# The effect of component-resolved diagnosis on specific immunotherapy prescription in children with hay fever

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**Background: Sensitization to profilins and other cross-reacting molecules might hinder proper specific immunotherapy (SIT) prescription in polysensitized patients with pollen-related allergic rhinitis (AR). In these patients, component-resolved diagnosis (CRD) might modify SIT prescription by improving the identification of the disease-eliciting pollen sources.**
**Objectives: We sought to measure the effect of CRD on SIT prescription in children with pollen-related AR.**
**Methods: Children (n = 651) with moderate-to-severe pollen-related AR were recruited between May 2009 and June 2011 in 16 Italian outpatient clinics. Skin prick test (SPT) reactivity to grass, cypress, olive, mugwort, pellitory, and/or Betulaceae pollen was considered clinically relevant if symptoms occurred during the corresponding peak pollen season. IgE sensitization to Phl p 1, Phl p 5, Bet v 1, Cup a 1, Art v 1, Ole e 1, Par j 2, and Phl p 12 (profilin) was measured by using ImmunoCAP. SIT prescription was modeled on SPT responses first and then remodeled considering also CRD according to GA$^2$LEN–European Academy of Allergology and Clinical Immunology guidelines and the opinions of 14 pediatric allergists.**
**Results: No IgE to the respective major allergens was detected in significant proportions of patients with supposed clinically relevant sensitization to mugwort (45/65 [69%]), Betulaceae (146/252 [60%]), pellitory (78/257 [30%]), olive (111/390 [28%]), cypress (28/184 [15%]), and grass (56/568 [10%]). IgE to profilins, polcalcins, or both could justify 173 (37%) of 464 of these SPT reactions. After CRD, the SPT-based decision on SIT prescription or composition was changed in 277 (42%) of 651 or 315 (48%) of 651 children according to the European or American approach, respectively, and in 305 (47%) of 651 children according to the opinion of the 14 local pediatric allergists.**
**Conclusions: In children with pollen-related AR, applying CRD leads to changes in a large proportion of SIT prescriptions as opposed to relying on clinical history and SPT alone. The hypothesis that CRD-guided prescription improves SIT efficacy deserves to be tested. (J Allergy Clin Immunol 2014;■■■:■■■-■■■.)**

***Key words:*** *Allergic rhinitis, children, component-resolved diagnosis, IgE, panallergens, pollen, profilin, specific immunotherapy*

Allergic rhinoconjunctivitis induced by pollens (pollen-related allergic rhinitis [AR]) affects millions of persons globally[1] and is particularly prevalent among children.[2] Allergen-specific immunotherapy (SIT) with pollen extracts can reduce pollen-related AR symptoms and prevent asthma comorbidity and is the only disease-modifying intervention.[3-5] Guidelines state that SIT efficacy requires proper matching of the SIT preparation against the pollen sources causing all or most symptoms in the individual patient.[6] Unfortunately, many patients with pollen allergy are today sensitized to many pollen sources with overlapping seasonality.[7] Moreover, many patients are sensitized to profilin or other highly cross-reacting molecules shared by many unrelated pollen sources and their extracts.[8] Thus the identification of the

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*Abbreviations used*
AR: Allergic rhinitis
ARIA: Allergic Rhinitis and its Impact on Asthma
CRD: Component-resolved diagnosis
EAACI: European Academy of Allergology and Clinical Immunology
SIT: Specific immunotherapy
SPT: Skin prick test

disease-eliciting pollen sources by means of extract-based skin prick tests (SPTs) in patients sensitized to multiple pollens with overlapping seasonality is often difficult.[9]

Measuring levels of IgE antibodies to major allergens makes it possible to decide whether SPT response positivity to a pollen source is "true" or "spurious" (ie, caused by corecognition of highly cross-reacting allergenic molecules).[10] Accordingly, it has been suggested that SIT to a pollen should be prescribed only when serum IgE antibodies to major allergenic molecular components of that pollen are detectable.[11] Hence component-resolved diagnosis (CRD) should make it possible to avoid either the isolated administration of irrelevant allergens or the "dilution" of the relevant ones in an SIT preparation.[12,13] For example, it was proposed that patients with SPT reactivity to grass pollen extracts should receive SIT for grass only in the presence of IgE antibodies to the major allergenic molecules Phl p 1, Phl p 5, or both.[14,15] Similarly, patients with SPT response positivity to the extract of pellitory, mugwort, Betulaceae, or olive should receive SIT only if they have IgE to Par j 2, Art v 1, Bet v 1, and Ole e 1, respectively.[14,15]

International guidelines for SIT still do not incorporate CRD in the diagnostic procedure, leading to SIT prescription.[6,16] To date, only 2 recent studies in adults evaluated whether therapeutic decisions are modified by CRD.[16,17] Moreover, the above-mentioned CRD algorithm has never been systematically tested, and to our knowledge, studies focusing on children are not yet available. Therefore we analyzed the data set of a large population of Italian children with pollen-related AR who had never received SIT[18] to test whether CRD results influence the prescription of SIT modeled according to international guidelines or pragmatically proposed by a pool of 14 pediatric allergists.

## METHODS

### Study population

Panallergens in Pediatrics (PAN-PED) is the first nationwide observational multicenter survey carried out by the Italian Pediatric Allergy Network. The Italian Pediatric Allergy Network is a large group of Italian specialists in pediatric allergy[18-20] created to investigate the effect of sensitization to highly cross-reacting allergenic pollen molecules on the management of respiratory allergies in childhood. Children were enrolled in 16 pediatric outpatient clinics in 14 Italian cities in the Po valley (Milan, Verona, Parma, and Bologna), Central Italy (Empoli and Ascoli Piceno), the Tyrrhenian coast and inlands (Genoa, 4 centers in Rome, Naples, and Benevento), and Southern Italy and islands (Cagliari, Palermo, and Crotone) between May 2009 and June 2011. Criteria for eligibility were (1) age 4 to 18 years; (2) a history of pollen-induced AR, asthma, or both in one of the 2 last pollen seasons; and (3) positive skin prick test (SPT) responses to the relevant pollen extracts. Exclusion criteria were (1) previous SIT for any pollen allergen and (2) any other severe chronic disease. Recruited children's parents answered questionnaires, and patients underwent SPTs (see below) and a blood draw. Parents or tutors of all participants provided informed written consent to clinical investigations. The study design and procedures were approved by the ethics committee of each participating center.

### Questionnaire and diagnostic criteria

Selected questions obtained from the following internationally validated questionnaires were administered to all participants: the International Study of Allergy and Asthma in Childhood,[21] Allergic Rhinitis and its Impact on Asthma (ARIA),[22] and the Global Initiative for Asthma.[23] A diagnosis of pollen-induced AR was made, as previously described,[18] in the presence of (1) nasal, eye, or both symptoms (apart from cold)[21] for at least 3 weeks during one of the 2 last pollen seasons and (2) a positive SPT response (wheal reaction of ≥3 mm) in accordance with clinical history and local pollination period. Pollen-induced AR was classified as mild or moderate to severe, as well as intermittent or persistent according to the ARIA classification.[22] An informatics platform (AllergyCARD; TPS Production, Rome, Italy) was used for data input.

### SPTs

SPTs were performed with a panel of commercial extracts (ALK-Abelló, Milan, Italy), including timothy grass, olive, cypress, mugwort, pellitory, and Betulaceae (birch and/or hazel). Histamine (0.1 mg/mL) and glycerol solution were positive and negative controls, respectively. Morrow-Brown needles were used to prick the skin, and wheal reactions were read after 15 minutes. A wheal of 3 mm or greater (or ≥5 mm when indicated) after subtraction of the negative control was regarded as positive.[24] A hierarchy of relevance was assigned to each of the 6 pollen sources by the locally recruiting doctors. A positive skin reaction was considered clinically relevant if reported symptoms occurred during the peak season of the respective pollen registered during 2001-2010.

### IgE assays

IgEs for allergenic molecules were tested in sera of patients with a wheal reaction of greater than 2 mm elicited by the corresponding allergenic source[18] by using the ImmunoCAP FEIA (TFS, Lund, Sweden). The following major allergenic molecules were selected, as previously suggested: Graminaceae (*Phleum pratense*, Phl p 1 and Phl p 5),[16] Oleaceae (*Olea europaea*, nOle e 1),[16] Cupressaceae (*Cupressus arizonica*, Cup a 1),[25] Betulaceae (*Betula verrucosa*, Bet v 1),[16] Urticaceae (*Parietaria judaica*, Par j 2),[16] and Compositae (*Artemisia vulgaris*, Art v 1).[26] Results were expressed in kilounits per liter and classified as positive if 0.7 kU/L or greater.

### GA²LEN–European Academy of Allergology and Clinical Immunology and alternative prescription models

Prescription of SIT was modeled according to the recently published GA²LEN–European Academy of Allergology and Clinical Immunology (EAACI) pocket guide.[6] Briefly, a subject was eligible for SIT if his or her pollen-related AR symptoms were (1) moderate to severe according to ARIA classification, (2) associated with SPT sensitization to pollen sources against which SIT is effective (timothy grass, birch, mugwort, olive, cypress, and pellitory), and (3) occurring during the local peak of pollen exposure.[6] In the European model, when 4 or more clinically relevant sensitizations were detected, the 3 most relevant allergens were selected on the basis of the opinion of the locally recruiting doctor.[6] Three additional SIT prescription models were taken into account (Table I). In the American model the number of allergenic sources to be mixed was unlimited.[27,28] In the monoallergenic model only the most important allergenic source was allowed,[28,29] and in the monosensitization model only patients with clinically relevant sensitization to 1 pollen source were eligible for SIT. All 4 prescription models described above were applied, again taking CRD into account, as previously proposed,[14] to measure the effect of CRD on SIT prescription. Briefly, SPT sensitization was considered irrelevant for SIT if not confirmed by a positive (≥0.7 kU/L) result to IgE testing to the respective major allergenic protein or proteins.[14]