Local allergic rhinitis in children: identification and characterization in a specialty outpatient clinic

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ABSTRACT

Background: Local Allergic Rhinitis (LAR) is a phenotype defined by rhinitis symptoms with negative responses to systemic sensitization tests but with an exclusively nasal allergic inflammatory response. Data on the pediatric age group is scarce, and no Latin American data has been published so far.

Methods: Nasal Allergen Challenge (NAC) was performed with *Dermatophagoides pteronyssinus* and *Blomia tropicalis* in six- to 18-year-old patients diagnosed with rhinitis and no systemic sensitization. NAC was monitored using subjective parameters and acoustic rhinometry. The study aimed to identify LAR in child and adolescent subjects previously diagnosed with non-allergic rhinitis (NAR) in a Brazilian specialty outpatient clinic (Allergy and Immunology).

Results: During the study period, we analyzed 758 skin prick tests (SPT). Of those, 517 (68.2%) were diagnosed with rhinitis. Among those, 18.4% (95/517) had a negative SPT, meeting the criteria for inclusion in the study. Twenty-five patients underwent NAC, and 40% (10/25) of them, previously considered to have NAR, had a positive test and were reclassified as having LAR. Based on the analyzed characteristics, clinically differentiating LAR from NAR was impossible.

Conclusion: This study represents the first investigation of LAR in child and adolescent subjects in Latin America, contributing significantly to the understanding of its prevalence and characteristics in this geographic area. Among a subgroup of patients lacking systemic sensitization submitted to NAC, 40% (10/25) demonstrated a positive NAC with *Dermatophagoides pteronyssinus* and *Blomia tropicalis*, warranting their reclassification to LAR. NAC with multiple allergens has been proven safe and viable in pediatric populations, affirming its critical role in the accurate diagnosis of LAR.

KEYWORDS

Rhinitis, acoustic rhinometry, nasal allergen challenge, house dust mite, children, child

IMPACT STATEMENT:

This is the first study to investigate LAR in child and adolescent subjects in Latin America, contributing to the understanding of its prevalence and characteristics in this geographic area.

INTRODUCTION

Rhinitis is defined as inflammation of the nasal mucosa, characterized by one or more of the following symptoms: nasal congestion, rhinorrhea, sneezing, nasal pruritus, and hyposmia (1).

Patients with chronic rhinitis are primarily classified into two main groups: allergic rhinitis (AR) and non-allergic rhinitis (NAR) (2). However, over the past decades, studies have indicated that numerous patients with rhinitis, despite negative responses to systemic sensitization tests, exhibit an exclusively nasal allergic inflammatory response (3). This response has been corroborated through Nasal Allergen Challenge (NAC) with

pollens and/or house dust mites (4, 5). These findings have led to the conceptualization of a new rhinitis phenotype, termed local allergic rhinitis (LAR) (6).

LAR appears to be a stable (7) and well-delineated phenotype in adult subjects, predominantly affecting young, eutrophic, nonsmoking women with a family history of atopy (8). However, limited data exists on LAR in the pediatric age group. A recent systematic review (9), encompassing ten studies with a total of 1,024 patients revealed significant variation in the prevalence rates of LAR (3.7% to 83.3%) among individuals previously classified as having non-allergic rhinitis (NAR). Notably, the prevalence rates in Eastern countries (3.7% to 16.6%) were considerably lower than those in Western countries (22.3% to 83.3%). Yet, no distinct clinical features have been identified that could explain this geographical discrepancy or differentiate between the various rhinitis phenotypes in childhood (4).

In adult patients, protocols involving conducting NAC with multiple allergens sequentially on the same day have shown favorable safety and result reproducibility when compared to performing a single NAC separately (10). Utilizing multiple allergens in NAC accelerates the procedure, simplifies it, and enhances comfort for both physicians and patients, thereby facilitating the screening for LAR. The selection of allergens for NAC, whether multiple or single, should be individualized based on the relevance of the allergens involved in the pathophysiology of AR, particularly in the region where the test is conducted.

In Brazil, there is a predominance of perennial AR, primarily triggered by household allergens. The most significant of these are the mites: *Dermatophagoides pteronyssinus* (Dp), *Dermatophagoides farinae* (Df), and *Blomia tropicalis* (Bt). Other household allergens include the epithelia of domestic animals (dogs and cats), cockroaches, and fungi (11).

The primary objectives of this study were twofold: (a) to ascertain the prevalence of child subjects presenting with rhinitis without systemic sensitization, and (b) to identify LAR in child and adolescent subjects previously diagnosed as NAR in a Brazilian specialty outpatient clinic (Allergy and Immunology). This differentiation was achieved by conducting NAC with multiple allergens. Additionally, the study aimed to pinpoint any clinical or demographic features that could effectively discriminate between patients with LAR and those with NAR.

MATERIAL AND METHODS

This cross-sectional study involved a retrospective selection of patients aged six to 18 years diagnosed with rhinitis in accordance with the Allergic Rhinitis and its Impact on Asthma (ARIA) (2) criteria, who were attending the Allergy and Clinical Immunology outpatient clinic and showed no evidence of systemic sensitization. Systemic sensitization was determined by a positive skin prick test (SPT) and the presence of serum-specific IgE for the following allergens: *Dermatophagoides pteronyssinus* (Dp), *Dermatophagoides farinae* (Df), *Blomia tropicalis* (Bt), animal epithelia (dog and cat), fungal mix, and *Periplaneta americana* (Pa). A positive result for the SPT was defined as a wheal with a diameter > 3 mm greater than the negative control. For serum-specific IgE levels (measured using ImmunoCAP; Thermofisher), values ≥ 0.35 kUA/L were considered positive.

Patients who had other pulmonary or cardiovascular diseases, uncontrolled asthma, significant anatomical defects of the upper airway affecting nasal patency (such as deviated septum, adenoid hypertrophy, and nasal polyposis), those on systemic corticosteroids within the last 15 days, and those with a history of upper airway infection in the previous 30 days were excluded from the study. Additionally, patients with any

motor or neurological inability to cooperate were also excluded.

During the study period (October 2017 to September 2022), patients were invited to the outpatient clinic to undergo voluntary NAC with Dp and Bt. Before the NAC, patients completed the total nasal symptom score (TNSS) based on the last seven days to assess the severity of AR. This assessment considered the following symptoms: runny nose, itching, nasal obstruction, and sneezing. Each symptom was scored on a scale: 0 = no symptoms, 1 = mild symptoms (when present for a short time and without impact on daily life), 2 = moderate symptoms (frequently present but without impact on daily life), and 3 = severe symptoms (when present most of the time with significant effect on daily activities or sleep). The TNSS, ranging from zero to 12 points, is categorized according to the sum of the scores for each item: mild symptoms (0–4), moderate symptoms (5–8), and severe symptoms (9–12) (13).

The present study was approved by the local Research Ethics Committee (#2.330.653).

Nasal allergen challenge with multiple aeroallergens

The NAC was conducted using extracts of Dp and Bt (FDA ALLERGENIC® - Brazil, 5,000 UBE/ml) diluted at different levels in 0.9% saline solution. The nasal response was monitored using acoustic rhinometry (A1, GM Instruments, Scotland - UK). Evaluations were conducted by the same observer (FM) in triplicate, adhering to international recommendations (14), and under standardized room conditions, including temperature and humidity. All patients were instructed to discontinue oral antihistamines, topical intranasal corticosteroids and antihistamines, chromones, leukotriene receptor antagonists, and decongestants for two weeks before the provocation test.

As noted earlier, the volume of the nasal cavity in its first five centimeters (V5)

was defined as the primary parameter for monitoring by AcR in child subjects (15). This parameter was calculated by summing the values from each nostril (16). Additionally, the two smallest cross-sectional areas (MCA1 and MCA2, cm^2) in each nostril were measured. To determine the concentrations and dilutions of Dp and Bt for NAC with multiple allergens, data from previous single NAC protocols with these allergens in the same age group were utilized (17).

Baseline measurements were taken following the instillation of 0.15 mL of saline solution (0.9%) into each nostril. If the initial result was negative, the administration of two consecutive allergen solutions, Dp and Bt, commenced. These were provided in two increasing dilutions (1:1,000 and 1:100) for each allergen, at an average interval of ten minutes, in the aforementioned order, bilaterally using a spray device delivering 0.15 mL per nostril. AcR measurements were taken ten minutes after each instillation. Subsequently, nasal symptoms were assessed and recorded using a standardized symptom score (17, 18) (Figure 1).

FIGURE 1

NAC symptom score

All patients were clinically evaluated on the day of the NAC and this assessment was considered as baseline for starting NAC. To monitor the test, a NAC symptom score previously adapted to Brazilian children (17) was used, assessing the following symptoms: nasal secretion assessed by anterior rhinoscopy, amount of sneezing, and presence of extranasal symptoms (eye tearing, conjunctivitis/chemosis, urticaria, cough/dyspnea) (18). This score assigns significance to values equal to or higher than three (Table I), the threshold for positive tests.

TABLE 1

NAC with multiple allergens was deemed positive if a reduction equal to or greater than 20% in V5 was observed, or when the symptoms score questionnaire was > 3 points. In cases of a positive NAC result with Dp (at any dilution), the patient was required to return after seven days for an NAC with Bt only. Regardless of the final NAC result, all patients remained under observation for 30 minutes following the conclusion of the test.

Statistical Analysis

The initial stage involved a descriptive analysis of the collected data. For categorical variables, both absolute and relative frequencies were tabulated. Numeric variables were presented in terms of averages and interquartile ranges. To compare results between groups, nonparametric tests, including the Mann-Whitney, Wilcoxon, and Fisher tests, were employed. In all instances, the threshold for rejecting the null hypothesis was established at a 5% level.

Data derived from the NAC with multiple allergens was systematically encoded, transferred to a database prepared in Microsoft Excel, and subsequently subjected to statistical analysis using the Statistical Package for the Social Sciences (SPSS) - version 29.0.

RESULTS

During the retroactive analysis period (January 2015 to December 2019), a total of 758 skin prick tests (SPTs) performed on patients attending the outpatient clinic were

analyzed. Of these, 517 (68.2%) patients were diagnosed with rhinitis according to the Allergic Rhinitis and its Impact on Asthma (ARIA) (2) criteria. Within this group, 422 patients had a positive SPT, indicating that 81.6% (422/517) of the rhinitis patients had allergic rhinitis (AR), while 18.4% (95/517) had a negative SPT, thereby meeting the criteria for inclusion in the study.

Out of the eligible patients, forty-five (47%) were successfully recruited via telephone; 27 of them underwent NAC with Dp and Bt, followed by an evaluation of the results. Among these, 7.4% (2/27) were excluded from the final analysis due to being diagnosed with nonspecific nasal hyperreactivity following saline instillation, which triggered NAC positivity before the instillation of the allergens (Figure 2).

FIGURE 2

The median age of the remaining 25 patients was nine years (range: 8.5–12.5 years), with the median age of symptom onset being two years (range: 1.5–5 years). Of these patients, 44% (11/25) were female, and they had a median TNSS of 5 (range: 3–7). All patients included in the study were clinically evaluated on the day of the NAC and had mild symptoms or were asymptomatic. This assessment was considered as baseline for starting NAC.

Following the NAC with multiple allergens, 40% (10/25) of the patients tested positive and were subsequently reclassified as having LAR. At the conclusion of the NAC, the median variation in V5 for the LAR group was -22.66% (range: -26.10% to -21.39%), while the NAR group showed a median variation of -7.59% (range: -10.09% to -1.07%), as illustrated in Figure 3. There was no significant difference in the variations of MCA1 and MCA2 between patients with positive and negative NAC outcomes (Table

II). Clinically, none of the patients undergoing NAC exhibited severe or pulmonary symptoms during or after the procedure.

FIGURE 3

Among the positive tests, nine were characterized by a greater than 20% reduction in V5, while only one was identified by a symptom score $\geq$ 3. Regarding the triggering allergens, one patient showed reactivity to both Dp and Bt, six exclusively to Dp, and three exclusively to Bt.

In the NAR group (n=15), the median age was nine years (range: 8–12 years), the median age of symptom onset was three years (range: 1–5 years), with 46.7% (7/15) being female, and the median TNSS recorded as seven (range: 5–8). Four of these patients did not exhibit signs or symptoms of other allergic diseases such as asthma, atopic dermatitis, or conjunctivitis.

Conversely, in the LAR group (n=10), the median age was 10.5 years (range: 8.5–13.5 years), the median age of symptom onset was two years (range: 1.8–3.5 years), with 40% (4/10) being female, and the median TNSS noted as three (range: 2.5–6.3). Only one patient in this group showed no signs or symptoms of other allergic diseases.

The NAR and LAR groups had similar characteristics, with no statistically significant difference in the AcR parameters (baseline V5, baseline MCA1, and MCA2) or the clinical variables evaluated (age, TNSS, age at onset of symptoms). The specific characteristics of these groups are detailed in Table II.

TABLE II

Patients in the NAR group demonstrated a trend (p = 0.06) towards having a higher TNSS compared to those in the LAR group (Figure 4).

FIGURE 4

DISCUSSION

To our knowledge, this study represents the first investigation of LAR in child and adolescent subjects in Latin America, contributing significantly to the understanding of its prevalence and characteristics in this demographic. This research facilitates comparisons with data from other parts of the world.

Dp and Bt were selected for the NAC based on the characteristics of AR in the Brazilian population. This choice underscores the dominant presence of perennial AR with sensitization to household allergens, particularly mites (11). As such, this protocol, if applied in populations with similar characteristics, enables reliable international comparisons.

In the present study, 18.4% of patients with rhinitis did not exhibit systemic sensitization. Prevalence studies of NAR are scarce in the pediatric population, due to the challenges in distinguishing NAR from viral infections, which are common in this age group. Despite these challenges, all of them indicate a decline in NAR prevalence throughout childhood (19, 20). Our study, being cross-sectional, did not allow for long-term evaluation of patient behavior. Nonetheless, the prevalence observed aligns with findings reported in other studies.

In the subset of patients who underwent NAC with Dp and Bt, 40% (10/25) tested positive, allowing for their reclassification as having LAR. The data is consistent with that obtained in Western countries (22.3% to 83.3%), as reported in a recent systematic

review (9) that included ten studies and 1,024 patients. These rates are remarkably higher than those found in Eastern countries (3.7% to 16.6%), and the reasons for these regional differences remain unclear.

Upon examining the characteristics of rhinitis in Brazil, which is predominantly perennial and triggered by house dust mites, it appears unlikely that the type of rhinitis (seasonal vs. perennial) or the different allergens (pollens vs. house dust mites) used in NAC account for the variance in prevalence. The characteristics of rhinitis in Brazil more closely resemble those in some tropical countries, such as Indonesia, than in Western countries like Spain or Italy, where seasonal rhinitis and pollen involvement are more prevalent in the etiology of LAR.

In our study, a trend was observed towards higher TNSS among patients with NAR compared to those with LAR, particularly among patients with mild and moderate symptoms. However, we were unable to identify any clinical or laboratory features that could distinctly differentiate these two rhinitis phenotypes. This finding is consistent with conclusions drawn by other authors and a recent systematic review (9).

Currently, the NAC is predominantly used as a laboratory investigation and research tool. Yet, with the identification of LAR, the development of more comprehensive NAC protocols incorporating multiple allergens could streamline and enhance the screening process for patients with this specific rhinitis phenotype. The primary advantage of such screening would be the early initiation of specific immunotherapy. This approach could significantly improve the quality of life for these patients during childhood, as the efficacy of this treatment has already been established in adult subjects (21).

It is important to highlight that the EAACI and AAAAI position papers on nasal allergen challenges (22, 23) were very important in standardizing NAC protocols, but

unfortunately, to date, there are no Brazilian or Latin America NAC guidelines. However, these recent recommendations are not specific to children, once the parameters recommended as clearly positive were based on data obtained mainly in adults. Therefore, to define the test as positive, we chose to use criteria obtained in a study carried out specifically in Brazilian children. In this study, performed during histamine nasal challenges, a 19%-21% drop in V5 were the cutoffs with highest sensitivity and specificity when compared with 100% increase in total nasal resistance measured by anterior active rhinomanometry (15). Furthermore, the symptom score used in our study to monitor the clinical response to NAC also differs from international recommendations. We used a symptom score previously employed to standardize NAC with Dp and Bt in children and adolescents in Brazil (17) in a study carried out before the publication of the current recommendations (22, 23).

The NAC protocol with Dp and Bt in child subjects was proven to be safe, as evidenced by the absence of significant pulmonary and extranasal symptoms during and after the procedure. This safety applied even to patients who had another allergic disease (asthma, atopic dermatitis, or conjunctivitis) alongside their rhinitis diagnosis. This result aligns with findings from other studies in adult subjects (10), indicating that NAC with multiple allergens does not increase the risk of cumulatively triggering positive results. In our study, both patients with LAR and NAR who exhibited clinical symptoms post-NAC predominantly presented nasal symptoms such as nasal secretion and sneezing, making it clinically challenging to differentiate between the two groups.

This study does have limitations, including its reliance on a convenience sample and a small number of patients from a tertiary service. The substantial number of patients who were not recruited (50/95) represents a notable constraint. However, the difficulty in recruiting these patients represents a challenge in specialized Allergy and Immunology

Services, particularly following negative systemic sensitization tests (*in vivo* and/or *in vitro*), which can lead to frustration and perceived lack of clarity in diagnosis for patients and their families, thus discouraging continued follow-up in allergy outpatient clinics. Another limitation is that the NAC with multiple allergens was limited to house dust mites, excluding other common indoor allergens like pet dander, cockroaches, and fungi, which are prevalent in our population. A Brazilian survey on sensitization in atopic child subjects found the following rates: Dp (67.8%), Df (66.5%), Bt (57.1%), cockroach (34.4%), cat epithelium (12.2%), dog epithelium (8.1%), fungi (3.1%) (11). The absence of established protocols for these allergens in the pediatric age group justified their exclusion. However, not testing for these allergens may have led to an underestimation of the frequency of LAR, potentially maintaining the NAR classification in patients who would have responded positively to other allergens.

CONCLUSION

In this study, we observed that 18% of child and adolescent subjects with rhinitis lacked systemic sensitization. Focusing on patients who underwent NAC, 40% (10/25) of them tested positive, enabling their reclassification as patients with LAR. Notably, we were unable to discern any clinical features that distinctly differentiate children with LAR from those with NAR. Additionally, our findings indicate that NAC with Dp and Bt is safe for use in child and adolescent subjects. However, further longitudinal studies are necessary to understand the reasons behind the decreasing prevalence rates of NAR throughout childhood and to clarify the disparities in LAR rates between Western and Eastern countries.

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Declaration of Conflicting Interests:

The authors declare that they have no competing interests with respect to the research, authorship, and/or publication of this article.

Contributions:

FYM and GFM are senior co-first authors and contributed equally to this work: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - original draft and Writing - review & editing.

TRTG: Data curation and investigation.

DS: Supervision, Validation, Visualization, Writing - original draft and Writing - review & editing.

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TABLE I NAC symptom score carried on to monitor NAC with *Dermatophagoides pteronyssinus* and *Blomia tropicalis*.

Symptoms		Points
Nasal secretion at anterior rhinoscopy (examiner's judgment)	As before / normal	0
	Slight increase / minor amounts visible	1
	Pronounced	2
Irritation	0-2 sneezes	0
	3-5 sneezes	1
	> 5 sneezes	2
Distant symptoms	None	0
	Watery eyes and/or Palatal itching and/or Deep aural itching	1
	Conjunctivitis and/or Chemosis and/or Urticaria and/or Cough and/or dyspnea	2

Min: 0 points; Max: 6 points; Positive NAC ≥ 3 points

TABLE II Demographic and clinical characteristics observed in non-allergic rhinitis (NAR) and local allergic rhinitis (LAR) patients

Characteristics	NAR group (n=15)	LAR group (n=10)	P
Age* (Years)	9 (8–12)	10.5 (8.5–13.5)	0.53
Female gender – N (%)	7 (46)	4 (40)	0.74
Baseline MCA1* (cm^2)	1.01 (0.84–1.32)	1.06 (0.91–1.22)	0.56
Baseline MCA2* (cm^2)	1.87 (1.14–2.24)	2.21 (1.31–3.5)	0.28
Baseline V5* (cm^3)	8.74 (7.17–10.80)	9.09 (7.82–11.93)	0.46
Age at symptom onset* (years)	3 (1–5)	2 (1.8–3.5)	0.64
Association with other allergic diseases – N (%)			
Asthma	6 (40)	7(70)	7(70)
Conjunctivitis	7 (46)	2 (20)	2 (20)
Atopic Dermatitis	3 (20)	4 (40)	4 (40)
TNSS*	7 (5–8)	3 (2.5–6.3)	0.06
Mild – N (%)	2 (13)	7 (70)	0.06
Moderate – N (%)	11 (74)	2 (20)	0.07
Severe – N (%)	2 (13)	1 (10)	0.80

V5: Volume of the first five centimeters of the nasal cavity; MCA1 and MCA2: The two smaller cross-sectional areas. TNSS: Total Sympton Score. Mean (IQR – Interquartile Range).

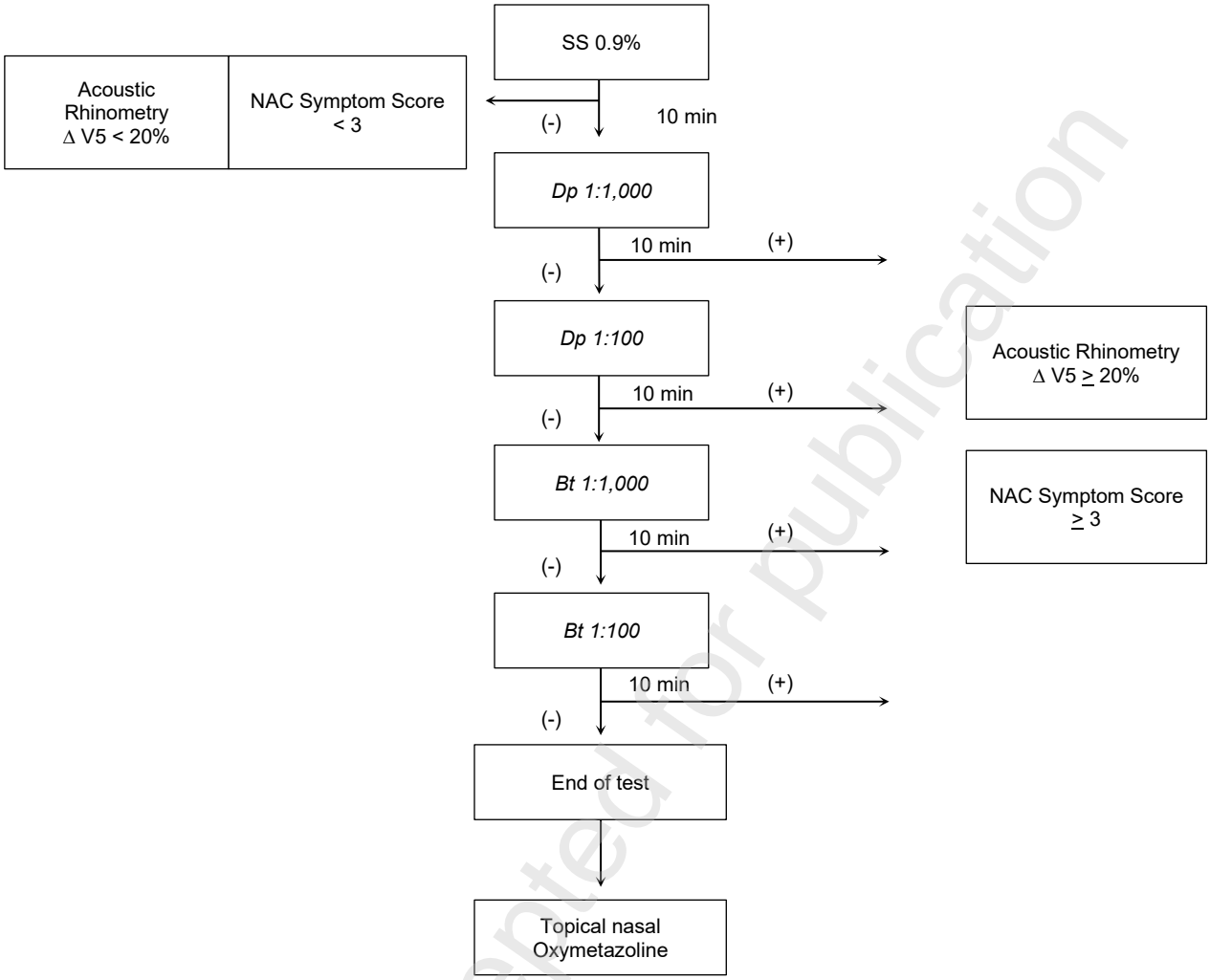

FIGURE 1 NAC with Dp (5,000 UBE/mL) and Bt (5,000 UBE/mL) in children and adolescents. Dp: *Dermatophagoides pteronyssinus*. Bt: *Blomia tropicalis.*

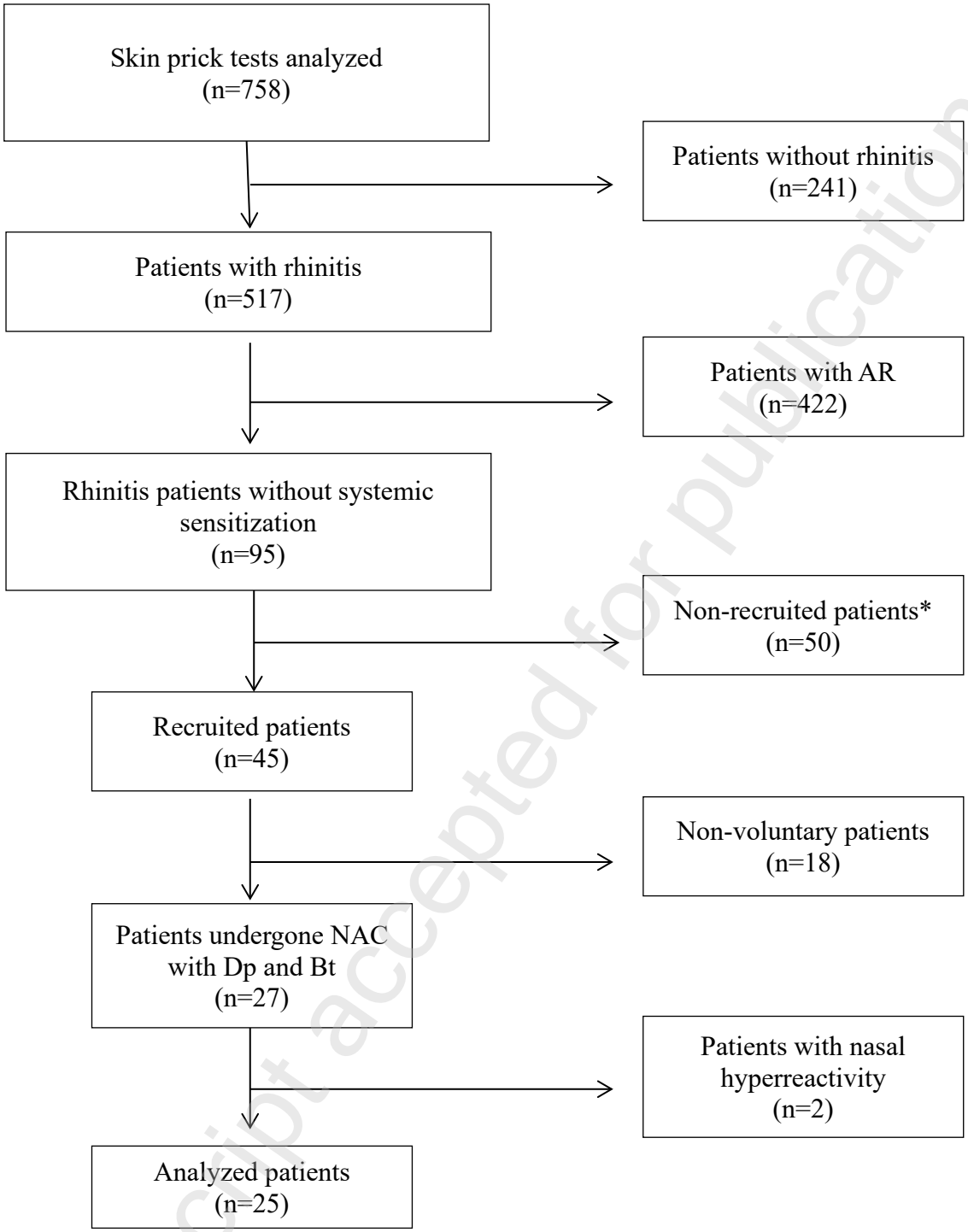

FIGURE 2 Patient recruitment flowchart. AR: Allergic Rhinitis.

* reasons for non-recruitment: Patient/family refusal to participate in the study, patients who were no longer regularly being monitored at the Allergy Clinic and/or who had outdated registration data, impossibility of carrying out NAC during the pandemic period by Sars-Cov-2.

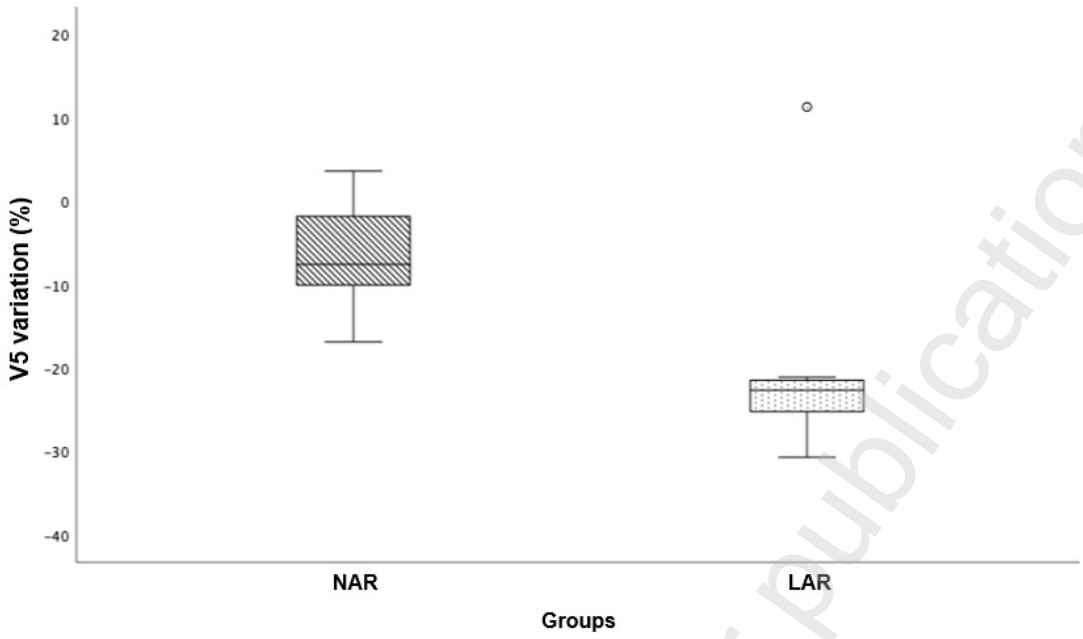

FIGURE 3 Variation in V5 (%) monitored by acoustic rhinometry, after NAC with Dp and Bt, in group NAR and group LAR. LAR: Local Allergic Rhinitis. NAR: Non-Allergic Rhinitis. $p < 0.001$.

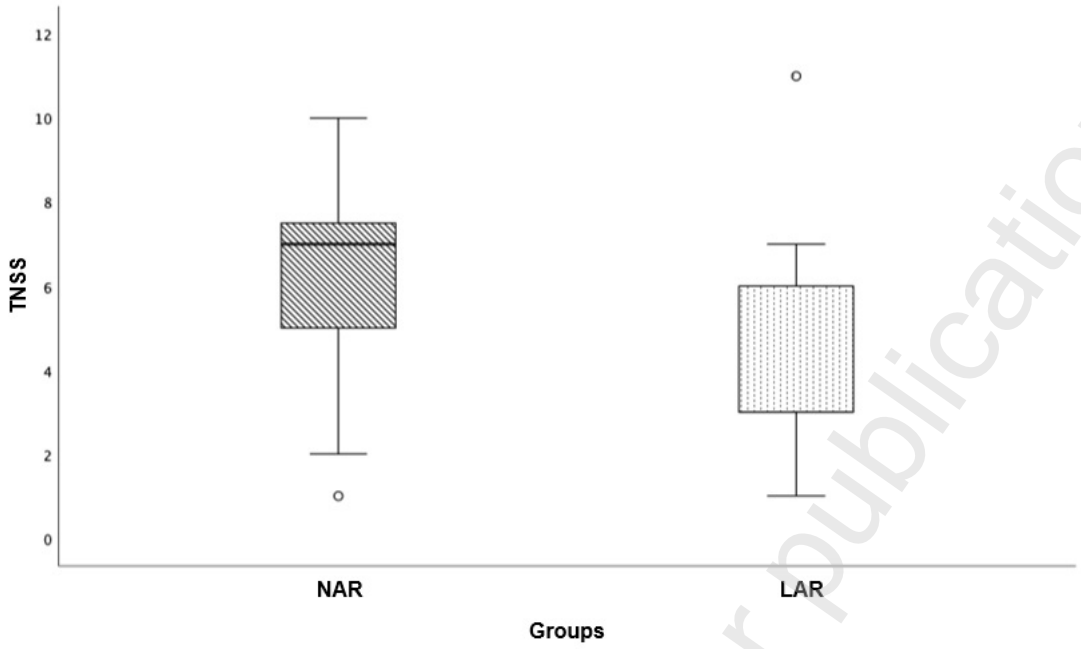

FIGURE 4 TNSS in LAR and NAR group. TNSS: Nasal Symptom Score. LAR: Local Allergic Rhinitis. NAR: Non-Allergic Rhinitis. p = 0.062.