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Algorithms in Allergy and Clinical Immunology

Algorithms in Allergy: Organ-Specific Allergen Challenges for the Phenotyping of Chronic Respiratory Diseases

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Organ-specific allergen challenges are meant to reproduce the response of the airway mucosa to an allergen in a controlled manner [1]. Standardized protocols for nasal, conjunctival, and bronchial allergen challenges (NAC, CAC, and BAC, respectively) have been recently published by EAACI [2–4]. The NAC should be monitored by a combination of symptom score

TABLE 1 | Recommended cutoffs for the different methods to monitor the nasal allergen challenge. Vol2-6 cm: Volume 2–6 cm, the area corresponding to the space between the nasal vestibule and the head of the lower turbinate in adults. References [S1–S8].

	Clearly positive	Moderately positive
Subjective parameter		
Lebel score	Increase ≥ 5 points	Increase ≥ 3 points
Linder score	Increase ≥ 5 points	Increase ≥ 3 points
Visual analog scale	Symptoms ≥ 55 mm	Symptoms ≥ 23 mm
Tonal nasal symptom score	Increase ≥ 5 points	Increase ≥ 3 points
Objective parameter		
Peak nasal inspiratory flow	Flow decrease ≥ 40%	Flow decrease ≥ 20%
Acoustic rhinometry	Bilateral decrease ≥ 40% in Vol2–6 cm	Bilateral decrease ≥ 27% in Vol2–6 cm
Active anterior rhinomanometry	Flow decrease ≥ 40% at 150 Pa	Flow decrease ≥ 20% at 150 Pa

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and objective measurement of nasal patency (through acoustic rhinometry, peak nasal inspiratory flow, etc.), and positivity is established by moderate changes in both parameters simultaneously or by clear changes in at least one parameter [2]. The cutoffs for moderate and clear changes rely on the method used to analyze the NAC [5, S1–S8] (Table 1). Conversely, CAC monitoring is based on the total ocular symptom score only, which evaluates redness, itching, tearing, and chemosis. Patients scoring ≥2 points in redness + itching or ≥5 points in the four symptoms after allergen instillation are considered positive [3]. Finally, BAC monitoring relies on lung function parameters only. A drop ≥20% in FEV1 respect to baseline identifies the early asthmatic response and is indicative of positivity [4]. For diagnostic purposes, one single allergen dose is administered during the NAC, whereas progressively increasing concentrations are given for BAC and CAC [1]. The administration of one allergen per session is generally recommended for allergen challenges, although a protocol with up to four allergens per session is also validated for NAC [S9]. Generally, a good asthma control (an asthma control test ≥20 points) is required for NAC and BAC, whereas more flexibility exists for CAC [1]. In any case, allergen challenges should be conducted by trained personnel

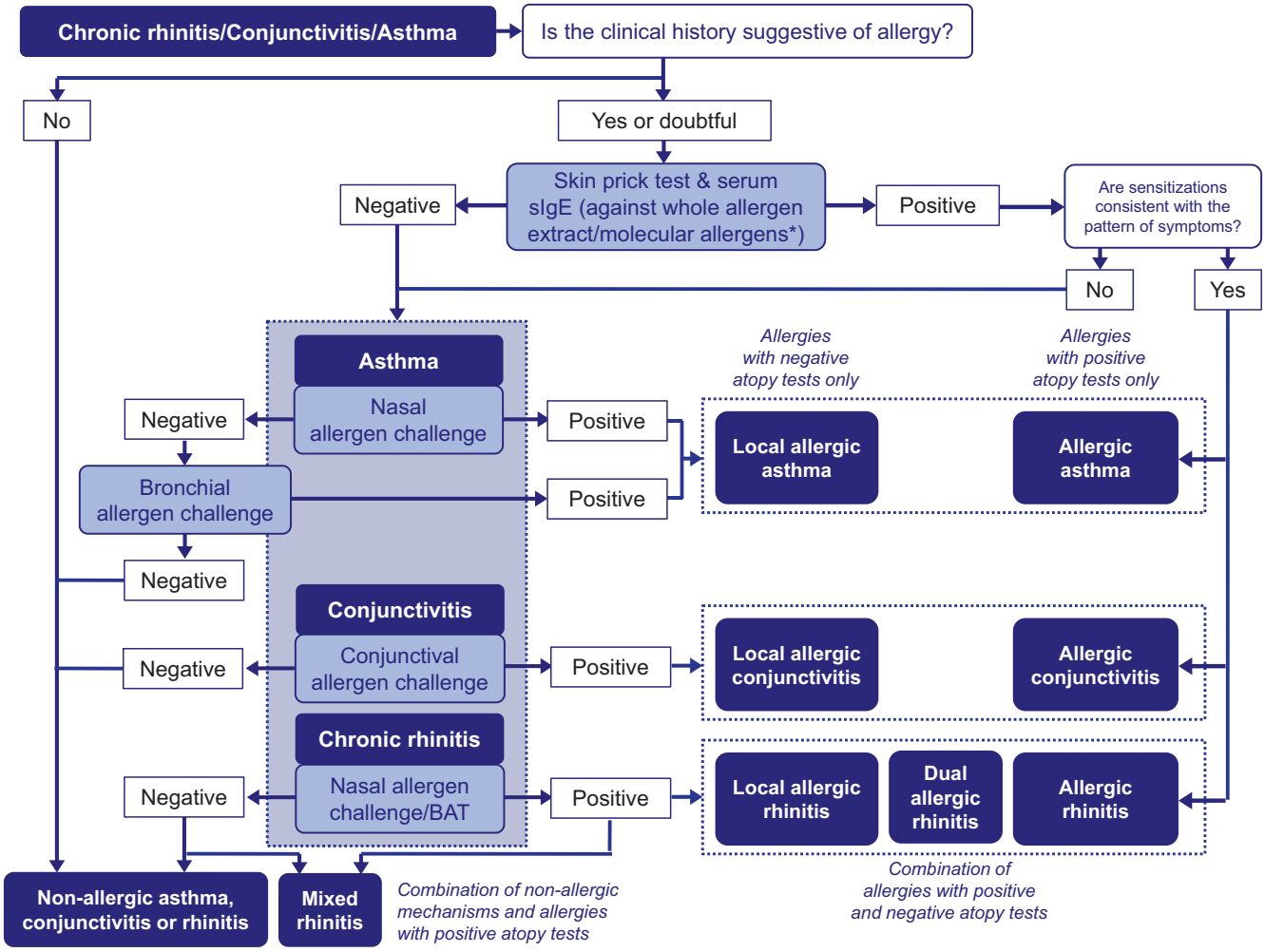

FIGURE 1 | A thorough clinical history should be conducted in all patients with chronic rhinitis, conjunctivitis, and asthma. If the clinical data are suggestive or compatible with an allergic etiology, the individuals should be subjected to skin prick test (SPT) and/or the quantification of specific (s)IgE against the whole allergenic extract in serum (collectively called atopy tests). The determination of sIgE against molecular allergens can also be considered in patients testing positive to the former tests. When the IgE sensitizations detected are consistent with the pattern of respiratory symptoms, the individual can be diagnosed with the allergic phenotype. Conversely, allergen challenges should be performed in cases with discrepancies between the clinical history and the results of IgE sensitization tests (e.g., nonatopic individual with suggestive clinical history or atopic subject whose symptoms are not consistent with the sensitizations detected). In asthma patients, a nasal allergen challenge (NAC) can be performed in a first step, followed by a bronchial allergen challenge in case of negativity of the former test. Together, these investigations can lead to the diagnosis of allergic (positive allergen challenge only with allergens testing positive in atopy tests), local allergic (positive allergen challenge only with allergens testing negative in atopy tests) or nonallergic (negative challenge with all allergens) asthma or conjunctivitis. In atopic individuals with rhinitis, a basophil activation test (BAT) can accurately replace the nasal allergen challenge (NAC) for the evaluation of the clinical relevance of IgE sensitizations. Conversely, a NAC will still be required to rule in/out the allergic etiology in nonatopic rhinitis patients who test negative to the BAT. In atopic individuals with rhinitis, the NAC (or BAT) can also identify the dual allergic phenotype (positive NAC to allergens with positive atopy tests and positive NAC to allergens with negative atopy tests) and the mixed phenotype (positive NAC to allergens with positive atopy tests and negative NAC to allergens with negative atopy tests). BAT, Basophil activation test; sIgE, Allergen-specific IgE. *The determination of specific IgE against molecular allergens should be conducted only in patients with positive SPT and/or detectable sIgE against the whole allergenic extract.

and in a clinical setting equipped with resources to treat bronchoconstriction and perform resuscitation [1].

The diagnostic process for airway allergy should start with a thorough clinical history, interrogating the seasonality, persistence, and triggers of respiratory symptoms, besides the presence of allergic multimorbidity [2–4]. If the clinical history is suggestive or compatible with an allergic etiology, the patient should be subjected to atopy tests (skin prick test [SPT] and serum allergen-specific (s)IgE) [1]. In case of positive results to multiple allergenic sources, the quantification of serum sIgE against molecular allergens can help discriminate between genuine sensitization and cross-reactivity [S10]. Conversely, when atopy tests are negative, an allergen challenge can be conducted to identify local allergic phenotypes. Moreover, in some atopic individuals, the determination of sIgE against molecular allergens is not sufficient to clarify the discrepancies between the results of atopy tests and the pattern of respiratory symptoms. In this case, allergen challenges can help investigate the clinical relevance of sensitizations and/or identify concurrent allergies with negative atopy tests [2–4]. Of note, patients with chronic nasal symptoms can suffer from dual allergic rhinitis (combination of allergies with positive and negative atopy tests) or mixed rhinitis (combination of nonallergic mechanisms and allergies with positive atopy tests) [6], in addition to the allergic, local allergic, and nonallergic phenotypes (Figure 1). Because the NAC is safer and less time-consuming than the BAC [7], the former test can be considered to evaluate the impact of allergen exposure on the bronchial mucosa following a "united airway" approach (see Supporting Informaiton for further elaboration) [8, S11–S15].

The clinical implementation of allergen provocations faces several issues including the shortage of allergen-based reagents and the insufficient number of trained specialists, besides reimbursement policies and local regulations [1]. Interestingly, the concordance rate between the basophil activation test (BAT) and the NAC is very high for allergies with positive atopy tests (allergic rhinitis and systemic component of DAR) [9]. On the other hand, 25%–75% of allergies with negative atopy tests (local allergic rhinitis and local component of DAR) are associated with positive BAT results [6, 9, S16–S21]. Thus, the BAT can accurately replace the NAC for the confirmation of the clinical relevance of sensitizations, and it can save a significant amount of NAC for the identification of allergies with negative atopy tests. Nevertheless, a NAC will be still required in case of negative BAT results to rule in/out the allergic etiology in nonatopic individuals [9]. Of note, the BAT is a more patient-friendly technique than the NAC and does not require a wash-out period for antiallergic medication.

The identification of the allergic triggers of rhinitis, conjunctivitis, and asthma will facilitate the selection of candidates for allergen immunotherapy (AIT). Besides its long-term effect for allergies with positive atopy tests, AIT can also alleviate symptoms and improve the quality of life of patients with local respiratory allergy [10, S22–S28]. In this regard, serum sIgE against molecular allergens can aid the selection of AIT composition in atopic individuals [S10], whereas the BAT with molecular allergens has been proposed for the same purpose for allergies with negative atopy tests [S17, S21].

Author Contributions

D.S.-T., A.T.-M., and G.B.-R. performed the literature review and extracted the main conclusions. M.J.T., R.M., and I.E.-G. drafted the manuscript and supervised the work of the other authors. The final version of this article was approved by all authors before submission.

Conflicts of Interest

The authors declare no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.