

# Difficulties in diagnosing allergic rhinitis in infants: a systematic review

*Dificuldades do diagnóstico de rinite alérgica em lactentes: revisão sistemática*

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## ABSTRACT

**Background:** Allergic rhinitis has been neglected in infants, mainly because the diagnosis is challenging. **Objective:** To identify the methods used to diagnose allergic rhinitis in infants. **Methods:** From April to August 2020, 2 independent reviewers systematically searched Scopus, PubMed/MEDLINE, SciELO, and LILACS databases using the following keywords: allergic rhinitis, diagnosis, and infant. The search considered original studies in English or Spanish involving children aged 0 to 2 years, regardless of publication date. **Results:** A critical analysis of the 5 included studies showed great heterogeneity in the definition of allergic rhinitis in children under 2 years of age. No studies were found that established an index test or gold standard, and there was no comparison between the available diagnostic methods. Because the clinical symptoms of allergic rhinitis in infants are variable and nonspecific and sensitization to aeroallergens is not necessarily clinically significant, making an accurate diagnosis of allergic rhinitis remains difficult in young children. **Conclusion:** Careful medical history and physical examination by the attending physician are essential for the diagnosis of allergic rhinitis in infants, as are the tests to be used for the detection of allergic sensitization, whose results should be correctly interpreted and correlated with the patient's medical history and physical examination.

**Keywords:** Allergic rhinitis, infant, diagnosis.

## RESUMO

**Introdução:** Rinite alérgica em lactentes é uma condição negligenciada, principalmente pelo seu diagnóstico desafiador. **Objetivo:** O presente estudo propõe identificar os métodos de investigação usados para o diagnóstico de rinite alérgica em lactentes. **Método:** Dois examinadores, de forma independente, realizaram busca sistemática da literatura, de abril a agosto de 2020, utilizando quatro bases de dados: Scopus, PubMed/MEDLINE, SciELO e LILACS. Foram usadas as seguintes palavras-chaves: rinite alérgica, diagnóstico e lactente. Foram pesquisados estudos originais na língua inglesa e espanhola, com crianças de 0 a 2 anos de idade, sem distinção de data de publicação. **Resultados:** Em análise crítica dos cinco estudos selecionados, percebeu-se grande heterogeneidade de definição de rinite alérgica em crianças menores de dois anos. Não foram encontrados estudos que estabeleceram um teste índice e o padrão ouro e não houve comparação entre os métodos diagnósticos disponíveis. A variabilidade e a inespecificidade de sintomas clínicos de rinite alérgica em lactentes, associadas ao fato de que a sensibilização a aeroalérgenos não tem necessariamente significado clínico, representam uma dificuldade para o correto diagnóstico de rinite alérgica em crianças pequenas. **Conclusão:** Para o diagnóstico de rinite alérgica em lactentes, é fundamental que o médico assistente realize cuidadosa anamnese e exame físico, além de testes para detectar sensibilização alérgica com correta interpretação do resultado e correlação com a história clínica e exame físico do paciente.

**Descritores:** Rinite alérgica, lactente, diagnóstico.

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## Introduction

Allergic rhinitis (AR) is an immunoglobulin E (IgE)-mediated disease that causes inflammation of the nasal sinus mucosa and is triggered by exposure to aeroallergens in individuals with a genetic predisposition.<sup>1,2</sup> Common symptoms include nasal congestion, rhinorrhea, sneezing, and itching.<sup>1-3</sup> Studies have reported a prevalence of AR ranging from 0% to 48% in infants, and this is not only due to geographic differences, but also to different criteria and definitions used to diagnose AR in young children.<sup>4</sup> The increase of AR in infants has become a problem, as AR is associated with sleep deprivation, fatigue, lack of concentration and learning difficulties, high medication expenses, and school absenteeism. It may also progress to asthma or exacerbate pre-existing asthma.<sup>2,3,5</sup> However, AR in infants is an unnoticed, mistreated, and misunderstood condition. It is neglected in all aspects, mainly because it is difficult to diagnose.<sup>2,6</sup>

It is challenging to diagnose AR in infants, both because of the similarity to upper airway infections, which are frequent in this age group, and the difficulty in performing tests to diagnose its etiology and assessing its subjective symptoms.<sup>2</sup> Infants with AR symptoms should have the following differential diagnoses excluded: cystic fibrosis, choanal atresia or stenosis, foreign body, inborn errors of immunity, and primary ciliary dyskinesia.<sup>1,2,7</sup>

The main international guidelines and the Brazilian consensus on rhinitis<sup>1</sup> consider a comprehensive medical history (clinical history, rhinitis symptoms, personal and family history of atopy), careful physical examination, and proof of allergic sensitization crucial for the diagnosis of AR. Thus, the diagnosis of AR is clinical and associated with identification of the possible causative allergen through skin prick test for immediate hypersensitivity or a serum specific IgE.<sup>1,3,8,9</sup> The Japanese consensus on AR includes a positive nasal eosinophil test.<sup>10</sup>

The present review aims to identify the criteria used to diagnose AR in infants in order to understand the current diagnostic variability, aid clinical practice, and guide future research. The review also aims to foster further research on AR in infants and to encourage the best diagnosis-based treatment for this age group.

## Methods

A systematic review was conducted to answer the question “what are the diagnostic criteria available

to diagnose AR in infants?”. The study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO), registration number CRD420209565.

A systematic literature search was performed from April to August 2020 using the following keywords and Boolean operators: diagnosis AND allergic AND rhinitis AND infant (Scopus); (“Rhinitis, Allergic” [MeSH]) AND “Diagnosis” [MeSH]) AND “Infant” [MeSH] (PubMed/MEDLINE); rhinitis, allergic AND diagnosis AND infant (SciELO); “Allergic Rhinitis” Infant Diagnosis (LILACS). We searched for original studies in English and Spanish including infants aged 0 to 2 years, regardless of publication date.

The results of the database searches were compiled, and 2 reviewers independently and concurrently screened titles and abstracts. The concordant articles were selected for full-text review, whereas the divergent ones were jointly reviewed, and a third reviewer resolved any discrepancies.

During full-text review, studies that did not provide information about the diagnosis of AR and that did not strictly address children under 2 years of age were excluded. Figure 1 shows the study selection process.

For data extraction, we analyzed methods, participants, clinical setting, definition of AR in the study, testing, and results. Data were extracted with a standardized form and compiled in tables, which allowed us to observe a variety of tests and results.

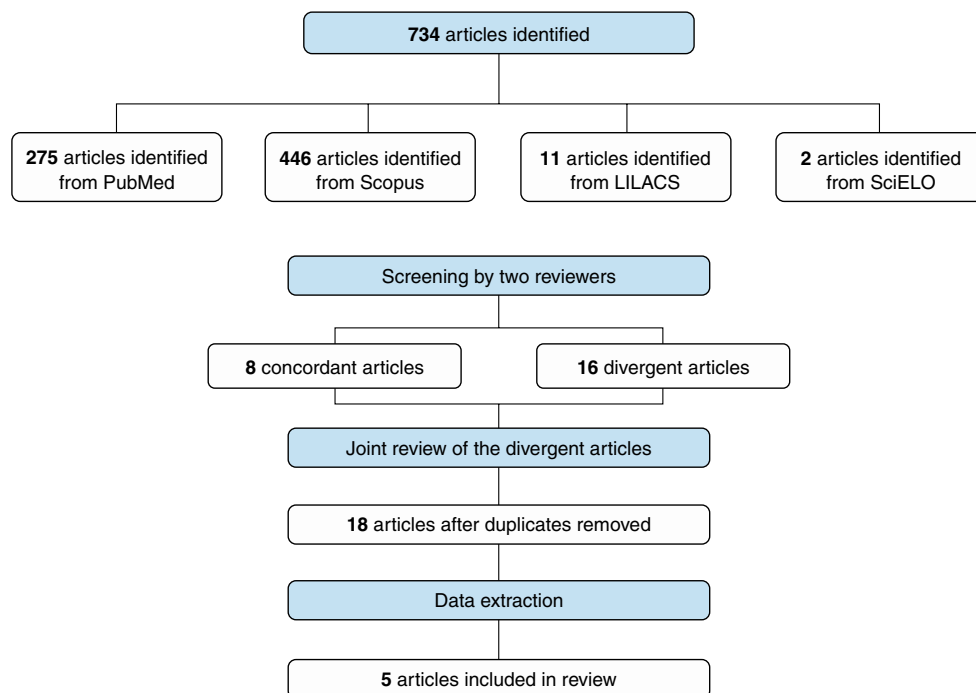
## Results

The systematic review of data on diagnostic criteria for AR in infants was not feasible. No primary studies were found to answer the question about the diagnostic criteria available to diagnose AR in infants.

The studies showed great heterogeneity in the definition of AR in children under 2 years of age. No studies were found that established an index test or gold standard, and there was no comparison between the available diagnostic criteria.

Therefore, the present study proposes a critical analysis of the 5 studies retrieved from the systematic search addressing the diagnosis of AR in infants. Table 1 shows the characteristics of each study.

Herr et al.<sup>11</sup> studied 1850 children in the PARIS birth cohort. AR symptoms (rhinorrhea, nasal obstruction, and sneezing without a cold) were collected through a standard questionnaire directed at



**Figure 1**  
Flowchart of the study selection process

the infants' caregivers. Parental history of allergy and blood markers of atopy (eosinophils  $\geq 470 \text{ mm}^3$ , IgE  $\geq 45 \text{ U/mL}$ , and presence of allergen-specific IgE) were analyzed. The prevalence of AR symptoms was 9.1% ( $n=169$ ), with no difference observed in either sex. The most commonly reported symptom was rhinorrhea (69.2%), followed by sneezing (32%) and nasal obstruction (20.7%). Symptoms were considered detrimental to the children's daily activities in 30 cases (17.8%). The authors suggested that universally accepted criteria to describe AR in infants are lacking. The study does not define diagnostic criteria for AR in infants; it investigates the association between AR symptoms, parental predisposition, and biological markers for atopy.

Chong et al.<sup>12</sup> reported that AR in young children is difficult to diagnose, and the symptoms are often confused with those of infectious rhinitis. However, symptoms that last longer than 2 weeks should prompt a search for causes other than infection. Chong et al.<sup>12</sup> studied 493 infants selected from a group of 1543 patients with asthma to assess the frequency of AR in infants with wheezing. Infants

with 2 or more nasal symptoms (sneezing, itching, congestion, and rhinorrhea) were considered to have rhinitis. They highlighted that 367 (74%) infants with asthma were diagnosed with rhinitis, and 131 (36%) had sensitization to aeroallergens detected by a skin prick test and were diagnosed with AR. The study showed that rhinitis is commonly present in infants with wheezing. The authors concluded that the diagnosis and definition of AR remains challenging in young children.

Chong et al.<sup>6</sup> verified the prevalence, clinical features, and treatment of AR symptoms in the first year of life using the International Study of Wheezing in Infancy (EISL) Phase III questionnaire with the addition of modified questions about AR from the International Study of Asthma and Allergies in Childhood (ISAAC). The following questions were directed at caregivers of 1003 children: (1) Has your baby ever had problem with sneezing, or a runny or blocked nose when he/she did not have a cold or the flu?; (2) Has your baby used antihistamines when he/she had problem with sneezing, or a runny or blocked nose when he/she did not have a cold or the flu?; (3)

**Table 1**  
Characteristics of the studies

Author/year	Country	Age	Sample size	Characteristics of the study	Diagnostic criteria	Definition of allergic rhinitis	Results
Herr M., et al., 2011	France	19 (SD, 2) months	1850	Cohort of children included in the PARIS birth control to describe the prevalence of symptoms suggestive of AR and to investigate the relationships between AR symptoms and atopy-related factors.	<ul style="list-style-type: none"> <li>Standard questionnaire directed at caregivers.</li> <li>Blood eosinophils by flow cytometry.</li> <li>Total serum immunoglobulin E (IgE).</li> <li>Specific IgE for food and aeroallergens.</li> </ul>	It does not define any criteria to diagnose AR in infants.	It reported an association between AR symptoms and biological markers of atopy (serum eosinophils and house dust mite sensitization). It suggested that AR may begin as early as 18 months.
Chong Neto H. J., et al., 2010	Brazil	0-24 months	493	Cross-sectional study to assess the frequency of rhinitis in infants with asthma.	<ul style="list-style-type: none"> <li>Standard questionnaire directed at caregivers.</li> <li>Skin prick test with aeroallergens.</li> </ul>	Rhinitis symptoms associated with sensitization to at least 1 aeroallergen through skin prick test.	367 infants (74%) were diagnosed with rhinitis and 131 (36%) with AR. Incidence of rhinitis in infants with asthma as well as atopic sensitization was similar to older children.
Chong Neto H. J., et al., 2014	Brazil	12-15 months	1003	Cross-sectional study to determine the prevalence, clinical characteristics, and treatment of AR symptoms in the first year of life.	<ul style="list-style-type: none"> <li>Standard questionnaire directed at caregivers: Phase III EISL questionnaire with the addition of modified questions from the ISAAC questionnaire.</li> </ul>	It does not define any criteria to diagnose AR in infants.	In their first year of life, 484 infants (48.3%) had at least 1 symptom of rhinitis, in the absence of a cold or the flu. High prevalence of early AR symptoms.
Otsuka H., et al., 2018	Japan	2-120 months	302	Cross-sectional study to diagnose AR in infants using a unique protocol.	<ul style="list-style-type: none"> <li>Clinical questionnaire directed at caregivers.</li> <li>Analysis of nasal cavity cells (neutrophils, eosinophils, and mast cells).</li> <li>Serum IgE specific for food and aeroallergen.</li> </ul>	Rhinitis symptom associated with eosinophils and/or mast cells on nasal swab and positive serum IgE for food and/or aeroallergen.	141 children < 2 years of age were diagnosed with AR. The association between sensitization to aeroallergens and AR in the age group under study is rare. Rhinitis symptoms and sensitization to food allergens may be associated in infants.
Osawa Y., et al., 2011	Japan	0-24 months	594	Cross-sectional study to evaluate the diagnosis of AR in infants.	<ul style="list-style-type: none"> <li>Clinical questionnaire directed at caregivers.</li> <li>Serum IgE for aeroallergen.</li> <li>Nasal eosinophils.</li> <li>Nasal changes assessed by anterior rhinoscopy.</li> </ul>	Aeroallergen sensitization associated with nasal eosinophils and intranasal examination with rhinorrhea and inferior turbinate hypertrophy.	The minimum prevalence of AR in children aged 18 months is estimated to be 1.5%. Diagnosis of AR in children < 2 years of age either by medical professionals or based on parent questionnaires is inaccurate.

AR = allergic rhinitis.

Has your baby used intranasal steroids when he/she had a problem with sneezing, or a runny or blocked nose when he/she did not have a cold or the flu?; and (4) Has your baby been diagnosed with AR by a doctor?. The study identified 484 babies (48.3%) who had at least 1 AR symptom in the first year of life and did not have an infection.

Otsuka et al.<sup>4</sup> stated that the onset of AR in infants is difficult to identify because it is challenging to make a conclusive diagnosis in young children. The authors conducted a study with 302 children (aged 2 to 120 months) to diagnose AR by combining different nasal cells and IgE for food and aeroallergens. Children with purulent rhinorrhea, common cold, systemic infectious disease, or eosinophilic syndrome were excluded. The study showed that 80% of children aged 2 to 14 months and 77% aged 15 to 24 months had rhinorrhea and only neutrophils on nasal swab, and the probable diagnosis was infectious rhinitis. No infants under 15 months of age had AR symptoms or specific IgE for an aeroallergen. However, AR symptoms were present in infants with sensitization to food allergens. The transition from food IgE response to aeroallergens occurred in infants older than 15 months, and sensitization to aeroallergens increased markedly after 25 months.

Osawa et al.<sup>5</sup> included 594 children (408 healthy infants and 186 who received medical care for various reasons) to determine the prevalence of sensitization to aeroallergens and the presence of nasal eosinophils in infants. In the group of healthy infants, 44 (10.7%) had allergen-specific IgE, 29 (7.1%) had nasal eosinophils, 8 (2%) had both, and 125 (30%) had rhinorrhea confirmed upon examination of the nasal cavity. Among the children who had sensitization to an aeroallergen in addition to nasal eosinophils, 6 (1.5%) had rhinorrhea confirmed upon physical examination. These children were diagnosed with AR. Among the 186 children who had attended the clinic, 5 (2.6%) had allergen-specific IgE and 6 (3.2%) had nasal eosinophils. No children had aeroallergen sensitization or nasal eosinophils. According to a questionnaire completed by the caregivers, 11 (2.7%) children had the diagnosis of AR made by a medical practitioner. However, sensitization to aeroallergen was confirmed in only 1 child, and none had nasal eosinophils. Thus, the authors stated that the diagnosis of AR based on parent questionnaires is unreliable. The authors concluded that diagnostic criteria for AR in children under 2 years of age need further definition to aid in early diagnosis and intervention.

## Discussion

In clinical practice, accurate etiologic diagnosis of rhinitis in infants is challenging, and only few studies have evaluated the natural history of AR in the pediatric population.<sup>8</sup> Most recommendations are extrapolated from studies of adults and/or older children.

We could observe from the studies included in the present review that the definition of AR is not homogeneous. Herr et al.<sup>11</sup> and Chong et al.<sup>6</sup> used the term AR symptoms but have not defined the diagnosis of AR. In a previous study conducted in 2010, Chong et al.<sup>12</sup> defined AR as the presence of rhinitis symptoms associated with the sensitization to at least one aeroallergen. Otsuka et al.<sup>4</sup> and Osawa et al.<sup>5</sup> highlight the importance of the analysis of nasal swabs in addition to clinical symptoms and allergic sensitization.

The ISAAC defines rhinitis based on a positive response from children's caregivers to the question, "In the past 12 months, has your child had a problem with sneezing, or a runny, or a blocked nose when he/she did not have a cold or the flu?". The questionnaire does not include a comprehensive medical history and allergic sensitization testing, which results in low accuracy for the diagnosis of AR. A Korean study reported an estimated accuracy of 60% for the ISAAC questionnaire and considered that it overestimates the true prevalence of AR.<sup>13</sup> Osawa et al.<sup>5</sup> doubt the accuracy of studies based on questionnaires directed at children's caregivers, because in their study none of the children whose parents reported that they had been medically diagnosed with AR were actually diagnosed when the diagnostic criteria for AR were used by the authors.

The guidelines of the Allergic Rhinitis and its Impact on Asthma (ARIA)<sup>14</sup> and the Brazilian consensus<sup>1</sup> consider a comprehensive medical history (clinical history, rhinitis symptoms, personal and family history of atopy) combined with a careful physical examination and proof of allergic sensitization crucial for the diagnosis of AR. The diagnosis of AR is therefore clinical and associated with identification of the possible causative allergen through skin prick test for immediate hypersensitivity or specific IgE.<sup>1,3,8,9</sup>

According to the Japanese consensus on AR, a definite diagnosis is based on symptoms (sneezing, itching, watery rhinorrhea, and nasal obstruction) combined with a positive nasal eosinophil test and identification of causative allergens (skin prick test for immediate hypersensitivity or allergen-specific



serum IgE).<sup>10</sup> Thus, Otsuka et al.<sup>4</sup> and Osawa et al.<sup>5</sup> agree with the definition established by the Japanese scientific community.

The European Forum for Research and Education in Allergy and Airways diseases<sup>2</sup> has developed a consensus guideline for AR in the pediatric population. According to the document, the diagnosis of AR in children is based on a detailed clinical history, physical examination and, if necessary, testing for allergen-specific IgE.<sup>2</sup>

AR symptoms may be persistent or intermittent, usually occurring within minutes of exposure to the allergen. In young children, AR symptoms may manifest less clearly and may be more subjective, as they depend on the caregiver's perception. In addition, young children are more likely to have infectious rhinitis, which adds to the challenge of diagnosing AR.<sup>2,8,9</sup>

The hypothesis of AR becomes more likely when the following conditions are present: ocular involvement, noticeable itching (allergic salute), symptoms exacerbated by a potential allergen, and family and/or personal history of atopy.<sup>2</sup> A specialist should also consider the following signs: children with unilateral symptoms refractory to treatment, such as severe nasal obstruction and sleep apnea; children with nasal polyps; children under 2 years of age; and children with nasal symptoms since birth.<sup>2</sup>

Examination of the nasal cavity with anterior rhinoscopy is key for the diagnosis of AR and should always be performed.<sup>8</sup> Classically, nasal examination shows hypertrophic, pale lower or middle turbinates with clear secretion.<sup>9</sup> Osawa et al.<sup>5</sup> highlight the importance of examining the nasal cavity and report that, in their study, the presence of rhinorrhea and hypertrophic turbinates allowed the identification of more children with AR than when infants were assessed based only on parent-reported symptoms.

Allergen-specific IgE detection can be performed in any age group by skin prick test for immediate hypersensitivity or allergen-specific serum IgE.<sup>2,15</sup> In a meta-analysis, the sensitivity of the skin prick test ranged from 68% to 100% and the specificity from 70% to 91%. However, studies of young children were not included.<sup>16</sup>

The poor agreement between skin prick test for immediate hypersensitivity and allergen-specific serum IgE and the poor correlation with clinical symptoms in young children suggest that allergy testing should be performed only in children with

symptoms of atopic disease, rather than as a diagnostic screening method.<sup>15</sup> Therefore, allergic sensitization test results should be interpreted in light of the clinical history, as both false-positive and false-negative results can occur.<sup>2</sup>

## Conclusion

Few studies have investigated diagnostic criteria for AR in infants, and consensus guidelines provide recommendations based on data extrapolated from older populations.

The variability and nonspecific nature of AR clinical symptoms in infants, combined with the fact that sensitization to aeroallergens does not necessarily have clinical significance, represent a challenge for the correct diagnosis of AR in young children. Thus, it is critical that the attending physician performs a careful history-taking and physical examination, including the nasal cavity, as well as tests to detect allergic sensitization (skin prick test for immediate hypersensitivity and/or allergen-specific serum IgE), whose results should be correctly interpreted and correlated with the patient's clinical history and physical examination. Differential diagnoses should also be considered.

AR in childhood has an impact on the quality of life of patients and their family members. In addition, it is a strong predictor of asthma in adolescents and adults.<sup>1,2</sup> Therefore, it is clear that accurate diagnosis and effective treatment of AR in childhood are highly important, with benefits that include not only improvement of patients' quality of life but also prevention of new atopic sensitizations.

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