

LITERATURE REVIEW

The united airway disease

Nuray Bayar Muluk

ENT Department, Faculty of Medicine, Kırıkkale University, Kırıkkale, Turkey

ABSTRACT

OBJECTIVES. The aim of this paper is to review the united airway concept.

MATERIAL AND METHODS. We searched Pubmed, Google, Google Scholar and Proquest Central database of Kırıkkale University.

RESULTS. Upper and lower airways are thought as a morphological and functional unit. There is a link between rhinitis and asthma. Over 80% of asthmatics have rhinitis and 10-40% of rhinitis patients have asthma. Rhinosinusitis is related to asthma in 34-50% of the patients. The relationship between rhinosinusitis and asthma may include “nasobronchial reflex, pharyngobronchial reflex, inhalation of dry, cold air and environmental pollutants inhalation”.

CONCLUSION. The united airway concept suggests that upper and lower airways are thought as a morphological and functional unit. It has been commonly accepted in recent years. Allergic rhinitis (AR) is a risk factor for asthma; and Allergic Rhinitis and Asthma (ARIA) suggest bronchial involvement in AR patients.

KEYWORDS: united airway, upper airway, lower airway, asthma, allergic rhinitis.

INTRODUCTION

Upper and lower airways are thought as a morphological and functional unit and the relationship between them has been observed for a long time^{1,2}. The nose is located in the passage of the airway and the underlying airway approaches as a strong ventilation to protect it from the destructive effects of the air. The nose warms, filters, humidifies and saturates the air, so at 37°C the natural air is sent to the lungs with full steam. During nasal breathing the collected particles with an aerodynamic equivalent diameter (AED) higher than 15 µm accumulate in the upper respiratory tract. Particles with AEDs > 2.5 µm are basically collected in the trachea and bronchus, while those with low AED enter the gas exchange area of the lungs³. The nose and the bronchial mucosa simulations are shown, and the strikingness among the most important aspects of nasal-lung communication is a practical complement to the lungs that provides nasal safety⁴. However, the upper respiratory tract elements and their communication with the lower respiratory tract are more extensive than air conditioning⁵.

Asthma and rhinitis patients tend to have a more serious disease with higher treatment costs, and

therefore the “airway disease” has a considerable effect, including the treatment and prophylaxis of these air distributions^{6,7}. Allergic rhinitis (AR) is a risk factor for asthma; Allergic Rhinitis and Asthma (ARIA) suggest bronchial involvement in AR patients^{8,9}.

In this paper, we review the united airway concept. We searched Pubmed, Google, Google Scholar and Proquest Central database of Kırıkkale University.

EPIDEMIOLOGY

AR is the most widely accepted phenomenon of all atopic diseases and although most patients may be of any age, most patients report the onset of symptoms before the age of 30, which is the most well-known conception in children⁴. AR can be seen as a significant general medical issue due to the patient’s personal satisfaction, work / school performance and profitability being dominated by monetary weight and influence^{4,5}.

AR is thought to be a risk factor for asthma⁴. Asthma is portrayed by the historical backdrop of episodic respiratory symptoms, for example, “wheezing, shortness of breath and chest torment”, and is related

with variable expiratory flow limitations^{5,10}. Non-AR patients (NAR) are at expanded risk of creating non-allergic asthma. NAR appears further in life than AR and it is not a solitary issue; however, it is made out of a heterogeneous gathering of diseases^{5,11}.

The link between rhinitis and asthma has been the subject of some epidemiological studies that reliably demonstrate an important implication of the two diseases¹². Despite asymptomatic asthma in approximately 19-38% of patients with AR and the fact that 30-80% of asthmatics had AR, late studies found that 98.9% of rhinitis was present in allergic asthmatics and 78.4% in non-allergic asthmatics¹³. The vast majority of AR patients have bronchial hyperreactivity (BHR)¹⁰.

Over 80% of asthmatics have rhinitis and 10-40% of rhinitis patients have asthma to suggest “one airway, one disease”⁴. Rhinitis findings are found in 98.9% of allergic asthmatics and 78.4% of non-allergic asthmatics. In addition, approximately 30% of patients with AR alone, without asthma, have either methacholine or histamine hypersensitivity^{2,4,5,14}.

Although allergic rhinitis is seen as a risk factor for the formation of asthma, it can be assumed that this term cannot be changed exactly; this can be explained by an initial time at which the upper airway disease (UAD) can go as far as asthma⁸.

PATHOPHYSIOLOGICAL EVIDENCE

The upper and the lower airways provide a continuum that allows air to enter and exit the lungs and share many anatomic and histological features². The ciliary epithelium, basement membrane, lamina propria, glands and goblet cells contain regular structures that shape the so-called united airway¹⁵. Then again, there are contrasts between the upper and the lower airways. The nasal mucosa, enriched with vessels, attached to the bone; the bronchial mucosa, enriched with smooth muscle cells, attached to the cartilage^{5,16}.

The upper respiratory tract is the main focus of allergens, physical and compound natural stimuli; thus, they have a tendency to be the first influenced by the allergic airway disease, and if the disease intensity is low, the upper respiratory tract might be the fundamental part of the influenced respiratory tract. Be that as it may, when the whole respiratory tract is included, rhinosinusitis and asthma begin after a parallel highway^{5,17}.

The allergic respiratory disease is caused by hypersensitivity or IgE-mediated responses when the inhaled allergen reacts with “mast cells and basophiles, the major effector cells, bearing IgE antibodies”. Concomitant cross-linking of allergen-specific IgE

molecules to cells by allergen particles allows granule-associated mediators (e.g., “histamine, tryptase”), “membrane lipid-derived mediators (i.e., leukotrienes)”, and cytokines to come^{18,19}.

AR and atopic asthma arise from an allergic response to an IgE response associated with variable strength airway aggravation⁴. Since the Ig displayed on the surface of B cells is IgM, it is of vital importance to convert IgM to IgE with the goal of creating allergic aggravation. IgE converting isotypes require antigen entry and two different signals²⁰. The first markers, IL-4R and IL-13R, are mediated by IL-13 as well as interleukin (IL) -4, which mediates STAT6 translating IgE isotypic interpretation. The flags are given by CD40 binding in CD40L B-cells in T-cells that mainly initiate DNA-key recombination²⁰. The IgE interfering safe reaction is initiated when allergens are taken up by cells presenting antigen through the cell surface Ig receptor. Subsequently, the T helper (TH) cells, which recognize and trigger the allergen – major histocompatibility complex II compound, are introduced into the major histocompatibility complex class II. The allergen-specific TH2 cells form IL-4 and IL-13 and exchange CD154 and require IgE class change^{5,20,21}.

When IgE is produced by the B cells, Ig binds to the high affinity receptor FcεR1 on mast cells and basophiles²⁰. In the future, contacts with polyvalent sensitizing allergens will result in FcεR1, initiating a quick-tip varnish response that is the focus of ARC and the pathogenesis of allergic asthma²⁰. The reaction has gone to a quick pace, triggered by the development of pre-built up and quickly incorporated mediators from mast cells and basophiles, activating occasions, for example, erythema, edema and skin itching in the upper respiratory tract, nasal obstruction in the upper respiratory tract, and cough, edema and mucus secretion in the lower respiratory tract²⁰. A late stage, which is intervened by cytokines and chemokines and described by edema and leukocytic union, can happen 6 to 24 hours after the coveted stage. Eosinophils, which are mainly produced by the IL-5 delivered by the TH2 cells, emerge and depend on the chronic inflammatory process and tissue harm^{5,20}.

Several components have been recommended to clarify the interaction between upper and lower airways^{5,22}. Most likely, inflammatory changes in the upper and lower airways lead to a basic reaction, involving bone marrow, which then leads to the arrival of the progenitor cells, which are recorded at tissue locations. The provocative discharges can be spread from the upper airway to the underlying area by postnasal diving and basic dissemination²⁰. An important confirmation of UAD interaction is the proximity of thickening of the epithelial basement membrane, which is a typical hallmark of the lower

respiratory tract remodelling in asthmatic atopic patients as well as in asthmatic patients. For each situation, the reestablishment has all the earmarks of being less extensive in the nasal mucosa than in the bronchial mucosa. The reason for this qualification might be cleared up by the production of particular cytokines of smooth muscle cells and their vicinity to embryological separation qualities in the lungs or by their diverse re-expression in asthma and rhinitis^{19,23}.

RISK FACTORS

Allergen exposure

Allergenic input is seen as a real risk factor for the recovery of UAD^{19,24}. Rhinitis and asthma are characterized by high sensitization to the usual allergens in the group, i.e. aeroallergens. When considering various air / breathing allergens, the most important qualities are the sufficiency between open air allergens (i.e., dust and forms), closed area allergens (e.g., cat, dog, puppies, parasites) and words related operators^{19,25}.

Hereditary Factors

The rate of allergic diseases in families is extraordinary: 35% to 95% for asthma, and 33% to 91% for AR²⁶. Focuses on the prevalence of allergic manifestations in relationship with family history indicate expanding increments with the risk of creating asthma or AR, with maybe a couple allergic diseases, and more than three allergic diseases have turned out to be more conspicuous if the allergic disease happens²⁶. A positive family history is one of the strictest devices for anticipating the allergic disease^{19,27}.

The relationship of asthma and AR with different chromosomal domains was found recently. Surely, there are roughly 161 diverse potential biomarkers engaged with respiratory irritation²⁷. For instance, Liu et al. have demonstrated that single nucleotide polymorphisms in TNFSF4 and FAM167A-BLK genes might be related with asthma and AR²⁸ and Zhao et al. reported the PBX2 gene in the 6p21.3 asthma susceptibility locus with an expanded risk for both AR and asthma^{19,29}.

REACTION TRIGGERS

There might be a few factors that trigger reflex airway responses. Infections and microbes are in charge of infectious rhinitis, rhinosinusitis, bronchiolitis and pneumonia. Chronic Obstructive Pulmonary Disease (COPD) and asthma exacerbations can happen related with them³⁰⁻³². Tobacco smoke and climatic or professional pollutants can likewise cause chronic aggravation of upper and lower respiratory

tracts, for example, chronic bronchitis, and can cause metaplasia and carcinogenic lesions. Tobacco smoke is the most vital hazard factor for COPD³³, laryngeal cancer, bronchial carcinoma, and rhinitis³⁴. The presentation of cadmium smoke to word related exposure may bring about the result of emphysema³⁵, while the exposure to asbestos may cause cancer³⁶.

Allergens are solid stimulants of allergic rhinitis and asthma. Indoor allergens, such as dust mites or animal proteins, are highly associated with asthma³⁷. Outdoor air allergens, e.g. pollens, are generally associated with rhinitis³⁸. Pollen particles are usually too large to enter the lower airways, but pollen grains are found in bronchial secretions and in the lung parenchyma³⁸. Asthma and rhinitis hypersensitivity reactions can be activated by beta blockers or aspirin, exposure to cold weather and physical exercise^{36,39,40}.

Neural reflexes

The presence of a naso-bronchial reflex starting from the sensory nerve endings, through the trigeminal nerve, goes to the central nervous system and follows an efferent pathway in the vagus nerve to deliver airway smooth muscle contraction^{5,17}.

Several studies in healthy subjects and in asthmatics have shown that airway resistance increases after cold and dry air is inhaled^{39,41}. Another important study showed an expansion of the AHR after nasal allergen induction in asthmatics, showing that asthma symptoms deteriorated after seasonal rhinitis exacerbation⁴². Remember that the traditional naso-bronchial reflex is part of the dive reflex⁴³. The cold water submersion of the head causes rapid respiration suppression (apnea), laryngospasm and bronchoconstriction to suppress the lower respiratory tract from the dive⁴³. Contingent upon the relaxation of the inspiratory muscles, the respiration of dust, contaminants, and aggravations through the nose may bring about prompt bronchoconstriction, while the expiratory airway is breathing at the stage⁴³. Consequently, in people with the allergic respiratory disease, this reflex may cause an expansion in asthma manifestations after nasal damage⁵.

THE LINK BETWEEN ALLERGIC RHINITIS AND ASTHMA

Allergic rhinitis is the most recognized agent of all atopic diseases, although it normally occurs before school age in patients who exhibited atopic dermatitis during the first years, and may occur at any age. Allergic rhinitis may be irregular or unstable with conditional or gentle or direct / extreme conditional side effects, leading to the severity of side effects experienced by the patient⁴⁴. Apart from traditional indications such as sniffing, nasal congestion, AR is

shown to be weakness and possibly restlessness in the personal satisfaction of patients, enthusiastic subjects, disability in exercises and social services⁴⁴⁻⁴⁶.

Asthma is defined as recurrent airway obstruction disease and it is analyzed using lung studies and bronchial hyperreactivity measurements. Primer findings include dry cough, expiratory wheezing, chest relaxation and dyspnea, intermittently activated with the exacerbation of allergies and diseases of the airways⁴⁷. Small airway pathology characterized by reduced forced expiratory flow (FEF) at 25-75% of the lung volume and abnormal spirometry has been suggested to be a sign of early allergic or inflammatory involvement of small airways with allergic diseases without asthma^{45,48}.

Allergic rhinitis is considered a risk factor for asthma, but in these cases it is thought that these terms cannot be fully resolved⁴⁸, as the united airway diseases that may lead to asthma may speak at the onset of the disease. Approximately 19% to 38% of allergic rhinitis patients have active asthma and 30-80% of asthmatics have allergic rhinitis. Nevertheless, this information is probably considered to be surprisingly low since rhinitis is present in 98.9% of the asthmatics and in 78.4% of non-allergic asthmatics^{13,45}.

Allergic rhinitis (AR) is now associated with asthma and regularly prevents bronchial hyperreactivity⁴⁸. Most patients with AR (up to 80% of cases) show bronchial hyperreactivity (BHR), no loss of lung function and no clinical signs of asthma^{10,49}, and this finding may be a prognostic factor for the progression of asthma^{36,50}.

THE LINK BETWEEN RHINOSINUSITIS AND ASTHMA

Rhinosinusitis and asthma are two unique expressions of a common pathological process that is typically not influenced by allergies, in which eosinophils and airway epithelium assume a part⁵¹. Late movement, in the consciousness airway pathology, has distinguished inflammation as a method for understanding these infections. Taken together, different diverse parts that link airway fragments from “the upper (nose, sinuses, larynx, pharynx, and trachea) and fundamental (bronchus and lungs)” can likewise be incorporated^{36,52}.

In children, the paranasal sinus diseases are thought to be a critical hazard factor for the treatment of lower respiratory tract illnesses, and rhinosinusitis and asthma seem to have framed two unique expressions in a common pathological process⁵³. The late advances in understanding the investigation of science of the airway diseases explained the role of inflammation in these two pathologies. There can be a few unique

systems that connect the “upper (nose, sinus, larynx, pharynx, and trachea) and lower (bronchus and lungs)” airway sections⁵².

Precipitation of asthma, as a rule, stimulates sinusitis, and then the connection between exacerbation of sinusitis and asthma can be an epiphenomenon⁵³. Rhinosinusitis is associated with asthma in 34% to half of patients⁵⁴. In patients with asthma, the occurrence of associated rhinosinusitis increases to 84%, especially with exacerbations of asthma^{45,55}.

It is vague whether rhinosinusitis is a quick trigger for asthma or whether the two conditions are demonstrative of a run of a typical underlying process. The conceivable clarifications of the relationship of rhinosinusitis and asthma may include the “naso-bronchial reflex, pharyngobronchial reflex, inhalation of dry, cold air and environmental pollutants inhalation”⁵⁴. To be sure, even bone marrow can give this connection between the upper and lower airways while making a run of the typical disease: blood eosinophils count is frequently connected with asthma development and asthma seriousness, though IL-5 might be a critical cytokine to facilitate the systemic interaction^{36,54,55}.

Now it is confirmed that rhinosinusitis without polyposis or eosinophilic inflammation is a quick stimulant for asthma, but rhinosinusitis with polyps and eosinophilic exacerbation suggests the main mechanisms of asthma⁴⁷. In essence, it is clear that the markers of bronchial irritation, commonly found in asthmatics, correspond to the severity of sinusitis^{36,56}.

CONCLUSIONS

The united airway concept suggests that upper and lower airways are thought as a morphological and functional unit. It has been commonly accepted in recent years. Allergic rhinitis (AR) is a risk factor for asthma; Allergic Rhinitis and Asthma (ARIA) suggest bronchial involvement in AR patients.

Ethics approval: There was no need to take Ethical Committee Approval.

Financial disclaimer: There is no financial disclosure of the author.

Conflict of interest: The author reports no conflicts of interest.

Contribution of authors:

Nuray Bayar Muluk: Planning, designing, literature survey, writing.

REFERENCES

- 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.
- Cingi C, Muluk NB, Cobanoglu B, Çatli T, Dikici O. Nasobronchial interaction. *World J Clin Cases*. 2015;3(6):499–503. DOI: 10.12998/wjcc.v3.i6.499.
- Eccles C. Anatomy and physiology of the nose and control of nasal airflow. In: Adkinson NF, Yunginger JW, Busse WW, et al, editors. *Middleton's Allergy: Principles and Practice*. 7th ed. Philadelphia: Elsevier; 2008, p.701–11.
- 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. DOI: 10.1111/j.1398-9995.2007.01620.x.
- Giavina-Bianchi P, Aun MV, Takejima P, Kalil J, Agondi RC. United airway disease: current perspectives. *J Asthma Allergy*. 2016;9:93–100. DOI: 10.2147/JAA.S81541. eCollection 2016.
- Yawn BP, Yunginger JW, Wollan PC, Reed CE, Silverstein MD, Harris AG. Allergic rhinitis in Rochester, Minnesota residents with asthma: frequency and impact on health care charges. *J Allergy Clin Immunol*. 1999;103(1 Pt 1):54–9.
- Kocevar VS, Bisgaard H, Jonsson L, Valovirta E, Kristensen F, Yin DD, et al. Variations in pediatric asthma hospitalization rates and costs between and within Nordic countries. *Chest*. 2004;125(5):1680–4.
- Compalati E, Ridolo E, Passalacqua G, Braido F, Villa E, Canonica GW. The link between allergic rhinitis and asthma: the united airways disease. *Expert Rev Clin Immunol*. 2010;6(3):413–23. DOI: 10.1586/eci.10.15.
- Bousquet J, van Cauwenberge P. ARIA. Allergic Rhinitis and its Impact on Asthma. Position paper in cooperation with WHO. *J Allergy Clin Immunol*. 2001;108(Suppl 5):S23–S35.
- Braman SS, Barrows AA, DeCotiis BA, Settignano GA, Corrao WM. Airways hyperresponsiveness in allergic rhinitis. A risk factor for asthma. *Chest*. 1987;91(5):671–4.
- Lieberman P, Pattanaik D. Nonallergic rhinitis. *Curr Allergy Asthma Rep*. 2014;14(6):439. DOI: 10.1007/s11882-014-0439-3.
- Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. [No authors listed]. [Internet]. *Lancet*. 1998;351(9111):1225–32. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/9643741>.
- Simons FE. Allergic rhinobronchitis: the asthma–allergic rhinitis link. *J Allergy Clin Immunol*. 1999;104(3 Pt 1):534–40.
- Crapo RO, Casaburi R, Coates AL, Enright PL, Hankinson JL, Irvin CG, et al. Guidelines for methacholine and exercise challenge testing – 1999. *Am J Respir Crit Care Med*. 2000;161(1):309–29.
- Feng CH, Miller MD, Simon RA. The united allergic airway: connections between allergic rhinitis, asthma, and chronic sinusitis. *Am J Rhinol Allergy*. 2012;26(3):187–90. DOI: 10.2500/ajra.2012.26.3762.
- Okano M, Kariya S, Ohta N, Imoto Y, Fujieda S, Nishizaki K. Association and management of eosinophilic inflammation in upper and lower airways. *Allergol Int*. 2015;64(2):131–8. DOI: 10.1016/j.alit.2015.01.004. Epub 2015 Feb 24.
- Togias A. Mechanisms of nose-lung interaction. *Allergy*. 1999;54(Suppl 57):94–105.
- Lin YT, Chen YC, Gau SS, Yeh TH, Fan HY, Hwang YY, et al. Associations between allergic diseases and attention deficit hyperactivity/ oppositional defiant disorders in children. *Pediatr Res*. 2016;80(4):480–5. DOI: 10.1038/pr.2016.111. Epub 2016 Jun 2.
- Licari A, Castagnoli R, Denicolò CF, Rossini L, Marseglia A, Marseglia GL. The nose and the lung: united airway disease? *Front Pediatr*. 2017;5:44. DOI: 10.3389/fped.2017.00044. eCollection 2017.
- Stone KD, Prussin C, Metcalfe DD. IgE, mast cells, basophils, and eosinophils. *J Allergy Clin Immunol*. 2010;125(2 Suppl 2):S73–S80. DOI: 10.1016/j.jaci.2009.11.017.
- Lambrecht BN, Hammad H. The immunology of asthma. *Nat Immunol*. 2015;16(1):45–56. DOI: 10.1038/ni.3049.
- Marseglia GL, Merli P, Caimmi D, Licari A, Labò E, Marseglia A, et al. Nasal disease and asthma. *Int J Immunopathol Pharmacol*. 2011;24(4 Suppl):7–12. DOI: 10.1177/03946320110240S402.
- Bousquet J, Jacot W, Vignola AM, Bachert C, Van Cauwenberge P. Allergic rhinitis: a disease remodeling the upper airways? *J Allergy Clin Immunol*. 2004;113(1):43–9. DOI: 10.1016/j.jaci.2003.09.047.
- Brambilla I, Pusateri A, Pagella F, Caimmi D, Caimmi S, Licari A, et al. Adenoids in children: advances in immunology, diagnosis, and surgery. *Clin Anat*. 2014;27(3):346–52. DOI: 10.1002/ca.22373. Epub 2014 Feb 18.
- Constantino Gde T, Mello JF Jr. Remodeling of the lower and upper airways. *Braz J Otorhinolaryngol*. 2009;75(1):151–6. DOI: 10.1016/S1808-8694(15)30847-8.
- Lockett GA, Huoman J, Holloway JW. Does allergy begin in utero? *Pediatr Allergy Immunol*. 2015;26(5):394–402. DOI: 10.1111/pai.12408.
- Ortiz RA, Barnes KC. Genetics of allergic diseases. *Immunol Allergy Clin North Am*. 2015;35(1):19–44. DOI: 10.1016/j.iac.2014.09.014.
- Liu Y, Ke X, Kang HY, Wang XQ, Shen Y, Hong SL. Genetic risk of TNFSF4 and FAM167A-BLK polymorphisms in children with asthma and allergic rhinitis in a Han Chinese population. *J Asthma*. 2016;53(6):567–75. DOI: 10.3109/02770903.2015.1108437. Epub 2016 Apr 18.
- Zhao Y, Zhang Y, Zhang L. Variant of PBX2 gene in the 6p21.3 asthma susceptibility locus is associated with allergic rhinitis in Chinese subjects. *Int Forum Allergy Rhinol*. 2016;6(5):537–43. DOI: 10.1002/alr.21725. Epub 2016 Feb 8.
- Gough H, Grabenhenrich L, Reich A, Eckers N, Nitsche O, Schramm D, et al. Allergic multimorbidity of asthma, rhinitis and eczema over 20 years in the German birth cohort MAS. *Pediatr Allergy Immunol*. 2015;26(5):431–7. DOI: 10.1111/pai.12410.
- Kim YH, Kim KW, Kim MJ, Sol IS, Yoon SH, Ahn HS, et al. Vitamin D levels in allergic rhinitis: a systematic review and meta-analysis. *Pediatr Allergy Immunol*. 2016;27(6):580–90. DOI: 10.1111/pai.12599. Epub 2016 Jun 21.
- Johnston SL, Pattemore PK, Sanderson G, Smith S, Lampe F, Josephs L, et al. Community study of role of viral infections in exacerbations of asthma in 9–11 year old children. *BMJ*. 1995;310(6989):1225–9.
- Buist AS. Risk factors for COPD. *Eur Respir Rev*. 1996;6(39):253–8.
- Kauffmann F, Neukirch F, Annesi I, Korobaeff M, Doré MF, Lelouch J. Relation of perceived nasal and bronchial hyperresponsiveness to FEV1, basophil counts, and methacholine response. *Thorax*. 1988;43(6):456–61. DOI: 10.1136/thx.43.6.456.
- Davison AG, Fayers PM, Taylor AJ, Venables KM, Darbyshire J, Pickering CA, et al. Cadmium fume inhalation and emphysema. *Lancet*. 1988;1(8587):663–7.
- Ciprandi G, Caimmi D, Miraglia del Giudice M, La Rosa M, Salpietro C, Marseglia GL. Recent developments in United airways disease. *Allergy Asthma Immunol Res*. 2012;4(4):171–7. DOI: 10.4168/air.2012.4.4.171. Epub 2012 Feb 8.

37. Platts-Mills TAE. The role of allergens in allergic airway disease. *J Allergy Clin Immunol.* 1998;101(2):S364-6. DOI: 10.1016/S0091-6749(98)70221-0.
38. Michel FB, Marty JP, Quet L, Cour P. Penetration of inhaled pollen into the respiratory tract. *Am Rev Respir Dis.* 1977;115(4):609-16.
39. Fontanari P, Zattara-Hartmann MC, Burnet H, Jammes Y. Nasal eupnoic inhalation of cold, dry air increases airway resistance in asthmatic patients. *Eur Respir J.* 1997;10(10):2250-4.
40. Saetta M, Maestrelli P, Di Stefano A, De Marzo N, Milani GF, Pivrotto F, et al. Effect of cessation of exposure to toluene diisocyanate (TDI) on bronchial mucosa of subjects with TDI-induced asthma. *Am Rev Respir Dis.* 1992;145(1):169-74.
41. Fontanari P, Burnet H, Zattara-Hartmann MC, Jammes Y. Changes in airway resistance induced by nasal inhalation of cold dry, dry, or moist air in normal individuals. *J Appl Physiol* (1985). 1996;81(4):1739-43.
42. Corren J, Adinoff AD, Irvin CG. Changes in bronchial responsiveness following nasal provocation with allergen. *J Allergy Clin Immunol.* 1992;89(2):611-8.
43. Baraniuk JN, Merck SJ. Nasal reflexes: implications for exercise, breathing, and sex. *Curr Allergy Asthma Rep.* 2008;8(2):147-53.
44. Bousquet J, Neukirch F, Bousquet PJ, Gehano P, Klossek JM, Le Gal M, et al. Severity and impairment of allergic rhinitis in patients consulting in primary care. *J Allergy Clin Immunol.* 2006;117(1):158-62. Epub 2005 Dec 2.
45. Caimmi D, Marseglia A, Pieri G, Benzo S, Bosa L, Caimmi S. Nose and lungs: one way, one disease. *Ital J Pediatr.* 2012;38:60. DOI: 10.1186/1824-7288-38-60.
46. Miraglia Del Giudice M, Marseglia A, Leonardi S, La Rosa M, Salpietro C, Brunese FP, et al. Allergic rhinitis and quality of life in children. *Int J Immunopathol Pharmacol.* 2011;24(Suppl 4):25-8.
47. Tosca MA, Riccio AM, Marseglia GL, Caligo G, Pallestrini E, Ameli F, et al. Nasal endoscopy in asthmatic children: assessment of rhinosinusitis and adenoiditis incidence, correlations with cytology and microbiology. *Clin Exp Allergy.* 2001;31(4):609-15.
48. Compalati E, Ridolo E, Passalacqua G, Braido F, Villa E, Canonica GW. The link between allergic rhinitis and asthma: the united airways disease. *Expert Rev Clin Immunol.* 2010;6(3):413-23. DOI: 10.1586/eci.10.15.
49. Riccio MM, Proud D. Evidence that enhanced nasal reactivity to bradykinin in patients with symptomatic allergy is mediated by neural reflexes. *J Allergy Clin Immunol.* 1996;97(6):1252-63.
50. Ciprandi G, Cirillo I. The lower airway pathology of rhinitis. *J Allergy Clin Immunol.* 2006;118(5):1105-9. Epub 2006 Jun 27.
51. Staikūniene J, Vaitkus S, Japertiene LM, Ryskiene S. Association of chronic rhinosinusitis with nasal polyps and asthma: clinical and radiological features, allergy and inflammation markers. *Medicina (Kaunas).* 2008;44(4):257-65.
52. Peroni DG, Piacentini GL, Ceravolo R, Boner AL. Difficult asthma: possible association with rhinosinusitis. *Pediatr Allergy Immunol.* 2007;18(Suppl 18):25-7. DOI: 10.1111/j.1399-3038.2007.00628.x.
53. Jani AL, Hamilos DL. Current thinking on the relationship between rhinosinusitis and asthma. *J Asthma.* 2005;42(1):1-7.
54. Barbi E, Longo G. Chronic and recurrent cough, sinusitis and asthma. Much ado about nothing. *Pediatr Allergy Immunol.* 2007;18(Suppl 18):22-4.
55. Bresciani M, Paradis L, Des Roches A, Vernhet H, Vachier I, Godard P, et al. Rhinosinusitis in severe asthma. *J Allergy Clin Immunol.* 2001;107(1):73-80.
56. ten Brinke A, Grootendorst DC, Schmidt JT, De Bruïne FT, van Buchem MA, Sterk PJ, et al. Chronic sinusitis in severe asthma is related to sputum eosinophilia. *J Allergy Clin Immunol.* 2002;109(4):621-6.