

# Allergic Rhinitis and its Impact on Asthma Update (ARIA 2008) The Perspective From Spain

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## ■ Abstract

Allergic rhinitis is a global health problem. Over 600 million patients suffer from this disease worldwide. ARIA (Allergic Rhinitis and its Impact on Asthma), an evidence-based document, was produced and published in 2001 using an extensive review of the available literature. The ARIA 2008 update was recently published and covers tertiary prevention of allergy, pharmacologic treatments, and immunotherapy. Nonallergic rhinitis is still a controversial area and may pose some treatment problems. Another important aspect of the ARIA update is the comorbidity of allergic rhinitis, in particular, asthma. The recommendations of the 2008 ARIA Update, as in 2001, are that patients with allergic rhinitis, particularly if persistent, should be evaluated for asthma, patients with asthma should be evaluated for rhinitis, and an effective and safe combination strategy should be used to treat diseases of the upper and lower airways. Over the last few years, several studies performed in Spain report new data on the prevalence of allergic rhinitis, sensitivity to common aeroallergens, comorbidity of allergic rhinitis and asthma, and impact on quality of life. The studies reviewed in this manuscript confirm—as do those from other developed countries—the enormous impact of the disease on society and health care in Spain.

**Key words:** Allergic rhinitis. Epidemiology. Comorbidities. Quality of life.

## ■ Resumen

La rinitis alérgica constituye un problema de salud global. Más de 600 millones de pacientes sufren esta enfermedad en todo el mundo. ARIA (Allergic Rhinitis and its Impact on Asthma), un documento basado en pruebas científicas, fue elaborado y publicado en 2001 mediante una revisión sistemática de la literatura disponible. La actualización 2008 de ARIA ha sido publicada recientemente y una amplia lista de terapias han sido abordadas y actualizadas en cuanto a la prevención de la alergia, el tratamiento farmacológico y la inmunoterapia. La rinitis no alérgica constituye todavía un tema de discusión pudiendo ofrecer problemas de tratamiento. Otro aspecto importante de la actualización de ARIA son las comorbilidades de la rinitis alérgica, el asma en particular. Las recomendaciones de la Actualización 2008 de ARIA, como en 2001, son que en los pacientes con rinitis alérgica, sobre todo si es persistente, debe estudiarse la presencia de asma; en los pacientes con asma debe investigarse la rinitis; y debe emplearse una estrategia para el tratamiento combinado de la rinitis y el asma en términos de eficacia y gravedad. Durante los últimos años se han realizado en España diversos estudios que han aportado nuevos datos sobre la prevalencia de la rinitis alérgica en nuestra población, la sensibilidad a aeroalérgenos, la comorbilidad de rinitis alérgica y asma, y el impacto sobre la calidad de vida. Estos estudios, revisados en este artículo, confirman, al igual que en otros países desarrollados, el enorme impacto social y sanitario que la rinitis tiene en España.

**Palabras clave:** Rinitis alérgica. Epidemiología. Comorbilidades. Calidad de vida.

## ARIA Update (2008)

Allergic rhinitis is a symptomatic disorder of the mucous membrane of the nose induced after allergen exposure due to an IgE-mediated inflammation of the membranes lining the nose. It was defined in 1929: "The three cardinal symptoms in nasal reactions occurring in allergy are sneezing, nasal obstruction and mucous discharge" [1].

Allergic rhinitis is a global health problem that affects patients of all ages and ethnic groups. It causes major illness and disability worldwide. Allergic rhinitis affects social life, sleep, and performance at school and work [2-5], and its economic impact is substantial. However, rhinitis is still underdiagnosed and undertreated [6].

Over 600 million patients suffer from this disease [7-10], but there are still differences between rural and urban areas, both in developed and developing countries [8,10-12], possibly due to differences in immune reactions [14].

In 1999, during the ARIA (Allergic Rhinitis and its Impact on Asthma) World Health Organization (WHO) workshop, an evidence-based document was produced using an extensive review of the literature available up to December 1999 [15]. The statements of evidence for the development of ARIA followed WHO rules and the recommendations of Shekelle et al [16].

The ARIA document presented the state-of-the-art for the specialist, general practitioner, and other health care professionals. Its aims were as follows:

- To update knowledge of allergic rhinitis
- To highlight the impact of allergic rhinitis on asthma
- To provide an evidence-based documented review of diagnostic methods
- To provide an evidence-based review of the treatments available
- To propose a stepwise approach to the management of the disease

However, an update of the ARIA guidelines was necessary for the following reasons:

- The large number of papers published over the last 7 years has increased our knowledge [17-22].
- The ARIA classification was proposed by an expert group and needed to be validated in terms of classification and management [14]. New studies showed consistently that "intermittent" and "persistent" are not synonymous with "seasonal" and "perennial" [23,24]. Several reports have now validated this classification [25,26], although some authors proposed extending the severity of allergic rhinitis to 3 levels [27,28]. However, since this would not lead to a difference in treatment, the ARIA experts proposed continuing to classify the severity of rhinitis as "mild" and "moderate/severe."
- New methods of diagnosis have been proposed for allergic and nonallergic rhinitis [29-32]. The diagnosis of allergic rhinitis is often easy, but in some cases it is problematic and many patients are still underdiagnosed, often because they do not perceive the symptoms of rhinitis as a disease.
- Gaps in our knowledge in the first ARIA document have now been filled. These include complementary and alternative medicine [18], sports and rhinitis in athletes [19,33,34], and rhinitis and its links with asthma in children [35-39].

The ARIA update began in 2004 and was published earlier this year [42]. Several chapters were extensively reviewed using the Shekelle evidence-based model [16], and papers published in peer-reviewed journals [17-22]. These papers cover the area of tertiary prevention of allergy, complementary and alternative medicine, pharmacotherapy and anti-IgE treatment, allergen-specific immunotherapy, links between rhinitis and asthma, and mechanisms of rhinitis. The need arose for a global document to highlight the interactions between the upper and the lower airways including diagnosis, epidemiology, common risk factors, management, and prevention. Moreover, attention was also given to allergy in developing countries [40,41].

The grading of evidence and the recommendation for an evidence-based management system in the ARIA 2008 update did not follow the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [43, 44]. It is expected that some of the recommendations offered by the 2008 ARIA update would differ if the GRADE approach had been applied.

A large list of treatments was considered in the ARIA 2008 update [42]. Intranasal corticosteroids are the first-line therapy in patients with moderate to severe disease and are also effective against ocular symptoms [45]. H<sub>1</sub>-antihistamines are important treatments for all patients and leukotriene receptor antagonists are particularly important for patients with rhinitis and asthma [46,47]. Tertiary prevention of allergy is still a matter of debate, since clinical trials do not usually show any efficacy of single allergen avoidance measures [17]. Sublingual immunotherapy has proven to be a safe and effective treatment [48-51], but clinical trials need to be standardized [52,53]. An algorithm of the management of allergic rhinitis is provided (Figure). However, our progress in understanding the mechanisms of allergic rhinitis is continuous and novel treatment approaches are constantly being published [54].

Nonallergic rhinitis is still a matter of discussion [55] and may pose some treatment problems [56].

Another important aspect of ARIA was to consider comorbid conditions of allergic rhinitis, in particular, asthma. Epidemiologic studies throughout the world have consistently shown that asthma and rhinitis often coexist in the same patient [57-60]. The vast majority of patients with asthma have rhinitis, but the prevalence of asthma in rhinitis patients still needs to be assessed [61,62]. The treatment of nasal symptoms has little effect on the lower airways, but there have been some compelling data suggesting that new studies with innovative methods need to be started [63,64]. Specific immunotherapy in patients with allergic rhinitis has a prolonged effect on the development of asthma when stopped [65].

The perception of patients and physicians regarding the links between asthma and rhinitis varies between countries, but this perception appears to be stronger than expected [66,67]. However, knowledge is not directly translated into practice, since fewer physicians coprescribe treatments for rhinitis and asthma.

The recommendations of the ARIA workshop in 1999 are still valid [15], and patients with allergic rhinitis, in particular persistent allergic rhinitis, should be evaluated for asthma. Patients with asthma should be evaluated for rhinitis, and an efficacious and combined strategy should be adopted to treat diseases of the upper and lower airway.

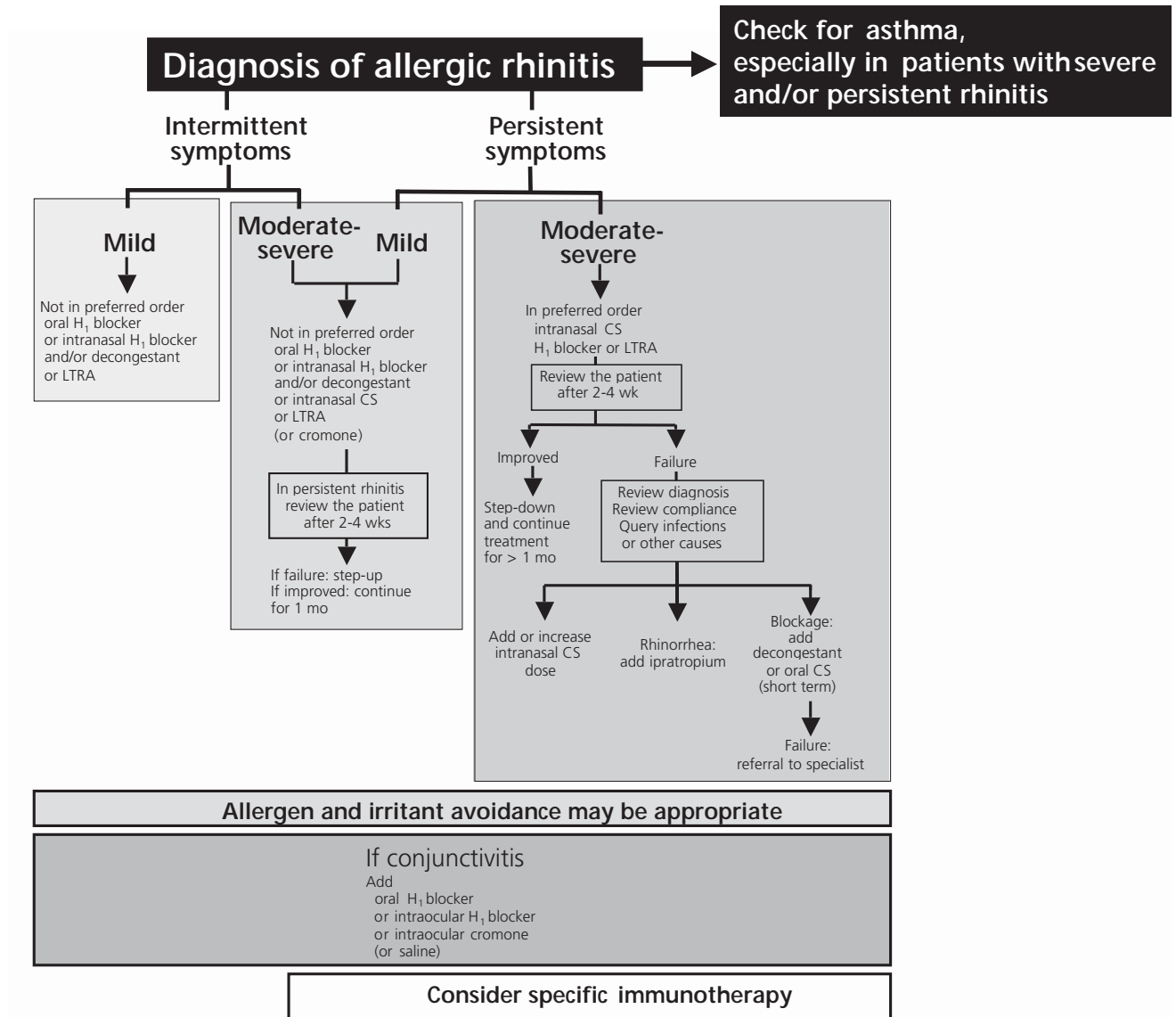


Figure. Management (diagnosis and treatment) scheme of allergic rhinitis according to the 2008 ARIA Update (with permission from reference 42). Abbreviations: CS, glucocorticosteroid; LTRA, leukotriene receptor antagonist.

## Allergic Rhinitis: the Perspective From Spain

Over the last few years, several Spanish studies have reported new data on the prevalence of allergic rhinitis, sensitivity to common aeroallergens, comorbidity of allergic rhinitis and asthma, and impact on quality of life. The results of these studies confirm (as is the case in other developed countries) the enormous impact of the disease on society and health care.

Bauchau and Durham [23] performed a pan-European epidemiological study on the prevalence of allergic rhinitis in 6 European countries (Belgium, France, Germany, Italy,

Spain, and the United Kingdom). The study was performed in 2 phases: during the first phase, 9646 subjects were surveyed by phone and, during the second, 725 subjects were selected and included in a clinical trial in which 411 subjects were diagnosed with allergic rhinitis.

The Estudio Ibérico [68], was a descriptive, observational, cross-sectional, population-based study carried out in Portugal and Spain in a population of allergic rhinitis patients to evaluate skin sensitization, characteristics of rhinitis, and comorbidity of rhinitis and asthma. The sample was composed of patients aged 10 to 50 years with allergic rhinitis consecutively attended at allergology centers. Patients were diagnosed using skin prick test to 20 standardized aeroallergens, and rhinitis was classified

according to ARIA and the etiological agent and asthma according to the Global Initiative for Asthma (GINA) [69].

The Spanish Society of Allergology and Clinical Immunology (SEAIC) developed 2 epidemiological studies, Alergológica, with the objective of obtaining information on allergic patients attended at outpatient allergology clinics. Those surveys were performed in 1992 and again in 2005 with the inclusion of 4005 and 4991 patients, respectively [70,71].

Two other prospective studies [72,73] have recently been performed in allergology (Oneair) and pneumology (Rinair) outpatient clinics to study the prevalence of allergic rhinitis among patients with diagnosed asthma from 2005 to 2006. Using an adequate geographic distribution, 170 specialists in allergology and 172 in pneumology participated in the studies. Demographic data, outcome of asthma and rhinitis, and classification according to GINA and ARIA were collected from 942 (Oneair) and 703 (Rinair) asthma patients.

To develop and validate a specific Spanish questionnaire for allergic rhinitis, the ESPRINT (ESTudio de la calidad de vida en Pacientes con RINOconjuntivitis) study was performed with the participation of over 40 centers and 800 patients, 413 in the item-reduction phase and 400 in the questionnaire-validation phase [74,75]. The inclusion criterion for patients with allergic rhinitis participating in the study was a total symptom score greater than 3 (score of 0 to 3 in each of nasal congestion, rhinorrhea, nasal itching, and sneezing). In the context of this project, new criteria to classify the severity of allergic rhinitis as mild, moderate, and severe according to ARIA severity items were also established [28].

### Epidemiology

The pan-European study reported a global prevalence of allergic rhinitis of 22.7% (95% confidence interval [95% CI]; 21.1-22.2) with a variation in European countries ranging from 16.9% (95% CI, 12.9-20.9) for Italy to 28.5% (95% CI, 24.5-32.5) for Belgium [23]. In the global survey, 45% of cases had no previous diagnosis (underdiagnosis) of allergic rhinitis. Five centers and cities (Barcelona, Bilbao, Madrid, Sevilla, Valencia) participated for Spain. In the first phase, 1600 telephone surveys were performed and, in the second phase, 100 subjects were studied to confirm the diagnosis of allergic rhinitis. The prevalence of allergic rhinitis in Spain was 21.5% (18.5-24.4).

The Estudio Ibérico studied 3225 subjects (2020 for Spain and 1205 for Portugal) [67] with a mean age of 27 years. Major house dust mites (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*) and grass and olive pollens were the most prevalent allergens, with skin polysensitization accounting for 95% of cases with a mean (SD) of 6.5 (3.7) sensitizations per subject. There were more cases of sensitization to pollens (n=2298) and house dust mites (n=2245) than to animal dander (n=1329) and mold (*Alternaria*) (n=399). Monosensitization accounted for 26% of cases for pollens and house dust mites and 2% of cases for animal dander and molds, while allergen group monosensitization accounted for 37% of cases (18% for pollens, 18% for house dust mites, 0.8% for animal dander, and 0.3% for *Alternaria*).

In the 1992 and 2005 Alergológica surveys [70,71], the prevalence of diagnosed allergic rhinitis was 52% and 55%, respectively, and 47% for the pediatric population (1992). The mean (SD) age of rhinoconjunctivitis patients was 32.1 (18) and 29.9 (15), respectively.

### Classification of Allergic Rhinitis According to the ARIA Criteria

Several studies performed in Spain over recent years have investigated the new classification of allergic rhinitis according to the ARIA criteria [15,23-26]. In the pan-European study, 21% (13.5-30.3) of allergic patients were classified as persistent in Spain while 29.3% (24.9-34.0) were persistent in the global study [23]. In the Estudio Ibérico, 64% of subjects with allergic rhinitis who visited allergy outpatient clinics (N=3225) were classified as persistent and 41% as moderate-to-severe [68].

In the Oneair study, 54% of asthmatic patients with allergic rhinitis were classified as persistent and 57% as moderate-to-severe (24% mild intermittent, 22% moderate/severe intermittent, 19% mild persistent, and 35% moderate/severe persistent) [72]. In the Rinair study, 43% of patients were classified as persistent and 74% as moderate-to-severe (9.2% mild intermittent, 47.4% moderate/severe intermittent, 16.3% mild persistent, and 27.1% moderate/severe persistent) [73].

In the ESPRINT study, 59% of the patients consulted with allergic rhinitis (N=400) in a specialist (allergology, otorhinolaryngology) outpatient clinic were classified as persistent [74,75]. To differentiate between moderate and severe allergic rhinitis, a new criterion was reported according to ARIA severity items [28]: patients with 1, 2, or 3 severity items affected continue to be classified as moderate, whereas patients with all 4 items affected are now classified as severe.

### Comorbidity of Rhinitis and Asthma

Most studies on the association between rhinitis and asthma evaluate the prevalence of asthma in patients with allergic rhinitis, while few assess the prevalence of rhinitis in patients with asthma. The prevalence of allergic rhinitis among asthma patients varies widely in published studies, ranging from 80% to 95% in the most recent [76]. In the Estudio Ibérico, 49% of patients with allergic rhinitis had concomitant asthma (56% intermittent, 44% persistent, 33% mild, 10% moderate, and 1% severe [68]). In the 2005 Alergológica study, 37% of patients with allergic rhinitis had concomitant asthma and 65% conjunctivitis [69].

In the Oneair (allergologists) and Rinair (pneumologists) studies, the prevalence of allergic rhinitis among asthma patients was 71% and 89.5%, respectively [72,73]. However, it is interesting to emphasize that, in the Rinair study, the prevalence was much higher among allergic (84%) than nonallergic (51%) asthmatics. In the Oneair study, the prevalence of asthma severity groups according to the GINA classification was 38.5% intermittent and 61.5% persistent (29.4% mild, 27.2% moderate, and 4.9% severe). In the Rinair study, the prevalence of asthma by severity was 24.5% intermittent and 75.5% persistent (35.4% mild, 32.7% moderate, and 7.4% severe).



In both studies, there was a significant correlation ( $P < .0001$ ) between the severity of rhinitis and of asthma. The prevalence of rhinitis decreased among older and more severely affected asthmatic patients.

Of the 400 allergic rhinitis patients for whom the ESPRINT questionnaire was validated, 39% had concomitant asthma and 53% conjunctivitis [74,75].

### Quality of Life

During the last few decades, considerable importance has been given not only to the symptoms present in a variety of diseases, but also to how these diseases affect the quality of life (QoL) of patients. Thus, generic and specific questionnaires have been developed to assess the QoL of allergic rhinitis patients [77-81].

The 2005 Alergológica study, which used the SF-12 generic questionnaire that assesses the impact on health-related QoL [82], showed that values for allergic rhinitis patients were located between the 25th percentile (physical component) and 20th percentile (mental component) for the general population of Spain, meaning that the QoL perceived by patients with allergic rhinitis was lower than that perceived by 75% of the general population [71].

In the ESPRINT study, a new specific questionnaire to assess the QoL in allergic rhinitis patients was developed and validated for the Spanish population. The ESPRINT questionnaire has 2 versions, a long version with 28 items to be used in research studies, and a short version with 15 items to be used in daily clinical practice. Using both long and short questionnaires has revealed an impact of allergic rhinitis on QoL, and this impact is higher in persistent than in intermittent allergic rhinitis. There was a significant correlation with the severity of allergic rhinitis according to the ARIA classification, which made it possible to differentiate between different levels of rhinitis severity [28,74,75].

### Socioeconomic Burden

Few studies have evaluated the economic and social burden of allergic rhinitis [2, 4, 83-85]. In Spain, no studies have been performed to date on the economic burden of allergic rhinitis. In the 2005 Alergológica study [71], 61% of patients visited their family physician during the last quarter with an average of 2.1 visits. During the last year, 29% of patients visited a specialist with an average of 1.7 visits, while 22% visited the emergency room, with an average of 1.9 visits per year (1.2% of patients had to be hospitalized). In allergic rhinitis/conjunctivitis patients, 6% reported absenteeism from work related to their disease, 66% with only 1 episode, and an average duration of 15.6 days. Among a population sample of 337 students, an average of 8 working days lost during the last year was reported. Work absenteeism by parents was reported in 15% of a pediatric sample ( $N=513$ ), with an average of 4 days/year. In general, good school performance was reported for 79% of children.

In conclusion, due to the high prevalence of allergic rhinitis, its impact on quality of life, and the social and health care burden, further investigation is necessary to obtain pharmaco-economic data on allergic rhinitis in Spain.

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