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DISSEMINATION AND IMPLEMENTATION OF THE ALLERGIC RHINITIS AND ITS IMPACT ON ASTHMA (ARIA) GUIDELINES FOR ALLERGIC RHINITIS IN GENERAL AND SPECIALIST PRACTICE

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- Van Hoecke H, Vastesaeger N, Dewulf L, De Bacquer D, Van Cauwenberge P. Is the allergic rhinitis and its impact on asthma classification useful in daily primary care practice? J Allergy Clin Immunol 2006;118(3):758-9.
- Van Cauwenberge P*, Van Hoecke H*, Kardos P, Price D, Waserman S. The current burden of allergic rhinitis amongst primary care practitioners and its impact on patient management. Prim Care Resp J 2009;18(1):27-33.
- Van Hoecke H, Van Cauwenberge P, Thas O, Watelet JB. The ARIA guidelines in specialist practice: a nationwide survey. Rhinology 2010;48(1):28-34.
- Van Hoecke H, Vandeplas G, Acke F, Thas O, De Sutter A, Gevaert P, Van Cauwenberge P, Dhooge I. Dissemination and implementation of the ARIA guidelines for allergic rhinitis in general practice. Submitted to Int Arch Allergy Immunol.

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LIST OF ABBREVIATIONS

AA: allergen avoidance
AGREE: Appraisal of Guidelines Research and Evaluation
ALT: antileukotriene
AR: allergic rhinitis
ARIA: Allergic Rhinitis and its Impact on Asthma
CRD: chronic respiratory disorder
CS: corticosteroid
EAACI: European Academy of Allergy and Clinical Immunology
EBM: evidence-based medicine
ECRHS: European Community Respiratory Health Survey
EFA: European Federation of Allergy and Airway Diseases Patients Association
GINA: Global Initiative for Asthma
GP: general practitioner
GRADE: Grading of Recommendation, Assessment, Development and Evaluation
HRQOL: health-related quality of life
HDM: house dust mite
IAR: intermittent allergic rhinitis
IGE: immunoglobulin E
IMCS: intramuscular corticosteroid
IPCRG: International Primary Care Respiratory Group
ISAAC: International Study on Asthma and Allergy in Childhood
IT: immunotherapy
NAH1: nasal H1-antihistamine
NCS: nasal corticosteroid
NDC: nasal decongestant
OAH1: oral H1-antihistamine
OCS: oral corticosteroid
ODC: oral decongestant
PAR: perennial allergic rhinitis
PER: persistent allergic rhinitis
QOL: quality of life
RCT: Randomized Controlled Trial
SAR: seasonal allergic rhinitis
SCIT: subcutaneous immunotherapy
SLIT: sublingual immunotherapy
TEM: topical eye medication
VAS: visual analogue scale
WHO: World Health Organization
WONCA: World Organization of National Colleges, Academies and Academic Associations of General Practitioners/Family Physicians

DEFINITIONS

ALLERGIC RHINITIS is a symptomatic disorder of the nose, resulting from an IgE-mediated inflammation of the membranes lining the nose, induced by allergen exposure.[1]

INTERMITTENT ALLERGIC RHINITIS (IN UNTREATED PATIENTS): allergic rhinitis with symptoms being present for less than 4 days a week or for less than 4 weeks.[2]

PERSISTENT ALLERGIC RHINITIS (IN UNTREATED PATIENTS): allergic rhinitis with symptoms being present for more than 4 days a week and for more than 4 weeks.[2]

MILD ALLERGIC RHINITIS (IN UNTREATED PATIENTS): allergic rhinitis with none of the following items being present:

- Sleep disturbance
- Impairment of daily activities, leisure and/or sport
- Impairment of school or work
- Troublesome symptoms.[2]

MODERATE-SEVERE ALLERGIC RHINITIS (IN UNTREATED PATIENTS): allergic rhinitis with one or more of the following items being present:

- Sleep disturbance
- Impairment of daily activities, leisure and/or sport
- Impairment of school or work
- Troublesome symptoms.[2]

EVIDENCE-BASED MEDICINE is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients. It means integrating individual clinical expertise with the best available external clinical evidence from systematic research.[3]

OPINION-BASED MEDICINE is medicine conducted based on unsystematically-compiled opinions of experts, based on clinical trails and mechanistic approaches.

CLINICAL GUIDELINES are systematically developed statements to assist practitioners and patients in making decisions about appropriate and effective healthcare in specific circumstances.[4]

DISSEMINATION is the targeted distribution of information and intervention materials to a specific public health or clinical practice audience. The intent is to spread knowledge and the associated (evidence-based) interventions.[5]

IMPLEMENTATION is the use of strategies to adopt and integrate (evidence-based) health interventions and change practice patterns within specific settings.[5]

REFERENCES

1. Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, et al. A revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization. J Allergy Clin Immunol 2004;113(5):823-6.
2. Bousquet J, Van Cauwenberge P, Khaltaev N; Aria Workshop Group; World Health Organization. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol 2001; 108(5 Suppl):S147-334.
3. Sackett DL, Rosenberg WM, Gray JA, Haynes RB Richardson WS. Evidence based medicine: what it is and what it isn't.BMJ 1996:13;312(7023):71-2.
4. Jackson R, Feder G. Guidelines for clinical guidelines. BMJ 1998;317:427-8.
5. National Heart, Lung, and Blood Institute; National Institutes of Health. http://www.nhlbi.nih.gov/funding/policies/dissemination&implementationR18.htm

CHAPTER I

GENERAL INTRODUCTION

PART 1
ALLERGIC RHINITIS: BURDEN OF DISEASE, DIAGNOSTIC AND THERAPEUTIC CHALLENGES AND THE NEED FOR GUIDANCE

INTRODUCTION

Allergic rhinitis (AR) is defined a symptomatic disorder of the nose, resulting from an IgE-mediated inflammation of the mucosal lining of the nose, induced by allergen exposure.[1] The burden of disease for both the patient and the society goes far beyond the nasal symptoms of rhinorrhea, nasal congestion, sneezing and pruritus. Nevertheless, the condition often remains regarded as trivial, un(der)-diagnosed and inadequately treated. Clinical practice guidelines aim to increase the awareness of AR and to optimize the diagnostic and treatment practices in order to improve the quality of patient care and healthcare outcomes.

ALLERGIC RHINITIS PREVALENCE HAS RISEN TO EPIDEMIC PROPORTIONS

Whereas the world health is generally improving, the prevalence of chronic respiratory disorders (CRDs) is still increasing. CRDs involve asthma, chronic obstructive pulmonary disease, respiratory allergies, occupational airway diseases and pulmonary hypertension, and represent the epidemic challenge of the 3rd millenium. AR is the most common CRD and affects an estimated 600 million of people worldwide.[2] Many large national and international studies[3-7] have increased our knowledge on the epidemiology of AR. It is important to remark, however, that heterogeneous definitions and diagnostic criteria for AR have been used throughout these different studies, which complicates the interpretation and comparison of results.

Monocentric studies have reported a prevalence of AR ranging from 1 up to 40 %.[8] Large multicentric surveys have confirmed this tremendous variation in the prevalence of AR symptoms among children and adults throughout the world, and reported the highest prevalence rates of AR (between 15 and 40%) in Western lifestyle countries: Western Europe, Australia, New Zealand and the USA.[3-4] Prevalence figures for AR in Belgium from various epidemiological surveys are represented in **TABLE 1**.

Although AR can occur at any age, most individuals develop the condition before the age of 20 years old[9] and the disease is usually clinically most active in young adults.[10] At child age, boys are more frequently affected than girls, at puberty this tendency reverses, and at adulthood men and women are equally affected.[11]

The prevalence of AR not only varies between regions and populations, but has also shown to vary over time. Over the last 40 years of the past millennium a steeply increasing trend in the prevalence of AR and other allergic diseases has been observed.[12] In recent years, there are some signs that this increase has leveled off, as the prevalence seems to be stabilizing or even slightly decreasing in high prevalence areas,[13-14] but still, a substantial rise in AR prevalence is noted in many countries undergoing rapid socio-economic development, where AR was

previously less common.[5] Although it is well-established that allergic diseases tend to occur within families and have a genetic basis, changes in gene pool require numerous generations and can not explain the observed prevalence gradients and time trends. The recent increase in prevalence of AR and other allergic diseases is largely attributed to changes in environmental en lifestyle factors such as higher socio-economic status, urbanization, reduced family size, increased allergen exposure, reduced early life microbial exposure, diet changes such as early introduction of foods or formula and possibly also alcohol consumption, tobacco smoke exposure, indoor and outdoor pollution. To meet the challenge of the growing impact of allergy and to allow the introduction of individualized prevention strategies, further assessment of the complex interactions between risk factors, including gene-environment interactions, is required.[18]

TABLE 1. *Prevalence of AR in Belgium as reported in different national and international studies. N= number of (Belgian) individuals recruited*

Author/ Study Group	Year	Study population	AR diagnosis	n	Prevalence AR
ISAAC		Children from randomly selected schools Antwerp area	Allergic rhinoconjunctivitis		
ISAAC I[4]	1992-98			1515	
		5-7 years old	Questionnaire for parents		**4.9%**
		13-14 years old	Questionnaire for child		**14.5%**
ISAAC III[5]	1999-04			5645	
		5-7 years old	Questionnaire for parents		**5.8%**
		13-14 years old	Questionnaire for child		**16.9%**
Bauchau[15]	2001	Random general population sample ≥ 18 years olds	1) Telephone interview 2) Clinical diagnosis and sIgE measurement	1) 1602 2) 187	**28.5%**
Bachert[16]	2003	Random general population sample ≥ 15 years olds	1) Screening questionnaire 2) Detailed questionnaire	1) 4959 2) 754	**29.8%**
Blomme[17]	2008	Public fair visitors 3-88 years old	Skin prick test and clinical history	2320	**30.9%**

ALLERGIC RHINITIS IS ACCOCIATED WITH COMORBIDITIES AND UNDERLIES COMPLICATIONS

AR is not an isolated disease. Findings from basic science and epidemiological studies have demonstrated that AR is not restricted to the nasal airway, but is associated with multiple comorbidities including asthma, rhinosinusitis, conjunctivitis and probably also otitis media. At a local level, nasal inflammation, congestion and dysfynction predisposes to inflammation and infection in the adjacent anatomical areas, but over the last years, it has also become clear that AR is part of a systemic inflammatory process and that common causal pathways and interactions result in allergic inflammatory disorders at different mucosal levels throughout the body.[8]

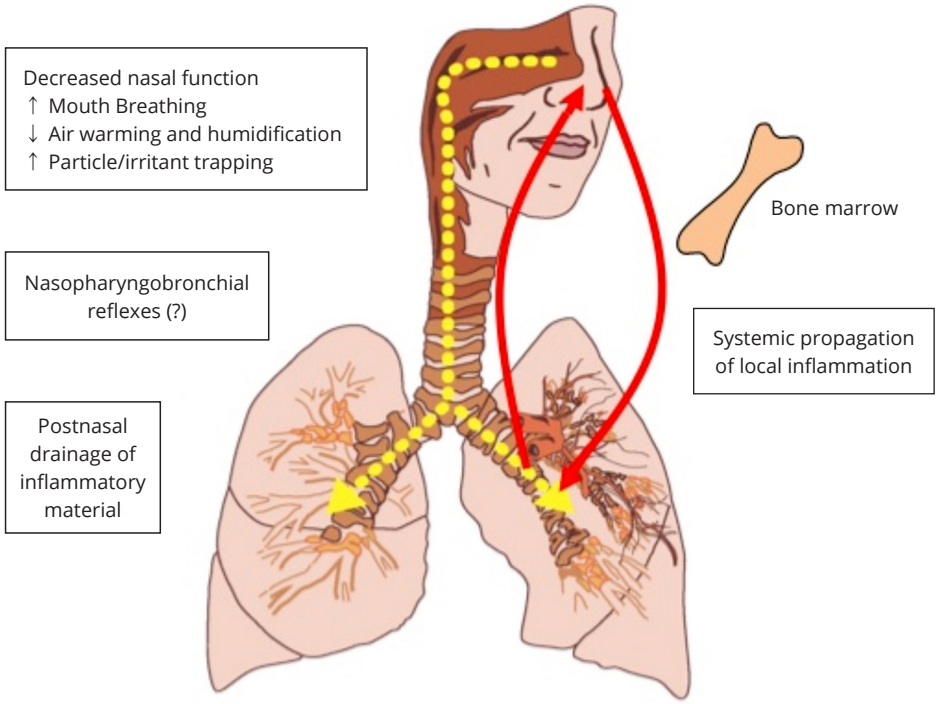
It is estimated that 42% of the patients with AR experience symptoms of allergic conjunctivitis and that 33-56% of the cases of allergic conjunctivitis occur in association with AR. This co-existence, referred to as 'allergic rhinoconjunctivitis', is a typical feature in patients with pollen allergy, where eye symptoms are present in up to 80% of the patients.[19] There is also good evidence to support a link between sinus disease and AR, as underlying AR can be found in 25-30% of individuals with acute rhinosinusitis, 40-60% with unilateral chronic rhinosinusitis and up to 80% with bilateral chronic rhinosinusitis.[20] Most epidemiological data also suggest an association between AR and otitis media, but controversy remains, as the available evidence is compromised by a possible patient referral bias and by a lack of prospective, controlled studies.[21]

Although the clinical association between AR and asthma was already described many centuries ago,[22] the comorbid relationship between both diseases was misregarded until the end of the previous century. Since then, repeated epidemiological, histological, physiological and immunopathological links have been reported and the concept of (allergic) rhinitis and asthma as part of a united airway disease is now well-established.[23] **FIGURE 1** represents potential pathophysiological interactions between the nose and the lower airways.

20-40% of the patients with AR have clinical asthma, whereas up to 80% of the patients with asthma demonstrate symptoms of rhinitis.[24] Both allergic and nonallergic rhinitis are risk factors for the development of asthma,[25] but patients with sensitization to indoor or outdoor allergens,[26] and patients with persistent and severe rhinitis[27] are most prone to have asthma as a comorbidity. In addition, moderate-severe rhinitis is related to poor asthma control.[28] Furthermore, it is important to consider that in patients with AR, even in case of subliminal exposure to the allergen(s) and in the absence of AR symptoms, a certain degree of inflammatory infiltration at the mucosal level persists. This 'minimal persistent inflammation'[29] synergizes with infective disease and explains why individuals with AR experience additional problems with viral colds, and with a higher rate and prolonged duration of respiratory symptoms.[30] In children and adults the

combination of a respiratory viral infection, allergic sensitization and allergen exposure have shown to significantly increase the risk (odds ratio of respectively 19 and 9) for hospital admisson for asthma exacerbation.[11, 31, 32]

FIGURE 1. *Potential pathophysiological interactions between the nose and the lower airways include the loss of nasal protective function, postnasal drip with pulmonary aspiration of nasal contents, the still contradictory presence of a nasal-bronchial reflex and probably most important: the systemic progression of local allergic inflammation. This bidirectional systemic inflammation is produced after local allergen provocation (in the nose or lower airways) leading to up-regulation and release of haemopoietic eosinophil/basophil progenitor cells from the bone marrow, which subsequently migrate to both nose and lungs and can undergo differentiation and activation. Adapted from Togias et al*[33].



ALLERGIC RHINITIS IMPAIRS THE QUALITY OF LIFE

AR comprises more than the classical symptoms of rhinorrhea, sneezing, nasal obstruction, itching and frequently associated non-nasal symptoms involving eye symptoms, sore throat, headache and cough. Both generic and disease-specific health-related quality of life (HRQOL) questionnaires have demonstrated that the disease causes a significant impairment of the physical, mental and psychosocial well-being in adults and children.[34-35] Furthermore, AR has shown to be at least as bothering as asthma in the patient's everyday life for concepts related to mental and social health, whereas asthma provides more physical limitations.[36] Poorly controlled symptoms of AR, especially nasal congestion, lead to sleep loss or disturbances and daytime fatigue and somnolence.[37]

In the US, symptoms of AR are estimated to be responsible for a loss of about 4 million work and school days a year.[38] Probably even more important than school and work absenteeism is presenteeism (being present, but not fully functioning), as it has well been demontrated that AR adversely affects the cognitive function,[39] learning and school performance[40-41] and work productivity[42]. Participation in leisure, sport and social activities can also be compromised, which especially in children can lead to emotional disturbances inluding frustration, sadness and anger.[43]

Comorbid diseases associated with AR add to the impact on the patient's quality of life. Adequate medical interventions have shown not only to improve the control of symptoms but also the health-related quality of life. However, certain treatments have also been found to provide increased functional impairments due to troublesome adverse events e.g. first-generation antihistamine-induced sedative effects.[43]

THE ECONOMIC CONSEQUENCES OF ALLERGIC RHINITIS ARE SUBSTANTIAL

Although the annual cost to manage AR might seem low relative to other chronic conditions, due to its high prevalence, AR poses a significant economic burden on the society. The overall healthcare costs, resulting from AR, comprise both direct and indirect costs. Direct costs are related to patient-care and include medical (e.g. medication, physician and hospital visits, diagnostic tests and medical procedures) and non-medical costs (e.g. transportation to and from healthcare provider, household modifications, special diets). Indirect costs are related to disease consequences, such as absenteeism and reduced productivity at work.[44] Estimates of the annual costs resulting from AR vary widely from study to study. This large variation is attributed to differences in identifying patients with AR, differences in cost calculations, limitations associated with available data (e.g. use of over-the-counter medications, complementary and alternative treatments)

and difficulties in assigning indirect costs of AR.[45] The majority of studies, however, agree that especially the indirect costs of AR are tremendous, which can be explained by the fact that AR peaks during the highly productive years of individuals (20-40 years old).

In Europe, the direct yearly costs for AR were reported to approximate 1.286 billion Euro, the indirect yearly costs 1.723 billion Euro.[45] Most economic analyses of AR were performed in the US with annual estimates of the direct cost varying from $US1.6 billion to $US4.9 billion and estimates of indirect costs ranging from $US0.1 billion to more than $US9.7 billion.[46] A large prevalence-based cost-of-illness study to estimate the direct healthcare costs for treating allergic rhinoconjunctivitis (as primary diagnosis) and/or associated comorbidities for all persons in the US in 1996 has demonstrated that the cost of allergic rhinoconjunctivitis was increased by 3.7 to 4.9 times when the costs attributable to the comorbid conditions were included.[44, 47]

THE DIAGNOSTIC CHALLENGE IN ALLERGIC RHINITIS

Rhinitis is characterized clinically by one or more of the following sympoms: rhinorrhea, nasal obstruction, nasal itch and sneezing. Additional nasal symptoms, including loss of smell, snoring and postnasal drip, are also frequently present. These symptoms, however, do not necessarily have an allergic origin. In about 50% of the cases, rhinitis is caused by allergy. In the differential diagnosis, AR must be differentiated from several types of non-allergic rhinitis and other nasal conditions **(TABLE 2)**.

CLINICAL HISTORY

A comprehensive clinical history, not only assessing the nasal symptomatology, but also associated and comorbid symptoms, such as eye symptoms (which have shown to have a high predictive value for differentiating AR from other types of rhinitis), oral and pharyngeal hypersensitivity symptoms after contact with fresh fruits or vegetables (suggestive for oral allergy syndrome in patients with pollen-induced AR) and lower airway symptoms is the first step in the (differential) diagnosis of AR. Special attention must be paid to symptoms not suggestive for AR and warranting specialist referral, such as unilateral nasal symptoms and recurrent epistaxis. A thorough history documents allergic and non-allergic triggers, family and occupational history, the severity and duration of the problem, the impact on the quality of life and response to treatment.[8, 11, 18]

TABLE 2. *Differential diagnosis of allergic rhinitis. Adapted from Greiner et al[11] and International Rhinitis Management Working Group[48].*

Allergic rhinitis
Infectious rhinitis, acute and chronic rhinosinusitis
Occupational rhinitis: allergic and non-allergic
Drug-induced rhinitis: e.g. aspirin, nasal decongestants, cocain
Hormonal rhinitis: puberty, pregnancy, menstruation, endocrine disorders
Emotional rhinitis
Atrophic rhinitis
Irritants-induced rhinitis
Food-induced rhinitis e.g. red pepper
NARES: non-allergic rhinitis with eosinophilic syndrome
Rhinitis associated with gastro-esophageal reflux
Idiopathic rhinitis
Mechanical factors
- Deviated septum
- Adenoid hyperplasia
- Hypertrophic turbinates
- Foreign bodies
- Choanal atresia
- Nasal valve dysfunction

Nasal or central nerve system tumours
- Benign
- Malignant

Multisystem diseases
- Wegener's granulomatosis
- Sarcoidosis
- Churg-Strauss syndrome

Relapsing polychondritis
- Systemic lupus erythematosus

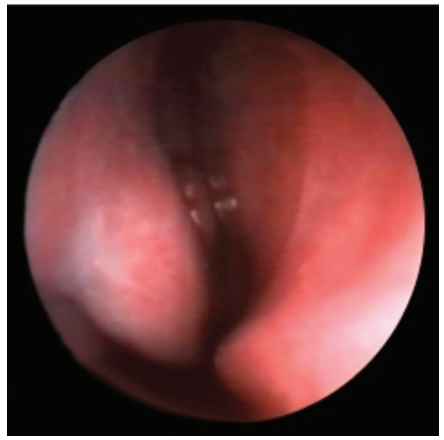
Ciliary defects
Cerebrospinal rhinorrhea

CLINICAL EXAMINATION

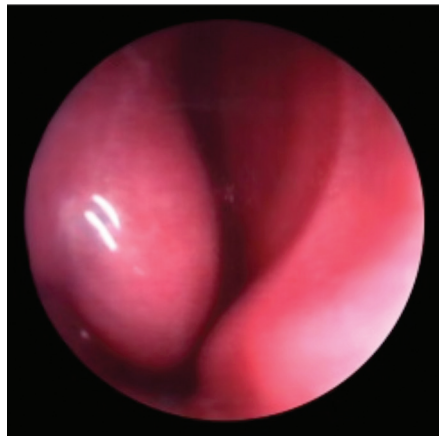
Clinical examination should include a thorough nasal examination. Anterior rhinoscopy can reveal typical changes in the nasal mucosa. During allergen exposure, the nasal mucosa of patients with AR can demonstrate swelling, and often changes in colour, from a purplish to a more common pale coloration, and an increase in vascularity are seen **(FIGURE 2)**. In absence of allergen exposure, the nasal mucosa may appear completely normal, but in patients who have suffered from AR for several years, irreversible mucosal hyperplasia and/or viscous hypersecretion may also occur. Nasal endoscopy, usually performed by specialists, allows a more thorough examination of the nose, including the

posterior nasal cavity and the middle meatus, which is not necessary to confirm AR, but to exclude other conditions, such as polyps, foreign bodies, tumours and septal deformations.[8, 18]

FIGURE 2. *Naso-endoscopic visualisation (right nasal cavity: Hopkins 30°) of nasal mucosa before and after allergen challenge in an allergic rhinitis patient. Image courtesy of Jean-Baptiste Watelet, MD, PhD.*



Before allergen challenge



After allergen challenge

ALLERGY TESTING

To confirm the allergic origin of rhinitis symptoms, specific IgE reactivity to airborne allergens needs to be recorded, via either skin-prick testing or by measuring specific IgE in serum. Both tests are of similar value, with a good sensitivity and specificity. Skin prick tests allow a wider selection of allergens, provide results within 20 minutes (whereas specific serum IgE measurements can take several days) and are more cost-effective than serum specific IgE testing. Specific serum IgE measurement, however, is the test of choice when the patient has dermographism or widespread dermatitis, when the patient is non compliant for skin testing or did not discontinue oral antihistamine treatment. The results of the allergy tests, however, must always be interpreted with the patient's history and clinical examination in mind. False positive and false negative allergy tests can occur, individuals can demonstrate sensitization without clinical symptoms of AR and some sensitizations can be irrelevant.[11]

Total serum IgE measurement lacks of specificity and has a poor predictive value for underlying allergy in rhinitis patients.

Nasal challenge tests are especially used for research purposes and are important in the diagnosis of occupational rhinitis.

DIAGNOSTIC ASSESSMENT OF COMORBIDITIES

The presence of comorbidities should also be assessed throughout the clinical history and clinical examination and if necessary additional investigations have to be performed (e.g. imaging of the paranasal sinuses, lung function measurement).

THE THERAPEUTIC CHALLENGE IN ALLERGIC RHINITIS

The therapeutic approach to AR includes patient education, environmental measures, pharmacotherapy and consideration of immunotherapy. Surgery is rarely needed. Optimal treatment is important, not only to obtain symptom control, but also to improve the quality of life, the academic and work performance and to minimize the risk of the development or exacerbation of comorbidities. Cost-effectiveness is also an important treament attribute, but, to date, there still is a lack of comprehensive cost-effectiveness analyses for many standard treatments for AR.

PATIENT EDUCATION

Education of the patient is critical in the management of any disease. Patients who understand their disease, treatment options and likelihood of treatment success are more likely to be compliant with their physicians' recommendations. As successful treatment of AR requires good long-term patient adherence, adequate patient education is also required to optimize treatment outcomes. To improve adherence, healthcare providers should educate, communicate and partnership with their patients about the nature of their disease and the likelihood of disease progression, the need for, aims, regimen and costs of treatment, the expected benefits and possible side-effects. Furthermore, it is very important to demonstrate and teach patients the proper technique using medicines. A correct technique for nasal delivery of corticosteroids for instance, enables effective treatment and reduction of adverse events. To opimize the partnership between healthcare provider and patient in the management of AR, patients should receive a written management plan and patients should give feedback about the control of their disease and compliance with the suggested management plan, preferentially by reporting in a diary.[11, 49]

ENVIRONMENTAL MEASURES

As symptoms of AR are clearly triggered by allergen exposure, the rationale of allergen avoidance is obvious. Significant reduction of allergen load can be achieved by physical and chemical means, but to date, there is little evidence that these reductions are sufficient to translate into clinical improvements of AR.[50]

Avoidance measures for house dust mite are the most investigated. They involve regular washing of bedding, pillows and duvets at 55-60°, encasing pillows and mattresses with protective coverings, reducing indoor humidity below 50°C, removing/reducing carpets, curtains and soft furnishings, removing, hot washing or freezing soft toys and use of vacuum cleaners with High Efficiency Particulate Air (HEPA) filters. At present there is no evidence to support the single use of one of these measures, but a multifaceted avoidance strategy might be beneficial in selected patients.[8, 50-52]

The only effective measure to avoid animal dander allergens in the home is to remove the pet and to subsequently and carefully vacuum-clean all carpets, mattresses and upholstered furniture.[8, 50, 52]

Although some methods have been developed to decrease the exposure to outdoor allergens (including filters and ventilation systems), avoidance of pollen and fungal spores is often impossible and impractical due to its ubiquitous nature.[8, 52]

Next to allergens, non-specific stimuli and irritants e.g. temperature changes, air conditioning and tobacco smoke, can lead to aggravation of symptoms in patients with AR. Although avoidance of these exposures seems logical, there is a lack of good evidence to support such environmental control measures.[8, 11]

PHARMACOTHERAPY

Pharmacological treatment of AR should take into account the spectrum of symptoms, the severity and duration of disease, the presence of comorbidities, the efficacy, safety and cost-effectiveness of the medications, the patient's preferences and the objective of treatment.

Pharmacological agents for AR or allergic rhinoconjunctivitis can be administered locally or systemically. Often agents are combined and some combined treatments e.g. an oral antihistamine and oral decongestant are commercially available.

A brief overview of the current standard pharmacotherapeutical treatments available for AR, their clinical effects, and advantages and disadvantages is provided in **TABLE 3**. The strength of evidence of these different AR treatments is represented in **TABLE 3** of Chapter 3.

TABLE 3. *Overview of pharmacological agents for the treatment of allergic rhinitis*[11, 53, 54]

Class name	Mechanism of action	Clinical effects and advantages	Side effects and disadvantages
Oral H1-antihistamines	Blockage of H1-receptor Inhibition of autacoid release in some new agents	Rapid (<1h) onset of action Effect on nasal symptoms of itch, sneezing, rhinorrhea; reduction of conjunctival, oral, and skin symptoms Second generation: favorable risk/benefit ratio	Poor effect on nasal congestion 'On demand' treatment less effective than regular therapy First generation: - anticholinergic effects - sedative effects with risk of behavior changes and reduced psychomotor performance Second generation: - mild sedative and anticholinergic effects in minority of patients
Local H1-antihistamines			
Nasal Ocular	Blockage of H1-receptor Inhibition of autacoid release in some new agents	Very rapid (<15min) effect on nasal itch, sneezing, rhinorrhea (nasal H1-antihistamine) or ocular symptoms (ocular antihistamine) Safe treatment	Only local beneficial effects Minor local side effects
Nasal anticholinergics	Blockage of acetylcholine receptor	Effective reduction of watery rhinorrhea Rare local or systemic side effects	Effective for reduction of watery rhinorrhea only Three applications a day Local dryness Occasional systemic anticholinergic effects
Nasal corticosteroids	Inhibits influx of inflammatory cells	Improvement of all nasal symptoms, some effects on eye symptoms Superior effect compared to other pharmacological treatments for AR Low bioavailability with new molecules	Effect starts after several hours, maximal effects only after 2 weeks Local side effects (5-10%): epistaxis, dryness Concerns about growth in children with prolonged use and/or combined inhaled corticosteroids

Class name	Mechanism of action	Clinical effects and advantages	Side effects and disadvantages
Oral corticosteroids	Inhibits influx of inflammatory cells	Rescue treatment for all AR symptoms	Adverse events related to oral corticosteroid use, only for rare and short-term use; not recommended in children
Nasal decongestants	Sympathicomimetic Vasoconstrictive	Potent effect on nasal obstruction Very rapid onset of action (<10 minutes)	Beneficial effects on nasal congestion only Overuse and addiction is common Risk of rhinitis medicamentosa with prolonged use (>10 days)
Oral decongestants	Sympathicomimetic Vasoconstrictive	Reduction of nasal obstruction Rapid onset of action (<30 minutes)	Beneficial effects on nasal congestion only Important risk of systemic side effects: hypertension, tachycardia, dry mouth, cental nerve stimulation with insomnia, tremor, agitation
Mastcell stabilizers			
Nasal Ocular	Inhibition of degranulation of sensitized mast cells	Nasal: Modest effect on nasal symptoms of AR Ocular: More effective relief of ocular symptoms Safe treatment	Nasal: Less effective than other treatments Several applications a day required Rare and mild local side effects
Antileukotrienes (oral)	Blockage of leukotriene receptor Inhibition of leukotriene synthesis	Effective for nasal obstruction, rhinorrhea, and conjunctival symptoms; effective for bronchial symptoms in patients with asthma Generally well tolerated	Less effective for nasal itch and sneezing Not consistently effective Occasional local or systemic side effects

Nasal saline irrigation is most commonly used in rhinosinusitis, but may also prove useful in AR, allowing a reduction in the amount of pharmacotherapy needed to control symptoms.[11]

Furthermore, increasing insights in the pathophysiology of AR, the roles of diverse cells and their cytokine products, receptors and mediators involved in allergic inflammation has provided new (potential) targets for pharmacotherapy.

Modulation of allergic response through anti-mediators and anti-receptors has gained much interest (e.g. anti-IgE, anti-IL-5, anti-CCR3). Omalizumab (anti-IgE) is a "humanized" monoclonal antibody that effectively hinders the interaction between IgEs and the high-affinity IgE receptor present on mast cells, basophils, and dendritic cells. At present this costly treatment is only licenced for the treatment of severe asthma, but placebo-controlled studies have shown benefits in the treatment of AR.[55, 56]

Two pharmacological treatments are not advised for patients with AR: first-generation antihistamines, that cause sedation, impair academic and work performance and are associated with traffic and industrial accidents, and intramuscular corticosteroid injections, that are associated with potentially severe systemic side-effects and subcutaneous and muscular necrosis.[11]

IMMUNOTHERAPY

Immunotherapy is the practice of administering gradually increasing doses of standardized allergen extract to an allergic patient. The treatment consists of a build-up and a maintenance phase, which is continued for at least 3 years. Where pharmacotherapy aims to suppress symptoms, immunotherapy aims to alter the immune system (inducing a shift away from a Th2 type response and generating regulatory T cells) and the natural disease course. Traditionally, allergen-specific immunotherapy is administrated subcutaneously (SCIT). There now is good evidence that SCIT with seasonal and perennial allergens is clinically effective for the treatment of AR in adults and children (over 5 years old) with long-term reduction of symptoms and medication requirements after treatment stop.[57] In addition, SCIT, when administrated early in the disease process, has also demonstrated to modify the long term progress of the allergic inflammation and disease, by preventing the development of new sensitizations[58] and by preventing the development of asthma.[59] As SCIT holds a small (<0.1% of treated patients) but definite risk of inducing systemic reactions (including severe asthma attacks and potentially fatal anaphylaxis), patients must be closely observed for at least 30 minutes after injection and SCIT can only be carried out in medical settings where the necessary expertise is avaible with direct access to rescue medication and equipment. As SCIT is a highly-demanding long-term treatment with potential serious side effects, it should only be considered in patients with severe symptoms of AR, when allergen avoidance and pharmacotherapy have failed to reduce symptoms or when pharmacotherapy has been associated with unacceptable side effects.[8]

More recently local administration routes for immunotherapy have been introduced. Sublingual immunotherapy (SLIT) has shown to be effective for children and adults with AR with clinical and immunological benefits persisting after 3 years of follow-up.[60, 61] SLIT appears to be safer than SCIT with merely local adverse effects and very rare systemic side effects, but no reported fatal

incidents. SLIT is a more patient-friendly treatment as only the first dosing requires medical supervision. Also promising and safe results have been reported with oral immunotherapy tablets containing grass pollen.[62] For the locally administered immunotherapy, however, further studies on the longevity and concordance, especially in children, and on the potential beneficial effects on subsequent sensitizations and development of asthma are required.[11]

SURGERY

Surgery does not relief allergic inflammation and is rarely indicated for the treatment of AR. It can, however, be considered to improve the nasal patency (and route for nasal treatment application) in case of turbinate hypertrophy, anatomical cartilaginous or bony obstruction. In these cases, a conchotomy, nasal valve surgery and/or septo(rhino)plasty is recommended. In case of secondary chronic rhinosinusitis disease, unresponsive to medical treatment, functional endoscopic sinus surgery can be performed.

ALLERGIC RHINITIS: THE NEED FOR GUIDANCE

Due to its high prevalence, impairment of the quality of life, important economic consequences and risk for comorbidities, AR represents a considerable burden for the patient and society as a whole. Consequently, early detection and optimal treatment of AR should be a priority. AR, however, often remains unrecognized and/or trivialized. A large study conducted in 6 European countries demonstrated that 45% of AR patients were previously undiagnosed[15]. This high rate of undiagnosed cases of AR can partly be explained by a high proportion of patients either neglecting or trivializing their symptoms and not seeking help (often patients with mild symptoms) and a high rate of patients not consulting a physician, but self-treating, using over-the-counter medication or alternative treatments.[63] On the other hand, there remains a significant proportion of AR patients undiagnosed in clinical practice, which might be explained by inadequate doctor-patient dialogue, insufficient attention or awareness of physicians about the condition or inadequate diagnostic skills.[64] Furthermore, several studies have demonstrated that, even in case of a diagnosis of AR, physicians tend to underestimate the severity and impact of disease and to overestimate the control of disease.[65-66] Although no studies have linked physician's perspectives on AR to their prescribing behavior, it is to be expected that physicians who consider AR a low priority disease, who do not acknowledge or underestimate the impact of the disease, also inadequately treat the condition.[67] In addition, clinicians are confronted with various treatment options for AR and are often not fully aware of their relative downsides and merits, leading to considerable variation in treatment practice for AR68 and resulting in insufficient patient outcomes.[69]

To raise awareness and to optimize the diagnostic and treatment practices of AR guidelines have been developed. The main goal of clinical practice guidelines is to improve the quality of patient care and healthcare outcomes, but additionally, the scope of clinical guidelines is to summarize research findings and make clinical decisions more transparent, to reduce inappropriate variation in practice, to promote efficient use of resources, to identify gaps in knowledge and prioritize research activities, to provide guidance for consumers and inform and empower patients, to inform public policy and to support quality control.[70]

In 2001 the first evidence-based guidelines for AR, the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines,[8] were published. The ARIA guidelines propose diagnostic recommendations and a stepwise treatment algorithm, based on a new classification for AR in terms of the duration of disease and its impact on quality of life. Limited information, however, is available on the impact of guidelines on clinical practice and, more specifically, the applicability, dissemination and implementation of the ARIA guidelines in general and specialist practice warrants further research.

REFERENCES

1. Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, et al. A revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization. J Allergy Clin Immunol 2004;113(5):823-6.
2. Bousquet J, Dahl R, Khaltaev N. Global Alliance against Chronic Respiratory Diseases. Eur Respir J 2007;29(2):233-9.
3. ECRHS. Variations in the prevalence of respiratory symptoms, self-reported asthma attacks, and use of asthma medication in the European Community Respiratory Health Survey (ECRHS). Eur Respir J 1996;9(4):687–95.
4. Strachan D, Sibbald B, Weiland S, Ait-Khaled N, Anabwani G, Anderson HR, et al. Worldwide variations in prevalence of symptoms of allergic rhinoconjunctivitis in children: the International Study of Asthma and Allergies in Childhood (ISAAC). Pediatr Allergy Immunol 1997;8(4):161–76.
5. Asher MI, Montefort S, Bjorksten B, Lai CK, Strachan DP, Weiland SK, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet 2006;368(9537):733–43.
6. Wuthrich B, Schindler C, Leuenberger P, Ackermann-Liebrich U. Prevalence of atopy and pollinosis in the adult population of Switzerland (SAPALDIA study). Swiss Study on Air Pollution and Lung Diseases in Adults. Int Arch Allergy Immunol 1995;106(2):149–56.
7. Braun-Fahrlander C, Gassner M, Grize L, Neu U, Sennhauser FH, Varonier HS, et al. Prevalence of hay fever and allergic sensitization in farmers children and their peers living in the same rural community. SCARPOL team. Swiss Study on Childhood Allergy and Respiratory Symptoms with Respect to Air Pollution. Clin Exp Allergy 1999;29(1):28–34.
8. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al; World Health Organization; GA(2)LEN; AllerGen. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy 2008;63 Suppl 86:8-160.
9. Skoner DP. Allergic rhinitis: definition, epidemiology. Pathophysiology, detection and diagnosis. J Allergy Clin Immunol 2001;108(1Suppl):S2-8
10. Greisner WA 3rd, Settipane RJ, Settipane GA. Natural history of hay fever: a 23-year follow-up of college students. Allergy Asthma Proc 1998;19(5):271-5.
11. Greiner AN, Hellings PW, Rotiroti G, Scadding GK. Allergic rhinitis. Lancet 2011;378(9809):2112-22.
12. Strachan DP. Epidemiology of rhinitis. In Asthma and Rhinitis (2nd edition). Eds. WW Busse and ST Holgate. Blackwell Science Ltd (London, UK) 2000;33-42.

13. Braun-Fahrländer C, Gassner M, Grize L, Takken-Sahli K, Neu U, Stricker T, et al. No further increase in asthma, hay fever and atopic sensitisation in adolescence living in Switzerland. Eur Respir J 2004;23(3):407-13.
14. Verlato G, Corsico A, Villani S, Cerveri I, Migliore E, Accordini S, et al. Is the prevalence of adult asthma and allergic rhinitis still increasing? Results of an Italian study. J Allergy Clin Immunol 2003;111(6):1232-8.
15. Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. Eur Respir J 2004;24(5):758-64.
16. Bachert C, van Cauwenberge P, Olbrecht J, van Schoor J. Prevalence, classification and perception of allergic and nonallergic rhinitis in Belgium. Allergy 2006;61(6):693-8.
17. Blomme K, Tomassen P, Lapeere H, Huvenne W, Bonny M, Acke F, Bachert C, Gevaert P. Prevalence of allergic sensitization versus allergic rhinitis symptoms in an unselected population. Int Arch Allergy Immunol 2013;160(2):200-7.
18. Van Cauwenberge P, Van Zele T, Watelet JB, Van Hoecke H. In: Laurent G, Shapiro S, Eds. Allergy: Allergic Rhinitis. Encyclopedia of Respiratory Medicine. Elsevier 2006;80-92.
19. Global Resources in Allergy (GLORIA): Allergic rhinitis and allergic conjunctivitis. http://www.worldallergy.org/educational_programs/gloria.
20. Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2012. Rhinol Suppl 2012;23:1-298.
21. Miceli SopoS, Zorzi G, Calvani M Jr. Should we screen every child with otitis media with effusion for allergic rhinitis? Arch Dis Child 2004;89(3):287–8.
22. Simons FER. Ancestors of allergy. New York: Global Medical Communications; 1994.
23. Simons FE. Allergic rhinobronchitis: the asthma-allergic rhinitis link. J Allergy Clin Immunol 1999;104(3 Pt 1):534-40.
24. Fireman P. Rhinitis and asthma connection: management of coexisting upper airway allergic disease and asthma. Allergy and Asthma Proc 2000;21(1):45-54.
25. Shaahban R, Zureik M, Soussan D, Neukirch C, Heinrich J, Sunyer J, et al. Rhinitis and onset of asthma: a longitudinal population-based study. Lancet 2008;372(9643):1049-57.
26. Leynaert B, Neukirch C, Kony S, Guenegou A, Bousquet J, Aubier M, et al. Association between asthma and rhinitis according to atopic sensitization in a population-based study. J Allergy Clin Immunol 2004;113(1):86–93.
27. Magnan A, Meunier JP, Saugnac C, Gasteau J, Neukirch F. Frequency and impact of allergic rhinitis in asthma patients in everyday general medical practice: a French observational cross-sectional study. Allergy 2008;63(3):292-8.

28. Ponte EV, Franco R, Nascimento HF, Souza-Machado A, Cunha S, Barreto ML, Naspitz C, Cruz AA. Lack of control of severe asthma is associated with co-existence of moderate-to-severe rhinitis. Allergy 2008;63(5):564-9.

29. Ciprandi G, Buscaglia S, Pesce G, Pronzato C, Ricca V, Parmiani S. Minimal persistent inflammation is present at mucosal level in patients with asymptomatic rhinitis and mite allergy. J Allergy Clin Immunol 1995;96(6Pt1):971-9.

30. Ponte EV, Franco R, Nascimento HF, Souza-Machado A, Cunha S, Barreto ML, et al. Lack of control of severe asthma is associated with co-existence of moderate-to-severe rhinitis. Allergy 2008;63(5):564-9.

31. Green RM, Custovic A, Sanderson G, Hunter J, Johnston SL, Woodcock A. Synergism between allergens and viruses and risk of hospital admission with asthma: case–control study. BMJ 2002;324(7340):763–6.

32. Murray CS, Simpson A, Custovic A. Allergens, viruses, and asthma exacerbations. Proc Am Thorac Soc 2004;1(2):99-104.

33. Togias A. Rhinitis and asthma: evidence for respiratory system integration. J Allergy Clin Immunol. 2003;111(6):1171-83.

34. Meltzer EO, Nathan RA, Selner JC, Storms W. Quality of life and rhinitic symptoms: results of a nationwide survey with the SF-36 and RQLQ questionnaires. J Allergy Clin Immunol 1997;99:S815-9.

35. Roberts G, Mylonopoulou M, Hurley C, Lack G. Impairment in quality of life is directly related to the level of allergen exposure and allergic airway inflammation. Clin Exp Allergy 2005;35(10):1295–300.

36. Leynaert B, Neukirch C, Liard R, Bousquet J, Neukirch F. Quality of life in allergic rhinitis and asthma. A population-based study of young adulys. Am J Respir Crit Care Med 2000;162(4Pt1):1391-6.

37. Santos CB, Pratt EL, Hanks C, McCann J, Craig TJ. Allergic rhinitis and its effect on sleep, fatigue, and daytime somnolence. Ann Allergy Asthma Immunol 2006;97(5):579–86.

38. Task Force on Allergic Disorders. The Allergy Report. Milwaukee, Wis: American Academy of Allergy, Asthma and Immunology;2000.

39. Marshall PS, O'Hara C, Steinberg P. Effects of seasonal allergic rhinitis on selected cognitive abilities. Ann Allergy Asthma Immunol 2000;84(4):403–10.

40. Sundberg R, Toren K, Hoglund D, Aberg N, Brisman J. Nasal symptoms are associated with school performance in adolescents. J Adolesc Health 2007;40(6):581–3.

41. Walker S, Khan-Wasti S, Fletcher M, Cullinan P, Harris J, Sheikh A. Seasonal allergic rhinitis is associated with a detrimental effect on examination performance in United Kingdom teenagers: a case-control study. J Allergy Clin Immunol 2007;120(2):381-7.

42. Reilly MC, Tanner A, Meltzer EO. Work, classroom and activity impairment instruments: validation studies in allergic rhinitis. Clin Drug Invest 1996;11(5):278-88.

43. Meltzer EO. Quality of life in adults and children with allergic rhinitis. J Allergy Clin Immunol 2001;108Suppl1:S45-53.

44. Arigo C. Epidemiology and economics of allergy treatment. Clin Exp Allergy Rev 2005;5(1):36-9.

45. Marshall JB. European Allergy White paper, UCB Institute of Allergy, 1997.

46. Reed S, Lee T, McCrory D. The Economic Burden of Allergic Rhinitis: A Critical Evaluation of the Literature. PharmacoEconomics 2004;22(6):345-61.

47. Ray NF, Baraniuk JN, Thamer M, Rinehart CS, Gergen PJ, Kaliner M. Direct expenditures for the treatment of allergic rhinoconjunctivitis in 1996, including the contributions of related airway illnesses. J Allergy Clin Immunol 1999; 103(3pt1):401-7.

48. International Rhinitis Management Working Group. International Consensus Report on the Diagnosis and Management of Rhinitis. Allergy 1994;49 (Suppl 9):5-34.

49. Blaiss MS. Important aspects in management of allergic rhinitis: compliance, cost, and quality of life. Allergy Asthma Proc 2003;24(4):231-8.

50. Prevention of allergy and allergic asthma. Chemical Immunonology and Allergy. Editors: SGO Johansson, T. Haahtela. World Allergy Organization Project Report and Guidelines, 2004. Karger.

51. Sheikh A, Hurwitz B. House dust mite avoidance measures for perennial allergic rhinitis: a systematic review of efficacy. Br J Gen Pract 2003;53(489):318-22.

52. Van Cauwenberge P, Van Hoecke H. Management of allergic rhinitis. B-ENT 2005;Suppl 1:45-62.

53. Bousquet J, Reid J, van Weel C, Baena Cagnani C, Canonica GW, Demoly P, et al. Allergic rhinitis management pocket reference 2008. Allergy 2008;63(8):990-6.

54. Plaut M, Valentine MD. Allergic rhinitis. N Engl J Med 2005;353(18):1934-44.

55. Greisner A. Allergic rhinitis. Ped ENT; Casale TB, Condemi J, LaForce C, Nayak A, Rowe M, Watrous M, et al; Omalizumab Seasonal Allergic Rhinitis Trail Group. Effect of omalizumab on symptoms of seasonal allergic rhinitis: a randomized controlled trial. JAMA 2001;28(23)6:2956-67.

56. Chervinsky P, Casale T, Townley R, Tripathy I, Hedgecock S, Fowler-Taylor A, et al. Omalizumab, an anti-IgE antibody, in the treatment of adults and adoles- cents with perennial allergic rhinitis. Ann Allergy Asthma Immunol 2003;91(2):160–7.

57. James LK, Durham SR. Update on mechanisms of allergen injection immunotherapy. Clin Exp Allergy 2008;38(7):1074–88.

58. Des-Roches A, Paradis L, Ménardo-Bouges S, Daurès J-P, Bousquet J. Immunotherapy with standardized Dermatophagoides pteronyssinus extract. VI. Specific immunotherapy prevents the onset of new sensitization in children. J Allergy Clin Immunol 1997;99(4):450-3.

59. Jacobsen L, Niggemann B, Dreborg S, Ferdousi HA, Halken S, Høst A, et al; The PAT investigator group. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow up on the PAT study. Allergy 2007;62(8):943–8.

60. Canonica GW, Bousquet J, Casale T, Lockey RF, Baena-Cagnani CE, Pawankar R, et al. Sub-lingual immunotherapy: World Allergy Organization Position Paper 2009. Allergy 2009;64(suppl 91):1–59.

61. Larenas-Linnemann D. Sublingual immunotherapy in children: complete and updated review supporting evidence of effect. Curr Opin Allergy Clin Immunol 2009;9(2):168–76.

62. Alesina R, Milani M, Pecora S. A multicenter, randomized, parallel-group trial assessing compliance, tolerability, safety, and efficacy to treatment with grass allergy tablets in 261 patients with grass pollen rhinoconjunctivitis. J Allergy (Cairo) 2012;2012:673502.

63. Scadding GK, Richards DH, Price MJ. Patient and physician perspectives on the impact and management of perennial and seasonal allergic rhinitis. Clin Otolaryngol 2000;25(6):551-7.

64. Maurer M, Zuberbier T. Undertreatment of rhinitis symptoms in Europe: findings from a cross-sectional questionnaire survey. Allergy 2007;62(9):1057-63.

65. Schatz M. A survey of the burden of allergic rhinitis in the USA. Allergy 2007;62Suppl 85:9-16.

66. Canonica GW, Bousquet J, Mullol J, Scadding GK, Virchow JC. A survey of the burden of allergic rhinitis in Europe. Allergy 2007;62Suppl 85:17-25.

67. Meltzer EO. Allergic rhinitis: the impact of discordant perspectives of patient and physician on treatment decisions. Clin Ther 2007;29(7):1428-40.

68. Bousquet J, Schünemann HJ, Zuberbier T, Bachert C, Baena-Cagnani CE, Bousquet PJ, et al; WHO Collaborating Center of Asthma and Rhinitis (Montpellier). Development and implementation of guidelines in allergic rhinitis – an ARIA-GA2LEN paper. Allergy 2010;65(10):1212-21.

69. Bousquet J, Lund VJ, van Cauwenberge P, Bremard-Oury C, Mounedji N, Stevens MT, El-Akkad T. Implementation of guidelines for seasonal allergic rhinitis: a randomized controlled trial. Allergy 2003;58(8):733-41.

70. Davis D, Goldman J, Palda VA. In: Toronto: Canadian Medical Association. Handbook on Clinical Practice Guidelines. 2007; Chapter 1: Introduction to clinical practice guidelines:1-4.

PART 2
AIMS OF THE STUDY AND THESIS OUTLINE

AIMS OF THE STUDY AND THESIS OUTLINE

The general aim of this thesis is to better understand the impact of guidelines on clinical practice. The impact of "the Allergic Rhinitis and its Impact on Asthma" (ARIA) guidelines for allergic rhinitis (AR) was studied in order to meet this goal.

AR represents a serious health problem and a social and economic burden to the patient and society. To raise awareness about the disease, to assist healthcare providers in the management of their patients and to improve the quality of healthcare, clinical practice guidelines have been developed. The first evidence-based guidelines for AR, the ARIA guidelines, were distributed worldwide to primary care practitioners and specialists dealing with AR. They propose diagnostic recommendations and a stepwise treatment algorithm, based on a new classification for AR in terms of the duration of disease and its impact on quality of life.

First of all, it is relevant to understand how guidelines are created. The development of guidelines in general and for AR specifically, is critically reviewed and evaluated in a literature study (Chapter 2). In addition, we look into the specific choices that were made upon the generation of a guideline, e.g. the ARIA classification of AR, and estimate the usefulness of these decisions and their adaptation to daily practice, by applying (Chapter 3) and critically appraising (Chapter 4) the ARIA classification in a large patient population of AR patients recruited in general practice.

Secondly, after publication and distribution of guidelines, monitoring of their use and their impact on healthcare is essential and should be evaluated. Very little information, however, is available on the dissemination and implementation of the ARIA guidelines in clinical practice. Results of a questionnaire-based survey are used to analyze to what extent physicians, both general practitioners (Chapter 6) and specialists (Chapter 5), are familiar with these guidelines, if their directives influence everyday practice and whether physician characteristics influence guideline compliance.

Finally, if differences in management of AR between healthcare providers exist, knowledge of and compliance with guidelines might not be the only explanation. Of interest, can personal factors, such as personal experience with AR, influence practitioners' choices for their patients? A questionnaire distributed among a large number of general practitioners with and without AR compares the management of AR patients between these 2 groups of healthcare providers (Chapter 7).

SPECIFIC AIMS OF THIS THESIS ARE:

1. To characterize the classes of AR described by ARIA in a large patient population (chapter 3) and to assess whether the ARIA classification at the basis of the ARIA treatment recommendations is useful in daily primary care practice (chapter 4)
2. To assess the management practices of AR in general and specialist practice and to compare them with the evidence-based guideline recommendations (chapters 3, 5 and 6)
3. To evaluate the knowledge and use of the ARIA guidelines among general practitioners and specialists and to gain information on physician characteristics that influence compliance with guideline recommendations (chapters 5 and 6)
4. To assess whether personal experience of healthcare providers with AR has an impact on the management of their AR patients (chapter 7)

Chapters 2, 3, 4, 5, 6 and 7 correspond to individual manuscripts. As each manuscript is self-containing some overlap between the chapters is possible.

CHAPTER II

CLINICAL GUIDELINES FOR ALLERGIC RHINITIS

Update of:

CRITICAL LOOK AT THE CLINICAL PRACTICE GUIDELINES FOR ALLERGIC RHINITIS.

Van Hoecke H, Van Cauwenberge P.
Respir Med 2007;101(4):706-14.

INTRODUCTION

Clinical guidelines are systematically developed statements to assist practitioners and patients in making decisions about appropriate and effective healthcare in specific circumstances.[1] Over the last 2 decades, clinical practice guidelines have gained much interest, both in clinical practice and in medical education, as a tool to synthesize clinical information and to improve the quality of healthcare. A large amount of national and international guidelines, covering diverse areas of medicine - including allergic rhinitis (AR) - have been published, and guideline users may even get overwhelmed and confused by this extensive offer.

To ensure the quality of clinical guidelines, increasing attention is paid to the methodology of guideline development[2] and standards, such as the validated AGREE (Appraisal of Guidelines, Research and Evaluation) instrument, are used by an increasing number of guideline developers and appraisers to assess the methodological quality of a guideline and the documentation of the guideline development process.[3, 4] **(TABLE 1)**

A rigorous and transparent methodology of guideline development is essential, but does not guarantee the validity and acceptance of clinical guidelines in the medical community.

In this review we discuss the clinical practice guidelines for AR, with a special focus on the international ARIA (Allergic Rhinitis and its Impact on Asthma) guidelines. We critically appraise the methodology of guideline development, the composition of the guideline development panel and the efficacy and applicability of guidelines for AR. Furthermore, we describe the barriers that may rise when translating scientific knowledge into relevant and accessible information for the practitioner and we discuss the importance of a carefully planned and multifaceted dissemination and implementation strategy.

TABLE 1. *The AGREE II Instrument, a 23-item tool comprising 6 quality domains to address the methodological quality and transparency of guideline development, adapted from Brouwers et al[4].*

Domain 1: Scope and Purpose
1. The overall objective(s) of the guideline is (are) specifically described
2. The health question(s) covered by the guidelines is (are) specifically described
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described
Domain 2: Stakeholder Involvement
1. The guideline development group includes individuals from all the relevant professional groups
2. The views and preferences of the target population (patients, public, etc.) have been sought
3. The target users of the guideline are clearly defined
Domain 3: Rigour of Development
1. Systematic methods were used to search for evidence
2. The criteria for selecting evidence are clearly described
3. The strengths and limitations of the body of evidence are clearly described
4. The methods for formulating the recommendations are clearly described
5. The health benefits, side effects and risks have been considered in formulating the recommendations
6. There is an explicit link between the recommendations and the supporting evidence
7. The guidelines has been externally reviewed by experts prior to its publication
8. A procedure for updating the guideline is provided
Domain 4: Clarity of Presentation
1. The recommendations are specific and unambiguous
2. The different options for the management of the condition or health issue are clearly presented
3. Key recommendations are easily identifiable
Domain 5: Applicability
1. The guideline describes facilitators and barriers to its application
2. The guideline provides advice and/or tools on how recommendations can be put into practice
3. The potential resource implications of applying the recommendations have been considered
4. The guideline presents monitoring and/or auditing criteria
Domain 6: Editorial Independence
1. The views of the funding body have not influenced the content of the guideline
2. Competing interests of guideline development group members have been recorded and addressed

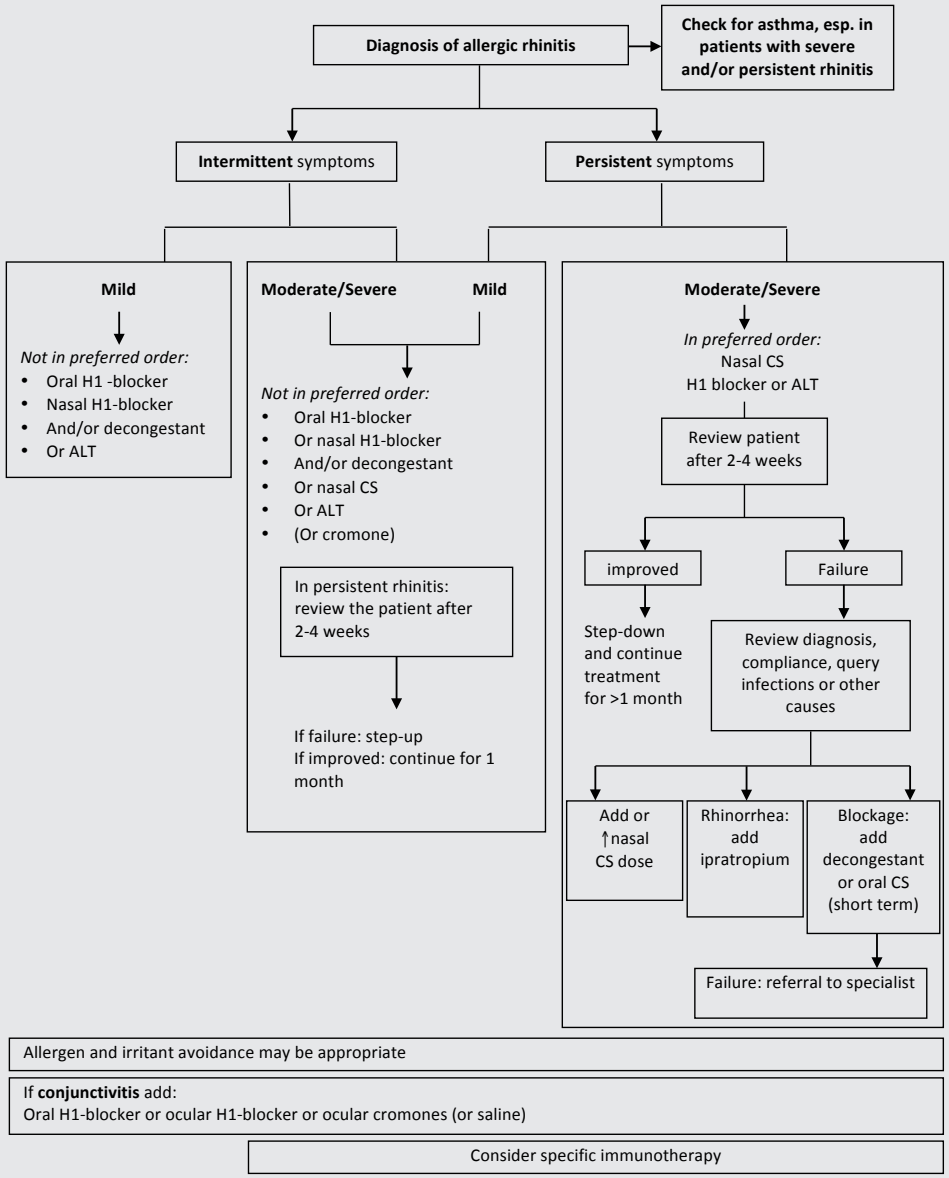
EVOLUTION OF CLINICAL GUIDELINES FOR ALLERGIC RHINITIS

Before 2000, guidelines for AR were predominantly derived from unsystematically-compiled opinions of experts, based on clinical trials and mechanistic approaches (opinion-based medicine).[5-8] Among these opinion-based guidelines, the US guidelines for (allergic) rhinitis[7, 8] represented a state-of-the-art revision of the clinical characteristics, the (differential) diagnosis and treatment options of rhinitis, but did not provide a practical flowchart, guiding practitioners in the management of their patients. The International Consensus on Rhinitis[5] and the Guidelines of the European Academy of Allergy and Clinical Immunology (EAACI)[6] contained very similar information to the US guidelines, but a prominent feature was that they included stepwise treatment algorithms for rhinitis, similar to the Global Inititiative for Asthma (GINA) guidelines for asthma.[9] Whereas the International Consensus Statement on Rhinitis was especially developed for general practitioners (GPs), and only accounted for patients with mild or moderate disease, the newer EAACI guidelines were also aimed for specialists and also included recommendations for patients with severe disease.

In 1999, the ARIA (Allergic Rhinitis and Its Impact on Asthma) Working Group was founded under the initiative of the WHO (World Health Organization). The ARIA guidelines, resulting from this collaboration and published in 2001,[10] were the first evidence-based guidelines. They were intended for GPs and specialists dealing with AR around the world and were innovative in:

- Developing guidelines in collaboration with all stakeholders, including primary care physicians and patients
- Including experts from developed and developing countries
- Highlighting the impact of AR on asthma and emphasizing that rhinitis and asthma are different manifestations of one ‘united airway disease’
- Proposing a new classification for AR based on the duration of sympoms, instead of the type of allergen, and on their impact on quality of life, rather than on rating (nasal) symptom scores
- Providing an evidence-based documented revision of diagnostic methods for AR
- Providing an evidence-based documented revision of treatments for AR and evidence-based therapeutic algorithm with step-up and step-down options **(FIGURE 1).**[11]

FIGURE 1. *Stepwise treatment algorithm for allergic rhinitis in adolescents and adults, as recommended in the ARIA 2008 Guideline Update. Adapted from Bousquet et al[12]. CS: corticosteroid, ALT: antileukotriene.*



After 2001, an evidence-based strategy, based on various evidence models, was used in the updated Practice Parameter for Rhinitis from the AAAAI (American Academy of Allergy, Asthma and Immunology) and the ACAAI (American College of Allergy, Asthma and Immunology),[13] in the International Primary Care Respiratory Group (IPCRG) Guideline on the management of AR in primary care[14] and of course in the updated ARIA guidelines,[12, 15] but also in national or local guidelines such as the Guidelines for the Management of Allergic and Non-allergic Rhinitis from the British Society of Allergy and Clinical Immunology (BSACI) in the UK[16] and the NHG Standard for allergic and non-allergic rhinitis, used in the Netherlands and Belgium.[17] Although all these guidelines are evidence-based, some important differences between their recommendations remain. These differences can be explained by the use of different evidence grading systems, different selection and interpretation of the available medical literature, different available or approved treatments and different target population.[18, 19]

The AR guidelines from the IPCRG[14] and the NHG Standard[17] took over the ARIA classification for AR, but the AAAAI/ACAAI[13] and BSACI[16] guidelines still classified AR into seasonal or perennial. Before the ARIA workshop, asthma and rhinitis comorbidity was disregarded, but after 2000 most guidelines for (allergic) rhinitis reported the link between rhinitis and asthma and made recommendations to assess the possibility of asthma in rhinitis patients. The ARIA Guidelines and its updates[10, 12, 15] and the Spanish Asthma Management Guide,[20] however, are the only guidelines that assess the management of patients with both asthma and rhinitis in the same document.

In 2009-2010, there was another important evolution in the development of AR guidelines with the ARIA 2010 update,[15] that incorporated the GRADE (Grading of Recommendation, Assessment, Development and Evaluation) approach.[21] The ARIA 2010 update presents an analysis of the key clinical questions about allergy prevention, management of AR and management of AR and asthma in the same patient. The recommendations are presented as answers on 48 PICO-based questions (Patient problem or Population – Intervention – Control - Outcome), developed by clinical experts and methodologists. While the previous evidence-based guidelines only based the strength of their recommendations on the quality of underlying evidence, the recommendations in the ARIA 2010 update, following the GRADE methodology, are also influenced by the balance between benefits and harms of following the recommended course of action, values and preferences of those for whom the guidelines are intended and considerations around resource utilization.[22]

EVIDENCE-BASED GUIDELINES: SEARCHING AND APPRAISING EVIDENCE, GRADING RECOMMENDATIONS

Evidence-based medicine (EBM) has become an increasingly important concept in medicine. The benefits of the methodology to provide a convenient logical framework from which the quality and relevance of clinical studies may be assessed in an unbiased manner are well described.[23]

For the healthcare practitioner, however, it is almost impossible to keep up-to-date with the medical literature. It is even more difficult to critically appraise the value of research findings and to apply evidence from research in medical practice. To allow clinicians to efficiently use the information from research in making decisions about the care of the individual patient, the process of preparing and providing clinical practice guidelines, based on the best-available evidence from research regarding the efficacy of various procedures and interventions, has become essential.[24] The recommendations of these 'evidence-based guidelines' are linked to a specific evidence background, which is identified through an extensive literature search, critically evaluated and rated by a specific grading system.[25]

SEARCHING AND APPRAISING EVIDENCE

Critical examination of evidence from clinical research is best done by performing a systematic evaluation of the literature. Ideally, evidence is based on results of randomized controlled trials (RCTs). Of course, not only the study design, but also the relevance and quality of the collected evidence must be assessed following pre-established criteria. The CONSORT (Consolidated Standards of Reporting Trials),[26] and the QUORUM (Quality of Reporting of Meta-analyses) and MOOSE (Meta-analysis Of Observational Studies in Epidemiology) statements[27, 28] in particular, are intended to improve the reporting of RCTs and meta-analyses respectively. In addition, they enable readers, reviewers, researchers and editors to understand a trial's conduct and to assess the validity of its results in a stepwise manner.[29]

It needs to be emphasized, however, that there are some obvious limitations when performing a systematic evaluation of the 'best available evidence'. For many clinical questions, such as the role of allergen avoidance in the treatment of AR and asthma, there remains a lack of large-scale, well-developed and well-conducted clinical trials and consequently a lack of evidence. On the other hand, despite a thorough and hand-based search, it is not always possible to have access to or to review all relevant study results. Furthermore, results from different original studies often disagree.

In these cases - and if available - systematic reviews can contribute to resolving uncertainty.[28] The Cochrane Library is a key source for systematic reviews of evidence on healthcare interventions. The Cochrane Collaboration is organized in more than 50 review groups, covering different areas of interest in medical research and provides methodological support in 16 methods groups.[31] In general, the comprehensive systematic reviews of the Cochrane Collaboration are more systematic and demonstrate less publication and reference bias than systematic reviews published in paper journals. A rigorous methodology is applied, characterized by an extensive review of published and pre-published data, obtained through database- and hand-searching, and the process of post-publication review is promoted.[32] Nevertheless, even systematic Cochrane reviews are not completely free of errors and bias, and still must be interpreted with caution.[21] Furthermore, systematic reviews are sometimes criticized for their failure to offer specific guidance, which is often due to few assessments of outcome measures in the primary studies that they analyze.[33]

GRADING RECOMMENDATIONS

For guideline users, it is important to know how much confidence they can place in guideline recommendations. Therefore, many guidelines use and disclose a method to grade the strength of their recommendations. Before the introduction of the GRADE methodology, the strength of guideline recommendations was exclusively based on the quality of the underlying evidence.

Several evidence grading systems have been developed. The ARIA 2001[10] and 2008[12] guidelines and the 2008 US Practice Parameter for Rhinitis[13] followed the grading system of the Agency for Health Care Policy and Research (AHCPR)[34] **(TABLE 2)**. Other grading systems include the SIGN (Scottish Intercollegiate Guidelines Network) system,[35] the OCEBM (Oxford Centre for Evidence-Based Medicine) system[36] and the evidence model of the Royal College of General Practitioners[37] that was used in the AR Guideline from the IPCRG[14]. Although these different classification systems all share the same basic structure, they demonstrate differences in terminology and in gradation of evidence from specific publication types, which is of course confusing and limits easy communication.[21, 25]

TABLE 2. *Evidence grading system of the Agency for Health Care Policy and Research (AHCPR)*[34]

Category of evidence	
Ia	Evidence from meta-analysis of randomized controlled trials
Ib	Evidence from at least one randomized controlled trial
IIa	Evidence from at least one controlled study without randomization
IIb	Evidence from at least one type other type of quasi-experimental study
III	Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies
IV	Evidence from expert committee reports or opinions or clinical experience of respected authorities or both
Strength of evidence of recommendations	
A	Directly based on category I evidence
B	Directly based on category II evidence or extrapolated recommendation from category I evidence
C	Directly based on category III evidence or extrapolated recommendation from category I or II evidence
D	Directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence

The grading of the recommended pharmacotherapy and immunotherapy in AR treatments as proposed in the ARIA 2008 guidelines[12] has shown to be particularly strong (category A for most treatments), whereas evidence supporting the benefits of allergen avoidance is very low (category D) **(TABLE 3)**. It is important to remark, however, that the collected evidence[12] is mostly based on trials that were carried out before the new classification of AR. Strength of evidence is therefore mainly reported for seasonal and perennial AR and cannot merely be extrapolated to intermittent and persistent AR.

But, there are more important shortcomings with this evidence grading methodology.

First, there is no grading for 'negative' results. E.g. RCTs have demonstrated that the combination of an oral H1-antihistamine and a leukotriene receptor antagonist does not increase the efficacy of any single drug.[38, 39] The AHCPR grading system,[34] however, does not provide a category that allows to grade the strength (or weakness) of recommending this combined treatment.

Second, the clinical relevance of the strength of evidence supporting a specific recommendation can be questioned. E.g. RCTs have demonstrated that cromones have modest effects in the treatment or prophylaxis of seasonal AR symptoms compared to placebo, which corresponds with a category A strength of evidence **(TABLE 3)**. In clinical practice, however, the use of cromones is limited, as they have demonstrated to be clearly less effective than other AR treatments such as H1-antihistamines and nasal corticosteroids. Nevertheless, the strength of

recommending an antihistamine, a nasal corticosteroid or a cromone in seasonal AR all receive the same "A" gradation.[12]

Third, the highest quality and strength of evidence from RCTs is often based on highly selected patients, that differ from the patient population seen in daily practice. Many clinicians feel that evidence-based recommendations are difficult to apply in a specific clinical setting and to integrate with individual clinical expertise.[40]

According to the definition of Sackett, however, EBM should not cancel the value of individual clinical expertise but should be regarded as "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of the individual patient. It means integrating individual clinical expertise with the best available external clinical evidence from systematic research".[41] This implies that an evidence-based approach to make healthcare decisions acknowledges that only relying on the quality of literature is insufficient, but that values and preferences, clinical circumstances and clinical expertise inevitably influence decisions.[42, 43]

TABLE 3. *Strength of evidence of different AR treatments in ARIA 2008 guidelines*[12] *according to AHCPR gradation.*[35] *SAR: seasonal allergic rhinitis, PAR: perennial allergic rhinitis, PER: persistent allergic rhinitis. OAH1: oral H1-antihistamine, NAH1: nasal H1-anthistamine, NCS: nasal corticosteroid, OCS: oral corticosteroid, ND: nasal decongestant, OD: oral decongestant, SCIT: subcutaneous immunotherapy, SLIT: sublingual immunotherapy, nda: no data available,* [(1)]*: evidence more recent than publication of ARIA 2008 guidelines*

Intervention	SAR Adult	SAR Children	SAR Adult	SAR Children	PER
OAH1	A	A	A	A	A
NAH1	A	A	A	A	nda
NCS	A	A	A	A	A[(1)]
OCS	A	B	B	B	nda
ND	C	C	C	C	nda
OD	A	nda	nda	nda	nda
Nasal cromone	A	A	A	B	nda
Ocular cromone	A	A	B	B	nda
ALT	A	A (>6y)	nda	nda	nda
SCIT	A	A	A	A	nda
SLIT	A	A	A	A	nda
Anti-IgE	A	A (>12y)	A	A	nda
Allergen avoidance	D	D	D	D	nda

The GRADE approach to developing clinical guidelines affirms that the quality of evidence is only one of the factors influencing the strength of a recommendation. The GRADE process starts with asking an explicit question, including specification of all important outcomes. After the evidence is collected and summarized, GRADE provides explicit criteria for rating the quality of evidence into 4 categories (high, moderate, low and very low) that include study design, risk of bias, imprecision, inconsistency, indirectness, and magnitude of effect. The strength of a recommendation is graded into 2 levels (strong or weak) according to the quality of the supporting evidence and the balance between desirable and undesirable consequences of the intervention and the alternative management options, resource utilization and user values and preferences.[44] **(FIGURE 2)**

As recommended by the "guidelines for WHO guidelines",[45] the GRADE methodology was used in the ARIA 2010 guidelines[15] **(TABLE 4)**. Separation of the strength of a recommendation and the quality of the supporting evidence allows:

- Strong recommendations supported by low quality evidence when other factors determining the strength of a recommendation suggest that this is the best course of action; e.g. ARIA 2010 makes a strong recommendation of total avoidance of environmental tobacco smoke in children and pregnant women to reduce the risk of developing allergy, wheezing or asthma despite only very low-quality evidence, as there is a clear balance between desirable and undesirable effects with this intervention.
- Weak recommendations in the presence of moderate or high quality of evidence for instance when there are potential important undesirable effects of an intervention; e.g. ARIA 2010 recommends not to use sublingual immunotherapy in children with AR caused by house dust mites as there is a relatively high chance of local adverse effects, despite moderate quality of evidence of reduction in nasal symptoms.[15, 46]

The GRADE Working Group believes that their grading of recommendations better reflects the way clinicians think or behave before undertaking action (balancing the pros and cons) and is closer to patient and physician's needs than former grading systems, that were only based on the quality of the underlying body of evidence. The GRADE classification has been adopted by over 50 major organizations worldwide.[46, 47] But, also the GRADE system has limitatons. Inevitably, categorizing recommendations as strong or weak can be 'arbitrary' and criticism concerning its effectiveness, validity and internal consistency has risen.[48]

It remains to be emphasized that, irrespective of the type of grading system that is used, transparent reporting of the evaluations and judgements that support guideline recommendations is absolutely necessary in order to allow the implementation of the recommendations in an individual clinical setting.

FIGURE 2. *Schematic view of GRADE's process for developing recommendations. RCT: randomized controlled trials, adapted from Guyatt et al[44]. S: study, OC: outcome, *also labeled 'conditional' or 'discretionary'.*

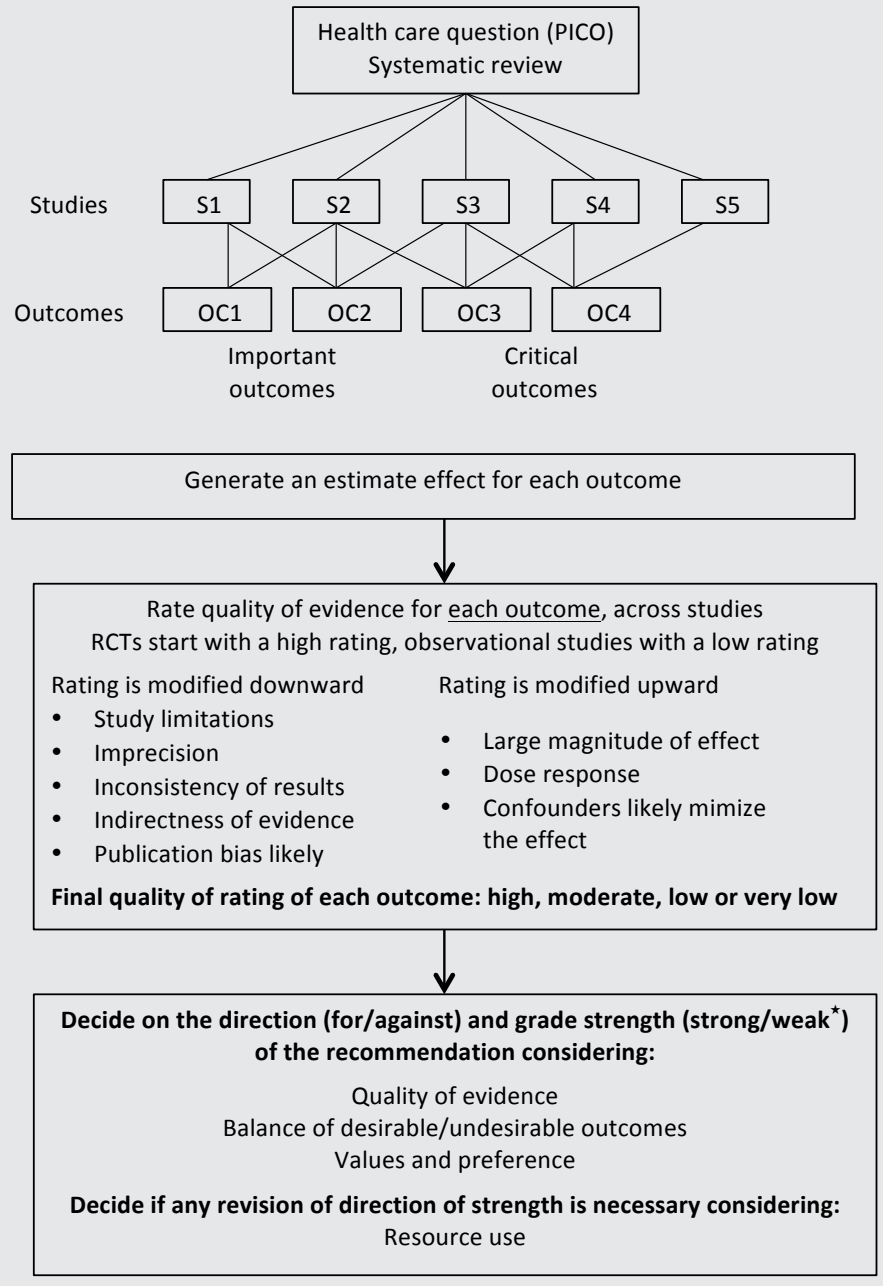


TABLE 4. *Overview of pharmacological agents for the treatment of allergic rhinitis*[11, 53, 54]

	Strength of recommendation and quality of evidence	Clarity of balance desirable / undesirable effects	Quality of supporting evidence	Implications
1A	Strong recommendation High-quality evidence	Desirable effects clearly outweigh undesirable effects, or vice versa	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies	Recommendation can apply to most patients in most circumstances. Further research is unlikely to change our confidence in the estimate of effect
1B	Strong recommendation Moderate-quality evidence		Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise) or unusually strong evidence from unbiased observational studies	Recommendation can apply to most patients in most circumstances. Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
1C	Strong recommendation Low-quality evidence		Evidence for at least one critical outcome from RCTs with serious flaws, observational studies, or indirect evidence	Recommendation may change when higher quality evidence becomes available. Further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
1D	Strong recommendation Very low-quality evidence (very rarely applicable)		Evidence for at least one of the critical outcomes from unsystematic clinical observation or very indirect evidence	Recommendation may change when higher quality evidence becomes available. Any estimate of the effect for at least one critical outcome is very uncertain
2A	Weak recommendation High-quality evidence	Desirable effects closely balanced with undesirable effects	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies	The best action may differ depending on circumstances or patients or societal views. Further research is very unlikely to change our confidence in the estimate of the effect
2B	Weak recommendation Moderate-quality evidence		Evidence from RCTs wit-h important limitations (inconsistent results, methodological flaws, indirect or imprecise) or unusually strong evidence from unbiased observational studies	Alternative approach likely to be better for some patients under some circumstances. Further research is likely to have an important impact on our confidence of the estimate of effect and may change the estimate
2C	Weak recommendation Low-quality evidence		Evidence for at least one critical outcome from RCTs with serious flaws, observational studies, or indirect evidence	Other alternatives may be equally reasonable. Further research is very likely to have important impact on our confidence in the estimate of effect and is likely to change the estimate
2D	Weak recommendation Very low-quality evidence		Evidence for at least one of the critical outcomes from unsystematic clinical observation or very indirect evidence	Other alternatives may be equally reasonable Any estimate of the effect for at least one critical outcome is very uncertain

THE GUIDELINE DEVELOPMENT GROUP

The guideline development group is a committee of people, each exerting a specific role in the guideline development process. Usually, the group consists of a team leader that co-ordinates the group process (ensuring that it functions effectively) and the group task (ensuring that it achieves its aims), a group of team members, representing the stakeholders and people providing expert resource, methodological, technical and administrative support.[34]

According to Shekelle[34] the panel should consist of at least 6, but no more than 12-15 members, as too few members limits adequate discussion and too many members hampers effective functioning of the group. Nevertheless, the recommendations on the number of panel members can be debated. Probably, large groups can also function adequately if the tasks are shared by subgroups, reporting the larger group at the end.

To allow a successful guideline development with a very large working group, many guideline panels, including the ARIA 2008[12] and 2010 panel[15], are organized into a guideline 'core group' undertaking the day to day running of the work and a larger group (or different subgroups) acting as consultants or reviewers and reporting to the core group.

STAKEHOLDER INVOLVEMENT

Probably more important than the number of guideline members, is the involvement of stakeholders. Identifying stakeholders involves identifying all the groups whose activities are covered by the guideline or who have other legitimate reasons for having an input into the process.[34] The representation of the stakeholders in the guideline development group is indeed of great value for the identification of the specific needs of those for whom the guidelines are intended and for the adaptation of data from research into useful and user-friendly recommendations. Furthermore, different backgrounds of the panel members may lead to a better balancing of individual biases, which in turn may lead to the production of more valid guidelines.

In a systematic review of 91 studies, Grimshaw and Russell concluded already 20 years ago that guidelines have the greatest chance of changing clinical behavior when they are developed by clinicians for whom they are intended.[49] Many clinical conditions, including allergy and AR, are preferentially managed in a multidisciplinary setting, and consequently, it is recommended that the expert panel has a multidisciplinary composition. Guidelines for the management of AR are not only aimed for specialists, but are intended to assist GPs in particular.[30] The important end-user group of GPs, however, was not represented in the guideline panel from the International Consensus Report[5] and the EAACI guidelines.[6] For the development of the ARIA guidelines,[10, 12, 15] on the other hand, both specialists (ENT-specialists, Allergologists, Pulmonologists, Paediatricians) and GPs were involved from the start. Furthermore, an ARIA pocket guide was developed with the World Organization of Primary Care Physicians (WONCA) and the IPCRG.[50]

Although often underestimated, not only GPs and specialists, but also pharmacists can play a key role in the prevention, recognition and treatment of AR. The involvement of pharmacists in the collaborative management of AR is also recognized by ARIA, and is sustained by the publication of the 'ARIA in the Pharmacy' guidelines.[51] This document is aimed as a practical stepwise guide for pharmacists and their staff in the recognition and management of patients suffering from AR. Pharmacists were part of this guideline working group.

As the stakeholder with the most to lose or to gain, the input of patients in the process of guideline development should not be neglected. In contrast to the preceding international guidelines for AR, patient organizations were involved in the development of the ARIA guidelines and pocket guides.[10, 12, 15, 51]

A BALANCED AND DIVERSE GUIDELINE PANEL

As mentioned above, different backgrounds of a guideline panel may lead to a better balancing of individual biases and to the production of more valid guidelines. The background of a guideline, however, not only refers to its stakeholder position, but is also influenced by type of affiliation and demographic factors such as age, gender and ethnicity.

If guidelines are intended for international use, it is necessary that experts and stakeholders from the different countries and continents are involved in their generation and formulation and in adapting them to meet local needs and local socio-economic and healthcare standards and resources. The ARIA guidelines were developed as a basis for the whole world and their global character is also reflected in the international and intercontinental composition of the ARIA panels.[10, 12, 15]

In most (allergic) rhinitis guideline groups,[5-8, 10, 12, 13, 15] on the other hand, women and members affiliated to non-university institutions are very poorly represented. It is possible that only few women and non-academics were candidate to be part of the guideline development groups, but the selection of a more balanced composition of the panel for gender and professional affiliation is definitely a point of discussion.

CONFLICT OF INTEREST

If guidelines are intended to be used as a basis for physicians and healthcare organizations, independence of pharmaceutical industry is strictly necessary. Instruments, such as AGREE, emphasize that guidelines need to include an explicit statement that views or interests of the funding body have not influenced the final recommendations and that all members of the guideline group have declared possible conflicts of interest.

Before 2001, conflict of interest among the members of the expert panels of AR guidelines was not disclosed. For the ARIA 2001 Working group, conflict of interest was reported to the WHO for all except one member, but this was not published in the ARIA report.[10] For the following ARIA 2008 and 2010 guidelines[12, 15] conflict of interest of the members of the guideline core group was reported, but not for the members of the review group.

EFFICACY AND APPLICABILITY OF GUIDELINES

The key role of guidelines is to assist healthcare providers in the management of their patients and to improve the patient care, compliance and satisfaction. Despite the vast number of guidelines and the increasing attention paid to the methodology of guideline development, there is limited evidence of the impact of guidelines on practice patterns, health outcomes and healthcare costs.[49]

Ideally, guidelines should be assessed for their efficacy and applicability in the target healthcare setting prior to its dissemination and implementation. This validation is rarely performed, but is nevertheless important as evidence-based recommendations in evidence-based guidelines are based on results from RCTs, which are often based on high selected patients, not representing the patient population seen in daily practice. The GRADE methodology that was used in the ARIA 2010 guidelines[15] partly addresses these concerns by grading guidelines recommendations not only on the underlying body of evidence, but also on the presumed balance between benefits and downsides, user values and preferences and considerations around costs. But, there remains a clear need to perform real-life studies to provide concrete proof that evidence-based results from mechanistic RCTs and evidence-based or 'strong' guideline recommendations also translate into relevant and beneficial effects in daily clinical practice. Furthermore, studies need to be conducted in 'special populations', that are usually excluded in clinical trials, including young children, elderly patients, patients with comorbidity and patients in low resource countries.[43]

EFFICACY OF GUIDELINES

At present, 2 guidelines for AR have been assessed for their effects on health outcomes in patients with AR induced by pollens in multicentre, randomized, parallel group studies. A first study in general practice showed that treatment according to the International Consensus on Rhinitis[3] was significantly better than treatment according to the GPs' free choice, as reflected by reduced symptom scores and increased quality of life scores, patient compliance and satisfaction[52].

A more recent pragmatic study in specialist practice demonstrated that treatment according to the ARIA guidelines[12] resulted in significant improvements in quality of life scores, work productivity and daily symptom scores in comparison to the free-choice treatment group.[53] Costs were not evaluated in both studies.

In these trials, however, GPs and specialists in the 'guideline group' were explicitely asked to follow the guideline recommendations, whereas, in real life, availability of guidelines does not ensure the use of guidelines. User-friendliness and applicability of guidelines and physician's attitude towards and adherence to clinical guidelines should therefore also be evaluated next to measuring effectiveness of clinical practice guidelines based on patient outcomes.

APPLICABILITY OF GUIDELINES

The applicability of guidelines refers to whether and how guidelines can be put into practice. It encompasses the provision of advice and/or tools to apply recommendations in the specific clinical setting and anticipation of resource implications of applying the recommendations. To make guidelines applicable in different local healthcare settings they may require adaptation, by reformatting

the recommendations at a local/national level, depending on the local values, available medications and interventions and costs.

As primary care practitioners diagnose and treat the majority of patients with AR, applicability of AR guidelines in primary care practice remains a major challenge. Whereas the ARIA guidelines, contrarely to the previous 'International', European and US Guidelines[5-8], were the first to involve GPs in the development and formulation of their recommendations, they still lack explicit description of barriers and facilitators, and provision of tools and advices to implement their recommendations in the primary care setting. Many (primary) healthcare organizations, however, have developed their own guidelines or adapted an existing guideline. The NHG Standard for allergic and non-allergic rhinitis[17] and the International Primary Care Respiratory Group (IPCRG) Guideline on the management of AR in primary care[14] were both modified from the ARIA guidelines with specific considerations of the primary care health setting and resources.

Another concern is the applicability of AR guidelines in developing countries. The EAACI guidelines[6] assumed that the recommended treatments were available and financially affordable to the patient, and did not consider these situations where the suggested first-choice treatment was not an option. The International Consensus Report5 did mention that all recommendations of treatment strategies depend upon local availability of the therapeutic interventions, but did not formulate any concrete suggestions or recommendations. One of the principal goals of ARIA was to optimize the management of AR worldwide. The first version of the ARIA guidelines[10] took into account the availability and affordability of medications, as well as the WHO essential list of medications.[54] In the WHO list that was available at the time of the 2001 ARIA guidelines, only first generation antihistamine chlorpheniramine was listed and consequently also recommended by the ARIA working group. In the 2010 ARIA revision[15] 16 experts from developing countries have drafted or reviewed the recommendations. Experts and reviewers have extensively discussed the relative risk/benefit ratio of first generation antihistamines,[55] the WHO list has listed alternative drugs and the latest ARIA guidelines strongly recommend the use of new- over old-generation antihistamines.[15]

To guarantee the global applicability of guidelines, not only differing healthcare resources and facilities, but also local values and cultural differences need to be considered. Furthermore, most of the (randomized controlled) studies at the basis of guideline recommendations have been carried out in developed, westernized countries. Different races, however, may metabolize drugs differently and risk versus benefit arguments regarding therapeutic decisions may also vary between populations. The risks associated with steroid therapy for instance, may possibly be greater when the patient is malnourished or pardoxically less when life expectancy is anyway low.[56]

UPDATING GUIDELINES

To be useful and valuable in clinical practice, it is particularly important that guidelines are based on current scientific knowledge and that they are regularly revised and updated.

There is, however, no consensus on the time interval and the methodology to perform a guideline update. Although guideline evaluators agree that periodic revision is important, 9 out of 18 guideline organizations reported that they lack formal procedures for keeping their guidelines up to date.[57]

Conducting a new, complete systematic literature review, starting from the end date of the original guideline search, is definitely the most thorough way to identify significant new evidence, but is very effort-, time- and money-consuming and has been identified as a major barrier to timely updates of guidelines.[58] A more feasible method, is to first assess whether guideline updating is required, as undertaking a full update prematurely is a waste of resources.

Shekelle et al described six situations that require a guideline or guideline recommendation to be updated (or even withdrawn) **(TABLE 5)** and proposed a pragmatic model to determine whether a guideline update should be performed.[59]

TABLE 5. *Situations that require a guideline to be updated, adapted from Shekelle et al*[59]

1. Changes in the available interventions
2. Changes in the evidence on the benefits and harms of existing interventions
3. Changes in the outcomes that are considered important
4. Changes in the values placed on outcomes
5. Changes in evidence that current practice is optimal
6. Changes in resources available for healthcare

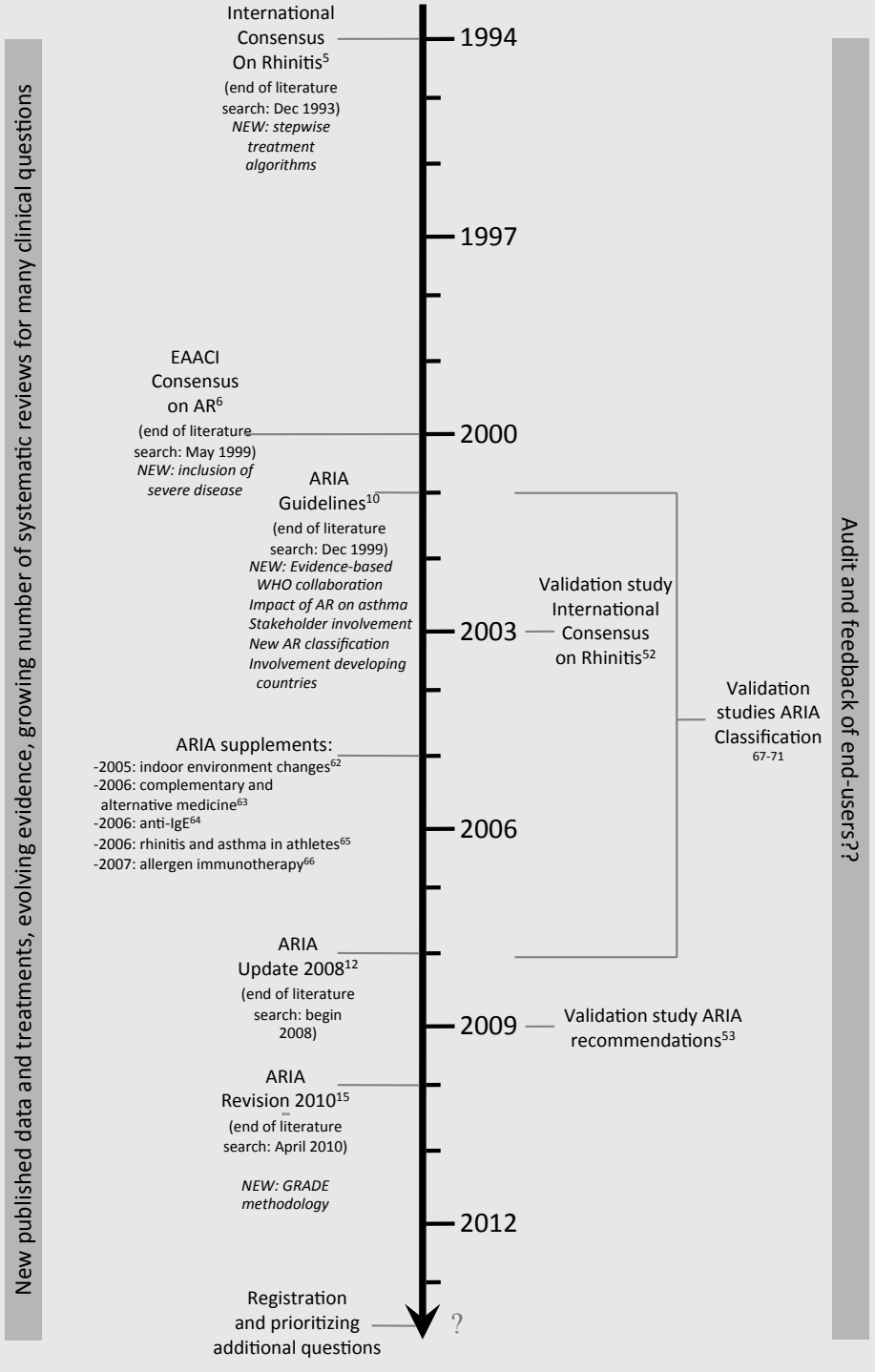
Shekelle's model is based on the assumption 'that evidence sufficient to invalidate an existing guideline' would be known to clinical experts and/or discussed in reviews, commentaries, and editorials in major journals of general or specialty interest[59] and has been validated as an efficient and acceptable method compared to a traditional systematic review method.[60] Applying this model, analysis of 17 clinical practice guidelines, published by the AHRQ (Agency for Healthcare Research and Quality), showed that about half of the guidelines become outdated in 5.8 years, whereas 90% of the guidelines are still valid 3.6 years after delivery of the guideline. Based on these findings the authors of this study suggest that the best interval to assess whether guidelines are still up-to-date should be conservatively after a 3 years time period, when 90% of the guidelines are estimated to be still valid. For topics that are characterized by rapid scientific advances, however, a shorter interval may be indicated, for topics that are more stable a longer interval.[61]

It is important to add that a first precondition to avoid a guideline to become to soon outdated is to minimize the time interval between the end date of the literature search and the publication date of the guideline. The first ARIA guidelines,[10] however, were based on a literature search that ended in December 1999, whereas the guideline report was only published 2 years later.

The chronology of the development and publication of the ARIA Guidelines and updates and the preceding International[5] and European[6] Consensus Report on (allergic) rhinitis is presented in **FIGURE 3**.

But, as guidelines are living documents guideline development and updating should preferably be performed as a continuous process, rather than as a discrete event. This ongoing process could consist of regular automated literature searches and revision of relevant citations by members or subgroups of the guideline panel, followed by evaluation of the impact of new evidence on the validity of an existing guideline. Furthermore, if guidelines are available in an electronic form on the Web, recommendations that are considered as outdated or invalid could easily and systematically be deleted or changed by updating the underlying inputs. In addition, a mechanism could be added to electronically alert interested parties that changes have been made to the guideline.[61]

FIGURE 3. *Chronology of AR guideline development*[62-71]



TRANSLATING RESEARCH INTO PRACTICE, DISSEMINATION AND IMPLEMENTATION OF GUIDELINES

A large gap between clinical research and clinical practice remains, and the development of clinical practice guidelines does not ensure their use in medical practice. Translating scientific knowledge into practical medicine is not straightforward and may be hampered by diverse structural, cultural, economic or behavioral barriers. Budgetary limitations, competing demands and restricted healthcare facilities in low-income countries have already been addressed. However, also in developed countries, allergy (and AR) has only recently gained a place on the agenda of Governments and Health Departments. In the individual patient care setting, physician adherence to guidelines may be restricted by lack of awareness, lack of familiarity, lack of self-efficacy, lack of outcome expectancy and by inertia of previous practice. Lack of time, lack of reimbursement for following guidelines or limited staff have also been put forward as barriers. Furthermore, physicians may experience difficulties in reconciling patient preferences with guideline recommendations, and sometimes guidelines themselves may be unclear or confusing.[56, 72] Finally, barriers may also rise at the level of the patient, in terms of compliance with the recommended therapeutic strategies.

To address the gap between research and practice, clinical guidelines should be simple, transparent, informative and adapted to the clinical setting, the cultural and socio-economical context. The main goal of guidelines is to assist physicians and to improve patient care. This implies that they should be developed and considered as a support for practitioners with space for flexibility, rather than as a set of constrained rules.[2]

There is no single effective way to introduce and ensure the use of guidelines into practice, but a carefully developed and multifaceted dissemination and implementation program should form an integrated part of the stepwise and continuous process of guideline production.

Dissemination usually starts with the publication of the full version guideline report in a professional journal. For practitioners - GPs in particular - taking care of patients with multiple diseases, however, it is impossible to read through these often very voluminous documents. The ARIA 2001 Workshop Report is 187 pages long,[10] the 2008 update counts 160 pages. Derivatives of guidelines such as summaries, pocket guides, web-based activities, documents and questionnaires are usually more useful and user-friendly and should follow the guideline recommendations exactly.

For the ARIA 2001 and 2008 guidelines, pocket guides were translated into more than 50 languages and distributed worldwide. The ARIA website[73] provides a copy of the guidelines and pocket guides, and interactive rhinitis and asthma questionnaires.[22]

Over the last years the World Wide Web has gained interest as an alternate medium for guideline developers to disseminate guidelines. Web-based guidelines can incorporate a greater complexity than that afforded by paper-based format while maintaining a consistent structure and orientation for the user. The level of detail displayed can be varied and easy linking to supporting material is possible.[74] Web-based guidelines allow distance-learning and are more easily distributed, modified and updated. Furthermore, there is a growing interest in Web-based models to create guidelines based on decision models that can be disseminated over the Web. Local guideline users could then alter the input underlying the decision model and tailor the guidelines to a particular patient population.[75] At present, however, research into Web-based guidelines is still in the early stages. The strengths and weaknesses of Web-based guidelines need to be further elucidated and the exact role of Web-based guidelines as a primary or secondary modality added to the traditional paper-based guidelines needs to be defined.

Furthermore, relatively passive methods of publication in professional journals or mailing to targeted healthcare professionals alone, are unlikely have an impact on professional acting.[76, 77] The dissemination and implementation process should be arranged to take the intervention closer to the doctor/patient setting. In a systematic review of 91 studies, Grimshaw and Russell concluded that guidelines have the greatest chance of changing clinical behavior when they are disseminated via specific educational interventions, followed by continuing medical education, and implemented via patient-specific reminders during the consultation.[78] A Cochrane Review analysed the effects of continuing education sessions and concluded that interactive workshops can result in moderately large changes in professional practice, whereas didactic sessions alone are unlikely to change professional practice.[79] Other professional interventions that may lead to further reinforcement of guideline messages are reminders, audit and feedback.[76] As for Web-based guidelines, Web-based learning in general possibly has a valuable educational contribution, but its full potential needs to be unlocked and its exact role needs to be established. Of course quality control of the disseminated information must be warranted and the principles of effective learning must be integrated.

At present, there is insufficient evidence to allow an estimation of the efficiency and cost-effectiveness of the diverse professional dissemination and implementation strategies in different circumstances. Further research in this area is required to develop and validate a coherent framework that may sustain the process of introducing and establishing guidelines into clinical practice and may consequently result in significant improvements in educational outcomes and healthcare practices.[80]

Organizational interventions (e.g. expanded role of the pharmacist), financial interventions (e.g. professional incentives) and regulatory interventions (e.g. giving GPs access to specific diagnostic tests) have also been suggested to facilitate or stimulate the use of guidelines in clinical practice.[81] However, caution should be paid to the implication of legal authorities or national health organizations in the process of guideline development, dissemination and implementation. Leaning on guidelines to guide or support governmental and healthcare policy decisions might generate discussions on the type of guidelines that should be used (e.g. national versus international). In addition, it is associated with a potential risk of basing such important decisions on outdated guidelines, and of course it may imply a restriction of medical freedom.

The final and most important step of putting guidelines into practice occurs at the level of the patient. Even if guidelines ensured the best clinical practice in the world, if patient's behavior and knowledge is inappropriate, the outcomes may not change much. Patients should be considered as effective partners in healthcare. Educating the patient regarding the nature and management of their disease, teaching them how to verify received information, how to present symptoms and clinical history, and how to assess outcomes can maximize compliance, increase satisfaction and optimize health outcomes. Furthermore, patient's feedback may act as a stimulus to health professional change.[82]

REFERENCES

1. Jackson R, Feder G. Guidelines for clinical guidelines. BMJ 1998;317(7156):427-8.
2. Bousquet J, Van Cauwenberge P. A critical appraisal of 'evidence-based medicine' in allergy and asthma. Allergy 2004;59 Suppl 78:12-20.
3. AGREE Collaboration. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. Qual Saf Health Care 2003;12(1):18-23.
4. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al; AGREE Next Steps Consortium. AGREE II: Advancing the guideline development, reporting and evaluation in healthcare. CMAJ 2010;182(18):E839-42.
5. International Rhinitis Management Working Group. International Consensus Report on the Diagnosis and Management of Rhinitis. Allergy 1994;49 (Suppl 9):5-34.
6. Van Cauwenberge P, Bachert C, Passalacqua G, Bousquet J, Canonica GW, Durham SR, et al. Consensus statement on the treatment of allergic rhinitis. Allergy 2000;55(2):116-134.
7. Fornadley JA, Corey JP, Osguthorpe JD, Powell JP, Emanuel IA, Boyles JH, et al. Allergic rhinitis: clinical practice guideline. Committee on Practice Standards, American Academy of Otolaryngic Allergy. Otolaryngol Head Neck Surg 1996;115(1):115-22.
8. Dykewicz MS, Fineman S, Skoner DP, Nicklas R, Lee R, Blessing-Moore J, et al. Diagnosis and Management of Rhinitis: Complete Guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. Ann Allergy Asthma Immunol 1998;81 (5Pt2):478-518.
9. Global Initiative for Asthma. Global strategy for asthma management and prevention. http://www.ginasthma.com/.
10. Bousquet J, van Cauwenberge P, Khaltaev N, ARIA Workshop Group. Allergic Rhinitis and its Impact on Asthma (ARIA). J Allergy Clin immunol 2001;108 (Suppl 5):S147-S333.
11. Bousquet J, Schünemann HJ, Samolinski B, Demoly P, Baena-Cagnani CE, Bachert C, et al; World Health Organization Collaborating Center for Asthma and Rhinitis. Allergic Rhinitis and its Impact on Asthma (ARIA): achievements in 10 years and future needs. J Allergy Clin Immunol 2012;130(5):1049-62.
12. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al: Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy 2008;63(Suppl 86):8-160.

13. Wallace DV, Dykewicz MS, Bernstein DI, Blessing-Moore J, Cox L, Khan DA et al. Joint Task Force on Practice; American Academy of Allergy; Asthma & Immunology; American College of Allergy; Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. The diagnosis and management of rhinitis: an updated practice parameter. J Allergy Clin Immunol 2008;122(2Suppl):S1-84.
14. Price D, Bond C, Bouchard J, Costa R, Keenan J, Levy ML, et al. International Primary Care Respiratory Group (IPCRG) Guidelines: management of allergic rhinitis. Prim Care Resp J 2006;15(1):58-70.
15. Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, et al: Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. J Allergy Clin Immunol 2010;126(3):466-76.
16. Scadding GK, Durham SR, Mirakian R, Jones NS, Leech SC, Farooque S et al. BSACI guidelines for the management of allergic and non-allergic rhinitis. Clin Exp Allergy 2008;38(1):19-42.
17. Sachs APE, Berger MY, Lucassen PLBJ, Van der Wal J, Van Balen JAM, Verduijn MM. [NHG Standard: allergic and non-allergic rhinitis]. Huisarts Wet 2006;49(5):254-65.
18. Chipps B, Spector S, Farrar J, Carr W, Meltzer, Storms W, et al. Differences in recommendations between the Allergic Rhinitis and its Impact on Asthma Update 2010 and US Rhinitis Practice Parameters. J Allergy Clin Immunology 2011;127(6):1640-1; author reply 1643-5.
19. Spector S, Wallace D, Nicklas R, Portnoy J, Blessing-Moore J, Bernstein D, et al. Comments on Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines. J Allergy Clin Immunol 2011;127(6):1641-2; author reply 1643-5.
20. GEMA. Spanish Asthma Management Guide. Arch Bronconeumol 2009;45(Suppl7):2-35.
21. GRADE Working Group. Grading quality of evidence and strength of recommendations. BMJ 2004;328(7454):1490-8.
22. Bousquet J, Schünemann HJ, Zuberbier T, Bachert C, Baena-Cagnani CE, Bousquet PJ, et al; WHO Collaborating Center of Asthma and Rhinitis (Montpellier). Development and implementation of guidelines in allergic rhinitis – an ARIA-GA2LEN paper. Allergy 2010;65(10):1212-21.
23. Barton S. Which clinical studies provide the best evidence? The best RCT still trumps the best observational study. BMJ 2000;321(7256):255-6.
24. Fletcher SW, Fletcher RH. Development of clinical guidelines. Lancet 1998;352(9144):1876.

25. Caracciolo B, van Rijn A, Bonini S. Practice evidence to put evidence into practice. Allergy 2004;59(11):1165-7.

26. Moher D, Schulz KF, Altman D; CONSORT Group (Consolidated Standards of Reporting Trials). The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA 2001;285(15):1987–91.

27. Clarke M. The QUORUM statement. Lancet 2000;355(9205):756–7.

28. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283(15):2008–12.

29. Tramer MR. CONSORT, QUOROM, and structured abstracts--new rules for authors, new tools for readers. Eur J Anaesthesiol. 2001;18(1):1-2.

30. Costa DJ, Bousquet PJ, Ryan D, Price D, Demoly P, Brozek J, et al. Guidelines for allergic rhinitis need to be used in primary care. J Prim Care Respir J 2009;18(4):250-7

31. http://www.cochrane.org

32. Olsen O, Middleton P, Ezzo J, Gotzsche PC, Hadhazy V, Herxheimer A, Kleijnen J, et al. Quality of Cochrane reviews: assessment of sample from 1998. BMJ 2001;323(7317):829-32.

33. Petticrew M. Why certain systematic reviews reach uncertain conclusions. BMJ 2003;326 (7392):756-8.

34. Shekelle PG, Woolf SH, Eccles M, Grimshaw J. Developing guidelines. BMJ 1999; 318(7183):593-6.

35. Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines. BMJ 2001;323(7308):334-6.

36. Oxford Centre for Evidence-based Medicine (CEBM). http://www.cebm.net

37. Royal College of General Practitioners. The development and implementation of clinical guidelines. Report of the Clinical Guidelines Working Group. London: Royal College of General Practitioners; 1995.

38. Pullerits T, Praks L, Ristioja V, Lotvall J. Comparison of a nasal glucocorticoid, antileukotriene, and a combination of antileukotriene and antihistamine in the treatment of seasonal allergic rhinitis. J Allergy Clin Immunol 2002;109(6):949–955.

39. Di Lorenzo G, Pacor ML, Pellit- teri ME, Morici G, Di Gregoli A, Lo Bianco C, et al. Randomized placebo-controlled trial comparing fluticasone aqueous nasal spray in monotherapy, fluticasone plus cetirizine, fluticasone plus montelukast and cetirizine plus montelukast for seasonal allergic rhinitis. Clin Exp Allergy 2004;34(8):259–67.

40. Bousquet J, Van Cauwenberge P. A critical appraisal of 'evidence-based medicine' in allergy and asthma. Allergy 2004;59 Suppl 78:12-20.

41. Sackett DL, Straus SE, Richardson WS, Rosenberg W, Haynes RB. Evidence-based medicine: how to practice and teach EBM. 2nd ed. Edinburgh: Churchill Livingstone; 2000.

42. Guyatt GH, Hayward R, Richardson WS, Green L, Wilson M, Sinclair J et al. Moving from evidence to action. In: Guyatt GH, Rennie D, editors. User's guides to medical literature: a manual for evidence-based practice. Chicago, IL; AMA Press 2002:175-199.

43. Brozek JL, Baena-Cagnani CE, Bonini S, Canonica GW, Rasi G, van Wijk RG, et al. Methodology for development of the Allergic Rhinitis and its Impact on Asthma guideline 2008 update. Allergy 2008;63(1):38-46.

44. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction - GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011;64(4): 383-94.

45. Global Programme on Evidence for Health Policy. Guidelines for WHO Guidelines. EIP/GPE/EQC/2003.1. Geneva, World Health Organization; 2003.

46. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336(7650):924-6.

47. Schunemann HJ, Oxman AD, Brozek J, Glasziou P, Jaeschke R, Vist GE, et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. BMJ 2008;336(7653):1106-10.

48. Kavanagh BP. The GRADE system for rating clinical guidelines. PLoS Med 2009;6(9):e1000094. doi: 10.1371/journal.pmed.1000094.

49. Grimshaw JM, Russell IT. Effect of clinical guidelines on medical practice: a systematic review of rigorous evaluations. Lancet 1993;342(8883):1317-22.

50. Bousquet J, Reid J, van Weel C, Baena Cagnani C, Canonica GW, Demoly P, et al. Allergic rhinitis management pocket reference 2008. Allergy 2008;63(8):990-6.

51. Members of the Workshops, Bousquet J, van Cauwenberge P, Khaltaev N. ARIA in the pharmacy: management of allergic rhinitis symptoms in the pharmacy. Allergic rhinitis and its impact on asthma. Allergy 2004;59(4):373-87.

52. Bousquet J, Lund VJ, van Cauwenberge P, Bremard-Oury C, Mounedji N, Stevens MT, El-Akkad T. Implementation of guidelines for seasonal allergic rhinitis: a randomized controlled trial. Allergy 2003;58(8):733-41.

53. Bousquet J, Bodez T, Gehano P, Klossek JM, Liard F, Neukirch F, Le Gal M, Janin N, Allaf B. Implementation of guidelines for allergic rhinitis in specialist practices. A randomized pragmatic controlled trial. Int Arch Allergy Immunol 2009;150(1):75-82.

54. http://www.who.int/medicines/publications/essentialmedicines

55. Church MK, Maurer M, Simons FR, Bindslev-Jensen C, Van Cauwenberge P, Bousquet J, et al. Risk of first generation H(1) antihistamines: a GA(2)LEN position paper. Allergy 2010:65(4):459-66.

56. Partridge M.R. Translating research into practice: how are guidelines implemented? Eur Respir J Suppl 2003;39:23s-29s.

57. Burgers JS, Grol R, Klazinga NS, Makela M, Zaat J. Towards evidence-based clinical practice: an international survey of 18 clinical guideline programs. Int J Qual Health Care 2003;15(1):31–45.

58. Clark E, Donovan EF, Schoettker P. From outdated to updated, keeping clinical guidelines valid. Int J Qual Health Care 2006;18(3):165-6.

59. Shekelle P, Eccles M, Grimshaw J, Woolf S. When should clinical guidelines be updated? BMJ 2001;323(7305):155-7.

60. Gartlehner G, West SL, Lohr KN, Kahwati L, Johnson JG, Harris RP, et al. Assessing the need to update prevention guidelines: a comparison of two methods. Int J Qual Health Care 2004;16(5):399-406.

61. Shekelle PG, Ortiz E, Rhodes S, Morton SC, Eccles MP, Grimshaw JM, Woolf SH.Validity of the Agency for Health care Research and Quality clinical practice guidelines: how quickly do guidelines become outdated? JAMA 2001;286(12):1461-7.

62. Custovic A, Wijk RG. The effectiveness of measures to change the indoor environment in the treatment of allergic rhinitis and asthma: ARIA update (in collaboration with GA(2) LEN). Allergy 2005;60(9):1112–5.

63. Passalacqua G, Bousquet PJ, Carlsen KH, Kemp J, Lockey RF, Niggemann B, et al. ARIA update: I. Systematic review of complementary and alternative medicine for rhinitis and asthma. J Allergy Clin Immunol 2006;117(5):1054–62.

64. Bousquet J, van Cauwenberge P, Ait Khaled N, Bachert C, Baena- Cagnani CE, Bouchard J, et al. Pharmacologic and anti-IgE treatment of allergic rhinitis ARIA update (in collaboration with GALEN). Allergy 2006;61(9):1086–96.

65. Bonini S, Bonini M, Bousquet J, Brusasco V, Canonica GW, Carl- sen KH, et al. Rhinitis and asthma in athletes: an ARIA document in collaboration with GA2LEN. Allergy 2006;61(6):681–92.

66. Passalacqua G, Durham SR. Allergic rhinitis and its impact on asthma update: allergen immunotherapy. J Allergy Clin Immunol 2007;119(4):881–91.

67. Demoly P, Allaert F-A, Lecasble M, Bousquet J, PRAGMA*. Validation of the classification of ARIA (allergic rhinitis and its impact on asthma). Allergy 2003;58(7):672-5.

68. Bauchau V, Durham SR. Epidemiological characterization of the intermittent and persistent types of allergic rhinitis. Allergy 2005;60(3):350-3.

69. Bousquet J, Annesi-Maesano I, Carat F, Léger D, Rugina M, Pribil C, et al. Characteristics of intermittent and persistent allergic rhinitis: DREAMS study group. Clin Exp Allergy 2005;35(6):728-32.

70. Bousquet P, Bousquet-Rouanet L, Co Minh HB, Urbinelli R, Allaert FA, Demoly P. ARIA (Allergic Rhinitis and its Impact on Asthma) classification of allergic rhinitis severity in clinical practice in France. Int Arch Allergy Immunol 2007;143(3):163-9.

71. Bousquet P, Combescure C, Neukirch F, Klossek JM, Méchin H, Daures JP, Bousquet J. Visual analog scales can assess the severity of rhinitis graded according to ARIA guidelines. Allergy 2007;62(4):367–72.

72. Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud PA, Rubin HR. Why don't physicians follow clinical practice guidelines? A framework for improvement. JAMA 1999;282(15):1458-65.

73. www.whair.org

74. Abendroth TW, Greenes RA, Joyce EA. Investigations in the use of clinical algorithms to organize medical knowledge. Proceedings of the 12th Annual Symposium on Computer Applications in Medical Care. IEEE Computer Society Press 1988;90–3.

75. Sanders GD, Nease RF Jr, Owens DK. Publishing web-based guidelines using interactive decision models. J Eval Clin Pract 2001;7(2):175-89.

76. Freemantle N, Harvey E, Grimshaw JM, Wolf F, Bero L, Grilli R, et al. The effectiveness of printed educational materials in changing the behaviour of health care professionals In: Cochrane Library, Issue 3; 1996. Chichester: Wiley.

77. Bero L, Grilli R, Grimshaw JM, Oxman AD, eds. The Cochrane Effective Practice and Organisation of Care Review Group. The Cochrane database of Systematic Reviews Issue 3. Oxford: Update Software, 1996.

78. Grimshaw JM, Russell IT. Implementing clinical practice guidelines: can guidelines be used to improve clinical practice? Effective Health Care 1994;8:1-12.

79. Thomson O'Brien MA, Freemantle N, Oxman AD, Wolf F, Davis DA, Herrin J. Continuing education meetings and workshops: effects of professional practice and health care outcomes (Cochrane Review). In: The Cochrane Library, Issue 2. Oxford, Update Software, 2002.

80. Grimshaw JM, Thomas RE, MacLennan G, Fraser C, Ramsay CR, Vale L, et al. Effectiveness and efficiency of guideline dissemination and implementation strategies. Health Technol Assess 2004; 8(6):1-72.

81. Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, et al. A revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization. J Allergy Clin Immunol 2004;113(5):823-6.

82. Feder G, Eccles M, Grol R, Griffiths C, Grimshaw J. Clinical guidelines: using clinical guidelines. BMJ 1999;318(7185):728-30.

CHAPTER III

CLASSIFICATION AND MANAGEMENT OF ALLERGIC RHINITIS IN GENERAL PRACTICE

CLASSIFICATION AND MANAGEMENT OF ALLERGIC RHINITIS PATIENTS IN GENERAL PRACTICE DURING POLLEN SEASON

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ABSTRACT

BACKGROUND

AR (allergic rhinitis) represents a major challenge in primary care. The ARIA (Allergic Rhinitis and its Impact on Asthma) group proposed a new classification for AR and developed evidence-based guidelines for the management of this disease. We conducted this study to further characterize the classes of AR described by ARIA, and to evaluate whether the management of AR in general practice is happening according to the ARIA guidelines.

METHODS

During the pollen season of 2003, 95 Belgian GPs (general practitioners) enrolled 804 patients, who presented with symptoms of AR. For each patient a questionnaire, comprising the clinical presentation and management was completed.

RESULTS

In 64% of the patients AR was classified as intermittent, in 36% as persistent. Persistent rhinitis caused more discomfort than intermittent rhinitis. Only 50% of the patients had ever undergone allergy testing. Among them, 51% were allergic to both seasonal and perennial allergens. 82% of the persistent rhinitics were allergic to at least one seasonal allergen and 72% of the intermittent rhinitics to at least one perennial allergen. When compared strictly with the ARIA recommendations, only 34.4% of the patients received a rhinitis treatment that was in accordance with the guidelines, 12.8% were undertreated and 52.7% were overtreated.

CONCLUSION

This study confirms that the previous classification of AR into seasonal and perennial is not satisfactory and that intermittent and persistent AR are not equivalent to seasonal and perennial AR respectively. Furthermore, persistent rhinitis has shown to be a distinct disease entity.

Further efforts are required to disseminate and implement evidence-based diagnostic and treatment guidelines for AR in primary care practice.

INTRODUCTION

Over the last decades, the prevalence of allergic disorders has risen to epidemic proportions. Allergic rhinitis (AR) is the most common allergic disease, worldwide affecting up to 25% of the population. Due to its high and increasing prevalence, the significant impact on quality of life (QOL), the association with multiple comorbidities and the considerable costs in terms of use of healthcare resources, school or work absenteeism and loss of productivity, the disease represents a major global health concern.

Nevertheless, the burden and consequences of AR are still often underestimated by healthcare providers, patients and their environment. Too often, the disease is underdiagnosed and remains mis- or un(der)treated, which leads to uncontrolled symptoms affecting work, home and social life.

To facilitate and standardize the management of AR and to improve the patient care -and consequently the patient satisfaction and compliance- several clinical guidelines have been developed. In 1994 and 2000, European guidelines for AR[1,2] were published, recommending a stepwise treatment approach. In 1999, the WHO initiative ARIA (Allergic Rhinitis and Its Impact on Asthma) Working Group was founded. The ARIA guidelines, resulting from this collaboration, are directed towards managing comorbid rhinitis and asthma as manifestations of one 'united airway disease', rather than as two separate diseases of the nose and lung. They also propose a stepwise treatment strategy for AR, but unlike the European guidelines, the ARIA guidelines are evidence-based.[3]

Whereas rhinitis was previously classified into seasonal and perennial (and by extension occupational), based on the type of exposure, the ARIA group reviewed and changed this classification into 'intermittent' or 'persistent' AR, on the basis of the duration of disease. The gradation of the severity of AR is based on the impact on QOL, rather than on (nasal) symptom scores.

For most patients suffering from AR, the GP (general practitioner) is the (first) point of contact and AR is identified as one of the top ten reasons for visits to primary care clinics.[4] Consequently, the management of AR and the dissemination and implementation of guidelines for AR in general practice should receive much attention.

Despite the evidence that a guided strategy is superior to a non-guided one,[5] the availability of rigorously developed guidelines does not ensure their use in clinical practice.[6] We conducted this survey to evaluate whether the current knowledge regarding diagnostic methods and treatment regimens for AR is applied in daily primary care practice and to further characterize the different classes of AR, as described by ARIA.

MATERIALS AND METHODS

DESIGN OF THE STUDY

In this cross-sectional pharmaco-epidemiological survey, Belgian GPs were asked to recruit consecutive patients who presented at their practice with symptoms of AR during the months February until July 2003, reflecting the tree- and grass pollen season. The GPs were instructed to include a maximum of 10 consecutive patients, to allow a fair distribution over the different practices. For every patient, a questionnaire was completed by the GP during the consultation. The questionnaire was designed in order to allow a classification of the patients according to ARIA and included following items:

- Patient demographics: age and gender
- Duration of AR symptoms (number of days per week and number of consecutive weeks per year)
- Impact of AR on the patient's QOL, assessed by the 4 ARIA questions defining the severity of AR3
- Clinical expression of AR and severity of symptoms, measured on a 4-point-scale, evaluating whether AR manifests by these symptoms 1=never/rarely, 2=occasionally, 3=frequently or 4=always.
- Most bothersome symptom (rhinorrhea, nasal congestion, nasal itch, sneezing or conjunctivitis)
- Method of allergy diagnosis (with or without allergy testing: radioallergosorbent test (RAST) and/or skin test)
- Triggering allergens (confirmed by positive allergy test)
- Treatment prescribed by GP: oral or nasal antihistamines, nasal decongestants, nasal or oral corticosteroids, ocular antihistamines or cromones
- Referral to specialist

PATIENT CHARACTERISTICS, INCLUSION AND EXCLUSION CRITERIA

In order to have an optimal reflection of the AR patient population in daily practice, the exclusion criteria were reduced to a minimum: patients currently receiving treatment for AR and pregnant women. To avoid data based on hetero-anamnesis, the patients had to be at least 14 years old. A total of 804 patients, 50.9% males and 49.1% females, aged 36.4 ± 16.1 years old, were enrolled.

RECRUITMENT OF GENERAL PRACTITIONERS

To allow maximal spread, 125 GPs were contacted and asked to participate in a total of 29 different geographical areas covering Belgium. 95 of the 125 contacted GPs agreed to participate, 77.9% males and 22.1% females. Among them, 63.8% worked in a solo practice, 36.2% in a group practice. The distribution of the participating GPs was homogeneous throughout Belgium: 56.8% worked in Flanders, 35.8% in Wallonia and 7.4% in Brussels. 27.4% of the GPs practiced in an area with a population density of < 250 inhabitants/km^2, 24.2% in an area with 251-500 inhabitants/km^2, 25.3% in an area with 501-1000 inhabitants/km^2 and 23.1% in an area with more than 1000 inhabitants/km^2.[7] On average, 8.5 patients per investigator were included.

STATISTICAL ANALYSIS

The descriptional part of the study uses conventional parameters: means ± standard deviations for quantitative variables; qualitative variables are represented in terms of percentages. Differences between subgroups are analyzed using Chi Squared Test for nominal or ordinal values, and Kruskal Wallis Test and Mann-Whitney U Test for quantitative values. The significance level was set with an α risk = 0.05. All analyses were completed using SPSS Inc Chicago, version 11.

RESULTS

DURATION, SEVERITY AND ARIA CLASSIFICATION OF AR

In 36.1% of the patients, symptoms of AR were present for more than 4 consecutive weeks and during more than 4 days a week. In 42.1% symptoms of AR were present for 4 or less consecutive weeks and in 21.8% symptoms of AR were present for more than 4 consecutive weeks, but only during 4 or less days a week. According to the ARIA classification, 36.1% of the patients were classified with persistent AR and 63.9% were classified with intermittent AR.

Abnormal sleep was reported by 37.1% of the patients, impairment of daily activities, sports or leisure by 71.3%, impairment of work or school by 53.2% and troublesome symptoms by 77.6%. One or more of these 4 QOL items was (were) disturbed in 89.3% of the patients, who were consequently categorized with moderate/severe rhinitis. **(TABLE 1)**

TABLE 1. *Classification of the patients (n=804) into the 4 classes, as defined by ARIA*

	Persistent	Intermittent	Total
Mild	17 (2.1%)	69 (8.6%)	86 (10.7%)
Moderate-Severe	273 (34.0%)	445 (55.3%)	718 (89.3%)
Total	290 (36.1%)	514 (63.9%)	804 (100%)

In the group of persistent rhinitics, all 4 QOL items were more frequently disturbed, when compared to the group of intermittent rhinitics. These differences reached significance for abnormal sleep and troublesome symptoms. Consequently, AR was significantly more often graded as moderate/severe in patients with persistent than in patients with intermittent disease. **(TABLE 2)**

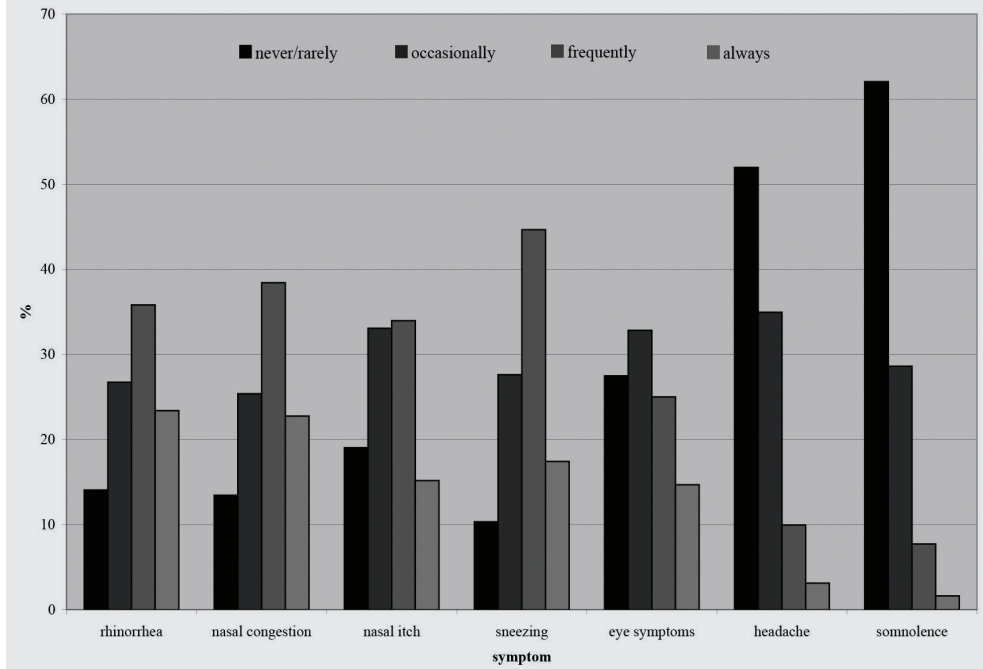
TABLE 2. *Clinical presentation of patients with intermittent versus persistent allergic rhinitis. NS: no statistical significance*

	Persistent (n=514)	Intermittent (n=290)	P-value
Male/female	1.05	1.01	NS
Age in years (mean ± SD)	36.1 (± 15.9)	36.8 (± 16.5)	NS
Impaired sleep (%)	33.5	43.4	0.006
Impaired daily activit/leisure/sports (%)	69.8	73.8	NS
Impaired school/work (%)	51.4	56.6	NS
Troublesome symptoms (%)	73.5	84.8	<0.001
Moderate/severe AR (%)	86.6	94.1	0.001
Symptom scores (% with score 3 or 4)			
Rhinorrhea	59.1	59.3	NS
Nasal congestion	58.4	66.2	0.03
Nasal itch	50.2	43.8	NS
Sneeze	61.9	62.4	NS
Conjunctivitis	37.4	43.8	0.09
Headache	11.7	15.5	NS
Somnolence	6.8	13.8	0.002

CLINICAL PRESENTATION OF ALLERGIC RHINITIS

AR was accompanied by sneezing in 89.7% of the patients, by nasal congestion in 86.6%, by rhinorrhea in 85.9%, by nasal itch in 81.0%, by conjunctivitis in 70.0%, by headache in 48.0% and by somnolence in 37.9%. **(FIGURE 1)**

FIGURE 1. *Symptomatology of allergic rhinitis and severity of the manifestations (n=804)*



Patients with moderate/severe rhinitis, demonstrated significantly higher symptom scores for rhinorrhea, nasal congestion, nasal itch, conjunctivitis, headache and somnolence compared to patients with mild rhinitis **(TABLE 3).** Patients with persistent rhinitis had significantly higher scores for nasal congestion and somnolence and borderline significantly higher scores for conjunctivitis compared to patients with intermittent rhinitis **(TABLE 2).**

TABLE 3. *Clinical presentation of patients with mild versus moderate/severe allergic rhinitis. NS: no statistical significance*

	Mild (n=86)	Mod/sev (n=718)	P-value
Male/female	1.05	1.01	NS
Age in years (mean ± SD)	38.8 (± 18.5)	36.1 (± 15.8)	NS
Symptom scores (% with score 3 or 4)			
Rhinorrhea	47.7	60.6	0.03
Nasal congestion	39.5	63.8	<0.001
Nasal itch	32.6	49.7	0.004
Sneeze	58.1	62.5	NS
Conjunctivitis	26.7	41.2	0.01
Headache	5.8	13.9	0.05
Somnolence	0.0	10.4	0.003

Of all patients, 38.3% were predominantly bothered by nasal congestion, 28.0% by rhinorrhea, 17.3% by conjunctivitis, 9.8% by sneezing and 6.6% by nasal itch. Patients predominantly suffering from nasal congestion reported significantly more abnormal sleep than all other patients (42.5% versus 33.7%, p=0.01), whereas patients especially bothered by conjunctivitis reported more impairment of daily activities, sport and leisure compared to all other patients (78.4% versus 69.6%, p=0.05).

ALLERGY DIAGNOSIS AND RESPONSIBLE ALLERGENS

Of all patients, 47% had never undergone allergy testing to confirm the allergic basis of rhinitis. In 32% RAST and/or skin tests had been performed within the last 2 years, and in 21% more than 2 years ago. The prevalence of allergy testing was significantly higher in the group of persistent rhinitics compared to intermittent rhinitics (69.3% versus 44.2%, p<0.001) and in the moderate/severe group compared to the mild AR group (54.6% versus 41.9%, p=0.03).

In 351 of the 428 'tested' patients the cause of allergy was known: 65.2% of the patients were allergic to grass pollen, 63.8% to tree pollen, 63.0% to house dust mite (HDM) and 37.0% to animal dander. No significant differences were found between intermittent and persistent rhinitics in the prevalence of allergy due to grass pollen (respectively 65.4% and 65.1%), tree pollen (respectively 62.7% and 53.6%), HDM (respectively 58.4% and 68.1%) or animal dander (respectively 34.6% and 39.8%).

Overall, 50.7% of the patients were allergic to both seasonal (grass and/or tree pollen) and perennial allergens (HDM and/or animal dander). In 82.5% of the persistent rhinitics, symptoms were provoked by at least one seasonal allergen (grass and/or tree pollen) and in 71.9% of those classified with intermittent rhinitis AR was triggered by at least one perennial allergen (HDM and/or animals).

PRESCRIBED TREATMENT AND SPECIALIST REFERRAL

None of the patients were on treatment for AR at the time of the visit (was part of the exclusion criteria). At the end of the visit, only 1 medication was prescribed in 29.6% of the patients, 67.2% received a combination therapy and 3.2% received no prescription for medication. Overall, topical treatment was recommended in 14.2%, oral therapy in 21.3%, while 61.3% received a combination of oral and topical medication. Oral antihistamines were the most frequently prescribed pharmacological agents (82.2%), followed by nasal corticosteroids (58.2%), nasal decongestants (18.6%), topical eye treatment (ocular antihistamine or cromone) (17.3%), nasal antihistamines (9.2%) and oral corticosteroids (5.3%).

9% of the patients were referred to a specialist. Specialist referral was significantly more often proposed in patients with persistent disease compared to patients with intermittent disease, but did not significantly differ between patients with mild or moderate/severe AR. Remarkably, 27.8% of the patients referred to a specialist did not receive any initial treatment from their GP.

Patients with mild AR more often received no medication than those with moderate/severe AR, but this difference only reached borderline significance. Corticosteroids were more often prescribed in persistent rhinitics than in intermittent rhinitics and in the moderate/severe group compared to the mild group. These differences reached significance for nasal corticosteroids, but not for oral corticosteroids. **(TABLES 4 AND 5)**

TABLE 4. *Therapeutic management of patients with intermittent versus persistent allergic rhinitis. NS: no statistical significance*

	Intermittent (n=514)	Persistent (n=290)	P-value
Oral antihistamines (%)	82.1	82.4	NS
Nasal antihistamines (%)	8.8	10	NS
Nasal corticosteroids (%)	53.1	67.2	<0.001
Oral corticosteroids (%)	4.9	6.2	NS
Nasal decongestants (%)	18.3	19.3	NS
Topical eye medication (%)	14.6	22.1	0.009
No medication prescribed (%)	3.3	3.1	NS
Specialist referral (%)	7.0	12.4	0.01

TABLE 5. *Therapeutic management of patients with mild versus moderate/severe allergic rhinitis. NS: no statistical significance*

	Mild (n=86)	Moderate/ Severe (n=290)	P-value
Oral antihistamines (%)	62.8	84.5	<0.001
Nasal antihistamines (%)	8.1	9.3	NS
Nasal corticosteroids (%)	40.7	60.3	<0.001
Oral corticosteroids (%)	1.2	5.8	NS
Nasal decongestants (%)	22.1	18.2	NS
Topical eye medication (%)	12.8	17.8	NS
No medication prescribed (%)	7.0	2.8	0.08
Specialist referral (%)	7.0	9.2	NS

We also compared the proposed medication for rhinitis symptoms in the different groups, defined by ARIA, with the recommendations of the ARIA guidelines **(TABLE 6)**. In total, only 34.4% of the patients received a rhinitis treatment that was in accordance with the evidence-based ARIA treatment recommendations, 12.8% were undertreated and 52.7% were overtreated.

TABLE 6. *Prescribed medication for rhinitis in the different patient groups, classified according to ARIA*

	Mild intermittent (n=69)	Mild persistent (n = 17)	Mod/sev intermitt (n = 445)	Mod/sev persistent (n = 273)
NDC	3 (4.3%)	/	5 (1.1%)	1 (0.4%)
AH1	21 (30.4%)	4 (23.5%)	134 (30.1%)	60 (22.0%)
AH1+NDC	15 (21.7%)	/	29 (6.5%)	10 (3.7%)
NCS	11 (15.9%)	7 (41.2%)	30 (6.7%)	16 (5.9%)
NCS+NDC	1 (1.4%)	/	4 (0.9%)	9 (3.3%)
NCS+AH1	10 (14.5%)	6 (35.3%)	178 (40%)	122 (44.7%)
NCS+AH1+NDC	/	/	27 (6.1%)	25 (9.2%)
OCS	/	/	/	/
OCS+AH1	1 (1.4%)	/	7 (1.6%)	5 (1.8%)
OCS+NDC	/	/	2 (0.4%)	/
OCS+AH1+NDC	/	/	4 (0.9%)	3 (1.1%)
OCS+NCS	/	/	1 (0.2%)	/
OCS+NCS+AH1	/	/	6 (1.3%)	2 (0.7%)
OCS+NCS+NDC	/	/	/	1 (0.3%)
OCS+NCS+AH1+NDC	/	/	5 (1.1%)	7 (2.6%)
No rhinitis medication	7 (10.1%)	/	13 (2.9%)	12 (4.4%)
Treated according to ARIA	39 (56.5%)	11 (64.7%)	202 (45.4%)	25 (9.2%)
'Undertreated'	7 (10.1%)	0 (0.0%)	13 (2.9%)	83 (30.4%)
'Overtreated'	23 (33.3%)	6 (35.3%)	230 (51.7%)	165 (60.4%)

NDC: nasal decongestant
AH1: oral or nasal H1-antihistamine
NCS: nasal corticosteroid
OCS: oral corticosteroid

Treated according to ARIA
Undertreated compared to ARIA recommendations
Overtreated compared to ARIA recommendations

ALLERGIC RHINITIS TREATMENT IN VIEW OF THE MAIN SYMPTOMATOLOGY.

Among the patients who predominantly suffered from nasal congestion 70.1% were prescribed a nasal corticosteroid, 20.8% a nasal decongestant and 4.2% an oral corticosteroid, whereas 19.8% received none of these potent anti-congestive agents. Overall, patients who considered nasal congestion as the most bothersome symptom more often received a nasal corticosteroid (70.1% versus 50.6%, $p<0.001$) compared to other patients, but no significant differences were found for nasal decongestants or oral corticosteroids.

Patients mostly bothered by eye symptoms received an ocular cromone or ocular antihistamine in 44.6% of the cases compared to 11.6% in the other patients ($p<0.001$); 48.5% did not receive topical eye medication, but were prescribed an oral antihistamine for the treatment of their allergic rhinoconjunctivitis.

DISCUSSION

For patients suffering from AR, the GP is often the first point of contact. As many rhinitis patients rely on their GP for the diagnosis and treatment of their symptoms, general healthcare practices represent an interesting and important target to evaluate the management of AR. The ARIA guidelines currently provide diagnostic and therapeutic recommendations for AR with the best available evidence. Our study was conducted 2 years after publication of the ARIA document,[3] primarily to assess whether the criteria for diagnosis and the standards for effective treatment are applied in daily primary care practice (in Belgium).

Whereas ARIA insists on performing highly sensitive and specific *in vivo* or *in vitro* allergy tests to confirm or exclude an allergic etiology of rhinitis, we found that only half of the patients diagnosed with AR by their GP, had ever undergone allergy testing. In addition, less than 10% were referred to a specialist for further diagnostic or therapeutic management. These figures are similar to previous results,[8, 9] and indicate that GPs do not commonly confirm or support their diagnosis of AR by skin or in vitro allergy tests and rarely ask advice from a specialist. In most cases, the diagnosis of AR is based on a typical clinical picture, consisting of sneezing, nasal congestion, rhinorrhea, nasal itch and often also conjunctivitis. In our study, these manifestations were part of the symptomatology in respectively 90%, 87%, 86%, 81% and 70% of the patients. Although allergy tests were not routinely performed, we may assume that the number of falsely diagnosed allergic rhinitics is rathersmall, as the predictive value of clinical history alone in the diagnosis of AR has shown to vary between 82% and 85% for seasonal allergens and to be at least 77% for perennial allergens.[10]

Similar to other pharmaco-epidemiological trials,[8, 11] oral antihistamines were by far the most commonly prescribed first-line medications (82%). Despite of previous

reports that GPs seem to have some reluctance to use nasal corticosteroids for the treatment of AR,[12] we found a rather high prescription rate, especially in patients with persistent (67%) or moderate/severe AR (60%) and in patients predominantly bothered by nasal congestion (70%). Currently, there is no proof for the additional beneficial effects of the combination of a nasal corticosteroid and an antihistamine compared to a nasal corticosteroid alone,[13] but many experts feel that such superior value exists.[2] This is also reflected in the pharmacological treatment, presented by the GPs in our study, with the combination of these 2 agents (with or without addition of a nasal decongestant) prescribed in 15% of the mild intermittent, 35% of the mild persistent, 46% of the moderate/severe intermittent and 54% of the moderate/severe persistent rhinitis patients.

Nasal decongestants are very effective for the rapid relief of nasal congestion, but as they do not improve nasal itch, sneezing or rhinorrhea and hold a significant risk for rebound rhinitis in case of prolonged administration, their use(fulness) is limited. The GPs in our study, nevertheless, prescribed these agents in 20% of the patients and, remarkably, a similar prescription rate was found in patients who were and who were not predominantly bothered by nasal congestion! Oral corticosteroids, on the other hand, are never recommended as first-line treatment options for AR, but are preserved for the more treatment-resistant cases of AR. Belgian GPs, however, prescribed them as first-line treatment in 5% of the patients. Only 34% of the patients received a rhinitis treatment that was in accordance with the evidence-based ARIA treatment recommendations, 13% were undertreated and 53% were overtreated. Overtreatment mainly consisted of the prescription of nasal corticosteroids in the mild intermittent group and the combination of a nasal corticosteroid and an antihistamine in the mild persistent and moderate/severe intermittent and persistent groups. For moderate/severe persistent rhinitis, on the other hand, nasal corticosteroids are the first-choice treatment, but almost one third of this patient group was insufficiently treated.

From comparing the treatment strategies proposed by the GPs with the ARIA recommendations, we might conclude that the guidelines are only followed to some extent by the GPs. Of course, it should be recognized that the prescribed treatment is a result of an agreement between doctor and patient, and therefore some deviations from the gold standard are to be expected. In addition, the choice of treatment may also be affected by the presence of comorbid disease or the use of concomitant medication. In patients with comorbid asthma and rhinitis GP's may prefer to prescribe a systemic treatment that is effective for both manifestations of the united airway disease and leads to increased compliance, instead of a combination of topical treatments. In patients, especially children, already treated with inhaled corticosteroids for asthma, on the other hand, they may want to limit the total corticosteroid dose by choosing other treatment options than nasal corticosteroids for AR.

The results of this survey also allow us to formulate some reflections on the previous AR classification, based on the type of exposure, and on the newer ARIA classification, based on the duration of symptoms and their impact on QOL. The inclusion period of our study was limited to the tree and grass pollen season and this trial has an obvious recruitment bias. An overrepresentation of tree and grass pollen-allergic patients is expected, and this spring survey can not be used as an epidemiological study to assess the proportion of patients suffering from seasonal or perennial AR. Nevertheless, our results do confirm that the previous classification of AR is not adherent to real life as more than half of the patients had a 'mixed' form of AR, being allergic to both seasonal and perennial allergens. The ARIA classification has been validated by Demoly et al in a medical practice-based study in France[14] and by Bauchau et al in a population-based cross-sectional study in 6 European countries[15, 16]. Both trials demonstrated that perennial allergens can cause intermittent symptoms and that seasonal allergens can cause persistent symptoms. We found 80% of the patients classified with persistent rhinitis to be allergic to tree- or grass pollen, and more than 70% of the intermittent rhinitics to be allergic to perennial allergens. These results, together and consistent with the findings of Demoly and Bauchau, demonstrate that persistent and intermittent AR are not equivalent to or interchangeable with perennial and seasonal AR respectively. Furthermore, persistent rhinitis has shown to be clearly different from and more debilitating than intermittent rhinitis. Bauchau et al reported a greater degree of self-awareness and previous diagnosis, more severe symptoms, a higher rate of doctor prescribed medication and a more regular use of medication in patients with persistent compared to intermittent rhinitis.16 We found that persistent rhinitics had a reduced QOL, marked by an increased rate of troublesome symptoms and impaired sleep, and that they reported more frequent symptoms of somnolence, conjunctivitis and nasal congestion compared to intermittent rhinitics. In addition, persistent rhinitis was associated with a higher degree of allergy testing and specialist referral.

Furthermore, in our study, moderate/severe AR was associated with higher symptom scores for nasal congestion, rhinorrhea, nasal itch, conjunctivitis, headache and somnolence and a higher rate of doctor prescribed medication compared to mild AR. This demonstrates that the two severity categories for AR defined by ARIA based on the impact of AR on QOL, indeed represent a different burden of disease, also reflected by other outcome measures. Another important observation, however, is that - similar to the data of Demoly[8, 11] - up to 90% of the patients were categorized with moderate/severe rhinitis. In addition, Bauchau reported that 45% of the AR patients in the general population are undiagnosed by a physician and that these previously undiagnosed patients have lower symptom severity.[15] It may therefore be suggested that patients consulting their physician are those with moderate/severe rhinitis, whereas those with mild rhinitis often do not seek advice from professional healthcare providers.

CONCLUSION

This study demonstrates that the ARIA guidelines are often not followed in general practice. To improve the management of a global health problem with increasing prevalence further efforts are required to disseminate and implement these evidence-based recommendations in primary care practice. In addition, our results support the validity of the ARIA classification and provide more information on the characteristics of AR patients in the different ARIA classification groups. A year-around assessment in the general population, however, is required to make an epidemiologically correct estimation of the proportion of AR patients in the four ARIA classes.

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REFERENCES

1. International Rhinitis Management Working Group. International Consensus Report on the Diagnosis and Management of Rhinitis. Allergy 1994;49(Suppl 9):5-34.
2. Van Cauwenberge P, Bachert C, Passalacqua G, Bousquet J, Canonica GW, Durham SR. et al. Consensus statement on the treatment of allergic rhinitis. Allergy 2000;55(2):116-34.
3. Bousquet J, van Cauwenberge P, Khaltaev N, ARIA Workshop Group. Allergic Rhinitis and its Impact on Asthma (ARIA). J Allergy Clin immunol 2001;108 (Suppl 5):S147-S333.
4. Gregory C, Cifaldi M, Tanner LA. Targeted intervention programs: creating a customized practice model to improve the treatment of AR in a managed care population. Am J Manag Care 1999;5(4):485-96.
5. Bousquet J, Lund VJ, van Cauwenberge P, Bremard-Oury C, Mounedji N, Stevens MT, et al. Implementation of guidelines for seasonal allergic rhinitis: a randomised controlled trial. Allergy 2003; 58(8):733-741.
6. Bousquet J, Van Cauwenberge P. A critical appraisal of 'evidence-based medicine' in allergy and asthma. Allergy 2004;59 Suppl 78:12-20.
7. http://statbel.fgov.be/figures/dsp2003_nl.asp
8. Demoly P, Allaert FA, Lecasble M; PRAGMA. ERASM, a pharmacoepidemiologic survey on management of intermittent allergic rhinitis in every day general medical practice in France. Allergy 2002;57(6):546-54.
9. Wang DY, Chan A, Smith D. Management of allergic rhinitis: a common part of practice in primary care practice. Allergy 2004;59(3):315-9.
10. Crobach MJ, Hermans J, Kaptein AA, Ridderikhoff J, Petri H, Mulder JD. The diagnosis of allergic rhinitis: how to combine the medical history with the results of radioallergosorbent tests and skin prick tests. Scand J Prim health Care 1998;16(1):30-6.
11. Demoly P, Allaert FA, Lecasble M, Klossek JM; Groupe Pragma. ERAP, a pharmaco-epidemiologic survey on perennial allergic rhinitis in every day medical practice in France. Presse Med. 2003;32(23):1066-73.
12. Fokkens WJ. Corticosteroids, first choice in moderate to severe allergic rhinitis. What prevents general practitioners from using them? Allergy 2003;58(8):724-6.
13. Nielsen LP, Mygind N, Dahl R. Intranasal corticosteroids for allergic rhinitis: superior relief? Drugs 2001;61(11):1563-79.
14. Demoly P, Allaert FA, Lecasble M, Bousquet J; PRAGMA. Validation of the classification of ARIA (allergic rhinitis and its impact on asthma). Allergy 2003;58(7):672-5.
15. Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. Eur Respir J 2004;24(5):758-64.
16. Bauchau V, Durham SR. Epidemiological characterisation of the intermittent and persistent types of allergic rhinitis. Allergy 2005;60(3):350-3.

CHAPTER IV

CRITICAL LOOK AT THE ARIA CLASSIFICATION

IS THE ARIA CLASSIFICATION USEFUL IN DAILY PRIMARY CARE PRACTICE?

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J Allergy Clin Immunol 2006;118(3):758-9

ABSTRACT

BACKGROUND

The Allergic Rhinitis and its Impact on Asthma (ARIA) group proposed a new classification for allergic rhinitis (AR) based on the duration and severity of disease.

AIM

As AR represents a major primary care problem and the ARIA guidelines were mainly developed to assist general practitioners, we wanted to assess whether the ARIA classification is applicable for the AR patient population in primary care practice.

METHODS

During the pollen season of 2003, 95 Belgian general practitioners enrolled 804 patients, who presented with symptoms of AR. For each patient a questionnaire, comprising the clinical presentation and management was completed.

RESULTS

As disease severity was graded as mild in only 10.7% and as moderate/severe in 89.3 %, we propose some suggestions to enlarge the criteria for 'mild' rhinitis and to subdivide 'moderate/severe' rhinitis into 'moderate' and 'severe'. Classification of the 804 AR patients according to this empirical model results in 3 important groups, with the 'moderate' group containing most patients. The difference in disease severity between these 3 newly defined groups is reflected by the increasing symptom scores, the more profound diagnostic and therapeutic management from mild over moderate to severe AR.

CONCLUSION

We propose to change the ARIA classification for severity of AR from 2 to 3 subgroups. Of course, this modification of the categorization of AR severity needs to be validated in large patient groups.

INTRODUCTION

In 2001, the Allergic Rhinitis and its Impact on Asthma (ARIA) initiative proposed a new classification for allergic rhinitis (AR) based on the duration of symptoms and their impact on the quality of life and formulated evidence-based guidelines for the treatment of this disease.[1] AR is a major primary healthcare problem, and the ARIA guidelines were developed primarily to assist general practitioners (GPs) in their management of this condition. The classification scheme is the basis of the stepwise treatment recommendations and should be tailored to the AR patient population in daily general practice.

During the pollen season of 2003 we conducted a cross-sectional survey in general practice in Belgium. Ninety-five Belgian GPs enrolled 804 patients, who presented with symptoms of AR. For each patient a questionnaire, comprising the duration, severity, symptomatology and management of the disease, was completed. In a previous article we described the characteristics of the patients in the different ARIA classification groups, and we compared the management of AR in daily primary care practice with the ARIA recommendations.[2] The results demonstrated that the classification of AR as persistent and intermittent, on the basis of the duration of disease, is not equivalent to the previous, unsatisfactory classification of AR as perennial or seasonal. These findings are similar to those from large epidemiological studies in the general population,[3, 4] in primary care practice[5] and in specialty practice[6]. On the other hand, the usefulness and validity of the classification of AR severity as mild or moderate-severe, based on the impact of AR on quality of life (QOL), are not verified with data. The results of our survey indicate that moderate-severe AR indeed represents a higher burden of disease than mild AR, as reflected by the higher scores for nasal and non-nasal symptoms accompanying AR and the more complicated diagnostic and therapeutic management in moderate-severe compared to mild rhinitis.[2] An important finding in our data is the disproportionate size of the classification, with the preponderance of subjects classified as moderate-severe rhinitis, 89.3%, and only 10.7% classified as mild.[2] These data are similar to results of a year round assessment in general practice in France, in which 93% of the 3052 AR patients enrolled were classified with moderate/severe rhinitis.[7]

We address the imbalance between mild and moderate/severe AR and propose a refinement of the current ARIA classification for AR severity.

RESULTS

Allergic Rhinitis and its Impact on Asthma defines the severity of AR on the basis of 4 quality of life items: (1) impairment of sleep; (2) impairment of daily activities, sports or leisure, (3) impairment of school or work; and (4) troublesome symptoms. If 1 or more of these items are present, rhinitis is classified as moderate/severe.[1] In our study, abnormal sleep was reported by 37.1% of the patients, impairment of daily activities, sports or leisure by 71.3%, impairment of work or school by 53.2% and troublesome symptoms by 77.6%.[2] Because 86.9% of the patients with moderate/severe AR considered their symptoms as troublesome and only 9.8% of the patients reported troublesome symptoms in absence of impairment of daily activities/sports/leisure, school/work or sleep, the report of troublesome symptoms does not add appreciably to the assessment of disease severity. Furthermore, impairment of daily activities/sports/leisure and impairment of school/work both lead to a diminished quality of the active daily life, and we found an important overlap between these 2 items. Although more patients experienced discomfort from AR during their personal than during their professional life, 91.1% of those who reported problems at school or work were also bothered during daily activities, sports or leisure.

On the basis of these findings, we suggest a modification in the current assessment of AR severity defined by ARIA. We propose to eliminate the question on troublesome symptoms as a key issue in the assessment of AR severity, and to recombine the question on impairment of daily activities, sports, leisure and the question on the impairment of school or work into 1 question evaluating the quality of the active daily life.

Taken together, this results in 2 questions to evaluate the severity of AR:

1. Do your symptoms of AR cause sleep disturbance?
2. Do your symptoms of AR cause impairment of your daily personal (daily activities, leisure, sports) and/or professional life (school, work)?

In this model, the severity of AR is classified into 3 groups, with patients responding ‘no’ to both questions classified as ‘mild’, patients answering ‘yes’ to 1 of the 2 questions as ‘moderate’ and patients answering ‘yes’ to both questions as ‘severe’.

Categorization of the 804 patients from our survey according to this empirical model resulted in 20.5% with 'mild' rhinitis, 45.9% with 'moderate' rhinitis and 33.6% with 'severe' rhinitis. Table 1 compares symptom scores and Table 2 the diagnostic and therapeutic management in the new 'mild', 'moderate' and 'severe' AR groups.

TABLE 1. *Symptom scores in the new 'mild', 'moderate' and 'severe' AR groups.*

	Mild AR (165)	Moderate AR (369)	Severe AR (270)	p
Rhinorrhea*	52.1	60.7	61.5	NS
Nasal congestion*	42.4	61.5	72.2	<0.0001
Nasal itch*	35.1	51.8	50.4	0.007
Sneeze*	55.8	61.0	67.4	0.01
Eye symptoms*	33.3	37.9	45.9	<0.0001
Headache*	4.2	12.5	19.2	<0.0001
Somnolence*	1.8	9.8	13.3	0.0001
Troublesome symptoms (%)	47.9	81.4	90.4	<0.0001

NS: not significant

Statistical analyses with Chi-square test for trends (Medcalc, version 8.1.0.0).

P<0.05 = statistically significant.

* Each symptom score is expressed as percentage of patients with score 3 or 4 (symptoms were scored on a 4-point-scale, evaluating whether AR manifests by these symptoms 1=never/rarely, 2=occasionally, 3=frequently or 4=always.)

TABLE 2. *Symptom scores in the new 'mild', 'moderate' and 'severe' AR groups.*

	Mild AR (165)	Moderate AR (369)	Severe AR (270)	p
Allergy testing (ever) (%)	43.6	51.2	64.4	<0.0001
Treatment prescribed (%)				
Oral antihistamines	70.3	84.8	85.9	0.0002
Nasal antihistamines	11.5	8.1	9.3	NS
Nasal corticosteroids	46.7	54.7	70.0	<0.0001
Oral corticosteroids	3.0	3.8	8.9	0.004
Nasal decongestants	17.6	15.4	23.7	NS
Topical eye medication	14.5	19.0	16.7	NS
Specialist referral (%)	7.9	6.2	13.3	0.02

NS: not siginificant

Statistical analyses with Chi-square test for trends (Medcalc version 8.1.0.0).

P<0.05 = statistically significant.

For all symptoms scores, except rhinorrhea, a linear increasing trend was found from mild to moderate to severe AR. Furthermore, the proportion of patients considering their symptoms as troublesome, the degree of allergy testing and the prescription rate of nasal and oral corticosteroids demonstrated a significant trend upwards with increasing AR severity category.

CONCLUSION

In conclusion, we propose to categorize the severity of AR into 3 instead of 2 groups, which in turn will allow a more gradual stepwise therapeutic approach. On the basis of the results of our study in general practice we suggest a modification in the current assessment of AR severity, using the 4 questions defined by ARIA. We here propose a very easy to use and to remember combination of two questions: one evaluating the patient's quality of daily life and one evaluating the patient's quality of sleep.

Classification of our patient population according to this empirical model results in 3 important groups, with the 'moderate' group containing most patients. The difference in disease severity between these 3 newly defined groups is reflected by the increasing symptom scores, the higher degree of allergy testing and increased prescription of corticosteroids from mild to moderate to severe AR. Of course, this proposed modification in classification for AR severity needs to be validated in large patient groups. As the ARIA guidelines were mainly developed for GPs it is particularly important that the classification is applicable to the patient population in primary care practice. However, it would also be interesting to evaluate which types of AR patients remain undiagnosed in the general population and which types are most commonly in a specialist practice.

REFERENCES

1. Bousquet J, van Cauwenberge P, Khaltaev N, ARIA Workshop Group. Allergic Rhinitis and its Impact on Asthma (ARIA). J Allergy Clin immunol 2001;108 (Suppl 5):S147-S333.
2. Van Hoecke H, Vastesaeger N, Dewulf L, Sys L, van Cauwenberge P. Classification and management of allergic rhinitis patients in general practice during pollen season. Allergy 2006;61(6):705-11.
3. Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. Eur Respir J 2004;24(5):758-64.
4. Bauchau V, Durham SR. Epidemiological characterisation of the intermittent and persistent types of allergic rhinitis. Allergy 2005;60(3):350-3.
5. Demoly P, Allaert FA, Lecasble M, Bousquet J; PRAGMA. Validation of the classification of ARIA (allergic rhinitis and its impact on asthma). Allergy 2003;58(7):672-5.
6. Bousquet J, Annesi-Maesano I, Carat F, Leger D, Rugina M, Pribil C, El Hasnaoui A, Chanal I. Characteristics of intermittent and persistent allergic rhinitis: DREAMS study group. Clin Exp Allergy 2005;35(6):728-32.
7. Bousquet J, Neukirch F, Bousquet PJ, Gehano P, Klossek JM, Le Gal M, Allaf B. Severity and impairment of allergic rhinitis in patients consulting in primary care. J Allergy Clin Immunol 2006;117(1):158-62.

CHAPTER V

DISSEMINATION AND IMPLEMENTATION OF THE ARIA GUIDELINES IN SPECIALIST PRACTICE

THE ARIA GUIDELINES IN SPECIALIST PRACTICE: A NATIONWIDE SURVEY

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ABSTRACT

PROBLEM

In 2001, the ARIA guidelines were published to assist healthcare practitioners in managing allergic rhinitis (AR) according to the best evidence. Very limited information, however, is available on the impact of these guidelines on clinical practice.

METHODS

All Belgian Otorhinolaryngologists were invited to complete a questionnaire, covering demographic and professional characteristics, knowledge, use and perception of the ARIA guidelines and 4 clinical case scenarios of AR.

RESULTS

Of the 258 (44%) Belgian Otorhinolaryngologists who participated, almost 90% had ever heard about ARIA and 64% had followed a lecture specifically dedicated to the ARIA guidelines. Furthermore, 62% stated to always or mostly follow the ARIA treatment algorithms in the daily management of AR patients. In the clinical case section, adherence to the ARIA guidelines raised with increased self-reported knowledge and use of the ARIA guidelines and among participants that considered the guidelines more user-friendly. Of the respondents, 51% were considered as good compliers. Younger age was a significant predictor for good compliance.

CONCLUSION

More efforts are required to improve the translation of scientific knowledge into clinical practice and to further identify which factors may influence guideline compliance.

INTRODUCTION

Allergic rhinitis (AR) affects one into four people worldwide, causes significant impairment of the personal, social and professional life and has substantial economic consequences.[1, 2] Despite the wealth of information available on the pathophysiology, diagnosis and treatment of AR, this disease remains too often unrecognized, underestimated and inadequately treated.[3, 4]

Over the last decades, clinical practice guidelines have gained a lot of interest as a support to synthesize clinical information, to assist health care providers in the management of their patients and to improve the quality of healthcare.

Several national and international guidelines, specifically dedicated to AR have been designed,[5-8] but it wasn't until 2001 that the first evidence-based guidelines for AR, the ARIA guidelines (Allergic Rhinitis and its Impact on Asthma) guidelines, were published.[9] The ARIA guidelines were developed in collaboration with the World Health Organization (WHO) and provide general practitioners (GPs) and specialists dealing with AR patients with stepwise treatment algorithms, based on a new classification of AR in terms of the duration and severity of disease.

It has previously been demonstrated that following guidelines has favorable effects on healthcare and patient outcomes. Implementation of the GINA guidelines in childhood asthma showed to reduce daytime and nighttime symptoms, activity limitations and drug use and to improve quality of life in patients and their families.[10] At the time of this publication, the only guidelines for AR that have been assessed for their effects on health outcomes are those from the International Rhinitis Management Group.[5] Application of these guidelines demonstrated to be significantly better than treatment according to the GPs' free choice, as reflected by reduced symptom scores and increased quality of life, patient compliance and satisfaction.[11] In these validation studies, however, healthcare providers were explicitly asked to follow the guideline recommendations, whereas, in real life, availability of guidelines does not ensure their use, and the impact of guidelines on daily practice patterns remains uncertain.

The translation of scientific knowledge into clinical practice and physician adherence to guidelines is often complicated by structural, cultural, socio-economic and behavioral barriers.[12-14] Physicians' knowledge of, attitude towards and compliance with clinical guidelines should therefore also be evaluated next to measuring effectiveness of clinical practice guidelines, based on patient outcomes.

As specialists of the upper respiratory tract, Otorhinolaryngologists play a key role in the management of AR and its several associated conditions in the upper airways, including rhinosinusitis, nasal polyps, adenoid hypertrophy, tubal dysfunction, otitis media with effusion and laryngitis.[15] Furthermore, they are often considered as a point of referral when rhinitis management in primary care practice remains unsatisfactory.

We conducted a survey 1) to assess treatment practices of AR in specialist practice, 2) to assess the knowledge and use of the ARIA guidelines among Belgian Otorhinolaryngologists, and 3) to gain information on physician characteristics that may influence compliance with the guideline recommendations.

MATERIALS AND METHODS

QUESTIONNAIRE DEVELOPMENT AND DATA COLLECTION

We designed a questionnaire in multiple response format that covered following items:

- Demographic and professional details;
- Dissemination of the ARIA guidelines;
- User-friendliness of the ARIA guidelines ;
- Self-reported knowledge of the ARIA classification and ARIA treatment recommendations, assessed with a four-point Likert scale (1: not at all familiar, 2: a little familiar, 3: somewhat familiar, 4: very familiar);
- Test question on the ARIA classification to detect potential bias in self-reported knowledge ('According to ARIA allergic rhinitis is classified into: 1: seasonal or perennial, 2: acute, chronic or recurrent 3: intermittent or persistent, 4: periodic or non-periodic);
- Self-reported use of the ARIA classification and ARIA treatment recommendations, assessed with a four-point Likert scale (1: never, 2: sometimes, 3: mostly, 4: always);
- Presentation of 4 clinical scenarios, representing different types of AR, where the respondents were asked to select the treatment or combination of treatments they would recommend (environmental control measures, oral H1-antihistamine, oral decongestant, oral corticosteroid, nasal H1-antihistamine, nasal decongestant, nasal corticosteroid, ocular H1-antihistamine, ocular cromone, (referral) for immunotherapy or other, with free text space to specify).

Initially, the questionnaire was developed in English and translated into French and Flemish, followed by back-translation into English, with modifications if necessary. The questionnaire was distributed in French and Flemish, the 2 major national languages. Additional minor amendments of the initial survey were made after the questionnaire was pilot tested among 15 Otorhinolaryngologists. In May 2005, the final questionnaire was sent to all fully-trained and practicing Belgian Otorhinolaryngologists (n=598). A reminder was sent to the non-respondents 4 weeks after the initial mailing. The physicians had the possibility to respond

by completing and sending back the anonymized postal questionnaire in an accompanying return-stamped envelope or by completing the questionnaire on a website for which they received a login.

The Ethics Committee of Ghent University Hospital approved the conditions and application of the survey.

CLINICAL CASE SECTION

For the 4 clinical scenarios the treatment proposed by the respondents was strictly compared with the treatment recommendations of the ARIA guidelines, available at that time[9] **(APPENDIX 1)**. A score of 0 (treatment not consistent with ARIA recommendations, resulting from over- or undertreatment) or 1 (treatment consistent with ARIA recommendations) was attributed per case, resulting in a total score ranging from 0 to 4 per respondent. Upon further analysis, compliance with the ARIA guidelines in the clinical scenarios was dichotomized into 'poor compliance' or 'good compliance'. Good compliance was set at a total score above the mean outcome.

STATISTICAL ANALYSIS

The descriptive part of the study uses conventional parameters: means ± standard deviations for quantitative variables; qualitative variables are represented in terms of percentages. Statistical differences for means of quantitative values were analyzed using the independent samples t-test. To assess a linear trend in proportions of nominal or ordinal values across subgroups Chi square test for trends was used.

The influence of demographic and professional variables on compliance with the ARIA guidelines in clinical case scenarios was assessed using multivariate logistic regression. The following demographic and professional characteristics were considered to potentially influence guideline compliance and were included in the regression analysis: gender, age, years of practice, specialty, proportion of AR patients in practice and type of practice. As age and years in practice were strongly correlated (Spearman correlation coefficient 0.98, $p<0.001$), only age was entered into the regression model.

Significance level was set at $\alpha = 0.05$. Analyses were completed using SPSS Inc (Chicago, ILL, USA; version 16.0, Nov 2007).

RESULTS

BASELINE CHARACTERISTICS OF THE RESPONDENTS

Of the 598 Otorhinolaryngologists that were contacted, 4 were ineligible because they were no longer practicing Otorhinolaryngology and 6 questionnaires were returned because of incorrect mail addresses. After 2 mailings, 258 questionnaires were returned, yielding an overall response rate of 43.9%. Demographic and professional details of the respondents are summarized in **TABLE 1**.

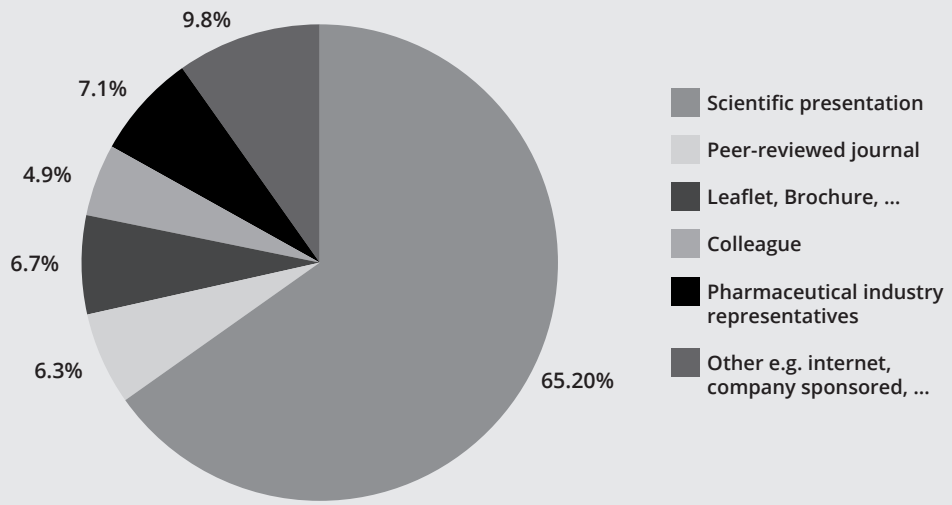
TABLE 1. *Demographic and professional details of the respondents*

	N	%	Mean (SD)	Range
Gender (male) (256 respondents)	166	64.8		
Age (years) (257 respondents)			47.9 (11.2)	31-77
Number of years in practice (years) (257 respondents)			17.8 (11)	1-48
Estimated proportion of AR patients among all patients treated (254 respondents)				
<10%	57	22.4		
10-20%	137	53.9		
20-30%	49	19.3		
>30%	11	4.3		
Practice type (258 respondents)				
University hospital	58	22.5		
Non-university, teaching hospital	46	17.8		
Non-university, non-teaching hospital	123	47.7		
Not hospital affiliated	31	12.0		

DISSEMINATION OF THE ARIA GUIDELINES

87.2% (224/257) of the respondents stated that they had ever heard about the ARIA guidelines and 64.2% (165/257) had ever followed a lecture specifically on this topic. For the group that had ever heard about ARIA, scientific presentations were the most frequently cited source to become aware of the guidelines, whereas the medical literature, representatives from the pharmaceutical industry, colleagues and the internet were less often mentioned **(FIG 1)**.

FIGURE 1. *Sources of initial contact with the ARIA guidelines. Among the respondents that had ever heard about the ARIA guidelines, sources of initial contact were scientific presentations (146/224), peer-reviewed journals (14/224), leaflets/brochures (15/224), colleagues (11/224), pharmaceutical industry representatives (16/224) and other sources including the internet and company sponsored events (22/224).*



42.6% (110/258) of the respondents considered the ARIA guidelines as very user-friendly, 26.7% (69/258) as moderately user-friendly and 15.9% (41/258) as not user-friendly, with an additional 14.7% (38/258) claiming they were not familiar enough with guidelines to formulate an opinion.

SELF-REPORTED KNOWLEDGE AND USE OF THE ARIA CLASSIFICATION AND ARIA TREATMENT RECOMMENDATIONS

26.4% (68/257) of the respondents reported to be very, 38.9% (100/257) somewhat, 18.7% (48/257) a little and 16.0% (41/257) not at all familiar with the ARIA classification. Similarly, 31.4% (81/258) responded to be very, 41.5% (107/258) somewhat, 12.4% (32/258) a little and 14.7% (38/258) not at all familiar with the ARIA treatment recommendations. To detect potential bias in self-reported knowledge, a test question on the ARIA classification was included. The correct response rate to this question significantly increased ($p<0.001$) with increased self-reported knowledge of the ARIA classification, and among participants claiming to be very familiar with the ARIA classification only 7.4% gave an incorrect answer **(TABLE 2)**.

TABLE 2. *Self-reported knowledge and use of the ARIA classification*

Self-reported knowledge of ARIA classification in % (n)	Self-reported use of ARIA classification (% using classification mostly or always)	ARIA classification test (% with correct response)
Not at all familiar 16.0 (n=41)	0.0	26.8
A little familiar 18.7 (n=48)	2.1	39.6
Somewhat familiar 38.9 (n=100)	27.0	70.0
Very familiar 26.5 (n=68)	75.0	92.6
Significance of linear trend (p)	<0.001	<0.001

10.5% (27/257) of the respondents reported to use the ARIA classification always, 20.2% (52/257) sometimes, 17.9% (46/257) mostly, but the majority of 51.4% (132/257), answered that they never used this classification. On the other hand, only 23.6% (61/258) of the respondents claimed they never followed the ARIA treatment recommendations, whereas 48.8% (126/258) reported to follow them mostly, 13.6% (35/258) always and 14.0% (36/258) sometimes.

Self-reported use of the ARIA classification and ARIA treatment recommendations significantly ($p<0.001$) increased with increased level of self-reported knowledge of the classification **(TABLE 2)** and the recommendations (results not displayed, $p<0.001$) respectively.

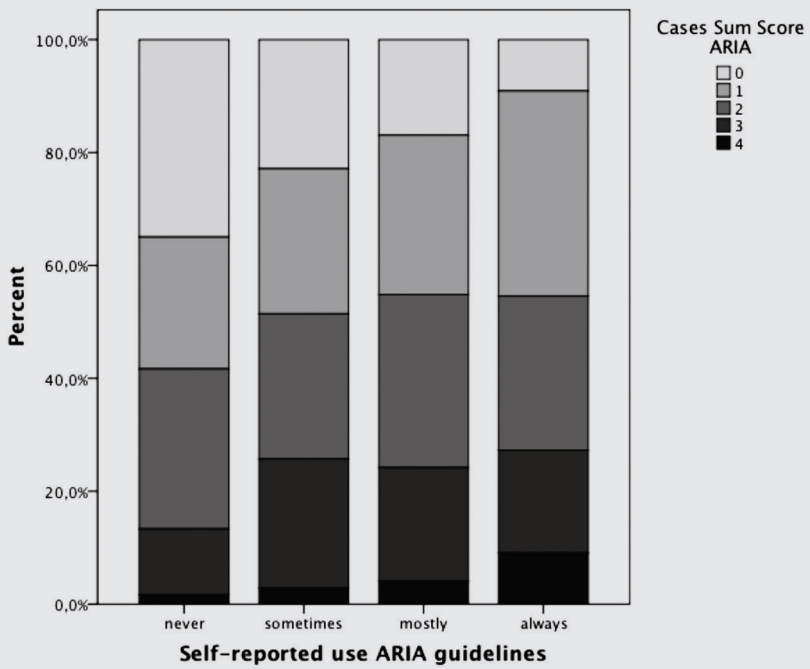
TREATMENT PRACTICES OF AR, COMPLIANCE WITH THE ARIA GUIDELINES IN CLINICAL CASE SCENARIOS

APPENDIX 2 represents the treatment modalities selected in the 4 clinical scenarios. A treatment consistent with the ARIA recommendations was proposed by 18.2% of the participants for scenario 1, 49.2% for scenario 2, 50.0% for scenario 3 and 47.2% for scenario 4. Upon calculation of the individual total scores obtained in

the 4 clinical scenarios, 21.0% (53/252) of the participants obtained a score of 0, 27.8% (70/252) a score of 1, 29.0% (73/252) a score of 2, 18.3% (46/252) a score of 3 and 4.0% (10/252) a score of 4.

Significantly higher scores were obtained by respondents self-reporting to be very or somewhat familiar with the ARIA treatment recommendations compared to those that were a little or not at all familiar with the recommendations (mean score of 1.67 ± 1.12 versus 1.27 ± 1.10, t = -2.46, p = 0.015) and by Otorhinolaryngologists that considered the ARIA guidelines as very user-friendly compared to those that considered them as moderately or not user-friendly (1.82 ± 1.09 versus 1.40 ± 1.14, t = -2.71, p = 0.007). Specialists self-reporting to always or mostly follow the ARIA recommendations scored significantly higher than those reporting to follow them sometimes or never (mean score of 1.69 ± 1.10 versus 1.35 ± 1.14, t = -2.39, p= 0.018). Nevertheless, only 9% (3/33) of the respondents claiming to always follow the ARIA recommendations proposed a treatment that was fully consistent with the ARIA guidelines in all 4 clinical case scenarios and still 45% (15/33) obtained a score of only 0 or 1 (indicating that they proposed a treatment was not consistent with the ARIA recommendations in respectively 4 or 3 of the 4 presented clinical scenarios). **(FIG 2)**

FIGURE 2. *Symptomatology of allergic rhinitis and severity of the manifestations (n=804)*



DETERMINANTS OF GUIDELINE COMPLIANCE

Good compliance with the ARIA guidelines was defined as obtaining a score of ≥ 2 in the clinical scenario section, resulting in 48.8% (123/252) poor compliers and 51.2% (129/252) good compliers. Multivariate logistic regression analysis showed no influence at the 5% significance level of gender, practice type, (sub)specialty or proportion of AR patients on compliance with the ARIA recommendations. Age, on the other hand, was identified as a significant predictor of compliance. For an increase of age with one year the odds of guideline compliance decreased with a factor 0.92 (95% confidence interval = 0.89 to 0.95). This conclusion is corrected for all other factors in the model **(TABLE 3).**

TABLE 3. *Adjusted odds ratio and confidence interval for compliance with ARIA guidelines in clinical case scenarios (* = p<0.001)*

	Odds ratio	95% confidence interval
Age	0.92	**0.89 to 0.95***
Gender		
Male	1.48	0.78 to 2.83
Female	1	
(Sub)specialisation		
General ENT specialist	0.61	0.25 to 1.46
Rhinologist/allergologist	0.96	0.4 to 2.3
Other subspecialist	1	
Proportion of AR patients		
<10%	0.85	0.19 to 3.80
10-20%	0.74	0.18 to 3.02
20-30%	0.74	0.17 to 3.18
>30%	1	
Practice type		
University hospital	0.63	0.19 to 2.06
Non university teaching hospital	0.44	0.14 to 1.39
Non university non teaching hospital	0.73	0.28 to 1.90
No hospital practice	1	

DISCUSSION

Four years after publication of the ARIA guidelines for AR, the dissemination and implementation of these guidelines among Otorhinolaryngologists were assessed for the first time. This study has some obvious limitations. First, results are based on the responses of Otorhinolaryngologists, who were willing to participate. Nothing can be said about the non-respondents, who made up 56 % of the original sample, why they did not return the questionnaire and whether they differ from those who did return it. Second, the study population was limited to Belgian Otorhinolaryngologists, whose behavior may vary from that of their colleagues in other parts of the world. Third, data are based on self-reports and responses to hypothetical case descriptions, which may be different from actual practice patterns. Well-constructed clinical case scenarios, however, have demonstrated to reflect the actual clinical behavior of a group of physicians.[16-18] Fourth, in the case scenario section, for every treatment that was not entirely consistent with the ARIA recommendations a score of 0 was attributed and no distinction was made between treatments that deviated 'strongly' or 'slightly' from the ARIA recommendations.

Despite these limitations, our results clearly show that there remains an apparent lack of influence of guidelines on health professionals' behavior. In this context, three broad areas of concern have to be considered: i) the methodology of guideline development, ii) the process of guideline dissemination and, finally, iii) the implementation of the guideline recommendations in daily medical practice.[19] For the ARIA guidelines, considerable attention has been paid to the development and dissemination processes. The ARIA guidelines are evidence-based, developed by a multidisciplinary, international panel and introduced a new classification for AR, whose benefits have already previously been validated.[20, 21] The guidelines have been widely distributed to healthcare providers dealing with AR patients, through publication of a full workshop report,[9] an executive summary,[22] ample citations in other articles, pocket guides in more than 20 languages and an impressive amount of lectures in all corners of the world. The extensive promulgation efforts are reflected in our survey, with 87% of the respondents having ever heard about ARIA, 64% having ever followed a scientific lecture on the ARIA guidelines, and 73% reporting to be very or somewhat familiar with the ARIA recommendations.

Whereas the dissemination process is focused on educational interventions that aim at influencing clinicians' awareness and understanding of the guidelines, implementation is much more complex, and involves strategies to translate knowledge into changes in medical practice, with impact on patient care. Very few data are available on the implementation of the ARIA guidelines, which should be evaluated as a continuum from dissemination, to awareness, to attitude, and finally, to adherence.[12] In the present survey, ENT-specialist's adherence to the ARIA guidelines was assessed in 4 clinical case scenarios. Overall, only 51% of

the respondents were considered as good compliers, but specialists, that were more familiar with the ARIA guidelines and that considered the ARIA guidelines as user-friendly, more often proposed a treatment consistent with the ARIA recommendations. However, we acknowledge that other factors than lack of awareness, lack of familiarity and lack of user-friendliness of guidelines can act as barriers to guideline implementation. In the future, the impact of agreement or disagreement with the specific guideline recommendations, outcome expectancy, self-efficacy, motivation, practice habits, time, resources, infrastructure, reimbursement strategies, organizational or regulatory framework and patient preferences on guideline compliance should also be evaluated.[12]

As expected, a higher self-reported use of the ARIA guidelines was also reflected in increased adherence to the ARIA treatment recommendations in the clinical case section. But still, among the Otorhinolaryngologists, self-reporting to always practice in accordance with the ARIA guidelines, only 9% proposed a treatment that was fully consistent with the ARIA recommendations. These findings could demonstrate that self-reported adherence to guidelines is subject to social desirability bias and interviewer bias, and in general represents an overestimation of actual guideline adherence.[23] On the other hand, it could also indicate that application of the ARIA guidelines in a clinical setting is not straightforward or that the ARIA recommendations are sometimes misinterpreted.

Whereas gender, subspecialty in rhinology/allergology, working at a University or teaching hospital and a higher proportion of AR patients in practice did not seem to influence compliance with the ARIA guidelines, we found that younger age was a significant predictor for good compliance. Similar findings of declining adherence to clinical practice standards and evidence-based guidelines with increasing age and experience have also been reported in other areas of medicine.[24, 25] A possible explanation is that the introduction of guidelines into clinical training and practice and the evolution of opinion-based to evidence-based medicine dates from the last 15 years. It is well known that physicians not easily change their longstanding prescribing patterns, and inertia of previous practice has been identified as a barrier to the incorporation of guidelines into practice.[12] On the other hand, we recognize that staying up-to-date can be difficult and even confusing when different guidelines, providing conflicting recommendations, are promoted within a short time interval. Less than 2 years before the publication of the ARIA guidelines, the 'Consensus statement on the treatment of allergic rhinitis' was developed by the European Academy of Allergology and Clinical Immunology (EAACI)[6]. Although not evidence-based, these guidelines also provide stepwise treatment algorithms for the management of AR. An important difference is that the EAACI guidelines recommend to combine an antihistamine and a nasal corticosteroid as a first-line treatment in severe cases of AR, whereas the ARIA guidelines follow a more stepwise approach and only recommend this combination if treatment with an

antihistamine or a nasal corticosteroid alone fails.[6, 9] In the clinical case scenarios we found that the combination of an antihistamine and a nasal corticosteroid as a first-line treatment was recommended by many specialists, and that the prescription of this combination accounted for one of the most frequent reasons of inconsistency with the ARIA guidelines.

CONCLUSION

Despite the wide promulgation of the ARIA guidelines, many specialists dealing with AR patients remain only poorly influenced by these evidence-based recommendations. Translation of scientific knowledge into clinical practice is not straightforward and adherence to guidelines is undermined by several barriers at the level of physicians' knowledge, attitudes and practice behavior.

We found that older, more experienced Otorhinolaryngologists were more unlikely to adhere to the guidelines than their younger colleagues and that younger age (or less clinical experience) was a significant and independent predictor for good compliance with the ARIA treatment recommendations. However, further research is needed to determine the factors influencing poor compliance before selecting effective interventions to change physicians' practice behavior.

Nevertheless, we recognize that a treatment remains a result of an agreement between doctor and patient and is always influenced by the individual context. The main goal of guidelines is to assist physicians and to improve patient care, which implies that they should be developed and considered as a support for practitioners with space for flexibility, rather than as a set of constrained rules.

ACKNOWLEDGEMENT

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REFERENCES

1. Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. Eur Respir J 2004;24(5):758-64.
2. Sly RM. Changing prevalence of allergic rhinitis and asthma. Ann Allergy Asthma Immunol 1999;82(3):233-48.
3. Nolte H, Nepper-Christensen S, Backer V. Unawareness and undertreatment of asthma and allergic rhinitis in a general population. Respir Med 2006;100(2):354-62.
4. Scadding GK, Williams A. The burden of allergic rhinitis as reported by UK patients compared with their doctors. Rhinology 2008;46(2):99-106.
5. International Rhinitis Management Working Group. International Consensus Report on the Diagnosis and Management of Rhinitis. Allergy 1994;49(Suppl 9):5-34.
6. Van Cauwenberge P, Bachert C, Passalacqua G, Bousquet J, Canonica GW, Durham SR, et al. Consensus statement on the treatment of allergic rhinitis. Allergy 2000;55(2):116-34.
7. Fornadley JA, Corey JP, Osguthorpe JD, Powell JP, Emanuel IA, Boyles JH, et al. Allergic rhinitis: clinical practice guideline. Committee on Practice Standards, American Academy of Otolaryngic Allergy. Otolaryngol Head Neck Surg 1996;115(1):115-22.
8. Dykewicz MS, Fineman S, Skoner DP, Nicklas R, Lee R, Blessing-Moore J, et al. Diagnosis and Management of Rhinitis: Complete Guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. Ann Allergy Asthma Immunol 1998;81(5Pt2):478-518.
9. Bousquet J, van Cauwenberge P, Khaltaev N, ARIA Workshop Group. Allergic Rhinitis and its Impact on Asthma (ARIA). J Allergy Clin immunol 2001;108 (Suppl 5):S147-S333.
10. Guarnaccia S, Lombardi A, Gaffurini A, Chiarini M, Domenighini S, D'Agata E, et al. Application and implementation of the GINA asthma guidelines by specialist and primary care physicians: a longitudinal follow-up study on 264 children. Prim Care Respir J 2007;16(6):357-62.
11. Bousquet J, Lund VJ, van Cauwenberge P, Bremard-Oury C, Mounedji N, Stevens MT, et al. Implementation of guidelines for seasonal allergic rhinitis: a randomized controlled trial. Allergy 2003;58(8):733-41.
12. Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud PA, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. JAMA 1999;282(15):1458–65.
13. Grimshaw JM, Russell IT. Effect of clinical guidelines on medical practice: a systematic review of rigorous evaluations. Lancet 1993;342(8883):317-22.

14. Lenfant C. Shattuck lecture--clinical research to clinical practice--lost in translation? N Engl J Med 2003;349(9):868-74.

15. Hellings PW, Fokkens WJ. Allergic rhinitis and its impact on otorhinolaryngology. Allergy. 2006;61(6):656-64.

16. Webster BS, Courtney TK, Huang YH, Matz S, Christiani DC. Physicians' initial management of acute low back pain versus evidence-based guidelines. Influence of sciatica. J Gen Intern Med 2005;20(12):1132-5.

17. Carey TS, Garrett J. Patterns of ordering diagnostic tests for patients with acute low back pain. Ann Intern Med 1996;125(10):807–14.

18. Homer CJ, Quintana JM, Baskin M, Goldman DA. Can we believe physicians' responses to clinical vignettes? (abstract) Arch Pediatr Adolesc Med 1994;148:35.

19. Langley C, Faulkner A, Watkins C, Gray S, Harvey I. Use of guidelines in primary care - practitioners' perspectives. Fam Pract 1998;15(2):105-11.

20. Demoly P, Allaert FA, Lecasble M, Bousquet J; PRAGMA. Validation of the classification of ARIA (allergic rhinitis and its impact on asthma). Allergy 2003;58(7):672-5.

21. Bousquet J, Annesi-Maesano I, Carat F, Léger D, Rugina M, Pribil C, et al. Characteristics of intermittent and persistent allergic rhinitis: DREAMS study group. Clin Exp Allergy 2005;35(6):728-32.

22. Bachert C, van Cauwenberge P, Khaltaev N; World Health Organization. Allergic rhinitis and its impact on asthma. In collaboration with the World Health Organization. Executive summary of the workshop report. 7-10 December 1999, Geneva, Switzerland. Allergy 2002;57(9):841-55.

23. Adams AS, Soumerai SB, Lomas J, Ross-Degnan D. Evidence of self-report bias in assessing adherence to guidelines. Int J Qual Health Care 1999;11(3):187-92.

24. Choudhry NK, Fletcher RH, Soumerai SB. The relationship between clinical experience and quality of health care. Ann Intern Med 2005;142(4):260–73.

25. Ward MM, Vaughn TE, Uden-Holman T, Doebbeling BN, Clarke WR, Woolson RF. Physician knowledge, attitudes and practices regarding a widely implemented guideline. J Eval Clin Pract 2002;8(2):155-62.

APPENDIX 1: *Treatment recommendations of the ARIA guidelines*[9] *for the different case scenarios. Decongestant*: short course of oral or nasal decongestant.*

	Case scenario	AR classification (according to ARIA)	Treatment recommended according to ARIA guidelines[9]
1	Currently untreated patient, allergic to house dust mite, who is suffering from rhinorrhea, sneezing and nasal congestion since 2 months. Symptoms interfere with the patient's quality of sleep.	Moderate-severe persistent AR	• Allergen avoidance • And nasal corticosteroid ± decongestant*
2	Currently untreated patient who has experienced sneezing, rhinorrhea, nasal congestion and red and tearing eyes for the last month, especially when he's working in the garden. Besides these symptoms, the patient has no complaints.	Mild intermittent AR with conjunctivitis	• (Allergen avoidance) • (And) oral H1-antihistamine ± decongestant* Or nasal H1-antihistamine + topical eye treatment ± decongestant*
3	Currently untreated patient, allergic to birch, who is especially suffering from nasal congestion for the last 2 weeks. The patient is having exams and says that he's bothered during studying.	Moderate-severe intermittent AR	• (Allergen avoidance) • (And) oral H1-antihistamine ± decongestant* Or nasal H1-antihistamine ± decongestant* Or decongestant Or nasal corticosteroid ± decongestant*
4	Patient with manifest symptoms of allergic rhinitis due to house dust mite and currently treated with an oral antihistamine. This treatment provides insufficient symptom relief.	Step up treatment oral antihistamine	• Allergen avoidance • And nasal corticosteroid ± decongestant* Or oral H1-antihistamine + nasal corticosteroid ± decongestant*

APPENDIX 2: *Treatment modalities selected in 4 case scenarios of allergic rhinitis. Treatments consistent with the ARIA guidelines[9] are in bold.*

Clinical scenario 1 Selected treatment or combination of treatments	% (n)
OAH1/NAH1 + NCS + AA	45.6 (115)
NCS + AA	**18.2 (46)**
IT*	9.9 (25)
OCS**	4.8 (12)
OAH1/NAH1 + NCS	5.6 (14)
OAH1/NAH1 + NCS + DC + AA	5.2 (13)
OAH1/NAH1 + AA	4.0 (10)
OAH1/NAH1	2.0 (5)
OAH1/NAH1 + NCS + DC	1.6 (4)
NCS	1.2 (3)
AA	1.2 (3)
Other	0.8 (2)
Consistent with ARIA recommendations	**18.2 (46)**

Clinical scenario 2 Selected treatment or combination of treatments	% (n)
OAH1 +/- TEM +/- AA	**42.5 (107)**
OAH1 + NCS +/- TEM +/- AA	30.6 (77)
NCS + TEM +/- AA	7.9 (20)
IT*	6.0 (15)
NAH1+ TEM +/- AA	**4.4 (11)**
OAH1 +/- TEM + DC +/- AA	**2.4 (6)**
NCS +/- AA	2.4 (6)
OCS**	1.6 (4)
Other	2.4 (6)
Consistent with ARIA recommendations	**49.2 (124)**

Clinical scenario 3 Selected treatment or combination of treatments	% (n)
OCS**	17.1 (43)
NCS +/-AA	**16.3 (41)**
OAH1/NAH1 + NCS +/- DC	14.7 (37)
NCS + DC +/- AA	**13.1 (33)**
OAH1/NAH1 + DC +/- AA	**10.7 (27)**
OAH1/NAH1 + NCS + DC +/- AA	10.7 (27)
OAH1/NAH1 + DC +/- AA	**5.2 (13)**
IT*	5.2 (13)
DC +/- AA	**4.8 (12)**
IMCS	2.4 (6)
Consistent with ARIA recommendations	**50.0 (126)**

Clinical scenario 4 Selected treatment or combination of treatments	% (n)
IT*	45.2 (114)
NCS + AA	**21.4 (54)**
OAH1/NAH1 + NCS + AA	**15.1 (38)**
NCS	**6.0 (15)**
OCS**	5.2 (13)
OAH1 + NCS	**3.2 (8)**
OAH1 + NCS + DC + AA	**1.6 (4)**
AA	1.6 (4)
Other	0.8 (2)
Consistent with ARIA recommendations	**47.2 (119)**

OAH1: oral H1-antihistamine
NAH1: nasal H1-antihistamine
NCS: nasal corticosteroid
OCS: oral corticosteroid (short course)
OCS**: usually proposed in combination with or followed by diverse anti-allergic medications
DC: oral or nasal decongestant (short course)
TEM: topical eye medication (ocular H1-antihistamine or cromone)
IMCS: intramuscular corticosteroid
IT: immunotherapy
IT*: usually proposed in initial combination with diverse anti-allergic medications
AA: allergen avoidance

CHAPTER VI

DISSEMINATION AND IMPLEMENTATION OF THE ARIA GUIDELINES IN GENERAL PRACTICE

DISSEMINATION AND IMPLEMENTATION OF THE ARIA GUIDELINES FOR ALLERGIC RHINITIS IN GENERAL PRACTICE

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ABSTRACT

BACKGROUND

Allergic rhinitis (AR) is a prevalent problem in general practice. The first evidence-based guidelines for AR, the ARIA guidelines, were published and repeatedly updated since 2001 in order to improve the care of AR patients. Very limited information, however, is available on the impact of these guidelines on everyday clinical practice. The aim of this study was to evaluate the dissemination and implementation of the ARIA guidelines in general practice.

METHODS

350 Flemish general practitioners (GPs) were recruited to complete a questionnaire, covering demographic and professional characteristics, awareness, perception and implementation of the ARIA guidelines. To assess compliance with the ARIA treatment recommendations, 4 fictitious case scenarios of AR were presented, in which the respondents were asked to select the treatment of choice.

RESULTS

Of the 350 included GPs, only 31% were aware of the ARIA guidelines and 10% stated to implement them. For the diagnosis of AR, 71% of the GPs ask specific IgE tests or perform skin prick tests, whereas only 29% perform an anterior rhinoscopy. ARIA users are more likely to screen for concomitant asthma. In the clinical case section there was a large variability in proposed therapeutic strategies. Adherence to the evidence-based ARIA treatment guidelines was low, but recent graduation was a significant predictor of compliance with these recommendations.

CONCLUSIONS

The ARIA guidelines remain relatively unknown among Flemish GPs and even those who are aware of them still tend to treat AR independently from the guideline recommendations.

INTRODUCTION

Allergic rhinitis (AR) is the most common chronic disease of the developed world, and is becoming increasingly important in developing countries.[1] AR is estimated to affect up to one into 4 people, has a serious impact on the personal and social well-being, the professional and academic performance, is associated with several coexisting conditions (e.g. asthma, sinusitis, conjunctivitis and otitis media), and represents an important source of direct and indirect costs for the individuals and the society. Nevertheless the disease often remains unrecognized, un(der) diagnosed, trivialized and inadequately treated.[2]

In 2001 the first evidence-based guidelines for AR were published: the ARIA (Allergic Rhinitis and its Impact on Asthma) guidelines.[3] They were developed by an international, multidisciplinary panel and provide diagnostic and therapeutic recommendations for the management of AR patients in primary and specialist healthcare settings throughout the world. The ARIA guidelines also changed the previous and unsatisfactory classification of AR based on the type of sensitization to cyclic pollens or year-around allergens (into seasonal or perennial) in a new classification based on the duration of the symptoms and their impact on the quality of life (QOL). Furthermore, the ARIA working group emphasized that AR is not an isolated disorder, but is often associated with asthma, as part of a 'united airway disease'. In the meanwhile the ARIA guidelines have been updated[4, 5] and the benefits on patient outcomes (symptom scores, QOL and work productivity) of following the ARIA recommendations compared to using a nonstandard treatment regimen have been validated in a pragmatic randomized study.[6]

Less than 50% of AR patients seek medical help for their condition,[7] but the majority of patients who do seek medical help, consult their general practitioner (GP), highlighting the key role of GPs in the diagnosis, treatment and follow-up of AR.[1] Nevertheless previous studies have demonstrated considerable scope for improvement in GP awareness, diagnostic skills and management of AR.[8]

Primary care physicians have always played an important role in the development of the ARIA guidelines[3-5] and the ARIA 2008 pocket guide was developed with the World Organization of Primary Care Physicians (WONCA).[9] Furthermore, the ARIA guidelines are not intended to be a global standard of care, but serve as a basis to develop relevant local guidelines adapted to the healthcare setting. The "NHG Standard for allergic and non-allergic rhinitis"[10] is such a local evidence-based guideline. The NHG clinical practice guidelines, written in Dutch, are developed by the Dutch College of General Practitioners and were initially intended for GPs in the Netherlands, but also became popular among the Dutch speaking (Flemish) GPs in the northern part of Belgium (Flanders). The recommendations of the NHG guideline for (allergic) rhinitis are in many ways very similar to the ARIA guidelines, proposing the same ARIA classification and the same first-line treatments according to the duration and severity of disease, but the NHG Standard is specifically adapted to the primary care setting.

Despite the availability of evidence-based guidelines for the management of AR and their proven effectiveness,[6] very little is known about the adoption of these guidelines in daily general practice.

We performed a questionnaire-based study among Flemish GPs 1) to assess the level of dissemination and penetration of clinical guidelines for AR in general practice, 2) to evaluate the diagnostic and therapeutic management of AR by GPs, 3) to compare these practices with the evidence-based ARIA guideline recommendations, and 4) to gain information on GPs' socio-professional characteristics that may influence guideline compliance.

MATERIAL AND METHODS

QUESTIONNAIRE DEVELOPMENT

We designed a questionnaire in multiple choice response format that covered following items:

- Demographic and professional details
- Classification of AR
- Diagnostic procedures for AR
- Self-reported use of clinical guidelines for AR in daily practice
- Awareness of, familiarity with and attitude towards the ARIA guidelines
- Therapeutic management of AR through presentation of 4 fictitious clinical scenarios.

The questionnaire was formulated in Dutch. Part of the questionnaire was similar to a previously performed survey among Belgian ear-, nose-, throat (ENT) specialists,[11] with some modifications to make it more suitable for the primary care setting. Prior to its distribution, the questionnaire was pilot tested among 15 GPs, resulting in some minor changes.

SAMPLE AND DATA COLLECTION

All Flemish local quality peer review groups (LQPRGs) of general practitioners that planned a group meeting between January and March 2009, were contacted through their chairs and were invited to participate in this study. In total 33 LQPRGs throughout Flanders participated. At the time of the LQPRG meeting, the paper-based questionnaires were individually and anonymously completed by all GPs attending the meeting, resulting in 350 participants. There were no non-responders. After completion, the questionnaires were collected by the chairman of the group and send back to the investigators in a prestamped envelop by the end of the study period (March 2009). All distributed questionnaires were recollected. There was no incentive for participation.

The Ethics Committee of Ghent University Hospital approved the contents, conditions and application of the survey.

CLINICAL CASE SECTION

For the 4 fictitious case scenarios the treatment proposed by the respondents was strictly compared with the treatment recommendations of the ARIA guidelines, available at the time of the study[4] **(APPENDIX 1)**. A score of 0 (treatment not consistent with ARIA recommendations) or 1 (treatment consistent with ARIA recommendations) was attributed per case, resulting in a total score ranging from 0 to 4 per respondent. Upon further analysis, compliance with the ARIA guidelines in the clinical scenarios was dichotomized into 'poor compliance' or 'good compliance'. Good compliance was set at a total score above the mean outcome.

STATISTICAL ANALYSIS

The descriptive part of the study uses conventional parameters: percentages for nominal and ordinal variables. Chi square test was used to analyze differences in nominal or ordinal values between 2 subgroups and to compare demographic characteristics of our sample group with the target group of all Flemish GPs. To assess a linear trend in proportions of nominal or ordinal values across more than 2 subgroups Chi square test for trends was used.

The influence of demographic and professional variables on compliance with the ARIA recommendations was assessed using multiple logistic regression analysis. The following demographic and professional characteristics were considered to potentially influence guideline compliance and were included in the regression analysis: gender, years of practice, type of practice, special interest in ENT pathology/allergology, peer-reviewed journal subscriptions, obtained continuing medical education (CME) credits and self-reported implementation of guidelines for AR. Significance level was set at $\alpha = 0.05$ throughout the whole study. Analyses were completed using SPSS Inc (Chicago, ILL, USA; version 19).

RESULTS

BASELINE CHARACTERISTICS OF THE RESPONDENTS

Demographic and professional details of the sample population of 350 GPs are summarized in **TABLES 1A** and **1B** and compared with the available demographics of the target population, all Flemish GPs, in **TABLE 1A**. For age and gender no significant differences were found between the sample and the target population, but there was a significant overrepresentation of GPs working in a group practice within our sample population.

TABLE 1A. *Demographics of the sample population of 350 participating GPs compared with the target population of all Flemish GPs. The latter was obtained through the annual report (2009) of Domus Medica, a Flemish association representing the interests of GPs. *statistically significant*

	Participating GPs (n=350)		All Flemish GPs (n = 7367)		P value
	%	n	%	n	
Gender					0.77
Male	68.6	240	67.6	4981	
Female	31.4	110	32.2	2374	
Unknown	0.0	0	0.2	12	
Years of practice					0.41
≤5 years	8.0	28	3.1	228	
6-10 years	8.9	31	12.4	915	
11-20 years	20.6	72	21.9	1615	
21-30 years	32.6	114	33.6	2473	
>30 years	30.0	105	28.8	2122	
Unknown			0.2	14	
Type of practice					<0.001*
Solo practice	46.6	163	72.3	5323	
Group practice	53.4	187	27.7	2044	

TABLE 1B. *Additional demographic and professional characteristics of the sample population (n = 350) (no data available for all Flemish GPs). CME credits = credits obtained for continuing medical education, 1 credit accounts for 1 hour of CME*

	Sample population (n=350)	
Number of patients/week	**%**	**n**
<50	5.1	18
50-100	39.1	137
100-200	48.3	169
>200	7.4	26
Special interest in ENT/ Allergology		
Yes	24.3	85
No	75.7	265
Peer reviewed journal subscriptions		
No	38.9	136
1 or 2	55.4	194
≥3	5.7	20
CME credits last year		
<20	8.9	31
20-40	75.4	264
>40	15.7	55

SELF-REPORTED AWARENESS OF ARIA GUIDELINES FOR ALLERGIC RHINITIS

Of all participants 31.1% knew about the ARIA guidelines. Among this group, 21.1% considered the ARIA guidelines as very user-friendly, 33.9% as moderately user-friendly, 1.8% as not user-friendly and 43.1% were insufficiently familiar with these guidelines to evaluate their user-friendliness.

Respondents that were aware of the ARIA guidelines, first heard about these guidelines through scientific lectures or postgraduate medical education (36.4%), representatives of pharmaceutical companies (32.7%), peer reviewed medical journals (16.4%), non-peer reviewed medical journals, leaflets or brochures (8.2%), colleagues (4.5%) or during medical training (1.8%).

Self-reported awareness of the ARIA guidelines was significantly higher among male compared to female GPs (35.8% versus 20.9%, p=0.006), among GPs with a specific interest in ENT pathology/allergology compared to the rest of GPs (43.5% versus 27.2%, p=0.007) and showed a significant increasing trend with increasing number of subscriptions to peer-reviewed journals (24.3% among GPs without peer reviewed journal subscription, 33.5% among GPs holding 1 or 2 subscriptions and 55.0% among those with 3 or more peer reviewed journal subscriptions, p=0.002) and with increasing number of obtained CME credits (19.4% among GPs that obtained <20 CME units the last year, 29.2% among those that obtained 20-40 CME units and 47.3% for those that obtained > 40 CME units, p =0.002).

SELF-REPORTED IMPLEMENTATION OF (ARIA) GUIDELINES FOR ALLERGIC RHINITIS

In total, 34.3% of the participants reported to follow clinical guidelines in the daily care of patients with AR. 7.4% of this group stated to strictly follow the guideline recommendations in the management of all AR patients 76.9% considered the guideline as a basis for the management of AR patients, which they adapt according to the specific context, and 15.7% stated to only implement the guidelines in special or difficult cases.

28.3% of the GPs, stating to implement AR guidelines, used paper or computer summaries, pocket guides or flowcharts of the guidelines during daily practice. Self-reported implementation of guidelines for AR was significantly higher among GPs with a special interest in ENT pathology/allergology compared to the rest of GPs (49.4% versus 29.4%, p=0.001) and showed a significant increasing trend with increasing number of peer reviewed journal subscriptions (26.5% among GPs without peer reviewed journal subscription, 37.1% among GPs holding 1 or 2 subscriptions and 60.0% among those with 3 or more peer reviewed journal subscriptions, p=0.001).

The majority of GPs (70.0%) reporting to implement guidelines for AR, followed the "NHG Standard for allergic and non-allergic rhinitis",[10] whereas only 29.2% (i.e. 32.1% of the GPs that were aware of the ARIA guidelines or 10.0% of all respondents), followed the ARIA guidelines in daily clinical practice. There were significantly more female GPs and significantly more GPs working in a group practice among the NHG standard users compared to the ARIA users (respectively 40.4% versus 17.1%, p=0.018 and 69.9% versus 40.0%, p<0.001)

CLASSIFICATION AND DIAGNOSIS OF ALLERGIC RHINITIS

Within our sample population, 30.6% of the GPs did not use a classification for AR in daily practice. 38.9% classified AR as seasonal or perennial. 11.4% classified AR consistent with the ARIA (and NHG) guidelines into intermittent or persistent and 19.1% stated to use another, spurious classification for AR. Of interest, 40% of the GPs that reported to follow the ARIA guidelines and 40.5% of those declaring to follow the NHG guidelines, still used the previous classification of AR into seasonal or perennial.

GPs' common practice(s) to diagnose AR are presented in **TABLE 2**. Almost all GPs perform a thorough clinical history, 71.1% ask additional serum allergen-specific IgE tests or perform skin prick tests, whereas only 28.6% perform an anterior rhinoscopy. Almost 50% of the respondents ask for a total serum IgE measurement. Anterior rhinoscopy, specific IgE measurement and skin prick tests were more frequently performed among the self-declared guideline user group, but these differences were not significant. Further analysis showed no significant differences in the diagnostic procedures for AR between ARIA users and the rest of the GPs, or between ARIA and NHG standard users (data not presented).

74.3% of all respondents reported to screen routinely for concomitant asthma in patients with AR. The screening rate for asthma was significantly higher among GPs that reported to implement AR guidelines than among those who did not (84.2% versus 69.1%, p=0.003), and was not significantly higher in the subgroup of GPs that reported to implement the ARIA guidelines compared to those using the NHG standards (94.3% versus 81.0%, p=0.091).

TABLE 2. *Common procedures, reported by GPs, to diagnose allergic rhinitis. Comparison is made between GPs that report to implement guidelines for AR and those who don't.*

	All respondents n=350	Guideline users n=120	Non-guideline users n=230	P value
Clinical history	342 (97.7%)	117 (97.5%)	225 (97.8%)	1.00
Anterior rhinoscopy	100 (28.6%)	40 (33.3%)	60 (26.1%)	0.17
Allergy testing				
Skin prick test	14 (4.0%)	7 (5.8%)	7 (3.0%)	0.25
Skin patch test	3 (0.9%)	2 (1.7%)	1 (0.4%)	0.55
Total IgE	174 (49.7%)	66 (55.0%)	108 (47.0%)	0.18
Specific IgE	235 (67.1%)	83 (69.2%)	152 (66.1%)	0.63
Eosinophilia	100 (28.6%)	36 (30.0%)	64 (27.8%)	0.71
Imaging paranasal sinuses	27 (7.7%)	12 (10.0%)	15 (6.5%)	0.29
Therapeutic trial	4 (1.1%)	0 (0.0%)	4 (1.7%)	0.30
Specialist referral	5 (1.4%)	2 (1.7%)	3 (1.3%)	1.00
Screening for asthma	260 (74.3%)	101 (84.2%)	159 (69.1%)	0.003
Clinical history	247 (70.6%)	92 (76.7%)	155 (67.4%)	0.09
Lung auscultation	166 (47.4%)	68 (56.7%)	98 (42.6%)	0.02
Peak flow measurement	114 (32.6%)	47 (39.2%)	67 (29.1%)	0.07
Thorax radiography	4 (1.1%)	3 (2.5%)	1 (0.4%)	0.23
Self-performed spirometry	28 (8.0%)	14 (11.7%)	14 (6.1%)	0.11
Referral to pulmonologist	45 (12.9%)	17 (14.2%)	28 (12.2%)	0.72

TREATMENT OF ALLERGIC RHINITIS AND COMPLIANCE WITH THE ARIA RECOMMENDATIONS

The treatment modalities selected by the respondents in the 4 clinical case scenarios are presented in Appendix 2 and compared with the ARIA recommendations.[4] A treatment consistent with the ARIA recommendations was proposed by 84.8% (297/350) of the participants for scenario 1, 34.0% (119/350) for scenario 2, 42.8% (150/350) for scenario 3 and 75.7% (265/350) for scenario 4.

For the 4 case scenarios in total 2.9% (10/350) of the participants obtained a total score of 0, while 12.9% (45/350) had a score of 1, 36.0% (126/350) a score of 2, 38.3% (134/350) a score of 3, and 10.0% (35/350) a score of 4. The mean score was 2.4. Respondents that obtained a score above the mean (i.e. 3 or 4) were considered as 'good compliers', resulting in 51.7% (181/350) poor compliers and 48.3% (169/350) good compliers.

Multiple logistic regression analysis revealed recent graduation (<5y of clinical experience) to be the only independent significant predictor of good compliance

with the ARIA guidelines **(P=0.049, TABLE 3)**. Compared to the group with more than 30 years of experience, compliance was increased with a factor 2.6. Gender, practice type, interest in ENT/allergology, journal subscription, CME credits and self-reported implementation of guidelines for AR showed no independent influence at the 5% significance level on compliance with the ARIA recommendations.

TABLE 3. *Adjusted odds ratios and confidence intervals for compliance with ARIA guidelines, based on the results of clinical case scenarios. Data were calculated using multiple logistic regression, *statistically significant.*

		Odds Ratio	95% confidence interval	P value
Gender	Male	0.620	0.363-1.059	0.080
	Female	1		ref
Experience	0-5y	2.618	1.004-6.830	**0.049***
	6-10y	1.481	0.612-3.586	0.384
	11-20y	1.695	0.866-3.318	0.124
	21-30y	1.372	0.790-2.381	0.261
	>30y	1		ref
Type of practice	Solo	1.206	0.748-1.943	0.442
	Group	1		ref
Special interest in ENT/allergology	No	0.958	0.570-1.609	0.871
	Yes	1		ref
Journal subscription	No	1.163	0.424-3.190	0.769
	Yes, 1-2	1.446	0.544-3.843	0.460
	Yes, >2	1		ref
CME	<20	0.813	0.317-2.086	0.666
	20-40	0.677	0.364-1.258	0.217
	>40	1		ref
Self-reported implementation of AR guidelines	No	1.129	0.699-1.823	0.619
	Yes	1		ref

DISCUSSION

Although AR is a prevalent problem in general practice and the ARIA guidelines have been developed to standardize and improve the quality of care of AR patients, the results of this survey demonstrate that the penetration of these guidelines among Flemish GPs remains very poor. The first barrier to physician adherence to guidelines is lack of awareness.[12] This barrier is obvious in our sample population, with more than two thirds of the participating GPs having never heard about the ARIA guidelines. Among GPs with a particular interest in ENT/allergology, a higher number of peer-reviewed journal subscriptions and increased CME credits, self-reported awareness of the ARIA guidelines was higher. When we compare our results with a similar study in France, where 48% of the GPs declared to be familiar with the ARIA guidelines[13] and a survey completed by Belgian ENT specialists, with up to 87% having ever heard about the ARIA guidelines[11], dissemination of the ARIA guidelines among Flemish GPs seems to have failed...

Awareness of a guideline, on the other hand, does not necessarily lead to its implementation. Guideline utilization is a stepwise process resulting from awareness, to agreement, to adoption, and finally adherence, with a variety of internal and external barriers that may raise at the different levels.[12] In our survey, only 32% of the GPs aware of the ARIA guidelines, reported to also use this guideline in the daily management of AR patients. The majority (70%) of GPs using a guideline for AR, preferred the NHG Standard from the Dutch College of General Practitioners.[10] It is well-known that physicians have more confidence in guidelines that are developed by their own specialty organization[14] and family physicians in particular prefer receiving guideline information from their own peer group[15]. The ARIA initiative never intended to be the universal standard of care and also recommends the 'best practice recommendations' to be tailored to local circumstances and population characteristics, including the healthcare system regulations. In this context adherence to a local evidence-based guideline can only be promoted. The NHG standard is evidence-based and in many ways very similar to the ARIA guidelines: it recommends the ARIA classification for AR based on the duration of symptoms and their impact on QOL, emphasizes on the comorbid relationship between rhinitis and asthma and recommends the same first-line treatment regimens. In terms of recommended diagnostic approach, however, there are some important differences. Whereas ARIA recommends to perform a nasal examination and additional allergy tests by means of skin prick tests or serum allergen-specific IgE measurements in all suspected AR patients, the NHG Standard states that a nasal examination in general practice by means of an anterior rhinoscopy has limited additional value and is only mandatory when suspicion of other diagnoses exists. Furthermore, the NHG Standard finds additional allergy tests unnecessary in case of straightforward and isolated grass or tree pollen induced AR symptoms, given the high predictive value of clinical history in these cases.[16]

In our sample population, 74% of all participants stated to routinely screen for asthma in AR patients and this raised to 84% among self-declared AR guideline users and 94% in the subgroup of self-declared ARIA users. These data indicate that overall awareness of the comorbid association between AR and asthma was high, with additional and positive attentiveness for the upper-lower airway link among guideline-users and ARIA users in particular.

More than 70% of the GPs indicated to routinely perform adequate allergy testing, but no significant differences were found between self-declared guideline or non-guideline users, ARIA or NHG users. Anterior rhinoscopy, on the other hand, was only done by 29% of the GPs, with no significant differences between self-declared guideline or non-guideline users, and, remarkably, neither between ARIA or NHG Standard users. On the other hand, total serum IgE measurement in suspected AR patients was still advised by almost 50% of the respondents (with no significant differences between self-declared guideline en non-guideline users), whereas the (ARIA and NHG) guidelines do not recommend this investigation, due to its lack of specificity.

Conflicting responses between self-reported and actual guideline adherence were also found when assessing the classification of AR, with 40% of the self-declared ARIA and NHG Standard users indicating to use the classification of AR based on the type of allergen, that is no longer recommended by the current guidelines, but, however, still appears in the literature. Also, in the fictitious case scenario section self-declared guideline users did not demonstrate higher compliance with the evidence-based (ARIA) guideline treatment recommendations. These data indicate that self-reported adherence must be interpreted with caution as it does not necessarily reflect actual practice and might be susceptible to social desirability bias and interviewer bias.[17] On the other hand, it could also indicate that application of guidelines in a clinical setting is not straightforward.[11]

In the clinical case scenarios we found a tremendous variability in the proposed treatment regimens, with only 10% of the GPs recommending a treatment entirely consistent with the evidence-based guidelines in all 4 case scenarios. Based on our scoring system, only 48% of the respondents were considered as 'good' compliers with the evidence-based treatment recommendations for AR. This indicates that next to a lack of dissemination and implementation of the ARIA guidelines in Flemish general practice, scientific evidence concerning AR management has not yet found its way into the daily routine of GPs. As discussed above, self-reported adherence to the ARIA or NHG guidelines did not lead to increased compliance with evidence-based treatment principles for AR, but neither did physician's interest in ENT/allergology, increased journal subscriptions, obtained CME credits, working in a group practice or gender. The only independent significant predictor of increased implementation of evidence was recent graduation, with ≤ 5 years of clinical experience. Although the less experienced GPs did not report a higher awareness of the ARIA guidelines, their treatment practices seem to be more

concordant with the underlying evidence of these guidelines compared to their more experienced colleagues. The same was found in our previous survey in ENT specialists, where younger age was a significant predictor of better compliance with the ARIA recommendations.[11] Similar findings of declining adherence to clinical practice standards and evidence-based recommendations with increasing age and experience have also been reported in other areas of medicine.[18-20] A possible explanation is that the evolution from opinion-based to evidence-based medicine dates from the last 15 years. It is well known that physicians not easily change their long- standing prescribing patterns and this has been identified as a barrier to the incorporation of scientific evidence and guidelines into practice.[12] Younger, less experienced physicians on the other hand, more often tend to rely on the current scientific knowledge to support their clinical practice.

Clinical practice guidelines like ARIA and the NHG Standard were developed to improve and facilitate the implementation of scientific evidence into clinical practice, but the impact of these guidelines on everyday clinical practice remains limited. There is no single effective way to introduce and ensure the use of guidelines into practice, but research into guideline implementation in primary care practice has suggested that strategies might be more effective when tailored to pre-identified barriers. Further research is needed to determine the factors that influence poor compliance and the barriers that raise at the different levels of guideline dissemination and implementation before selecting effective interventions to change physicians' practice behavior.[21]

LIMITATIONS OF THE STUDY

There are some obvious limitations to this study.

First, results are based on responses of a sample population of 350 Flemish GPs. The knowledge and behavior of Flemish GPs might differ from that of colleagues elsewhere, and obviously our results cannot merely be extrapolated to the international GP population. Although our sample was quite representative for the total Flemish GP population, there was an overrepresentation of GPs working in a group practice. Type of practice, however, did not demonstrate an important influence on our results. Furthermore the setting of recruitment at a LQPRG meeting, whose mission is to promote interprofessional dialogue, to organize continued medical education and to improve the quality of care, might have led to bias in the results. On the other hand, in Flanders it is compulsory for GPs to be part of a LQPRG and to regularly participate at the group meetings. Additionally, all GPs present at the meetings completed the survey, which excludes a non-respondent bias.

Second, the data are based on self-reports and fictitious case scenarios. The limits of self-reported guideline adherence and the risk of social desirability bias are already discussed above. We, however, tried to limit social desirability bias by conducting and handling the surveys under complete anonymous conditions.

By using hypothetical clinical situations we gained information on the physician's intention to treat, resulting from their integrated knowledge of scientific evidence or guideline recommendations. However, this might differ from actual treatment practices in the daily clinical setting, which is much more influenced by the individual context and patient preferences.[22] Nevertheless, well-constructed clinical case scenarios have demonstrated to reflect the actual clinical behavior of a group of physicians[23, 24] and have the advantage of being much less time and cost consuming and lead to a more straightforward interpretation compared to assessing physician's treatment practices based on medical patient files.[22]

Third, in assessment of the diagnostic strategy for AR and screening for asthma, we asked to indicate the diagnostic modalities of choice from a proposed list and we directly questioned whether or not the participant screened for asthma. This may have forced reply and possibly led to interviewer bias and an increased reporting of routine allergy testing and screening for asthma.

Fourth, in the case scenario section, for every treatment that was not entirely consistent with the ARIA recommendations[4] a score of 0 was attributed. No distinction was made between treatments that deviated 'strongly' or 'slightly' from the guideline recommendations. This stern scoring system probably contributed to the overall low compliance rates.

CONCLUSION

In summary, the ARIA guidelines remain relatively unknown among Flemish GPs. Although GPs are familiar with general concepts about AR, such as the upper-lower airway link, their daily treatment practices often differ from the evidence-based recommendations. More efforts are required to translate scientific evidence into practice and to increase the implementation of evidence-based guidelines adapted to the end-user group and healthcare setting.

REFERENCES

1. Ryan D, van Weel C, Bousquet J, Toskala E, Ahlstedt S, Palkonen S, er al. Primary care: the cornerstone of diagnosis of allergic rhinitis. Allergy 2008;63(8):981-9.
2. Greiner AN, Hellings PW, Rotiroti G, Scadding GK. Allergic rhinitis. Lancet 2011;378(9809):2112-22.
3. Bousquet J, Van Cauwenberge P, Khaltaev N; Aria Workshop Group; World Health Organization. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol 2001;108(5 Suppl): S147-334.
4. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy 2008;63(Suppl 86):8-160.
5. Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. J Allergy Clin Immunol 2010;126(3):466-76.
6. Bousquet J, Bodez T, Gehano P, Klossek JM, Liard F, Neukirch F, Le Gal M, Janin N, Allaf B. Implementation of guidelines for allergic rhinitis in specialist practices. A randomized pragmatic controlled trial. Int Arch Allergy Immunol 2009;150(1):75-82.
7. Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. Eur Respir J 2004;24(5):758–64.
8. Ryan D, Grant-Casey J, Scadding G, Pereira S, Pinnock H, Sheikh A. Management of allergic rhinitis in UK primary care: baseline audit. Prim Care Respir J 2005;14(4):204-9.
9. Bousquet J, Reid J, van Weel C, Baena Cagnani C, Canonica GW, Demoly P, et al. Allergic rhinitis management pocket reference 2008. Allergy 2008;63(8):990-6.
10. Sachs APE, Berger MY, Lucassen PLBJ, Van der Wal J, Van Balen JAM, Verduijn MM. [NHG Standard: allergic and non-allergic rhinitis]. Huisarts Wet 2006;49(5):254-65.
11. Van Hoecke H, Van Cauwenberge P, Thas O, Watelet JB. The ARIA guidelines in specialist practice: a nationwide survey. Rhinology 2010;48(1):28-34.
12. Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud PA, Rubin HR. Why don't physicians follow clinical practice guidelines? A framework for improvement. JAMA 1999;282(15):1458–65.
13. Demoly P, Concas V, Urbinelli R, Allaert FA. Spreading and impact of the World Health Organization's Allergic Rhinitis and its impact on asthma guidelines in everyday medical practice in France. Ernani survey. Clin Exp Allergy 2008;38(11):1803-7
14. Cabana MD, Abu-Isa H, Thyne SM, Yawn B. Specialty differences in prescribing inhaled corticosteroids for children. Clin Pediatr (Phila) 2007;46(8):698-705.

15. Freed GL, Bordley WC, Clark SJ, Konrad TR. Universal hepatitis B immunization of infants: reactions of paediatricians and family physicians over time. Pediatrics 1994;93(5):747-51.

16. Crobach MJ, Hermans J, Kaptein AA, Ridderikhoff J, Petri H, Mulder JD. The diagnosis of allergic rhinitis: how to combine the medical history with the results of radioallergosorbent tests and skin prick tests. Scand J Prim Health Care 1998;16(1):30-6.

17. Adams AS, Soumerai SB, Lomas J, Ross-Degnan D. Evidence of self-report bias in assessing adherence to guidelines. Int J Qual Health Care 1999;11(3):187-192.

18. Choudhry NK, Fletcher RH, Soumerai SB. The relationship between clinical experience and quality of health care. Ann Intern Med 2005;142(4):260-73.

19. Ward MM, Vaughn TE, Uden-Holman T, Doebbeling BN, Clarke WR, Woolson RF. Physician knowledge, attitudes and practices regarding a widely implemented guideline. J Eval Clin Pract 2002;8(2):155-62.

20. Heidrich J, Behrens T, Raspe F, Keil U. Knowledge and perception of guidelines and secondary prevention of coronary heart disease among general practitioners and internists. Results from a physician survey in Germany. Eur J Cardiovasc Prev Rehabil 2005;12(6):521-9.

21. Tan WC, Ait-Khaled N. Dissemination and implementation of guidelines for the treatment of asthma. Int J Tuberc Lung Dis 2006;10(7):710-6.

22. Couraud S, Fournel P, Moro-Sibilot D, Pérol M, Souquet PJ. Are clinical guidelines applied in routine daily practice?: a French regional survey of physicians' clinical practices in lung cancer management (EPOTRA). Clin Lung Cancer 2011;12(5):298-306.

23. Webster BS, Courtney TK, Huang YH, Matz S, Christiani DC. Physicians' initial management of acute low back pain versus evidence-based guidelines. Influence of sciatica. J Gen Intern Med 2005;20(12):1132-5.

24. Carey TS, Garrett J. Patterns of ordering diagnostic tests for patients with acute low back pain. Ann Intern Med 1996;125(10):807-14.

APPENDIX 1: *Treatment recommended by the ARIA guidelines[4] for the 4 fictitious case scenarios (decongestant*: a short course (<10 days) of oral or nasal decongestant; ALT: antileukotriene).*

1	**Patient, currently untreated, is allergic to house dust mite and suffering from rhinorrhea, sneezing and nasal congestion since 2 months. Symptoms impair the quality of sleep.**	
	ARIA classification group	Moderate-severe persistent allergic rhinitis
	Treatment recommended by ARIA guidelines	Nasal corticosteroid ± H1-antihistamine or ALT ± decongestant* ± allergen avoidance
2	**Patient, currently untreated, with symptoms of sneezing, runny nose, red and tearing eyes since 1 month, especially when he's working in the garden. Besides these symptoms, the patient has no complaints.**	
	ARIA classification group	Mild intermittent allergic rhinoconjunctivitis
	Treatment recommended by ARIA guidelines	Oral H1-antihistamine ± decongestant* ± allergen avoidance or Nasal H1-antihistamine or ALT + ocular cromone or H1-antihistamine ± decongestant* ± allergen avoidance
3	**Patient, currently untreated, allergic to birch, is especially suffering from nasal congestion for the last 2 weeks. The patient is having exams and says that he's bothered during studying.**	
	ARIA classification group	Moderate-severe intermittent allergic rhinitis
	Treatment recommended by ARIA guidelines	Oral or nasal H1-antihistamine or ALT ± decongestant* ± allergen avoidance or Decongestant* ± allergen avoidance or Nasal corticosteroid ± decongestant* ± allergen avoidance
4	**Patient with severe symptoms of allergic rhinitis due to house dust mite for many years. Current treatment with oral antihistamine provides insufficient symptom relief.**	
	ARIA classification group	Moderate-severe persistent allergic rhinitis, step-up treatment oral antihistamine
	Treatment recommended by ARIA guidelines	Nasal corticosteroid ± decongestant* ± allergen avoidance or Nasal corticosteroid + oral or nasal H1-antihistamine or ALT ± decongestant* ± allergen avoidance

APPENDIX 2: *Treatment modalities selected in 4 case scenarios of allergic rhinitis. Treatments consistent with the ARIA guidelines[4] are in bold.*

Clinical scenario 1 Selected treatment or combination of treatments	% (n)
AA + OAH1/NAH1 + NCS	**38.3 % (134)**
OAH1/NAH1 + NCS	**16.3% (57)**
AA + OAH1/NAH1 + ODC/NDC + NCS	**9.7% (34)**
AA + NCS	**9.1% (32)**
OAH1/NAH1 + ODC/NDC + NCS	**5.7% (20)**
NCS	**4.6% (16)**
AA + OAH1/NAH1	3.1% (11)
AA + OAH1/NAH1 + ODC/NDC	3.1% (11)
OGCS	1.7% (6)
OAH1/NAH1 + ODC/NDC	1.4% (5)
OAH1/NAH1	1.4% (5)
AA + ODC/NDC + NCS	**0.8% (3)**
IT	0.6% (2)
AA + NCS + ALT	**0.3% (1)**
OAH1 + NCS + ALT +/- AA	0.6% (2)
Other	3.1% (11)
Consistent with ARIA recommendations	**84.8% (297)**

Clinical scenario 2 Selected treatment or combination of treatments	% (n)
OAH1 + NCS +/- TEM +/- AA	32.8% (115)
OAH1 +/- TEM +/- AA	**30.3% (106)**
NCS +/- AA	9.4% (33)
No treatment	6.3% (22)
OAH1 + ODC/NDC + NCS +/- AA	5.7% (20)
AA	3.1% (11)
OAH1 + ODC/NDC +/- TEM +/- AA	**3.1% (11)**
NCS + TEM +/- AA	2.3% (8)
OCS	0.8% (3)
NAH + TEM	**0.6% (2)**
ODC/NDC +/- AA	0.6% (2)
TEM	0.6% (2)
OAH1 + NCS + ALT + /- TEM +/- AA	0.6% (2)
Other	3.7% (13)
Consistent with ARIA recommendations	**34.0% (119)**

Clinical scenario 3 Selected treatment or combination of treatments	% (n)
OAH1/NAH1 + NCS +/- AA	26,6% (93)
OAH1/NAH1 + ODC/NDC + NCS +/- AA	20.8% (73)
NCS +/- AA	**17.7% (62)**
OAH1/NAH1 + ODC/NDC +/- AA	**11.4% (40)**
OAH1/NAH1 +/- AA	**7.4% (26)**
OCS	6.6% (23)
ODC/NDC + NCS +/- AA	**4.6% (16)**
ODC/NDC	**1.7% (6)**
No treatment	1.1% (4)
Other	2.0% (7)
Consistent with ARIA recommendations	**42.8% (150)**

Clinical scenario 4 Selected treatment or combination of treatments	% (n)
AA + NCS +/- OAH1/NAH1	42.6% (149)
NCS +/- OAH1/NAH1	**24.6% (86)**
AA + ODC/NDC + NCS +/- OAH/NAH	**4.8% (17)**
IT	**4.8% (17)**
OGCS	4.6% (16)
AA +/- OAH1/NAH1	**3.4% (12)**
ODC/NDC +/- OAH1/NAH1	**2.3% (8)**
ODC/NDC + NCS +/- OAH1/NAH1	2.0% (7)
NCS + ALT +/- AA	1.1% (4)
ODC/NDC + NCS	0.6% (2)
AA + ODC/NDC +/- OAH1/NAH1	0.6% (2)
NAH1	0.3% (1)
No treatment	0.3% (1)
NCS + OAH1 + ODC + ALT +/- AA	0.6% (2)
Other	7.4% (26)
Consistent with ARIA recommendations	**75.7% (265)**

AA: allergen avoidance
OAH1: oral H1-antihistamine
NAH1: nasal H1-antihistamine,
ALT: antileukotriene,
NCS: nasal corticosteroid
OCS: oral corticosteroid (short course)
ODC: oral decongestant (short course)
NDC: nasal decongestant
TEM: topical eye medication (ocular H1-antihistamine or cromone)
IT: immunotherapy

CHAPTER VII

BURDEN OF ALLERGIC RHINITIS AMONG GENERAL PRACTITIONERS AND IMPACT ON PATIENT MANAGEMENT

THE CURRENT BURDEN OF ALLERGIC RHINITIS AMONG GENERAL PRACTITIONERS AND ITS IMPACT ON PATIENT MANAGEMENT

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ABSTRACT

AIMS

To investigate the burden of allergic rhinitis (AR) among general practitioners (GPs), the impact of AR on GPs' professional lives, and the effect of GPs' personal experience of AR on the management of AR patients.

METHODS

An on-line questionnaire was completed by 1201 GPs (50% AR sufferers) from eight countries.

RESULTS

21% of GPs reported very well controlled symptoms and 66% quite good control. Six hours work per week, on average, were missed by GPs whose AR symptoms resulted in absence. AR symptoms affected concentration, stress level, mood, time spent with patients and physical contact with patients. GPs with AR reported a significantly higher proportion of AR patients in their practice. In the management of their AR patients, they gave a significantly higher ranking to patient requests for specific treatment and emotional well-being of the patient, and a significantly lower ranking to preventing comorbidity development and providing a treatment most likely to result in high patient compliance.

DISCUSSION

This is the first study demonstrating the impact of AR on GPs and showing association with lost productivity, absenteeism and reduction in professional performance. Personal experience of AR might influence GPs' management of AR, but first qualitative research, followed by additional quantitive research is required.

INTRODUCTION

Allergic rhinitis (AR) is a common, symptomatic disorder induced by allergen exposure and is due to an IgE-mediated inflammation of the membranes lining the nose.[1] In 2001, the Allergic Rhinitis and its Impact on Asthma (ARIA) Workshop Group, in collaboration with the World Health Organization (WHO), introduced a new classification which subdivided AR as either intermittent or persistent, and mild or moderate-severe, depending on the duration, severity and impact of symptoms on quality of life **(TABLE 1)**.[1]

Although many sufferers self-treat and seek medical help only when their symptoms become intolerable,[2] AR remains among the top ten reasons for visits to primary care clinics[3] and updated management guidelines have been published by the International Primary Care Respiratory Group (IPCRG)[4]. Several studies have examined the detrimental effects of AR on the working lives of sufferers among the general population,[5-9] but to date there has been no published research investigating the effects of AR symptoms on the professional lives of general practitioners (GPs) themselves.

TABLE 1. *ARIA classification of allergic rhinitis*[1].

Intermittent	Symptoms are present: • Less than 4 days a week • Or for less than 4 weeks
Persistent	Symptoms are present: • More than 4 days a week • And for more than 4 weeks
Mild	None of the following items are present • Sleep disturbance • Impairment of daily activities, leisure and/or sport • Impairment of school or work • Troublesome symptoms
Moderate-severe	One or more of the following items are present: • Sleep disturbance • Impairment of daily activities, leisure and/or sport • Impairment of school or work • Troublesome symptoms

Therefore, the aim of this study was to investigate whether suffering from AR has a negative impact on the professional lives and performance of GPs and to examine if personal experience of AR influences their management of patients with the disease.

METHODS

DESIGN OF THE STUDY

The questionnaire, which was quantitative and devised for on-line completion, was derived from existing and validated questionnaires,[10] with the addition of a number of novel questions covering: demographic details, GPs' personal experience of AR, self-treatment, impact of AR on their working lives as well as their management of patients with AR. In order to test the viability and technical functionality of the electronic questionnaire, 10 pilot online interviews were conducted among GPs who qualified according to the eligibility criteria for the main study as described below. Amendment of the initial questionnaire resulted in a final version **(APPENDIX)**, which consisted of 21 closed questions. GPs were advised that the questionnaire would take approximately 15 minutes to complete, that it would be available for completion for a period of four weeks, and that those who participated would receive a small cash payment for completing the questionnaire. The questionnaire was translated from English into five other languages (French, German, Italian, Portuguese and Spanish), but there was no allowance made for regional variations in English or French.

RECRUITMENT AND ELIGIBILITY OF GPS

In order to ensure sufficiently high numbers of participants from eight countries, GPs were recruited from a panel of healthcare professionals, of all specialties, who were prepared to take part in such studies, but were not pre-selected for health-related or other reasons. The panel was managed by an independent group specializing in healthcare recruitment. All GPs on the panel received a personal invitation and were eligible for inclusion if at the time of participation they were aged 25-65 years, were qualified and currently practising, had been in practice for 2-30 years, and had not participated in research on allergies of any kind in the previous three months.

In order to be able to compare GPs with and without AR, 50% of the total sample from each country had to be AR sufferers and 50% AR non-sufferers. AR status was probably most often self-diagnosed by the GPs. Self-diagnosis by GPs of AR for the purposes of this study reflects normal clinical practice for such conditions.The GPs were also asked to classify their AR into intermittent or persistent according to the ARIA classification, that was outlined in the questionnaire.

The total sample was designed to include 1200 GPs, recruited from eight countries (Australia, Brazil, Canada, France, Germany, Italy, Spain and the UK).

STATISTICAL ANALYSIS

Data were entered into QPSMR software (Wallingford, UK) and tabulated for analysis. Statistical differences were assessed for means using t-testing of two independent sample means. This method was selected as use of a t-test is standard practice in market research when analyzing rating scales. Although the data are not strictly of interval form and often not normally distributed, the t-test was considered robust enough to allow for this. For proportions z-testing of two independent sample proportions was used. Statistical significance was recognized at the 5% level in all cases. For Question 11 of the questionnaire (impact of AR symptoms on ability to perform daily tasks), the following statistical method was used: GPs rated only the symptoms they personally experienced for their impact on ability to perform daily tasks. As the number of symptoms varied for each individual, each symptom was allocated a new rank value on a comparable scale ranging from 1 to 3. The impact of each symptom was determined from its prevalence in the top, middle or bottom third of individual rankings, with symptoms appearing more frequently in the top third than bottom third considered as being more impactful on the GP population suffering from AR as a whole.

RESULTS

DEMOGRAPHICS OF THE STUDY POPULATION

Of the 2817 GPs assessed for eligibility, 894 were unable or unwilling to complete the study. A further 343 GPs did not meet the eligibility criteria. The last 379 GPs were excluded because the pre-specified populations with or without AR had been achieved by the time of their recruitment.

The total study population consisted of 1201 GPs from the eight countries - Australia, Brazil, Canada, France, Germany, Italy, Spain and the UK - with 150 GPs from each, with the exception of Brazil where the online program closed when one extra GP above the required 150 had completed the questionnaire. The mean age of the GPs was 47 years; with 7% aged 25 to 34 years, 29% aged 35 to 44 years, 46% aged 45 to 54 years and 18% aged 55 to 65 years. Seventy three per cent were male and 27% were female. Of the 600 GPs (self-) diagnosed with AR, 70% reported to have intermittent AR, 25% persistent AR and 5% reported having both intermittent AR and persistent AR.

PERCEIVED SYMPTOM CONTROL AMONGST GPS WITH AR

Nasal symptoms of sneezing, and runny, blocked or itchy nose, were the most commonly reported symptoms by GPs **(TABLE 2)**. Both nasal and ocular symptoms were reported by 55% (n=326) of the GPs, 41% (n = 248) had nasal symptoms only, and 1% (n = 5) ocular symptoms only.

Oral antihistamines were the most frequently used treatment (66%), followed by nasal corticosteroids (44%), environmental control measures (29%) and nasal decongestants (26%) **(TABLE 3)**. GPs using oral antihistamines were significantly more likely to report that their AR symptoms were quite or very well controlled than quite or very poorly controlled ($p = 0.037$). GPs using environmental control measures or nasal decongestants were significantly less likely to report that their symptoms were quite or very well controlled than quite or very poorly controlled ($p = 0.013$ for environment control measures; $p < 0.0001$ for nasal decongestants). Overall, 21% of GPs considered their symptoms to be very well controlled and 66% reported quite good control. No significant difference in the perception of the level of symptom control was demonstrated between GPs with nasal symptoms only and GPs with both nasal and ocular symptoms and the results obtained for symptom control were very similar between countries (data not displayed).

TABLE 2. *Symptoms reported by GPs with AR (when not taking medication).*

Symptoms suffered	Percentage of GP AR sufferers (n=600)
Sneezing	72%
Runny nose	66%
Blocked nose	59%
Itchy nose	58%
Itchy/red eyes	45%
Watery eyes	39%
Post nasal drip	33%
Itchy palate	29%
Cough	26%
Headache	23%
Snoring	22%
Sinus pressure	21%
Waking at night	19%
Sore throat	17%
Wheezing	15%

TABLE 3. *Treatment use and symptom control reported by GPs with AR.*

Treatment type	All GPs (n=600)	Symptom control reported by GPs: Very poorly controlled (n=8)	Quite poorly controlled (n=69)	Quite well controlled (n=371)	Very well controlled (n=116)
Oral antihistamines	66%	63%	59%	72%	69%
Nasal corticosteroids	44%	75%	43%	46%	49%
Environmental control	29%	63%	41%	32%	20%
Nasal decongenstants	26%	63%	45%	27%	16%
Oral decongestants	19%	63%	25%	21%	12%
Nasal antihistamines	14%	25%	14%	16%	9%
Asthma treatments	13%	25%	19%	13%	13%
Ocular antihistamine	12%	13%	13%	14%	9%
Oral corticosteroids	8%	13%	6%	9%	8%
Ocular cromone	6%	13%	9%	6%	4%
Immunotherapy (referral)	5%	25%	4%	4%	6%
None of the above	6%	N/A	N/A	N/A	N/A

EFFECTS OF AR SYMPTOMS ON GPS' PROFESSIONAL LIVES

27% of GPs said their AR symptoms resulted in absence from work, late arrival or early departure. This group reported an average of six hours work missed per week during a typical week encountering AR symptoms.

GPs reporting very good symptom control were significantly more likely to report no time lost from work compared with those reporting very poor control (85% versus 50%; p = 0.010). The results indicated that, compared to those who were not self-employed, self-employed GPs were significantly less likely to miss work (p = 0.022) and also missed significantly fewer hours of work a week during a week of symptoms (0.8 hours versus 1.8 hours; p = 0.001) due to AR, although this was independent of the level of symptom control. Compared with nasal symptoms alone, the presence of both ocular and nasal symptoms was also significantly associated with time missed from work (23% versus 31%; p = 0.031).

Ability to perform daily tasks was affected most by runny or blocked nose and itchy red eyes. GPs reported that their AR symptoms moderately or considerably affected their concentration (31%), stress level (31%), general mood when dealing with patients (28%), level of physical contact with patients (22%), time spent with each patient (18%) and the number of patients that they saw (16%) **(TABLE 4)**.

TABLE 4. *Effect of AR symptoms on the ability of GPs to perform daily tasks.*

Task	Percentage of GPs reporting effect of AR on ability to perform daily tasks (n=600): No effect	Limited effect	Moderate effect	Considerable effect
Concentration	32%	37%	23%	8%
Number of patients seen	59%	26%	12%	4%
Time with patient	50%	33%	14%	4%
Level of physical contact with patient	42%	36%	16%	6%
Stress	39%	31%	22%	9%
Mood	33%	39%	21%	7%

INFLUENCE OF PERSONAL EXPERIENCE OF AR ON GPS' MANAGEMENT OF AR PATIENTS

The mean reported prevalence of AR patients in the GPs' practice populations was 16.5% (with a mean estimated distribution of 66% patients with intermittent AR and 34% with persistent AR), though there was a wide variation in the reported prevalence. GPs with AR reported a slightly, but significantly, higher mean proportion of AR patients in their practice than those not suffering from AR (17.7% and 15.3% respectively; p = 0.015). Results were broadly similar between countries, although GPs from Brazil did report a higher proportion of patients suffering from persistent AR (40%) compared to the other countries (30%-35%).

Awareness of the ARIA guidelines was not significantly affected by the GPs AR status or classification type, with 41% being unaware of the guidelines and 29% stating that they preferred to treat patients' individual needs irrespective of the guidelines. GPs from Australia (46.9%), Canada (44.7%) and the UK (49.3%) were significantly more likely to be unaware of the ARIA guidelines when compared to the other countries. Only 3% of all of the GPs stated to follow the guidelines for all AR patients, with a further 27% reporting to base their management on the guidelines, but adapting them according to the individual patient.

The results of the questionnaire indicated that the relative importance given by GPs to patient-relevant factors of AR treatment was very similar between GPs with and without AR, for example improvement in their AR patients' overall quality of life was the most important patient-relevant factor to all physicians **(TABLE 5)**. Some significant differences were, however, highlighted. Compared to GPs without AR, those with the disease gave a significantly higher ranking to patients' requests for a specific treatment ($p = 0.011$) and emotional well-being ($p = 0.008$), and a significantly lower ranking to preventing the onset or development of comorbidities ($p < 0.0001$) and providing a treatment most likely to result in high patient compliance ($p = 0.005$).

When considering treatment attributes, the two groups were also similar with safety and effectiveness being the most important for all GPs. However, some specific differences were again identified, for example GPs with AR ranked treatment costs to their practice or state health service slightly, but significantly, higher than GPs without AR ($p = 0.012$) **(TABLE 6)**, although the cost of treatment did not rank highly when compared to some other treatment attributes for both GPs suffering with AR and those without the disease.

TABLE 5. *Importance to GPs (with and without AR) of patient-relevant factors of AR treatment (the lower score indicates the higher level of importance).*

	Importance to GPs of patient-relevant factors		
Patient-relevant factors of treatment	Total (n=1201)	AR sufferer (n=600)	Non AR sufferer (n=601)
Improving patient quality of life	2.1	2.2	2.0
Providing a treatment most likely to result in high patient compliance	3.5	3.6	3.3
Preventing the onset of or development of comorbidities of AR	3.5	3.8	3.3
Patient emotional well being	5.0	4.8	5.1
Providing affordable treatment for patients	5.2	5.2	5.1
Demands on patients from their professional lives	5.3	5.2	5.4
Demands on patients from their personal lives	5.5	5.5	5.6
Patient requests for specific treatment	5.9	5.8	6.1

TABLE 6. *Importance to GPs (with and without AR) of AR treatment attributes (the lower score indicates the higher level of importance)*

	Importance to GPs of treatment attributes		
Treatment attributes	Total (n=1201)	AR sufferer (n=600)	Non AR sufferer (n=601)
Reduction of symptom severity	2.6	2.7	2.6
Safety /side effects	3.5	3.6	3.5
Speed of onset of action	4.0	4.1	4.0
Experience of GP with the treatment	4.7	4.6	4.7
Ease of administration	4.8	4.8	4.9
Duration of action	5.0	4.9	5.0
Guideline recommendation	6.0	6.0	6.0
Treatment cost to practice or state health service	7.0	6.8	7.1
Formulary recommendation	7.3	7.4	7.3

When using monotherapy to treat mild AR, all GPs were most likely to recommend or prescribe oral antihistamines (64%) as their first-choice treatment. GPs without AR, however, were significantly more likely to recommend environmental control measures (53% versus 38% of GPs with AR; $p < 0.0001$), a nasal antihistamine (29% versus 19%; $p = 0.0001$), and a nasal decongestant (28% versus 22%; $p = 0.010$). There was no difference between GPs with and without AR in their first-choice monotherapy for moderate-severe AR, which was equally likely an oral antihistamine (54%) or a nasal corticosteroid (52%). Compared to GPs with AR, GPs without the disease were significantly more likely to recommend a nasal corticosteroid (55% versus 48%; $p = 0.009$), a nasal decongestant (23% versus 17%; $p = 0.003$) and environmental control measures (33% versus 27%; $p = 0.001$).

There was no difference between GPs with and without AR in their choice of combination therapy for either mild or moderate-severe AR. Significantly fewer GPs would prescribe or recommend combination therapy for mild AR than for moderate-severe AR (93% versus 99%; $p < 0.0001$). GPs using combination therapy for mild AR suggested over 300 different combinations but, the most frequent choice (by 15% of GPs; n=177) was an oral antihistamine plus a nasal corticosteroid. GPs chose over 450 different combinations for moderate-severe AR, but again the most frequent combination (recommended or prescribed by 9% of GPs; n=112) was an oral antihistamine plus a nasal corticosteroid.

DISCUSSION

EFFECTS OF AR ON GPS' WORKING LIVES

This is the first study to examine the impact of AR on the lives of GPs. It shows that AR is associated with lost productivity, work absenteeism and presenteeism (present at work, but not fully functioning), similar to AR sufferers in the general population.[5-9]

Over one quarter of GPs with AR reported losing an average of six hours of work a week during a typical week of AR symptoms. Yet, those who did not miss work also reported detrimental effects on their professional effectiveness during their contact with patients. The study indicated an association between AR symptoms, symptom control and lost productivity, and that effective control of AR symptoms significantly reduced the likelihood of absence from work. There was a significant association between self-employment status and continuing presence at work by GPs, although this was not influenced by AR symptom severity. This reflects research in the general European population, demonstrating relatively low rates of absenteeism among self-employed sole traders and small employers despite their higher rates of stress and fatigue compared to employed individuals.[11] Self-employment status was, however, less influential than AR symptom control, and so the burden of AR symptoms appears to be a more important contributor to absenteeism among GPs in our study.

INFLUENCE OF GPS' PERSONAL EXPERIENCE OF AR ON THEIR MANAGEMENT OF AR PATIENTS

This is the first study to show that personal experience of AR influences GPs' management of patients with the disease. All GPs aim to provide the most effective treatment for their patients, but those with AR assigned a higher ranking to patients' requests for a specific treatment and their emotional well-being. It was therefore surprising that, when choosing a specific treatment, GPs with AR appeared to be more influenced than their colleagues without AR by costs to the practice or state health service. Although significant, the difference between the two groups remained small, and cost was still a relatively minor consideration compared to the main influences of effectiveness and safety.

The results also suggest that personal experience of AR may improve a GP's ability to recognize the disease amongst their patients, since the AR patient population was slightly, but significantly, higher for GPs with AR compared to those without AR. It remains unclear whether this was due to GPs' greater awareness of the disease and superior diagnostic abilities, or because AR patients were more likely to consult them. GPs with AR were significantly less likely than GPs without the disease to recommend a nasal antihistamine, a nasal decongestant or environmental control measures, possibly because of less favorable personal experience with these interventions and classes of drug. Further explanations

could be the cost implications of these therapies or that environment control measures can be complicated, time-consuming, costly and not always practical to incorporate into everyday life.

In contrast, personal experience of AR did not influence GPs' most frequent first choice of monotherapy or combination therapy in either mild or moderate-severe AR. There is similarly no indication that GPs with AR are more likely to incorporate current evidence-based guidelines into their clinical practice when treating either themselves or their AR patients. Indeed, it is remarkable GPs with AR were less likely than GPs without AR to recommend a nasal corticosteroid, the most effective treatment for moderate-severe AR.

Some GPs may have been following the ARIA guidelines without being aware of the fact, since the guidelines' provisions have been included in national AR guidelines in some of the countries included in the study. Previous studies have, however, also demonstrated suboptimal management of AR patients in primary care[12,13] and GPs' lack of awareness of, or adherence to the ARIA guidelines is confirmed in our study by their low ranking of guideline recommendations, first-line choice of treatment and the hundreds of reported therapy combinations.

LIMITATIONS OF THE STUDY

The results of this survey are based on self-reports and personal estimations of the participating GPs, which obviously can differ from actual figures and practice habits.

The study population was drawn from a panel of healthcare professionals, with no special interest in AR, but willing to be involved in research. This method, rather than approaching the general population of healthcare professionals, was employed in order to obtain the large study population required by the study and to provide the wide geographical spread of countries, but may have induced bias as this population might not entirely be representative for the general population of GPs.

The balance between persistent AR and intermittent AR in our study is equivalent to that in the general population,[1, 15] but the preponderance of male GPs (73% versus 27% female) does not reflect the epidemiology of AR, and is greater than the mean of 62% amongst GPs in the countries included in the study (data unavailable in Brazil).[16] In the general population, women are absent from work more often than men in similar employment[17] but, since gender was not included in the eligibility criteria for our study, it is not possible to conclude that gender imbalance led us to underestimate AR-related absenteeism among the GPs in our study.

Some subsets of the total large study population, for example AR sufferers whose symptoms were poorly controlled, were very small resulting in a low sample base for that group of GPs.

This study only provides a first snapshot of the influence of AR on the professional lives of healthcare providers and the impact on the management of patients suffering from the same disease. In order to enable more detailed investigation qualitative research is also needed to resolve important questions highlighted by our study, including the reasons for GPs' choice of treatment, the influence of personal experience of AR symptoms on the management of their patients with AR, and their attitudes to the use of evidence-based guidelines when managing their own and their patients' AR.

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REFERENCES

1. Bousquet J, Van Cauwenberge P, Khaltaev N, ARIA Workshop Group, World Health Organisation. AR and its impact on asthma. J Allergy Clin Immunol 2001;108(Suppl 5):S147-334.
2. Maurer M, Zuberbier T. Undertreatment of rhinitis symptoms in Europe: findings from a cross-sectional survey. Allergy 2007;62(9):1057-63.
3. Gregory C, Cifaldi M, Tanner LA. Targeted intervention programs. Creating a customized practice model to improve treatment of allergic rhinitis in a managed care population. Am J Managed Care 1999;5(4):485-96.
4. Price D, Bond C, Bouchard J, Costa R, Keenan J, Levy M, et al. International Primary Care Respiratory Group (IPCRG) Guidelines: Management of allergic rhinitis. Primary Care Respiratory Journal. 2006;15(1):58-70.
5. Burton WN, Conti DJ, Chen CY, Schultz AB, Edington DW. The impact of allergies and allergy treatment on worker productivity. J Occup Environ Med 2001;43(1):64-71.
6. Kessler RC, Almeida DM, Berglund P, Stang P. Pollen and mold exposure impairs the work performance of employees with allergic rhinitis. Ann Allergy Asthma Immunol 2001;87(4):289-95.
7. Lamb CE, Ratner PH, Johnson CE, Ambegaonkar AJ, Joshi AV, Day D, et al. Economic impact of workplace productivity losses due to allergic rhinitis compared with select medical conditions in the United States from an employer perspective. Curr Med Res Opin 2006;22(6):1203-10.
8. Shedden A. Impact of nasal congestion on the quality of life and work productivity in allergic rhinitis: findings from a large online survey. Treat Respir Med 2005;4(6):439-46.
9. Szeinbach SL, Seoane-Vasquez EC, Beyer A, Williams PB. The impact of rhinitis on work productivity. Prim Care Respir J 2007;16(2):98-105.
10. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics 1993;4(5):353-65.
11. Benavides FG, Benach J, Diez-Roux, Roman C. How do types of employment relate to health indicators? Findings from the Second European Survey on Working Conditions. J Epidemiol Community Health 2000;54(7):494-501.
12. Ryan D, Grant-Casey J, Scadding G, Pereira S, Pinnock H, Sheikh A. Management of allergic rhinitis in UK primary care: baseline audit. Prim Care Respir J 2005;14(4):204-9.
13. Scadding GK, Richards DH, Price MJ. Patient and physician perspectives on the impact and management of perennial and seasonal allergic rhinitis. Clin Otolaryngol Allied Sci 2000;25(6):551-7.

14. Bachau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. Eur Respir J 2004;24(5):758-64.

15. Bauchau V, Durham SR. Epidemiological characterization of the intermittent and persistent types of allergic rhinitis. Allergy 2005;60(3):350-3.

16. European Pharmaceutical Market Research Association - Doctor Universe Statistics In Major Markets. http://www.ephmra.org/PDF/Dr%20Universereportpdf19December03.pdf

17. Mastekaasa A, Olsen KM. Gender, absenteeism and job characteristics. Work Occupation 1998;25(2):195-228.

APPENDIX: GENERAL PRACTITIONERS' STUDY ONLINE QUESTIONNAIRE *All GPs answered questions 1-8 and 16-21, while questions 10-15 were answered only by GPs with AR.*

SECTION 1: RESPONDENT PROFILE (ALL RESPONDENTS)

1. Which, if any, of the following areas have you participated in any market research on within the past 3 months?

☐ Asthma
☐ Allergies
☐ Acid-peptic disorders and treatments
☐ Emollients and antipruritics
☐ Diabetes
☐ Oncology

2. Are you male / female?

3. What is your age?

4. How many years have you been practicing as a general practitioner?

5. What is your current working status? Please check as many boxes as are applicable.

☐ Full-time ☐ Part-time ☐ Retired ☐ Self-employed ☐ Other

6 How many hours do you normally work in a week?

7 How many other general practitioners are there in the practice in which you work?

8 Approximately, how many patients do you have on your personal list?

SECTION 2: GP AR SUFFERERS (ALL RESPONDENTS)

9. We would now like to ask you about your own experience of any of the following symptoms. Which, if any, of the following do you suffer from?

☐ Intermittent allergic rhinitis (IAR)
☐ Both IAR and PER
☐ Persistent allergic rhinitis (PER)
☐ None of the above

10 Thinking about allergic rhinitis (AR), which, if any, of the following do you suffer from when not taking AR medication?

☐ Cough
☐ Itchy palate
☐ Itchy / red eyes
☐ Sore throat
☐ Runny nose
☐ Snoring as a result of any of the above
☐ Headache
☐ Blocked nose
☐ Sneezing
☐ Itchy nose
☐ Waking up in the night as a result of any of the above
☐ Wheezing
☐ Post nasal drip
☐ Watery eyes
☐ Sinus pressure

11 For each of the symptoms you've mentioned, please rank this in order of the degree of impact they have on your ability to perform your daily tasks, where 1 means this symptom has the most impact.

☐ Cough
☐ Watery eyes
☐ Post nasal drip
☐ Sore throat
☐ Itchy palate
☐ Sinus pressure
☐ Headache
☐ Runny nose
☐ Itchy / red eyes
☐ Sneezing
☐ Blocked nose
☐ Snoring
☐ Wheezing
☐ Itchy nose
☐ Waking up in the night

12 Which, if any, of the following do you use to treat these symptoms that you experience?

- ☐ Oral antihistamine
- ☐ Oral decongestant
- ☐ Oral corticosteroid
- ☐ Ocular antihistamine
- ☐ Ocular cromone
- ☐ Nasal antihistamine
- ☐ Nasal decongestant
- ☐ Nasal corticosteroid
- ☐ Referral for diagnostics / possible immunotherapy
- ☐ Treatment for asthma
- ☐ Environmental control measures e.g. lifestyle changes

13 How well do you feel your symptoms are controlled with this medication?

- ☐ Not at all well controlled
- ☐ Not very well controlled
- ☐ Quite well controlled
- ☐ Very well controlled

SECTION 3: IMPACT ON WORK FOR GP AR SUFFERERS (AR SUFFERERS ONLY)

14 For this next question, please think about a week when you typically encounter the symptoms you have described experiencing yourself.

During this week, how many hours did you miss from work because of these problems typically associated with these symptoms? Please include hours you missed on sick days, times you went in late, left early etc. because of these symptoms.

Hours missed in a week because of these typical symptoms

15 To what extent do these symptoms affect you in the following ways?

		My symptoms affect me considerably	My symptoms affect me moderately	My symptoms affect me to a limited extent	My symptoms do not affect me at all
a	My concentration at work				
b	The number of patients I see				
c	The time I spend with each patient				
d	My level of physical patient contact (e.g. touching, handling)				
e	My stress level at work				
f	My general mood when dealing with patients				

SECTION 4: IMPACT ON PATIENT MANAGEMENT (ALL RESPONDENTS)

16 A. Of all your patients, approximately what percentage has any form of allergic rhinitis?

B. And of all your patients with allergic rhinitis, what percentage has intermittent allergic rhinitis and what percentage of patients have persistent allergic rhinitis?

Percentage of patients with intermittent allergic rhinitis (IAR)

Percentage of patients with persistent allergic rhinitis (PER)

17 To what extent do you follow the ARIA-guidelines in the treatment of allergic rhinitis?

- ☐ I follow them for all AR patients
- ☐ I base the management my AR patients on these guidelines and I adapt according to the individual situation
- ☐ I prefer not to treat patients' individual needs irrespective of the ARIA-guidelines
- ☐ I am not aware of the ARIA-guideline

18 Please rank the following factors in order of importance to you, where 1 is the most important to you and 8 is the least important to you

- ☐ Improving patients' overall quality of life
- ☐ Preventing the onset or development of comorbidities of allergic rhinitis (AR) e.g. asthma
- ☐ Providing a treatment that is most l likely to result in high patient compliance
- ☐ Patient requests for specific treatment
- ☐ Providing affordable treatments for patients
- ☐ Demand on patients' personal lives e.g. family commitments
- ☐ Demands on patients' professional lives
- ☐ Patients' emotional well-being

19 A. Which of the following treatments, if any, would you prescribe or recommend as a <u>monotherapy</u> for a patient with *mild* AR?

Please indicate any treatments you would prescribe or recommend as stand alone treatment for *mild* AR.

- ☐ Environmental control measures e.g. lifestyle changes
- ☐ Oral antihistamine
- ☐ Oral decongestant
- ☐ Oral corticosteroid
- ☐ Nasal antihistamine
- ☐ Nasal decongestant
- ☐ Nasal corticosteroid
- ☐ Ocular antihistamine
- ☐ Ocular cromone
- ☐ (Referral for) immunotherapy
- ☐ Intramuscular corticosteroid treatment
- ☐ Ocular decongestant
- ☐ Ocular corticosteroid
- ☐ I would not recommend any stand-alone treatment for a patient with mild AR
- ☐ I would not recommend any treatment for a patient with mild AR

B. Which of the following treatments, if any, would you prescribe or recommend as a <u>combination</u> therapy for a patient with *mild* AR?

Please indicate which <u>2 or more treatments</u> that you would typically prescribe or recommend in combination for a patient with *mild* AR.

- ☐ Environmental control measures e.g. lifestyle changes
- ☐ Oral antihistamine
- ☐ Oral decongestant
- ☐ Oral corticosteroid
- ☐ Nasal antihistamine
- ☐ Nasal decongestant
- ☐ Nasal corticosteroid
- ☐ Ocular antihistamine
- ☐ Ocular cromone
- ☐ (Referral for) immunotherapy
- ☐ Intramuscular corticosteroid treatment
- ☐ Ocular decongestant
- ☐ Ocular corticosteroid
- ☐ I would not recommend any combination treatment for a patient with mild AR

20 **A. Which of the following treatments, if any, would you prescribe or recommend as a monotherapy for a patient with *moderate-severe* AR?**

Please indicate any treatments you would prescribe or recommend as stand alone treatment for *moderate to severe* AR.

- ☐ Environmental control measures e.g. lifestyle changes
- ☐ Oral antihistamine
- ☐ Oral decongestant
- ☐ Oral corticosteroid
- ☐ Nasal antihistamine
- ☐ Nasal decongestant
- ☐ Nasal corticosteroid
- ☐ Ocular antihistamine
- ☐ Ocular cromone
- ☐ (Referral for) immunotherapy
- ☐ Intramuscular corticosteroid treatment
- ☐ Ocular decongestant
- ☐ Ocular corticosteroid
- ☐ I would not recommend any stand-alone treatment for a patient with *moderate-severe* AR
- ☐ I would not recommend any treatment for a patient with *moderate-severe* AR

B. Which of the following treatments, if any, would you prescribe or recommend as a combination therapy for a patient *moderate to severe* AR?

Please indicate which 2 or more treatments that you would typically prescribe or recommend in combination for a patient with *moderate-severe* AR.

- ☐ Environmental control measures e.g. lifestyle changes
- ☐ Oral antihistamine
- ☐ Oral decongestant
- ☐ Oral corticosteroid
- ☐ Nasal antihistamine
- ☐ Nasal decongestant
- ☐ Nasal corticosteroid
- ☐ Ocular antihistamine
- ☐ Ocular cromone
- ☐ (Referral for) immunotherapy
- ☐ Intramuscular corticosteroid treatment
- ☐ Ocular decongestant
- ☐ Ocular corticosteroid
- ☐ I would not recommend any combination treatment for a patient with *moderate-severe* AR

21 **Please rank the following treatment attributes in order of importance to you when considering treatment options for patients suffering from allergic rhinitis. 1 means this treatment attribute is most important to you and 9 means this treatment attribute is least important to you.**

- ☐ Reduction of symptom severity
- ☐ Duration of action
- ☐ Speed of onset of action
- ☐ Safety / side effects
- ☐ Ease of administration
- ☐ Treatment cost to your practice or state health service
- ☐ Your experience with the treatment
- ☐ Guideline recommendation
- ☐ Formulary recommendation

CHAPTER VIII

DISCUSSION AND FUTURE PERSPECTIVES

PART 1
DISCUSSION

Allergic rhinitis (AR) is the most common chronic respiratory disease. If poorly controlled, the disease is known to result in significant disease morbidity and reduced quality of life (QOL). It can lead to the development or exacerbation of comorbidities and has important economic consequences.

In 2001, the first ARIA guidelines[1] for AR were published to assist physicians in ameliorating the management of their patients by providing them with a guide for optimal clinical practices, based on a systematic review of the available evidence about the diagnostic and treatment options for AR. The main goal of this thesis was to assess the impact of the ARIA guidelines on clinical practice.

We started this work by a critical review of the ARIA guidelines **(CHAPTER 2)**. In this review, also the latest ARIA 2010 guideline, that was developed using the GRADE methodology,[2] was included. The advantages of the GRADE approach are that it focuses on outcomes that are important to patients, explicitly considers patient values and preferences, uses a systematic approach to collecting the evidence, clearly separates the quality of evidence and the strength of recommendations, and transparantly reports the decision process.[3] This GRADING of recommendations seems to better reflect the way clinicians make decisions and to come closer to the individual patient's needs. On the other hand, it leaves much more place for individual interpretation and judgement and does not provide a framework that eliminates disagreements in interpreting evidence and in deciding on the best among alternative courses of action, making them also very difficult to implement when evaluating or auditing clinical practice.[4] The ARIA 2010 guideline, furthermore, only addressed a limited number of clinical questions and recommendations on additional questions e.g. covering the outcome of combination treatments and step-up or step-down regimens should be prioritized. The ARIA 2010 guideline, however, was not included in the further scope of this work, as it was not yet available when we performed our surveys.

At present, no guideline for AR has been subjected to an independent quality appraisal according to the validated AGREE instrument,[5] and there is a urgent need to perform such a systematic analysis. Based on our updated review,[6] however, we can assume that the ARIA 2001[1] and 2008 guidelines,[7] that were used in our surveys, meet the quality domains defined by AGREE as 'purpose and scope', 'stakeholder involvement' and 'editorial independence'.

When we consider their 'rigour of development', we can conclude that systematic methods were used to describe evidence and that the criteria for selecting evidence, the strengths and limitations of the body of evidence are clearly described. The practical treatment recommendations of the ARIA guidelines, on the other hand, are formulated as a stepwise treatment algorithm, based on a new classification for AR, developed by the ARIA working group. As the collected evidence underlying the therapeutic choices is mainly based on trials that were carried out before the new classification for AR, there is no explicit link between the treatment algorithm and the supporting evidence. Furthermore, although the

shortcomings of the previous AR classification, based on the time of exposure to the offending allergen(s), were extensively described in the ARIA Workshop Report,[1] the new ARIA classification, based on the duration of symptoms and their impact on QOL was developed empirically and based on expert consensus and had not been evaluated and validated in a patient population prior to the publication of the ARIA guidelines.

The AGREE collaboration also emphasizes that the implementability of a guideline should already be anticipated on at the time of the development of the guideline by ensuring a clear presentation of the guideline recommendations and considering the applicability of the guideline. The latter, however, was not clearly addressed in the ARIA reports and, still very little is known about the implementation of the ARIA guidelines and factors that may influence this process.

Assessment of the ARIA classification in a large patient population and evaluation of the implementation of the ARIA guidelines by general practitioners and specialists were the 2 main topics of this thesis, resulting in some interesting conclusions and hypotheses, but also raising additional questions and opening future research perspectives. The discussion on 'the ARIA classification for allergic rhinitis' and 'the implementation of the ARIA guidelines for allergic rhinitis' will separately be addressed in this chapter.

THE ARIA CLASSIFICATION FOR ALLERGIC RHINITIS

In **CHAPTER 3** we classified a large AR patient population, recruited in general practice and untreated at the time of presentation, according to the ARIA classification. Similar to previous studies performed in the general population[8] and in medical practice[9], we found that the classification of AR into persistent and intermittent AR is not synonymous and interchangeable with the former classification into seasonal and perennial AR, and that intermittent and persistent AR represent distinct disease categories in terms of clinical symptoms, impact on QOL and recommended therapeutic management.

We, however, were the first to report that not only the classification of AR based on duration of symptoms, but also the gradation of severity, based on impact on 4 health-related QOL items (1. sleep disturbance, 2. impairment of daily activities, leisure and/or sport, 3. impairment of school or work, 4. troublesome symptoms; see definitions) into mild and moderate-severe in an untreated patient population (see definitions of ARIA classification) has significant discriminating capacity, supporting its validity to stratify AR patients. This was confirmed in other large clinical trials conducted in general and specialist practice, but mostly including both treated and untreated patients. These studies also analyzed the ARIA grading for disease severity and reported significantly higher prevalence[10, 11] and severity[12, 13] of nasal and non-nasal AR symptoms and visual analogue scale (VAS) scores for disease severity,[12-14] significantly reduced outcome on validated QOL,[12, 14] sleep[11]

and work performance[11] questionnaires, and increased asthma prevalence[11, 12] in the moderate-severe compared to the mild AR patient group.

On the other hand, we noted a clear disproportion in the distribution of patients graded as mild or moderate-severe among our patient population, with almost 90% classified as moderate-severe. Other epidemiological trials performed in general and specialist practice[10, 11, 13] reported a similar high proportion of patients classified with moderate-severe AR, raising the question whether this large group of patients with moderate-severe AR does not demonstrate wide heterogeneity in disease severity and whether it would not be beneficial to further stratify this severity gradation into two separate moderate and severe AR groups.

In **CHAPTER 4** we made a proposition to adapt the ARIA classification of AR severity by differentiating 3 severity categories: mild, moderate, severe. In our model, the definition of AR severity was in many ways very similar to the original ARIA definition, but we omitted one of the 4 QOL items from the original ARIA classification, namely the absence or presence of troublesome symptoms, as this was found to be the least discriminative, and combined the 2 QOL items assessing the impact on the daily life into 1 item, resulting in following definitions:

- 'Mild' AR: symptoms of AR cause no sleep disturbance and no impairment of daily personal (daily activities, leisure, sports) and/or professional (school, work) life
- 'Moderate' AR: symptoms of AR cause sleep disturbance or impairment of daily personal (daily activities, leisure, sports) and/ or professional (school, work) life
- 'Severe' AR: symptoms of AR cause sleep disturbance and impairment of daily personal (daily activities, leisure, sports) and/or professional (school, work) life

When applying this 'modified' ARIA classification in our patient group of 804 patients, 20.5% of our patients were classified with mild AR, 45.9% with moderate AR and 33.6% with severe AR. A significant linear increasing trend in severity scores of all assessed symptoms, except rhinorrhea, was found from mild to moderate to severe AR and the degree of allergy testing and prescription of nasal and oral corticosteroids significantly increased with increased AR severity category.

Demoly et al applied our modified ARIA severity classification to a large AR patient group (n=5140) recruited in French general and specialist practice and classified them as 'mild', 'moderate' or 'severe' according to our definitions resulting in 48.6% patients classified as moderate and 44.4% as severe.[15] For the prevalence of nasal and eye symptoms the mild and moderate group were found to be very similar (with overlap of the 95% confidence interval), compared to the severe group that demonstrated significantly more nasal obstruction,

loss of olfaction and eye symptoms (watering, itching and redness). The severe group also demonstrated significantly more lung symptoms (cough, wheezing), pharyngeal irritation, fatigue and headache than the moderate group, which in turn reported significantly more wheezing, pharyngeal irritation and fatigue than the mild group. None of the nasal or non-nasal symptoms were more prevalent in the mild than in the moderate group or in the moderate group compared to the severe group. Furthermore, a significant increase in use of oral corticosteroids was noted in the moderate compared to the mild group and in the severe compared to the moderate group. Although the authors concluded that the observed statistical differences were mainly because of the very large sample size and that no clear clinically relevant trends were observed to support the need for a distinction between mild, moderate and severe AR patients, the main goal of our proposed 'modified ARIA severity classification' was to further differentiate the large group of patients with moderate-severe AR. From this perspective we dare to conclude that the observed increased prevalence of almost all assessed non-nasal symptoms and the higher use of oral corticosteroids in the severe compared to the moderate group support the idea that the moderate-severe group, as defined by the original ARIA classification, demonstrates significant internal heterogeneity in disease severity. Furthermore, it needs to be noted, that the large patient group from Demoly[15] was assessed for the presence of symptoms and not for the severity of symptoms, as in our patient group, making both studies difficult to compare.

Shortly after publication of our proposition of a modified ARIA severity classification, Valero et al[16] also reported substantial heterogeneity in terms of nasal symptom scores and QOL impairment in a group of 141 untreated moderate-severe AR patients, recruited in specialist practice, and formulated a proposal to differentiate moderate from severe AR, that, however, was different from our proposal. Based on a linear regression model, they measured a significant effect from the number of affected ARIA-QOL domains on nasal symptom and QOL scores, with the clearest distinction between patients that were affected with 4 versus 3, 2 or 1 items. The latter criterion was used to define respectively severe and moderate AR. No change was proposed to the definition of mild AR. The group of Valero performed validation studies of their modified ARIA severity classification in a large group of untreated pediatric AR patients (n=1269), recruited in specialist practice, [17] and a large group of untreated (1058) and treated (1066) adult AR patients, recruited in general and specialist practice.[18] In the pediatric patient group the modified ARIA severity classification was found to be useful to discriminate severe (30.5% of patients) from moderate (59.5% of patients) from mild AR (10% of patients) with significantly worse T4SS (Total 4 Symptom Scores) and VAS scores for disease severity in the severe compared to the moderate and moderate compared to mild group. Also in both the untreated (with 17.8%, 63.1% and 19.1% classified as respectively mild, moderate and severe) and treated adult AR patient group (with 8.9%, 62.2% and 28.9% classified as respectively mild, moderate and severe) the modified ARIA severity classification proved to have discriminative value with significantly worse T4SS among the different severity grades and QOL scores (assessed with the validated AR-specific ESPRINT-15 questionnaire) in the severe compared to the moderate and the moderate compared to the mild AR group.

CONCLUSIONS AND UNANSWERED QUESTIONS

We can conclude that the moderate-severe AR patient group, as defined by ARIA, represents a very large proportion of the patients presenting in medical practice and undoubtedly encompasses heterogeneity in disease severity.

Proposals by our group and by the group of Valero have been made to differentiate moderate from severe AR. Our proposed 'modified AR severity gradation' was applied on our own patient group, recruited in general practice, and by Demoly et al[15] on a large patient group and has shown to have discriminative value between the 'modified' mild, moderate and severe group in terms of severity and prevalence of several nasal and paranasal symptoms and (suggested) medical treatment practices. On the other hand, we acknowledge that further assessment of this classification and its discriminative impact on validated symptom and QOL scores is required.

In contrast to our proposal, the modified AR severity classification by Valero[16] did not alter the definition of mild AR and preserved the 4 ARIA-QOL items, which might be an advantage, as the original ARIA classification was widely distributed and less change might have beneficial effects in acceptance of a modification. Furthermore, Valero validated the stratification of moderate and severe AR in both an adult and pediatric AR patient population and demonstrated the discriminative impact on validated disease severity scores (T4SS, VAS and ESPRINT-15).[17, 18]

Irrespective of which modified ARIA severity classification has the most benefit, there remain some unresolved questions that definitely require to be addressed in future research before deciding that the original ARIA classification should be adapted.

- First, an assessment of the original and modified ARIA severity classifications should be performed in the general AR population to evaluate the distribution and characteristics of the different severity grades. It is known that many AR patients do not seek medical help or even remain undiagnosed. There are indications that this group of patients probably has lower symptom severity[19] and might represent an important group of 'mild' AR patients, that are 'underrepresented' in medical practice but, at present, clear data are lacking.

- Second, current studies evaluating the ARIA classification were mainly performed in Western countries and there still is a paucity of data analyzing the ARIA classification in the rest of the world.[20, 21] As the ARIA guidelines were intended as a basis for the entire world, these studies are absolutely required.
- Third, the phenotype of moderate-severe (or severe) AR should be further characterized. By now, we know that this group of patients has more invalidating symptoms and per definition impaired quality of life, affecting social functioning, sleep, and school/work performance. However, there is a need of more objective evaluation tools for disease severity. In this context, also the identification and characterization of biological markers for endotypes that might be used in the diagnosis, but also in the severity classification, follow up and treatment monitoring, have been defined as future research needs, not only for AR, but for all allergic diseases.[22]
- Fourth, we have to keep in mind that the main purpose of classifying AR patients is to inititiate an appropriate treatment. At present, it is absolutely not clear whether the heterogeneous group of moderate-severe AR patients would also benefit from a stratified therapeutic approach and consequently whether a modification of the ARIA classification would result in a different therapeutic algorithm.
- Fifth, as originally defined by the ARIA Working Group, the ARIA classification is intended for untreated patients. Although most studies evaluating or 'validating' the ARIA classification also included patients that were already treated, it is not sure what the impact of treatment is on the validity of the ARIA classification and on the conclusions that resulted from these studies. By analogy to trends in the management of asthma and other respiratory or allergic diseases, it seems appropriate or even essential to also introduce the concept "control of AR" as a complementary instrument next to the ARIA classification for purposes of follow-up, to evaluate the status of disease and plan future treatment, especially for patients already under treatment. There is no single definition of "disease control". Demoly et al proposed a very complete definition of disease control in AR, combining measurements of the severity and/or frequency of daily or nocturnal symptoms, impairments in social, physical, professional and educational activities, respiratory function monitoring and exacerbations.[23] Different instruments for assessing disease control in AR have already been developed and underwent validation studies, but at present no comparative studies of these different control instruments have been performed[23-29] and the AR control concept is not yet integrated in clinical AR guidelines. The introduction of the asthma control concept and simple tools to assess

control have shown to be beneficial in clinical decision making, has increased awareness of the important partnership between patient and caregiver when setting and aiming treatment goals, and probably also increased the guideline penetration in the medical community when the level of asthma control was incorporated in the GINA 2006 guidelines to guide treatment.[30]

IMPLEMENTATION OF THE ARIA GUIDELINES IN CLINICAL PRACTICE

The ARIA guidelines were intended to improve the quality of AR patient care by optimizing the practice patterns of healthcare providers dealing with AR patients. A first step to improving the quality of care, is to know whether current practice patterns differ from those that are thought to be optimal.

In **CHAPTER 3** we described the results of a cross-sectional survey in Belgium, that evaluated the diagnostic and therapeutic management of 804 AR patients by 95 GPs. We chose to perform this study in general practice, as most people who do seek medical help for AR, consult their GP, making AR a very prevalent condition in general practice and supporting the necessity to investigate the management practices of AR in this healthcare setting.

Whereas the ARIA guidelines recommend that the diagnosis of AR should be supported by highly sensitive and specific *in vivo* or *in vitro* allergy tests, only 50% of the patients diagnosed by their GP with AR, underwent allergy testing. These figures are similar to the results of a pharmacoepidemiological survey of intermittent AR patients presenting in everyday medical practice in France, where the diagnosis of AR was confirmed with allergy tests in only 50% of the patients.[31]

Only 33.4% of the patients received a rhinitis treatment that was in accordance with the evidence-based ARIA treatment recommendations, available at the time of the survey,[1] 12.8% were undertreated and 52.7% were overtreated. Many GPs immediately prescribed the combination of an antihistamine and a nasal corticosteroid, which was the most popular treatment regimen and was initiated in 45.5% of the patients, instead of following a stepwise treatment regimen. Despite the costs of this combined treatment and the lack of evidence supporting the superior value of immediately adding an antihistamine to a nasal corticosteroid, the high prescription rate of this combined treatment was also reported in other European studies[32, 33] and was also found in our studies assessing the proposed treatment for AR by GPs and ENT-specialists in clinical case scenarios **(CHAPTER 5 AND 6)**. Nevertheless the co-prescription of a nasal steroid and an antihistamine remains an important topic of debate.[32] Also guideline recommendations seem conflicting, with the opinion-based EAACI guidelines,[34] preceding the first ARIA guidelines, recommending to combine an antihistamine and a nasal steroid as a first-line treatment in severe cases of AR, the ARIA 2001 guidelines recommending a stepwise approach and only recommending this combination if treatment with

an antihistamine or a nasal steroid alone fails[1] and the ARIA 2008 guidelines allowing to immediately combine a nasal steroid and an antihistamine in patients with moderate-severe persistent AR when symptoms are severe[7] (without further specification of 'severe' and not clearly supported by evidence!). The ARIA 2010 revision does not formulate recommendations concerning this combined treatment.[2]

From chapter 3 we can conclude that the management practices for AR in Belgian general practice often differ from the ARIA recommendations, but we did not gain information on the practioners' awareness of and intention to comply with these guidelines.

This led to the surveys, described in **CHAPTER 5 AND 6**, that were specifically developed to evaluate the dissemination and implementation of the ARIA guidelines in Belgian general and specialist practice.

In these surveys, the spreading of the ARIA guidelines to the GPs was found to be very poor with only 31.1% of them being aware of the ARIA guidelines compared to 87.2% of the Belgian ENT-specialists. Data from a French cross-sectional study also reported a higher familiarity with the ARIA guideline among French ENT-specialists (65.0%) compared to GPs (48.4%),[35] but also indicate that, in France, the ARIA guidelines seem to have better reached the GP population than in Belgium (Flanders). Possibly, in France, more initiatives were undertaken for a wide dissemination of the ARIA guidelines, under the impulse of the French ARIA Chairmanship (Prof. Jean Bousquet). For Belgium, on the other hand, the particularly high awareness among Belgian ENT-specialists can probably be explained by the fact that the co-chair of the ARIA initiative (Prof. Paul Van Cauwenberge) is a renowned Belgian ENT-specialist, leading to specific dissemination initiatives and interest in the ARIA guidelines within this specialist group. Furthermore, the French and the Belgian surveys cannot strictly be compared, as we assessed 'awareness of' the ARIA guidelines, whereas Demoly[35] questioned 'familiarity with the ARIA guidelines', which are not exactly synonyms.

Spreading and awareness of and familiarity with the ARIA guidelines, on the other hand, does not necessarily lead to adherence with these guideline recommendations in clinical practice. 62% of the ENT specialists, and only 10% of the GPs in our surveys stated to follow the ARIA recommendations in their daily practice. An additional 24% of the GPs, however reported to follow the 'NHG Standard for Allergic and Non-allergic Rhinitis",[36] developed by the Dutch College of General Practitioners, in the daily management of their AR patients. The recommendations of the NHG guideline for (allergic) rhinitis[36] are also supported by evidence and in many ways very similar to the ARIA guidelines, proposing the same classification and the same first-line treatments according to the duration

and severity of disease, but are specifically addressed and adapated to the primary care health setting. It is well-known that physicians, and GPs in particular, prefer receiving guideline information from their own peer group.[37] If these guidelines are well-developed and evidence-based, the implementation of guidelines that are tailored to local circumstances, patient population characteristics and healthcare system regulations can only be encouraged.

Nevertheless, the self-reported use or implementation of any guideline for AR among our GP population remains very poor (34.3%). Of course, we need to consider that GPs in particular manage many different illnesses and that many might not consider AR among their priorities. Indeed, the self-reported implementation of guidelines for AR was significantly higher among GPs with a special interest in ENT pathology/allergology compared to the rest of GPs (49.4% versus 29.4%). But, on the other hand, AR is known to be among the top 10 reasons for a doctor's visit in general practice,[38] and this important patient group is entitled to receive the best standards of care.

Furthermore, it is well-known that self-reported adherence to guidelines must be interpreted with caution, might be susceptible to social desirability and interviewer bias and does not necessarily reflect actual practice.[39] In our surveys we found that that physicians who self-reported to implement the ARIA (or NHG) guidelines only to a limited extent adhered to the guideline recommendations when we further questioned their diagnostic management (only performed in GP survey) and treatment strategies for AR.

Whereas the ARIA guidelines recommend to perform a nasal examination as a standard part of the diagnosis of AR, only one third of the 'ARIA users' indicated to routinely perform this examination. Allergen testing and screening for asthma, on the other hand, were indicated as a routine part of the diagnostic work-out of AR patients by the majority of GPs (respectively 71% and 74%), but only screening for asthma was significantly more performed by the self-reported guideline users (84.2%) (and ARIA users in particular (94.3%)) compared to the rest of the GPs (69.1%). We acknowledge that these results must be interpreted with caution because of the low number of self-reported guideline (and ARIA in particular) users and the explicit questioning about diagnostic procedures, which may have forced reply and probably contributed to the overall high reporting of asthma screening and allergen testing, compared to what is found in most epidemiological studies evaluating the diagnostic management of AR patients in general practice.[35, 38, 40]

Also, when assessing the treatment strategies proposed by GPs and ENT-specialists in 4 fictitious clinical scenarios, we found that self-reported use of the ARIA (or NHG) guidelines was not a good predictor of adherence to the stepwise ARIA treatment recommendations. In the specialist survey self-declared ARIA users still demonstrated some higher scores indicative for better compliance with the ARIA guidelines compared to the self-declared non-users, but in both the GP

as the ENT survey overall compliance with the ARIA recommendations was poor and great diversity in treatments and treatment combinations was found, both among self-declared guideline users and non-users.

In both surveys we analyzed whether certain demographic and professional physician characteristics influenced compliance with the evidence-based treatment recommendations for AR and, consistently, in both the GP as the ENT survey, we found that younger age (or less clinical experience) was a significant and independent predictor of good compliance. Similar findings of declining adherence to clinical practice standards and evidence-based recommendations with increasing age and experience have also been reported in other areas of medicine.[41-43] A possible explanation is that the evolution from opinion-based to evidence-based medicine dates from the last 15 years. It is well known that physicians not easily change their long-standing prescribing patterns and this has been identified as a barrier to the incorporation of scientific evidence and guidelines into practice.[38] Younger, less experienced physicians on the other hand, more often tend to rely on the current scientific knowledge to support their clinical practice.

Unfortunately, comparisons between GPs and ENT-specialists concerning guideline compliance or adherence to the evidence-based treatment principles of AR could not be made because in the interval between the surveys an update of the ARIA guidelines[7] was published with some modifications in the treatment algorithm. Depending on the ARIA guideline version used to score physician's compliance with the ARIA recommendations (and to assess ARIA guideline implementation) in the surveys described in chapters 5 and 6 our results would differ. Especially the above mentioned immediate combined treatment of a nasal steroid and an antihistamine in moderate-severe persistent AR, that is consistent with the ARIA 2008 guidelines, but not with the ARIA 2001 guidelines, explains the higher overall ARIA compliance scores in the clinical case sections in the GP survey (chapter 6, using ARIA 2008 guidelines), compared to the ENT survey (chapter 5, using ARIA 2001 guidelines).

Similarly, also in chapter 3 , less 'overtreatment' would have been reported if we would have compared GPs' prescription habits with the later ARIA 2008 instead of the ARIA 2001 guidelines, that were available at the time of the survey.

However, as defined in the methodology of our surveys, assessment of compliance with the ARIA recommendations was performed by strictly comparing the physician's proposed treatments with the recommendations of the ARIA guidelines, available at the time of the survey.

CONCLUSIONS AND UNANSWERED QUESTIONS

From the surveys described in chapters 3, 5 and 6, and discussed in the above section, we can conclude that the management of AR in Belgian general and specialist practice often differs from the evidence-based recommendations, and that there remains a lack of influence of clinical guidelines on health professionals' behavior.

On the other hand, we acknowledge that our results provide only a snapshot of how GPs and specialists deliver care to AR patients, are subject to some limitations and raise additional research questions.

Evaluating healthcare practices through questionnaires obviously has some limitations

- First, only a limited number of items can be addressed.
- Second, results are based on the answers of respondents and can be subject to non-response bias. We, however, tried to limit this bias by obtaining a relatively high response rate (ENT survey) or a sample population that is representative for the entire target population (GP survey).
- Third, results are based on self-reports, making them vulnerable to interviewer and social desirability bias. Interviewer bias cannot be ruled out, and we are aware that some types of questions (and proposed answers) may have forced reply. We tried to limit social desirability bias by conducting and handling the surveys under complete anonymous conditions.
- Fourth, in the questionnaires, the respondents' choice for diagnostic and treatment indicates their practice intentions and intentions to treat in clinical case scenarios. The real life setting, however, is much more complex and decisions not only depend on physician's intentions, but are also influenced by the individual context, patient comorbidity and patient preferences. Nevertheless, well-constructed clinical case scenarios have demonstrated to reflect the actual clinical behavior of a group of physicians[45-47] and have the advantage of being much less time and cost consuming and lead to a more straightforward interpretation compared to assessing physician's treatment practices based on medical patient files.[48]

Our data are limited to Belgian ENT-specialists and Flemish GPs. Concordant to our results, a limited number of studies, conducted in westernized countries, have also revealed considerable scope of improvement in the management of AR in general and specialist practice[38, 49, 50] and have shown that the implementation of the ARIA guidelines remains poor.[35, 51] Of course, it would be interesting to see how GPs, specialists, but also pharmacists in different parts of the world manage the prevalent condition of AR and to which extent the evidence-based recommendations are disseminated and implemented.

Dissemination and implementation of guidelines are closely linked. The dissemination process focuses on educational interventions, that aim at improving awareness, knowledge, understanding and skills and influencing attitudes towards recommendations. Implementation, on the other hand, is more complex and implies strategies to translate changes in knowledge and attitude into changes in practice, and aim at the adoption and adherence of recommendations in daily routines.[52-54] As dissemination is a first step towards implementation, both processes are often addressed together, using the terminology of 'implementation'.

From our research we can conclude that the translation of scientific evidence concerning AR management into clinical practice and the implementation of the ARIA guidelines is unsatisfactory. It remains to be analyzed, however, why this implementation process remains inadequate and how it can be improved.

Cabana et al developed a theoretical framework of the potential barriers to physician adherence to clinical guidelines, operating at the level of the practitioner, the level of the patient, the organizational context, and the social and cultural context. In total, he identified 293 (!) potential barriers that are able to influence (or impair) physician's knowledge, attitudes and behavior.[55] The aim of identifying barriers is to develop a tailored implementation plan, as it has been shown that implementation strategies are more effective when tailored to pre-identified barriers.[56] Cabana's model has been applied in qualitative and quantitative surveys to analyze barriers towards a (group of) guideline(s), or specific guideline recommendations and often resulting in suggested interventions to overcome these barriers and improve the feasibility and success of guideline implementation.[57-60] **(TABLE 1)**

TABLE 1: *Perceived barriers and suggested interventions in surveys addressing barriers to guideline implementation*[53, 54, 57-60]

	Perceived barriers	Suggested interventions
Knowledge related barriers		
Lack of awareness/familiarity	Inadequate spreading of or access to guidelines	Use of clinical practice guidelines in professional development and continuous medical education Small group, interactive educational sessions Computerization Reminder systems
Attitude related barriers		
Lack of agreement	Arguing supporting evidence	Detailed and transparant information on supporting evidence
Lack of self-efficacy	Insufficient training or experience	Small group education/training
Lack of outcome expectancy	Belief that applying guideline recommendations will not result in patient benefits	
Inertia of previous practice/lack of motivation	Difficult to overcome habits and routines	
External barriers		
Patient factors	Conflicting patient preferences, abilities and needs	Use of decision aids to support the flexible use of guidelines to individual patients in practice
Guideline factors	Unclear/ambiguous Incomplete/not up to date Not user-friendly/too complex	User-friendly format and presentation of guidelines Choose guidelines that are validated according to AGREE Development of locally adapted guidelines
Environmental factors	Lack of time/time pressure Lack of resources/material Organizational constraints Lack of reimbursement	Professional incentives, referral privileges

Barriers, however, largely differ between guidelines, but also across recommendations within guidelines. Furthermore, they vary depending on the healthcare setting and analysis of barriers to implementation among the different groups of target users is advocated. Every implementation project should therefore be tailor made.[57] In order to increase the success of implementation, the closely linked processes of guideline development, dissemination and implementation should not be phased, but should be prepared and proceed together.[61]

In our studies there are indications that lack of awareness of/familiarity with the ARIA guidelines among the GP population, inertia of practice among the seasoned GPs and ENT specialists and poor uptake of the ARIA treatment algorithm (due to insufficient clarity? Complexity?) are barriers to effective implementation. Our questionnaires, however, were not specifically developed to evaluate perceived barriers to guideline implementation and our data are insufficient to draw firm conclusions.

Finally, it is important to understand that variations in clinical outcomes can not only be explained by variations in medical practice process and implementation of evidence-based guidelines by healthcare providers, but are largely driven by individual responses to treatments and patient compliance. Patients should be considered as effective partners in healthcare and the patient's voice should also be heard in the development of guidelines. Patient education and involvement is critical in the management of any disease and patient feedback can act as a stimulus to health professional change. Adequate patient-doctor dialogue can maximize compliance, increase satisfaction and optimize health outcomes.

For many diseases, however, conflicting perspectives are identified between patients and physicians.[62, 63] The available literature indicates that physicians underestimate the impact of AR, leading to inadequate patient-physician dialogue and discordant treatment decisions. In **CHAPTER 7** we investigated whether a better understanding of the burden of AR by physicians, due to personal experience of AR, influenced the management of patients suffering from the same disease. We found that GPs with AR might better recognize AR patients within their practice and, when making treatment decisions, gave a significantly higher ranking to patient requests for specific treatment and emotional well-being of the patient, compared to their non-AR colleagues. In order to try to optimize healthcare outcomes, further inquiry to the decision processes shared by healthcare providers and patients is necessary.

REFERENCES

1. Bousquet J, van Cauwenberge P, Khaltaev N, ARIA Workshop Group. Allergic Rhinitis and its Impact on Asthma (ARIA). J Allergy Clin immunol 2001;108 (Suppl 5):S147-S333.
2. Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, et al: Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. J Allergy Clin Immunol 2010;126(3):466-76.
3. Brożek JL, Akl EA, Compalati E, Kreis J, Terracciano L, Fiocchi A, Ueffing E, et al; GRADE Working Group. Grading quality of evidence and strength of recommendations in clinical practice guidelines part 3 of 3. The GRADE approach to developing recommendations. Allergy. 2011;66(5):588-95.
4. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, Norris S, Falck-Ytter Y, Glasziou P, DeBeer H, Jaeschke R, Rind D, Meerpohl J, Dahm P, Schünemann HJ. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011;64(4):383-94.
5. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al; AGREE Next Steps Consortium. AGREE II: Advancing the guideline development, reporting and evaluation in healthcare. CMAJ 2010;182(18):E839-42.
6. Van Hoecke H, Van Cauwenberge P. Critical look at the clinical practice guidelines for allergic rhinitis. Respir Med 2007;101(4):706-14.
7. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al: Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy 2008;63(Suppl 86):8-160.)
8. Bauchau V, Durham SR. Epidemiological characterization of the intermittent and persistent types of allergic rhinitis. Allergy 2005;60(3):350-3.
9. Demoly P, Allaert FA, Lecasble M, Bousquet J; PRAGMA. Validation of the classification of ARIA (allergic rhinitis and its impact on asthma). Allergy 2003;58(7):672-5.
10. Bousquet PJ, Bousquet-Rouanet L, Co Minh HB, Urbinelli R, Allaert FA, Demoly P. ARIA (Allergic Rhinitis and Its Impact on Asthma) classification of allergic rhinitis severity in clinical practice in France. Int Arch Allergy Immunol 2007;143(3):163-9.
11. Bousquet J, Neukirch F, Bousquet PJ, Gehano P, Klossek JM, Le Gal M, Allaf B. Severity and impairment of allergic rhinitis in patients consulting in primary care. J Allergy Clin Immunol 2006;117(1):158-62.
12. del Cuvillo A, Montoro J, Bartra J, Valero A, Ferrer M, Jauregui I, et al. Validation of ARIA duration and severity classifications in Spanish allergic rhinitis patients - The ADRIAL cohort study. Rhinology 2010;48(2):201-5.

13. Jáuregui I, Dávila I, Sastre J, Bartra J, del Cuvillo A, Ferrer M, et al. Validation of ARIA (Allergic Rhinitis and its Impact on Asthma) classification in a pediatric population: the PEDRIAL study. Pediatr Allergy Immunol 2011;22(4):388-92.

14. Bousquet PJ, Combescure C, Neukirch F, Klossek JM, Méchin H, Daures JP, Bousquet J. Visual analog scales can assess the severity of rhinitis graded according to ARIA guidelines. Allergy 2007;62(4):367-72.

15. Demoly P, Urbinelli R, Allaert FA, Bousquet PJ. Should we modify the allergic rhinitis and its impact on asthma dichotomic classification of severity? Allergy 2010;65(11):1488-90.

16. Valero A, Ferrer M, Sastre J, Navarro AM, Monclús L, Martí-Guadaño E, et al. A new criterion by which to discriminate between patients with moderate allergic rhinitis and patients with severe allergic rhinitis based on the Allergic Rhinitis and its Impact on Asthma severity items. J Allergy Clin Immunol 2007;120(2):359-65.

17. Montoro J, Del Cuvillo A, Mullol J, Molina X, Bartra J, Dávila I, et al. Validation of the modified allergic rhinitis and its impact on asthma (ARIA) severity classification in allergic rhinitis children: the PEDRIAL study. Allergy 2012;67(11):1437-42.

18. Valero A, Ferrer M, Baró E, Sastre J, Navarro AM, Martí-Guadaño E, et al. Discrimination between moderate and severe disease may be used in patients with either treated or untreated allergic rhinitis. Allergy 2010;65(12):1609-13.

19. Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. Eur Respir J 2004;24(5):758-64.

20. Asha'ari ZA, Yusof S, Ismail R, Che Hussin CM. Clinical features of allergic rhinitis and skin prick test analysis based on the ARIA classification: a preliminary study in Malaysia. Ann Acad Med Singapore 2010;39(8):619-24.

21. Lee CH, Jang JH, Lee HJ, Kim IT, Chu MJ, Kim CD, Won YS, Kim JW. Clinical characteristics of allergic rhinitis according to allergic rhinitis and its impact on asthma guidelines. Clin Exp Otorhinolaryngol 2008;1(4):196-200.

22. Papadopoulos NG, Agache I, Bavbek S, Bilo BM, Braido F, Cardona V, et al. Research needs in allergy: an EAACI position paper, in collaboration with EFA.Clin Transl Allergy 2012;2(1):21.

23. Demoly P, Calderon MA, Casale T, Scadding G, Annesi-Maesano I, Braun JJ, et al. Assessment of disease control in allergic rhinitis. Clin Transl Allergy 2013;3(1):7.

24. Nogueira-Silva L, Martins SV, Cruz-Correia R, Azevedo LF, Morais-Almeida M, Bugalho-Almeida A, et al. Control of allergic rhinitis and asthma test–a formal approach to the development of a measuring tool. Respir Res 2009;10:52.

25. Fonseca JA, Nogueira-Silva L, Morais-Almeida M, Azevedo L, Sa-Sousa A, Branco- Ferreira M, Fernandes L, Bousquet J. Validation of a questionnaire (CARAT10) to assess rhinitis and asthma in patients with asthma. Allergy 2010;65(8):1042–8.

26. Fonseca JA, Nogueira-Silva L, Morais-Almeida M, Sa-Sousa A, Azevedo LF, Ferreira J, et al. Control of Allergic Rhinitis and Asthma Test (CARAT) can be used to assess individual patients over time. Clin Transl Allergy 2012;2(1):16.

27. Nathan RA, Dalal AA, Stanford RH, Meltzer EO, Schatz M, Derebery J, et al. Qualitative Development of the Rhinitis Control Assessment Test (RCAT), an Instrument for Evaluating Rhinitis Symptom Control. Patient 2010;3(2):91-9.

28. Schatz M, Meltzer EO, Nathan R, Derebery MJ, Mintz M, Stanford RH, et al. Psychometric validation of the rhinitis control assessment test: a brief patient-completed instrument for evaluating rhinitis symptom control. Ann Allergy Asthma Immunol 2010;104(2):118–24.

29. Demoly P, Jankowski R, Chassany O, Bessah Y, Allaert FA. Validation of a self- questionnaire for assessing the control of allergic rhinitis. Clin Exp Allergy 2011; 41(6):860–8.

30. Kroegel C. Global Initiative for Asthma (GINA) guidelines: 15 years of application. Expert Rev Clin Immunol 2009;5(3):239-49.

31. Demoly P, Allaert FA, Lecasble M; PRAGMA. ERASM, a pharmacoepidemiologic survey on management of intermittent allergic rhinitis in every day general medical practice in France. Allergy 2002;57(6):546-54.

32. Ramirez LF, Urbinelli R, Allaert FA, Demoly P. Combining H1-antihistamines and nasal corticosteroids to treat allergic rhinitis in general practice. Allergy 2011;66(11):1501-2.

33. Canonica GW, Bousquet J, Mullol J, Scadding GK, Virchow JC. A survey of the burden of allergic rhinitis in Europe. Allergy 2007;62Suppl85:S17–S25.

34. Van Cauwenberge P, Bachert C, Passalacqua G, Bousquet J, Canonica GW, Durham SR, et al. Consensus statement on the treatment of allergic rhinitis. Allergy 2000;55(2):116-134.

35. Demoly P, Concas V, Urbinelli R, Allaert FA. Spreading and impact of the World Health Organization's Allergic Rhinitis and its impact on asthma guidelines in everyday medical practice in France. Ernani survey. Clin Exp Allergy 2008;38(11):1803-7.

36. Sachs APE, Berger MY, Lucassen PLBJ, Van der Wal J, Van Balen JAM, Verduijn MM. [NHG Standard: allergic and non-allergic rhinitis]. Huisarts Wet 2006;49(5):254-65.

37. Freed GL, Bordley WC, Clark SJ, Konrad TR. Universal hepatitis B immunization of infants: reactions of paediatricians and family physicians over time. Pediatrics 1994;93(5):747-51.

38. Wang DY, Chan A, Smith JD. Management of allergic rhinitis: a common part of practice in primary care clinics. Allergy 2004;59(3):315-9.

39. Adams AS, Soumerai SB, Lomas J, Ross-Degnan D. Evidence of self-report bias in assessing adherence to guidelines. Int J Qual Health Care 1999;11(3):187-192.

40. Van Hoecke H, Vastesaeger N, Dewulf L, Sys L, van Cauwenberge P. Classification and management of allergic rhinitis patients in general practice during pollen season. Allergy 2006;61(6):705-11.

41. Choudhry NK, Fletcher RH, Soumerai SB. The relationship between clinical experience and quality of health care. Ann Intern Med 2005;142(4):260-73.

42. Ward MM, Vaughn TE, Uden-Holman T, Doebbeling BN, Clarke WR, Woolson RF. Physician knowledge, attitudes and practices regarding a widely implemented guideline. J Eval Clin Pract 2002;8(2):155-62.

43. Heidrich J, Behrens T, Raspe F, Keil U. Knowledge and perception of guidelines and secondary prevention of coronary heart disease among general practitioners and internists. Results from a physician survey in Germany. Eur J Cardiovasc Prev Rehabil 2005;12(6):521-9.

44. Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud PA, Rubin HR. Why don't physicians follow clinical practice guidelines? A framework for improvement. JAMA 1999;282(15):1458–65.

45. Webster BS, Courtney TK, Huang YH, Matz S, Christiani DC. Physicians' initial management of acute low back pain versus evidence-based guidelines. Influence of sciatica. J Gen Intern Med 2005;20(12):1132-5.

46. Carey TS, Garrett J. Patterns of ordering diagnostic tests for patients with acute low back pain. Ann Intern Med 1996;125(10):807–14.

47. Homer CJ, Quintana JM, Baskin M, Goldman DA. Can we believe physicians' responses to clinical vignettes? (abstract) Arch Pediatr Adolesc Med 1994;148:35.

48. Couraud S, Fournel P, Moro-Sibilot D, Pérol M, Souquet PJ. Are clinical guidelines applied in routine daily practice?: a French regional survey of physicians' clinical practices in lung cancer management (EPOTRA). Clin Lung Cancer 2011;12(5):298-306.

49. Ryan D, Grant-Casey J, Scadding G, Pereira S, Pinnock H, Sheikh A. Management of allergic rhinitis in UK primary care: baseline audit. Prim Care Respir J 2005;14(4):204-9.

50. Natt RS, Karkos PD, Natt DK, Theochari EG, Karkanevatos A. Treatment trends in allergic rhinitis and asthma: a British ENT survey. BMC Ear Nose Throat Disord 2011;11:3.

51. Maio S, Simoni M, Baldacci S, Angino A, Martini F, Cerrai S, Sarno G, Silvi P, Borbotti M, Pala AP, Bresciani M, Paggiaro PL, Viegi G.The ARGA study with Italian general practitioners: prescriptions for allergic rhinitis and adherence to ARIA guidelines. Curr Med Res Opin 2012;28(10):1743-51.

52. Davis D, Tailor-Vaisey A. Translating guidelines into practice: a systematic review of theoretic concepts, practical experience and research evidence in the adoption of clinical practice guidelines. CMAJ 1997;157(4):408-16.

53. Eccles MP, Grimshaw JM. Selecting, presenting and delivering clinical guidelines: are there any "magic bullets"? Med J Aust 2004;180(6 Suppl):S52-4.

54. Tan WC, Aït-Khaled N. Dissemination and implementation of guidelines for the treatment of asthma. Int J Tuberc Lung Dis 2006;10(7):710-6.

55. Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud PA, Rubin HR. Why don't physicians follow clinical practice guidelines? A framework for improvement. JAMA 1999;282(15):1458–65.

56. Baker R, Reddish S, Robertson N, Hearnshaw H, Jones B. Randomised controlled trial of tailored strategies to implement guidelines for the management of patients with depression in general practice. Br J Gen Pract 2001;51(470):737-41.

57. Lugtenberg M, Zegers-van Schaick JM, Westert GP, Burgers JS. Why don't physicians adhere to guideline recommendations in practice? An analysis of barriers among Dutch general practitioners. Implement Sci 2009;4:54.

58. Lugtenberg M, Burgers JS, Zegers-van Schaick JM, Westert GP. Guidelines on uncomplicated urinary tract infections are difficult to follow: perceived barriers and suggested interventions. BMC Fam Pract 2010;11:51.

59. Lugtenberg M, Burgers JS, Besters CF, Han D, Westert GP. Perceived barriers to guideline adherence: a survey among general practitioners. BMC Fam Pract 2011;12:98.

60. Wiener-Ogilvie S, Pinnock H, Huby G, Sheikh A, Partridge MR, Gillies J. Do practices comply with key recommendations of the British Asthma Guideline? If not, why not? Prim Care Respir J 2007;16(6):369-77.

61. Grimshaw JM, Russell IT. Achieving health gain through clinical guidelines II: Ensuring guidelines change medical practice. Qual Health Care 1994;3(1):45-52.

62. Scadding GK, Richards DH, Price MJ. Patient and physician perspectives on the impact and management of perennial and seasonal allergic rhinitis. Clin Otolaryngol Allied Sci 2000;25(6):551-7.

63. Meltzer EO. Allergic rhinitis: the impact of discordant perspectives of patient and physician on treatment decisions. Clin Ther 2007;29(7):1428-40.

PART 2
FUTURE PERSPECTIVES

From our unresolved questions some future research perspectives are prioritized.

There is an urgent need for a systematic quality appraisal of the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines and other available allergic rhinitis (AR) guidelines. The standardized AGREE instrument will be used for this purpose.

Further assessment of the ARIA classification and the modified ARIA classifications, proposed by our group and the group of Valero, needs to be performed in large groups of AR patients, recruited in different settings: the general population, general practice and specialist practice. The different (modified) ARIA classification groups will be compared for validated symptom and quality of life scores and the presence of well-defined comorbidities. As, at present, least data on the ARIA classification are available from the general allergic rhinitis population, the first focus lies on this patient group.

In untreated, but especially also in treated AR patients, we want to compare AR control scores, measured by a validated and easy to administer instrument, such as the Allergic Rhinitis Control Test (ARCT), with AR severity as defined by the (modified) ARIA classification(s) and to analyze potential correlations between AR control and severity and physician-recommended (change in) treatment.

In order to better understand why the implementation of the ARIA guidelines remains inadequate, it is necessary to perform a systematic evaluation of perceived barriers to the implementation of the ARIA guidelines and suggestions to improvement. This work will start by qualitative studies e.g. by conducting focus group studies among the different target user groups, and eventually expanding to larger quantitative studies. The information resulting from this research might provide valuable information to improve the implementation process of the current or any future ARIA guideline update or local adaptation, that ideally should be accompanied by a simultaneous implementation plan.

SUMMARY

Allergic rhinitis (AR) is the most common chronic respiratory disease, affecting up to 25% of the population worldwide. The burden of disease goes far beyond the nasal symptoms of rhinorrhea, nasal congestion, sneezing and pruritus. AR causes significant impairment of the quality of life, is associated with multiple comorbidities and has important economic consequences. Nevertheless, the disease often remains regarded as trivial, un(der)diagnosed and inadequately treated.

In 2001, the first evidence-based guidelines for AR, the ARIA guidelines, were published to assist physicians in improving the management of their patients by providing them a guide for 'optimal clinical practices'. The ARIA guidelines propose diagnostic recommendations and a stepwise treatment algorithm, based on a new classification for AR in terms of the duration of disease (into intermittent and persistent) and its impact on quality of life (into mild and moderate-severe).

The main goals of this thesis were to assess the validity and applicability of the ARIA classification in a large patient population and the implementation of the ARIA guidelines by general practioners (GPs) and ENT-specialists.

In our patient group we confirmed the benefits of classifying AR into intermittent or persistent. On the other hand, gradation of severity, into mild or moderate-severe, showed some important limitations, due to a clear disproportion in the distribution of patients, with almost 90% being classified as moderate-severe, and the heterogeneity in disease severity within the moderate-severe group. Based on these findings, we proposed an adaptation and simplification of the ARIA gradation of AR severity, differentiating 3 severity categories: mild, moderate, severe.

To evaluate the implementation of the ARIA guidelines in clinical practice, we first performed an exploratory study in Belgian general practice, showing that diagnostic and treatment practices for AR often differ from the evidence-based ARIA recommendations. Further surveys addressed to Flemish GPs and Belgian ENT-specialists confirmed that there remains a lack of influence of clinical guidelines on health professional's behavior. Among the GPs, awareness of the ARIA guidelines was very poor. Compliance with the stepwise treatment algorithm for AR was poor among both GPs and ENT-specialists, and even among those that reported to follow the ARIA guidelines in their daily practice. In both surveys young age (and less clinical experience) of the physician was found to be a significant and independent predictor for good compliance with the evidence-based AR treatment recommendations.

Further research perspectives will aim at evaluating the original and adapted ARIA classification in different patient groups, the additional value of assessing AR control in treated patients and the impact of these different instruments on the treatment algorithm.

Systematic analysis of perceived barriers to the implementation of the ARIA guidelines among the different target user groups is necessary to better understand and improve the implementation process.

Finally, the decision processes shared by healthcare providers and patients, their impact on patient compliance and clinical outcomes need to be further explored.

SAMENVATTING

Allergische rhinitis (AR) is de meest voorkomende chronische respiratoire ziekte, die ongeveer 25% van de wereldbevolking treft. De impact van de ziekte gaat veel verder dan de typische neussymptomen, bestaande uit neusloop, neusverstopping, niezen en jeuk. AR heeft een significante invloed op de levenskwaliteit, is geassocieerd met vele comorbiditeiten en heeft belangrijke economische gevolgen. Desondanks wordt de aandoening vaak gebanaliseerd, niet- of ondergediagnosticeerd en inadequaat behandeld.

In 2001 werden de eerste evidence-based richtlijnen voor AR gepubliceerd, de ARIA richtlijnen. De ARIA richtlijnen werden ontwikkeld om artsen/zorgverleners te helpen de zorg voor hun patiënten te optimaliseren. De ARIA richtlijnen formuleren diagnostische aanbevelingen en stellen een stapsgewijs behandelingsalgoritme voor, dat gebaseerd is op een nieuwe classificatie for AR, op basis van de duur van de aandoening (in intermittent en persistent) en de impact op de levenskwaliteit (in mild en matig-ernstig).

De belangrijkste doelstellingen van deze thesis waren de evaluatie van de validiteit en toepasselijkheid van de ARIA classificatie in een grote patiëntengroep en de implementatie van de ARIA richtlijnen door huisarten en NKO-specialisten.

De voordelen van een classificatie van AR op basis van de duur van de symptomen, met onderscheid tussen intermittent en persistent, werden binnen onze patiëntengroep bevestigd. Anderzijds, vertoonde de classificatie (of gradatie) van ernst in de groepen mild of matig-ernstig, toch een aantal belangrijke beperkingen. Enerzijds vonden we een duidelijke disproportie tussen deze 2 groepen, met bijna 90% van de patiënten die als matig-ernstig werd geclassificeerd, en anderzijds was er binnen de matig-ernstige groep toch een belangrijke heterogeniteit in ziekte-ernst. Op basis van deze bevindingen stelden we een modificatie en vereenvoudiging van de ARIA classificatie voor ernst van AR voor, met onderscheid tussen 3 ziekte-ernst categorieën: mild, matig, ernstig.

Om de implementatie van de ARIA richtlijnen in de klinische praktijk te evalueren, werd eerst een verkennende studie in de Belgische huisartsenpraktijk uitgevoerd, die aantoonde dat de diagnostische en therapeutische aanpak van AR vaak afwijkt van de evidence-based ARIA aanbevelingen. In een tweede fase ondervroegen we Vlaamse huisarten en Belgische NKO-specialisten en werd de gebrekkige impact van klinische guidelines op de praktijkgewoonten van de arts bevestigd. De huisartsen bleken bijzonder slecht op de hoogte van (het bestaan van) de ARIA richtlijnen. Zowel bij de huisartsen als bij de NKO-artsen was compliance met het stapsgewijs ARIA behandelingsalgoritme voor AR zwak, en dit zelfs bij de artsen die zelf eerder hadden aangegeven de ARIA richtlijnen te volgen in hun dagelijkse praktijk. Zowel bij de huisartsen als specialisten bleek jongere leeftijd (en minder

klinische ervaring) van de arts een significante en onafhankelijke predictor te zijn voor goede compliance met de evidence-based aanbevelingen voor de behandeling van AR.

Toekomstige onderzoeksperspectieven zullen gericht zijn op een verdere evaluatie van de originele en 'gemodificeerde' ARIA classificatie in diverse patiëntengroepen, de bijkomende waarde van het meten van 'controle van AR' bij behandelde patiënten en de impact van deze verschillende meetinstrumenten op het behandelingsalgoritme van AR.

Een systematische analyse van de barrières tot implementatie van de ARIA richtlijnen bij de verschillende groepen eindgebruikers is noodzakelijk om het implementatieproces beter te begrijpen en te verbeteren.

Tot slot is meer inzicht nodig omtrent de impact van gemeenschappelijke besluitvorming of 'shared decision making' tussen artsen en patiënten op patiënt compliance en klinische outcomes.

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PUBLICATIES

A1 Artikels opgenomen in ISI Web of Science

1. Mansbach AL, Brihaye P, Casimir G, Dhooge I, Gordts F, Halewyck S, Hanssens L, Lemkens N, Lemkens P, Leupe P, Mulier S, Van Crombrugge L, Van Der Veken P, Van Hoecke H. Clinical aspects of chronic ENT inflammation in children.B-ENT 2012;8 Suppl 19:83-101.
2. Van Hoecke H, Bauters T, Coppens M, Robays H, Van Hoecke E, Dhooge I. Basic principles for pediatric care: what the ENT professionals should know. B-ENT 2012;8 Suppl 19:125-31.

3. Van Hoecke H, Van Cauwenberge P, Thas O, Watelet JB. The ARIA guidelines in specialist practice: a nationwide survey. Rhinology 2010;48(1):28-34.
4. Van Hoecke H, Piette A, De Leenheer E, Lagasse N, Struelens P, Verschraegen G, Dhooge I. Destructive otomastoiditis by MRSA from porcine origin. Laryngoscope 2009;39(9):1338-47.
5. Van Cauwenberge P, Van Hoecke H, Kardos P, Price D, Waserman S. The current burden of allergic rhinitis amongst primary care practitioners and its impact on patient management. Prim Care Resp J 2009;8(1):27-33.
6. Van Hoecke H, Vandenbulcke L, Van Cauwenberge P. Histamine and leukotriene receptor antagonism in the treatment of allergic rhinitis: an update. Drugs 2007;67(18):2717-26.
7. Van Hoecke H, Van Cauwenberge P. Critical took at the clinical practice guidelines for allergic rhinitis. Respir Med 2007;101(4):706-14.
8. Van Cauwenberge P, Van Hoecke H, Bachert C. Pathogenesis of chronic rhinosinusitis. Curr Allergy Asthma Rep 2006;6(6):487-94.
9. Van Hoecke H, Vastesaeger N, Dewulf L, De Bacquer D, Van Cauwenberge P. Is the allergic rhinitis and its impact on asthma classification useful in daily primary care practice? J Allergy Clin Immunol. 2006;118(3):758-9.
10. Van Hoecke H, Vastesaeger N, Dewulf L, Sys L, Van Cauwenberge P. Classification and management of allergic rhinitis patients in general practice during pollen season. Allergy 2006;61(6):705-11.
11. Deventer K, Mikulcíková P, Van Hoecke H, Van Eenoo P, Delbeke FT. Detection of budesonide in human urine after inhalation by liquid chromatography-mass spectrometry. J Pharm Biomed Anal 2006;42(4):474-9.
12. Van Cauwenberge P, Van Hoecke H. Management of allergic rhinitis. B-ENT. 2005;Suppl 1:45-62; quiz 63-4.
13. Heinzerling L, Frew AJ, Bindslev-Jensen C, Bonini S, Bousquet J, Bresciani M, Carlsen KH, Van Cauwenberge P, Darsow U, Fokkens WJ, Haahtela T, van Hoecke H et al. Standard skin prick testing and sensitization to inhalant allergens across Europe--a survey from the GALEN network. Allergy 2005;60(10):1287-300.
14. Claeys S, Van Hoecke H, Holtappels G, Gevaert P, De Belder T, Verhasselt B, Van Cauwenberge P, Bachert C. Nasal polyps in patients with and without cystic fibrosis: a differentiation by innate markers and inflammatory mediators Clin Exp Allergy 2005;35(4):467-72.
15. Karapantzos I, Tsimpiris N, Goulis DG, Van Hoecke H, Van Cauwenberge P, Danielides V. Management of epistaxis in hereditary hemorrhagic telangiectasia by Nd:YAG laser and quality of life assessment using the HR-QoL questionnaire. Eur Arch Otorhinolaryngol 2005;262(10):830-3.

A2, A3: Artikels in tijdschriften met leescomité, niet opgenomen in ISI Web of Science

1. Van Crombrugge L, Van Hoecke H, Roche N, Dhooge I. A rare case of necrotizing fasciitis of the external ear. IJPORL Extra 2013;8:44-6.
2. Van Hoecke H, Dhooge I, De Leenheer E. Oor- en gehoorproblemen bij het Syndroom van Turner. Symposium: Van Turner Adolescentie tot Volwassen Vrouw. TVG 2011;67(11):554-6.
3. Claeys S, Van Hoecke H, Dhaeseleer E, Van Lierde K. Multidisciplinaire diagnostiek en behandeling stemplooidisfunctie. Ned Tijdschr KNO 2008;2:87-93.

4. Joos GF, Brusselle GG, Van Hoecke H, Van Cauwenberge P, Bousquet J, Pauwels RA. Positioning of glucocorticosteroids in asthma and allergic rhinitis guidelines (versus other therapies). Immunol Allergy Clin North Am 2005;25(3):597-612.
5. Van Cauwenberge P, Van Hoecke H, Vandenbulcke L, Van Zele T, Bachert C. Glucocorticosteroids in allergic inflammation: clinical benefits in allergic rhinitis, rhinosinusitis, and otitis media. Immunol Allergy Clin North Am 2005;25(3):489-509.
6. Van Cauwenberge P, Gevaert P, Van Hoecke H, Van Zele T, Bachert C. [New insights into the pathology of nasal polyposis: the role of superantigens and IgE].Verh K Acad Geneeskd Belg 2005;67(1):5-28; discussion 29-32.
7. Van Cauwenberge P, Van Hoecke H. Preface: We come from far but still have a long way to go. Clinical & Experimental Allergy Reviews 2005;5(1):1.

B2: Hoofdstukken in boeken

1. Takes R, Dhooge I, Van Hoecke H. Farynx. In: De Vries N, Van de Heyning PH, Leemans CR, editors. Leerboek Keel-Neus- Oorheelkunde en Hoofd-Halschirurgie. Bohn Stafleu Van Loghum 2013.
2. Van Cauwenberge P, Van Zele T, Watelet JB, Van Hoecke H. Allergy: Allergic Rhinitis. In: Laurent G, Shapiro S, editors. Encyclopedia of Respiratory Medicine. Elsevier 2006;80-92.
3. Van Cauwenberge P, Van Hoecke H, Bousquet J. Allergic rhinitis and its impact on asthma. In: Sih T, Clement P, editors. Pediatric Nasal and Sinus Disorders. Taylor & Francis 2005;401-420.
4. Van Cauwenberge P, Van Hoecke H, Bachert J, Mullol J. Rinitis alergica. In: Mullol J, Montserrat JR, editors. Rinitis, Rinosinusitis, Poliposis Nasi. Ponencia oficial de la SEORL Y PCF 2005;509-28.
5. Van Cauwenberge P, Van Hoecke H, Bachert C, Mullol J. Guias terapeuticas para la rinitis. In: Mullol J, Montserrat JR, editors. Rinitis, Rinosinusitis, Poliposis Nasi. Ponencia oficial de la SEORL Y PCF 2005;973-86.

WETENSCHAPPELIJKE PRIJZEN

- NVWPO prijs voor casusvoorstelling. Systemic disease mimicking otomastoiditis. Van Hoecke H, De Leenheer E, Dhooge I. Vergadering Nederlands-Vlaamse Werkgroep voor Pediatrische Otorhinolayngologie, oktober 2008.
- GLAXO Smith Kline scientific ENT Award. Expression of innate markers and cytokine profile in nasal polyps from children with cystic fibrosis. Van Hoecke H, Claeys S, De Belder T, Holtappels G, Gevaert P, Verhasselt B, Van Cauwenberge P, Bachert C. Spring Meeting, Koninklijke Belgische Vereniging voor NKO, februari 2004.

BEURZEN

- EAACI Junior Member Travel Grant, EAACI Vienna, juni 2006
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MONDELINGE VOORDRACHTEN OP WETENSCHAPPELIJKE CONGRESSEN

November 2012: Basic principles for pediatric care: what ENT professionals should know. Van Hoecke H, Bauters T, Coppens M, Robays H, Van Hoecke E, Dhooge I. Vergadering Belgische Vereniging NKO, Wilrijk.

Mei 2011: Bovenste luchtwegobstructie bij het kind. Van Hoecke H, Bonte K. G-ENT Rounds, Zwijnaarde.

Oktober 2009: Oor- en gehoorproblemen bij Turner syndroom. Van Hoecke H. Turner Symposium, Gent.

Mei 2008: Desctructive otomastoiditis by MRSA from porcine origin. Van Hoecke H, Piette A, De Leenheer E, Verschraegen G, Dhooge I. Wetenschappelijke Vergadering Belgische Vereniging NKO, Brussel.

Oktober 2008: Systemic disease mimicking otomastoiditis. Van Hoecke H, De Leenheer E, Dhooge I. Vergadering Nederlands-Vlaamse Werkgroep voor Pediatrische Otorhinolayngologie, Antwerpen.

November 2005: Use of ARIA by Belgian ENT-Specialists. Spring Meeting, Koninklijke Belgische Vereniging voor NKO, Luik.

Mei 2004: Pathophysiology of pollenosis. Van Hoecke H. Dag van de Allergie, Belgische Vereniging Kinderlongartsen, Genval.

Februari 2004: Expression of innate markers and cytokine profile in nasal polyps from children with cystic fibrosis. Van Hoecke H, Claeys S, De Belder T, Holtappels G, Gevaert P, Verhasselt B, Van Cauwenberge P, Bachert C. Spring Meeting, Koninklijke Belgische Vereniging voor NKO, Brussel.

November 2003: Innate markers in upper airway disease. Van Hoecke H, Claeys S, De Belder T, Holtappels G, Gevaert P, Verhasselt B, Van Cauwenberge P, Bachert C. SERIN, Week of Allergy, Ghent, Belgium.

POSTERPRESENTATIES

Juni 2008: Burden of allergic rhinitis amongst primary care practitioners and its impact on patient management. Van Hoecke H, Van Cauwenberge P, Kardos P, Waserman S, Price D. EAACI, Barcelona.

Juni 2006: Dissemination and implementation of the ARIA Guidelines among ENT-specialists. Van Hoecke H, Watelet JB, Van Cauwenberge P. EAACI, Vienna.

Februari 2005: Nasal polyps in patients with and without cystic fibrosis: differentiation by inflammatory mediators and macrophage phenotype heterogeneity. Claeys S, Van Hoecke H, Holtappels G, Van Zele T, Van Cauwenberge P, Bachert C. 3rd EAACI Davos Meeting in Basic Immunology in Allergy and Clinical Immunology.

Januari 2004: Expression of innate markers and cytokine profile in upper airway disease. Claeys S, Van Hoecke H, De Belder T, Holtappels G, Gevaert P, Verhasselt B, Van Cauwenberge P, Bachert C, Wetenschapsdag Universiteit Gent.

Maart 2004: The Macrophage Mannose Receptor and Toll-likeReceptor 2 and 4 in Chronic Sinus Disease. Claeys S, Van Hoecke H, De Belder T, Holtappels G, Gevaert P, Verhasselt B, Van Cauwenberge P, Bachert C. AAAAI Annual Meeting, San Francisco.

Juni 2004: Nasal polyps in patients with versus without cystic fibrosis: a differentiation by innate and adaptive defence markers. Van Hoecke H, Claeys S, De Belder T, Holtappels G, Gevaert P, Verhasselt B, Van Cauwenberge P, Bachert C. EAACI, Amsterdam.