                                |
| Weeds                 | 91.2<br>88.2                                  | 84–95<br>85–94                              | 86–96<br>86–100                          | 75<br>95                                 |
| HDM                   | 91.2<br>88.2                                  | 84–100<br>76–96                             | 86–96<br>86–100                          | 82<br>95                                 |
| Mold                  | 91.2<br>88.2                                  | 84–95<br>85–94                              | 86–96<br>86–100                          | 69<br>88                                 |
| Cat                   | 91.2<br>88.2                                  | 84–95<br>85–94                              | 86–96<br>86–100                          | 82<br>100                                |
| Dog                   | 91.2<br>88.2                                  | 84–95<br>85–94                              | 86–96<br>86–100                          | 68<br>97                                 |
| Atopic dermatitis     |                                               |                                             |                                          |                                          |
| HDM                   | 91.2<br>88.2                                  | 84–100<br>76–96                             | Not included                             | 82<br>95                                 |
| Animal dander         | 91.2<br>88.2                                  | 84–95<br>85–94                              | Not included                             | 75<br>98                                 |
| Milk                  | 91.2<br>88.2                                  |                                             | Not included                             | Not available                            |
| Egg                   | 91.2<br>88.2                                  |                                             | Not included                             | Not available                            |
| Soy                   | 91.2<br>88.2                                  |                                             | Not included                             | Not available                            |
| Vegetables and fruits | 91.2<br>88.2                                  |                                             | Not included                             | Not available                            |
| Food allergy          |                                               |                                             |                                          |                                          |
| Food allergens        | 91.2<br>88.2                                  | 44–93<br>89–100                             | Not included                             | Not available                            |

\*Sensitivity and specificity as compared with ImmunoCAP.

†Suitable as Doctor's office test.

‡Sensitivity and specificity is compared with skin prick test.

### Factors influencing test results

The result depends upon sample handling, the quality and contents of the allergen components, the sensitivity of the detection system, the cut-off value, and the unit in which the results are expressed. The price per test can limit the number of allergen extracts used for testing and thus affect the final diagnosis.

### Usefulness of serologic *in vitro* diagnostic tests in PC

There is no general consensus on the feasibility of GPs performing serologic diagnostics for IgE, which can be helpful in the diagnosis of AR, atopic asthma, food allergy and insect venom hypersensitivity. The positive results should be critically revised in relation to the occurrence of clinical symptoms.

Allergen-specific IgE assays performed with different systems display results that are not interchangeable. It is

therefore important that the method used is specified. A choice between different manufacturers is challenging.

### Which tests give best value for the money?

There is a wide range of cost per test within and between countries due to differences in culture, government policies (e.g. reimbursement), size of laboratory, staffing, number of tests, company-supported placement of equipment. Comparison of pricing from a GPs perspective is hampered by the situation that only a few, often only one, diagnostic system is offered by laboratories in close vicinity to the GPs.

### Management pathways for allergic diseases in a PC setting

Management pathways were constructed for the allergic diseases identified as most frequently seen and treated in a

PC setting: AR, asthma, food allergy, urticaria and contact dermatitis.

### Allergic rhinitis

The medical history is the mainstay of the diagnosis, as it allows the evaluation of the presence, severity and duration of nasal symptoms (Fig. 1). AR is defined as having two of the listed symptoms for >1 h/day for >2 weeks (25, 26). Usually these symptoms follow allergen exposure, however, non-allergic factors (cigarette smoke, medications, alcohol, spices) may be the sole cause (26). History should include specific questions related to timing and severity of symptoms, alleviating factors, seasonal aggravation, and signs of atopy in other organs. AR and asthma frequently co-exist, thus bronchial symptoms need to be enquired.

Clinical examination consists of external and internal nasal examination, revealing mucosal pathology without signs of infection and without major anatomic abnormalities. In PC, anterior rhinoscopy is the first step as it allows the inspection of the first half of the endonasal cavity. Mucosal pathology in AR consists of mucosal congestion and/or transparent secretions, but may be normal in treated patients. In case of unilateral pathology, major crusting or bleeding, headache, smell disorder or suspicion of rhinosinusitis, patients should be referred for nasal evaluation by a specialist (27).

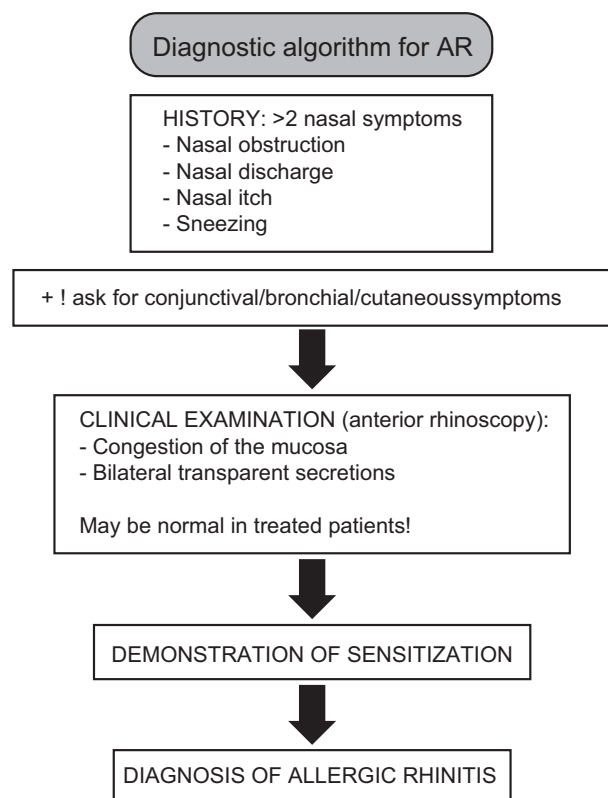


**Figure 1** Pathway for allergic rhinitis diagnosis.

The diagnosis (Fig. 1) is based upon the concordance between a typical history, clinical examination and demonstration of sensitization (25, 28). The demonstration of sensitization is not always necessary in PC, particularly when the symptoms occur in conjunction with seasonal norms or when there is a good response to treatment. Several arguments support the demonstration of IgE sensitization such as demonstration of hypersensitivity to the patient, evaluation of the feasibility of allergen avoidance and of immunotherapy.

### Asthma

In common with all diseases, a careful history is critical factor for the correct diagnosis (Fig. 2). Commonly asthma is typified by symptoms of dyspnoea, cough, wheezing and chest tightness. The administration of a short acting beta2 agonist (SABA) may demonstrate reversible airflow obstruction (29). In specialist care, the most used methods for asthma diagnosing are spirometry and bronchial challenge. In Western Europe, spirometry is increasingly performed in PC settings, but the quality is questionable (30, 31). In a recent study, 22% of spirometric tests carried out in PC setting showed no ERS/ATS guideline adherence, despite intensive training (32).

Objective tests to measure airway obstruction are recommended as the correlation between pulmonary symptoms and lung function (LF) is poor (33–35). Measuring LF in PC is needed for the diagnosis of asthma and for guiding subsequent management. This can be accomplished roughly by PEF measurements. Demonstrating reversibility may be quite simple with a dramatic improvement in LF to a few puffs of a SABA. However, patients presenting in the late afternoon may have optimal LF and not demonstrate reversibility, owing to the exaggerated diurnal rhythm witnessed in poorly controlled asthma. In this situation, serial (twice or more often) PEF readings may assist the diagnosis. Spirometers are much more accurate than PEF measurements (3 vs 10%) and FEV1 is less effort-dependent, thus PEF measurement is less recommended nowadays (32), but may be useful when spirometry is not available, in occupational asthma or for asthma monitoring at home. The cost is much lower than that of office spirometry. Nevertheless, there is a case for improving access to quality spirometry accessible by or delivered by GP, as accurate assessment leads to better clinical decision making and more appropriate prescribing (31).

The FEV1 is the most reproducible LF variable: the short term, within-subject coefficient of variation is 3–5%. It gives very useful information, but only if it's performed and interpreted correctly. The specificity for diagnosing airway obstruction is high (90%), but the sensitivity is much lower (29%). Therefore, asthma cannot be ruled out only using spirometry (Fig. 2).

There are no absolute contraindications for spirometry testing. Patients must respect the bronchodilators washout requirements for diagnosing asthma, but not for evaluating the response to treatment.

The technical requirements of spirometry devices are standardized. It is important that the spirometer offers the

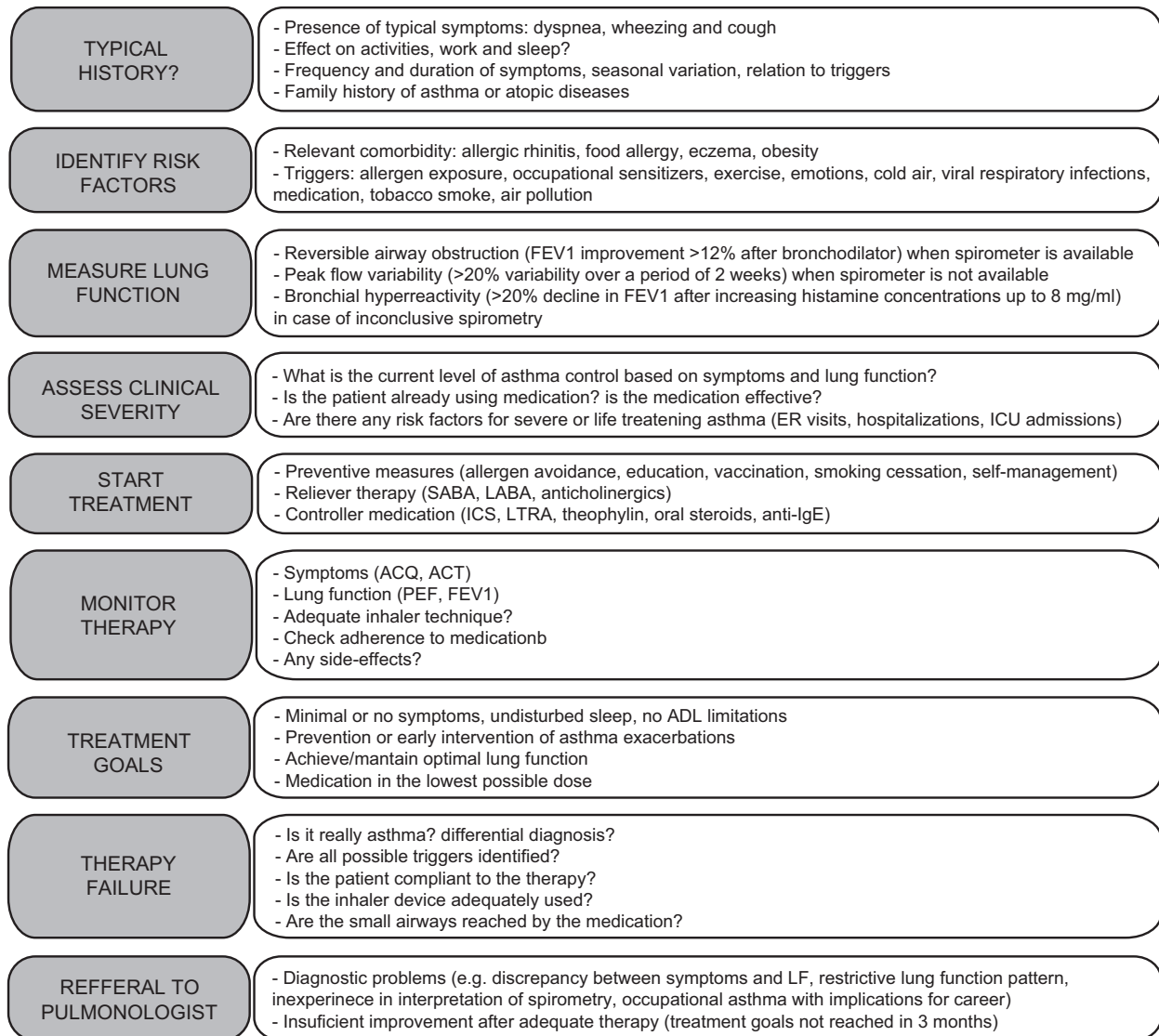


**Figure 2** Pathway for asthma diagnosis and management.

possibility of seeing the flow-volume (FV) loop and the volume-time curve together as the first one allows the analysis of the initial effort and the second checks if the expiratory effort is long enough for the VC maneuver. Guidelines recommend three technically acceptable measurements and no more than eight tries. The technical aspects of spirometry involve 'curve's morphology' such as steep rising part FV-curve, pointed or curved peak and 'smooth' course of the curve (36, 37). ATS/ERS guidelines recommend FEV1 variations up to 150 ml as reproducible. To ensure that FEV1 is obtained by a maximal effort, the back extrapolated volume must be <5% of FVC or <0.15L.

Patients with inconclusive spirometric results should be referred for additional tests, such as nitric oxide (NO) measurement and/or bronchial provocation. After the recent introduction of small, portable analyzers, NO measurement

is also feasible in PC (38). Airway hyper-responsiveness (AHR) to histamine or methacholine is widely used for the diagnosis of asthma, especially when baseline spirometry is normal. The methacholine challenge test is very sensitive for diagnosis, but specificity is much lower, as AHR is also increased in AR, COPD and other chronic respiratory diseases, congestive heart failure. The methacholine challenge test has good reproducibility and normative values from healthy persons are available for all age groups. The test is fairly safe, but requires experienced staff and is more time-consuming than spirometry. It is usually performed in dedicated LF laboratories. Indirect testing for AHR with mannitol to guide inhaled corticosteroid treatment was demonstrated feasible and acceptable in PC (39).

In children a typical history, the presence of atopy and wheezing are important findings that support the diagnosis.

Wheezing, however, is very common in children before the age of 6 years, in particular following an upper respiratory tract infection (viral associated wheeze). The majority of children that have postinfectious wheezing become symptom free after the age of 6 years. Apart from transient infantile wheeze, other clinical phenotypes in children are multitrigger wheeze, atopic asthma and exercised-induced asthma (40, 41). Three or more episodes of wheezing should raise the suspicion of asthma.

Spirometry is indicated in the work-up for asthma in all patients  $\geq 6$  years old to test for airway obstruction, severity and reversibility. However, the sensitivity is rather low as in most children with asthma spirometry is normal. Reproducibility of the FEV1 is usually lower than in adults due to a short attention span or poor cooperation and the cut-off value for FEV1/FVC is higher. In children with controlled asthma, it is recommended to perform LF at least once a year. Asthma severity and flow limitation in childhood are strongly predictive for persistent asthma and airway obstruction in adulthood (42).

Exhaled NO is currently the only measurement for airway inflammation that can be used to monitor asthmatic children from the age of 4 years. The cut-off values in children are lower than in adults. There are no studies that have positioned the role of FeNO measurement in PC for diagnosis and monitoring of young children with asthma.

Most children with asthma can be treated by GP's. Special considerations need to be taken into account for children under the age of 1 year as the differential diagnosis is more extended. Monitoring of height and weight is important.

Inhaler medication is the cornerstone of asthma treatment. There are several types of inhalers that vary in dose delivery, deposition and particle size, flow dependency and convenience. Several aspects need to be considered when prescribing an inhaler: asthma severity, cooperation, inspiratory flow, hand-mouth coordination, type of medication (bronchodilators, anti-inflammatory) and location of the disease process and receptors in the lung. Teaching optimal inhaler technique requires repeated visits and guidance by experienced health care workers.

### Food allergy

Food allergy (FA) is 'an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food' (43). Immune mechanisms can result in the production of increased levels of specific IgE (IgE-mediated FA) and/or changes in patterns of regulatory T lymphocytes and cytokines (non-IgE-mediated FA).

The prevalence of FA ranges from 2% to 10% of the population and time trends in westernized countries show a sevenfold increase of food-related severe reactions in the last 10 years, especially in children. FA might not solve spontaneously, as previously appreciated. FA is the leading cause of anaphylaxis in the community, and severe reactions need prompt recognition and treatment with life-saving drugs.

Anytime there is the suspicion of a severe reaction to a food, the diagnostic evaluation should be undertaken promptly. Whenever the patient complains of food-related

adverse effects, an effort toward proper diagnosis avoids useless self-prescribed avoidance diets with potential malnutrition, especially in children.

The diagnosis of food allergy integrates medical history, clinical symptoms, detection of specific IgE, endoscopy with biopsy and, when needed, the outcome of the elimination diet and of the oral challenge with the suspected food (Fig. 3).

The medical history continues to be the mainstay of diagnostic, defining culprit food(s), time course of reaction, ancillary factors (aspirin, exercise and alcohol) and thresholds for small or large quantities. The specificity is low: only 2% of 35% patients self-reporting FA were confirmed by the oral challenge. Clinical manifestations can overlap with other diseases and vary according to the age, with gastrointestinal and cutaneous symptoms (such as atopic dermatitis) more prevalent in the infant/child and acute reactions of the oro-pharynx more common later on. Respiratory symptoms such as laryngeal edema and wheezing accompany severe reactions.

IgE sensitization should always be evaluated as it might influence the treatment and the prognosis. The IgE-mediated FA can trigger more severe reactions and persist longer. The detection of food-specific IgE can be performed with the SPTs or *in vitro*. IgG/IgG4 is not recommended in the work-up of food allergy.

The endoscopy with biopsy should be performed for gastrointestinal symptoms suggestive of FA, especially in absence of food-specific IgE, with the aim to diagnose eosinophilic gastrointestinal disease.

When there is a strong suspicion for the food(s) to elicit reactions, a trial with an elimination diet is recommended for a period suitable to achieve resolution of symptoms, ranging from 15 days in case of acute manifestations, to 4 weeks for atopic dermatitis and up to 8 weeks for gastrointestinal chronic symptoms. Patients should be monitored for nutritional and caloric intake. The improvement of symptoms should be confirmed through the reintroduction of the offending food with an oral food challenge. Due to the possibility of misinterpretation and occurrence of severe, unexpected reactions, the food challenge should be performed in a setting properly equipped to face emergencies, by an experienced physician with competence in allergy and in dealing with severe reactions. Caution is mandatory in this regard and oral food challenges in an outpatient clinic without facilities for resuscitation should be firmly discouraged (44).

Patients with confounding clinical manifestations may require a thorough evaluation by an allergist with expertise in FA. Multiple or severe FA, for whom the management requires a multidisciplinary approach (allergist, gastroenterologist, dietician), benefit from referral to a second-tertiary level center. It is recommended to refer for food challenges due to the risk for severe anaphylactic reactions (45). It is also recommended to provide an emergency kit with copy of anaphylaxis emergency action plan and medications for self-treatment, for example,

- adrenaline auto-injector for treating anaphylaxis, where appropriate;
- fast acting, nonsedating, antihistamine for treating cutaneous allergic reactions, where appropriate.

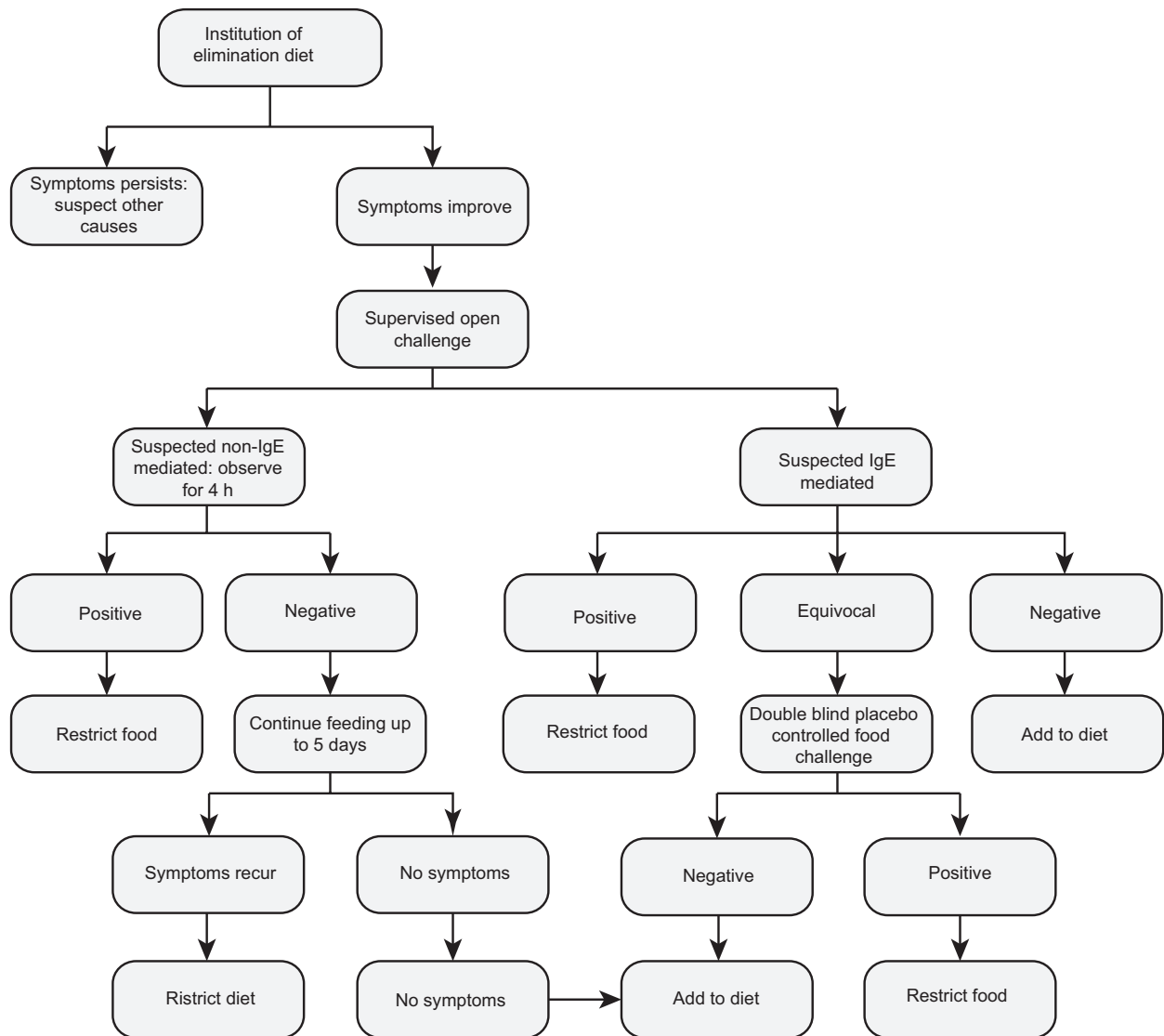


**Figure 3** Pathway for food allergy diagnosis and management.

### Urticaria and angioedema

Urticaria is common: the lifetime prevalence for any subtype is approximately 20%. Chronic forms of urticaria decrease in quality of life and affect performance at work and school. Angioedema is a subentity of urticaria. Testing for hereditary angioedema is only required in angioedema without wheals.

Urticaria is a heterogeneous group of diseases. In many patients with spontaneous urticaria allergen sensitization cannot be demonstrated and an autoimmune background is postulated (46).

Of all the diagnostic procedures, a thorough history, including all possible eliciting factors (Table 3) is the most important. Asking for a symptom diary and photos of rash might be helpful (47).

For acute urticaria, first episode, without associated symptoms, no diagnostic work-up is needed and only symptomatic treatment is recommended.

For chronic urticaria, testing for pressure-inducible urticaria component is useful. The following lab panel is suggested: CRP and differential blood count; serum tryptase; complement factors C3, C4; urinalysis, hepatitis B and C and *Helicobacter pylori* serology; immunoglobulin electrophoresis; anti-TPO and TRAB antibodies, ANA, ANCA, RF, D-Dimer test. Allergen-specific IgE measurement is recommended according to clinical history (47).

In general urticaria is quite similar in childhood, but acute and parainfectious urticaria are much more common. A first episode of acute urticaria does not require any diagnostic work-up if no signs of systemic anaphylaxis are associated. In chronic urticaria physical causes are predominating. Cold- and

**Table 3** Thorough history for the diagnosis of urticaria

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|                                                                                                    |
|----------------------------------------------------------------------------------------------------|
| 1. Time of onset                                                                                   |
| 2. Frequency and duration of wheals (if > 24 h suspicion of urticaria vasculitis)                  |
| 3. Shape, size, and distribution of wheals                                                         |
| 4. Associated angioedema                                                                           |
| 5. Associated symptoms such as itch, pain, fever                                                   |
| 6. Occurrence in relation to weekends, holidays or travel                                          |
| 7. Diurnal variation                                                                               |
| 8. Family and personal history of urticaria, angioedema, atopy                                     |
| 9. Previous or current diseases                                                                    |
| 10. Psychosomatic and psychiatric diseases                                                         |
| 11. Surgical implantations and events during surgery                                               |
| 12. Gastric/intestinal problems (stool, flatulence)                                                |
| 13. Induction by physical agents (pressure, cold, heat, vibration) or exercise                     |
| 14. Use of drugs (NSAIDs, immunizations, hormones, laxatives, suppositories, alternative remedies) |
| 15. Observed correlation to food or to menstrual cycle                                             |
| 16. Occupational exposure                                                                          |
| 17. Hobbies                                                                                        |
| 18. Stress                                                                                         |
| 19. Quality of life, emotional impact                                                              |
| 20. Response to therapy                                                                            |

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exercise-induced urticaria and cholinergic urticaria are typically found in older children and adolescents. Very rarely an immunologic disease is beginning or is accompanied by urticaria. Finally, as hereditary angioedema is often first manifesting at puberty it has to be ruled out in cases of relapsing angioedema, especially in association with a family history.

### Contact allergy

Contact allergy usually refers to the type IV allergic reaction seen as a subtype of contact dermatitis (or contact eczema). Subtypes are irritant CD (wet work), allergic CD (daily life products such as cosmetics, metal, rubber, leather), the type I allergic variant protein CD (caused by food), photo CD (either toxic or an allergic reaction to a cosmetic or to a systemic medication, e.g. an antibiotic.) The classical type IV allergic CD is a T-cell mediated reaction against small molecular weight substances (<500 Da), which easily penetrate the skin.

In PC contact dermatitis (CD) is very frequent (48). In addition, acute reactions against contact allergens mainly lead to emergency visits to the GP. Allergic CD is frequent in people treated for atopic dermatitis due to the impairment of the skin barrier and the frequent use of different external emollients (49).

The diagnosis of CD is limited to the use of a skin patch test. This test uses a wide battery of contact allergens, normally diluted in petroleum.

The test is applied to the back for 48 h and read twice after 48 and 72 h. The time-course may vary: reaction to corticosteroids have a slower time course and the test needs to be read at 96 h or even later.

**Table 4** Task force key recommendations for use of allergy diagnosis tests in PC

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|                                                                                                                                                 |
|-------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. Specific IgE measurement can be performed in PC or referred (depending on local conditions), but only in light of a precise patients history |
| 2. SPT are not recommended without a proper training and the risk of anaphylaxis should be considered                                           |
| 3. Total IgE as a single parameter measurement is not recommended                                                                               |
| 4. IgG measurement is not recommended                                                                                                           |
| 5. Seasonal and easily responsible to treatment AR should not be IgE tested                                                                     |
| 6. Use of management pathways adapted for PC is strongly recommended                                                                            |

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PC, Primary care.

The most frequent contact allergens are combined in European or national standard series, however, the skill in diagnosis is detecting the more rare allergens. In selected occupational settings, it is crucial to have the relevant allergens available for testing. The patch test can be performed with the patient's own products with previous dilution.

The major difficulty in reading the patch test is due to the irritant nature of contact allergens per se. The skin patch test needs to be postponed if very severe and acute reactions are present, because a patch test might provoke a flare of an already active eczema. If the patch test is performed too early false positive reactions due to the activated skin immune system ('angry back') may hamper the diagnosis. An 'angry back' should be suspected if more than seven nonrelated contact allergic reactions appear in a patch test. UV light reduces the skin immune functions so after tanning of the skin patch testing should thus be postponed for 4–6 weeks.

While a more sophisticated testing for contact allergic reactions need a referral to a dermatologist, already at the GPs office a good workup can be ensured by checking closely the patient's history or already asking the patient to start writing a diary on when these reactions happen, reminding the patient that contact allergic reactions are delayed, usually at 12–72 h after the application of the possible ingredient.

### Conclusions and recommendations

The diagnosis of allergic diseases involves a thorough clinical history, further supported by *in vivo* or *in vitro* testing. Additional procedures such as challenge tests are needed to establish the correct diagnosis (Table 4).

In accordance with the significant workload in a PC setting, simplified pathways for recognition and diagnosis of allergic diseases are proposed, that should be further adapted to local (national) conditions.

### Conflicts of interest

The authors declare no conflicts of interest.

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