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Frequency and Patterns of New Allergen Sensitization in Patients with Recurrent Allergic Symptoms During Subcutaneous Allergen Immunotherapy

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ABSTRACT**Background:** Allergen immunotherapy (AIT) remains the sole disease-modifying intervention for allergic respiratory diseases. Nevertheless, symptom recurrence occurs in some patients during therapy, possibly due to new allergen sensitizations.**Objective:** To determine the frequency and patterns of new allergen sensitization among patients with respiratory allergic diseases who experience recurrence of allergic symptoms during subcutaneous allergen immunotherapy (SCIT).**Methodology:** This multicentre observational study was conducted at four healthcare centres in Rawalpindi and Islamabad, Pakistan, from January 2024 to December 2024. The study included 422 patients with allergic rhinitis and/or bronchial asthma who had received SCIT for at least two years and subsequently experienced symptom recurrence following initial improvement. Skin prick testing (SPT) was repeated to identify new sensitization patterns. Data analysis was performed using SPSS version 26.**Results:** Allergic symptom recurrence during SCIT was observed in 22.8% (422/1850) of patients screened. Among those with symptom recurrence, new sensitization was identified in 51.2% (216/422). Pollen sensitization was the most prevalent, occurring in 31.6% of patients, followed by sensitization to house dust mites (18.5%) and molds (12.0%). Most new sensitizations were detected in patients who experienced symptom recurrence during the third year of therapy (45.8%). No statistically significant association was observed between new sensitization and age, sex, diagnosis, or immunotherapy duration.**Conclusion:** New sensitization frequently develops in patients who experience symptom recurrence during SCIT. Repeating SPT to identify evolving sensitization patterns is recommended for these patients, especially for those with symptom recurrence during the third year of therapy.**Keywords:** Allergen Sensitization; New Sensitization; Subcutaneous Immunotherapy; Symptom Recurrence; Allergic Rhinitis; Bronchial Asthma

Introduction

Allergic respiratory diseases, including allergic rhinitis (AR) and allergic bronchial asthma, represent some of the most prevalent chronic conditions worldwide. They significantly affect quality of life, daily functioning, and healthcare utilization. These diseases arise from abnormal immune responses to common environmental allergens such as pollens, house dust mites, molds, and animal dander, influenced by both genetic and environmental factors. Allergic rhinitis is particularly widespread and is generally managed through allergen avoidance, pharmacotherapy, and, when appropriate, allergen immunotherapy (AIT).^{1,2} Allergen immunotherapy is distinct among treatment modalities because it can alter the underlying immune response rather than merely controlling symptoms. AIT is particularly indicated for patients with allergic rhinitis or asthma whose symptoms persist despite standard therapies.³ Subcutaneous allergen immunotherapy (SCIT), a widely used form of AIT, involves administering repeated doses of allergen extracts to induce and maintain immune tolerance. This approach can reduce both symptoms and medication requirements, with benefits that may persist after cessation of therapy.^{4,5} Both subcutaneous and sublingual forms of AIT have demonstrated efficacy for respiratory allergens, including pollens and house dust mites.^{6,7} SCIT remains a key option for patients with well-defined allergen triggers who are able to adhere to long-term therapy. However, patient responses vary; some individuals experience sustained improvement, while others achieve only partial benefit or encounter symptom recurrence. Outcomes are influenced by factors such as treatment adherence, relevance of the targeted allergen, duration of therapy, and individual biological differences.^{6,8} Recurrence of allergic symptoms during SCIT is clinically significant and may result from inadequate therapeutic response, suboptimal adherence, environmental changes, disease progression, or the development of new sensitizations. Therefore, symptom recurrence does not necessarily indicate SCIT failure. A thorough reassessment of the patient's clinical history and sensitization profile is recommended, and immunotherapy should continue to target clinically relevant, confirmed allergens.⁹ A key but less understood issue is whether new allergen sensitizations can develop during or after AIT. While AIT is thought to reduce the risk of new sensitizations, evidence is mixed. A 2021 study in children found some differences in new sensitization rates between AIT and control groups, but the protective effect was not consistent after adjusting for other factors.¹⁰ This suggests the relationship is complex and may depend on patient age, disease, allergen exposure, and treatment details. It is important to note that new sensitizations may develop over time as a result of changing environmental

exposures and individual susceptibility, rather than as a direct consequence of immunotherapy. Some studies have documented new sensitizations during SCIT, whereas other research suggests that AIT may reduce this risk.^{5,10,11} The overall impact of AIT on new sensitization remains uncertain. This issue is particularly relevant for patients who initially respond to SCIT but subsequently experience symptom recurrence. The development of new sensitizations may render previously negative allergens clinically significant. Therefore, reassessment of sensitization status can offer valuable insights for the management of recurrent symptoms.

Skin-prick testing (SPT) is a standard method for assessing sensitization to aeroallergens. Comparing baseline and follow-up SPT results can identify new sensitizations, particularly when consistent allergen panels are used. However, these results should always be interpreted in conjunction with clinical symptoms and exposure history.^{6,9}

Evolving sensitization patterns have significant implications for clinical management. Patients undergoing SCIT may be exposed to new allergens over time as a result of changes in environment, lifestyle, or geographic location, which increases the likelihood that the allergen profile at the time of symptom recurrence will differ from baseline. Despite growing awareness, there is limited data on how often and in what patterns new sensitizations develop in patients with recurrent symptoms during SCIT. Most research has focused on prevention, not on those who relapse after initial improvement, and often involves small samples or limited allergen panels. This leaves a knowledge gap in real-world settings. For this reason, this study was planned to conduct to evaluate the development of new allergen sensitizations in patients with allergic rhinitis or asthma who received SCIT for a minimum of two years, demonstrated initial improvement, and subsequently experienced recurrent symptoms. The rationale for this study is to elucidate the reasons underlying recurrence of allergic symptoms in patients undergoing SCIT. Identifying new sensitizations may explain these relapses and support more individualized follow-up and allergen testing during extended immunotherapy.

Objective

To determine the frequency and patterns of new allergen sensitization among patients with respiratory allergic diseases who experience recurrence of allergic symptoms during subcutaneous allergen immunotherapy (SCIT).

Methodology

This multicentre observational study was conducted at four allergy and respiratory medicine centres in

Rawalpindi and Islamabad, Pakistan, from January 2024 to December 2024. This study included patients with respiratory allergic diseases, such as allergic rhinitis (with or without conjunctivitis) and/or allergic bronchial asthma, who were receiving subcutaneous allergen immunotherapy (SCIT) at participating centres. Inclusion criteria required a minimum of two years of SCIT, initial clinical improvement, and subsequent recurrence of allergic respiratory symptoms. The primary objective was to determine whether symptom recurrence was associated with the development of sensitization to new allergens not present prior to SCIT. Eligible patients were consecutively recruited from participating centres throughout the study period.

The sample size was calculated based on the primary outcome, which was the detection of new allergen sensitization among patients experiencing recurrent allergic symptoms during SCIT. Using a previously reported new sensitization rate of 56.2%, a 95% confidence level, and 5% absolute precision, the required sample size was determined to be 379 patients. To account for an anticipated 10% rate of incomplete or missing data, the target sample size was increased to 422 participants. Eligible patients were consecutively recruited from participating centres until the target was achieved.

Participants aged 6 years or older with a diagnosis of allergic rhinitis and/or allergic bronchial asthma who had received subcutaneous immunotherapy (SCIT) for at least two years were included if they experienced recurrence of previously controlled allergic respiratory symptoms during therapy. The precise duration of SCIT was recorded for each participant, rather than limiting inclusion to those with exactly two years of treatment. Clinical records were reviewed to determine the indication for SCIT, baseline sensitization profile, treatment adherence, initial response, timing and type of recurrence, and repeat sensitization results. At enrollment, standardized assessments collected data on allergic diagnosis, disease duration, SCIT regimen, adherence, initial response, and recurrence, with confirmation through clinical records or patient interviews. Initial improvement was defined as a documented reduction in allergic symptoms following initiation of SCIT. Recurrence was defined as the reappearance or worsening of previously controlled symptoms during SCIT, including sneezing, nasal itching, rhinorrhea, nasal obstruction, cough, wheezing, and dyspnea. Symptom scores or standardized clinical assessments before and after SCIT were reviewed when available. SCIT duration was calculated from therapy initiation to repeat assessment or enrollment. Adherence was assessed using immunotherapy records, including documentation of injections, missed visits, interruptions, and reasons for interruptions. Patients with significant treatment interruptions that affected response assessment were excluded. The type and composition of SCIT,

including the specific allergens in the formulation, were also recorded to facilitate interpretation of new sensitizations relative to the original regimen.

The baseline or pre-subcutaneous immunotherapy (SCIT) allergen sensitization profile was obtained from patients' medical records. Baseline sensitization was primarily determined by skin-prick testing (SPT) conducted prior to SCIT initiation. The baseline assessment identified specific allergens to which each patient was sensitized, as well as those eliciting negative responses before immunotherapy. If baseline SPT results were unavailable, we used a previously documented, valid allergen-specific sensitization assessment performed before SCIT initiation that provided sufficient data for comparison with repeat assessments. Patients lacking a reliable baseline sensitization profile were excluded, as new sensitizations could not be established without knowledge of pre-immunotherapy sensitization status.

After recurrence of allergic respiratory symptoms, participants underwent repeat allergen sensitization assessment, preferably by SPT, following the standard protocol of the participating allergy center. Testing utilized standardized commercial allergen extracts selected based on the local aeroallergen profile and each patient's clinical history. The allergen panel was maintained as consistently as possible between baseline and repeat testing to enable direct comparison. The panel included clinically relevant aeroallergens, such as house dust mites, pollens, molds, animal dander, and other locally significant environmental allergens. Each SPT session included a negative control (appropriate diluent) and a positive control (typically histamine) to confirm test validity. Testing was conducted on the volar aspect of the forearm or another standard anatomical site, with individual allergens spaced to prevent reaction overlap.

Trained personnel conducted the SPT using standardized procedures. After application of allergen extracts and controls, the skin was punctured with sterile, single-use lancets. Test reactions were evaluated after the designated waiting period, following the manufacturer's instructions and institutional protocol. The largest wheal diameter and its perpendicular diameter were measured, and the mean wheal diameter was recorded. A test was considered positive if the wheal response met the predefined laboratory or kit-specific positivity criterion compared to the negative control, with an adequate positive-control response. The same interpretation criteria were consistently applied to both baseline and repeat assessments when corresponding data were available. Participants taking medications that could interfere with SPT interpretation were managed according to standard clinical practice, and testing was postponed until an adequate medication washout period had been achieved, when clinically appropriate.

The pattern of newly developed sensitization was evaluated by comparing each participant's baseline and follow-up sensitization profiles. Participants were

classified as having either no new sensitization or at least one new sensitization. For those with new sensitization, both the total number and specific types of newly positive allergens were documented. When sufficient data were available, new sensitization was further classified by whether the newly detected allergen was biologically or clinically related to the participant's original sensitization profile and whether it was included in the SCIT formulation. The distribution of mono-sensitization and polysensitization patterns was also characterized. This methodology enabled assessment of both the frequency and specific patterns of new sensitization emerging during SCIT.

Data were collected using a standardized, structured data collection form. Demographic variables comprised age and sex. Clinical variables encompassed allergic diagnosis, duration of allergic disease, history of allergic conjunctivitis, asthma status, baseline allergic manifestations, and characteristics of recurrent symptoms. Immunotherapy-related variables included subcutaneous immunotherapy (SCIT) duration, allergen extract type and composition, treatment adherence, treatment interruptions, and documented initial clinical response. Sensitization-related variables included baseline allergen sensitization, repeat sensitization results, the number of newly detected allergens, the specific newly sensitized allergens, and whether the newly identified allergen was included in the original SCIT formulation. The intervals

between initiation of SCIT, initial clinical improvement, symptom recurrence, and repeat sensitization testing were also recorded when available.

Potential factors influencing the development or detection of new sensitization were evaluated during the analysis. These factors included age, sex, allergic diagnosis, duration of allergic disease, duration of subcutaneous immunotherapy (SCIT), adherence to immunotherapy, baseline number of sensitized allergens, initial allergen sensitization pattern, type of allergens included in SCIT, environmental exposure, and the interval between baseline and repeat sensitization testing. Relevant comorbid allergic conditions and changes in environmental or occupational exposure were documented when such information was available.

Data analysis was conducted using SPSS version 26. Continuous variables were evaluated for distribution and reported as mean $\pm$ standard deviation for normally distributed data or as median with interquartile range for non-normally distributed data. Categorical variables were summarized as frequencies and percentages. Patterns and types of newly detected allergens were also described using frequencies and percentages.

Comparisons between participants with and without new allergen sensitization were performed using the independent-samples t test or Mann-Whitney U test for continuous variables, depending on data distribution, and the chi-square test or Fisher's exact test for categorical

Table 1. Characteristics of the study participants

Parameter	Frequency (%)
Sex	
Male	169 (40.0)
Female	253 (60.0)
Age (years)	
Median (min–max)	31 (5–64)
Diagnosis	
Allergic Rhinitis (AR)	138 (32.7)
Bronchial Asthma (BA)	170 (40.3)
AR and BA	114 (27.0)
Duration of treatment (years)	
Median (min–max)	3 (2–9)

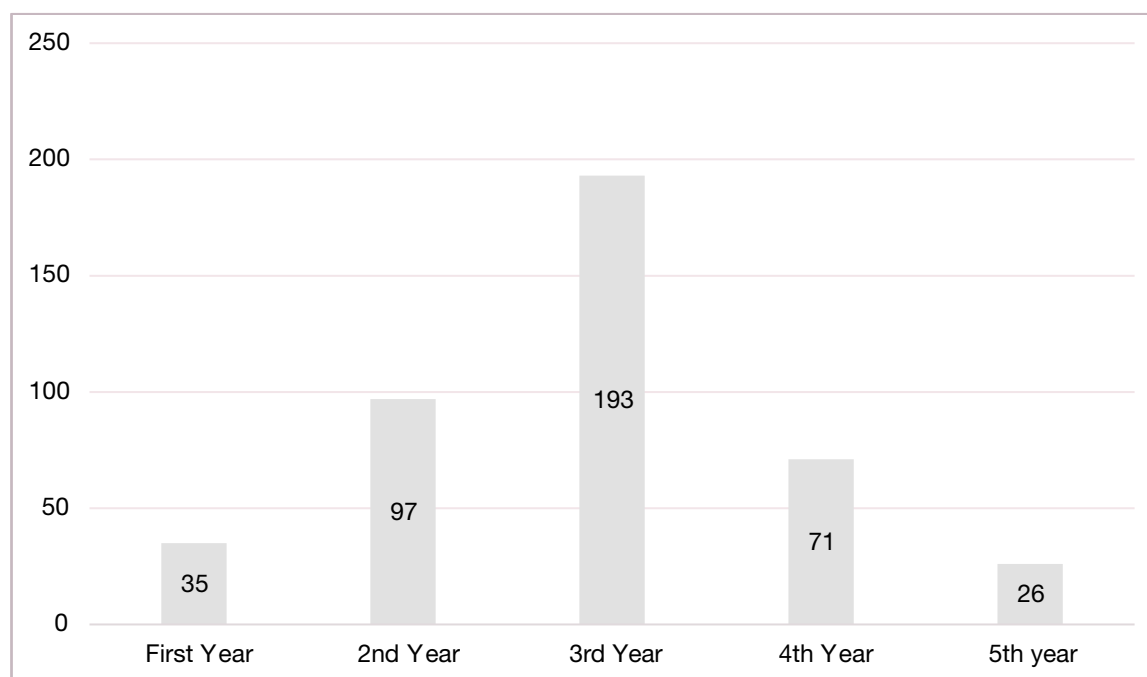


Figure 1. Onset of symptom recurrence during SCIT (n = 422)

variables. Associations between the number or type of newly developed sensitizations and clinically relevant factors, including age, sex, allergic diagnosis, duration of subcutaneous immunotherapy (SCIT), baseline number of sensitized allergens, and treatment adherence, were initially evaluated using univariate analyses. Variables showing clinically relevant associations or meeting a predefined significance threshold in univariate analysis were subsequently included in a multivariable logistic regression model to identify independent predictors of new allergen sensitization. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were reported. Statistical significance was defined as a two-sided p value less than 0.05.

Ethical approval (IRB/PIMS/37/23) was granted by the institutional review boards of the Pakistan Institute of Medical Sciences. Written informed consent was secured from participants or their legally authorized representatives, as appropriate, especially for prospective repeat testing and the collection of clinical information.

Results

A total of 1,850 patients with allergic airway diseases who received subcutaneous allergen immunotherapy (SCIT) were screened at four participating centres in Rawalpindi and Islamabad. Among these, 422 patients (22.8%) experienced a recurrence of allergic symptoms following initial improvement during SCIT and were included in the final analysis. Of the 422 patients with symptom

recurrence, 253 (60.0%) were female, and 169 (40.0%) were male. The median age was 31 years (range: 5–64 years). By diagnosis, 138 patients (32.7%) had allergic rhinitis (AR) alone, 170 (40.3%) had bronchial asthma (BA) alone, and 114 (27.0%) had both AR and BA. The median duration of SCIT was 3 years (range: 2–9 years) (Table 1). Recurrence was most common in the third year of SCIT, affecting 45.8%. Recurrence occurred in 97 patients (23.0%) during the second year and in 71 patients (16.8%) during the fourth year. Fewer patients experienced recurrence in the first year (35 patients, 8.3%) and the fifth year (26 patients, 6.2%) of therapy (Figure 1).

Of the 422 patients with recurrent symptoms, 216 (51.2%) demonstrated new sensitization. The other 206 patients (48.8%) exhibited no evidence of new sensitization on repeat skin prick testing (SPT) (Figure 2).

Pollen sensitization represented the most frequently detected new sensitization, identified in 133 (31.6%) of patients. Specifically, pollen 1 sensitization, which includes *Chenopodium album*, *Conyza*, and *Tamarix aphylla*, was observed in 75 (17.8%). In contrast, pollen 2 sensitization, comprising *Polypogon monspeliensis*, *Cynodon dactylon*, and *Arundo donax*, was detected in 58 (13.8%). House dust mite sensitization was the second most common new sensitization, identified in 78 (18.5%) of patients. Straw sensitization occurred in 65 (15.4%), and hay dust sensitization was detected in 58 (13.7%). Mould sensitization was present in 12.0% of patients, with *Aspergillus* species, *Alternaria alternata*, and *Candida albicans* representing the most prevalent mould

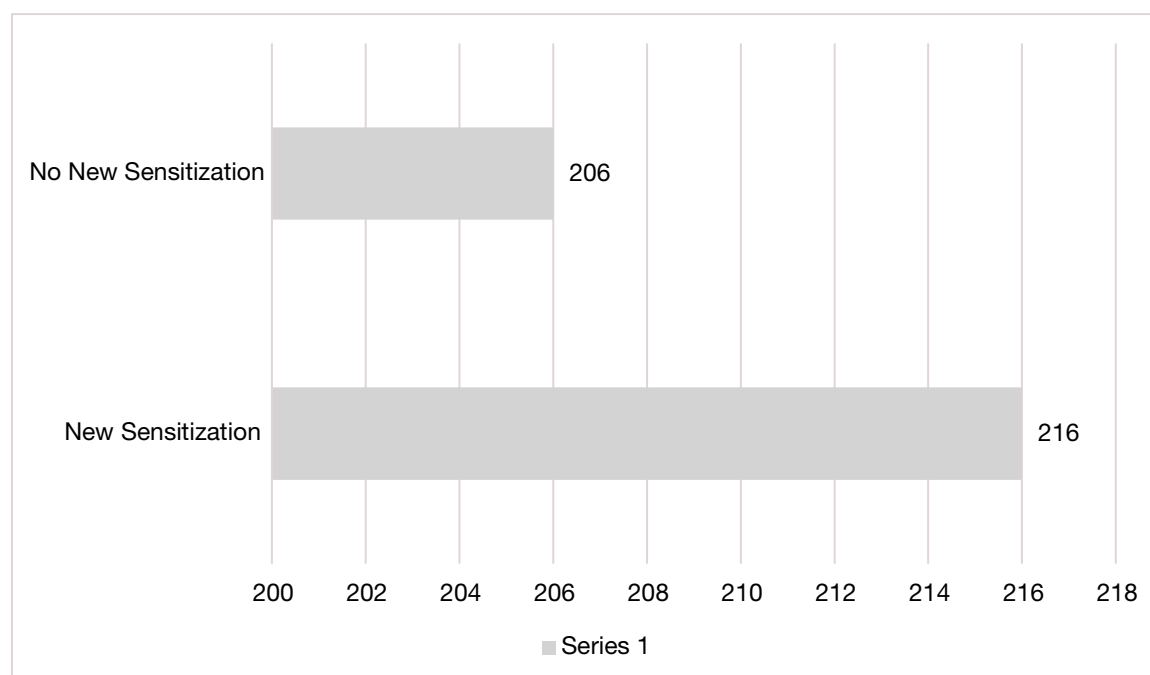


Figure 2. Proportion of patients with new sensitization (n = 422)

allergens. Animal dander sensitization was observed, with cat hair sensitization in 44 (10.4%) patients, followed by goat hair and dog hair. Pigeon feather sensitization was the least common, detected in 11 (2.6%) of patients (Table 2; Figure 3).

The majority of new pollen sensitizations occurred in patients with symptom recurrence during the third year of therapy. Among the 193 patients with third-year recurrence, pollen 1 sensitization was identified in 26.9% (n=52), and pollen 2 sensitization in 20.7% (n=40). Straw sensitization was also most prevalent in the third year, affecting 22.8% (n=44) of these patients. House dust mite sensitization was most frequently observed in patients with symptom recurrence during the second year (12.4%, n=12) and the third year (14.0%, n=27). Mould sensitization demonstrated a comparable pattern, with higher frequencies in the second (10.3%, n=10) and third (12.4%, n=24) years.

Although no statistically significant differences were observed in the distribution of specific allergen sensitizations across the years of recurrence onset (all $p > 0.05$), a trend toward higher frequencies of pollen and straw sensitizations was evident among patients with symptom recurrence in the third year of therapy (Table 3; Figure 4). Among the 216 patients with new sensitization, 60.6% were female and 39.4% were male. The gender distribution in the group without new sensitization (n=206) was comparable. The median ages in the two groups were 30 and 33 years, respectively, with no significant difference observed. The distribution of diagnoses (AR,

BA, or both), change of residence, and median duration of subcutaneous immunotherapy (SCIT) were also comparable between groups. None of these factors demonstrated a statistically significant association with new sensitization (Table 4).

A multivariable logistic regression analysis was conducted to identify independent predictors of new sensitization among patients experiencing symptom recurrence. The model included age, sex, diagnosis, duration of subcutaneous immunotherapy (SCIT), and change in residence as variables. None of these variables showed statistically significant independent associations with the development of new sensitization (Table 5).

Discussion

This multicentre observational study evaluated the development of new allergen sensitizations among patients with recurrent allergic respiratory symptoms during subcutaneous allergen immunotherapy (SCIT). Among 1,850 SCIT patients across four centres, 422 (22.8%) experienced symptom recurrence following initial improvement. Repeat allergen testing revealed that 216 of these patients (51.2%) developed at least one new sensitization, most frequently to pollens, followed by house dust mites, straw, hay dust, and molds. These findings suggest that recurrence during SCIT is often associated with new sensitizations rather than solely a loss of the original therapeutic response. The 22.8% recurrence rate is clinically significant and underscores

Table 2. New sensitization patterns in patients with symptom recurrence (n = 422)

Parameter	Frequency (%)
Allergens*	
Mould	51 (12.0)
Pollens (pollen 1 and pollen 2)	133 (31.6)
Pollen 1	75 (17.8)
Pollen 2	58 (13.8)
Hay dust	58 (13.7)
Cotton pollen	33 (7.8)
Barely	22 (5.2)
Pigeon feather	11 (2.6)
Dog hair	20 (4.7)
House dust mite	78 (18.5)
Wheat	27 (6.4)
Cat hair	44 (10.4)
Straw	65 (15.4)
Goat hair	35 (8.3)
New sensitization (overall)	216 (51.2)

*Groups are not mutually exclusive; patients may have multiple new sensitizations.

the variability in SCIT effectiveness among patients. Previous research has established SCIT's disease-modifying potential, although individual responses may fluctuate over time.^{11,12} The present study specifically examined patients who initially improved and subsequently relapsed, which differs from prior investigations. Therefore, the observed recurrence rate pertains to those with secondary symptoms rather than representing overall SCIT failure. These results highlight the importance of individualized management and continuous monitoring during long-term SCIT.

In this study, 51.2% of patients with recurrent symptoms developed at least one new allergen sensitization on repeat testing, which is higher than the 24% reported by Gellrich et al.¹³ This discrepancy likely results from methodological differences: Gellrich et al. employed

molecular allergen-component testing focused on SCIT-related components, whereas the present study utilized repeat skin-prick testing for a broader range of allergens. Additionally, the current analysis focused on patients with recurrent symptoms, while Gellrich et al. included all patients before and after SCIT. Therefore, the higher frequency observed may reflect clinical enrichment for individuals more likely to develop new sensitizations.

These findings contribute to the ongoing debate regarding the ability of allergen immunotherapy (AIT) to prevent new sensitizations. Çekiç et al. reported no significant difference in overall new sensitization rates between immunotherapy and control groups, although immunotherapy reduced new tree- and weed-pollen sensitizations in certain cases.¹⁰ This indicates that the effect of AIT is complex and not uniformly protective.

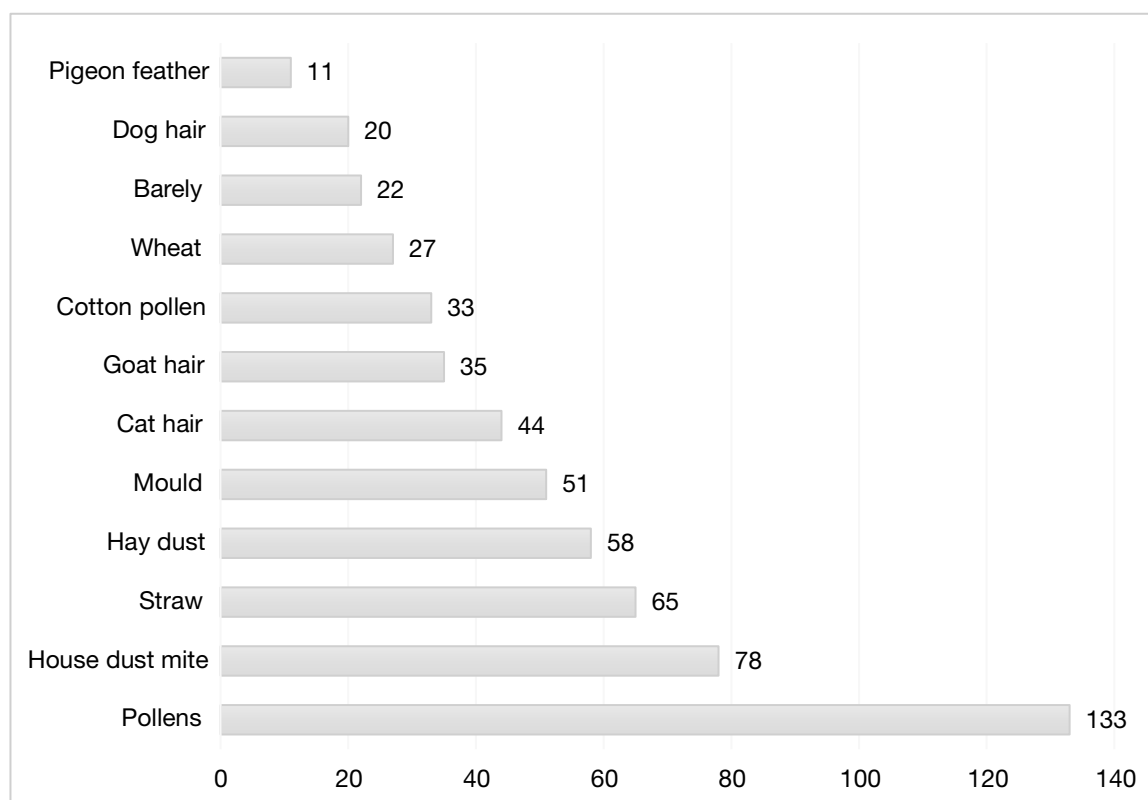


Figure 3. Overall distribution of newly identified allergen sensitizations among patients with recurrent allergic symptoms during subcutaneous allergen immunotherapy (n = 422). Categories were not mutually exclusive; therefore, patients could have sensitization to more than one allergen

Similarly, new sensitizations were observed during prolonged SCIT among patients with recurrent symptoms; however, in the absence of a control group, it is not possible to determine whether SCIT alters the risk of new sensitization.

Pollen was the most frequently newly detected allergen in this study, identified in 31.6% of participants. Sensitizations to pollen 1 and pollen 2 were observed in 17.8% and 13.8% of participants, respectively. These findings are consistent with the results of Ükrü et al., who also reported pollen sensitization as a common new sensitization, particularly to tree and weed pollens.¹⁰ Although there are differences in study design, participant age, and geographic focus, the predominance of pollen sensitization is a consistent finding across studies. The high frequency of pollen sensitization may be attributed to environmental exposure, seasonal variation, and local aerobiological factors. Patients may develop sensitivity to pollens not included in their initial subcutaneous immunotherapy (SCIT) formulation.¹⁴ Current recommendations emphasize tailoring immunotherapy to clinically relevant and region-specific allergens; therefore, new pollen sensitization may result from exposure to additional environmental allergens rather than from

immunotherapy failure. House dust mite (HDM) was the second most common new sensitization, detected in 18.5% of patients. HDM is a major perennial aeroallergen and is frequently targeted by SCIT, with evidence supporting its efficacy in allergic rhinitis and asthma.¹⁵ The development of HDM sensitization in previously negative patients indicates evolving sensitization profiles and highlights the need for ongoing monitoring and adjustment of immunotherapy formulations.

Straw (15.4%) and hay-dust (13.7%) sensitization were relatively common, particularly among individuals with agricultural, rural, or occupational exposure. However, this study did not identify a significant association between residential relocation and the development of new sensitizations. Environmental and occupational exposures are heterogeneous, and repeated contact with previously unrecognized allergens may contribute to the emergence of new sensitizations. Therefore, regularly updating environmental and occupational histories is essential for subcutaneous immunotherapy (SCIT) patients who experience recurrent symptoms. Mold sensitization was observed in 12.0% of patients. Gellrich et al. reported that SCIT can modify sensitization profiles to multiple allergen components, and the complexity of

Table 3. New sensitization patterns in relation to recurrence onset (n = 422)

Parameter	1st Year (n=35)	2nd Year (n=97)	3rd Year (n=193)	4th Year (n=71)	5th Year (n=26)	Significance*
Mould	2 (5.7%)	10 (10.3%)	24 (12.4%)	11 (15.5%)	4 (15.4%)	χ^2 : 4.2, p: 0.4
Pollen 1	5 (14.3%)	13 (13.4%)	52 (26.9%)	3 (4.2%)	2 (7.7%)	χ^2 : 9.8, p: 0.06
Pollen 2	3 (8.6%)	10 (10.3%)	40 (20.7%)	3 (4.2%)	2 (7.7%)	χ^2 : 8.4, p: 0.08
Hay dust	3 (8.6%)	11 (11.3%)	31 (16.1%)	9 (12.7%)	4 (15.4%)	χ^2 : 5.6, p: 0.3
Cotton pollen	2 (5.7%)	8 (8.2%)	12 (6.2%)	8 (11.3%)	3 (11.5%)	χ^2 : 4.1, p: 0.4
Barely	1 (2.9%)	5 (5.2%)	9 (4.7%)	5 (7.0%)	2 (7.7%)	χ^2 : 3.2, p: 0.5
Straw	4 (11.4%)	12 (12.4%)	44 (22.8%)	3 (4.2%)	2 (7.7%)	χ^2 : 7.2, p: 0.1
House dust mite	4 (11.4%)	12 (12.4%)	27 (14.0%)	23 (32.4%)	12 (46.2%)	χ^2 : 6.4, p: 0.2

* χ^2 test used; groups are not mutually exclusive.

allergen extracts complicates prediction.¹³ The present findings extend these observations to a broader range of environmental allergens. It remains unclear whether new mold sensitization represents a truly new occurrence, a previously undetected sensitization, or increased exposure. Additional animal dander sensitizations were

identified, including cat (10.4%), goat (8.3%), and dog (4.7%) hair, highlighting the evolving diversity of sensitization patterns over time. Current allergen immunotherapy (AIT) guidelines recommend targeting only clinically relevant allergens rather than all positive test results.¹⁴ New positive skin prick tests (SPTs) should

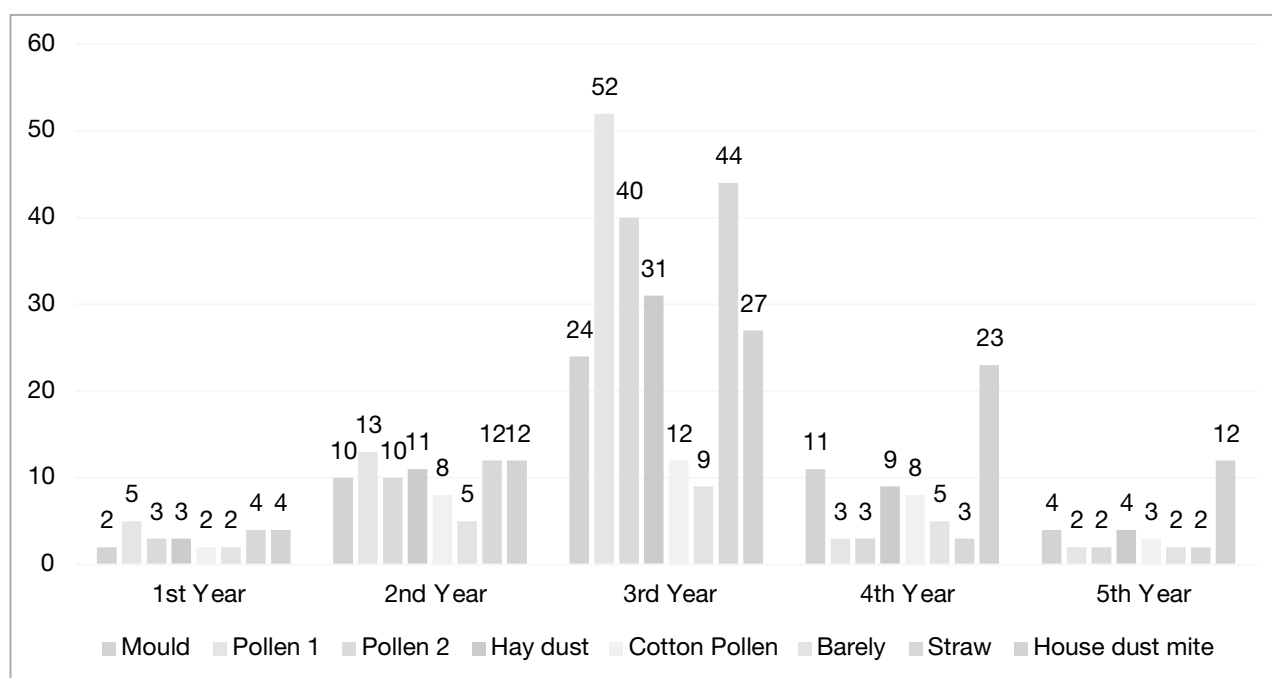


Figure 4. New sensitization patterns in relation to onset of symptom recurrence

be interpreted in the context of clinical symptoms and exposure history before modifying immunotherapy regimens.

A key finding was the temporal pattern of symptom recurrence, with the highest proportion observed in the third year of SCIT (193 patients, 45.8%). New pollen and straw sensitizations were most frequent in this group; however, year-to-year differences were not statistically significant. Although third-year recurrence demonstrates a notable trend, it does not represent a statistically confirmed increase in sensitization over time. The predominance of recurrence in the third year may be clinically relevant, given that SCIT is typically administered for 3 to 5 years to achieve sustained benefits.^{11,14} Recurrence during the third year should prompt a review of treatment response, adherence, environmental exposures, and allergen relevance. Liu et al. reported that the three-year response is associated with earlier outcomes, emphasizing the third year as a critical point for assessing long-term effectiveness.¹² These results

differ from those of Şükrü et al., who evaluated whether immunotherapy prevented new sensitization over time, rather than its emergence at the point of recurrence.¹⁰ This distinction likely results from the present study's focus on patients with clinical recurrence, which enables targeted analysis of recurrence timing and sensitization patterns.

In this study, new sensitization was not significantly associated with age. The median age of patients with new sensitization was 30 years, compared to 33 years among those without new sensitization ($p=0.4$). Similarly, sex was not significantly associated with new sensitization; females accounted for 60.6% of patients with new sensitization and 59.2% of those without new sensitization ($p=0.7$). These results suggest that demographic characteristics did not account for the development of new sensitization in this cohort. This finding aligns with the results of Gellrich et al., who did not identify a clear clinical predictor of de novo sensitization during SCIT.¹³ Their study also indicated that demographic and clinical characteristics alone may not reliably identify patients

Table 4. New sensitization in relation to patient parameters (n = 422)

Parameter	Absence of New Sensitization (n=206)	Presence of New Sensitization (n=216)	Significance
Gender			
Male	84 (40.8%)	85 (39.4%)	χ^2 : 0.12, p: 0.7*
Female	122 (59.2%)	131 (60.6%)	
Age (years)			
Median (min-max)	33 (6–64)	30 (5–62)	Z: -0.8, p: 0.4†
Diagnosis			
AR	69 (33.5%)	69 (31.9%)	χ^2 : 0.6, p: 0.7‡
BA	84 (40.8%)	86 (39.8%)	
AR and BA	53 (25.7%)	61 (28.2%)	
Change in residence			
No	178 (86.4%)	185 (85.6%)	χ^2 : 0.08, p: 0.8*
Yes	28 (13.6%)	31 (14.4%)	
Duration of immunotherapy (years)			
Median (min-max)	3 (2–9)	3 (2–8)	Z: -0.5, p: 0.6†

*Fisher's Exact test used; †Mann-Whitney U Test used; ‡ χ^2 test used.

Table 5. Multivariable logistic regression analysis for predictors of new sensitization

Variable	Adjusted Odds Ratio	95% Confidence Interval	p-value
Age (per year increase)	0.98	0.96–1.01	0.3
Sex (Female vs. Male)	1.08	0.72–1.62	0.7
Diagnosis (AR vs. BA)	0.92	0.56–1.51	0.7
Diagnosis (AR+BA vs. BA)	1.15	0.68–1.94	0.6
Duration of SCIT (per year increase)	1.04	0.93–1.17	0.5
Change in residence (Yes vs. No)	1.12	0.62–2.04	0.7

who develop new sensitization. The lack of a significant association with age or sex in the present study supports the hypothesis that environmental exposure, baseline sensitization profile, allergen composition, and individual immunological factors may play a more substantial role.

No significant association was observed between underlying diagnosis and new sensitization. The proportions of allergic rhinitis, bronchial asthma, or both among patients with and without new sensitization were similar ($p=0.7$). Multivariable analysis confirmed the absence of an independent association. This finding contrasts with the results of Şükrü et al., who reported that asthma increased the risk of new sensitization in children.¹⁰ The discrepancy may be attributable to differences in age range, study population, allergen exposure, or outcome definitions. Additionally, the present cohort included patients with recurrence during SCIT, which may have influenced this relationship.

The median duration of SCIT was three years in both groups, with no significant difference in new sensitization rates ($p=0.6$). Multivariable analysis confirmed no independent association between treatment duration and new sensitization (adjusted OR 1.04, 95% CI 0.93–1.17; $p=0.5$). These findings are consistent with Gellrich et al.,¹³ who reported 24% de novo sensitization after a median of 2.8 years of SCIT but found no evidence that longer treatment independently causes sensitization. Therefore, SCIT duration alone does not account for new sensitization. Current evidence supports individualized treatment courses of approximately three years or longer to achieve sustained benefit.^{14,16}

Only 14.4% of patients with new sensitization and 13.6% of those without reported a change of residence, with no significant association between residence change and new sensitization ($p=0.8$). Although environmental changes may alter aeroallergen exposure, residence change is a crude measure that does not account for other relevant factors. Therefore, the lack of association should not diminish the importance of comprehensive

environmental assessment. Current AIT guidance and these findings, which highlight pollen, straw, and hay-dust sensitization, emphasize the need for individualized and detailed environmental evaluation when selecting allergens and managing recurrent symptoms.¹⁴

A principal strength of this study is the concurrent evaluation of demographic and clinical predictors through multivariable logistic regression. None of the variables assessed, including age, sex, diagnosis, duration of subcutaneous immunotherapy (SCIT), or change in residence, demonstrated an independent association with new sensitization. Adjusted odds ratios for all variables approximated 1 and were not statistically significant. These results are consistent with the findings of Gellrich et al., who also identified no definitive clinical predictor of de novo sensitization,¹³ whereas Şükrü et al. reported associations with asthma and weed-pollen sensitization.¹⁰ These discrepancies suggest that predictors of sensitization changes may be specific to particular populations and influenced by methodological differences, allergen panels, and definitional criteria.

The findings indicate that changes in allergen sensitization frequently occur among patients experiencing recurrent respiratory allergic symptoms during extended SCIT. More than half of those with recurrence developed at least one new sensitization, most commonly to pollens, which is consistent with previous studies,^{10,13} although the frequency observed in this study was higher. Demographic factors, diagnosis, treatment duration, and change in residence were not independent predictors of new sensitization. These results support the need for individualized reassessment, including environmental evaluation and repeat allergen testing, rather than presuming that recurrence signifies immunotherapy failure.

Clinical implications

These findings underscore the importance of reassessing

allergen sensitization in patients undergoing prolonged subcutaneous immunotherapy (SCIT) who experience recurrent symptoms, particularly in the context of changing environmental exposures.^{14,17} More than half of these patients in the present study demonstrated new positive test results; however, recurrence does not necessarily indicate treatment failure. Adjustments to SCIT should be considered only when new sensitizations are clinically relevant, as a positive skin prick test (SPT) does not always confirm allergy, particularly in polysensitized individuals.

Strengths

This research possesses several notable strengths. The large multicentre design (1,850 patients across four centers) enabled a focused investigation of recurrent allergic respiratory symptoms during subcutaneous immunotherapy (SCIT). The study assessed several allergen sensitizations and used multivariable analysis to identify independent demographic and clinical associations. Evaluating long-term SCIT treatment increases the real-world applicability of the findings. Consideration of multiple environmental allergens provides clinically relevant information for patient reassessment. Collectively, the study addresses a significant and understudied issue in allergy management, supporting clinicians in treating recurrent respiratory allergy during immunotherapy.

Limitations

This study has several limitations to consider when interpreting its findings. This observational study cannot establish causality, as it lacks a non-SCIT control group. Selection bias exists because we included only patients with recurrent symptoms during SCIT. Testing identified new sensitizations, but their clinical relevance is uncertain without symptom correlation. Incomplete environmental exposure data may have affected the results. Further prospective studies with control groups and detailed exposure assessment are needed to clarify SCIT's impact on new sensitization.

Conclusion

This study showed that new allergen sensitization frequently occurred among patients who experienced recurrent allergic respiratory symptoms during ongoing subcutaneous allergen immunotherapy (SCIT). Over half of these patients had at least one detected sensitization, with pollens being the most prevalent, followed by dust mites, straw, hay dust, and molds. Age, sex, underlying allergic diagnosis, SCIT duration, and change of residence were not significantly associated with new

sensitization. These results indicate that symptom recurrence during prolonged SCIT should not be automatically interpreted as treatment failure. Reassessing clinical history, environmental exposures, and allergen sensitization profiles may help identify newly relevant allergens and inform individualized management strategies. Additional prospective studies with appropriate non-immunotherapy control groups are required to elucidate the natural course of new sensitization and to determine whether SCIT exerts any protective or modifying effects on its development.

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