

REVIEW

Testing for inhalant allergy in asthma

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Introduction

In asthma the inflammatory process [1,2] is strongly related to atopy. It is estimated that more than 70% of the asthmatic population under the age of 55 is atopic, due to the production of specific immunoglobulin E (IgE) antibodies against inhalant allergens [3]. The severity of the asthmatic inflammatory process as indicated by the presence of inflammatory cells in the bronchi is reflected in the level of bronchial hyperresponsiveness (BHR) to histamine, metacholine or other stimuli [4]. It is still unclear whether the level of BHR on itself is related to the clinical manifestations of asthma [5]. In the population a relationship exists between atopic status and BHR, dependent on age [6–8]. There are strong indications that the individual's atopic status, in combination with the degree of BHR, is indicative of the severity of the bronchial response to inhaled antigen in that individual and thus of the clinical manifestation of allergic asthma [9,10]. In about 60% of the atopic asthmatics a late asthmatic response occurs, the process of which greatly increases BHR [11,12], resulting in a lower threshold to further allergen exposure [13], and a consecutive further increase in asthmatic symptoms.

In view of these facts it is argued that in a patient with symptoms suggestive of asthma it is essential to be informed both on the atopic status and on the degree of BHR. To assess the atopic status in a patient, *in vivo* testing and *in vitro* testing are at the disposal of the clinician. In the last decade(s) both methods have been modified and improved with regard to standardization of allergenic extracts and methodology.

In vivo testing for inhalant allergy

Skin tests

In skin testing the presence or absence of specific IgE antibodies on skin mast cells is investigated as well as the releasability of the mast cells and the reactivity of the surrounding tissues to the mediators released from these cells. It is a longstanding method with many variables which may affect the results [14]. Two methods for skin

testing are currently in use, the intracutaneous or intradermal test (ICT) and the epicutaneous (epidermal) or skin-prick test (SPT). The choice between SPT and ICT is not really an issue [15,16], although in the routine diagnosis of allergy the SPT is preferred [17].

In the SPT method the skin is punctured through a minute amount of allergenic extract applied onto the skin, using a standardized needle with a 1 mm tip [18–20]. In the ICT method a test solution is injected into the superficial layer of the epidermis, the indicated amount varying from 0.01 to 0.05 ml [15,20,21].

In the last decade the quality of the allergenic extracts as well as the biological standardization has been especially a focus of research to minimize the batch to batch variation and the difference in potency between different extracts [22–24]. The concentration of an allergenic extract should be given in biological activity. Biological standardization of allergenic preparations are, according to the Nordic guidelines, expressed as biological units per ml (BU/ml) or as histamine equivalent in skin-prick testing (HEP) [17,22]. A concentration of 1000 BU/ml or 1 HEP denotes the potency of an extract that elicits an identical reaction as to histamine dihydrochloride 1 mg/ml in most individuals who are allergic to the material in the skin-prick test [22]. However, a reference concentration of histamine at a level of 10 mg/ml might be more accurate for defining the HEP unit, because of less variability of its skin reaction [25]. In the U.S.A. the Food and Drug Administration Laboratory of Allergenic Products has defined the biological activity of allergenic extracts in allergy units (AU) per ml, and the HEP system is not (yet) accepted as a biological method of standardizing allergen extracts [20].

The methods of reading the skin reaction (weal, flare, or both) and recording (mean, sum, or product of the longest and the midpoint orthogonal diameters) vary. The scoring of skin-test results with clinical interpretation and cut off limits are not yet standardized, but efforts are being made [26–28]. A negative control (saline solution or phosphate-buffered diluents) should always be incorporated to evaluate unspecific reactions of the skin, and a positive control to document normal reactivity of the skin. As a positive control in SPT histamine dihydrochloride 1 mg/ml or preferably 10 mg/ml is recommended, and in ICT histamine dihydrochloride 0.01 mg/ml or

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preferably 0.1 mg/ml [17]. To correct for differences in operator technique the test result can be related to the histamine weal size and expressed as percentage or in HEWS (Histamine Equivalent Weal Size), i.e. the allergen skin-test result divided by the histamine skin-test result [17,20]. These methods of interpretation of the test results are especially important in the follow-up of an individual's sensitivity [29], or when comparing test results between individuals of different ages [30].

Inhalation provocation tests with allergen

Although inhalation provocation testing can be useful in the investigation of occupational asthma, it is to be considered of limited clinical value in the daily practice of diagnosing inhalant allergies [31]. One can predict the test result from the provocation test with histamine or metacholine and skin test or *in vitro* results, and thus avoiding the possible risk of a severe asthmatic reaction [10].

In vitro testing for inhalant allergy

Serological tests

In vitro testing detects the presence or absence of circulating IgE antibodies in the serum. Since the discovery of IgE in 1966, the diagnostic possibilities with radio- and enzyme-labelled immunoassays have markedly increased [32,33]. Although a high level of total IgE concentration in serum is suggestive of an allergic origin of the asthmatic disease, normal levels can not exclude allergy. The normal values presented in the literature vary, especially in children [34,35], the estimation depending on the selection of the study population. It has been suggested that reference laboratories use their own normal values for children of different age groups [35]. In adults it is proposed that IgE mediated allergic asthma is unlikely when total IgE concentration is below the level of 25 kilo Units (kU)/l and likely when above the level of 100 kU/l [36].

The initially introduced Phadebas Radio Allergo-Sorbent Test (RAST) to determine specific IgE antibodies in the serum has been updated through the years to increase the sensitivity and specificity. The results, based on a reference system, can be expressed in arbitrary Phadebas RAST Units (PRU/ml) or percentage binding [37]. For clinical use these units are divided into classes from 0 to 4. Class 2 and more is thought to denote a clinically relevant sensitization to the allergen tested in the RAST [38,39], and class 1 a potential clinical relevance. Recently a new three dimensional solid phase carrier with high binding capacity, the Pharmacia CAP system, has been developed. This test system is found to enhance the

sensitivity of the RAST with little or no reduction in specificity [40–44]. The assay is calibrated against the World Health Organization standard for total IgE and the results can be expressed in kU_A/l (kilo units of allergen specific IgE/l), or in classes 0–6. In the past, various other systems based on the allergosorbent principle have been developed, such as the fluoro-allergo-sorbent test (FAST), and more recently the (multiple) allergosorbent chemiluminescent assays (MAST CLA and Magic Lite) [45–48]. These tests vary in type of solid support used to produce the allergosorbent and in method to label the anti-human IgE antibody [49]. The different tests lack comparability, and it has been suggested that quality control by reference laboratories to enhance their validity and reproducibility should be stimulated [20,49].

Recently multiple allergen screening tests became available. The Phadiatop test—a single yes/no screening test—carries a balanced mixture of relevant allergens to common inhalant allergy. Its results showed very good correlations with the results of a RAST panel [50–55], and its sensitivity and specificity for a clinically diagnosed inhalant allergy also proved to be high [52,56–58]. Especially for use in young children and infants the Phadiatop Paediatric was developed. This test screens efficiently for the most relevant food and inhalant allergens in childhood [59]. The QUIDEL Allergy Screen (QAS) is a multi-allergen dipstick enzyme immunoassay for measuring IgE antibodies against a maximum of 10 allergens, offering a good comparison to the RAST [60], but further improvement of some allergen preparations seems to be necessary in the assay [61].

Cellular tests

Histamine release from allergen sensitized basophils can be measured in the—fresh—blood of the patient as a 'biological signal' of allergy, by methods of chemical and enzyme-isotopic assays, that have been modified to increase the sensitivity and specificity [20]. Recently a glass fibre-based basophil histamine release test has become commercially available. Evaluation of its diagnostic value is recommended [62], and the test is rather a research tool at present.

General considerations

There has been much discussion regarding the relative merits of *in vivo* and *in vitro* testing for allergic status. Skin testing is a rapid technique, but it is operator dependent and it requires experienced personnel in order to obtain consistent results. Skin testing is contra-indicated in some skin diseases [20], and is susceptible to the inhibitory effects of anti-allergic medications [63]. Modern methods

for *in vitro* measurements of specific IgE can now yield a (semi-) quantitative result and have enhanced the sensitivity, the cost of *in vitro* testing, however, being obviously higher than of skin testing. The choice between *in vivo* and *in vitro* testing depends on practical grounds [64], with the prerequisite that standardized methods and allergenic extracts, wherever possible, are properly applied [20]. It is generally accepted that the clinical history is the cornerstone of the allergy diagnosis [65,66]. However, discrepancies do occur between history and sensitization to (specific) allergen(s), the history being rather specific than sensitive [39,67–70]. The relationship between history and sensitization might also be confused by a concomitant increase in nonspecific bronchial reactivity which is associated with the late allergic response [11,71].

In the management of the patient allergy testing, guided by the clinical case history, will contribute to the confirmation or exclusion of atopy as one of the possible causes of the asthmatic symptoms. Identification of the relevant allergen(s) is needed, because the first step in the therapeutic approach should be trying to lower the level

of exposure and to avoid contact with the allergen(s) involved in the allergic process [71,72], the focus being in particular on house dust mites and domestic pets [73]. Determination of atopy is particularly important as atopy can be considered a risk factor in the developing of active or chronic asthma in childhood [74,75], and in the occurrence of acute severe attacks of asthma [76,77]. The provision of (semi-)quantitative indicators in allergy testing is worthwhile in view of the interrelationship between allergic reaction and non-specific bronchial reactivity, in which the atopic status, judged by the number of positive tests or levels of specific IgE antibodies, appears to be an important determinant [71,78,79]. Furthermore, an association has been found between degree of atopy and severity of asthma in childhood [80], and between a high grade of atopy and the need of a more intensive therapeutic approach [75,80].

Screening procedures can be of value in the clinical setting to exclude allergy, especially when the case history is inconclusive. In this respect the Phadiatop test proved to be superior to total IgE determination [50,53–58]. In

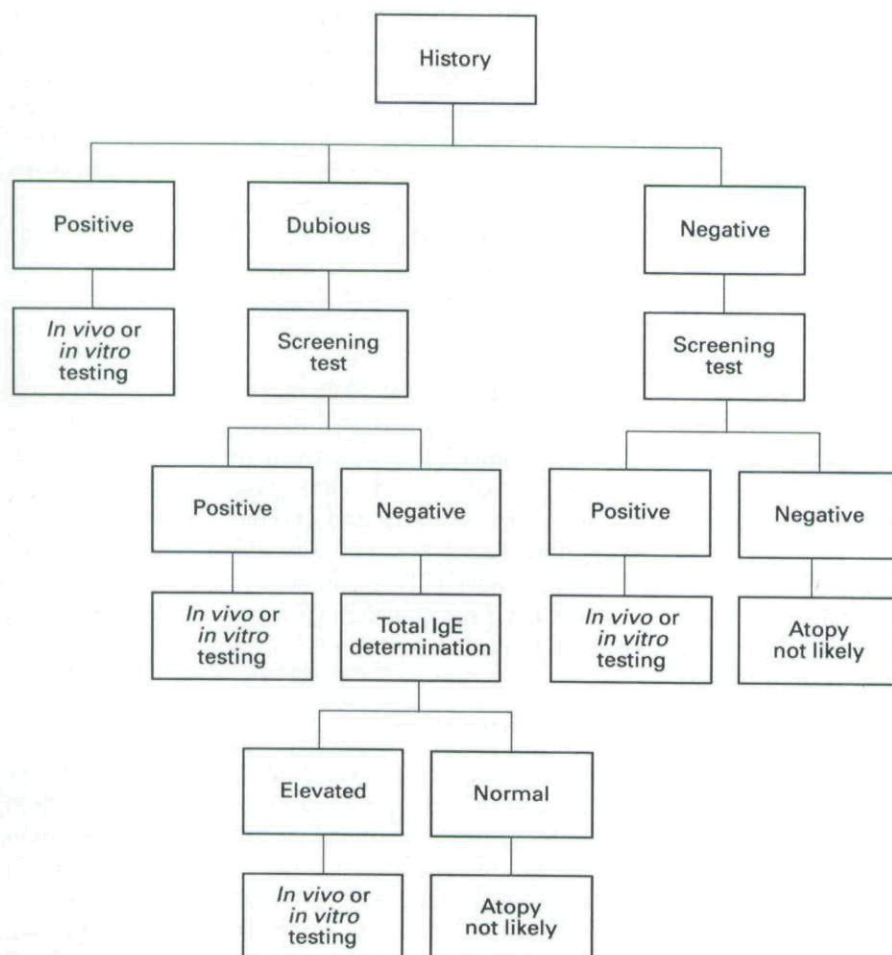


Fig. 1. A practical flow chart for testing in the diagnostic process of inhalant allergy.

case of a positive test result further allergy testing is indicated and can be determined in the same serum if stored at -20°C . A practical flow chart for testing in the diagnostic process of inhalant allergy is proposed in Figure 1.

In conclusion, for patients with asthmatic symptoms, allergy testing offers the potential to improve the management of the patient. However, it is acknowledged that this is an area that should be further studied systematically.

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