Local specific Immunoglobulin E among patients with non-allergic rhinitis: a systematic review*

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Background: Allergen specific immunoglobulin can be present in the nasal mucosa of patients with non-allergic rhinitis (NAR). This condition is defined as local allergic rhinitis. However, the reported presence of nasal specific immunoglobulin E (nspIgE) among NAR is variable. The aim of this review was to summarize the studies which reported the presence of nspIgE among patients diagnosed as NAR.

Methods: Embase (1947-) and Medline (1946-) were searched until 6th June 2017. A search strategy was utilized to identify studies on nspIgE among patients with NAR. The target population was patients with symptoms of rhinitis, but negative systemic allergen sensitization. Studies with original data on detectable nspIgE among the NAR population were included. Meta-analysis of single proportions as a weighted probability %(95%CI) was performed. Heterogeneity was explored amongst studies.

Results: A search strategy returned 2286 studies and 21 were included. These studies involved 648 participants with NAR. NspIgE was detected using either; 1. nasal secretions, 2. epithelial mucosa sampling, 3. tissue biopsies or 4. In-situ tests. Meta-analysis was performed on studies with nasal secretions. The weighted proportion of detectable nspIgE in nasal secretions within patients with NAR was 10.2 (7.4-13.4) %. Population definitions partly explained variability. Detection of nspIgE was lower in patients without a history suggestive of allergy compared to those with a positive allergic history (0 (0-3.1) % v 19.8 (14.5-25.6) %, p<0.01).

Conclusion: NAR with positive allergy history suggests presence of nspIgE. These patients warrant further allergology evaluation to confirm localized nasal allergy, as they benefit from allergy therapy such as immunotherapy.

Key words: Immunoglobulin E, allergens, rhinitis, non-allergic rhinitis, local allergic rhinitis

Introduction

Diagnosis of allergic rhinitis (AR) involves demonstrating the presence of specific Immunoglobuin E (spIgE) in a person with nasal symptoms. Standard allergology evaluation employs systemic assessments, either skin prick testing (SPT) or by serological detection of spIgE [(1)]. Those who test negative for these systemic tests are diagnosed with non-allergic rhinitis (NAR). However, there has been compelling evidence suggesting that in certain NAR patients, spIgE can be present only in the nose, and is not detectable via routine systemic blood assessment or SPT. The term entopy or local allergic rhinitis (LAR) [(2)] has been used to describe this group of rhinitis patients. In published studies, there is a very wide range in the percentage of NAR patients who have a positive result for the presence of nasal

splgE (nsplgE) [3].

A systematic review of the literature was performed to identify studies that investigated nsplgE among patients with NAR. The primary objective was to assess for evidence of nsplgE among rhinitis patients with negative systemic allergy. The secondary objective was to determine if presence of nsplgE was influenced definitions of NAR.

Materials and methods

A systematic review was performed to identify studies on patients diagnosed as NAR with reported outcomes on nasal sampling for nsplgE. This review was done in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)[4]. Methods from the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy[5] was followed where applicable.

Eligibility criteria

Studies which assessed for nsplgE among rhinitis patients with negative systemic allergy status were included. Participants were rhinitis patients of any age, with a history of physician diagnosed rhinitis or chronic symptoms of rhinitis. These patients must have undergone systemic evaluation for allergy (either SPT or serum splgE) and nasal sampling which was tested for nsplgE. Studies were excluded if the nasal test did not include any nsplgEs for aeroallergens, or if participants were diagnosed with chronic rhinosinusitis, asthma without rhinitis or infectious rhinitis. Only studies with data reported as proportions were included. Study designs were diagnostic studies of either case series, case-control or cross-sectional design. Only manuscripts published in English were considered; case reports, reviews, guidelines, letters and editorials with no original data were excluded as well as animal studies. The outcome of interest was the proportion of patients with detectable nsplgE among the NAR population.

Information sources

A systematic electronic search was performed on both the Embase (1947-) and Medline (1946-) databases until 6th June 2017. A search strategy was designed for each database (Appendix 1) to identify all studies on a rhinitis population with nasal assessment for allergy. Missing studies were searched manually from the bibliography of included studies.

Study selection

The search results were reviewed by two authors (AWH and RJH) and selected according to the eligibility criteria. Titles were screened for relevant articles followed by abstract review. Uncertain abstracts were then discussed between the reviewers. Full texts of the selected abstracts were then analyzed and excluded if they did not fulfil the selection criteria.

Data collection

An Excel standardized data-sheet was used to extract relevant data from the selected studies. Variables recorded were: study type, study location, number of subjects, definition of NAR and its baseline characteristics (when available), type of sampling methods, timing of sampling, test used to measure nsplgE and the outcome.

Data synthesis

Descriptive data was presented in percentages and proportions. Meta-analysis of single proportions was done for a selected group of studies. This data was analyzed using Excel 2016 (Microsoft, Redmond, WA, USA) with a statistical add-on application package MIX2.0 (BiostatXL, 2016, CA, USA)[6]. The frequency of detectable nasal splgE among NAR population (n/N) in these studies was transformed using the Freeman Tukey transformation. Data output was generated as a weighted probability both within individual studies and as overall cumulative tests. The data was presented as a percentage with a 95% confidence interval. Heterogeneity was assessed by the I2 test and explored for discrepancies.

Results

Study selection

The search strategy yielded a total of 2286 studies. Studies were reduced to 1690 after 596 duplicates were removed. These titles were then screened which left 500 abstracts for assessment. There were 135 full text studies which were assessed for eligibility, of which 21 studies were included (Figure 1). Of these, four studies were duplicated. These studies involved 648 participants with NAR.

Characteristics of included studies

The included studies consisted mainly of case controls (n=16) [7-22] and case series (n=5) [23-27]. All were original articles except for one conference abstract [26]. The characteristics of included studies are available in Appendix 2.

Population

Studies were conducted in Europe except for seven studies [15, 16, 18, 22, 24, 26, 27]. All studies included NAR populations with minimum criteria of rhinitis symptoms but negative serum splgE and/or skin prick test. The majority of studies were on adults while six studies [8-10, 14, 23] involved children. There were two studies which exclusively studied patients with non-allergic rhinitis with eosinophilia (NARES) [7, 24].

Systemic tests to rule out allergy among NAR

All studies defined their NAR population as having symptoms of rhinitis but negative systemic tests. There were 13 studies which used dual systemic test (both negative serum splgE and skin

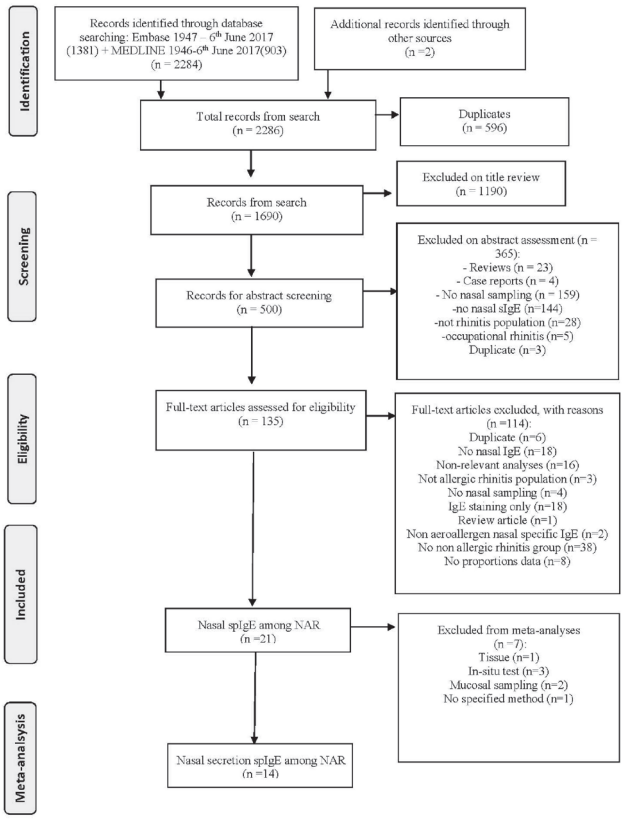

Figure 1. PRISMA flowchart of the study selection process.

prick test) [7, 11-13, 16, 18-24, 27] to rule out systemic sensitization. The other studies used only a single test, where six studies defined their NAR population as having negative SPT [9-10, 14, 15, 17, 26] and two studies defined NAR as having negative serum spIgE [8, 25].

Definition of NAR within the target population

The baseline characteristics of the NAR population were available for 13 studies and assessed. This descriptive data was grouped into either positive, negative or uncertain clinical allergic characteristics. Studies were defined to have NAR patients with positive allergy characteristics when there was either an identifiable aeroallergen which triggered the nasal symptoms [10, 12, 13, 16, 20, 21, 23] or if there was seasonality of symptoms [10, 20, 21, 23]. Studies were defined to have patients with negative allergy characteristics if a history of allergy was specifically ruled out (no family history of allergy, no allergen triggers or no allergic co-morbidities) [7, 18, 24]. Studies which did not give the above details but gave data which could suggest allergy (co-morbidities and family history of atopy) were defined as having uncertain allergic characteristics [11, 19, 27] (Table 1). Other studies did not report any baseline characteristics of their NAR population [8, 9, 14, 15, 17, 22, 25, 26].

Intervention: sampling method

Most studies sampled the nasal secretions to assess for nspIgE except for seven studies (one study biopsied the inferior turbinate tissue [16] and two studies performed nasal mucosal sampling (either using a cytology brush [27] or nasal curette [11], three studies used a unique method of in-situ testing [9, 10, 14] and one study did not specify it's sampling method [26]). In-situ tests involved incubation of solid phase coupled allergen directly on nasal mucosa. Nasal secretions were sampled either by nasal lavage/washings [13, 19-21, 23] or direct collection of nasal secretions. Direct collection of nasal secretion was done either by collecting spontaneous secretions [24], by suctioned secretions [22], by absorbing nasal secretions in the nasal cavity (using filter paper [12,15]

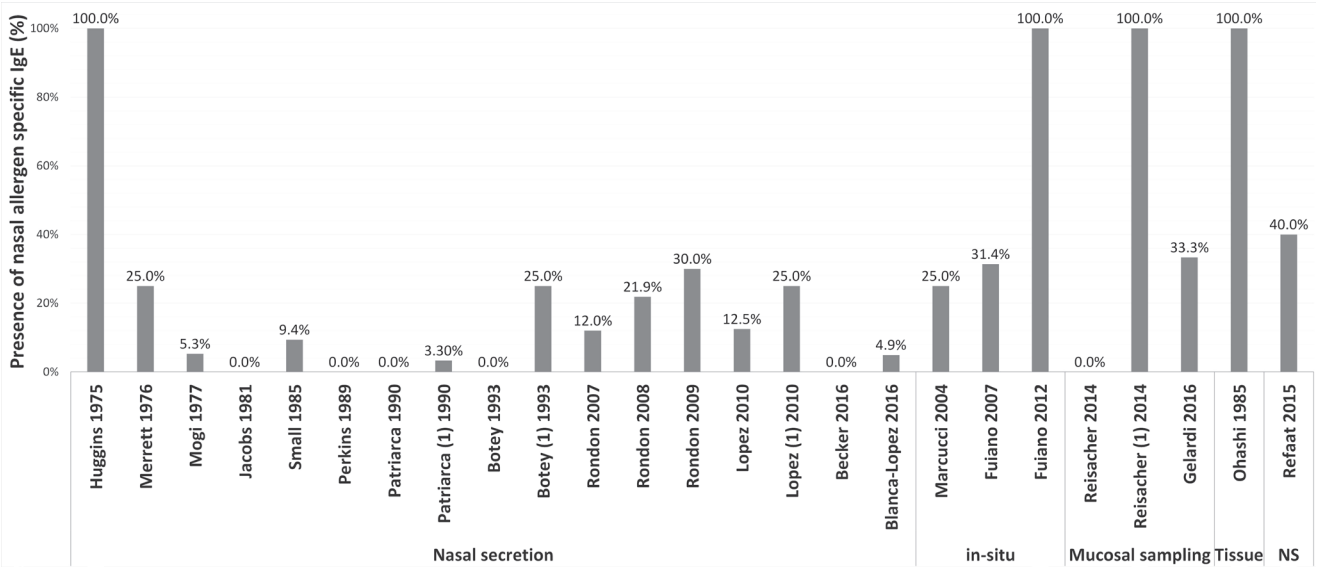

Figure 2. The proportion (%) of detectable nasal specific Immunoglobulin E (spIgE) among patients diagnosed as non-allergic rhinitis. Studies were grouped by the sampling method used to obtain nasal specimens for the detection of spIgE. The studies were then ordered by the year of publication.

Table 1. The definitions of the non-allergic rhinitis population in included studies.

Author (year)	n	Age (years)	FHA (%)	Asthma (%)	Conjuncti-vitis (%)	Seasonal symptoms	Identifiable allergen trigger	Other
Positive allergic characterisitics								
Fuiano 2012 [10]	36	137.5±43.2	-	-	-	Yes	Pollen	-
Huggins 1975 [12]	12	-	-	-	-	No	Dust	-
Lopez 2010 [13]	40	18-63	70	33	25	No	90% trigger Dust	-
Ohashi 1985 [16]	4	-	-	-	-	-	Dust	-
Rondon 2008 [20]	32	41±18	46	31	62	Yes	Pollen	-
Rondon 2009 [21]	30	39±15	43	47	57	Yes	Pollen	-
Blanca Lopez 2016 [23]	61	Range:7-67	62	44.26	95	Yes	Pollen	-
Negative allergic characteristics								
Becker 2016 [7]	19	29(9-57),	-	-	-	-	-	No allergy like history
Perkins 1989 [18]	10	54	0	-	-	-	-	No clinical history of allergy
Jacobs 1981 [24]	19	NA	50	-	-	No	None	Unknown trigger: 42%, weather trigger: 31%, pollen, food or epthelium: 0%, dust or smoke: 12%
Uncertain allergic characteristics								
Rondon 2007 [19]	50	39±16	-	32	48	No	-	-
Gelardi 2016 [11]	12	32.4±15.2	33.3	16.7	-	No	-	-
Reisacher 2014 [27]	20	23-59	-	30	75	Yes (65%)	-	-

NA: not applicable, NAPT: nasal allergen provocation test.

or cotton wool pieces [7, 17, 18] or by first stimulating the nasal cavity with hypertonic solution followed by collection of produced nasal secretions [8,25]. The summary of nspIgE found in secretions, nasal mucosa or tissue are summarized in Figure 2.

Type of allergen

There were three studies which tested for pollen allergens [20, 21, 23] seven studies tested for dust mites or house dust [8, 12, 13, 15, 16, 19, 24] while the other studies tested for a panel of common aeroallergens [7, 9, 10, 14, 18, 22, 25, 27].

Time of sampling

Most studies performed nasal sampling at random (no specified point of time) except for four studies, which sampled the nasal mucosa at both baseline period prior to and after nasal allergen provocation test (NAPT)[13], after NAPT only [21], or during the pollen season [10, 20].

Positivity criteria for detectable nasal specific Immunoglobulin E

The presence of nspIgE was tested using commercial lab methods by either radioimmunoassay (and utilized the radioallergosorbent test (RAST), mostly during the pre-90s period), or used the fluoroenzyme immunoassay (FEIA) (ImmunoCAP®/uniCAP® system). The exceptions were two studies which used the in-situ methods and measured the response directly based on their own protocol. The RAST method reported the outcome using the ordinal class system (class 0 to 4). Class 0 being undetectable. Class 1 and above was determined as positive presence of nspIgE. The FEIA reported its outcome as continuous data, where a value of 0.35kU/L or more was used to define presence of nspIgE [13,14,19-21,23]. There were two studies which used a lower cut-off of 0.1kUA/L[27] and 0.17kUA/L[11].

Meta-analyses: presence of nasal spIgE in nasal secretions

Only studies which sampled nasal secretions (n=14) [7-8,12-13,15,17-18, 19-25] were pooled for a total of 484 NAR subjects. The pooled summary estimate for the presence of nspIgE in nasal secretions among NAR was 10.2 (7.4-13.4) %.

Heterogeneity of studies

This group of studies were heterogenous with I2 value 84.7(76.9 -89.9)%.

Subgroup analysis

A subgroup analyses was done to explore the heterogeneity. To

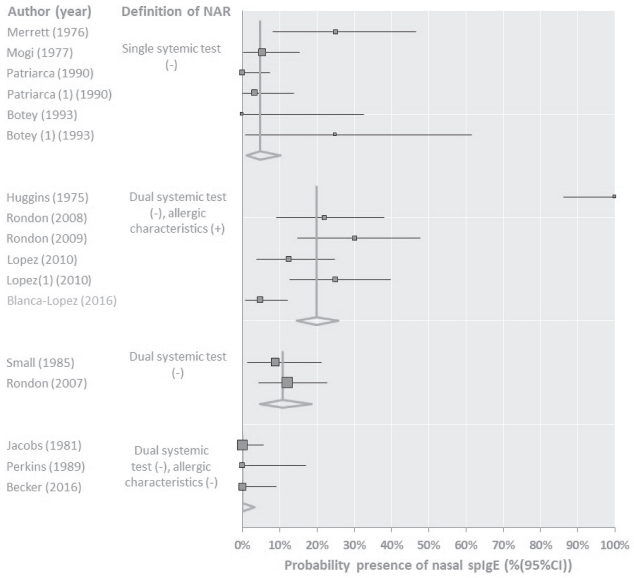

Figure 3. Forest plot representation of detectable nasal specific Immunoglobulin E (nspIgE) among patients with non-allergic rhinitis (NAR) with subgroup analysis of the definitions of NAR. Studies were primarily ordered by their definition of NAR, then by year of publication. The weighted probability of detecting nspIgE in the individual studies with 95% confidence intervals (error bars) was represented as boxes. Diamonds represented pooled summary estimates for each definition of NAR.

describe heterogeneity based on definitions of NAR, the studies were grouped into one of four types of definitions. 1. Studies which defined NAR by ruling out allergy with a single systemic test (these studies also did not have information for allergic characteristics), 2. Studies which ruled out allergy using dual tests and among NAR patients with positive allergic characteristics, 3. Studies which ruled out allergy using dual tests (but incomplete data on allergic characteristics) 4. Studies which ruled out allergy using dual tests among NAR patients with negative allergic characteristics. A subgroup analysis was done to compare these four definitions of NAR (Figure 3). Studies with negative allergic characteristics all gave negative results compared to those with positive allergic characteristics (0 (0-3.1) v 19.8 (14.5-25.6) %, $p<0.01$).

Discussion

The presence of nspIgE among patients with NAR showed extreme variability with reported values from 0 to 100%. This highly variable result was partly due to the definition of NAR. Patients who lacked a suggestive allergy history and had negative systemic allergy tests, on summary proportions, had zero probability of having detectable nspIgE (0 (0-3.1) %). On the other hand, those with a history suspicious for allergy, which could not be confirmed with conventional systemic testing, had a 19.8 (14.5-25.6) % pooled probability of detecting nasal spIgE. A history of seasonality, pollen reactivity, identifiable triggers, additional sites of allergic disease (asthma, dermatitis) and family history made the likelihood of detecting nspIge higher. The "Swiss Study on Childhood Allergy and Respiratory Symptoms with Respect to Air Pollution, Climate and Pollen" (SCARPOL) reported that allergen sensitization is strongly associated with either the diagnosis of seasonal allergic rhinitis (OR= 5.7), eye symptoms (OR=4.4) or symptoms during pollen season (OR=4.9) [28]. Studies have also shown that a positive family history of atopy was significantly higher among patients with LAR compared to those with NAR [29, 30]. Furthermore, prior studies which reported more than 50% prevalence of LAR diagnosed by NAPT, involved subjects with seasonality of symptoms [20, 23, 31] or identified an allergen trigger [32]. Potentially, only those with a suggestive allergic history but negative SPTs and/or serum spIgEs, warrant further investigation in order to embark on allergen reduction interventions or immunotherapy. Prior studies have confirmed that LAR and AR share similar clinical characteristics, underlying inflammatory pattern and both respond well to intranasal steroid as well as immunotherapy [20,33]. This leads to a question whether good response to intranasal corticosteroids could differentiate LAR from AR. Similar to AR, topical nasal steroids and oral antihistamine is the recommended treatment of LAR [34]. AR generally responds well to intranasal corticosteroids, however studies on its benefit in NAR had been variable. This may be due to lack of identification of NAR subtypes, including LAR [35]. Up to date, LAR is considered a NAR subtype, owing to its negative systemic sensitization [36]. The absence of practical local diagnostic test, have resulted in most LAR cases being undiagnosed. Essentially, LAR and AR are both IgE mediated nasal inflammatory diseases and the clinical characteristics associated with allergy may be used to direct clinical suspicion towards LAR, when systemic tests have been reported as negative.

In this current review, the majority of studies were conducted in Europe. Of note, studies conducted in Spain [8,13,19-21,23] gave more consistent results where most investigations detected 12-30% nasal spIgE in nasal secretions of their NAR patients. Apart from patient selection with history suggestive of allergy, geographical variations may be a contributing factor. The prevalence of LAR diagnosed based on NAPT had been reported to be lower in Asian countries compared to western countries [33]. This may be due to climate factor where seasonal allergens more closely associated with LAR [37], are more prevalent in temperate conditions. Furthermore, only few studies have been conducted outside of Europe which may be a confounder.

LAR is thought to occur due to local spIgE synthesis in the nasal mucosa itself. The mechanism of allergen spIgE production (class switch recombination, somatic hypermutation, B cell affinity maturation before differentiating into IgE producing plasma cells) have been studied in the human nasal mucosa [38]. These studies show compelling evidence that the nasal mucosa

is a capable primary site for highly selected and refined spIgE production. It has also been reported that only 1% of the spIgEs in serum are derived from peripheral blood mononuclear cells suggesting other major sites of spIgE production [39]. Locally produced allergen spIgE will first bind to nasal tissue mast cells and the excess spIgE will be released into the nasal secretions and circulation [40] and these spIgE may escape systemic detection. Therefore, assessment for allergy at the primary site has become an increasingly important test. Unfortunately, local nasal assessment is marred by some yet unresolved complexities.

NAPT is the established method to diagnose LAR. However, whether an induced allergen provocation in a controlled setting reflects the disease state upon natural exposure remains questionable. NAPT is also time consuming, requires special patient preparation and trained personnel to perform the procedure. Furthermore, only one allergen can be tested at a time and the methodology remains broad with differing recommendations regarding allergen dose, mode of application and interpretation of nasal response [38]. A relatively non-invasive method to sample the nasal mucosa would be a much more practical alternative. However, this method of assessment is still in research phase.

One of the issues faced with testing for nasal spIgE is the low sensitivity. In this study, 10% of NAR population was estimated to have detectable nasal secretion spIgE which is less than half of previously reported value in another systematic review where 24.7% of patients diagnosed as NAR had a positive NAPT [37]. This is due to the low SpIgE concentrations detected in nasal samples compared to serum [8,41,42]. This low concentration could be a consequence of the assay sensitivity. Nasal tissues or secretions contain mucin (not present in serum) which may hamper the binding process of fluoroenzyme immunoassay. IgA which is the predominant antibody class in nasal secretions may also interfere with IgE detection in nasal samples by ImmunoCAP that have been optimized for serum (where IgG is the most abundant antibody class). Dilution of nasal secretions also plays a role where up to 2ml have been used to mobilize absorbed nasal secretion or 8-10ml of saline have been used for nasal lavage [21,23]. Also, little is known about local nspIgE half-life and degradation process which may differ from serum spIgE. Therefore, the cut-off value of 0.35kUA/L determined for serum may not be suitable for nasal samples. Further studies are still needed to define the role of nspIgE in determining LAR and establish its diagnostic utility and appropriate threshold.

Conclusion

Local allergic rhinitis or nasal allergy is a condition currently underdiagnosed via conventional systemic allergen testing. NAR patients with a history of seasonality, pollen reactivity, identifiable triggers, additional sites of allergic disease (asthma, dermatitis) and family history of atopy should be considered for local allergen assessment. These patients need to be identified as they will benefit from allergy treatment such as immunotherapy.

Authorship contribution

AWH performed the data collection, data analysis, data interpretation and drafted the article. JR and WS were involved with the conception of the work, data interpretation and made critical revision of the article. SH and RA were involved in data interpretation and drafting of the article. JT made critical revision of the article. LK and RJH were involved in design of study, data collection, study selection and made critical revision. All authors gave final approval of the version to be published

Conflict of interest

This is an unfunded project. Richard J. Harvey is a consultant with Medtronic, Olympus and NeilMed pharmaceuticals. He has also been on the speakers' bureau for Glaxo-Smith-Kline, Seqirus and Astra-Zeneca. Janet Rimmer has honoraria with Sanofi Aventis, Novartis, Mundipharma, BioCSL, Stallergenes. Larry Kalish is on the speaker bureau for Meda Pharmaceuticals, Care Pharmaceuticals and Bayer Pharmaceuticals. All other authors have no financial disclosures or conflicts of interest.

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Appendix 1. Search strategy used in MEDLINE (OVID) (1946 until 6th June 2017).

No.	Search terms (number of studies)
1.	exp ALLERGIC RHINITIS/ (19757)
2.	RHINITIS/ (11227)
3.	Rhinit*.tw. (21653)
4.	2 or 3 (28715)
5.	exp HYPERSENSITIVITY/ (317374)
6.	(allerg* or hypersensitiv*).tw. (206883)
7.	5 or 6 (398764)
8.	4 and 7 (20059)
9.	(perennial or persistent or nonseasonal or nose or nasal or cat* or fur or hair* or dander or dust* or mite* or pet* or dog* or cockroach*).ti. (633806)
10.	(seasonal or intermittent or spring or summer or pollen or grass* or birch or ragweed or tree* or weed* or mugwort or willow or alder).ti. (83295)
11.	9 or 10 (713313)
12.	4 or 7 (407420)
13.	11 and 12 (27233)
14.	(hayfever or hay fever or pollenosis or pollinosis or SAR).tw. (16845)
15.	1 or 8 or 13 or 14 (59909)
16.	exp VASOMOTOR RHINITIS/ (608)
17.	(NARES or NAR or LAR or NANIPER).tw. (5444)
18.	Idiopathic rhinitis.tw. (51)
19.	Non-allergic rhinitis.tw. (350)
20.	Rhinoconjunctivitis.tw. (1789)
21.	(local adj2 rhinit$).mp. (67)
22.	entopy.tw. (10)
23.	((Entop$ or non?atopic or gustatory or exercise induced or mixed) adj rhinitis).mp. (44)
24.	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 (8129)
25.	15 or 24 (65673)
26.	NASAL MUCOSA/ (17006)
27.	TURBINATE/ (3019)
28.	turbinate$.tw. (4470)
29.	(nasal or nose or rhino$).tw. (131734)
30.	(tissue or mucosa).tw. (1201861)
31.	((nasal or nose or rhino$) adj2 (tissue or mucosa)).tw. (8259)
32.	26 or 27 or 28 or 29 or 31 (136562)
33.	IMMUNOGLOBULIN E/ (38172)
34.	(IgE or immunoglobulin E).tw. (47126)
35.	(IgE adj2 specifi$).tw. (12692)
36.	(IgE adj2 local).tw. (152)
37.	33 or 34 or 35 or 36 (56413)
38.	32 and 37 (3378)
39.	(secret$ or Lavage$ or Blow$ or Mucus or mucous or wash$ or Biopsy or Brush$ or incubat$ or smear$ or filter disc or aspirat$ or scrap$ or rhinopro$ or test).tw. (2270843)
40.	32 and 39 (26400)
41.	38 and 40 (1596)
42.	25 and 41 (1223)
43.	limit 42 to (english language and humans) (959)

AR: Allergic rhinitis, D: Data duplicated in these studies, FHA: family history atopy, NAR: Non allergic rhinitis, , NA: not applicable, NS: not specified

Appendix 2. Characteristics of included studies.

Author year	- Study design - Location	Study Population(s)	- NAR definition - NAR population characteristics	- Intervention - Nasal sampling method (Time) - Tested nasal allergen	- Test (unit) for nasal samples - Positive cut-off value for nasal specific IgE -Outcome
Becker 2016[7]	- Case control - Munich, Germany	- 19 NAR - 53 AR	- Symptoms, > 1 year, Serum spIgE (-), SPT (-) towards aeroallergen, Allergen component negative, NARES (nasal ECP>200ng/ml)) - Mean(range) age: 29(9-57), 53%F,	- Secretory total and spIgE - Nasal secretion: absorbed nasal secretion (NS time) - 51 allergen component (aeroallergens)	- ImmunoCAP® ISAC (ISU) , - Positive cutoff NS - Nasal spIgE component: Proportion
Botey 1993[8] (D)	- Case control - Spain	- 5 NAR - 12 AR	- Perennial history (+) rhinitis, RAST(-) towards DP (extracted from initial 17 patients with rhinitis) - Age: 7-19years *Duplicate: 8 patients with same definition but only SPT (-).	- Secretory spIgE -Nasal secretion: stimulated nasal secretion (NS time) - *Dermatophagoides pteronyssinus*	- RAST(PRU/ml) - Positive cutoff NS - Nasal spIgE: Proportion
Fuiano 2007[9]	- Case control - Italy	- 51 NAR - 74 AR	- Patients referred for rhinitis, SPT(-) <3mm aeroallergen (extracted from 125 rhinitis patients) - Age:3-47 (all rhinitis)	- Secretory spIgE - In situ Nasal test (NS time) - Aeroallergens	- Calorimetric reaction (class 0-4) -positive ≥1 - Nasal spIgE: Proportio
Fuiano 2012[10]	- Case control - Italy	- 36 NAR - 20 AR	- Seasonal symptoms ≥ 2 years during alternaria period , SPT (-) Alternaria. (extracted from 56 children with rhinitis) - Age mean (SD): 137.5±43.2 month (all rhinitis)	- Secretory spIgE - In situ incubation (during seasonal exposure) - Alternaria	- Calorimetric reaction (class 0 -4) - Positive cut-off ≥ 1 - Nasal spIgE: Proportion
Gelardi 2016[11]	- Case control - Italy	- 12 NAR - 15 AR - 14 Control	- Adults with rhinitis, SPT(-), serum spIgE<0.35 - Mean(SD) age: 32.4(15.2), 50%F, asthma:16.7%, FHA:33.3%, Aspirin sensitivity:0%	- Secretory total and spIgE - Mucosal sampling: nasal scraping in 0.5ml saline (NS time) Aeroallergens (parietera, olive, dust mite, cypress and grasses)	- Immunocap(kU/L) - Positive cut-off 0.17kU/L - Nasal spIgE: proportion
Huggins 1975[12]	- Case control - London	- 12 NAR - 8 AR - 5 Control	- Rhinitis symptom due to house dust, SPT(-) , RAST (-), NAPT (+) DP - Not described	- Concentrated secretory spIgE - Nasal secretion: absorbed nasal secretion (NS time) - *Dermatophagoides pteronyssinus*	- RAST - cut-off not stated - Nasal spIgE: Proportion
Lopez 2010[13] (D)	- Case control - Spain	-40 NAR -50 Control	- Previously diagnosed local allergic rhinitis, SPT(-), serum spIgE(-), ID(-), NAPT(+) towards DP - Age:25(18-63), 70%F, disease duration:3.5 years, FHA:70%, urban dwelling:63%, asthma:33%, conjunctivitis:25%, dust trigger:90% *Duplicate: Data for pre and Post NAPT	- Secretory spIgE - Nasal secretion: nasal lavage, 8mls saline (pre and post NAPT) - *Dermatophagoides pteronyssinus*	- UniCAP(kU/L) - Positive cutoff ≥0.35 - Nasal spIgE: Proportion
Marcucci 2004 [14]	- Case control - Perugia, Italy	- 4 NAR - 12 AR	- Questionnaire defined Symptom rhinitis, SPT(-) <3mm towards aeroallergen (extracted from 126 children, of these 16 had rhinitis) - Age:6-12(total population)	- Secretory spIgE - In situ incubation (NS time) - Aeroallergens (Phleum pratanse G6,Perietaria judaica W19, Oleo eropoea T9,Dermatophagoided pteronyssinusD1,cat E1 and dog E5	- CAP system reference (own lab protocol) kU/L - Positive cut-off ≥0.35 - Nasal spIgE: Proportion
Mogi 1977[15]	- Case control - Japan	- 38 NAR - 112 AR - 50 Control	- Patients with nasal allergy and asthma, SPT(-) dust (extracted from nasal allergy group) - Not described	- Secretory spIgE - Nasal secretion: absorbed nasal secretion eluted in 2 ml saline (NS time) - House dust	- RAST(Class 0-4) - Positive if ≥1 - Nasal total IgE: mean±2SEM Nasal spIgE: Proportion

Author year	- Study design - Location	Study Population(s)	- NAR definition - NAR population characteristics	- Intervention - Nasal sampling method (Time) - Tested nasal allergen	- Test (unit) for nasal samples - Positive cut-off value for nasal specific IgE -Outcome
Ohashi 1985[16]	- Case control - Osaka, Japan	- 4 NAR - 8 AR - 10 Control	- Perennial symptoms, SPT (-) or RAST(-) but NAPT (+)-House dust (Extracted from total rhinitis population) - Not described	- Tissue splgE - Inferior turbinate biopsy homogenized in 20ml saline (NS time) - House dust	- RAST (PRU/g) - Positive cut-off NS - Nasal splgE: Proportion
Patriarca 1990 [17] (D)	- Case control - Rome, Italy	- 24 NAR - 21 AR	- Patients with rhinitis, SPT (-) (Extracted from total rhinitis group) - Age:16-26 years (total rhinitis)	- Secretory splgE - Nasal secretion: absorbed nasal secretion (NS time) - not specified	- RAST (class 0-4) - Positive if ≥1 - Nasal splgE: Proportion
Perkins 1989 [18]	- Case control - Madigan Army medical center	- 10 NAR - 10 AR - 10 Control	- Patients diagnosed as NAR, SPT(-), RAST(-) aeroallergen, no clinical history of allergy, no FHA - Age (average): 54	- Concentrated Secretory splgE - Nasal secretion: absorbed nasal secretion eluted in 2ml saline (NS time) -R elevent allergen (from skin test or seven common aeroallergen if SPT negative guided by history)	- RAST (class0-4) - Positive cut-off NS - Nasal splgE: Proportion
Rondon 2007 [19]	- Case control - Malaga, Spain	- 50 NAR - 30 AR - 30 Control	- Persistent symptom >2 years, SPT (-) serum splgE (-) perennial aeroallergen, ID (-) DP, no vasomotor symptoms - Age:39(16), 66%F, asthma:32%, conjunctivitis:48%, dermatitis:2%, severe rhinitis:37.5%	- Secretory total and splgE - Nasal secretion: nasal lavage, 10 ml (NS time) *Dermatophagoides pterynissinus*	- Immunocap - Positive cutoff >0.35kU/L - Nasal splgE: Proportion
Rondon 2008[20]	- Case control - Malaga, Spain	- 32 NAR - 35 AR - 50 Control	- Symptom exclusively during pollen season > 2 years, SPT (-) , serum splgE (-) aeroallergens and ID (-) grass and O. europea pollen, good response to medication - Age: 41(18), 59%F, FHA:46%, asthma:31%conjunctivitis:62%, smoking:0%,	- Secretory total and splgE - Nasal secretion: nasal lavage, 10ml (During season) - Grass and olive	- UniCAP - Positive cutoff >0.35 kU/L - Nasal splgE: proportions
Rondon 2009[21]	- Case control - Malaga, Spain	- 30 NAR - 30 Control	- Seasonal Symptom ≥ 2yrs, NAPT (+) , SPT(-), serum splgE (-) common aeroallergen and ID (-) grass (all LAR) - Age:39(15), 63%F, FHA:43%, asthma:47%, conjunctivitis:57%, trigger pollen:100%	- Secretory splgE - Nasal secretion: nasal lavage, 10ml (post NAPT) - Grass	- Unicap (kU/L) - Positive cutoff ≥0.35 kUA/L - Nasal splgE: Proportion
Small 1985[22]	- Case control - Montreal, Canada	- 32 NAR - 21 AR	- Symptom(+), SPT(-) and/or RAST (-) aeroallergen (extracted from 53 rhinitis patients) - Age:15-56 (total rhinitis group)	- Secretory splgE - Nasal secretion: suctioned nasal secretions (NS time) - Aeroallergen (dust, ragweed, grass, tress)	- RAST (0-3+) - Positive cut-off NS -Nasal splgE: Proportion
Blanca-Lopez 2016 [23]	- Case series - Central Spain	- 61 NAR	- Seasonal history > 2years, SPT(-), serum splgE(-), towards aeroallergen, ID (-) phleum pollen, 37 NAPT (+) and 24 NAPT - towards phleum pollen, adult and children - Age (mean(SD), range): 36.15(15.89), 7-67, 62%F ,FH atopy:62%, asthma:44.26%, mild-mod:83.6%, smoker or Ex: 52.4%, drug allergy:3.27%, food allergy: 3.27%, conjunctivitis:95%	- Secretory splgE - Nasal secretion: nasal lavage, 8ml saline (baseline and 1 H post NAPT) - Phleum pollen	- Unicap - Positive cutoff: 0.35 kUA/L - Nasal splgE: Proportion

Author year	- Study design - Location	Study Population(s)	- NAR definition - NAR population characteristics	- Intervention - Nasal sampling method (Time) - Tested nasal allergen	- Test (unit) for nasal samples - Positive cut-off value for nasal specific IgE -Outcome
Jacobs 1981[24]	- Case series - Texas, US, study	- 19 NAR	- Rhinitis symptom, SPT(-), ID(-) towards aeroallergens, nasal eosinophilia >20% (NARES) - Not described(for subpopulation with nasal sampling) for whole 52 NARES patients: FHA:50%, 57.6%F, Unknown trigger:42%, weather trigger:31%, pollen, food or epthelium:0%, dust or smoke:12%	- Secretory spIgE - Nasal secretion:10 collected nasal secretion (diluted 1:1 with saline) and 9 nasal washes with 10mls saline (NS time) - Six perennial aeroallergens	- RAST - Positive cut-off NS - Nasal spIgE: Proportion
Merrett 1976[25]	- Case series - Kent, England	- 20 NAR	- Subjects with mild or recently acquired allergy, RAST (-) aeroallergen - Not described	- Secretory spIgE - Nasal secretion: stimulated nasal secretion (NS time) - Aeroallergen	- RAST (class 0-4) - Positive if ≥1) - Nasal spIgE: Proportion
Refaat 2015[26]	- Case series (Abstract) - Cairo, Egypt	- 40 NAR	- Rhinitis patients, SPT(-) and normal total IgE (NS) - Not described	- Secretory spIgE - NS - NS	- NS - NS - Nasal spIgE: Proportion
Reisacher 2014 [27] (D)	- Case series - New York, US	- 20 NAR	- Clinical history of idiopathic NAR, SPT (-)<3mm and/ or serum spIgE (-) <0.35kU/L aeroallergen - Age:38(23-59), 90%F, seasonal sx:65%, eye sx:75%, wheezing/ chest tightness:30% *Duplicate data: Two cut-offs used	- Mucosal spIgE - Mucosal sampling: mucosal brushings (NS time) - Aeroallergen	- Immunocap - Positive cutoff ≥ 0.1 kU/L and ≥0.35 kU/L - Nasal total IgE: Mean±SD, Nasal spIgE: Proportion

AR: Allergic rhinitis, D: Data duplicated in these studies, FHA: family history atopy, NAR: Non allergic rhinitis, , NA: not applicable, NS: not specified .