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## Allergic Rhinitis and its Impact on Asthma (ARIA) 2008

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## Abstract

Allergic rhinitis is a symptomatic disorder of the nose induced after allergen exposure by an IgE-mediated inflammation of the membranes lining the nose. It is a global health problem that causes major illness and disability worldwide. Over 600 million patients from all countries, all ethnic groups and of all ages suffer from allergic rhinitis. It affects social life, sleep, school and work and its economic impact is substantial.

Risk factors for allergic rhinitis are well identified. Indoor and outdoor allergens as well as occupational agents cause rhinitis and other allergic diseases. The role of indoor and outdoor pollution is probably very important, but has yet to be fully understood both for the occurrence of the disease and its manifestations.

In 1999, during the Allergic Rhinitis and its Impact on Asthma (ARIA) WHO workshop, the expert panel proposed a new classification for allergic rhinitis which was subdivided into 'intermittent' or 'persistent' disease. This classification is now validated.

The diagnosis of allergic rhinitis is often quite easy, but in some cases it may cause problems and many patients are still under-diagnosed, often because they do not perceive the symptoms of rhinitis as a disease impairing their social life, school and work.

The management of allergic rhinitis is well established and the ARIA expert panel based its recommendations on evidence using an extensive review of the literature available up to December 1999. The statements of evidence for the development of these guidelines followed WHO rules and were based on those of Shekelle et al. A large number of papers have been published since 2000 and are extensively reviewed in the 2008 Update using the same evidence-based system. Recommendations for the management of allergic rhinitis are similar in both the ARIA workshop report and the 2008 Update. In the future, the GRADE approach will be used, but is not yet available.

Another important aspect of the ARIA guidelines was to consider co-morbidities. Both allergic rhinitis and asthma are systemic inflammatory conditions and often co-exist in the same patients. In the 2008 Update, these links have been confirmed.

The ARIA document is not intended to be a standard-of-care document for individual countries. It is provided as a basis for physicians, health care professionals and organizations involved in the treatment of allergic rhinitis and asthma in various countries to facilitate the development of relevant local standard-of-care documents for patients.

## Review article

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## 1. Introduction

Allergic rhinitis is a symptomatic disorder of the nose induced after allergen exposure by an immunoglobulin E (IgE)-mediated inflammation of the membranes lining the nose (1). It was defined in 1929 (2): ‘The three cardinal symptoms in nasal reactions occurring in allergy are sneezing, nasal obstruction and mucous discharge’.

Allergic rhinitis is a global health problem that causes major illness and disability worldwide. Patients from all

countries, all ethnic groups and of all ages suffer from allergic rhinitis. It affects social life, sleep, school and work. The economic impact of allergic rhinitis is often underestimated because the disease does not induce elevated direct costs. However, the indirect costs are substantial (1). Both allergic rhinitis and asthma are systemic inflammatory conditions and are often co-morbidities.

Although asthma and other forms of allergic disease have been described in antiquity, ‘hay fever’ is surprisingly modern. Very rare descriptions can be traced back to

*Abbreviations:* AAAAI, American Academy of Allergy, Asthma and Immunology; ABPA, allergic bronchopulmonary aspergillosis; ACAA, American College of Allergy, Asthma and Immunology; AGREE, Appraisal of Guideline Research & Evaluation; AIA, aspirin-induced asthma; AIANE, European Network on Aspirin-Induced Asthma; ANAES, Agence Nationale de l’Accréditation et d’Evaluation en Santé; AOM, acute otitis media; AQLQ questionnaire, asthma quality of life questionnaire; ARIA, Allergic Rhinitis and its Impact on Asthma; ATS, American Thoracic Society; BCG, Bacille de Calmette et Guérin; Bet v 1, *Betula verucosa* antigen 1 (major birch pollen allergen); CAM, complementary and alternative medicine; CD, Cluster of Differentiation; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; CNS, central nervous system; CO, carbon monoxide; CO<sub>2</sub>, carbon dioxide; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; CRD, chronic respiratory diseases; CRS, chronic rhinosinusitis; CT scan, computerized tomography scan; CXCR, CXC chemokine receptor; CysLT, cysteinyl leukotrienes; DALY, disability-adjusted life years; Der f, *Dermatophagoides farinae*; Der p 1, *Dermatophagoides pteronyssinus* antigen 1 (major HDM allergen); DPT, Diphtheria-Tetanus-Pertussis; EAACI, European Academy of Allergy and Clinical Immunology; EBM, evidence-based medicine; ECRHS, European Community Respiratory Health Survey; ECM, extracellular matrix; ECP, eosinophil cationic protein; EFA, European Federation of Allergy & Airway diseases patients association; EIA, exercise-induced asthma; EIB, exercise-induced bronchoconstriction; Equ c, *Equus caballus* (horse); ETS, environmental tobacco smoke; Eur m, *Euroglyphus maynei*; EVH, Eucapnic Voluntary Hyperventilation; FceRI, high affinity receptor for IgE; FceRII, low affinity receptor for IgE (CD23); Fel d 1, *Felix domesticus* allergen 1 (major cat allergen); FEV<sub>1</sub>, forced expiratory volume in 1 s; FLAP, 5-lipoxygenase (LO) activating protein; FVC, forced vital capacity; GARD, WHO Global Alliance against chronic Respiratory Diseases; GER, gastro-oesophageal reflux; GM-CSF, granulocyte, monocyte colony-stimulating factor; GR, glucocorticosteroid receptor; GRADE, Grading of Recommendations Assessment, Development and Evaluation; GRE, glucocorticosteroid receptor responsive element; HDM, house dust mite; HEPA, High Efficiency Particulate Air Filter; HETE, hydroxyeicosatetraenoic acid; HPA axis, hypothalamic-pituitary-adrenal axis; HPETE, hydroperoxyeicosatetraenoic acid; HRQOL, health-related quality of life; IAR, intermittent allergic rhinitis; IPAG, International Primary Care Airways Group; IPCRG, International Primary Care Respiratory Group; ISAAC, International Study on Asthma and Allergy in Childhood; IU, International Unit; IUIS, International Union of Immunological Societies; Lep d, *Lepidoglyphus destructor*; LTC<sub>4</sub>, leukotriene C<sub>4</sub>; LTD<sub>4</sub>, leukotriene D<sub>4</sub>; LRT, lower respiratory tract; mAb, monoclonal antibody; MAS, German Multi-center Allergy Study; MMR, Measle-Mumps-Rubella; MMPs, Matrix Metallo Proteinases; mRNA, messenger ribonucleic acid; Mus m, *Mus musculus*; NANC, nonadrenergic, noncholinergic; NAR, nasal airway resistance; NARES, nonallergic rhinitis with eosinophilia syndrome; NHANES II, second National Health and Nutrition Examination Survey (USA); NIH, National Institutes of Health; NO, nitric oxide; NO<sub>2</sub>, nitrogen dioxide; NP, nasal polyp; NSAID, nonsteroidal anti-inflammatory drug; OAD, occupational asthma; OME, otitis media with effusion; OR, odds ratio; Ory c, *Oryctolagus cuniculus*; OSAS, obstructive sleep apnoea syndrome; OTC, over-the-counter; PADQLQ, Paediatric Allergic Disease Quality of Life Questionnaire; PCR, polymerase chain reaction; PDGF, platelet-derived growth factor; PedsQL, paediatric quality of life inventory; PEF, peak expiratory flow; PEFr, peak expiratory flow rate; PAR, persistent allergic rhinitis; PG, prostaglandin; Phl p, *Phleum pratense*; PIAMA, Prevention and Incidence of Asthma in Mite Allergy; PM10, particulate matter < 10 µm; PNIF, peak nasal inspiratory flow; PRIST, paper radioimmunosorbent test; PRN, as needed; QALY, quality-adjusted life years; QOL, quality of life; QTc, QT interval; Rat n, *Rattus norvegicus*; RAST, radioallergosorbent test; RCT, randomized-controlled trial; RQLQ, rhinoconjunctivitis quality of life questionnaire; RSV, respiratory syncytial virus; SAPALDIA, Swiss Study on Air Pollution and Lung Diseases in Adults; SCARPOL, Swiss Study on Childhood Allergy and Respiratory Symptoms with Respect to Air Pollution, Climate and Pollen; SCIT, subcutaneous immunotherapy; SF36, medical outcome short form 36 questions; SIGN, Scottish intercollegiate network; SIT, specific immunotherapy; SLIT, sublingual immunotherapy; SO<sub>2</sub>, sulphur dioxide; Th, T helper lymphocyte; UDA, Usual Daily Activity; URT, upper respiratory tract; VAS, visual analogue scale; VCAM-1, vascular cellular adhesion molecule 1; VEGF, Vascular Endothelial Growth Factor; VOC, volatile organic compound; WHO, World Health Organization; WRAD, work-related occupational disease.

Islamic texts of the 9th century and European texts of the 16th century. It was only in the early 19th century that the disease was carefully described, and at that time it was regarded as most unusual (3). In the 19th century, the disease followed the industrialization of westernized countries (4). By the end of the 19th century it had become commonplace in both Europe and North America. However, the prevalence of allergic rhinitis was still low and has considerably increased during the past 50 years. In some countries, over 50% of adolescents are reporting symptoms of allergic rhinitis (5). Using a conservative estimate, allergic rhinitis occurs in over 500 million people around the world. The prevalence of allergic rhinitis is increasing in most countries of the world, and particularly in areas with low or medium levels of prevalence. However, it may be plateauing or even decreasing in the highest prevalence areas. Rhinitis and allergic diseases are now taken seriously and the European Union (6) or countries such as Canada have specific programs to better understand, manage and prevent allergic diseases.

Risk factors for allergic rhinitis are well identified. In the middle of the 19th century, the cause of hay fever was ascribed to pollens (7, 8). Indoor and outdoor allergens as well as occupational agents cause rhinitis and other allergic diseases. The role of indoor and outdoor pollution is probably very important, but has yet to be fully understood both for the occurrence of the disease and its manifestations.

The diagnosis of allergic rhinitis is often easy, but in some cases it may cause problems and many patients are still underdiagnosed, often because they do not perceive the symptoms of rhinitis as a disease impairing their social life, school and work.

The management of allergic rhinitis is well established and many guidelines have been issued although the first ones were not evidence based (9–11).

### 1.1. The ARIA workshop

In 1999, during the Allergic Rhinitis and its Impact on Asthma (ARIA) World Health Organization (WHO) workshop, the suggestions were made by a panel of experts and based on evidence using an extensive review of the literature available up to December 1999 (1). The statements of evidence for the development of these guidelines followed WHO rules and were based on those of Shekelle et al. (12).

The second important achievement of ARIA was to propose a new classification for allergic rhinitis which was subdivided into ‘intermittent’ (IAR) or ‘persistent’ (PER) disease (1).

Moreover, it is now recognized that allergic rhinitis comprises more than the classical symptoms of sneezing, rhinorrhoea and nasal obstruction. It is associated with impairments in how patients function in day-to-day life. The severity of allergic rhinitis was therefore classified as ‘mild’ or ‘moderate/severe’ depending on symptoms but also on quality of life (QOL; 1).

Another important aspect of the ARIA guidelines was to consider co-morbidities of allergic rhinitis. Eye involvement in allergic rhinitis has been described for a long time (13). The nasal airways and their closely-associated paranasal sinuses are an integral part of the respiratory tract (1, 14–16). In the second century, *Claudius Galenus*, one of the fathers of modern respiratory physiology, defined the nose as a ‘respiratory instrument’ in his work *De usu partium* [on the usefulness of the (body) parts (17)]. The co-morbidities between the upper and lower airways were described with the clinical description of allergic rhinitis (3, 8). The nasal and bronchial mucosa present similarities, and one of the most important concepts regarding nose–lung interactions is the functional complementarity (14). Interactions between the lower and the upper airways are well known and have been extensively studied since 1990. Over 80% of asthmatics have rhinitis and 10–40% of patients with rhinitis have asthma (1). Most patients with asthma have rhinitis (18) suggesting the concept of ‘one airway one disease’ although there are differences between rhinitis and asthma (19, 20).

The ARIA document was intended to be a state-of-the-art for the specialist as well as for the general practitioner and other healthcare professionals:

- to update their knowledge of allergic rhinitis;
- to highlight the impact of allergic rhinitis on asthma;
- to provide an evidence-based documented revision on diagnostic methods;
- to provide an evidence-based revision on treatments and
- to propose a stepwise approach to management.

The ARIA document was not intended to be a standard-of-care document for individual countries. It was provided as a basis for doctors, healthcare professionals and organizations involved in the treatment of allergic rhinitis and asthma in various countries to facilitate the development of relevant local standard-of-care documents for patients.

The ARIA workshop held at the WHO headquarters proposed the recommendations shown in Table 1.

### 1.2. Need for an ARIA update

An update of the ARIA guidelines was needed because:

- a large number of papers have been published over the past 7 years extending our knowledge on the epidemiology, diagnosis, management and co-morbidities of allergic rhinitis. Other guidelines have been produced since 1999 (21), but these did not review the ongoing literature extensively using an evidence-based model;
- the ARIA recommendations were proposed by an expert group and needed to be validated in terms of classification and management;