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## **National Impact of Allergies**

The most common allergic disorder, allergic rhinitis (AR), is a lifelong debilitating condition which, if untreated, results in significant health and economic consequences (1-5). In this article, I detail how a lack of access and non-adherence to effective AR treatment incurs these consequences and reinforces the need for patient education and evidence-based treatment and prevention guidelines.

Approximately 60 million Americans are affected by allergic diseases, ranking AR as the third-leading chronic disease in the U.S. among individuals younger than 45, and the fifth leading cause of chronic disease among all Americans (2, 4). Up to 30 percent of all adults and 40 percent of all children suffer from AR (1, 3, 4). Internationally, the prevalence of AR is increasing, particularly in developed countries (3-5). This upsurge in prevalence is demonstrated by noting that since 1995, the number of Americans suffering with AR has doubled to 37 million (6). This increased prevalence of AR has led to a concomitant enhancement of direct and indirect health-related costs that should encourage aggressive intervention to ensure clinically favorable and cost-effective outcomes (1-5).

## **The Economic Impact of Allergies**

When considering the impact of lost productivity and days off from work on the 60 million Americans with AR, the health related-expenditures attributable to AR are significant. In 2010, Americans with AR spent approximately \$17.5 billion on health related costs, lost more than six million work and school days and made 16 million visits to the doctor (7). Outpatient visits account for approximately one-third (36 percent) of AR-related direct costs and prescription medications account for nearly the entire remainder (7). It is not uncommon for over-the-counter (OTC) and prescription medications to be used in combination to treat the bothersome symptoms of nasal allergies (4, 7, 8). In fact, a recent survey reported that many adults with AR use two to four medications simultaneously to control their AR symptoms (8). When parents were surveyed about which medications their children used for allergy symptom relief, more than half (54 percent) reported the use of an OTC medicine, whereas slightly fewer (48 percent) reported use of prescription medications. Because costs for OTC medications are not usually included in the estimated expenditures and are reportedly equivalent to costs for prescription medications, health care expenditures attributable to AR may be underestimated (4, 8, 9, 12).

AR usually precedes and is associated with other chronic related allergic and non-allergic diatheses, including asthma, chronic sinusitis, otitis media with effusion, upper respiratory tract infections and sleep disorders (4, 9, 10). The presence of AR with such comorbidities, particularly in association with asthma, significantly increases health service utilization and health-related expenditures (9-11).

U.S. patients are in dire need of a proven and long lasting treatment for seasonal and perennial AR. Since 1995 the number of Americans suffering from AR alone has doubled to 37 million (6). This collective upsurge in the prevalence of all seasonal and perennial AR in the U.S. has further led to increased direct and indirect medical-related costs.

In contrast to symptomatic drug treatment (e.g. antihistamines and nasal steroids), which only temporarily relieves allergy symptoms (4, 5, 9, 12-14) allergen-specific subcutaneous immunotherapy (SCIT) is a disease-modifying therapeutic modality, thereby reducing the need for long-term treatment, the progression of allergic rhinitis to asthma (15- 17) and the development of new allergies (18-20). The clinical benefits of SCIT have been shown to persist for an additional three to 12 years after discontinuation of a 2.5- to 5.0-year treatment course (21, 22). It therefore stands to reason that the clinical benefits of SCIT also encompass economic benefits (12).

## **Allergic Rhinitis and Comorbidities**

AR is characterized as a substantial clinical burden and manifested by congestion, rhinorrhea, sneezing, and nasal and ocular pruritis (4, 9, 23). Also characteristic, although less common, are dry cough, sleep disturbance, headache, facial pain, and ear pain (4, 9). Symptoms of the illness can significantly reduce quality of life. Adults and children demonstrate physical discomfort, psychomotor dysfunction; disrupted sleep results in daytime somnolence and reduced alertness; impaired cognitive functioning, job performance, and learning often are diminished; and lost time from work, school, and leisure activities occurs (8, 24, 25). Historically, investigators have documented an association between allergic rhinitis and asthma, sinusitis, otitis media with effusion, recurrent respiratory tract infections and sleep disorders (9).

## **Relationship between Allergic Rhinitis and Comorbidities**

### **A. Asthma**

The incidence of allergic rhinitis in asthmatic adults can be as high as 58 percent (9). Investigators have documented the frequent association of AR with asthma. Allergen exposure and AR development often precedes the development and onset of asthma suggesting an etiologic association (26-33). In particular, AR and positive allergy skin tests have been thoroughly studied and defined by investigators as risk factors for the development of asthma (30-33). Of note, the treatment of AR reduces the incidence and severity of asthma (34-37). There is a significant increased global prevalence of AR and Asthma which has lead to a concomitant enhancement of direct and indirect health-related costs (4). Remarkably, the initiation of SCIT treatment effectively addresses the core pathophysiology of AR and investigators demonstrated that SCIT prevents the onset of asthma in patients with AR (15-17) and in others; it diminishes the asthmatic severity and morbidity (32-37). Thus, SCIT treatment diminishes health care expenditures for this large patient population (5, 12-14).

### **B. Sinusitis**

Acute and chronic sinusitis are identified in 31 million Americans each year (38). AR has been documented to be a predisposing factor in 30 percent of patients with acute maxillary sinusitis (39), in 78 percent of individuals suffering with extensive sinusitis (40), and in up to 67 percent of patients who had symptoms of chronic sinusitis with unilateral involvement (9, 41). In contrast, 80 percent of patients with bilateral sinusitis suffered with AR (9, 42-45). Furthermore, an association between extensive sinus disease and asthma was documented in 71 percent of patients. Because of the significant association of AR with sinusitis (9, 38-45), the effective treatment of individuals with AR should diminish the development of sinusitis and thereby diminish health care-related costs.

### **C. Otitis Media with Effusion & Dental disorders**

Acute otitis media with effusion (OME) is an inflammatory disorder of the middle ear frequently associated with eustachian tube dysfunction and the loss of hearing in children (9). OME is commonly linked with AR (46-49). This AR-linkage is corroborated by observing that the prevalence AR in children with OME ranges up to 50 percent (9, 48, 49).

Allergic rhinitis is a risk factor for the development of orthodontic malocclusions. The incidence of malocclusions is almost three times greater in obligate mouth breathers (a common finding in moderate and severe AR) than in unaffected individuals (9, 50).

### **D. Respiratory infections**

There is a reciprocal relationship between AR and respiratory viral infections (9). Childhood viral infections have been reported as risk factors for the development of allergic rhinitis and asthma (9, 51-56). In contrast, the expression of intercellular adhesion molecule 1, which is the receptor for 90 percent of human rhinoviruses, is up

regulated upon allergen exposure. This may in turn enhance the susceptibility of atopic individuals to rhinovirus infections (4, 9).

Nasal mucociliary clearance is the first line of defense of the respiratory tract ciliated epithelium against inhaled pathogens (57). AR, as a rhinopathic disorder is in part, characterized by alterations in nasal mucociliary clearance. In AR, the rhinopathic consequence is impaired mucociliary clearance which investigators have associated with a predisposition to respiratory infections (57, 58).

## **E. Sleep disorders**

AR has a profound effect on normal nocturnal breathing. This in turn contributes to aberrant patterns of sleep (4, 59, 60). Approximately 57 percent of adult patients and 88 percent of pediatric patients with AR experience sleep disruptions (4, 60, 61). These sleep disruptions contribute to daytime fatigue, learning performance disorders, work inefficiency, behavioral disorders, and attention-deficit disorders (4, 9, 59-62).

AR is a risk factor for obstructive sleep apnea syndrome (OSAS) due to the associated nasal obstruction, enlarged tonsils and adenoids, and an elongated face characteristic of chronic AR, all of which constitute a smaller upper airway size. The size of the upper airway determines the severity of the OSAS. Thus, adequate treatment of AR would diminish the severity of OSAS. Effective treatment of AR may prevent the occurrence of OSAS and reduce the severity of existing OSAS (63, 64).

## **Treatment with Allergen-Immunotherapy**

Most allergy sufferers spend their entire lives battling their symptoms without knowing the exact cause of their reactions. Often, they treat their undiagnosed allergies with over-the-counter and prescription drugs that only mask the symptoms (4, 5, 9, 12-14). Over 100 years of scientific research and medical practice (4, 5, 9) have proven that the only lasting relief from allergies is immunotherapy, which induces immunologic tolerance by introducing a patient to the administration of safely increased doses of an allergen(s).

Allergen Immunotherapy (IT) is a therapeutic modality directed towards diminishing a patient's sensitivity to allergens. It involves introducing the patient to increasing amounts of an allergen (e.g. pollen, mold) through a series of customized single-injections, over the course of several years. Immunotherapy desensitizes the patient to the allergen that triggers their symptoms, ultimately allowing patients to be exposed to these allergens without any subsequent allergic reaction.

IT is the only known disease-modifying treatment for allergies. The results of IT can be life-changing and significantly increase the quality of life while simultaneously diminishing morbidity (4, 5, 9, 65). IT has been shown to diminish symptoms of allergic rhino conjunctivitis (4, 5, 9), and decrease the severity of allergic-asthma (32, 33, 35-37). Remarkably, IT also prevents the onset of new allergies and allergic asthma (15-20).

## **The Economic Impact of Immunotherapy**

In the majority of cases, immunotherapy, results in: significant clinical improvement, the diminished utilization of antihistamines and nasal steroids, diminishing the severity of allergic asthma and reducing the utilization of asthma medications, and diminishing the severity of the other comorbidities of sinusitis, OME, respiratory infections and sleep disorders (4,5,9). As a consequence, there are fewer physician visits, and fewer hospitalizations. These outcomes diminish the economic-burden associated with AR and comorbidity treatment.

Numerous studies have examined the potential economic benefit of AR treatment with SCIT. The vast majority of study outcomes demonstrated significant savings to patients, government agencies, and insurance companies when SCIT was utilized. Hankin et al. completed 3 economic studies (12-14), the longest a retrospective 11-year (1997–2008), matched cohort, claims analysis of Florida Medicaid adult enrollees with AR (14). After 18 months, total mean health care costs for inpatient (\$10,352 vs. \$14,796,  $P = .003$ ), outpatient (\$2466 vs. \$4181,  $P < .0001$ ), pharmacy (\$5636 vs. \$6321,  $P < .0001$ ) and total health care services (\$10,626 vs. \$17,912,  $P < .0001$ ) were significantly lower for patients who were administered SCIT. Significant total health care savings were realized within 3 months of SCIT initiation (\$1932 vs. \$3189,  $P < .0001$ ). Remarkably, 18-month total cost savings per patient with SCIT were 41 percent (14). Similar results were promulgated by several European investigators (66-69). In conclusion, the unambiguous principle is that SCIT provides significant cost benefits. In the US, total health care cost savings of 33 percent and 41 percent have been reported for US children and adults with AR (with or without asthma), respectively, within 18 months of SCIT initiation (12-14). Considering the suboptimal duration of SCIT treatment reported for US patients (12, 13) estimated US cost savings conferred by SCIT are likely to be greater among patients who adhere to the suggested 3-year minimum course of treatment.

The initial course of immunotherapy is one year, but maximal benefits are achieved after three to five years of SCIT administration (4, 13). Immunotherapy is very effective in greatly decreasing or eliminating the symptoms of allergies. Up to 85 percent of patients receive a complete elimination or significant reduction in allergy symptoms using immunotherapy (71). Most insurance plans cover allergy testing and immunotherapy.

### **Shortage of Allergists to Administer Immunotherapy**

There is a growing shortage of allergists in the United States. Without intervention, it is estimated that the number of full-time equivalent (FTE) allergist/immunologists will decline about 7 percent from 3,660 in 2006 to 3,400 in 2020. Meanwhile, demand for these physicians is projected to increase by 35 percent over the same period (to more than 5,550 in 2020). While seasonal and perennial AR generates considerable health-related costs, reduces the patient's quality of life, and workforce and school productivity, not nearly enough specialists exist to treat the number of patients in need.

Until now, the only disease-modifying and long term relief for allergies, in the form of IT, has remained primarily in the hands of allergists. However, the majority of patients with AR are treated by primary care providers and not Board Certified Allergists (4, 5). In addition, recent studies (70) demonstrated the ability of primary care physicians to diagnose and assess individuals with AR.

## REFERENCES

1. Schoenwetter WF. Economic impact and quality-of-life burden of allergic rhinitis. *Curr Med Res Opin* 20(3): 305-17, 2004.
2. Chronic conditions - a challenge for the 21st century. National Academy on an Aging Society Washington, DC 1999.
3. Schoenwetter W.F. Allergic rhinitis: epidemiology and natural history. *Allergy Asthma Proc* 21. (1): 1-6, 2000.
4. Meltzer E.O., Blaiss M.S., Derebery M.J., et al. Burden of allergic rhinitis: results from the Pediatric Allergies in America survey. *J Allergy Clin Immunol* 124. (Suppl 3): S43-S70, 2009.
5. Hankin C.S., Cox, L., Bronstone A. The Health Economics of Allergen Immunotherapy. *Immunol Allergy Clin North Amer.* 31(2):325-41,2011.
7. Lindner, Melanie. "When Allergies Attack." *Fortune* 26 July 2010.
8. Soni, A. Allergic rhinitis: trends in use and expenditures, 2000 and 2005; Statistical brief #204. Agency for Healthcare Research and Quality Bethesda (MD), 2008.  
New survey suggests patients want fast, long relief of allergy symptoms. PRN Newswire. March 20, 2006.
9. Meltzer E.O.: Quality of life in adults and children with allergic rhinitis. *J Allergy Clin Immunol* 108. (1): S45-S53, 2001.
10. S.L. Spector. Overview of comorbid associations of allergic rhinitis, *J Allergy Clin Immunol* 99 (suppl): S773-S780, 1997.
11. Halpern M.T., Schmier J.K., Richner R., et al: Allergic rhinitis: a potential cause of increased asthma medication use, costs, and morbidity. *J Asthma* 41. (1): 117-126.2004;
12. Thomas M., Kocevar V.S., Zhang Q., et al: Asthma-related health care resource use among asthmatic children with and without concomitant allergic rhinitis. *Pediatrics* 115. (1): 129-134.2005
13. Hankin C.S., Cox L., Lang D., et al. Allergen immunotherapy and health care cost benefits for children with allergic rhinitis: a large-scale, retrospective, matched cohort study. *Ann Allergy Asthma Immunol* 104. 79-85, 2010.
14. Hankin C.S., Cox L., Lang D., et al. Allergy immunotherapy among Medicaid-enrolled children with allergic rhinitis: patterns of care, resource use, and costs. *J Allergy Clin Immunol* 121 (1): 227-232, 2008.
15. Hankin CS, Cox L, Wang Z, et al. Does allergen-specific immunotherapy provide cost benefits for children and adults with allergic rhinitis? Results from large-scale retrospective analyses jointly funded by AAAAI

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16. C. Moller, S. Dreborg, H.A. Ferdousi, S. Halken, A. Host and L. Jacobsen *et al.*, Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). *J Allergy Clin Immunol* **109**: 251–256, 2002.
17. Nayak, A.S. The asthma and allergic rhinitis link. *Allergy Asthma Proc* **24**:395–402, 2003.
17. Casale , T.B. and Dykewicz, M.S. Clinical implications of the allergic rhinitis-asthma link. *Am J Med Sci* **327**: 127–138, 2004.
18. Pajno, GB, Barberio, G, De Luca, F et al. Prevention of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy: a six-year follow-up study. *Clin Exp Allergy* 31:1392–1397, 2001.
19. Purello-D'Ambrosio, F, Gangemi, S, Merendino, RA et al. Prevention of new sensitizations in monosensitized subjects submitted to specific immunotherapy or not: a retrospective study. *Clin Exp Allergy* 31:1295-1302, 2001.
20. Halken, S. Prevention of allergic disease in childhood: clinical and epidemiological aspects of primary and secondary allergy prevention. *Pediatr Allergy Immunol.* 15 (Suppl. 16): 9–32, 2004.
21. Eng, PA, Reinhold, M, and Gnehm, HP. Long-term efficacy of pre-seasonal grass pollen immunotherapy in children. *Allergy* **57**: 306–312, 2002.
22. Eng, PA, Borer-Reinhold, M, Heijnen, I, et al. Twelve-year follow-up after discontinuation of pre-seasonal grass pollen immunotherapy in childhood, *Allergy* 61: 198–201, 2006.
23. Wallace D., Dykewicz M., Bernstein D., et al. The diagnosis and management of rhinitis: an updated practice parameter. *J Allergy Clin Immunol* 122 (2): S1-S8, .2008.
24. Bousquet, J, Bullinger, M, Fayol, C, et al. Assessment of quality of life in patients with perennial allergic rhinitis with the French version of the SF-36 Health Status Questionnaire, *J Allergy Clin Immunol* **94**:182–188, 1994.
25. Bousquet, J, Knani J, Dhivert H, et al. Quality of life in asthma. I. Internal consistency and validity of the SF-36 questionnaire. *Am J Respir Crit Care Med* **149**: 371–75, 1994.
26. Sporik, R, Holgate, ST, Platts-Mills, TAE. Et al. Exposure to house-dust mite allergen (*Der p 1*) and the development of asthma in childhood, *N Engl J Med* **323**: 502–507, 1990.
27. Van der Heide, S, de Monchy, JGR, de Vries, K, et al. Seasonal variation in airway hyperresponsiveness and natural exposure to house dust mite allergens in patients with asthma, *J Allergy Clin Immunol* **93**: 470–475, 1994

28. Corren, J, Adinoff, AD, and Irvin, CG. Changes in bronchial responsiveness following nasal provocation with allergen. *J Allergy Clin Immunol* **89**: 611–618, 1992.
29. Newacheck PW, and Stoddard, JJ. Prevalence and impact of multiple childhood chronic illnesses. *J Pediatr* **124**: 40–48, 1994.
30. Sibbald, B, and Strachan, DP. Epidemiology of rhinitis. In: WW Busse and ST Holgate, Editors, *Asthma and rhinitis*. Blackwell Scientific Publications, Boston: 32–43, 1995.
31. Anderson, HR, Pottier, AC, and Strachan, DP. Asthma from birth to age 23: incidence and relation to prior and concurrent atopic disease. *Thorax* **47**:537–542, 1992.
32. Settipane, R, Hagy, GW, and Settipane, GA. Long-term risk factors for developing asthma and allergic rhinitis: a 23-year follow-up study of college students. *Allergy Proc* **15**:21–25, 1994.
33. Gergen PJ, and Turkeltaub, PC. The association of individual allergen reactivity with respiratory disease in a national sample: data from the second National Health and Nutrition Examination Survey, 1976-80 (NHANES II). *J Allergy Clin Immunol* **90**: 579–588, 1992.
34. Polosa R, Li Gotti F, Mangano G, Paolino G, Mastruzzo C, Vancheri C, et al. Effect of immunotherapy on asthma progression, BHR and sputum eosinophils in allergic rhinitis. *Allergy* **59**:1224-8m 2004.
35. Johnstone DE, Dutton A. The value of hyposensitization therapy for bronchial asthma in children: a 14-year study. *Pediatrics*. **42**:793-802, 1968.
36. Jacobsen L. Preventive aspects of immunotherapy: prevention for children at risk of developing asthma. *Ann Allergy Asthma Immunol*. **87**:43-6, 2001.
37. Polosa R, Al-Delaimy WK, Russo C, Piccillo G, Sarva M. Greater risk of incident asthma cases in adults with allergic rhinitis and effect of allergen immunotherapy: a retrospective cohort study. *Respir Res*. **6**:153, 2005.
38. Moss, AJ, and Parsons, VL. Current estimates from the National Health Interview Survey, United States, 1985, *Vital Health Stat* **10**: 1–82, 1986.
39. Savolainen, S. Allergy in patients with acute maxillary sinusitis. *Allergy* **44**: 116–122., 1989.
40. Hisamatsu, K, Ganbo, T, and Nakazawa, T, et al. Cytotoxicity in human eosinophil granule major basic protein to human nasal sinus mucosa in vitro. *J Allergy Clin Immunol* **86**: 52–63, 1990.
41. Newman, LJ, Platts-Mills, TAE and Phillips, CD et al. Chronic sinusitis: relationship of computed tomographic findings to allergy, asthma, and eosinophilia. *JAMA* **271**: 363–367, 1994.
42. van Dishoeck, HA, and Franssen, MB. The incidence and correlation of allergy and chronic maxillary sinusitis. *Practica Oto-Rhino-Laryngologica (Basel)* **19**: 502–506, 1957.

43. van Dishoeck, HA. Allergy and infection in the paranasal sinuses. *Adv Otorhinolaryngol* **10**: 1–29, 1961.
44. Davis, WE, Templer, JW, and Lamear, WR, et al. Middle meatus antrostomy: patency rates and risk factors. *Otolaryngol Head Neck Surg* **104**: 467–72, 1991.
45. Conner BL, Roach, ES, Laster, W, et al. Magnetic resonance imaging of the paranasal sinuses: frequency and type of abnormalities. *Ann Allergy* **62**: 457–460, 1989.
46. Hurst, DS, and Venge, P. The presence of eosinophil cationic protein in middle ear effusion. *Otolaryngol Head Neck Surg* **108**: 711–22, 1993.
47. Fireman, P. The role of antihistamines in otitis. *J Allergy Clin Immunol* **86**: 638–41, 1990.
48. Tomonaga, K, Kurono, Y, and Mogi, G. The role of nasal allergy in otitis media with effusion: a clinical study. *Acta Otolaryngol* **458**: S41–S47, 1988.
49. Bernstein, J, Lee, J, and Conboy, K, et al. Further observations on the role of IgE-mediated hypersensitivity in recurrent otitis media with effusion. *Otolaryngol Head Neck Surg* **93**:611–15, 1985.
50. Bresolin, D, Shapiro, PA, Shapiro, GG, et al. MD Mouth breathing in allergic children: its relationship to dentofacial development, *Am J Orthod* **83**: 334–40, 1983.
51. Pullan, CR, and Hey, EN. Wheezing, asthma, and pulmonary dysfunction 10 years after infection with syncytial virus in infancy. *Br Med J* **284**: 1665–69, 1982.
52. Sims, DG, Downham, MAPS, and Gardener, PS, et al. Study of 8-year-old children with a history of respiratory syncytial virus bronchiolitis in infancy. *Br Med J* **1**: 11–14, 1978.
53. Welliver, RC, Wong, DT, and Sun, M, et al. Parainfluenza virus bronchiolitis: epidemiology and pathogenesis. *Am J Dis Child* **140**: 34–40, 1986.
54. McConnochie, MK, and Roghmann, KJ. Bronchiolitis a possible cause of wheezing in childhood: new evidence. *Pediatrics* **74**: 1–10, 1984.
55. Gurwitz, D, Corey, M, and Levison, H. Pulmonary function and bronchial reactivity in children after croup. *Am Rev Respir Dis* **122**: 95–99, 1980.
56. Minor, TE, Baker, JW, and Dick, EC et al. Greater frequency of viral respiratory infections in asthmatic children as compared with their non-asthmatic siblings. *J Pediatr* **85**: 472–77, 1974.
57. **Vlastos I, Athanasopoulos I, Mastronikolis NS, et al. Impaired mucociliary clearance in allergic rhinitis patients is related to a predisposition to rhinosinusitis.** *Ear Nose Throat J*.88(4):E17-9, 2009.
58. **Sun SS, Hsieh JF, Tsai SC, Ho YJ, Kao CH.** Evaluation of nasal mucociliary clearance function in allergic rhinitis patients with technetium 99m-labeled macroaggregated albumin rhinoscintigraphy. *Ann Otol Rhinol Laryngol*. 111(1):77-9, 2002.

59. Golbin, A, Bernales, R, and Lim, D. Perennial allergic rhinitis (PAR), and sleep disorders [abstract], *Ann Allergy* 68: 85, 1992.
60. Klossek, JM, Gohler, C, Vervloet, D, et al. Epidemiology of seasonal spring-time allergic rhinitis in adults in France. *Presse Med* 34: 348–352, 2005.
61. Gozal, D. Sleep-disordered breathing and school performance in children. *Pediatrics* 102: 616–20, 1998.
62. Owens, J, Opiari, L, Nobile, C, and Spirito, A. Sleep and daytime behavior in children with obstructive sleep apnea and behavioral sleep disorders. *Pediatrics* 102:1178–84, 1998.
63. [Kalpaklıoğlu AF](#), [Kavut AB](#), [Ekici M](#). Allergic and nonallergic rhinitis: the threat for obstructive sleep apnea. *Ann Allergy Asthma Immunol*.103(1):20-5, 2009.
64. [Ng DK](#), [Chan CH](#), [Hwang GY](#), [Chow PY](#), [Kwok KL](#). A review of the roles of allergic rhinitis in childhood obstructive sleep apnea syndrome. *Allergy Asthma Proc*. 2006. 27(3):240-2.
65. Bousquet, J, Bullinger, M, Fayol, C. Assessment of quality of life in patients with perennial allergic rhinitis with the French version of the SF-36 Health Status Questionnaire, *J Allergy Clin Immunol* **94**: 182–88, 1994.
66. Buchner K., Siepe M.: Nutzen der Hyposensibilierung unter wirtschaftlichen Aspekten. *Allergo J* 4: 156-63, 1995.
67. Schädlich P.K., Brecht J.G.: Economic evaluation of specific immunotherapy versus symptomatic treatment of allergic rhinitis in Germany. *Pharmacoeconomics* 17. (1): 37-52, 2000.
68. Ariano R., Berto P., Tracci D., et al: Pharmacoeconomics of allergen immunotherapy compared with symptomatic drug treatment in patients with allergic rhinitis and asthma. *Allergy Asthma Proc* 27. (2): 159-163, 2006.
69. Keiding H., Jorgensen K.P. A cost-effectiveness analysis of immunotherapy with SQ allergen extract for patients with seasonal allergic rhinoconjunctivitis in selected European countries. *Curr Med Res Opin* 23. (5): 1113-20, 2007.
70. Smith, HE, Hogger, C, Lallemand, C, et al. Is structured allergy history sufficient when assessing patients with asthma and rhinitis in general practice? *J Allergy Clin Immunol*. 123(3): 646-50, 2009.
71. Airborne allergens: Something in the air. National Institute of Allergy and Infectious Diseases. NIH Publication No. 03-7045. 2003.