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Alternatives to the allergen-specific nasal provocation test: role of molecular allergens for grasses in poly-sensitized children with seasonal allergic rhinitis

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Mario Barreto[1], Auro Della Giustina[2], Ifigenia Sfika[3], Stefano Pattini[4], Alessandro Travaglini[5], Maria Antonia Brighetti[5], Denise De Franco[5], Alessandro Di Menno Di Bucchianico[6], Velia Malizia[7], Salvatore Tripodi (coordinator)[8]

[1] NESMOS Department, Faculty of Medicine and Psychology, Pediatric Unit Sant'Andrea Hospital, "Sapienza" University, Rome, Italy; [2] Private Practice, Parma, Italy; [3] Private Practice, Rome, Italy; [4] Pediatric Unit, Department of Medical and Surgical Sciences of the Mother, Children and Adults, University of Modena and Reggio Emilia, Modena, Italy; [5] Department of Biology, Tor Vergata University, Rome, Italy; [6] Italian National Institute for Environmental Protection and Research (ISPRA), Rome, Italy; [7] Institute of Translational Pharmacology, National Research Council (CNR), Palermo, Italy; [8] Allergology Service, Policlinico Casilino, Rome, Italy

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CORRESPONDENCE

Mario Barreto
mario.barreto@fondazione.uniroma1.it

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SUMMARY

Allergic rhinitis (AR) affects 10-30% of the global population, notably children and adolescents, leading to reduced quality of life and comorbidities like asthma. An Italian multicenter study indicated that 85% of children tested positive for multiple pollen allergens, with Timothy grass predominant. IgE antibodies against *Phleum Pratense, Bermuda grass*, olive, and cypress are highly prevalent in southern Europe, where overlapping pollination periods complicate the identification of specific seasonal allergens in poly-sensitized patients. For some patients, allergen-specific immunotherapy is necessary when symptomatic therapy is insufficient. Molecular diagnostics and nasal provocation testing (NPT) are crucial to identify relevant allergens. NPT remains the gold standard for documenting clinical relevance in seasonal AR, but is challenging in poly-sensitized children. Non-invasive strategies, e-Diary for symptoms, and IgE-specific activity analysis are being explored. This summary reviews the predictive value of clinical and biological data for NPT outcomes in pediatric patients co-sensitized to grasses and other seasonal pollens. Clinical data assessed with the visual analogue scale can predict NPT outcomes. Biological data, including specific IgE levels and skin prick tests, have shown varying predictive values. Combining clinical scores and biological markers, such as IgE-specific activity for grass-pollen molecules, enhances prediction accuracy for positive NPT outcomes.

KEYWORDS: Allergic rhinitis, AllergyMonitor, nasal provocation test, grass pollens, poly-sensitized children

Allergic rhinitis (AR) impacts approximately 10-30% of the world's population, especially children and adolescents; ocular-nasal, systemic symptoms and those secondary to therapies

characterize it. The most severe symptoms are associated with reduced quality of life, school absenteeism, outdoor sports limitations, and comorbidities such as asthma [1,2].

Data from an Italian multicenter study revealed that nearly 85% of children tested positive for at least 3 allergens, with *Timothy grass* being the dominant allergen in about 90% of cases [3]. Recently, a high prevalence of IgE antibodies against major molecules from *Phleum Pratense* (Phl p 1 and Phl p 5), *Bermuda grass* (Cyn d 1), olive (Ole 1), and cypress (Cup A 1) was described in 9 centers across southern Europe. The distribution was more heterogeneous for other pollen molecules, and variability was observed in pollen sensitization profiles and clinical manifestations [4].

Poly-sensitization makes it challenging to identify the specific allergen responsible for AR symptoms during the pollen season [5]. Even when aerobiological data are available to assess the correlation between symptoms and pollen concentrations, the difficulty is exacerbated by overlapping pollination periods, especially in southern European regions [4,6]. In contrast, central-northern areas exhibit more sequential pollination periods for grasses and other pollens (e.g., birch) [4].

For some patients, symptomatic therapy alone is insufficient to control the severity of seasonal rhinitis, necessitating allergen-specific immunotherapy (AIT) [5]. Molecular diagnostics (CRD) allows the identification of the most relevant allergenic molecules and optimizing AIT prescription [7]. Other patients do not show a serum sensitization profile corresponding to the local, causal symptoms, and nasal provocation testing (NPT) is necessary [2, 8].

NPT remains the 'gold standard' for documenting the clinical relevance of a specific allergen in patients with seasonal AR [8]. However, choosing the appropriate allergen is challenging in patients who are poly-sensitized to pollens, and performing the NPT can be cumbersome in children. Additionally, execution of the NPT requires standardizing environmental and procedural conditions, and clinical-therapeutic patient monitoring [8,9].

An alternative non-invasive strategy to NPT can be studied using algorithms that incorporate quantitative and semi-quantitative parameters, including digital symptom assessment technologies and analysis of IgE-specific activity for grass-pollen molecules as their percentage fraction from total IgE [10].

This summary outlines experiences from various studies regarding the predictive value of clinical and biological data for NPT outcomes. Specifically, it discusses the diagnostic value of NPT surrogates in pediatric patients who are co-sensitized to grasses and other seasonal pollens, whose severe AR symptoms justify AIT prescription.

PREDICTIVE PARAMETERS FOR A POSITIVE NPT OUTCOME

Clinical Data

There are various semi-quantitative methods for retrospective or prospective self-assessment of symptoms related to pollen seasons. These methods help guide pharmacological therapy and evaluate the effectiveness of allergen immunotherapy (AIT) [7,9,11]. However, studies on the value of psychometric scales in predicting a positive response to NPT for grasses remain scarce [12,13]. The development of apps such as MASK or AllergyMonitor has made patient follow-up easier through an "e-diary" [14,15]. Within the "AllergyMonitor" app (AM) (TPS Production, Rome, Italy), three self-assessment methods — the "Rhinoconjunctivitis Total Symptoms Score" (RTSS, 0-18), the "Combined Symptom and Medication Score" (CSMS, 0-6), and the "Visual Analogue Scale" (VAS, 0-10) — allow patients to enter detailed scores for nasal and ocular symptoms as well as medication use (RTSS, CSMS) and assess their clinical progress (VAS) daily [15-20].

The VAS is a psychometric scale that is considered simple to use and well correlated to the ARIA criteria [21]. This scale can be applied to rate the severity of each AR symptom (e.g., nasal obstruction, runny nose, itching, sneezing) or the overall symptoms' severity by asking: "How much did your allergy symptoms bother you today?". In addition to monitoring, VAS is useful for assessing the total symptoms' severity relating to the previous pollen season.

Recently, in allergen poly-sensitized pediatric patients with AR, we have found that clinical VAS scores (overall symptoms) assessed daily and those referring to the previous pollen season were comparably useful in predicting the NPT outcome [13]. A close relationship between the e-diary and retrospective ARIA data has been previously reported [22].

Patient data of the AM App were analyzed as maximum values and coefficients of variation (CV=100* SD/mean) for RTSS, CSMS, and VAS during days with high pollen concentrations (>30/m^3) following the EAACI criteria [23,24]. VAS (AM), but not RTSS or CSMS, was predictive of NPT outcome; VAS maximum value: sensitivity (Se) 72.1%, specificity (Sp) 63.6%; VAS CV%: Se 80.3%, Sp 63.6%. Furthermore, the overall VAS on the previous pollen season (retrospective) showed a modest Se (60.7%) and good Sp (81.8%) for a positive NPT.

In contrast to our results, a prior study in adult patients found no relationship between the VAS referring to the previous pollen season and the outcome of NPT titrated to increasing concentrations of grass extract [12]. Of note, we performed the NPT with an undiluted extract, more suitable for clinical use, as per current international guidelines [8].

Biological data

Biological data considered for AIT include skin prick tests (SPT), specific serum IgE, and more recently, CRD [5,7,25]. The substitutive value of biological data to NPT has been the subject of numerous studies. Regarding SPT positivity (defined differently by individual studies), a recent meta-analysis of 7 studies on various airborne allergens described pooled sensitivity and specificity of 70% and 86% respectively [26]; three of these studies reported dissimilar values (sensitivity between 68-97% and specificity between 70-86%) for the positive response to NPT with Timothy grass extract [27-29]. The extent of allergic sensitization understood as the wheals' size or the specific IgE levels, has also been reported to be predictive for the NPT outcome to various inhalant allergens (*Dpt*, cat, *Salsola K.* pollen) [30 -34]. On the other hand, the diameter of the skin reaction to *Timothy grass* was not

shown to be predictive of NPT, but only the cut-off (0.35 kUA/L) for specific IgE to the same allergen [35].

A study in 101 adult patients evaluated serum IgE against eight *Phleum pratense* molecules (Phl p: 1, 2, 4, 5b, 6, 7, 11, and 12); the authors found that increased numbers of sensitizations exceeding the cut-off 0.35 kUA/L predicted NPT and conjunctival challenge positive results [36]. From our recent study in 72 poly-sensitized children, only serum Phl p 5 concentrations ≥ 0.35 kUA/L were common in NPT-positive patients (64% *vs* 18.2% in TPN-negatives); instead, Phl p 1 and Phl p 4 were equally frequent and others (Phl p 7 and Phl p 12) were infrequent in both groups examined [13]. This is consistent with the recognized allergenic capacity of Phl p 5, attributable to the numerous epitopes of this molecule [37], as well as the high risk of developing asthma in patients who are sensitized to it [38].

A few years ago, quantification of IgE-specific activity for a given allergen was proposed [10]. This approach calculates for each specific IgE its percentage of total serum IgE, i.e., (specific IgE/total IgE) *100 [39]. The index provides an estimate of the degree of allergic sensitization and, ultimately, the clinical impact on the patient; this approach has proven useful to evaluate the development of tolerance in food allergies and the effectiveness of AIT [40, 41]. IgE-specific activity is part of the parameters of the humoral immune response that act in the release of mediators from mast cells and basophils, together with IgE concentrations, affinity, and heterogeneity in specific epitopes of the antibody [42].

We hypothesized that the measurement of the serum IgE-specific activity for grasses is a useful tool to improve the predictive capacity of the response to NPT. For the challenge, the allergenic extract Graminacee blend, 300 SRU/ml (ALK Abellò - Milan, Italy), which has an allergen concentration of Phl p 5 equal to 26 mcg/ml, was administered [13]. We estimated the predictive value of specific IgE for *Phleum pratense* and *Bermuda grass* and the molecules Phl p 5 and Cyn d 1 and their IgE-specific activity in determining a positive NPT result. The IgE-specific activities for each of these molecules were found to be more predictive of the NPT outcome than the IgE-specific activities for *Phleum* and *Bermuda*, also compared to the diameter of the SPT wheal reactions for the two allergens. The combined IgE-specific activity for both molecules, i.e., (specific IgE for Phl p 5+Cyn d 1/total IgE)*100, reached the highest predictive value for TPN outcome; for a cut-off ≥ 7.25%: Se 70.5%, Sp 90.9% [13].

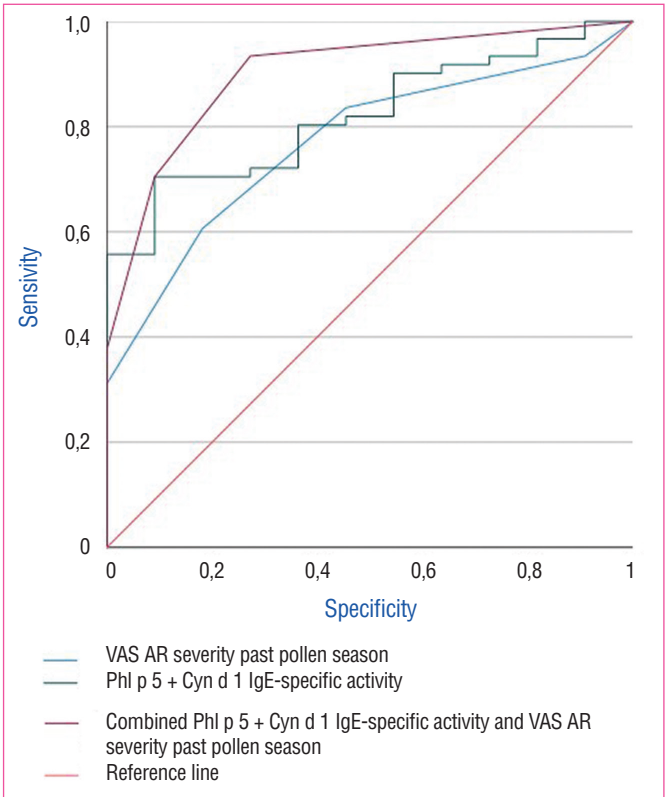

FIGURE 1. "Receiver operating characteristic" (ROC) curves and areas under the curve (AUCs) for allergen sensitization to combined grass molecules and AR visual analog scales (VAS) as predictors of the nasal provocation test (NPT) result. Combined IgE-specific activity to Phl p 5 + Cyn d 1, AUC= 0.82, p < 0.01; VAS for AR severity in the previous pollen season, AUC= 0.77, p < 0.01; Diagnostic algorithm using threshold values for the combined IgE-specific activity to Phl p 5 + Cyn d 1 (≥ 7.25%) and VAS for AR severity in the previous pollen season (≥ 7), AUC = 0.90, p < 0.001 (Modified with permission from [Figure 2]: Barreto M, Tripodi S, Arasi S, Landi M, Montesano M, Pelosi S, Potapova E, Sfika I, Villella V, Travaglini A, Brighetti MA, Matricardi PM, Dramburg S. Factors predicting the outcome of allergen-specific nasal provocation test in children with grass pollen allergic rhinitis. Front Allergy 2023;4:1186353. https://doi.org/10.3389/falgy.2023.1186353).

Clinical-biological algorithms

From what has been stated, it appears possible to identify pediatric patients who are candidates for AIT without resorting to NPT. Combining clinical scores (prospective and retrospective) and biological biomarkers can be useful in making decisions for poly-sensitized patients with seasonal AR. To this end, we tried to optimize the prediction of a positive NPT by considering both the VAS outcome (on days of high pollen concentration or summary of the previous season) and the combined serum IgE-specific activity for main grass-pollen molecules Phl p 5 and Cyn d 1 [13].

In patients with a VAS score ≥7 for AR severity and IgE-specific activity for both grass molecules (Phl p 5+Cyn d 1) ≥7.25%, a positive outcome for NPT was predicted with a sensitivity of 93% and a specificity of 73% (Fig. 1).

Future possibilities

The correlation between symptom burden and environmental pollen concentrations in patients with seasonal RA is well known [6,43]. As is obvious, clinical scores are not allergen-specific and, especially in poly-sensitized patients, may reflect both the immunological

"priming" of cross-reactive allergens and the effect of overlapping pollination from various allergenic sources [6]. Pollen allergenicity changes with environmental factors such as pollution, humidity, precipitation/storms, and other factors induced by climate change [44]. For instance, the rain osmotic impact on the surface of the granules and the cytoplasm releases microparticles that are capable of multiplying the stimulus on sensitive subjects, as happens during periods of asthma exacerbations [44].

Recent studies show that seasonal symptoms, rather than the count of suspected pollen granules, are more related to the aerial concentrations of its most allergenic molecules [45]. This suggests that evaluating clinical scales during periods that are "rich" in airborne allergens and measuring the serum IgE-specific activity for these molecules could increase the predictive power for the NPT outcome in pediatric patients. However, this is not the case for all patients with seasonal symptoms, as some have normal serum IgE levels and are classifiable as local AR (so-called "LAR"), thus representing a diagnosis of exclusion.

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Conflicts of interest statement

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Authors' contribution

BM and TS: prepared the first manuscript draft; all co-authors were actively involved in the discussion and critical review of the manuscript. All authors contributed to the article and approved the submitted version.

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