

SPECIAL ARTICLE

Allergic Rhinitis and Its Impact on Asthma Update (ARIA 2008) - Western and Asian-Pacific Perspective

Ruby Pawankar¹, Chaweewan Bunnag², Yuzhi Chen³, Takeshi Fukuda⁴, You-Young Kim⁵, Lan Thi Tuyet Le⁶, Le Thi Thu Huong⁷, Robyn E O'Hehir⁸, Ken Ohta⁹, Pakit Vichyanond², De-Yun Wang¹⁰, Nanshan Zhong¹¹, Nikolai Khaltayev¹² and Jean Bousquet^{13,*}

SUMMARY The prevalence of allergic diseases such as allergic rhinitis (AR) and asthma is markedly increasing worldwide as societies adopt western life styles. Allergic sensitization is an important risk factor for asthma and AR, and asthma often co-exists with AR. An estimated 300 million people worldwide have asthma, about 50% of whom live in developing countries and about 400 million people suffer from AR. Yet, AR is often under-diagnosed and under-treated due to a lack of appreciation of the disease burden and its impact on quality of life, as well as its social impact at school and at the workplace. However, AR with or without asthma is a huge economic burden. Thus, there was clearly a need for a global evidence-based document which would highlight the interactions between the upper and lower airways including diagnosis, epidemiology, common risk factors, management and prevention. The Allergic Rhinitis and its Impact on Asthma (ARIA) document was first published in 2001 as a state-of-the-art guideline for the specialist, the general practitioner and other health care professionals. Subsequent new evidence regarding the pathomechanisms, new drugs and increased knowledge have resulted in the publication of the ARIA 2008 update. The present review summarizes the ARIA update with particular emphasis on the current status of AR and asthma in the Asia-Pacific region and discusses the Western and Asian perspective.

Allergic rhinitis (AR) and asthma are the most common allergic airway diseases with epidemic proportions. AR is an IgE-mediated symptomatic disorder of the nose due to the interaction of an allergen with IgE resulting in the release of a variety of mediators that induce the typical symptoms of rhinorrhea, sneezing, itching and nasal blockage. IgE-mediated inflammation of the airways can either manifest as AR, asthma or both. Globally, over 400 million people suffer from AR¹⁻⁴ with differences between rural and urban areas, developed and developing countries.^{3,5-7} These differences may in part be explained by differences in their immune responses.⁸ Allergic rhinitis markedly affects social life,

sleep, school and work⁸⁻¹¹ and its economic impact is

From the ¹Nippon Medical School, Tokyo, Japan, ²Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, ³National Cooperative Group of Pediatric Research on Asthma, Asthma Clinic and Education Center of the Capital Institute of Pediatrics, Peking, China, ⁴Dokkyo University, Tochigi, Japan, ⁵Seoul National University College of Medicine, Seoul, Korea, ⁶University of Medicine and Pharmacy, Ho Chi Minh City, Vietnam, ⁷Nhan Dan Gia Dinh Hospital, Ho Chi Minh City, Vietnam, ⁸Alfred Hospital and Monash University, Melbourne, Australia, ⁹Teikyo University School of Medicine, Tokyo, Japan, ¹⁰Yong Loo Lin School of Medicine, National University of Singapore, Singapore, ¹¹First Affiliated Hospital of Guangzhou Medical College, Guangzhou, China, ¹²Geneva, Switzerland, ¹³University Hospital and INSERM, Montpellier, France.
Correspondence: Ruby Pawankar
E-mail: rpawankar@gmail.com

substantial. However, rhinitis is often under-diagnosed, misdiagnosed and/or under-treated.¹²

Moreover, many patients with asthma have rhinitis, and rhinitis is a major risk factor for asthma and often precedes it. Increasing evidence on the link between allergic rhinitis and asthma comes from epidemiologic, immunologic and clinical studies. Epidemiologically, up to 40% of patients with AR also have asthma, and up to 80% of patients with asthma experience nasal symptoms. Both AR and asthma are chronic inflammatory diseases of the airways and their inflammatory mechanisms are characterized by an inflammatory infiltrate made up of eosinophils, T cells, and mast cells that release several mediators, chemokines and cytokines, inducing local and systemic IgE synthesis, and activate a systemic link via the bone marrow. Studies have shown that patients with AR exhibit bronchial hyper-responsiveness (BHR) and an increase in inflammatory cells, and that a nasal allergen challenge further increases this hyper-reactivity. Results of several retrospective studies indicated, that for patients with asthma the presence of co-morbid allergic rhinitis is associated with higher annual medical costs, as well as an increased likelihood of asthma-related hospital admissions and emergency visits. These findings highlight the potential for improving asthma outcomes by treating co-morbid AR. This link may be due to cross talk between the upper and lower airways, the direct impact of inflammatory mediators released locally and to the systemic link between the two.

Epidemiologic studies done in different parts of the world have consistently shown that asthma and rhinitis often co-exist in the same patients.¹³⁻¹⁶ Adults and children with asthma and concomitant AR experience more asthma-related hospitalizations and physician visits, incur higher asthma drug costs than patients with asthma alone¹⁷⁻²⁰ and experience more frequent absences from work and decreased productivity with few exceptions.²¹

Based on the strength of the above, the first ever evidence-based position paper on rhinitis devoted to the relationship between rhinitis and asthma and its therapeutic implications entitled ARIA: 'Allergic Rhinitis and its Impact on Asthma' emphasizing the importance of treating allergic rhinitis and

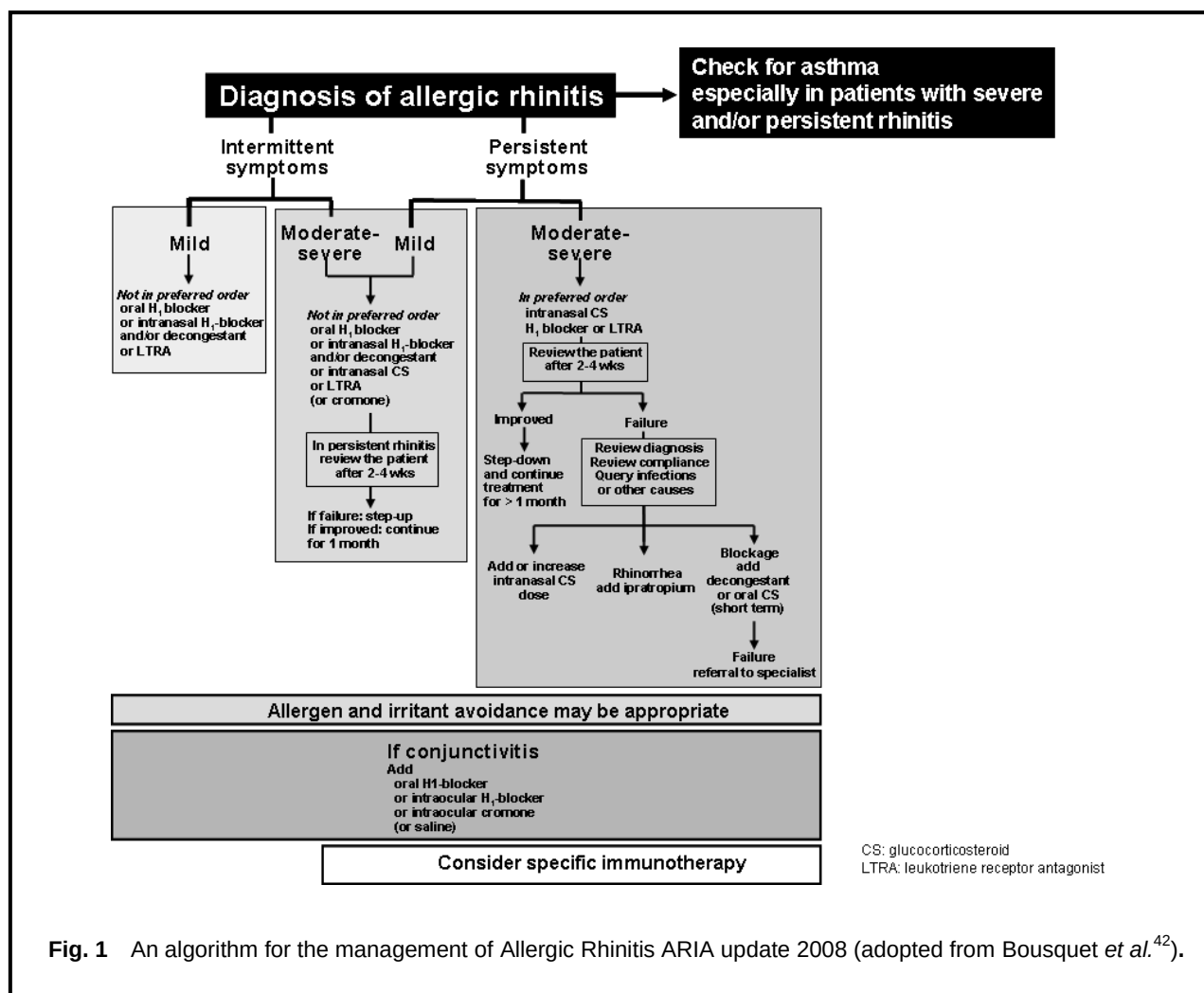
asthma globally as 'One Airway One Disease' was developed. The ARIA initiative was developed as a state-of-the-art guideline for the specialist as well as for the general practitioner in order to update their knowledge of allergic rhinitis, emphasize the impact of allergic rhinitis on asthma, provide an evidence-based document on the diagnostic methods and an evidence-based revision of the presently available treatments. It clearly proposes a stepwise strategy for the management of allergic rhinitis. Moreover, a new classification is also proposed for allergic rhinitis namely "intermittent" or "persistent" rhinitis based on the duration of the disease and "mild" and "moderate-severe" based on the severity of symptoms and quality of life.

ARIA update

A large number of papers were published since the ARIA was first developed thus extending our knowledge.²²⁻²⁷ The ARIA classification was validated^{15,23-26} although some proposed a three level classification of the severity of AR.^{27,28} New evidence on the pathomechanisms, new methods of diagnosis, new drugs, and new evidence on the safety or side effects of existing drugs have been published.²⁹⁻³² Hence, the need to update the ARIA guidelines. The ARIA Update also covers aspects of treatment with complementary and alternative medicine,¹⁸ sports and rhinitis in athletes,^{19,33,34} the link between rhinitis and asthma in children³⁵⁻³⁹ and specific information on developing countries.⁴⁰⁻⁴² The grading of evidence and management recommendations of the ARIA 2008 update used the Shekelle and not the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach.^{43,44} Therefore, recommendations made by the 2008 ARIA update may change once the GRADE approach is incorporated. A stepwise approach for the management of AR is proposed in Fig. 1.

Asthma and allergic rhinitis in Asia Pacific and the Asian perspective

The prevalence of allergic diseases in Asia varied widely but was found to be rising (asthma 29.1%; AR up to 45%) mostly in low- and mid-income countries.^{45,46} In Thailand, the prevalence of all three major allergic diseases increased significantly from the ISAAC phase I survey



performed in 1995, *i.e.* asthma increased from 12.2% to 14.5%, AR from 37.9% to 50.6% and eczema from 9.8% to 15.7%.⁴⁷ In Japan, rhinitis has increased from 3.8% in 1984 to 32% and asthma from 4.6% in 1992⁴⁸ to 9.1% (Akasawa A. 2006; unpublished) and more than 42% of patients with asthma have AR. The prevalence of childhood asthma in Taiwan has increased from 1.3% in 1974 to 5.07% in 1985⁴⁹ and more recently, the overall cumulative and 12-month prevalence of wheezing and rhinitis in the younger children was 8.2% and 44.4%, respectively; and in the older children, 6.9% and 42.2%.⁵⁰ Similarly, in Singaporean preschoolers, the cumulative and previous-12-months prevalence of wheezing was 27.5% and 16.0%, respectively, and the current asthma and rhinitis prevalence was 11.7% and 25.3%, respectively. By contrast, the prevalence of current wheezing, diagnosed asthma and allergic rhinoconjunctivitis in Tibet was 0.8%, 1.1%, and 5.2%, re-

spectively.⁵¹ While the asthma prevalence in rural Bangladesh was 16.1%⁵² and in Pakistan there was a doubling of the prevalence of AR and asthma in ISAAC III as compared to ISAAC I, a study in urban India presented the overall prevalence of asthma with 2.38%.⁵³ The prevalence of allergic rhinitis in 5-11yr children in Vietnam was 34.9 %⁵⁴ and the prevalence of allergic rhinitis in patients with asthma was 48.54% (Le Van Khang, *et al.* Study of sensitivity, specificity of house dust mite allergen made in Vietnam for the diagnosis of asthma, Ministry of Health of Vietnam, Jan 2002 to Dec 2004, www.cimsi.org.vn). The asthma prevalence in Australia increased from 8% in 1989-90 to 11% in 1995 but the prevalence plateaued in recent years with 2004 prevalence of asthma at 14-16% in children and 10-12% in adults (Australian Centre for Asthma Monitoring, www.asthamonitoring.org).

Although overall regional data for adults are scant, it is estimated that 1-10% have asthma and 10-32% have AR. In a more recent study, the self-reported prevalence of AR in China had wide variations, ranging from < 10% to > 20% with about 15% suffering from persistent AR.⁵⁵ More recent data showed an increase in the prevalence of AR in Korea from 6 -10% to > 20%⁵⁶ in the adult population. The distribution of the severity of AR was mild intermittent (25.7%), moderate to severe intermittent (16.4%), mild persistent (16.4%) and moderate to severe persistent (41.2%).⁵⁷

Recent data showed a very high co-morbidity of asthma and rhinitis as 60-80% of asthma patients had rhinitis symptoms.⁵⁸ The younger asthmatic patients had a higher co-morbidity (80%) than the elderly patients (60%) moreover, asthmatic patients with rhinitis presented more severe clinical symptoms in both adult and children indicating that rhinitis may affect asthma severity and outcome.⁵⁸

Although aeroallergens that trigger allergy and asthma in Asia Pacific vary from area to area house dust mites are the major triggering allergen in most of Asia followed by pollens, insects, molds and fungi.⁵⁹

In a study on patient perceptions of asthma management across Asia, patients reported frequent and unnecessary symptoms and exacerbations because of a lack of adequate asthma control.⁶⁰ Twenty-seven percent of adults and 37% of children with asthma reported absences from work or school in the previous year due to asthma, and 40% required hospitalization, emergency department visits, or unscheduled emergency visits to other health care facilities in the previous year.⁶⁰ Asthma severity varied, with Vietnam and China reporting the most patients with severe, persistent symptoms. Absenteeism from work was highest in the Philippines (46.6%) and lowest in South Korea (7.5%). In a survey of parents of children with asthma in four Asian countries, most children with asthma (73%) had preexisting symptoms of AR and asthma with co-morbid AR substantially affecting their quality of life and worsening their asthma symptoms.⁶¹ However, awareness of the co-morbidity of AR and asthma amongst the parents of asthmatic children was only about 50%.

The socio-economic burden via annual costs of treating asthma and AR - both direct costs (hospitalization, medications) and indirect costs (time lost from work, premature death) - are substantial, and represent an even heavier burden in societies with emerging economies. In eight countries in Asia Pacific, the annual per-patient direct costs ranged from US\$ 108 to US\$ 1,010.⁶² Total per-patient costs, including productivity costs, ranged from US\$ 184 to US\$ 1,189. Urgent care costs were 18% to 90% of the total per-patient direct costs. The total cost of asthma in Singapore was estimated to be about US \$33.93 million per annum, based on figures from 1992-1993.⁶³ Of this amount, US\$ 17.22 million was incurred in direct costs and US\$ 16.71 million from indirect costs. In-patient hospitalization accounted for the largest proportion of direct costs (approximately US \$8.55 million) and loss of work productivity (US\$ 12.7 million) comprised the major proportion of indirect costs. The total medical cost of asthma in Korea was 2.04 billion US dollars in 2004. Direct costs and indirect costs equally contributed to total costs (0.96 and 1.08 billion dollars respectively). If intangible costs (willing to pay method) were included, total costs inflated to 4.11 billion US dollars, which were nearly equivalent to 0.44% of its GDP in 2004.

From the evidence listed in this summary, it is clear that there is a close linkage between asthma and AR. It is therefore recommended that patients with persistent AR should be evaluated for asthma, including appropriate history taking and spirometric parameters, at an early stage. On the other hand, patients with asthma should be evaluated for rhinitis. Unfortunately in reality there is a gap in this practice in many countries in the region. Partly this is due to the lack of allergy medicine as a recognized specialty in some countries as well as to governmental regulations restricting specialists to practice as organ-based specialists. To resolve this problem and to have an integrated therapeutic strategy is one of the major challenges in the Asia Pacific region.

Based on these constraints we also need to consider treatment strategies that can really treat both the upper and the lower airway diseases. Leukotriene receptor antagonists are recommended for patients with both rhinitis and asthma in this ARIA summary. As the only established etiological

treatment for allergic diseases, allergen-specific immunotherapy (SIT) needs to be highlighted as well. Allergen-specific immunotherapy should be considered not only after unsatisfactory traditional pharmacologic treatments but also for patients who have a clear IgE-mediated allergic disease based on history and positive SPT as an early adjunct to standard pharmacotherapy.

Subcutaneous immunotherapy has been found to be effective and safe, and sublingual immunotherapy is now becoming more popular, because of its convenience and lower side effects but the use of standardized vaccines and higher allergen doses (50-200 higher than subcutaneous) in the maintenance stage should be emphasized.

CONCLUSION

The prevalence of asthma and AR is increasing in the Asia Pacific region and the prevalence of co-morbidity is high.⁶⁴ The perception of patients and physicians regarding the link between asthma and rhinitis varies between countries, but seems to be higher than expected.⁶⁴ However, knowledge is not directly translated into practice since few physicians co-prescribe treatments for rhinitis and asthma in the same patient.

The recommendations of the ARIA workshop in 1999 are still valid,¹⁵ and in particular, it is recommended that all patients with AR, particularly if it is persistent, should be evaluated for asthma. AR is not only a risk factor for underlying asthma but could be a risk factor for asthma exacerbations. Patients with asthma should likewise be evaluated for rhinitis, and a combined strategy should ideally be used to treat the upper and lower airway diseases in terms of efficacy and safety.

REFERENCES

1. Bousquet J, Dahl R, Khaltaev N. Global alliance against chronic respiratory diseases. *Allergy* 2007; 62: 216-23.
2. Bousquet J, Khaltaev N. Global surveillance, prevention and control of Chronic Respiratory Diseases. A comprehensive approach. Global Alliance against Chronic Respiratory Diseases. World Health Organization. ISBN 978 92 4 156346 8. 2007.
3. Asher MI, Montefort S, Bjorksten B, *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: 733-43.
4. Ait-Khaled N, Odhiambo J, Pearce N, *et al.* Prevalence of symptoms of asthma, rhinitis and eczema in 13- to 14-year-old children in Africa: the International Study of Asthma and Allergies in Childhood Phase III. *Allergy* 2007; 62: 247-58.
5. Pekkarinen PT, von Hertzen L, Laatikainen T, *et al.* A disparity in the association of asthma, rhinitis, and eczema with allergen-specific IgE between Finnish and Russian Karelia. *Allergy* 2007; 62:281-7.
6. Majkowska-Wojciechowska B, Pelka J, Korzon L, *et al.* Prevalence of allergy, patterns of allergic sensitization and allergy risk factors in rural and urban children. *Allergy* 2007;62:1044-50.
7. Viinanen A, Munhbayarlah S, Zevgee T, *et al.* The protective effect of rural living against atopy in Mongolia. *Allergy* 2007; 62:272-80.
8. Canonica GW, Bousquet J, Mullol J, Scadding GK, Virchow JC. A survey of the burden of allergic rhinitis in Europe. *Allergy* 2007; 62 Suppl 85:17-25.
9. van Oene CM, van Reij EJ, Sprangers MA, Fokkens WJ. Quality-assessment of disease-specific quality of life questionnaires for rhinitis and rhinosinusitis: a systematic review. *Allergy* 2007; 62:1359-71.
10. Schatz M. A survey of the burden of allergic rhinitis in the USA. *Allergy* 2007; 62 Suppl 85: 9-16.
11. 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: case-control study. *J Allergy Clin Immunol.* 2007;120:381-7.
12. Maurer M, Zuberbier T. Undertreatment of rhinitis symptoms in Europe: findings from a cross-sectional questionnaire survey. *Allergy* 2007; 62: 1057-63.
13. Terreehorst I, Oosting AJ, Tempels-Pavlica Z, *et al.* Prevalence and severity of allergic rhinitis in house dust mite-allergic patients with bronchial asthma or atopic dermatitis. *Clin Exp Allergy* 2002; 32: 1160-5.
14. Georgy V, Fahim HI, El Gaafary M, Walters S. Prevalence and socioeconomic associations of asthma and allergic rhinitis in northern Africa. *Eur Respir J* 2006; 28:1292-97
15. Kuyucu S, Saraclar Y, Tuncer A, *et al.* Epidemiologic characteristics of rhinitis in Turkish children: the International Study of Asthma and Allergies in Childhood (ISAAC) phase 2. *Pediatr Allergy Immunol* 2006; 17: 269-77.
16. Bousquet J, Gaugris S, Koccevar VS, *et al.* Increased risk of asthma attacks and emergency visits among asthma patients with allergic rhinitis: a subgroup analysis of the improving asthma control trial. *Clin Exp Allergy* 2005; 35: 723-7.
17. Price D, Zhang Q, Koccevar VS, Yin DD, Thomas M. Effect of a concomitant diagnosis of allergic rhinitis on asthma-related health care use by adults. *Clin Exp Allergy* 2005; 35: 282-7.
18. Gaugris S, Sazonov-Koccevar V, Thomas M. Burden of concomitant allergic rhinitis in adults with asthma. *J Asthma* 2006; 43: 1-7.
19. Sole D, Camelo-Nunes IC, Wandalsen GF, Melo KC, Nas-pitz CK. Is rhinitis alone or associated with atopic eczema a risk factor for severe asthma in children? *Pediatr Allergy Immunol* 2005; 16: 121-5.

20. Kanani AS, Broder I, Greene JM, Tarlo SM. Correlation between nasal symptoms and asthma severity in patients with atopic and nonatopic asthma. *Ann Allergy Asthma Immunol* 2005; 94: 341-7.
21. van Ree R, Yazdanbakhsh M. Allergic disorders in African countries: linking immunology to accurate phenotype. *Allergy* 2007; 62: 237-46.
22. Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001; 108: S147-334.
23. 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: 1112-5.
24. Juniper EF, Riis B, Juniper BA. Development and validation of an electronic version of the rhinoconjunctivitis quality of life questionnaire. *Allergy* 2007; 62: 1091-3.
25. Nizankowska-Mogilnicka E, Bochenek G, Mastalerz L, *et al.* Aspirin provocation tests for diagnosis of aspirin sensitivity. EAACI/GA2LEN guideline. *Allergy* 2007; 62: 1111-8.
26. Passalacqua G, Bousquet PJ, Carlsen KH, *et al.* ARIA update: I - systematic review of complementary and alternative medicine for rhinitis and asthma. *J Allergy Clin Immunol* 2006; 117: 1054-62.
27. Bonini S, Bonini M, Bousquet J, *et al.* Rhinitis and asthma in athletes: an ARIA document in collaboration with GA2LEN. *Allergy* 2006; 61: 681-92.
28. Bousquet J, van Cauwenberge P, Ait Khaled N, *et al.* Pharmacologic and anti-IgE treatment of allergic rhinitis ARIA update (in collaboration with GALEN). *Allergy* 2006; 6: 1086-96.
29. Passalacqua G, Durham SR. Allergic rhinitis and its impact on asthma update: allergen immunotherapy. *J Allergy Clin Immunol* 2007; 119: 881-91.
30. Cruz AA, Popov T, Pawankar R, *et al.* Common characteristics of upper and lower airways in rhinitis and asthma: ARIA update, in collaboration with GA(2)LEN. *Allergy* 2007; 62 Suppl 84: 1-41.
31. Demoly P, Allaert FA, Lecasble M, Bousquet J. Validation of the classification of ARIA (allergic rhinitis and its impact on asthma). *Allergy* 2003; 58: 672-5.
32. 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: 758-9.
33. Valero A, Ferrer M, Sastre J, *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: 359-65.
34. Bousquet PJ, Combescure C, Neukirch F, *et al.* Visual analog scales can assess the severity of rhinitis graded according to ARIA guidelines. *Allergy* 2007; 62: 367-72.
35. Boot JD, de Kam ML, Mascelli MA, *et al.* Nasal nitric oxide: longitudinal reproducibility and the effects of a nasal allergen challenge in patients with allergic rhinitis. *Allergy* 2007; 62: 378-84.
36. Juniper EF, Riis B, Juniper BA. Development and validation of an electronic version of the Rhinoconjunctivitis Quality of Life Questionnaire. *Allergy* 2007; 62:1091-3.
37. Nizankowska-Mogilnicka E, Bochenek G, Mastalerz L, *et al.* Aspirin provocation tests for diagnosis of aspirin sensitivity. EAACI/GA2LEN guideline. *Allergy* 2007; 62: 1111-8.
38. Bonini M, Lapucci G, Petrelli G, *et al.* Predictive value of allergy and pulmonary function tests for the diagnosis of asthma in elite athletes. *Allergy* 2007; 62:1166-70.
39. Burgess JA, Walters EH, Byrnes GB, *et al.* Childhood allergic rhinitis predicts asthma incidence and persistence to middle age: a longitudinal study. *J Allergy Clin Immunol* 2007;120:863-9.
40. Bateman ED, Jithoo A. Asthma and allergy - a global perspective. *Allergy* 2007;62:213-5.
41. English RG, Fairall LR, Bateman ED. Keeping allergy on the agenda: integrated guidelines for respiratory disease in developing countries. *Allergy* 2007; 62:224-9.
42. Bousquet J, Khaltaev N, Cruz A, *et al.* ARIA Update. *Allergy* 2008; 63 Suppl 86: 8-160.
43. Schunemann HJ, Hill SR, Kakad M, *et al.* Transparent development of the WHO rapid advice guidelines. *PLoS Med* 2007; 4: e119.
44. Brozek JL, Baena-Cagnani CE, Bonini S, *et al.* Methodology for development of the Allergic Rhinitis and its Impact on Asthma. *Allergy* 2008; 63: 38-46.
45. Bjorksten B, Clayton T, Ellwood P, *et al.*, for the Phase III Study Group II. Worldwide time trends for symptoms of rhinitis and conjunctivitis: Phase III of the International Study of Asthma and Allergies in Childhood. *Pediatr Allergy Immunol* 2008; 19: 110-24.
46. Pearce N, Ait-Khaled N, Beasley R, *et al.*, for the ISAAC Phase Three Study Group. Worldwide trends in the prevalence of asthma symptoms: Phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax* 2007; 62: 758-66.
47. Trakultivakorn M, Sangsupawanich P, Vichyanond P. Time trends of the prevalence of asthma, rhinitis and eczema in Thai Children - ISAAC Phase III. *J Asthma* 2007; 44: 609-11.
48. Nishima S. A study on the prevalence of bronchial asthma in school children in western districts of Japan - comparison between the studies in 1982 and in 1992 with the same methods and same districts. *Arerugi* 1993; 42: 192-204.
49. Hsieh KE, Shen JJ. Prevalence of childhood asthma in Taipei, Taiwan and other Asian Pacific countries. *J Asthma* 1988; 25: 73-82.
50. Chiang LC, Chen YH, Hsueh KC, Huang JL. Prevalence and severity of symptoms of asthma, allergic rhinitis, and eczema in 10- to 15-year-old schoolchildren in central Taiwan. *Asian Pac J Allergy Immunol* 2007; 25: 1-5.
51. Droma Y, Kunii O, Yangzom Y, *et al.* Prevalence and severity of asthma and allergies in schoolchildren in Lhasa, Tibet. *Clin Exp Allergy* 2007; 37: 1326-33.
52. Zaman K, Takeuchi H, Yunus MD, *et al.* Asthma in rural Bangladeshi children. *Indian J Pediatr* 2007; 74: 539-43.
53. Aggarwal AN, Chaudhry K, SK Chhabra, *et al.* Prevalence and risk factors for bronchial asthma in Indian adults: a multicentre study. *Indian J Chest Dis Allied Sci* 2006; 48: 13-22.
54. Nga NN, Chai SK, Bihn TT, *et al.* ISAAC-based asthma and atopic symptoms among Hanoi schoolchildren. *Pediatr Allergy Immunol* 2003; 14: 272-9.

55. Zhang L, Han D, Huang D, *et al.* Prevalence of self-reported allergic rhinitis in China. *Int Archives Allergy Appl Immunol* 2009; 149: 47-57.
56. Kim YM, Lee CH, Kim JH, *et al.* Prevalence of allergic rhinitis on the basis of ARIA classification. *Korean J Otolaryngol - Head Neck Surg* 2006; 49: 623-8.
57. Kim TB, Kim YK, Chang YS, *et al.* Association between sensitization to outdoor spider mites and clinical manifestations of asthma and rhinitis in the general population of adults. *J Korean Med Sci* 2006; 21: 247-52.
58. Kim CW, Lee CW, Hur GY, Ye YM, Park HS. CARINA Study Group. Evaluation and control of allergic rhinitis in adult patients with asthma (CARINA) in Korea. *Korean J Asthma Allergy Clin Immunol* 2007; 27: 248-56.
59. Daengsuwan T, Lee BW, Visitsunton N, *et al.* Allergen sensitization to aeroallergens including *Blomia tropicalis* among adult and childhood asthmatics in Thailand. *Asian Pac J Allergy Immunol* 2003; 21: 199-204.
60. Zainudin BM, Lai CK, Soriano JB, *et al.* for the Asthma Insights and Reality in Asia-Pacific (AIRIAP) Steering Committee. Asthma control in adults in Asia-Pacific. *Respirology* 2005; 10: 579-86.
61. Valovirta E, Pawankar R. Survey on the impact of comorbid allergic rhinitis in patients with asthma. *BMC Pulm Med* 2006; 30: S3.1-10.
62. Lai CKW, Kim YY, Kuo SH, *et al.* Cost of asthma in the Asia-Pacific region. *Eur Respir Rev* 2006; 15: 10-6.
63. Chew CT, Goh DYT, Lee BW. The economic cost of asthma in Singapore. *Aust NZ J Med* 1999; 29: 228-33.
64. Pawankar R, Baena-Cagnani C, Bousquet J, *et al.* State of world allergy report 2008: allergy and chronic respiratory diseases. *WAO J* 2008; 1: S4-S17.