ALLERGIC DISEASES
IN R. MACEDONIA

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PREFACE

The interest of the author of these lines and his collaborators for the frequency of the allergic disorders in our country is dating back twenty years ago. The causes were professional, pragmatic and also due to the fact that we didn’t want to accept the usually delivered sentence “Unfortunately there is no relevant data for Macedonia concerning the prevalence of ….”. Such explanation for certain entities was most frequently illustrated with exact figures for the elaborated occurrence in some countries as for example in the U.S.A., Australia, European countries as well as countries of our neighborhood.

In 1993 analyzing the group of almost 700 randomly selected patients we received the first piece of information for allergic rhinitis. In 1994 our research was enriched with many distinctions of this occurrence, but in both cases the data were only for the city of Skopje.

The team at the Institute for Occupational Health in collaboration with the Occupational Health Services, during 1995 and 1996 accomplished a polycentric study for the extension of bronchial asthma in 11 towns of the Republic of Macedonia. These reasons and taking into consideration the previous experiences and already established collaboration with the medical doctors from other towns in Macedonia, urged us to realize the Project No. 400998 approved by the Ministry for Education and Science. The research duration was 5 years (from 1998 to 2003) and was conducted in six towns. The Project’s results are elaborated in this publication.

Since the editors were not announcing their strong intention to distribute this particular publication to all Collaborating Centers of Occupational Health with WHO and National Association for allergy and clinic immunology, the attitude pointed out by the author of this lines would be completely diminished as of 1998 he critically reviewed and emphasized the discontent of the nomenclature of allergic entities with the one of the ICD-10 of WHO of 1992. This condition became more complex when the European Academy for Allergology and Clinic Immunology in 2001 proclaimed a new revised nomenclature and classification of allergic disorders. In relation to this update, Mr. Van Cauwenberge as a title of one of his disputes set the question: “New nomenclature, is it a fashion or a need?” Our answer would be: “It is certainly not a fashion, but at this moment it is not a need, too”.

We have been trying to present the results of this research various aspects, emphasizing the public health features. Have we succeeded?

Editor and Principal Investigator of the Project
Prof. Vladimir Cvetanov, M.D., Ph.D.
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Professor Vladimir Cvetanov, M.D., Ph.D. was born in Skopje in 1935. He graduated in 1961 at the Medical Faculty in Skopje. From 1962 until 1965 he worked as a general practitioner at the Health Station of the Radusha pit. During 1965 to 1966 he attended post-graduate studies at “Andrija Stampar” Medical School in Zagreb, while in 1967 he passed his specialist exams of occupational health. In 1970 he completed his master studies becoming the first Master of Science at the Medical Faculty in Skopje. In 1979 he completed his Ph.D. thesis particularly focusing on hypersensitive pneumonitis. Results obtained and presented in this study are named as “Macedonian Study” by some Scandinavian authors. In 1984 was conferred the degree sub-specialist of allergology and clinical immunology and 1993 he added allergology and pulmology to the list of his specialties.

Since 1993 he is a regular Full-time Professor at the Chair of Hygiene and Occupational Health at the Medical Faculty in Skopje. Simultaneously he was actively participating in the teaching process of subspecialty in allergology and pulmology. During one period of time, he was also lecturing at the post-graduate studies in Ljubljana and Sarajevo.

Professor Cvetanov is considered as a promoter of the Institute of Occupational Health back in 1972 and in 1986 of the Allergy Center within the same Institute. He was a Director of the Institute until his retirement in 2000.

He is the author of 207 scientific publications focused on the occupational pathology and allergology.

When in the newly constructed building of the Institute of Occupational Health in 1977, all optimum conditions were provided; the Institute turned into a teaching basis of the Medical Faculty. Professor Cvetanov introduced the modern functional diagnostics of the respiratory system in 1967, while the experiences gained by the "small spirometry" were summarized and published in 1969. In 1970, in the publication “Allergies and Asthma”, he published the application of skin tests with workplace allergens in detection of bronchial asthma in workers exposed to flour dust.

In 1976 he set the test for determination of precipitins with dual immune diffusion on gel-agar, indirect test on basophil deregulation, in 1978 the actual test for diagnosis of penicillin and drug hypersensitivity, while in 1980 he introduced LIF test in the diagnosis of occupational contact dermatitis. In 1991, at the Institute of Occupational Health an aeropalinological research survey started resulting in 1993 with its final results publication and knowledge of the first official facts about the city of Skopje. In 1994 at this Institute the use of rhinomanometry was induced as an additional and important test in diagnostics of allergic rhinitis.

He received the first award for his poster presented at the Balkan Congress for Allergology held in Sofia (Bulgaria) on 28-30 May, 1998, entitled “The link between allergic manifestations of airways and actual microflora in Macedonia”.


Professor Cvetanov is the principal investigator and participant of two projects related to epidemiological allergic rhinitis (1993/1994), polycentric study for bronchial asthma (1995/96) and the Project No.400998 (1998-2003).

He was the President of the First Macedonian Immunology Congress in 1996 and of the Macedonian Society of Basic and Clinical Immunology and Allergology in the period between 1996 and 2000.

For his work he was awarded the highest certificate of gratitude by the Macedonian Medical Association in 1996.
Professor Jovanka Karadzinska-Bislimovska, M.D., Ph.D. was born in Belgrade in 1955. She graduated at the Medical Faculty in Skopje in 1979. She completed the specialization in occupational health in 1988, and the subspecialty in pulmology and allergology in 2003. She completed postgraduate studies in 1986 and acquired the degree Master of Science. In 1990, by presenting her Ph.D. thesis entitled “Defining the level of allergic sensitivity and occurrence of pulmonary disorder with allergic etiology in workers involved in rice processing industry” she acquired the degree Ph.D. in Medical Science.

She has realized several study visits in Stockholm (Sweden) in 2000, Oxford (Great Britain) in 2001, and Jerusalem (Israel) in 2005.

Starting 1980 she has been employed at the Institute of Occupational Health at the Department for Cardiorespiratory Functional Diagnostics, and since 2003 she is the Director of the Institute. In 1986 she was appointed junior assistant at the Chair of Hygiene with Social Medicine and Occupational Health, Medical Faculty, while in 2002 she became full time regular professor at the same Chair. She is the Head of the Chair of Occupational Health and Coordinator of the Project for Development of the School for Public Health, assigned with the Medical Faculty in Skopje.

She is one of the authors of the handbook “Health Condition and Work Ability” (Skopje, 1989), the monographic publication “Allergic Diseases – Management (Skopje, 1998), the handbook for teachers, researchers and health professionals “Health Determinants in the Scope of New Public Health” (Sofia, 2005) and “Public Health: A Tool for Regional Development” (Bucharest, 2006).

She is the author of the chapter “Immuoallergic aspects of occupational allergic disorders” in the monograph “Clinical Immunology” (Belgrade, 2002). She is also the author and co-author of more than 130 professional and scientific articles.

Professor Karadzinska-Bislimovska is a member of the European Respiratory Society and of the European Academy of Allergology and Clinical Immunology. She is an actual deputy president of the Macedonian Society for Basic and Clinical Immunology and Allergology.

For her work she was awarded with the Declaration of “Dr. Trifun Panovski” by the Macedonian Medical Association in 2005.
Professor Elisaveta Stikova, M.D., Ph.D. was born in Skopje in 1956. She graduated at the Medical Faculty in 1980. In 1987 she completed her specialization in occupational health. During 1988 she completed the post-graduate studies and became Master of Science. In 1990 after presenting her doctoral thesis she has got her Ph.D. degree. In 1986 she was elected as a junior assistant at the Chair of Hygiene with Social Medicine and Occupational Health at the Medical Faculty in Skopje. Since 2002 she is a regular full time professor at the same Chair. She is also a responsible teacher for subjects related to medical ecology at the Faculty of Stomatology, as well as for school and pre-school hygiene at the Pedagogy Faculty in Skopje.

She has realized several study visits to France and Spain (2002), U.S.A (2003) and Israel (2005).

In 1980 she started to work at the Institute of Occupational Health. During the period between 1994 and 2004 she was appointed a Director of the Republic Institute for Health Protection. Currently she is still working in the same Institute.

She is one of the authors of the handbook “Health Condition and Working Ability” (Skopje, 1989), the handbook for teachers, researchers and health professionals “Health Determinants in the Scope of New Public Health” (Sofia, 2005); she is also the author of the student’s handbook “Hygiene” (Skopje, 2003) and handbooks for regular nutrition (Skopje, 2001), Health for All database indicators (Skopje, 2001), Codex Alimentarius (Skopje, 2003), as well as her latest handbook “Medical Ecology” (Skopje, 2006) which is the first book of this scope written in Macedonia.

Professor Stikova was engaged as a WHO national collaborator for topics related to nutrition and food safety. She was also the first President of the National Committee for Food and of the Codex Alimentarius Committee in the Republic of Macedonia. As a temporary collaborator of WHO she was closely involved in issues related to health statistics and evaluation of sensitivity and adaptation on climatic changes.

Professor Stikova is an author and co-author of more than 130 scientific and professional articles, principal researcher and participant in 7 international scientific-research projects. She is a regional co-coordinator of SCOPES Project “Development of Core Curriculum Health” and co-director of NATO Project “Strengthening National Public Health Preparedness and Response for Chemical, Biological and Radiological Agents Threats”.

She is a member of the International Committee for Occupational Medicine, and a member of the National Board Committee.
Jordan Minov, M.D., Ph.D. was born in Skopje in 1960. He graduated in 1984 at the Medical Faculty in Skopje. In 2002 he completed the specialization in internal medicine and in 2006 he completed the specialization in occupational health. During 2001 he completed his master studies and acquired the degree Master of Science, while in 2006 after public presentation of the doctoral thesis “Influence of Specific Occupational Exposure on the Bronchial Asthma Development in Pharmaceutical Industry Workers”, he acquired the degree Ph.D. in Medical Science.

Currently he is employed at the Department for Cardiorespiratory Functional Diagnostics within the Institute of Occupational Health – WHO Collaborating Center.

He participates in the teaching process of the post-graduate studies (Occupational Health Course) at the School of Public Health within the Medical Faculty in Skopje. Functional diagnostics of respiratory system and occupational and non-occupational chronic obstructive pulmonary disorders are scope of special professional and scientific interest in his devoted work.

He is one of the authors of the chapter “Occupational Lung Disorders as a Public Health Problem” of the Handbook for teachers, researchers and health professionals “Health Determinants in the Scope of New Public Health” (Sofia, 2005), as well as other 110 professional and scientific articles published in domestic and foreign publications and presented on congresses in our country and abroad. He is involved in many national and international projects, programs and workshops.

He is a member of the European Respiratory Society, European Academy of Allergology and Clinical Immunology, World Allergy Organization, Macedonian Respiratory Society and Macedonian Society for Basic and Clinical Immunology and Allergology.

Primarius Neda Ezova, M.D. was born in Rakle – Prilep in 1944. She graduated at the Medical Faculty in 1971. In 1981 she passed the specialization exam in occupational health, while in 2002 she completed her sub-specialist exam in pulmology and allergology.

In 1987 Teaching-Scientific Council of the Medical Faculty promoted her to assistant at the Chair for Hygiene with Social Medicine and Occupational Health. The title Primarius was awarded to her in 1994.

Currently she is employed at the Allergy Center within the Institute of Occupational Health – WHO Collaborating Center.

Her long-term professional activity is related to the scope of diagnostics, introduction and practical conduction of several methods and tests in allergology and pulmology. Management of allergic disorders, occupational and non-occupational chronic obstructive pulmonary disorders, as well as work-related diseases are targets of special scientific interest in her professional involvement.

She is the author and co-author of 130 professional and scientific articles published in national and international journals and presented in our country and abroad. She is one of the authors of the book “Allergic Diseases – Management” and “Macedonian National Consensus for Allergic Rhinitis”.

She is a member of the European Respiratory Society, Macedonian Respiratory Society and Macedonian Society for Basic and Clinical Immunology and Allergology.
Snezana Milkovska, Ph.D. was born in Skopje in 1962. She graduated in 1987 at the Faculty of Natural and Mathematical Sciences, Department of Biology in Skopje. In 1998 she completed her post-graduate studies, while in 2002 she acquired her Ph.D. in Biology at the same faculty. Her study visits were conducted at the Institute for Epidemic and Parasitic Diseases (Department for Allergy and Aeropalinology) in Sofia, Bulgaria and in 2005 in Lion, France during her stay she acquired European Certificate for Aerobiology and Aeropalinology.

Currently she is employed at the Allergy Center of the Institute of Occupational Health – WHO Collaborating Center where she actively participates in the scientific and research tasks. Her scope of special interest is focused to aeropalinology, epidemiology of allergic diseases, ecology and sustainable development. Being the only specialist in aeropalinology in the country, she is also devoted to its development in Macedonia. In 1993 she completed Pollen calendar for the city of Skopje. During the same year she also prepared calendars for the towns of Ohrid, Prilep, Pehchevo, Debar and Dojran and successfully defined allergic pallet of actual allergens for skin tests in Macedonia.

As an author and co-author she has published about 70 professional and scientific articles. She is a member of the Board of the Macedonian National Consensus for Allergic Rhinitis, a member of the Society of Occupational Health, Society of Basic and Clinical Immunology and Allergology, Society of Environment and Ecology in Macedonia and of the European Academy for Allergology and Clinical Immunology. She actively participates in the project LEAP of the city of Skopje, as well as in the project “Epidemiological characteristics of the allergic rhinitis in the Republic of Macedonia in correlation with the pollen micro flora”.

She was a member of the Scientific and Organizational Board of the First Macedonian Immunology Congress in 2000 and a secretary general of the First Macedonian Congress of Occupational Health with International Participation in 2004.

Assistant professor Snezana Risteska-Kuc, M.D., M.Sc. was born in Skopje in 1960. She graduated in 1988 at the Medical Faculty in Skopje. In the year 2000 she completed the specialization in occupational health and in 2003 she acquired her degree MSc in Medicine focusing on the occupational health.

She is employed at the Department for Industrial Toxicology within the Institute of Occupational Health – WHO Collaborating Center. As an assistant, starting from 1998, she has been participating in teaching process conducting practical courses for students at the Chair of the Occupational Health.

Her professional and research interests are focused mainly on two targets of the occupational health: occupational immunoallergology and industrial toxicology, while her special attention is focused on the occupational rhinitis and functional nasal diagnostics with the rhinomanometric method.

She is one of the authors of the “Macedonian National Consensus of Allergic Rhinitis” (1999) and the handbook for teachers, researchers and health professionals “Health Determinants in the Scope of New Public Health” (2005). Dr Kus is actively involved in numerous scientific and applicative projects, programs and workshops of national and international significance.

She has published more than 70 professional and scientific articles, some of them presented on congresses in the country and abroad.

Ass. M.D. Snezana M.Risteska-Kuc is a member of the Macedonian Medical Association, Macedonian Society of Occupational Medicine, Macedonian Society of Basic and Clinical Immunology and Allergology, European Respiratory Society and Macedonian Respiratory Society.
Olivera Spasovska, M.D. was born in Struga in 1957. She graduated at the Medical Faculty in 1985. In 2001 she completed her specialization in ophthalmology.

She is employed at the Department of Ophthalmology within the Institute of Occupational Health – WHO Collaborating Center.

Her special scope of professional and scientific interest is prevention and early detection and treatment of eye disorders, particularly those of allergic etiology.

As an author and coauthor she has published 20 professional and scientific articles. Within the frames of the health-education process at the Institute of Occupational Health, she participates in the education process of students of medicine and medical doctors on their specialization interim. She is a member of the Macedonian Ophthalmology Society.

Mimoza Marsenic, M.D. was born in Kumanovo in 1951. She graduated at the Medical Faculty in Skopje in 1978 and specialized clinical immunology with allergology in 1984 at the Military Medical Academy in Belgrade.

At the Clinic for Pulmonary Disorder and Tuberculosis in Nis she spent 17 years, being in charge for the Department of Immunoallergology and Management of Asthma.

Over the last eight years she has been employed at the Allergy Center within the Institute of Occupational Health – WHO Collaborating Center.

Allergic and immunologic tests with special attention to drug hypersensitivity as well as conducting specific and nonspecific immunotherapy are the major targets of interests in her work.

She is the author and co-author of more than 60 professional and scientific articles presented on congresses and other specialized gatherings in the country and abroad.

She is a member of the Macedonian Society for Basic and Clinic Immunology and Allergology and an active participant of several scientific projects.

Valentina Petreska, M.D. was born in Ohrid in 1952. She graduated at the Medical Faculty in Skopje in 1977, and in 1986 she completed her specialization in occupational health.

She is currently the director of the Occupational Health Service within the Health Institute in Ohrid. Health promotion at the workplace is her special professional target.

She is an author and co-author of about 15 professional articles presented on congresses in the country and abroad. She is a member of the Managing Board of the Society of Occupational Health within the Macedonian Medical Association.
Ljubica Andonovska, M.D. was born in Ohrid in 1950. She graduated in 1975 at the Medical Faculty in Skopje. She got her specialization in primary health care in 1981 and during 1983 completed her professional improvement of pulmology and allergology.

Since 1983 she has been employed at the Department of Pulmology and Allergology within the Department of Internal Medicine of the General Hospital in Ohrid. Respiratory and allergic disorders are major target of her professional interest.

She is a member of the Macedonian Respiratory Society and Macedonian Society for Basic and Clinical Immunology and Allergology.

Roza Naumoska, M.D. was born in Prilep in 1954. She graduated at the Medical Faculty in Skopje in 1980 and in 1992 she completed her specialization in occupational health.

Since 1981 she has been employed at the Occupational Health Service within the Medical Center in Prilep and her working tasks are related to the issues of the occupational medicine, especially targeted on the first aid factory’s units. Since 1995 she has been appointed as head of the Service. Her special professional interest is aimed at pulmonary disorders and allergology.

It has to be particularly emphasized her contribution and involvement in the preparation of documents for the National Strategy of Occupational Health and in organization and functioning of the occupational health services. Her involvement in the Project for preparation of the manual for verification, application and registration of occupational diseases and other related activities, is also worth to be stressed.

She is the author and co-author of more than 30 articles presented on congresses and seminars in the country and abroad. She participated in a two-week seminar for health and safety at work in Sweden. She actively participates by lecturing and conducting workshops of the projects “Healthy nutrition”, “Mental hygiene” and LEAP.

During the period between 1998 and 2002 she was the President of the Society of Occupational Health within the Macedonian Medical Association. Since 2002 she has been the Vice President and the member of the Managing Board of the Society and a member of the editorial board of the Bulletin where she also participates with her publications, comments and translations of professional literature.

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As an author or co-author she has published about ten professional works presented on congresses within the country. She is the member of the Macedonian Respiratory Society and Macedonian Society for Basic and Clinical Immunology and Allergology.

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Since 1988 he has been employed at the Medical Center in Debar. President or a member is of several committees, related to the health issues as well as of several NGOs. For his devoted work he has achieved few recognitions and acknowledgement. Presenting professional articles he participated on few congresses and seminars.

The Macedonian Chamber of Medicine has appointed him to conduct the exam required for licencing of graduated medical workers.

He is a member of the Macedonian Chamber of Medicine, a member of the Albanian American Academy of Science in U.S.A., of the Society of the Occupational Health and of the Association of Medical Doctors of Albanian Nationality in Macedonia.

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The influence of the living environment on human health with particular focus on the microclimate of Dojran is a specific target of his professional involvement. He participated in the preparation of the LEAP Project (Local Ecological Action Plan for the Municipality of Dojran), especially working on and evaluating the influence of the living environment on human health.

He is a member of the Macedonian Respiratory Society.

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Part I
Introduction
Redefinition of the facts and concepts concerning allergic diseases

Allergic diseases represent one of the most common chronic pathological conditions throughout the world, as well as a serious challenge both to health care systems and to society as a whole. In 1997, the European Allergy White Book (EAWP) reported that almost one-third of the population of the planet suffers from one or more allergic diseases.

The rising prevalence of the allergic diseases in the last decades caused intensive investigations and significant improvement of the knowledge about their pathogenesis, diagnostics and treatment options. Despite increasing knowledge, the gap between achieved improvement and satisfactory management still exists. From the patients’ point of view, there are also unmet needs.

In the late 1990s has started the polycentric project Global Approach to the Patient (GAP) started and it was focused on the systemic nature of the allergic diseases and the need of uniformed and standardized approach in their diagnostics and treatment. Having in mind the increased knowledge about the allergological mechanisms, and sometimes confusing terminology used by allergologists and organ specialists, a revision of the classification and nomenclature was necessary. The report prepared by the European Academy of Allergology and Clinical Immunology (EAACI) nomenclature task force representing the five EAACI sections and the EAACI Executive Committee was published in 2001. The aim of the report was to propose a revised nomenclature for allergic and related reactions that can be used independently of target organ or patient age group. The nomenclature was based on the actual knowledge of the mechanisms which initiate and mediate allergic reactions.

Despite the fact that allergic diseases were identified in the antique period, the terms “allergy” and “atopy” were introduced at the beginning of the last century. The term “allergy” was promoted by von Pirquet in 1905 for altered (unexpected) reactions in some people following the exposure to environmental agents which were absolutely harmless for others. Atopy, derived from a Greek word meaning “out of place”, was introduced by Coca & Cooke in the 1920s to describe a familial predisposition to develop several diseases including asthma, eczema and rhinitis. In the 1930s, atopic dermatitis, considered one manifestation of hypersensitivity, was subsequently defined by Wise and Sulzberger. At the same time, immediate skin reaction in normal subjects following administration of serum from atopic subjects was reported by Prausnitz & Küstner. Cooke and Grove indicated presence of heat-labile substances, referred to as “reagins”, in the serum of atopic patients. The cytophylity of the reagins, i.e. their activation after interaction with other cells, was suggested by Otto. In 1948, corticosteroids were introduced as a treatment option for asthma and other allergic diseases. The role of histamine in the immediate type of allergic reaction was determined in 1953.

The field of allergy has developed rapidly during the last 50 years. In the 1960s, Ishizaka & Ishizaka and Bennich & Johansson suggested that reagins should be a new class of immunoglobulins. In 1968, the WHO International Reference Center for
Immunoglobulins decided that enough critical data were available to announce the presence of the fifth immunoglobulin isotype, immunoglobulin E (IgE). At the same time, Coombs & Gell produced their classification of allergic reactions, i.e. familiar types I – IV hypersensitivities. Although too much emphasis has been given to the supposedly distinct and mutually exclusive roles of antibodies and immunocompetent cells, the Coombs & Gell classification is still useful. In the mid-1980s, the role of leukotrienes in the allergic reaction was determined.

**Actual knowledge about pathogenesis of allergic diseases**

Actual knowledge about pathogenesis of allergic diseases is focused on the hypothesis of dynamic immune response, as orchestrated by dendritic cells and T helper lymphocytes (Th), and mediated by effector cells of several types, antibodies, chemokines, and cytokines. According to the currently favored hypothesis of how the immune system is controlled, there is a balance between two subpopulations of Th, Th$_1$ and Th$_2$ cells. Th$_1$ promote immune protection against bacterial and viral infections, and Th$_2$ protect the body from helminth infestations and perhaps also maintain pregnancy.

In atopic individuals the balance between Th$_1$ and Th$_2$ is altered with predomination of Th$_2$ type of immune response. In these individuals, exposure to certain environmental allergens leads to Th$_2$ activation and production of specific cytokines, such as interleukin 3 (IL-3), IL-4, IL-5, and IL-13, i.e. to activation of the allergic cascade. IL-4 is critical in switching B-lymphocytes to produce specific IgE antibodies directed against certain allergen. The specific IgE antibodies coat the surface of the mast cell present in the nasal and bronchial mucosa or in the skin. When the specific allergen (e.g. a specific pollen grain) is inhaled into nose, it can bind to the IgE on the mast cell, leading to its degranulation and release of the mediators (histamine, leukotrienes, prostaglandin D2) responsible for the early allergic reaction that occurs within 1-2 hours following the exposure to allergen (Figure 1). IL-5 is of critical importance in the differentiation, survival, as well as in the recruitment of eosinophils in the target tissue (nasal and bronchial mucosa, skin). The eosinophil mediators, such as eosinophil cationic protein (ECP), major basic protein (MBP), and eosinophil peroxydase, are of great importance in late allergic reaction and chronic allergic inflammation. The most important cells of the allergic cascade include Th$_2$ cells, B-lymphocytes, mast cells, eosinophils, and structural cells (epithelial and endothelial cells, fibroblasts), as well as dendritic cells which act as antigen-presenting cells (APC).
Various agents can act as adjuvants in the activation of allergic cascade, such as enterotoxins of *Staphylococcus aureus* (it seems to stimulate eosinophilic inflammation and a polyclonal IgE response in atopic dermatitis), tobacco smoke, indoor and outdoor air pollutants, etc. In some cases the cascade should be activated by unknown agent (e.g. infective agent, unknown allergen) causing inflammation that does not differ from the allergen-induced inflammation in the classic allergic diseases (e.g. nonallergic asthma, nonallergic rhinitis, nonallergic urticaria).

Typical allergic symptoms include asthma, rhinoconjunctivitis, gastrointestinal symptoms, and characteristic skin lesions, which are usually refer to as “atopic diseases”. An atopic individual may develop a spectrum of atopic diseases with age, sometimes refer to as “the atopic march”. During the first years gastrointestinal and eczematous skin symptoms, usually caused by food allergens, predominate. Allergic diseases caused by inhalant allergens (e.g. asthma and rhinitis) develop later.

Atopy is defined as a personal or familial predisposition for production of specific IgE antibodies following the exposure to environmental allergens that may lead to clinical manifestations of allergic symptoms. The tendency to develop allergic, or IgE-mediated, reactions to extrinsic allergens has a genetic component. The risk of a child to develop an IgE-mediated allergy is estimated to 40-60% if both parents are atopic and to 5-10% if both parents are nonatopic. Up to now, association between several gene loci and high IgE levels, asthma and bronchial hyperresponsiveness has been reported, but no specific genetic marker for atopy has been identified. There are suggestions that besides increased IgE production, atopy may include some kind of higher sensitivity of the target organs, such as bronchial hyperresponsiveness in subjects with allergic asthma, and disturbed barrier function of the skin in subjects with allergic skin diseases, etc.

The atopic individual can not be identified before developing allergen-specific sensitization. The atopy is a condition, not a disease. The presencee of IgE antibodies does not necessarily mean clinically active disease. On the other hand, IgE-mediated allergic reactions may occur also in nonatopic subjects (e.g. reactions to drugs and insect venoms).
Revised classification and nomenclature of allergic diseases

Revised classification and nomenclature of the allergic diseases according to the European Academy of Allergy and Clinical Immunology (EAACI) Position Paper is given on Figure 2.

Hypersensitivity

Hypersensitivity is defined as a presence of objectively reproducible symptoms or signs, initiated by exposure to a defined stimulus at a dose tolerated by normal subjects. This definition does not accommodate classical responses to infection, autoimmunity, or toxic reactions, but emphasizes the link between the symptoms and the environmental factors to which the subjects attribute their symptoms. The old terms, such as “idiosyncrasy”, “intolerance”, or “hyperreactivity”, are no longer needed.

Figure 2. Classification of the hypersensitivity reactions
Atopy

Atopy is defined as a personal or familial tendency to produce IgE antibodies in response to low doses of allergens, usually proteins, and to develop typical symptoms such as asthma, rhinoconjunctivitis, or eczema/dermatitis. The terms positive prick-tests subjects or IgE-sensitized subjects should be used for asymptomatic subjects with positive prick tests and/or increased IgE serum levels.

According to the results of our polycentric study, the prevalence of atopy in adults in R. Macedonia was 34.8%.

Allergy

Allergy is defined as a hypersensitivity reaction initiated by immunologic mechanisms. Allergy can be antibody- or cell- mediated. In most cases, the allergic reaction is mediated by IgE antibodies (e.g. the antibody responsible for the allergic reaction belongs to IgE isotype) and these subjects may be said to suffer from IgE-mediated allergy. IgE-mediated reactions may also occur in nonatopic subjects (i.e. insect sting allergy, drug allergy, etc). Non-IgE-mediated allergy may be caused by antibodies IgE classes other than IgE, usually IgG (e.g. serum sickness, allergic alveolitis) or may be mediated by sensitized lymphocytes (e.g. allergic contact dermatitis, celiac disease).

Hipersensitivity reactions caused by nonimmunological mechanisms (e.g. hypersensitivity reaction to aspirin) should be called nonallergic hypersensitivity.

According to the current study, the prevalence of allergic diseases in R. Macedonia was 35.6%, 41.4% in adults and 25.1% in children.

Allergens

Allergens are defined as antigens stimulating hypersensitivity mediated by an immunologic mechanism. Most allergens reacting with IgE and IgG antibodies are proteins (molecular weight from 10,000 to 40,000 daltons), usually with carbohydrate side chains, but they also may be pure carbohydrates. In rare instances, allergens that cause IgE-mediated reaction may be a low-molecular-weight chemical, such as isocyanates and anhydrides, acting as haptens. In the cases of cell-mediated allergic reactions (e.g. allergic contact dermatitis), allergens are also low-molecular-weight chemicals such as nickel, chromium, formaldehyde, etc.
Allergic rhinitis

Allergic rhinitis is defined as rhinitis caused by immunological mechanisms. If we wish to highlight the role of IgE, we should use the term IgE-mediated allergic rhinitis. The World Health Organization (WHO) document “Allergic Rhinitis and its Impact on Asthma” (ARIA) recommends that the terms “seasonal” and “perennial” should be replaced by the terms intermittent allergic rhinitis and persistent allergic rhinitis, respectively. All other forms of chronic rhinitis caused by nonimmunological mechanisms (e.g. vasomotor rhinitis, hyperreflectory rhinopathy, etc) should be called nonallergic rhinitis.

According to the present study, the prevalence of allergic rhinitis in R. Macedonia was 20.8%, 23.1% in adults and 16.5% in children.

Allergic conjunctivitis

Allergic conjunctivitis is defined as conjunctival inflammation caused by immunological mechanisms. IgE-mediated allergic conjunctivitis may be divided into intermittent and persistent allergic conjunctivitis, as in the subdivision of allergic rhinitis. In the cases of allergic conjunctivitis combined with allergic rhinitis, the term allergic rhinoconjunctivitis should be used.

According to the current study, the prevalence of allergic conjunctivitis in adults in R. Macedonia was 12.9%.

Asthma

The term allergic asthma should be used for asthma caused by allergic mechanisms. Other nonallergic types of asthma should be called nonallergic asthma. The old terms, “extrinsic”, “intrinsic”, “exogenous”, and “endogenous” should no longer be used.

According to the results of our polycentric study, the prevalence of asthma in the age group 20-44 in R. Macedonia was 5.4%.

There are a variety of allergic diseases of the skin with distinctly different pathogenic mechanisms. The most common allergic skin diseases include atopic eczema/dermatitis, urticaria, angioedema, allergic contact eczema/dermatitis, and exanthematous drug eruptions.
Atopic eczema/dermatitis syndrome (AEDS)

Allergic AEDS is eczematous hypersensitivity reaction in the skin. **IgE-associated AEDS** is a subgroup of allergic AEDS in which the clinical selection is based on Hanifin & Rajka criterion, “family history or simultaneous occurrence of symptoms of atopy”. The word “associated” should be used instead of the word “mediated” due to the lack of knowledge about the precise role of IgE antibodies initiating the disease. **T-cell-associated AEDS** is another subgroup of allergic AEDS, characterized by positive atopy patch tests to aero- and food allergens or allergen-specific T cells in the peripheral blood or in skin biopsies, but in absence of IgE sensitization. AEDS caused by nonimmunological mechanisms should be called **nonallergic AEDS**. The old term “intrinsic/cryptogenic AEDS” is no longer needed.

**According to the present study, the prevalence of atopic eczema/dermatitis syndrome in children in R. Macedonia was 3.8%.**

Urticaria

**Allergic urticaria** is defined as urticaria caused by immunological mechanisms. If we wish to highlight the role of IgE, the term **IgE-mediated allergic urticaria** should be used. Urticaria caused by nonimmunological mechanisms should be called **nonallergic urticaria**.

Contact eczema/dermatitis

**Allergic contact eczema/dermatitis** is a subgroup of contact eczema/dermatitis caused by immunological mechanisms, predominantly cellular (Th1) related. The term **irritant/toxic contact eczema/dermatitis** should be used when there are no immune mechanisms involved.

Hypersensitivity to drugs, food, and venoms

In the situation of hypersensitivity to drugs, food, and insect venoms, the organ-based classification is not adequate. The main reason is a different multisystem response pattern when an individual is exposed to high allergen/antigen dosage (milligram to gram) via mucosal membranes, as by food and drugs, or by injection, as by Hymenoptera venoms and drugs.
Food allergy or allergic food hypersensitivity is a subdivision of food hypersensitivity caused by immunological mechanisms. If the role of IgE is demonstrated, the term is IgE-mediated food allergy. All other reactions should be referred to as nonallergic food hypersensitivity. Similar terms should be used in the cases of hypersensitivity to drugs and insect venoms.

According to the results of our polycentric study, the prevalence of drug hypersensitivity in R. Macedonia was 10.5%, 11.2% in adults and 9.8% in children.

According to the results of our polycentric study, the prevalence of food hypersensitivity in R. Macedonia was 4.2%, 3.3% in adults and 5.0% in children.

According to the results of our polycentric study, the prevalence of insect venom allergy in R. Macedonia was 3.1%, 2.5% in adults and 3.8% in children.

Anaphylaxis

Anaphylaxis is a severe, life-threatening, generalized or systemic hypersensitivity reaction. The reaction usually develops gradually, starting with itching of the throat, the palms, or the soles, and local urticaria, developing to a multiple organ reaction often dominated by severe asthma, culminating in hypotension and shock. Hypotension and bronchospasm do not have to be present for a reaction to be classified as anaphylaxis.

Allergic anaphylaxis is a term which should be used for anaphylaxis caused by immunological mechanisms. Allergic anaphylaxis usually is caused by IgE-mediated mechanism (IgE-mediated anaphylaxis), but also may be caused by IgG- or cell-mediated mechanisms. Another cases, which are much less common, should be called nonallergic anaphylaxis. The term “anaphylactoid” should not be used.

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Relevancy of the national statistics system for evaluation of allergic diseases

Actual condition in the Republic of Macedonia

Determining of specific health indicators and its easy and fast collection is a basis for establishing sustainable system for allergic diseases management.

There is a Law for health evidence in R. Macedonia (Official Gazette no. 37/79) that defines the obligation to establish an appropriate health-statistics system dedicated to monitoring of morbidity, mortality, capacity use, staff and data about conditions in health care organizations and health care system in general.

At the same time, there is a tradition in collecting, analyzing and publication of the health-statistics data.

Hence, there are expectations that official health-statistics system can offer usable data for analyses, planning of the needs, and assessment of the direct and indirect expenses
for prevention, diagnosis and treatment for a special health-ecological problem, such as allergic diseases of different organs and systems. Unfortunately, opposite of all well based prerequisites (legal and sub legal basis, regular collecting and reporting the data), it is a fact that the collected data practically cannot be used. The reason for this may be located in two groups of problems:

1. Weaknesses and deficiencies in conducting of legally based obligations for adequate reporting of registered diseases-conditions in different functional units of the health care system, especially in the private segment,
2. Inadequate system, approach and instruments for collection, analysis and report of the data

Structure of the health care system and possibilities for collecting and analyzing of the health-statistics data

According to the basic principles for availability, efficiency and rationality, ambulatory-policlinics and hospital health care in the Republic of Macedonia are provided on three levels - primary, secondary and tertiary health care. The provision of health care to different categories-population groups of inhabitants is based on establishing several functional categories:

- health care of children
- health care of school children and youth
- health care of adults
- health care of workers
- health care of women

Therefore, determining the conditions due to frequency and dynamics of disease incidence, including diseases with allergic etiology, needs analysis of morbidity in each functional category of health care system establishment. Additionally, routine statistics data are collected separately for population living in urban and rural areas.

Although it seems that this kind of morbidity statistics is fractured, incoherent and without possibility for global estimation, the fact that it gives opportunity for analysis of some conditions in different population groups with some demographic and socio-economical characteristics due to the registered morbidity is incomparable. However, the question about functionality of established national health statistics about data for diseases of interest for the policy makers and evidence based health policy, remains open. **Data presented in this book are a clear argument that diseases with allergic etiology refer to negative response about this issue.**

On the other hand, this complex system is completely open to a large number of subjective weaknesses that often bring into question the relevance of collected data. The gaunt dots are located in regular reporting and registering of detected conditions in health organizations, collecting and delivering to authorized specialized public health organizations on regional level, and then on national level, their analysis, and accessibility of the published data.
Finally, technological aspect of the setting makes this system highly sensitive to possibility for errors and omissions. Unfortunately, health evidence is manually performed almost in all health care segments. In spite of the presence of information technology in all segments, the absence of unique software solution and networking of all health-statistics subjects makes this system highly nonfunctional for the needs of its users.

Application of international classification of diseases and diseases with allergic etiology

Speaking about advantages and weaknesses in providing information for allergic diseases morbidity, it is necessary to make some comments on the possibilities of the official system for recording of diseases and conditions and their implementation in the national evidence system and morbidity registration. During the last 10 years, the International Statistical Classification of Diseases (ICD 10) has been used in Macedonia. This classification is based on alphanumeric scheme of coding which contains one letter followed by 3 numbers with possibility of disease classification on three- or four signed level.

The existing standard Tabular List for the morbidity, as an integral part of ICD-10 is of special importance and is in favor of increased possibility to compare the collected data. Therefore, in the national Tabular Lists for data tabling with a few exceptions as a result of certain specificities in some functional categories of health care system, these standard Tabular Lists are in use. The conditions due to some allergic entities that are discussed in this study in the light of possibilities given by ICD-10 are presented below.

Allergic rhinitis

According to the ICD-10 this entity belongs to the group of other diseases of the respiratory tract classified in the category J30-J39. Using the 3 signed classification, allergic rhinitis belongs in the group J30- vasomotor and allergic rhinitis. Using the 4 signed classification there is a possibility of additional classification of all important diagnostic aspects of this entity:

- J30.0 vasomotor rhinitis
- J30.1 allergic rhinitis caused by pollen (the used synonyms are: pollen allergy, hay fever and pollenosis)
- J30.2 other seasonal allergic rhinitis
- J30.3 other allergic rhinitis (long-term allergic rhinitis)
- J30.4 allergic rhinitis, unsigned

The categories according to which morbidity is presented in the health care segment for youth and children, school medicine and youth and services for general practice and workers health care are in line with ICD-10 Tabular List of Morbidity. Therefore, allergic rhinitis is shown together within a wide group of entities referring to nose and nasal sinuses diseases and are signed as J30-J31, J33-J34.
Hence, allergic rhinitis as a specific entity can not be analyzed in correspondence to its frequency having in mind that in official health statistics it appears as a sum placed in a large group of diseases that are significant in the structure of respiratory illnesses in all population groups.

Available data referring to respiratory morbidity in ambulatory-policlinic sector in R. Macedonia comprising allergic rhinitis for the period 1998-2000 are presented in a continuum.

| Vasomotor and allergic rhinitis, chronic rhinitis, nasopharyngitis and pharyngitis and other nasal and nasal sinuses diseases in Republic of Macedonia in the period 1998 - 2000 |
|--------------------------------------|------------------|------------------|------------------|
| J30-J31                              | Number | Rate/10000 | Number | Rate/10000 | Number | Rate/10000 |
| J33-J34                              |        |            |        |            |        |            |
|                                      | 1998   |           | 1999   |           | 2000   |           |
|                                      | Males  |          | Males  |          | Males  |          |
| Males                                | 535    | 49.35    | 881    | 81.27    | 947    | 87.36    |
| Females                              | 401    | 39.7     | 733    | 72.57    | 828    | 81.97    |
| Total                                | 936    | 44.7     | 1614   | 77.07    | 1775   | 84.76    |
| School                               | Males  |          | Males  |          | Males  |          |
| Males                                | 556    | 41.16    | 895    | 66.26    | 746    | 55.22    |
| Females                              | 502    | 39.42    | 791    | 62.11    | 695    | 54.58    |
| Total                                | 1058   | 40.32    | 1686   | 64.25    | 1441   | 54.91    |
| General                              | Males  |          | Males  |          | Males  |          |
| Males                                | 1504   | 19.53    | 1346   | 17.48    | 2024   | 26.28    |
| Females                              | 1049   | 13.4     | 1438   | 18.36    | 1881   | 24.02    |
| Total                                | 2553   | 16.44    | 2784   | 17.92    | 3905   | 25.14    |
| Occupational Medicine                | Males  |          | Males  |          | Males  |          |
| Males                                | 4615   | 67.5     | 3761   | 55.01    | 3565   | 52.14    |
| Females                              | 4233   | 62.55    | 3190   | 47.14    | 2920   | 43.15    |
| Total                                | 8848   | 65.04    | 6951   | 51.1     | 6485   | 47.67    |

The data are in favor of the previous fact that official health-statistics data are practically not useful when talking about monitoring the frequency and developing tendency of allergic rhinitis. This disease is shown in the large group of other nasal and nasal sinuses diseases. But hereby, we should mention the fact that each year there is an increased frequency in some of the functional categories of the health system (children health care, school children health care and adults).

**Allergic conjunctivitis**

According to ICD-10 this entity belongs to the groups of conjunctival diseases that are classified into the category H10-H13, having in mind that H10 is divided into:

- H10.0 mucous-purulent conjunctivitis
- H10.1 acute atopic conjunctivitis
- X10.2 other acute conjunctivitis
- H10.3 acute conjunctivitis, unsigned
- H10.4 chronic conjunctivitis
- X10.5 blepharoconjunctivitis
- X10.8 other conjunctivitis
- H10.9 conjunctivitis, unsigned

Having this in mind it is clear that although using the 4 signed classifications, ICD-10 gives no opportunity for allergic conjunctivitis classification but it is placed into category of other conjunctivitis (H10.8).

The categories according to which the registered morbidity of children, school children and youth and workers health care sectors is presented, emanate from ICD-10 Tabular List of Morbidity.

Therefore, allergic conjunctivitis is shown as a large group of conjunctival diseases (H10-H13) where besides allergic conjunctivitis, other diseases of conjunctiva are placed as well.

Available data referring to the condition of allergic conjunctivitis in R. Macedonia for the period 1998-2000 are presented in a continuum.

### Registered conjunctivitis morbidity and other diseases of the conjunctiva in Republic of Macedonia in the period 1998 - 2000

<table>
<thead>
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<th>1998</th>
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<td></td>
<td>Number</td>
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<tr>
<td>Total</td>
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<td>23.14</td>
<td>2787</td>
</tr>
</tbody>
</table>

### Asthma

According to ICD-10 allergic asthma is presented with a 3 signed category J45 having the following 4 signed categories:

- J45.0 predominant allergic asthma, comprising following categories - allergic bronchitis, rhinitis with asthma, atopic asthma, extrinsic atopic asthma and hay fever with asthma
- J45.1 non-allergic asthma
- J45.8 mixed asthma
- J45.9 asthma, unsigned
The category J46 according to ICD-10 is reserved for asthmatic status (acute severe asthma). According to ICD-10 Tabular List, categories J45 and J46 are presented together. This approach is also used in the national lists for data collection in the children, school children, youth and general practice health services.

Having in mind the specificity of worker population morbidity, besides J45-J46 categories there is also a 4 signed category J45.0.

<table>
<thead>
<tr>
<th>Asthma in Republic of Macedonia in the period 1998 - 2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>J45.0</td>
</tr>
<tr>
<td>Number</td>
</tr>
<tr>
<td>General</td>
</tr>
<tr>
<td>Males</td>
</tr>
<tr>
<td>Females</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Occupational medicine</td>
</tr>
<tr>
<td>Males</td>
</tr>
<tr>
<td>Females</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Asthma in Republic of Macedonia in the Occupational Health Services in the period 1998 - 2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>J45-J46 (without J45.0)</td>
</tr>
<tr>
<td>Number</td>
</tr>
<tr>
<td>Occupational medicine</td>
</tr>
<tr>
<td>Males</td>
</tr>
<tr>
<td>Females</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

Due to the fact that the Lists for tabling, collecting, analyzing and reporting the data for asthma are designed to give access to the asthma (total) and allergic asthma condition, such data can offer possibilities for current status evaluation. So, the conclusion is that the morbidity rate of predominant allergic asthma in adults in the Republic of Macedonia is 45/10000, without any significant difference due to gender and variations in the three years period. Opposite to this the morbidity rate in occupationally exposed workers is almost ten times lower than in the adults in the period between 1998 and 2000 showing decreasing tendency. Even if we manage to explain the ten times decreased morbidity rate in workers health care services as a result of organizational changes, the ten times decreased asthma incidence in occupationally exposed workers is almost impossible to be logically explained. The reasons may be located in the methodology for collecting and analyzing the data, significant decreasing in Occupational Health Services and the number of active population.
Atopic dermatitis

According to ICD-10 a 3 signed category L20 is reserved for atopic dermatitis:

- L20.0 Besnier’s prurigo
- L20.8 Other atopic dermatitis (includes-eczema and neurodermatitis)
- L20.9 Atopic dermatitis, unsigned

Allergic contact dermatitis is coded with the 3 signed category L23. But, this category excludes unsigned allergy (T78.4), unsigned dermatitis (L30.9), unsigned occupational contact dermatitis and eczema (L25), napkin (L22), non-infectious allergic dermatitis of the eyelid (H01.1), irritant contact dermatitis (L24) and some other entities without significance for this study.

In ICD-10 Tabular List these diseases are put into a large group of skin and subcutaneous diseases (L-10 –L99).

Dermatitis and eczema (L20-L30) and urticaria (L50) are placed in the national tabling lists of children, school children and youth health care services. In the general health care service data for allergic contact dermatitis (L23), urticaria-total (L50) and especially allergic urticaria are collected separately. Obviously this disease has a special attention during determining of the national tabling lists of diseases in Occupational Health Services, where data for allergic contact dermatitis (L23), irritant contact dermatitis (L24), urticariatotal (L50) and allergic urticaria are listed (tabling) separately.

Available data referring to the registered morbidity in ambulatory-policlinic sector in R Macedonia comprising atopic and other types of dermatitis for the period 1998-2000 are presented in a continuum.

<table>
<thead>
<tr>
<th>L20-L30</th>
<th>1998</th>
<th>1999</th>
<th>2000</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Rate/10000</td>
<td>Number</td>
</tr>
<tr>
<td>0-6 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>4008</td>
<td>369,73</td>
<td>4367</td>
</tr>
<tr>
<td>Females</td>
<td>3690</td>
<td>365,3</td>
<td>3939</td>
</tr>
<tr>
<td>Total</td>
<td>7698</td>
<td>367,59</td>
<td>8306</td>
</tr>
<tr>
<td>School</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>3572</td>
<td>264,44</td>
<td>3445</td>
</tr>
<tr>
<td>Females</td>
<td>3969</td>
<td>311,65</td>
<td>4088</td>
</tr>
<tr>
<td>Total</td>
<td>7541</td>
<td>287,35</td>
<td>7533</td>
</tr>
</tbody>
</table>

The data referring to the registered morbidity of allergic contact dermatitis in the adults health care services and occupational health services (occupationally exposed workers) as well as unsigned dermatitis in the occupational health services for the period 1998-2000 are presented in a continuum.
Allergic contact dermatitis in Republic of Macedonia in the occupational and general health services in the period 1998 - 2000

<table>
<thead>
<tr>
<th></th>
<th>1998</th>
<th>1999</th>
<th>2000</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Rate/10000</td>
<td>Number</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>3336</td>
<td>43.32</td>
<td>3664</td>
</tr>
<tr>
<td>Females</td>
<td>3979</td>
<td>50.81</td>
<td>3867</td>
</tr>
<tr>
<td>Total</td>
<td>7315</td>
<td>47.1</td>
<td>7531</td>
</tr>
<tr>
<td>Occupational medicine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>737</td>
<td>10.78</td>
<td>651</td>
</tr>
<tr>
<td>Females</td>
<td>612</td>
<td>9.04</td>
<td>557</td>
</tr>
<tr>
<td>Total</td>
<td>1349</td>
<td>9.92</td>
<td>1208</td>
</tr>
</tbody>
</table>

Unsigned contact dermatitis registered in Republic of Macedonia in the occupational health services in the period 1998 - 2000

<table>
<thead>
<tr>
<th></th>
<th>1998</th>
<th>1999</th>
<th>2000</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Rate/10000</td>
<td>Number</td>
</tr>
<tr>
<td>Occupational medicine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>88</td>
<td>1.29</td>
<td>98</td>
</tr>
<tr>
<td>Females</td>
<td>96</td>
<td>1.42</td>
<td>99</td>
</tr>
<tr>
<td>Total</td>
<td>184</td>
<td>1.35</td>
<td>197</td>
</tr>
</tbody>
</table>

Drug hypersensitivity

Drug allergy (hypersensitivity to an adequate medicament or medicament that is properly applied) is signed with T88.7 in ICD-10. It is a 4 signed category by the group of other surgical and medical care complications that are not classified elsewhere (T88), comprising:

- T88.0 Infection after immunization
- T88.1 Other immunization complications (excludes anaphylactic shock and other serum reactions)
- T88.2 Shock caused by anesthesia
- T88.3 Malignant hyperthermia caused by anesthesia
- T88.4 Unsuccessful or difficult intubations
- T88.5 Other complications due to anesthesia
- T88.6 Anaphylactic shock as an adverse effect caused by adequate medicament or medicament that is properly applied, excluding the anaphylactic shock caused by serum (T80.5)
- T88.7 Unsigned adverse drug or medicament effect, including allergic reaction, hypersensitivity and idiosyncrasy
- T88.8 Other complications
- T88.9 Complications caused by surgical and medical care, unsigned

It should be mentioned that ICD-10 gives the opportunity for classification of photoallergic (L56.1) as well as phototoxic response to drug (L56.0).
Drug hypersensitivity is classified in the tabling lists in a large group of conditions as signed as certain trauma and surgical and medical care complications that are not classified elsewhere, signed with 3 signed categories T79-T88. The national tabling and data collecting lists contains a special category of complications caused by surgical and medical care (T80-T88), which restrict the possibility of obtaining national data for epidemiology and other characteristics connected to drug hypersensitivity.

Drug hypersensitivity data in the national morbidity statistics are presented as a large group of diseases and conditions caused by surgical and medical care only with their 3 signed codes that completely disables the endeavors of collecting relevant national data for epidemiology of drug hypersensitivity.

**Food hypersensitivity**

According to ICD-10, food hypersensitivity can be determined by food contact of the human body. The following pathologic reactions can be manifested:

- **L23 - allergic contact dermatitis**
  - L23.6 - allergic dermatitis caused by contact of food with skin, excluding dermatitis by ingested food L27.2

- **L25 - unsigned dermatitis**
  - L25.4 - unsigned contact dermatitis caused by contact of food with skin

- **L27 - dermatitis caused by internally imported substances**
  (Excluding - reaction to food, except dermatitis T88.7)
  - L27.2 dermatitis caused by ingested food

- **T78 - Adverse effects, unclassified elsewhere**
  - T78.0 anaphylactic shock caused by adverse reaction to food
  - T78.1 other adverse reaction to food, unclassified elsewhere
  - T78.2 anaphylactic shock, unsigned
  - T78.3 angioneurotic edema
  - T78.4 allergy, unsigned
  - T78.8 other adverse effects, unsigned elsewhere
  - T78.9 adverse effect, unsigned

A large category (L10-L99), is reserved for all forms of dermatitis (atopic dermatitis, unsigned dermatitis and dermatitis caused by internally imported substances) according to the tabling lists in ICD-10, signed as other skin and subcutaneous diseases. Anaphylactic shock caused by adverse reaction to food, unclassified elsewhere, should be put in the category - certain early complications caused by trauma, surgical and medical care, unclassified elsewhere with all 3 and 4 signed categories from T79 to T88.
There are several possibilities incorporated in the national lists for tabling and presenting the data. The data for dermatitis and eczema (L20-L30) in children, school children and youth health services are collected and presented separately. There is a special 3 signed category for the data of complications due to surgical and medical care (T80-T88). In the Occupational Health Services these groups of diagnoses are divided and presented separately, such as allergic contact dermatitis (L23), and other diseases and conditions of the skin caused by a contact or food intake that are listed in the group of other skin and subcutaneous diseases (L10-L22, L24-L45, L51-L99).

It has to be pointed out once again that the data are listed only by their 3 signed codes which disable the intentions of collecting relevant national data for epidemiology of food hypersensitivity.

**Insect allergy**

Insect allergy can be classified in the group of toxic effects caused by contact with poison of animals (T63), according to ICD-10:

- T63.0 snake poison
- T63.1 other reptile’s poison
- T63.2 scorpion poison
- T63.3 spider poison
- T63.4 other arthropods poison (insect bite, poison)
- T63.5 toxic effect caused by fish contact

ICD-10 also recommends 3 signed category X23 for coding insect allergy, being a part of the large group of conditions assigned as contact with poison of animals and plants (X20-X29).

Due to the special tabling lists by ICD-10 there is a possibility to put the insect allergy into the large group of conditions known as toxic effects caused by mostly non-medical substances considering the source (T51-T65), which is at the same time used in the national lists for tabling, collecting and publishing the data. Contacts with poison of animals and plants, according to the special ICD-10 morbidity and mortality tabling are not planned, and in the national lists this category (X23) is placed in the large group of 3 signed coded diseases and conditions known as other causes for accidental injury (W00 - X30 and X39-X59).

Speaking about insect allergy, the same conclusion is imposed for the previous entities, that national available data for disease epidemiology are completely inadequate for the purpose of determining the basic epidemiological characteristics, frequency and dynamics.
The need of epidemiological research

Having in mind these reasons, in order to determine the frequency of some allergic entities, epidemiological-clinical research based on a previously made program that offers optimal meticulous objectivity and comparison of data, is being done. These were the basic ongoing goals in our research as well.

On the other hand, planning, conducting and evaluation of population epidemiological studies is a long-term process, giving valuable, comprehensive and plausible data. They are irreplaceable instrument for determining the prevalence of some conditions, but also for analysis of specific characteristics of the examined event. But, due to their design and mode of conduction, they require a perfectly organized network of institutions in the research, experienced and adequately trained researchers as well as adequately designed instruments pertinent for collecting relevant data. Therefore, this kind of epidemiological study is performed incidentally and in line with the needs and research potential of the research teams. The fact that they could be interrupted by financial barriers should always be considered by the institutions, teams or individuals involved.

It is necessary to emphasize the fact that epidemiological cross-sectional studies, like this one, according to its design enable collection of data about the prevalence of some conditions, but however can not give an entire review of their developing tendency. The data about decreasing or increasing of the disease frequency in a longer period of time are basic indicators for health policy planning in the area.

Having in mind the allergic diseases the problem becomes bigger and more actual considering the fact that the disease prevalence is increasing with an amazing speed in all population groups - children, adults, occupationally exposed workers. On the other hand, biomedical investigations and technological achievements are in a significant progress which requires new technical performances of the necessary medical equipment aimed to quick, correct and etiologic diagnosis and treatment of the diseases.

The intensive development of scientific and technological achievements opposite to the increasing trend of the allergic diseases and conditions frequency, is an acceptable reason to seek for easy and available sources of exact and relevant data as a basis for prevention and adequate risk management of allergic diseases.

Contrary to the advantages of some kind of epidemiological studies, they mostly offer data that are not completely comparable because of the chosen design and the basic aim of the conducted research. They are focused on different target groups, diagnosis and trigger factors that are determined by the purpose and research interest of the principal investigator. The experience of a large number of meta-analyses has confirmed this observation.
References:


Aeropallinological and epidemiological studies in R. Macedonia

The given contemplations and facts imposed the necessity of continuation in the cross-sectional epidemiological study of allergic diseases in order to gain a relevant aeropallinological information about the whole country. It resulted in the preparation and realization of the study “Epidemiological Characteristics of the Allergic Rhinitis in Republic of Macedonia in Correlation with the Pollen Microflora”, which was approved and financed by the Ministry of Science and Education of the Republic of Macedonia. The Project was performed under the code 400998 with the contract number 08-3564 from 08.07.1998 and contract annex 40079998 by 01.10.1999. Besides the epidemiological research of allergic rhinitis and aeropallinological studies, with the previous experience of the members from the Institute and other cities in Macedonia, the project enabled research on other allergic diseases in the whole country as well.

The basic aims of the study were aeropallinological monitoring and design of pollen calendars and maps, as well as forming of a palette of the most important allergens in our country for the use of allergy centers and determining the basic epidemiologic characteristics of pollenosis and other most common allergic diseases in the Republic of Macedonia, and the factors in favor of their occurrence.

The study incorporated two complementary segments, making one whole, aeropallinological and epidemiological segment. It had a polycentric character and was performed in 6 centers in the Republic of Macedonia: Skopje, Dojran, Ohrid, Prilep, Debar and Pehchevo, with different characteristics which resulted in getting a real impression of the research area.

In addition to basic analysis for qualitative-quantitative relations in the pollen specter, based on the 10-days average values of the dominant taxa in the pollen aero sediment, pollen calendars were made for each of the cities, and values were shown in a standard pillar diagram according to the EPI recommendations.

The dynamics of the total pollen grains count was analyzed and compared to the data given by the Republic Hydro-metrological Institute (meteorological stations: Zajcev Rid, Dojran, Ohrid, Prilep, Mavrovi Anovi and Berovo).

Statistical analysis of the data was made by analysis of variance (ANOVA), regression correlative analysis, cluster analysis and t-test.
Characteristics of the centers where the study was conducted

The selection of the centers for aeropallinological monitoring was made based on the criteria by their climate-vegetation-soil characteristics, horticultural treasure, economic and tourist importance and their specific location in the Republic of Macedonia (Figure 3). The selection also gratifies the criteria for the clinical-epidemiological segment of the study considering the fact that they are cities with different magnitude, depository and economic potential as well as different kind of standard of living of their inhabitants.

Skopje (Sk)

The Skopje ravine is a relatively well differentiated, situated in the north part of the Republic of Macedonia, taking the upper flow of the river Vardar. It comprises a surface of 1924,215 km$^2$, which is 7,6% of the total surface of the Republic of Macedonia.

The city of Skopje is an urban center with a wide gravitational radius and the most important center in Macedonia, having concentrated one quarter of its total population. According to the State Statistical Office, by the 2002 census Skopje has 506. 926 citizens. It takes the middle part of the Skopje ravine and belongs to warm continental zone. The average year temperature is 12°C and the average rain quantity is about 501,7 mm per year.

It is clear that the influence of the Continental-Mediterranean climate (as well as its modifications with the effects of mountain climate) is one of the most dominant factors on the vegetation of the given territory.

Based on the data analysis given by the Ministry of Agriculture, Forestry and Water Supply, vertical profile of the Skopje ravine and the classification by some of our authors, there are seven registered climate-vegetation-soil areas. They are a result of the regional climate conditions of place-growth, different ecological conditions and finally influence of anthropogenic factors.

Dojran (Do)

The Dojran ravine is a wide space placed in the southeast part of the Republic of Macedonia. It is a borderline and ecological region, having the lowest part of the down flow of river Vardar.

The city of Dojran is a tourist center with a wide gravitational radius. According to the 2002 census, Dojran has 3.426 inhabitants. The city is placed on the shore of the Lake Dojran 180 meters above the sea level in the sub-Mediterranean area. The average year temperature is 14,2°C and the average rain quantity is about 645 mm per year. According to the 1998 Spatial plan of the Republic of Macedonia this city has a low degree of aeropollution.
There are 8 registered climate-vegetation-soil areas in the Dojran ravine, which are a result of hydrologic, different ecologic conditions as well as influence of the anthropogenic factors.

**Ohrid (Oh)**

The Ohrid-Struga ravine is a relatively good differentiated space placed in the southwest part of the Republic of Macedonia comprising a part of the river Crn Drim flow. The city of Ohrid is situated on the flat surface between the ravine and the Lake Ohrid rising up to the next hill to the middle age Fortress. Today, Ohrid is the biggest and most attractive urban tourist center in this area with a wide gravitation radius and about 760 meters above the sea level. According to the 2002 census Ohrid has 55,749 inhabitants.

The city belongs to the warm continental zone. The average year temperature is 11,2°C and the average rain quantity is about 689 mm per year.

There are 6 registered climate-vegetation-soil areas in the Ohrid-Struga ravine, which are a result of regional climate place-growth, ecological conditions and influence of the anthropogenic factors as well.

**Prilep (Pr)**

Prilep ravine is a wide space placed in the central part of the Republic of Macedonia, surrounded by mountains (except towards south), occupying the field of Prilep (lowest part). It comprises parts of the Crna and Old river flows, having two cities, Prilep and Krushevo.

The city of Prilep is placed in the eastern part of the Prilep ravine. It is an urban center with a wide gravitation radius, 673 meters above the sea level. According to the 2002 census Prilep has 76,768 inhabitants. The city belongs to the warm continental zone, having average year temperature of 11,2°C and the average rain quantity is about 557 mm per year.

There are 6 registered climate-vegetation-soil areas in the Prilep ravine, which are a result of regional climate conditions and the influence of the anthropogenic factors as well.

**Debar (De)**

Debar ravine is a border area to the Republic of Albania, placed in the western part of Macedonia, surrounded by mountains. It comprises parts of the Crn Drim and Radika river flows.
The city of Debar is a functional center for the area with a small gravitation radius. It is placed about 675 meters above the sea level, nearby Lake Debar. According to the 2002 census Debar has 19,542 inhabitants.

This city belongs to the warm continental zone. There is not a meteorological station in the city of Debar, but according to the data taken from the station in Mavrovi Anovi, the average year temperature is 11,8°C and the average rain quantity is about 890 mm per year.

There are 6 registered climate-vegetation-soil areas in the Debar ravine, which are a result of regional climate place-growth, different ecological conditions and the influence of the anthropogenic factors as well.

**Pehchevo (Pe)**

Pehcevo ravine is a border area to the Republic of Bulgaria, placed in the eastern part of the Republic of Macedonia, surrounded by mountains (Picture 3). It comprises parts of the river Bregalnica flow. There are two cities in the research territory, Pehchevo and Berovo.

The city of Pehchevo is with a small gravitation radius, functional center for its immediate ambience and less developed secondary activities.

According to the 2002 census Pehchevo has 5,517 inhabitants. This city belongs to the cold continental zone.

There is no meteorological station in the city of Pehchevo, but according to the data taken from the station in Berovo, the average year temperature is 8,8°C and the average rain quantity is about 632 mm per year.

There are 5 registered climate-vegetation-soil areas in the Pehchevo ravine (Picture 3). They are a result of the regional climate place-growth, different ecological conditions and the influence of the anthropogenic factors, which resulted in other species of forests and cattle yards, but outnumbered in this ravine.
Part II

Aeropallinological monitoring
1.0. Outdoor aeroallergens

Monitoring of pollen contents (aeropollinologic microflora) in the air, as a pollenosis etiology factor, is directly connected to the pollenosis problem evaluation and conducting the preventive actions. In most European countries pollen monitoring is a tradition of many years. European monitoring system through EPI (European Pollen Information) enables local, regional and international coordination of aeropollinology centers by follow-up of the pollen grains distribution and provision of stipulation models. The need for creation aeropollinologic calendar of some region results from the climate, vegetation, topography, orography and hydrographic characteristics of that region. Since 1993, aeropollinologic research has been performed at the Institute of Occupational Health - Skopje. First observations comprised data about the city of Skopje without any representative statistics about the entire territory of R. Macedonia.

Atmospheric air contains different industrial and biologic pollutants. It is necessary to perform detailed monitoring of biologic pollutants in R. Macedonia together with examinations of industrial components which have already given comparable and relevant data. These data are of extensive importance in biologic, ecologic and allergologic researches.

Pollen grains (PG) together with other aerosols are continuously present in the air, especially in the pollen period and have specific effects on the health. They constitute generative elements necessary in the process of reproduction. Pollen is released from anemophilic taxa in large amounts in the period of pollination and is spread on the earth ground as a “pollen rain”. Some of the PG are close to the earth ground and have short period of sedimentation and deposition. But, pollen spread under the influence of dilution and turbulence on the distance far from the source is very important in the process of resolving questions on etiology of allergic diseases.

1.1. Definition

According to the British Aerobiologic Federation “aeropollinology is a scientific discipline which studies PG transport through the atmosphere, especially the source of PG, their release in the atmosphere, dispersion and deposition as well as their influence on vegetable, animal and human systems”, so aeropollinology as a segment of aerobiology studies pollen microflora in the free atmosphere.

1.2. Aeropollinological methods

One of the most important discussions in aeropollinology examinations is sampler selection. According to the physical principles of their construction there are, generally, two types of samplers. The first type (Gravimetric method) is simple; it is based on free sedimentation of pollen rain and has historical importance. The second type (Volumetric method) is based on forced pollen sedimentation mediated by vacuum pumps and shock forces. These sampling methods collect PG directly from the air flow which is minimal and adequate to the sedimentation velocity.
Today, both methods are used in aeropallinological practice. There are no great differences in data obtained and both methods have some practical importance.

Efforts for construction of more effective PG sampler continue and today there is large number of them.

The latest researches are focused on detecting and immunochemical quantification of micron and submicron allergens using radioisotope-marked antibodies. They can be detected by filters with cascade impactors which divide particles according to dimensions or flow intensity, but although these methods give more precise results, they have no wider use due to complex technique.

We have used gravimetric method (Durham) for aeropallinological monitoring, and for the city of Skopje both volumetric and gravimetric methods.

The gravimetric method is older one, based on free sedimentation of “pollen rain”, and performed by Durham apparatus (Figure 1). The advantages of this method are possibilities of placing on different locations and conditions (for e.g. places without electricity).

The volumetric method is a new method used worldwide, based on forced pollen sedimentation mediated by vacuum pumps and shock forces. The obtained results are comparable throughout world. It is usually done by Lanzoni VPPS 2000 apparatus (Figure 2).

The observation period started in the beginning of January 1998 and lasted till the end of 2000, with glass replacement each day and 24 hour duration of sedimentation period. Pollen grains identification and counting were performed on 2 cm\(^2\) surface.

Figure 1. Gravimetric Durham apparatus for aerosedimentation


1.3. Methodology of aeropallinological research

Aeropallinological research was performed in six cities of R. Macedonia: Skopje, Dojran, Ohrid, Prilep, Debar and Pehchevo. Selection of the cities was based on many criteria, such as: climate-vegetation-soil characteristics, horticultural wealth, economic and tourist importance as well as characteristic location in R. Macedonia (Figure 3).

Durham sedimentation method was applied during aeropallinological examination. The observation period started in the beginning of January 1998 and lasted till the end of 2000, with glass replacement each day and 24 hour duration of sedimentation period. Pollen grains identification and counting were performed on 2 cm² surface.

Among basic analyzes for quality-quantity relations in pollen spectrum, pollen calendars were constructed for each city, according to the 10 day-interval average values of dominant taxa in the pollen aerosediment, and data were shown on standard column chart as the most appropriate one, according to EPI recommendations.

Dynamics of the total daily PG number was analyzed and compared with the meteorology data (Republic Hydrometeorology Institute - Meteorology stations: Zajchev Rid, Dojran,
Ohrid, Prilep, Mavrovi Anovi and Berovo). Skopje meteorology station was located at region Zajchev Rid, Debar data were taken from meteorology station in Mavrovi Anovi, and Pehchevo data were taken from the station in Berovo.

Data obtained were statistically analyzed by analysis of variance (ANOVA), regression correlation analysis, cluster analysis and t-test.

Figure 3. Map of climate regions and location of apparatus for aeropallinological monitoring

1.4. Influence of aeropollution on pollen grains concentration and dissemination

Aeropollution. The term “aeropollution” means wide spectrum of chemical and biological components in outdoor and indoor atmosphere. *Aeropollutant is every substance which modifies natural contents of the atmospheric air.*

International meteorology organization research (Intergovernmental Panel on Climatic Change) (1992) and ecology associations focused on: increased \( \text{SO}_2 \) concentration in the atmosphere, gases of “green house”, CFC presence as well as new technologies as factors which have influence on pollen spectrum. They are producing changes in timing and magnitudes of pollen period and have implications on pollenosis appearance.
Under the influence of UV waves, aeropollution (SO$_2$, NO$_2$, CO, diesel particulates, heavy metals) changes the surface structure of pollen grains, increases the number of cytosol allergy proteins, and pollen becomes intensively allergenic. Total PG number in the air is associated with total aerosediment amount and the correlation is significant (Figure 4). In conditions of unavailable fundamental research, the data obtained through continuous monitoring and some researches give opportunity to determine the association between aerosediment amount and PG number for some area. Statistical analysis of these parameters in 2000 for the city of Skopje showed high degree of statistical association and coefficient of positive correlation (0,97). These data are expected and logical and significant correlation enables PG number assessment according to the aerosediment amount. This assessment could be valuable guide to the pollen potential evaluation of some area but comparative advantages of aeropallinologic methods are irreplaceable.

![Figure 4. Correlation between total monthly PG number and total monthly aerosediment amount (mg/m$^2$) registered in Skopje, 2000](image)

Nevertheless, statistically significant correlation was not determined in the case of ambrosia (Figure 5). The answer is somewhere between the presence of ambrosia PG in summary pollen structure on one side to the gravimetric and other characteristics of ambrosia PG on the other side.
The anatomy of nasal cavities enables deposition of inhaled particles, larger than 10 mcm, they are caught on the nasal filter and there they express effects, such as pollen rhinitis. After raining, pollen grains release submicron pollen particles (leucoplasts) which penetrate in lower airways and cause spreading allergic inflammation. Under the influence of UV waves, aeropollution (SO\textsubscript{2}, NO\textsubscript{2}, ozone) changes the surface structure of pollen grains, increases the number of cytosol allergy proteins, and pollen becomes intensively allergenic. The problems of aeropollution and its effects on the processes of allergic senzibilisation and inflammation are global ones. Table 1 shows the results of aerosediment measurements in the Republic of Macedonia, performed by the Republic Institute for Health Protection, Skopje (2003). It is obvious that large number of samples (20%) had aerosediment values above the maximum permitted concentration.
<table>
<thead>
<tr>
<th>Institute for Health Protection</th>
<th>Number of measurement sites</th>
<th>Number of samples</th>
<th>Average annual concentration (mg/m²)</th>
<th>Minimum-Maximum (mg/m²)</th>
<th>Number of samples above MPC*</th>
</tr>
</thead>
<tbody>
<tr>
<td>SKOPJE</td>
<td>30</td>
<td>338</td>
<td>182.1</td>
<td>32.1-707.2</td>
<td>42</td>
</tr>
<tr>
<td>VELES</td>
<td>7</td>
<td>82</td>
<td>176.7</td>
<td>0.3-1508.0</td>
<td>14</td>
</tr>
<tr>
<td>v. Ivankovci</td>
<td>1</td>
<td>12</td>
<td>191.0</td>
<td>6.0-686.1</td>
<td>2</td>
</tr>
<tr>
<td>PRILEP</td>
<td>5</td>
<td>60</td>
<td>177.45</td>
<td>127.0-229.3</td>
<td>13</td>
</tr>
<tr>
<td>T.U.Krushevo</td>
<td>2</td>
<td>24</td>
<td>119.5</td>
<td>95.75-136.25</td>
<td>0</td>
</tr>
<tr>
<td>OHRID</td>
<td>3</td>
<td>29</td>
<td>229.9</td>
<td>26.61-616.62</td>
<td>6</td>
</tr>
<tr>
<td>T.E.Struga</td>
<td>2</td>
<td>24</td>
<td>248.86</td>
<td>33.6-818.2</td>
<td>10</td>
</tr>
<tr>
<td>BITOLA</td>
<td>4</td>
<td>46</td>
<td>114.58</td>
<td>27.15-325.53</td>
<td>2</td>
</tr>
<tr>
<td>KOCHANI</td>
<td>4</td>
<td>48</td>
<td>72.67</td>
<td>11.83-242.08</td>
<td>0</td>
</tr>
<tr>
<td>KUMANNOVO</td>
<td>4</td>
<td>48</td>
<td>135.0</td>
<td>16.0-457.1</td>
<td>3</td>
</tr>
<tr>
<td>STRUMICA</td>
<td>4</td>
<td>47</td>
<td>290.0</td>
<td>117.0-682.0</td>
<td>17</td>
</tr>
<tr>
<td>TETOVO</td>
<td>4</td>
<td>47</td>
<td>126.16</td>
<td>11.58-379.40</td>
<td>1</td>
</tr>
<tr>
<td>SHTIP</td>
<td>6</td>
<td>70</td>
<td>243.9</td>
<td>35.38-659.31</td>
<td>60</td>
</tr>
<tr>
<td>R. MACEDONIA</td>
<td>76</td>
<td>870</td>
<td>177.52</td>
<td>41.56-572.85</td>
<td>170</td>
</tr>
</tbody>
</table>

* MPC-Maximum Permitted Concentration (300 mg/m²);

Table 1. Hygiene quality of air in R. Macedonia during 2003 - aeropollutant aerosediment

Statistical analysis showed significant correlation between total PG number and aerosediment concentration in 2003 in the city of Skopje (Figure 6).

![Figure 6. Correlation between total PG number and aerosediment concentration in 2003 in the city of Skopje](image-url)
Multicenter strategy is indispensable in order to solve the problem with the allergic diseases due to their high prevalence both in our country and in the world. The importance of such strategy is emphasized because of the wide range of industrial and biologic pollutants which are detected as allergogens and because of their synergistic actions.

The motive for performing such study is related either to the critical notification of disadvantages linked to the first epidemiological and aeropallinological examinations in our country or to the necessity for representative pollenosis data for the whole country. Therefore, besides Skopje, cities of Dojran, Ohrid, Prilep, Debar and Pehchevo were included in our research and pollen monitoring and clinical-epidemiological research for the whole country showed the true significance of a multicenter study.

1.5. Results

1.5.1. Skopje. Skopje apparatus was located on flat roof on the building of the Institute of Occupational Health at 7.5 m height above the ground level, coordinates: $\lambda=21^\circ27'09''$; $\varphi=42^\circ01'16''$; and $Z=275$ m above the sea level.

The city of Skopje is characterized by rich horticultural diversity. During the examined period, the highest values were detected for: *Betula* (birch), *Pinaceae* (pine), *Cedrus* (cedar), *Platanus* (plane), *Cupressaceae* (cypress), *Quercus* (oak), and *Fraxinus* (ash) as dendrofloral taxas, and *Poaceae* (cereal), *Urticaceae* (nettles), *Plantago* (plantain), and *Chenopodiaceae/Amaranthaceae* (orach/barren) as greens.

The highest concentrations of: *Cedrus* (cedar), *Betula* (birch), *Platanus* (plane), *Acer* (maple), *Populus* (polar), *Morus* (mulberry) and *Fraxinus* (ash), and low concentrations of *Fagus* (beech) were registered in Skopje in comparison with other examined cities.

<table>
<thead>
<tr>
<th>SKOPJE</th>
<th>Pollen %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dendroflora Trees</td>
<td>88,4</td>
</tr>
<tr>
<td>Poaceae Cereal</td>
<td>6,1</td>
</tr>
<tr>
<td>Chenopodiaceae Orach</td>
<td>1,1</td>
</tr>
<tr>
<td>Artemisia Wormwood</td>
<td>0,2</td>
</tr>
<tr>
<td>Urticaceae Nettle</td>
<td>1,5</td>
</tr>
<tr>
<td>Plantago Plantain</td>
<td>1,1</td>
</tr>
<tr>
<td>Ambrosia Ambrosia</td>
<td>0,2</td>
</tr>
</tbody>
</table>

Table 2. Average annual relative presence of pollen grains of seven taxa in the city of Skopje

1.5.2. Dojran. Sampling apparatus in Dojran was located at the Barracks court with coordinates $\lambda=22^\circ42'44''$; $\varphi=41^\circ10'42''$ and $Z=160$ m above the sea level.

The city of Dojran is characterized by the presence of taxa of riverside and swamp vegetation. During the investigation period, the highest values were detected for:
Cupressaceae (cypress), Pinaceae (pine), Cedrus (cedar), Quercus (oak), Ulmus (elm), Platanus (plane), and Juglans (walnut) as dendrofloral taxa, and Poaceae (cereal), Urticaceae (nettle), Asteraceae, Plantago (plantain), and Rumex (sorrel) as greens.

The highest concentrations of Ulmus (elm) and Sambucus (elder), typical only for the region of Dojran were registered, followed by high concentrations of Rosaceae (rose), Fabaceae, Olea (olive), Myrtus (Greek tea), and Koelreuteria, as well as Urticaceae (nettle), Chenopodiaceae/Amaranthaceae (orach/barren) and Apiaceae. The highest concentrations of Morus (mulberry), Platanus (plane), Cupressaceae (cypress), Juglans (walnut) and low concentrations of Tilia (lime) were registered at this location. Here, pollen period starts earlier and finishes later in comparison with other locations.

<table>
<thead>
<tr>
<th>DOJRAN</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Taxa</strong></td>
<td><strong>Pollen %</strong></td>
<td></td>
</tr>
<tr>
<td>Dendroflora</td>
<td>Trees</td>
<td>70,9</td>
</tr>
<tr>
<td>Poaceae</td>
<td>Grasses</td>
<td>8,6</td>
</tr>
<tr>
<td>Chenopodiaceae</td>
<td>Oraches</td>
<td>4,4</td>
</tr>
<tr>
<td>Artemisia</td>
<td>Wormwood</td>
<td>0,9</td>
</tr>
<tr>
<td>Urticaceae</td>
<td>Nettles</td>
<td>8,4</td>
</tr>
<tr>
<td>Plantago</td>
<td>Plantain</td>
<td>0,5</td>
</tr>
<tr>
<td>Ambrosia</td>
<td>Ragweed</td>
<td>0,1</td>
</tr>
</tbody>
</table>

Table 3. Average annual relative presence of pollen grains of seven taxa in the city of Dojran

1.5.3. Ohrid. Sampling apparatus in Ohrid was located on the plain roof of the Medical Center building at 8,5 m from the surface with the following coordinates: λ= 20° 49'20'"; φ=41° 06'56'" and Ζ=705 m above the sea level.

In the city of Ohrid, the highest values of pollen grains from dendrofloric taxa were detected for Pinaceae (pine), Cupressaceae (cypress), Betula (birch), Quercus (oak), Juglans (walnut) and Corylus (hazel), whereas the most prevalent grass and weed pollens were: Poaceae, Asteraceae, Plantago (plantain), Rumex (sorrel) and Urticaceae (nettle) pollen grains.

This city is characterized by a rich horticultural diversity, but also by a presence of swamp and water vegetables and higher pollen grains concentration of Asteraceae. In this city, compared to others, the highest concentrations were registered for Pinaceae (pine) and Sambucus (elder), and the lowest for Fagus (beech).

<table>
<thead>
<tr>
<th>OHRID</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Taxa</strong></td>
<td><strong>Pollen %</strong></td>
</tr>
<tr>
<td>Dendroflora</td>
<td>Trees</td>
</tr>
<tr>
<td>Poaceae</td>
<td>Grasses</td>
</tr>
<tr>
<td>Chenopodiaceae</td>
<td>Oraches</td>
</tr>
<tr>
<td>Artemisia</td>
<td>Wormwood</td>
</tr>
<tr>
<td>Urticaceae</td>
<td>Nettles</td>
</tr>
<tr>
<td>Plantago</td>
<td>Plantain</td>
</tr>
<tr>
<td>Ambrosia</td>
<td>Ragweed</td>
</tr>
</tbody>
</table>

Table 4. Average annual relative presence of pollen grains of seven taxa in the city of Ohrid
1.5.4. **Prilep.** Sampling apparatus in Prilep was located on the plain roof of the Medical Center building, 8,5 m from the surface with the following coordinates: $\lambda=21^\circ \ 34'07''$; $\varphi=41^\circ \ 20'39''$ and $Z=660$ meters above the sea level.

The highest values of pollen grains were detected for Cupressaceae (cypress), Quercus (oak), Pinaceae (pine), Tilia (lime) and Corylus (hazel) of dendrofloric taxaees, as well as for Poaceae (cereal), Plantago (plantain), Rumex (sorrel), Chenopodiaceae/Amaranthaceae, Urticaceae (nettle) and Asteraceae of grass and weed pollens in the city of Prilep, in the examined period.

This city, compared to others, is characterized with higher concentrations of Corylus (hazel), Tilia (lime), Populus (poplar), Quercus (oak) and Koelreuteria, as well as high prevalence of grass and weed taxa, with dominance of Poaceae (cereal), Rumex (sorrel), Chenopodiaceae/Amaranthaceae and Plantago (plantain). The most important taxa registered in the city of Prilep and their seasonal and concentration characteristics are presented in the pollen calendar for Prilep.

<table>
<thead>
<tr>
<th>TAXA</th>
<th>POLLEN%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dendroflora</td>
<td>Trees</td>
</tr>
<tr>
<td>Poaceae</td>
<td>Grasses</td>
</tr>
<tr>
<td>Chenopodiaceae</td>
<td>Oraches</td>
</tr>
<tr>
<td>Artemisia</td>
<td>Wormwood</td>
</tr>
<tr>
<td>Urticaceae</td>
<td>Nettles</td>
</tr>
<tr>
<td>Plantago</td>
<td>Plantain</td>
</tr>
<tr>
<td>Ambrosia</td>
<td>Ragweed</td>
</tr>
</tbody>
</table>

**Table 5.** Average annual relative presence of pollen grains of seven taxa in the city of Prilep

1.5.5. **Debar.** Sampling apparatus in Debar was located on the plain roof of the Medical Center building, 8,5 m from the surface with the following coordinates: $\lambda= 20^\circ \ 32'03''$; $\varphi=41^\circ \ 31'19''$; $Z= 675$ meters above the sea level.

The highest values of tree pollens were detected for Cupressaceae, Pinaceae (pine), Tilia (lime) and Quercus (oak), as well as for Poaceae (cereal), Urticaceae (nettle), Plantago (plantain) and Asteraceae of grass and weed pollens in the city of Debar, in the examined period.

This city, compared to others, is characterized with the highest concentrations of Salix (willow), Tilia (lime), Corylus (hazel) and Castanea (chestnut), as well as Urticaceae (nettle) and Plantago (plantain), also with presence of higher concentrations of pollen grains of Fabaceae and Ericaceae, compared to other cities, and lower of Platanus (plane).
Table 6. Average annual relative presence of pollen grains of seven taxa in the city of Debar

<table>
<thead>
<tr>
<th>Taxa</th>
<th>Pollen%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dendroflora</td>
<td>Trees</td>
</tr>
<tr>
<td>Poaceae</td>
<td>Grasses</td>
</tr>
<tr>
<td>Chenopodiaceae</td>
<td>Oraches</td>
</tr>
<tr>
<td>Artemisia</td>
<td>Wormwood</td>
</tr>
<tr>
<td>Urticaceae</td>
<td>Nettles</td>
</tr>
<tr>
<td>Plantago</td>
<td>Plantain</td>
</tr>
<tr>
<td>Ambrosia</td>
<td>Ragweed</td>
</tr>
</tbody>
</table>

1.5.6. Pehchevo. Sampling apparatus in Pehchevo was located on the plain roof of the Health Center building, 8 m from the soil surface with the following coordinates: $\lambda = 22^\circ 52' 30''$; $\phi = 41^\circ 45' 37''$; $Z = 1000$ meters above the sea level.

During the investigation period, the highest values of tree pollen grains were detected for Pinaceae (pine), Cupressacea (cypress), Betula (birch), Quercus (oak), Fagus (beech) and Salix (willow), as well as Poaceae (cereal), Urticaceae (nettle), Plantago (plantain) and Artemisia (mugwort) of grass and weed pollens in the city of Pehchevo.

This city, compared to others, is characterized with the higher prevalence of weed pollens, such as nettle and plantain, as well as higher pollen grains concentrations for Pinaceae (pine), Fagus (beech), Betula (birch) and Alnus (alder), but lower concentrations for Tilia (lime).

Table 7. Average annual relative presence of pollen grains of seven taxa in the city of Pehchevo

<table>
<thead>
<tr>
<th>Taxa</th>
<th>Pollen%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dendroflora</td>
<td>Trees</td>
</tr>
<tr>
<td>Poaceae</td>
<td>Grasses</td>
</tr>
<tr>
<td>Chenopodiaceae</td>
<td>Oraches</td>
</tr>
<tr>
<td>Artemisia</td>
<td>Wormwood</td>
</tr>
<tr>
<td>Urticaceae</td>
<td>Nettles</td>
</tr>
<tr>
<td>Plantago</td>
<td>Plantain</td>
</tr>
<tr>
<td>Ambrosia</td>
<td>Ragweed</td>
</tr>
</tbody>
</table>

The pollen period begins earliest in the city of Dojran and the latest in the city of Pehchevo as a result of the climate and geographical conditions.
1.5.7. Concentration and distribution of pollen grains in R. Macedonia

The pollen specter found in the examined cities showed rich qualitative and quantitative composition. There are 98 registered taxa in R. Macedonia (59 families), 51 of them (27 families) are representatives of the dendroflora.

From the total number of registered pollen grains in R. Macedonia (521127 pollen grains), most of them belong to the dendroflora taxa, predominantly: Cupressaceae (cypress - 23,6% of the total registered pollen grains), Pinaceae (pine - 17,25%), Betula (birch - 8,5%) and Quercus (oak). They participate with more than 60% in the total amount of detected tree pollens. Dominant taxa from the group of grasses and weeds were Poaceae (10,45%), followed by: Urticaceae (nettles-4,39%), Chenopodiaceae/ Amaranthaceae (fat hen-1,94%), and Plantago (plantain-1,94%).

<table>
<thead>
<tr>
<th>Taxa</th>
<th>Pollen%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dendroflora</td>
<td>77,2</td>
</tr>
<tr>
<td>Poaceae</td>
<td>10,4</td>
</tr>
<tr>
<td>Chenopodiaceae</td>
<td>1,5</td>
</tr>
<tr>
<td>Artemisia</td>
<td>0,8</td>
</tr>
<tr>
<td>Urticaceae</td>
<td>3,7</td>
</tr>
<tr>
<td>Plantago</td>
<td>2,0</td>
</tr>
<tr>
<td>Ambrosia</td>
<td>0,1</td>
</tr>
</tbody>
</table>

Table 8. Average annual relative presence of pollen grains of seven taxa in the Republic of Macedonia

1.5.8. Sensitization-relation to pollen grains

Considering the sensitization prevalence to pollen allergens that was 27,5% in adults, the highest prevalence was registered for weed pollens (19,4%), with the prevalence of 13,0% for fat hen (Chenopodium sp.) as the most potent allergen (Table 8). Its participation in examined population with manifested seasonal allergic rhinitis was 30,5%, whereas in allergic asthma it was 58,3%. The sensitization prevalence in the group of grasses was 18%, and 11,9% in the group of trees.

The highest prevalence of pollen sensitization was registered in examinees with allergic conjunctivitis (87,2%).
Figure 7. Atopy in examined population

<table>
<thead>
<tr>
<th>Taxon</th>
<th>Pollen%</th>
<th>Positive SPT %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dendroflora Trees</td>
<td>77,2</td>
<td>11,9</td>
</tr>
<tr>
<td>Poaceae Grasses</td>
<td>10,4</td>
<td>18</td>
</tr>
<tr>
<td>Chenopodiaceae</td>
<td>1,5</td>
<td>13,0</td>
</tr>
<tr>
<td>Fat Hen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Artemisia Mugwort</td>
<td>0,8</td>
<td>11,4</td>
</tr>
<tr>
<td>Urticaceae</td>
<td>3,7</td>
<td>7,5</td>
</tr>
<tr>
<td>Nettle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plantago Plantain</td>
<td>2,0</td>
<td>4,8</td>
</tr>
<tr>
<td>Ambrosia</td>
<td>0,1</td>
<td>4,1</td>
</tr>
<tr>
<td>Ragweed</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 9. Average annual relative presence of pollen grains of seven taxa and positive skin prick tests in the Republic of Macedonia
1.5.9. Sensitization-relation to pollen grains in the examined cities

<table>
<thead>
<tr>
<th>City</th>
<th>Pollen in %</th>
<th>Positive SPT in %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skopje</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dendroflora</td>
<td>88.4</td>
<td>5.5</td>
</tr>
<tr>
<td>Poaceae</td>
<td>6.1</td>
<td>13</td>
</tr>
<tr>
<td>Chenopodiaceae</td>
<td>1.1</td>
<td>15</td>
</tr>
<tr>
<td>Artemisia</td>
<td>0.2</td>
<td>15</td>
</tr>
<tr>
<td>Urticaceae</td>
<td>1.5</td>
<td>8.5</td>
</tr>
<tr>
<td>Plantago</td>
<td>1.1</td>
<td>6.5</td>
</tr>
<tr>
<td>Ambrosia</td>
<td>0.2</td>
<td>6.5</td>
</tr>
<tr>
<td><strong>Dorjan</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dendroflora</td>
<td>70.9</td>
<td>21.3</td>
</tr>
<tr>
<td>Poaceae</td>
<td>8.6</td>
<td>25.5</td>
</tr>
<tr>
<td>Chenopodiaceae</td>
<td>4.4</td>
<td>11.7</td>
</tr>
<tr>
<td>Artemisia</td>
<td>0.9</td>
<td>11.7</td>
</tr>
<tr>
<td>Urticaceae</td>
<td>8.4</td>
<td>5.3</td>
</tr>
<tr>
<td>Plantago</td>
<td>0.5</td>
<td>5.3</td>
</tr>
<tr>
<td>Ambrosia</td>
<td>0.1</td>
<td>4.3</td>
</tr>
<tr>
<td><strong>Ohrid</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dendroflora</td>
<td>83.9</td>
<td>19</td>
</tr>
<tr>
<td>Poaceae</td>
<td>8.3</td>
<td>10</td>
</tr>
<tr>
<td>Chenopodiaceae</td>
<td>0.2</td>
<td>5</td>
</tr>
<tr>
<td>Artemisia</td>
<td>0.9</td>
<td>4</td>
</tr>
<tr>
<td>Urticaceae</td>
<td>0.5</td>
<td>8</td>
</tr>
<tr>
<td>Plantago</td>
<td>0.9</td>
<td>3</td>
</tr>
<tr>
<td>Ambrosia</td>
<td>0.1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Prilep</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dendroflora</td>
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<td>9.3</td>
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Table 10. Average annual relative presence of pollen grains of seven taxa and positive skin prick tests in the six examined cities
Figure 8. Average annual relative presence of pollen grains of seven taxa and positive skin prick tests in the city of Ohrid

Figure 9. Correlation between average annual relative presence and sensitization to the adequate pollen allergens in the city of Ohrid \((r = 0.90; \, p<0.01)\)
1.5.10. Analysis of aeropollinological monitoring and sensitization effect among adult population in R. Macedonia

Analyzing the pollen microflora and sensitization of the examined adult population in R. Macedonia (Table 9), it is evident that tree taxaes are with the biggest average annual relative prevalence in the air (77.2%), while the sensitization to the tree allergens in the examinees is only 18.9%. On the other hand, the grass taxa have the highest prevalence of positive skin tests (Poaceae) with 17.9%, participating in the average annual relative prevalence in the air with 10.4% (right next to the tree taxa). The taxa Chenopodiaceae, Artemisia, Urticaceae, Plantago and Ambrosia have higher prevalence of positive skin tests related to their prevalence in the air. Besides that, the statistical analysis of the average annual relative prevalence of pollen grains for all 7 taxa and sensitization to them, show no relevant statistical correlation (r=0.245; for p>0.05).

The analysis of average relative pollen grains prevalence and positive skin tests in examinees from different cities shows that the highest air prevalence have the tree pollen grains (over 70%) in all 6 cities (Table 10), followed by grasses (Poaceae) ranging from 6.1% in Skopje to 16.6% in Prilep. The tree taxa do not dominate with their sensitization prevalence in the examined cities except in Ohrid with 19.0% (Table 10; Graph 6). There is the highest prevalence of the grass pollen taxa sensitization in Prilep (35.6%), followed by Dojran (25.5%), Pehchevo (17.8) and Debar (7.7%). In the city of Skopje the highest sensitization prevalence is registered for Chenopodiaceae and Artemisia with 15.0%. There is no correlation found between average annual relative presence and sensitization to the pollen allergens for the centers in Dojran, Skopje, Prilep, Debar and Pehchevo. This correlation is registered (Figure 9) only for the city of Ohrid (r=0.90, p<0.01).

The basic approach in the examination is evaluation and correlation of two connected segments: aeropollinological monitoring and clinical results.

A rich pollen specter, with total number of 98 taxa by 59 families, is registered using the aeropollinological monitoring. The dendroflora containing 51 taxa (27 families) has a dominant place in the total number of taxa. Most of the pollen grains belong to the dendroflora taxa but the most dominant are Cupressaceae (cypress)-23.6%, and cereals (fam. Poaceae) in the group of the grasses (10.4%). The constructed pollen calendars for each center separately, show the pollen taxa types, the period of appearance and their maximal concentrations. The pollen period in Dojran is the earliest one compared to the latest one in Pehchevo, considering the climate characteristics.

As a result of the climate-vegetation characteristics Macedonian pollen calendar has some similarities with the pollen calendar of Bulgaria. The differences of the pollen calendars in the Mediterranean countries and the Nordic region are significant, both in qualitative and quantitative point of view, timing and the magnitudes of the pollen periods and the present taxa.

Considering the distribution by cities in Macedonia, it is registered that in Prilep seasonal allergic rhinitis (SAR) has the highest prevalence (29.7%), whereas in Skopje it is the
lowest (8.5%). If we compare this prevalence for the city of Skopje with the results in 1996, when the prevalence of SAR was 7.1%, it is evident that the prevalence has slightly increased. The reasons for the different prevalence of SAR, the highest in the city of Prilep, are not quite clear. From the aeropallinological point of view, Prilep is characterized with higher concentrations of Corylus (hazel), Tilia (lime), Populus (poplar), Quercus (oak) and Koelreuteria compared to the other cities, as well as high prevalence of grass and weed pollens, with predominance of Poaceae (cereal), Chenopodiaceae/Amaranthaceae (fat hen) and Plantago (plantain). It is possible that these original pollen allergogenic composition and concentrations are one of the factors for the high SAR prevalence, although some other factors such as genetic, meteorologic, climate and geographic should be taken into account.

It is registered that the younger age and urban environment are factors in favor for SAR in adults, and lung problems are statistically significantly related to SAR (p<0.01). This relation points out to the necessity of integral approach during evaluation of upper and lower airways.

If the SAR prevalence in adults in Skopje (8.5%) is compared to the one registered in children, it is obvious that SAR is more present in the youth than in the adult population. The reason for this may be in the sensitivity of the child organism to the intensive urban pollution in the context of aero-biological pollution of the city of Skopje, having in mind that perhaps the genetic predisposition for SAR is manifested earlier compared to the other cities in the Republic of Macedonia. The early sensitization in children is supported by the presence of high pollen grains concentrations that are severe allergenic.

On the other hand, the prevalence of the perennial allergic rhinitis in children is 8.3% which is very similar to the seasonal allergic rhinitis, and it is the highest in Skopje (10.6%) and lowest in Debar (4.8%).

The atopy prevalence is 34.8% which is an expected value, according to the literature data. The highest sensitization prevalence is registered for weeds as a group (19.4%), followed by grasses with 17.9% in adults. The same is with the SAR, weeds with 7.6% and grasses 6.8%. These data confirm the fact that weeds and grasses have the greatest allergenicity in the examined population.

However, the aeropallinological data show that tree pollens taxa are with the highest concentrations in the Republic of Macedonia (77.2%), but sensitization to these pollens is found in 10.8% of the examined subjects. This fact shows that allergenic concentration is not the only factor for pollen sensitization.

It is evident that allergenicity of the weed and grass pollens is much more expressed than tree pollen taxa. This is proved by the data that if the weeds as a group are distributed due to single taxa (Chenopodiaceae, Artemisia, Urticaceae, Plantago, Ambrosia), higher prevalence of skin prick tests are registered related to average relative air prevalence, respectively.
According to these data, statistical analysis has also shown no correlation on the country level (totally and each city separately) between the annual relative prevalence of pollen grains of 7 taxa and sensitization to them in the examined population, except for the city of Ohrid where such correlation is found ($r=0.90$, $p<0.01$). In the city of Ohrid the highest is the average annual relative prevalence of the tree pollen taxa (83.9%), but the sensitization to them is also the highest (19.0%), followed by grass and weed pollens. Which is the reason for this, it is not yet clear enough, having in mind that the unique geographic-climate factors have their own influence. The high concentration of the dendrofloric taxa in Ohrid is the result of the rich alohtone horticulture; together with the high relative humidity contributing to the accelerated sedimentation of the grass and weed pollen grains sedimentation and making the lowest average annual relative prevalence compared to the other cities. So, the lower pollen grains concentrations of grasses and weeds decrease the relative sensitization in skin prick tests contributing to obtaining positive correlation. However, further aero-biological and epidemiological research in the city of Ohrid is needed, in order to receive the necessary answers to all open questions.

1.5.11. Proposal of the List of allergens for clinical use

By the clinical aspect of view, the highest sensitization was obtained for weed and grass pollen grains. In the pollen structure grasses are ranged as second, right behind the tree pollen taxa with average annual relative air prevalence of 10.4%. Therefore, if allergologic-aerobiologic assessment is in question, the priority would be determining of the grass and weed taxa air concentration in the Republic of Macedonia, and then of the tree taxa as well. From the practical point of view, using the integration of the aerobiological and epidemiological data, a List of allergens for practical use in allergy centers is proposed (Table 11).

Table 11. Proposal of the List of allergens for practical use in the allergy centers

<table>
<thead>
<tr>
<th>Latin terminology</th>
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<tbody>
<tr>
<td>Planatago lanceolata</td>
<td>Plantain</td>
</tr>
<tr>
<td>Urtica dioica</td>
<td>Nettle</td>
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<tr>
<td>Parietaria officinalis</td>
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<tr>
<td>Rumex sp.</td>
<td>Dock (Sorrel)</td>
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<td>Artemisia vulgaris</td>
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<td>Ambrosia sp.</td>
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<td>Chenopodium sp.</td>
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<td>Salsola kali</td>
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### Grass Pollen

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<td>Phleum pratense</td>
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<td>Alopecurus pratensis</td>
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<td>Arrhenatherum elatior</td>
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<td>Dactylis glomerata</td>
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### Tree Pollen

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<td>Quercus robur</td>
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<tr>
<td>Betula pendula</td>
<td>Birch (Silver)</td>
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<tr>
<td>Corylus avellana</td>
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<tr>
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<td>Cupressus sempervirens</td>
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1.6. Pollen calendar(s)

It is necessary to construct aeropallinology calendar resulting from climate, vegetation and topography characteristics of certain region as well as from its orography and hydrography. Our country has specific climate features, rich and specific vegetation and has unique aerobiologic characteristics.

Therefore, continual monitoring and reporting on pollen appearance in the air have long-term tradition in many countries and their pollen calendars differ from each other and have great differences between separate areas, too.

European monitoring system (European Pollen Information - EPI) provides regional, national and international coordination of aeropallinology centers by follow-up of pollen grains distribution and by provision of prediction models.

Our aeropallinologic data aim to provide and to predict majority of main aeropallinologic allergens in order to control the environment which is an important procedure, incorporated in the principles of prevention and therapy of allergic diseases. The data obtained in researches performed in our country will contribute to fulfil the gap in EPI information. One of the possible ways in solving this problem is establishment of monitoring network for contents and concentration follow-up of air allergens. It is important to increase the number of monitoring objects and to implement contemporary methods in air microflora research in order to receive relevant data.

The reported results could be used in theoretical interpretations of phenology, pollen production, different factors influencing changes on pollen contents and pollen quantity. Pollen calendar construction and modified set of allergen-diagnostics preparations are important for clinical allergology in allergic respiratory diseases examination as well as for their adequate prophylaxis and treatment. Also, it will help tourists and foreign business partners to choose place and time for accommodation in R. Macedonia.
1.6.1. Pollen calendar of the city of Skopje

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Concentration of the tree, grass, and weed pollens in the city of Dojran in the period January-December (1 - XII), 2000
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1.6.4. Pollen calendar of the city of Prilep

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1.6.5. Pollen calendar of the city of Debar

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Concentration of the tree, grass, and weed pollens in the city of Debar in the period January-December (I - XII), 2000

Evaluation of annual concentration of PG
1.6.6. Pollen calendar of the city of Pehchevo

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Number of PG: <1, 1-5, 5-19, 20-99, 100-1000, >1000
Concentration of the tree, grass, and weed pollens in the city of Pehchevo in the period January-December (I - XII), 2000
1.7. Conclusions

1. The constructed pollen calendars for each city separately have shown different pollen taxa, period of their appeal, and their maximal concentrations. It is registered that pollen calendar in the city of Dojran is the earliest and the one in Pehchevo is the latest which is, of course, reflection of the climate characteristics of those regions;

2. The highest sensitization prevalence of the examined population has been noted for weed pollens (19,4%), followed by the grass pollens with 17,7%. Similar is with the sensitization among the individuals with SAR (weed 7,6% and grass 6,8%);

3. The tree pollen taxa have the highest air concentrations in the Republic of Macedonia (77,2%), but sensitization to them is only 10,8%. Weed and grass pollen allergenicity is far more expressed, which make them much more important in the aerobiology specter of the Republic of Macedonia;

4. The correlation between the average annual relative pollen prevalence and positive skin prick tests is found in the city of Ohrid (r=0,90, p<0,01), having the highest annual relative prevalence of the tree pollen taxa (83,9%), as well as the sensitization to them (19,0%), followed by grass and weed pollens;

5. A high prevalence of pollenoses has been registered in the city of Prilep (SAR-29,7%) which is a result of the high grass pollen grains concentration;

6. The registered high SAR prevalence in the examined children in the city of Skopje reveals the connection between aero-pollution and the high allergen concentration and alohtone pollen grains;

7. Integrating of the aerobiological and epidemiological data, a List of allergens for practical use in allergy centers is proposed, in order to help in diagnostics, therapy and prevention of pollenoses;

8. A continuous monitoring with a multi-centric approach is necessary, including strategic following of invasive and allergenic species and restrictive implementation of allergenic and alohtone species (not to cultivate birch, linden and fetid tree);

9. It is necessary to incorporate the preventive measures in the public health programs (measures, principles and tools for elimination or reduction of the contact with allergens, sensitizing substances, irritants and other environmental provocative and factors in favor, staying outdoors when the concentrations are low, professional orientation, pre- and postnatal prevention etc.).
1.8. References:

3. European Allergy White Paper. The USB Institute of Allergy, Belgium, 1997
2.0. Indoor aeroallergens

2.1. Moulds

Moulds (fungi) can act as both indoor and outdoor airborne allergens. *Penicillium*, *Aspergillus* and *Candida* can be found indoors, while *Alternaria* and *Cladosporium* can be found both indoors and outdoors (Figure 10 and 11). Among these, *Alternaria* (Figure 12) is of special importance, being established as a risk factor for asthma in various populations, as well as a risk factor for asthma death in the United States.

Dark, humid, and poorly ventilated areas are optimal for indoor fungal growth. Moulds also grow well within the systems used for cooling, heating, and humidification, with house humidifiers providing a special risk for indoor fungal growth and air contamination. Outdoor moulds are particularly prevalent in the dry and windy conditions, where they usually grow on grasses and grains. They usually peak in the summer months and early fall, but their dispersion and airborne prevalence largely vary depending on climate.

Table 12 presents the mold species and its airborne prevalence in R. Macedonia.

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<th>Species</th>
<th>Growth area</th>
<th>Prevalence in R. Macedonia</th>
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<tr>
<td><em>Alternaria alternata</em></td>
<td>Humid walls, grains</td>
<td>High</td>
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<td><em>Aspergillus niger</em></td>
<td>Foods, grains</td>
<td>Very high</td>
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<td><em>Aspergillus fumigatus</em></td>
<td>Foods, grains</td>
<td>Very high</td>
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<tr>
<td><em>Botrytis cinerea</em></td>
<td>Grains</td>
<td>High</td>
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<tr>
<td><em>Chaetomium glabosum</em></td>
<td>Dispersed by wind; no growth in R. Macedonia</td>
<td>Low</td>
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<td><em>Eoicoccus purpurascens</em></td>
<td>Dispersed by wind</td>
<td>Low</td>
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<td><em>Fusarium spp.</em></td>
<td>Grains, grasses</td>
<td>High</td>
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<td><em>Neurospora sitophila</em></td>
<td>Dispersed by wind</td>
<td>Low</td>
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<td><em>Paecilmyces margundii</em></td>
<td>Dispersed by wind</td>
<td>Low</td>
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<tr>
<td><em>Cladosporium cladosporoides</em></td>
<td>Humid walls, grains</td>
<td>High</td>
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<tr>
<td><em>Penicillium notatum</em></td>
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<td><em>Phoma betae</em></td>
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<td><em>Rhizopus nigricans</em></td>
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<td><em>Sporobolomyces roseus</em></td>
<td>Dispersed by wind</td>
<td>Low</td>
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Table 12. Mold species and its airborne prevalence in R. Macedonia
Figure 10. Mold fruiting structures and spores of *Penicillium notatum*
Adapted from: Moulds. Available at: http://www.denniskunkel.com/DK/DK/Fungi_and_Slime_Moulds/

Figure 11. *Aspergillus fumigatus* spores
Adapted from: Moulds. Available at: http://www.denniskunkel.com/DK/DK/Fungi_and_Slime_Moulds/

Figure 12. Filamentous structure of *Alternaria alternata*
Adapted from: Alternaria alternata. Available at: http://www.alamy.com/stock_photography/
In the study of allergic sensitization to mold allergens, carried out at the Institute of Occupational Health Skopje in 2001 including 46 subjects with respiratory allergic diseases (allergic rhinoconjunctivitis and/or asthma) and 32 healthy subjects, we found similar prevalence in both groups (17.4% and 25.0%, respectively). The highest prevalence in both subjects with respiratory allergies and healthy subjects was found for sensitization to Neutrospora sitophila (10.8% and 8.6%, respectively) and Penicillium notatum (15.6% in both groups) (Figure 13).

![Figure 13](image)

**Figure 13.** Allergic sensitization to mold allergens in subjects with respiratory allergies and healthy subjects

### 2.1.1. Results of current study of sensitization to moulds in adults in R. Macedonia

Sensitization to Alternaria was detected in 3.6% of the examined adults (Figure 14).

![Figure 14](image)

**Figure 14.** Sensitization to Alternaria in the examined adults
The highest prevalence of subjects sensitized to *Alternaria* was detected among adults in Skopje (5.5%), and the lowest one among adults in Dojran (1.1%) (Figure 15). The difference is probably due to the different climate conditions in certain centers.

![Figure 15. Sensitization to *Alternaria* among adults in certain centers](image)

Prevalence of sensitization to *Alternaria* in the adults with perennial allergic rhinitis, perennial allergic conjunctivitis, and allergic asthma was 14.9%, 12.8%, and 25.0%, respectively (Figure 16).

![Figure 16. Sensitization to *Alternaria* in all examined adults, and in the Subjects with perennial allergic rhinitis, perennial allergic conjunctivitis, and allergic asthma](image)
Sensitization to *Penicillium notatum* was detected in 3.9% of the examined adults (Figure 17).

![Pie chart showing 3.9% sensitivity to Penicillium](image)

**Figure 17.** Prevalence of the sensitization to *Penicillium* in examined adults

As with *Alternaria*, the highest prevalence of adults sensitized to *Penicillium* was observed in Skopje (5.7%), and the lowest one in Debar (2.0%) (Figure 18).

![Bar chart showing sensitization rates](image)

**Figure 18.** Sensitization to *Penicillium* among adults in certain centers

Prevalence of sensitization to *Penicillium* in the adults with perennial allergic rhinitis, perennial allergic conjunctivitis, and allergic asthma was 14.9%, 11.2%, and 16.7%, respectively (Figure 19).
Figure 19. Sensitization to *Penicillium* in all examined adults, and in the subjects with perennial allergic rhinitis, perennial allergic conjunctivitis, and allergic asthma.

### 2.2. House dust mites

House dust (domestic) mite allergens are considered as the most important indoor sensitizing agents worldwide. Sensitization to house dust mites may be manifested by allergic asthma, allergic rhinoconjunctivitis and/or atopic dermatitis.

House dust is composed of several organic and inorganic compounds, including fibers, mold spores, insect and insect feces, mammalian danders, and mites and mites feces. Dust mites feed on organic material in households, particularly the skin that is shed from humans and pets. They can be found in carpets, upholstered furniture, pillows, mattresses, comforters, and stuffed toys. While they thrive in warmer temperatures (22-26°C) and high humidity (higher than 55%), they can be found year-round in many households. There are 2,000 to 15,000 mites per gram of mattresses dust.

The principal mite species include: *Dermatophagoides pteronyssinus, Dermatophagoides farinae, Dermatophagoides microceras,* and *Eurogluphus mainei.* *Dermatophagoides pteronyssinus* (Figure 20, A and B) is dominant mite in constantly damp climates (Europe, including R. Macedonia, and the Pacific Northwest).
In 1967 it was considered that allergenicity to house dust is associated with house dust mite allergens. House dust mite allergens are present in various parts of mite bodies, secretion, and excretion, constituting the main source of dust-derived allergens. The house dust mite allergens have been identified as proteolytic enzymes from mite feces, such as cysteine proteases (group I allergens: *D. pteronyssinus* I, *D. farinae* I, and *D. microceras* I), serine proteases (group III allergens), and amylase (group IV allergens). The group II allergens are derived mainly from mite bodies (*D. pteronyssinus* II and *D. farinae* II). The predominant allergens in house dust are from the groups I and III. A concentration of mite allergen above 0.5 mcg of *D. pteronyssinus* I per gram of house dust seems to be a significant risk factor for mite sensitization in susceptible individuals.

Mite sensitization is considered as a major risk factor for development of respiratory allergic diseases. Prevalence of mite sensitization is estimated to 100 million individuals worldwide. Results from the ECRHS local data sets showed that mite sensitization was found to be the allergen most strongly associated with asthma or bronchial hyperresponsiveness in 16 centers from Europe, North America, and Australia, mite and cat equally in one, cat in eight, timothy in eight, and *Cladosporium* in two. Mite sensitization was also found to be the most important individual allergen in the subjects with allergic asthma in our previous study of asthma in 1995.

Many published studies suggested strong link between mite sensitization and childhood asthma. According to the results of the prospective studies which investigated childhood asthma pathogenesis, a positive correlation between risk of childhood asthma and level of exposure was observed. The study of childhood asthma carried out in R. Macedonia at the end of the 1990s showed significant association between the level of exposure and severity of bronchial hyperresponsiveness, severity of asthma, and course of the disease. The mean concentration of mite allergen was found to be 11.8 mcg per gram of house dust that was 20 times higher concentration in respect to concentration of mite allergen considered as a risk factor for allergic sensitization in susceptible individuals.

Figure 20. A. and B. *Dermatophagoides pteronyssinus*  
(B. Isolated by S. Milkovska, 1996)  
Adapted from: Cvetanov V, et al. Alergiski bolesti-Lekuvanje  
[Allergic diseases – Treatment, in Macedonian]  
2.2.1. Results of the current study of mite sensitization in adults in R. Macedonia

Sensitization to *Dermatophagoides pteronyssinus* was detected in 13.9% of the examined adults (Figure 21).

**Figure 21.** Sensitization to *Dermatophagoides pteronyssinus* in the examined adults

Prevalence of mite sensitization among adults in certain centers varied from 14.4% in Skopje to 11.6% in Debar (Figure 22).

**Figure 22.** Prevalence of mite sensitization among adults in certain centers

Mite sensitization was the most important individual allergen in the adults with respiratory allergic diseases (Figure 23).
2.3. Pets

Household warm-blooded animals and birds release allergens in secretions, excretions, and danders.

2.3.1. Sensitization to cats

Cat allergens are potent sensitizing agents. The main cat allergen (Fel d1) is found in cat pelt, especially in the facial area, sebaceous secretions, and urine.

The cat allergen is carried on small particles (3-4 mm in diameter) that easily become airborne and enable rapid onset of the respiratory symptoms in sensitized subjects entering an indoor environment containing a cat. Although households with a cat contain high concentration of the cat allergen, homes without a cat may also contain its sufficient concentration to trigger symptoms in highly sensitized subjects. The clothes of cat owners constitute the vehicle of passive transport of cat allergen to cat-free environments.

Results of the published studies indicated approximately 6 million individuals in the USA which are sensitized to cat fur. The ECRHS data set from Sweden and the Netherlands suggested significant association of cat sensitization and bronchial hyperresponsiveness and asthma. On the other side, the ECRHS data set from Spain indicated that cat sensitization was a predictor of airflow limitation (lower FEV1 value) that was independent of smoking and bronchial hyperresponsiveness.
2.3.1.1. Results of the actual study of cat sensitization in adults in R. Macedonia

Sensitization to cat fur was detected in 5.5% of the examined adults (Figure 24).

Figure 24. Sensitization to cat fur in all examined adults

Prevalence of cat sensitization among adults in certain centers varied from 7.4% in Skopje to 2.4% in Debar (Figure 25).

Figure 25. Cat sensitization among examined adults in certain centers

Prevalence of cat sensitization in the adults with perennial allergic rhinitis, perennial allergic conjunctivitis, and allergic asthma was 34.0%, 16.7%, and 21.6%, respectively (Figure 26).
2.3.2. Sensitization to dogs

Dogs produce two important allergens, Can f1 and Can f2, found in dog hair and dander. The dog allergens characteristics are similar to cat allergens but they have lower allergenic potential. There is a slight degree of cross-reactivity between dog and cat allergens.

Sensitization to dog hair is registered in up to 30% of atotics in developed countries.

2.3.2.1. Results of the actual study of sensitization to dog hair in adults in R. Macedonia

Sensitization to dog allergens was detected in 2.8% of the examined subjects (Figure 27)
Prevalence of sensitization to dog hair among adults in certain centers varied from 4.2% in Skopje to 1.0% in Debar that probably depended on the prevalence of pets ownership in certain centers (Figure 28).

Figure 28. Sensitization to dog hair among adults in certain centers

Prevalence of sensitization to dog hair in the adults with perennial allergic rhinitis, perennial allergic conjunctivitis, and allergic asthma was 23.1%, 18.4%, and 10.0%, respectively (Figure 29).

Figure 29. Prevalence of sensitization to dog hair in all examined adults, and in subjects with perennial allergic rhinitis, perennial allergic conjunctivitis, and allergic asthma
2.3.3. Sensitization to birds

Sensitization to birds kept as indoor pets (parrots, canaries, pigeons) is considered as sensitization to allergens of mites which feed in their feather.

According to the published data, the prevalence of sensitization to feathers is not high. However, exposure to feathers may trigger severe nasal, ocular and/or asthma symptoms in sensitized individuals.

2.3.3.1. Results of the actual study of sensitization to feathers in adults in R. Macedonia

Sensitization to feathers was detected in 3.9% of the examined subjects (Figure 30).

![Pie chart showing 3.9% sensitization to feathers.]

Figure 30. Sensitization to feathers in all examined adults

Prevalence of sensitization to feathers among adults in certain centers varied from 4.4% in Skopje to 1.4% in Debar (Figure 31).
Prevalence of sensitization to feathers in the adults with perennial allergic rhinitis, perennial allergic conjunctivitis, and allergic asthma was 23.1%, 18.4%, and 10.0%, respectively (Figure 32).

Figure 31. Sensitization to feathers among adults in certain centers

Figure 32. Prevalence of sensitization to feathers in all examined adults, and in subjects with perennial allergic rhinitis, perennial allergic conjunctivitis, and allergic asthma
2.3.4. Sensitization to cockroach

Sensitization to cockroach (Figure 33, A and B) is considered as an important trigger of asthma symptoms in sensitized subjects in the USA, the UK, and Australia. Most species of cockroaches live in tropical climates, but central heating has enabled them to thrive outside their normal habitat. The most common species are the American cockroach (*Periplaneta americana*), Australian cockroach (*Periplaneta australasiae*), Asian cockroach (*Blatella orientalis*), etc. The German cockroach (*Blatella germanica*) lives in Europe and in R. Macedonia.

![Cockroach](image1.jpg)  ![Cockroach](image2.jpg)

**Figure 33. A. and B. Cockroach**
Adapted from: *Cockroach. Available at: http://en.wikipedia.org/wiki/

Allergens from the *Blatella germanica* and *Periplaneta americana* are characteristic, and the presence in house dust can be measured by using specific monoclonal antibodies.

### 2.3.4.1. Results of the actual study of sensitization to cockroach allergens in adults in R. Macedonia

Sensitization to cockroach allergens was detected in 3.2% of the examined subjects (Figure 34).

![Pie Chart](chart1.png)

**Figure 34.** Sensitization to cockroach in all examined subjects
Prevalence of sensitization to cockroach among adults in certain centers varied from 4.4% in Skopje to 1.4% in Debar (Figure 35).

**Figure 35.** Sensitization to cockroach among adults in certain centers

Prevalence of sensitization to cockroach in the adults with perennial allergic rhinitis, perennial allergic conjunctivitis, and allergic asthma was 11.6%, 10.0%, and 10.0%, respectively (Figure 36).

**Figure 36.** Prevalence of sensitization to cockroach in all examined adults, and in subjects with perennial allergic rhinitis, perennial allergic conjunctivitis, and allergic asthma
2.4. Conclusions

1. Sensitization to moulds was not frequent in the examined adults, however, they were considered as an important risk factor for perennial allergic rhinitis and allergic asthma.

2. Our data confirm the importance of mite sensitization as a risk factor for respiratory allergic diseases. The prevalence of mite sensitization in the examined adults was found to be 13.9%, which is approximately 200,000 subjects with mite sensitization in R. Macedonia. Mite sensitization was detected in 90% of the subjects with perennial allergic rhinitis and in above 60% of the subjects with allergic asthma.

3. Prevalence of sensitization to pet allergens in R. Macedonia was lower than in the developed countries that is probably due to the lower prevalence of pets ownership. However, sensitization to pet allergens was considered as an important risk factor for respiratory allergic diseases.

4. The initial results of sensitization to cockroach allergens in adults in R. Macedonia have suggested that it must be taken into consideration in allergologic evaluation of the subjects with respiratory allergic diseases.

2.5. References:

Part III

Epidemiological survey
A cross-sectional study (study of prevalence) was carried out in six centers in R. Macedonia, including Skopje, Dojran, Ohrid, Prilep, Debar, and Pehchevo, in the period February-June 2002. The study included 1121 randomly selected subjects (i.e. approximately 0.6% of the population in R. Macedonia), 722 adults (283 males and 439 females, mean age 39.6 ± 13.5) and 399 children (196 boys and 203 girls, mean age 11.01 ± 2.61).

Evaluation of the examined adults on site included completion of a questionnaire and skin prick tests (SPT) to common inhalant allergens. The interviewer-led questionnaires for adults and children were designed using the models of the ECRHS and ISAAC questionnaire. The questionnaires included questions about allergic and respiratory symptoms, life style, housing, smoking habit, environmental and workplace exposures, medication use, and family history of allergic and respiratory disorders (Appendix 2). SPT to 13 common inhalant allergens were performed on the volar part of the forearm using allergen extracts (Bencard Allergie GmbH, Germany)) of tree pollens, grass pollens, mugwort, goosefoot, plantain, Ambrosia eliator, Penicillinum notatum, Alternaria alternata, Dermatophagoides pteronyssinus, cat fur, dog hair, feathers, and cockroach. All tests included positive (1 mg/mL histamine) and negative (0.9 % saline) controls. Following the recommendations of the European Academy of Allergology and Clinical Immunology (EAACI), the SPT were considered positive if the mean wheal diameter 20 min after allergen application was larger than 3 mm.

Lung function tests were performed in the Institute of Occupational Health, Skopje-WHO Collaborating Center in the examined adults aged 20-44 who reported symptoms suggestive of asthma. Spirometry, including measures of forced vital capacity (FVC), forced expiratory volume in one second (FEV1), FEV1/FVC ratio, maximal expiratory flow at 50 %, 25% and 25-75% of FVC (MEF50, MEF25 and MEF25-75, respectively), was performed recording the best of three measurements. The results were expressed as percentages of the predicted values, according to the European Community for Coal and Steel (ECCS) norms. Histamine challenge was performed according to the European Respiratory Society (ERS)/ American Thoracic Society (ATS) recommendations. The test was considered positive if provocative concentration 20 - PC20 (i.e. the concentration of histamine causing a 20% fall in FEV1) was equal or less than 4 mg/mL. In the subjects with reduced lung function, bronchodilator test with inhaled salbutamol was performed. According to the British Thoracic Society (BTS) recommendations, the test was considered positive if the increase of the FEV1 value after bronchodilator application was equal or more than 12% compared to the baseline value.

Evaluation of the examined children included completion of a questionnaire on allergic and respiratory symptoms, birth weight, presence of siblings, type of feeding in the infancy, life style, housing conditions, environmental exposures, medication use, and family history of allergic and respiratory diseases (Appendix 3). The interviewer-led questionnaire was completed on site by the children’s parents.

The data obtained were statistically processed by descriptive and inferential methods (χ2-test, Fisher’s exact-test, Mann-Whitney U-test, t-test for independent samples, and linear regression) using statistic program SPSS 11.
1.0. Diagnostic criteria for certain allergic entities

**Atopy in adults** was defined as at least one positive SPT to common inhalant allergens.

**Allergic rhinitis in adults** was defined by positive history of one or more rhinitis symptoms associated with positive SPT to common inhalant allergens.

**Seasonal allergic rhinitis in adults** was defined by positive history of rhinitis symptoms associated with positive SPT to seasonal inhalant allergens.

**Perennial allergic rhinitis in adults** was defined by positive history of rhinitis symptoms associated with positive SPT to domestic inhalant allergens.

**Seasonal allergic rhinitis in children** was defined by positive history of seasonal rhinitis symptoms, whereas **perennial allergic rhinitis in children** was defined by positive history of persistent rhinitis symptoms.

**Allergic conjunctivitis in adults** was defined by positive history of one or more conjunctivitis symptoms associated with SPT to common inhalant allergens.

**Asthma in the age group 20-44** was defined by history of one or more asthmatic symptoms or use of asthma medications associated with positive histamine challenge or positive bronchodilator test in the subjects with reduced lung function.

**Atopic dermatitis in children** was defined as an itching rash coming and going for at least six months.

**Hypersensitivity to drugs, food and insect sting in adults and children** was defined by history of adverse reaction after drug intake, food consumption, and **Hymenoptera** insect sting.

1.1. Characteristics of the examined subjects

1.1.1. Characteristics of the examined adults

The group of examined adults included 722 randomly selected subjects, 283 males (38.6%) and 439 females (61.4%). **Sex** distribution of the examined adults is shown in Figure 37.
The examined adults were aged between 18 and 78 years, mean age $39.56 \pm 13.5$. Age distribution of the examined adults is shown in Figure 38.

Distribution of the examined subjects by certain centers is shown Table 39.
Macedonians and Albanians were the majority of the examined adults (79.7% and 13.6%, respectively). Distribution of the examined adults by ethnicity is shown in Figure 40.

Figure 39. Distribution of the examined adults by certain centers

Figure 40. Distribution of the examined subjects by ethnicity
There was higher prevalence of subjects with urban than with rural residence (85.4% vs. 14.6%) (Figure 41).

Distribution of the examined subjects by educational level and employment status is shown in Tables 42 and 43.

Figure 41. Distribution of the examined adults by residence

Figure 42. Distribution of the examined adults by educational level

Figure 43. Distribution of the examined adults by employment status
Prevalence of daily smokers was 34.2% (Figure 44). The highest prevalence of daily smokers was registered among examined subjects in Skopje (45.7%) and the lowest one among examined subjects in Dojran (25.6%) (Figure 45).

![Figure 44. Distribution of the examined adults by smoking status](image)

Living in a house was the dominant housing type (Figure 46), and wood heating was the dominant heating type in the examined adults (Figure 47).

![Figure 46. Distribution of the examined adults by housing type](image)

![Figure 47. Distribution of the examined adults by heating type](image)

Housing in the environment rich with green plants was reported by 67.2% of the examined adults (Figure 48). The highest prevalence of subjects with reported green plants outdoors was registered in Dojran and Pehchevo (92.3% and 84.3%, respectively) (Figure 49).
Presence of green plants at home was reported by 77.2% of the examined adults (Figure 50). The highest prevalence of subjects with reported green plants indoors was registered in Pehchevo and Ohrid (85.9% and 84.3%, respectively) (Figure 51).

Pets ownership was reported by 35.3% of the examined adults (Figure 52). The highest prevalence of pets owners was registered in Dojran and Skopje (45.4% and 40.5%, respectively) (Figure 53).

Exposure to environmental air pollutants (e.g. traffic and/or industrial pollution) was reported by 38.3% of the examined adults (Figure 54). The highest prevalence of subjects exposed to air pollutants was registered in Skopje, and the lowest in Dojran (45.2% vs. 14.6%) (Figure 55).
Exposure to workplace air pollutants was reported by 43.8% of the examined adults (Figure 56). The highest prevalence of the subjects with reported workplace exposure to air pollutants was registered in Skopje (57.5%) and the lowest one in Dojran (24.1%) (Figure 57).

1.1.2. Characteristics of the examined children

The study included 399 children aged 0-15 years, 196 boys (48.9%) and 203 girls (51.1%). Sex distribution of the examined children is shown in Figure 58.
The mean age of the examined children was 11,0 ± 2,6 years. Approximately 40% of the examined children were younger than 7 years (Figure 59).

Figure 59. Age distribution of the examined children

Figure 60 shows the distribution of the examined children by certain centers.

Figure 60. Distribution of the examined children by certain centers

As in the examined adults, the majority of the examined children were Macedonians (78.7%), followed by Albanians (14.5%). Distribution of the examined children by ethnicity is shown in Figure 61.

Figure 61. Distribution of the examined children by ethnicity
There was a higher prevalence of children with urban than with rural residence (81.9% and 18.1%, respectively) (Figure 62).

Figure 62. Distribution of the examined children by residence

Living in a house was the dominant housing type (Figure 63), and wood heating the most dominant heating type in the examined children (Figure 64).

Figure 63. Distribution of the examined children by housing type

Figure 64. Distribution of the examined children by heating type

Maternal smoking during pregnancy was reported by 12.1% of the examined children (Figure 65). The highest prevalence of maternal smoking during pregnancy was registered among examined children in Dojran and Skopje (17.6% and 15.6%, respectively), and the lowest one among examined children in Pehchevo (2.0%) (Figure 66).

Figure 65. Distribution of the examined children by maternal smoking during pregnancy

Figure 66. Maternal smoking during pregnancy in certain centers
Breast-feeding in the infancy was reported by 91.0% of the examined children (Figure 67). The highest prevalence was registered among examined children in Dojran (Figure 68). The majority of the examined children was breastfed during the period of infancy (Figure 69).

![Breast-feeding in the infancy](image)

**Figure 67.** Distribution of the examined children by feeding in the infancy

![Breast-feeding in the infancy](image)

**Figure 68.** Breast-feeding in the infancy prevalence among examined children in certain centers

![Duration of breast-feeding (months)](image)

**Figure 69.** Duration of breast-feeding (months)

Birth weight in the majority of the examined children was 3,000-4,200 g. (Figure 70).

![Distribution of the examined children by birth weight (g.)](image)

**Figure 70.** Distribution of the examined children by birth weight (g.)

Sibship was reported by 55.0% of the examined children (Figure 71). The highest prevalence was registered in Ohrid (66.6%) (Figure 72).
A day-care attendance during the preschool period was reported by 42.8% of the examined children (Figure 73). The highest prevalence of children that had attended a day-care was registered in Skopje (57.1%) (Figure 74).

Presence of the green plants outdoors was reported by 79.7% of the examined children (Figure 75). The highest prevalence was registered among examined children in Dojran (Figure 76).

Presence of green plants indoors was reported by 71.4% of the examined children (Figure 77). The highest prevalence was also registered in Dojran (92.7%) (Figure 78).
Pets ownership was reported by 34.4% of the examined children (Figure 79). As in the adults, the highest prevalence was registered in Dojran (Figure 80).

Exposure to environmental tobacco smoke was reported by 60.7% of the examined children (Figure 81). The highest prevalence was registered in Pehchevo (Figure 82).

Exposure to environmental air pollutants (traffic pollution, industrial pollution) was reported by 20.1% of the examined children (Figure 83). As in the examined adults, the highest prevalence of children exposed to environmental air pollutants was registered in Skopje (34.2%), and the lowest one in Dojran (5.9%) (Figure 84).
Figure 83. Distribution of the examined children by exposure to environmental air pollutants

Figure 84. Exposure to environmental air pollutants/prevalence among examined children in certain centers

References:


2.0. Allergic rhinitis - ICD - 10; J 30.4

2.1. Definition

Allergic rhinitis (AR) is defined as an inflammation of nasal mucosa in which many cells and cellular elements are involved.

The inflammation leads to increased nasal response to different specific and nonspecific stimuli and to symptom complex that consists of any combination of sneezing, nasal itching, rhinorrhea, and nasal blockage.

2.2. Classification

For a period of time AR has been subdivided, based on time of exposure, into seasonal and perennial AR. According to the new classification, based on duration of symptoms, AR is subdivided into intermittent and persistent AR. Intermittent AR is characterized by symptoms occurrence in less than four days per week or in less than four weeks per year. Persistent AR is characterized by symptoms occurrence in a longer period (e.g. in more than four days per week or in more than four weeks per year).

Seasonal AR (SAR, J 30.1) is defined as an inflammation of the nasal mucosa characterized by intermittent nasal symptoms that occur in sensitized subjects following exposure to outdoor allergens (pollens and certain moulds).

Perennial AR (PAR, J 30.3) is defined as an inflammation and hypertrophy of the nasal mucosa characterized by nasal symptoms that persist round-year.

Occupational AR, which can be seasonal, perennial, or sporadic, is defined as an inflammation of the nasal mucosa caused by IgE-mediated reaction to the allergen from the workplace.

According to the classification based on severity, AR is subdivided into mild and moderate-severe depending on symptoms and quality of life.

2.3. Pathogenesis

2.3.1. Seasonal Allergic Rhinitis (SAR)

The inflammation of the nasal mucosa in SAR results from an IgE-mediated response to extrinsic allergens. An inflammatory infiltrate is made up of different cells. The cellular response includes chemotaxis, selective recruitment and trans-endothelial migration of cells (T-lymphocytes, eosinophils, neutrophils); release of cytokines (IL 4, IL 5, IL 13); activation and differentiation of various cell types including mast cells, T-lymphocytes, eosinophils, and epithelial cells; prolongation of their survival; and release of mediators by
activated cells among which histamine and cysteinyl-leukotrienes are the most important. The response includes early or immediate phase, that occurs in minutes following the allergen exposure, and late phase, that occurs over 4-8 hours and may persist for hours or days.

SAR is commonly caused by allergy to seasonal pollens and outdoor moulds.

Tree pollens, which vary by geographic location, are typically present in high counts during spring, although some species produce their pollens in fall. Common tree families associated with SAR include birch, lime, alder, hazel, oak, olive, and willow. Grass pollens also vary by geographic location. Most of the common grass species are associated with SAR, including *Zea mays*, *Secale cereale*, *Poa pratensis*, and *Triticum spp*. A number of these grasses are cross-reactive, meaning that they have similar antigenic structure. Consequently, an individual which is sensitized to one species is also likely to be sensitive to other species. The grass pollens are most prominent from late spring during fall. Weed pollens also vary geographically. Common weeds associated with SAR include mugwort, plantain, goosefoot, nettle, and ragweed. Many of the weeds are most prominent in the late summer and fall.

Outdoor moulds, such as *Alternaria* and *Cladosporium* are also associated with SAR. Their airborne prevalence vary depending on climate and season. *Alternaria* and *Cladosporium* are particularly prevalent in the dry and windy conditions. *Aspergillus* and *Penicillium* can be found both outdoors and indoors (particularly in humid households), with variable growth depending on the season and climate.

Cold air, physical exercise, and emotional stress are considered as contributing factors in the development of SAR. A number of environmental and workplace air pollutants also play a role enhancing the formation of IgE and allergic inflammation. Indoor air pollution, particularly tobacco smoke, is of great importance since subjects in industrialized countries spend over 80% of their time indoors. Outdoor pollutants, including pollutants of automobile origin, ozone, oxides of nitrogen, and sulfur dioxide, may also be involved in the aggravation of nasal symptoms.

### 2.3.2. Perennial Allergic Rhinitis (PAR)

Similarly to SAR, inflammation of the nasal mucosa caused by IgE-mediated reaction to extrinsic allergens, including early and late response, is the basis of the pathogenesis of PAR.

PAR is usually caused by allergens found at home. Domestic allergens, such as allergens from the house dust (*Dermatophagoides pteronyssinus*), indoor moulds (*Alternaria, Penicillium*), pets (dog hair, cat fur, feathers), and insects (cockroach) are the most important allergens in the development of PAR.
Nonspecific stimuli, such as cold air, physical exercise, environmental and workplace air pollutants, strong smells, and emotional factors contribute to its development and severity.

2.4. Clinical manifestations

2.4.1. Seasonal Allergic Rhinitis (SAR)

Sneezing, nasal itching, and watery rhinorrhea, often accompanied by nasal congestion are the typical symptoms of SAR. The eyes, ears, sinuses, and throat can also be involved. Systemic effects, including fatigue, sleepiness, and malaise, can occur as a result of the inflammatory response. These symptoms often contribute to impaired quality of life. In about 10 – 20% of the subjects with SAR accompanied asthma is present, and in about 1% the disease is associated with skin and gastrointestinal manifestations.

- Seasonal occurrence of the symptoms, following the exposure to certain allergens (pollens or moulds) is typical for SAR.
- Severity of the symptoms depends upon the pollen concentration.
- Severity of the symptoms usually decreases with age.
- Occurrence of the symptoms out of certain season usually is caused by transport of the pollen grains from other areas.

2.4.2. Perennial Allergic Rhinitis (PAR)

- Hypersecretion of thick mucus or nasal blockage commonly dominate in the clinical picture of PAR (runners or blockers), whereas sneezing and nasal itching are less expressed.

- Symptoms occur at a consistent level thorough the year, usually being more severe in the fall-winter period.

- Sinusitis occurs quite frequently in the subjects with PAR. Sinonasal polyposis, as well as otitis media can also be associated with PAR. PAR is associated with asthma and is considered to be a risk factor for asthma.

2.5. Diagnosis

Diagnosis of AR is based on history, physical examination, functional assessment, and skin and laboratory tests.
2.5.1. Clinical history

Clinical history is essential for an accurate diagnosis of rhinitis, assessment of its severity, and likely response to treatment. Important elements include an evaluation of the nature, duration, and time course of symptoms, possible triggers for symptoms, response to medications, comorbid conditions, family history of allergic diseases, environmental and occupational exposures, and effects on quality of life. A thorough history may help identify specific triggers, suggesting an allergic etiology for rhinitis.

2.5.2. ENT status

The physical examination is focused on the nose, but examination of eyes, ears, oropharynx, neck, lungs, and skin is also important. Looking for physical findings that may be consistent with a systemic disease that is associated with rhinitis (e.g. sarcoidosis, hypothyroidism, ciliary dyskinesia syndrome) is recommended. The nasal examination includes rhinoscopy and nasal endoscopy. Anterior rhinoscopy using a speculum and mirror usually gives limited information. Nasal endoscopy is more useful.

The mucosa of the nasal turbinates is swollen and has a pale, bluish-gray color. While pale, boggy, blue-gray mucosa is typical for AR, mucosal examination findings cannot definitely distinguish between allergic and nonallergic causes of rhinitis. Thin and watery secretions are frequently associated with SAR, while thick and purulent secretions are usually associated with sinusitis. By examination of the nasal cavity may also be detected septal deviation, polyps, tumors, foreign bodies, etc. Polyps are firm gray masses that are often attached by a stalk which may not be visible. Polyps do not shrink after nasal decongestant application, while the surrounding nasal mucosa shrinks.

2.5.3. Functional diagnostics

2.5.3.1. Rhinomanometry

Rhinomanometry is a routinely applicable functional method for assessment of nasal patency (nasal resistance) through measurements of nasal airflow and differential pressure which can produce qualitative (Figure 85) and quantitative parameters for evaluation.
Rhinomanometric parameters for quantitative evaluation of nasal function for the Rhinotest MP 500 (Figure 86) are the flow parameters, percent of flow increase upon doubling the differential pressure (aerodinamical assessment), flow ratio (functional comparison of both nasal sides) and resistance parameters. Decongestion test and allergen specific nasal provocation test can be applied as well.

**Figure 85.** Normal and pathological rhinomanometric results

**Figure 86.** Rhinotest MP 500 device

### 2.5.3.2 Acustic rhinometry

Acustic rhinomanometry is a method for assessment of parameters of nasal turbinates that enables quantification of abnormalities. The method is based on analyses of the reflected sound wave that was emitted into nose.
2.5.4. Skin tests (immediate hypersensitivity testing)

Testing for reaction to specific allergens can be helpful to confirm the diagnosis of AR and to determine specific allergic triggers. If specific allergic triggers are known, then appropriate avoidance measures can be recommended and allergen-specific immunotherapy can be performed.

The allergens may be introduced percutaneously (prick tests) or intradermally. Skin prick tests (SPT), performed according to the actual recommendation of the European Academy of Allergology and Clinical Immunology (EAACI) are usually used for allergy testing. Drugs, such as antihistamines and corticosteroids, older age, seasonal variations of allergen, and skin changes, such as urticaria, dermographism, and atopic dermatitis, can change the skin reaction to introduced allergen.

2.5.5. Laboratory tests

Measurement of the total level of IgE in the blood (regardless of specificity) is neither sensitive nor specific for AR, so this test is not recommended in the diagnostic procedure.

Measurement of the level of specific IgE to a particular antigen in the blood by radioallergosorbent test (RAST) or CAP specific IgE assay is a useful test for demonstration of allergic sensitization. Since specific IgE is detected in different tissues (i.e. skin and blood) there is no correlation between in vivo and in vitro tests in approximately 30% of the cases.

Measurement of the markers of allergic inflammation, such as measurement of the eosinophil count in the nasal smear and in the blood, as well as the levels of inflammatory mediators (leukotrienes, prostaglandins, histamine) in the blood and urine, may help in establish the diagnosis of AR.

While radiographic studies (radiography, CT scanning, and MRI) are not needed to establish the diagnosis of AR, they can be helpful for evaluating possible structural abnormalities or to help detect complications or comorbid conditions, such as sinusitis or adenoid hypertrophy.

2.5.6. Differential diagnosis

Other problems that should be considered in the subjects with chronic nasal symptoms include vasomotor rhinitis, rhinitis medicamentosa (e.g. due to topical decongestants, antihypertensives, cocaine abuse), infectious rhinitis, hormonal rhinitis (e.g. related to pregnancy, hypothyroidism, oral contraceptive use), immotile cilia syndrome (ciliar dyskinesis), nasal polyps, and granulomatous rhinitis (e.g. sarcoidosis, Wegener granulomatosis).
2.6. Management of Allergic Rhinitis

The management of AR consists of environmental control measures, pharmacological treatment, allergen-specific immunotherapy, and other types of therapy.

2.6.1. Environmental control measures

Environmental control measures involve both the avoidance of allergen to which the patient has IgE-mediated hypersensitivity and avoidance of nonspecific triggers. However, global environmental control without identification of specific triggers is inappropriate.

2.6.1.1. Seasonal Allergic Rhinitis (SAR):

- To consider pollen counts when planning outdoor activities. It is helpful to limit the outdoor activities when pollen and mold counts are at their highest;
- To keep doors and windows of the house and car shut as much as possible during the pollen season;
- To take a shower after outdoor exposure for removing pollen grains that are stuck to the hair and skin;
- To use an air conditioner to cool the home instead of coolers or fans that bring in outside air.

2.6.1.2. Perennial Allergic Rhinitis (PAR):

- No furry or feathered pets at home;
- Remove the carpets or clean carpets and rugs by vacuum cleaning;
- Wash pillows, sheets, and blankets weekly in hot water;
- Cover mattress and pillows with impermeable covers;
- Reduce excessive humidity and to removal standing water;
- Exterminate cockroaches by insecticides;
- Avoid situations that may aggravate symptoms of PAR, such as exposure to tobacco smoke, strong perfumes, and rapid changes in temperature;
- Keep doors and windows shut during the pollen season since the exposure to pollens may aggravate symptoms of PAR.

2.6.2. Pharmacological treatment

The goals for successful pharmacological treatment of AR are to:

- Achieve and maintain control of symptoms;
- Prevent exacerbations, chronicity, and complications;
- Improve quality of life;
- Avoid adverse effects from rhinitis medications.
Pharmacological treatment of AR includes antihistamines, decongestants, anticholinergics, and anti-inflammatory medications. The most important AR medications are presented in Appendix 4. The effects of certain medications on rhinitis symptoms are shown in Appendix 5.

2.6.2.1. Antihistamines

Antihistamines are often preferred for the first-line therapy of AR, especially for seasonal symptoms, because of their excellent efficacy and safety profile.

- All antihistamines are efficacious in controlling sneezing, itching, and rhinorrhea, but do not significantly improve nasal congestion;
- They compete with histamine for histamine receptor type 1 (H₁) receptor sites in the blood vessels, gastrointestinal (GI) tract, and respiratory tract, which, in turn, inhibits physiologic effects that histamine normally indices at the H₁ receptor sites;
- Second-generation antihistamines (also referred to as the nonsedating antihistamines) are usually administered. The older, first-generation antihistamines, are effective in reducing most symptoms of AR, but they produce a number of adverse effects (e.g. sedation, impairment of cognition, anticholinergic effects);
- There are systemic and topical preparations of antihistamines.

2.6.2.2. Decongestants

Decongestants stimulate vasoconstriction by directly activating α adrenergic receptors of the respiratory mucosa. They are used alone or in combination with antihistamines to treat nasal congestion. Decongestants should be administered with precautions in subjects with hypertension, cardiac disease, diabetes, glaucoma, GI obstruction, urinary obstruction, elderly patients, pregnancy and lactation. They may also produce anxiety and insomnia. Local decongestants should not be used as a long-term treatment since they may cause rebound effect or atrophy of the nasal mucosa (i.e. rhinitis medicamentosa).

2.6.2.3. Anticholinergics

Anticholinergics, such as ipratropium bromide, may be helpful for decreasing symptoms of a runny nose.

2.6.2.4. Anti-inflammatory medications

Anti-inflammatory medications, including cromones, leukotriene receptor antagonists, and corticosteroids) control inflammation of the nasal mucosa.
Cromones, such as disodium cromoglycate and nedocromil sodium, produce mast cell stabilization and antiallergic effects that inhibit degranulation of mast cells. Used as local preparations they are effective for prophylaxis of AR, just before exposure to a known allergen (e.g. pollen, animal, occupational). Cromones produce modest effect compared with that of intranasal corticosteroids, their protective effect lasts 4-8 hours and thus frequent dosing is necessary. Cromones have an excellent safety profile and are thought to be safe for use in children and pregnancy.

Leukotriene receptor antagonists, such as montelukast, selectively prevent action of leukotrienes released by mast cells and eosinophils. When used as a single agent, montelukast produces modest improvement of symptoms, similar in degree to second-generation antihistamines. **Local corticosteroids** are highly efficacious in treating AR. They control the four major symptoms of AR (i.e. sneezing, itching, rhinorrhea, and nasal obstruction). They are effective as monotherapy and studies have shown that nasal corticosteroids are more effective than monotherapy with nasal cromones or antihistamines. Greater benefit may occur when local corticosteroids are used with other classes of medications (e.g. antihistamines). They are safe and are not associated with systemic adverse effects. Local adverse effects of nasal corticosteroids are limited to minor irritation of the nose or throat and nasal bleeding, which resolve with temporary discontinuation of the medication. Safety during pregnancy has not been established, but clinical experience suggests that their use is not associated with adverse fetal effects.

Due to the possibility of serious systemic adverse effects **systemic corticosteroids** are recommended only as a short-course treatment in subjects with severe AR symptoms.

### 2.6.2.5. Specific immunotherapy

Allergen-specific immunotherapy (ASIT), also referred to as desensitization, allergy vaccination (AV) or allergy shots, for the first time was used in the treatment of AR by Noon and Freeman in 1911. Since then, a considerable body of clinical research has established the effectiveness of ASIT in reducing symptoms and medication requirements. ASIT has been considered as an established treatment of SAR, PAR, allergic rhinoconjunctivitis, asthma, and insect sting allergy. The success rates have been demonstrated to be as high as 80-90% for certain allergens.

In 1997 the initiative of J. Bousquet and R. Lockey, resulted in publishing *Allergen Immunotherapy: therapeutic vaccines for allergic diseases. The WHO Position Paper* that includes recommendations for indications, contraindications, and standardized therapeutic protocols. ASIT as a therapeutic modality in the treatment of allergic diseases has been used in R. Macedonia for a long period of time and its principles have been incorporated in the *Macedonian National Consensus for Allergic Rhinitis* and in the *Macedonian National Consensus for Asthma and Chronic Obstructive Pulmonary Disease*, both published in 1999.
**Definition.** SIT is defined as a high allergen dose vaccination strategy, which reprogrammed the peripheral tolerance against allergen.

The classic subcutaneous immunotherapy (SCIT) consists of a series of injections (shots) with an increasing concentration of allergen extracts reaching the dose that is effective for reducing the symptoms associated with exposure to certain allergen. The treatment usually begins with a weak solution that is applied once or twice a week. The strength of the solution is gradually increased with each dose. Once the strongest dose is reached, the injections are given once a month. At this point, the sensitivity to certain allergen is decreased and the maintenance level is reached.

**Mechanism.** Controversy remains about the mechanism of ASIT. There is no conclusive evidence as to exact mechanism of ASIT, though there are several theories. The most plausible current theory emphasizes the balance between effector and regulatory T cell population, which regulates peripheral tolerance (Figure 87).

![Mechanistical sequence of specific immunotherapy](image)

**Figure 87.** Current concept of regulatory T-cell induction underlying ASIT


Allergic diseases result from an unbalanced response of the specific immune system, generating allergen-specific antibodies, which mediate various clinical symptoms. The generation of allergen-specific IgE by B ly depends on the generation of IL-4 producing Th 2 cells. The existence of allergen-specific Th 2 cells is not sufficient for allergy pathogenesis, because these cells are also found in healthy individuals. In contrast, allergen-specific regulatory T cells (Tregs) occur at a higher frequency than their effector counterparts in healthy individuals, and are capable of suppressing the proliferation and cytokine expression of Th 1 and Th 2 cells, also acting on APC. Tregs are defined on the basis of their function, in contrast to Th 1 and Th 2 cells, which are characterized by their gene products. Allergen-specific Tregs are induced after the initiation of ASIT, and are assumed to suppress Th 2 cells directly mediating allergic inflammation.
**Goal.** The basic goal of ASIT is to achieve allergic tolerance and to reduce symptoms of the disease by decreasing the level of specific IgE directed against certain allergen. ASIT represents the only curative treatment of specific allergy, i.e. the only treatment that can modify the natural course of the disease.

**Indications.** ASIT should be administered with allergens to which the patient is known to be sensitive and that are present in the patient’s environment and cannot be easily avoided. ASIT may be considered more strongly with severe disease, poor response to other management options, and the presence of comorbid conditions or complications. The value of the ASIT for **pollens**, **dust mites**, **cats**, and **Hymenoptera venom** is well established. The value of the ASIT for **dogs** and **moulds** is less well established. ASIT is not a useful method for the treatment of food allergy.

**ASIT with undefined allergens, such is house dust, should not be performed.**

Before starting the ASIT the allergic sensitization to certain allergen in each patient has to be demonstrated by history, positive SPT and/or increased specific IgE levels, and nasal provocation test.

The most important indications for ASIT include:

- Cases of SAR with poor response to other management options;
- Cases of SAR with prolonged exposure to pollens (3-5 months);
- Cases of PAR caused by mite sensitization with poor response to other management options;
- Cases of clinical manifested insect sting allergy and demonstrated allergic sensitization to Hymenoptera venom.

**Contraindications**

ASIT should only be performed in selected patients by individuals who have been appropriately trained, who institute appropriate precautions, and who are equipped for potential adverse effects. A number of potential contraindications for ASIT exist and need to be considered.

The most important contraindications for ASIT include:

- Cases of SAR in which adequate allergen avoidance may be achieved;
- Cases of SAR characterized by sporadic exposure to allergen;
- Nasal polyposis;
- Cardiovascular diseases;
- Treatment with β blockers;
- All conditions in which administration of adrenaline is contraindicated (arterial hypertension, arrhythmias);
- Autoimmune diseases;
- Pregnancy;
- Uncontrolled asthma.
**Duration.** Administration of the ASIT is a long-term process. A noticeable improvement often is not observed for 6-12 months. If helpful, therapy should be continued for 3-5 years. ASIT is not without risk because severe systemic allergic reactions (i.e. life-threatening anaphylactic shock) can occur. For these reasons, the risk and benefits of ASIT in each patient should be carefully considered in respect to the risks and benefits of the other management options.

**ASIT modalities.** In the last decades many treatment schedules, aimed at satisfactory protection, minimal side-effects, optimal convenience, and minimal costs, have been developed.

There are several ASIT protocols in which the initial phase (i.e. the period in which the maintenance dose should be reached) is markedly shortened. The patients who underwent these ASIT protocols had to be hospitalized due to the possibility of adverse effects. In the rush ASIT protocol the maintenance dose is reached within 4 - 7 days, whereas in the ultrarush ASIT protocol the maintenance dose is reached within 2 days.

**Sublingual immunotherapy (SLIT)**

Although SCIT has proven efficacy and a good safety record, disadvantages include requirement for injections, which are especially problematic in children, as well as the need for injections administering at the doctor’s office. These factors provide a rationale to seek alternative treatment approaches, and SLIT shows considerable promise in this regard.

SLIT technique involves putting large doses of allergen extracts under the tongue, where the allergen is adsorbed and subsequently induces immune response that may promote peripheral tolerance. One of the main advantages of this technique is the ability to have patients self-administrate the extracts at home.

Oral allergen extracts have been used in randomized clinical trials, which began to appear in the literature around 1985. There has been a considerable clinical experience with SLIT until today. The published data indicate the efficacy of SLIT in treatment of AR, asthma, and insect sting hypersensitivity, as well as a good safety profile in both adults and children. The questions that have to be answered to optimize this therapy include defining the optimal dose and administration schedule for each extract, determining how long-term efficacy is best achieved, and working toward a better understanding of the local immune response and immunologic mechanisms underlying the SLIT-induced tolerance.

**2.7. Frequency of allergic rhinitis**

The prevalence of AR varies among and within countries that is due to geographic differences in the types and potency of different allergens, as well as to type and design of the study. However, published data indicate AR prevalence from 3.8 to 20.6% of the
general population (13-15% in Finland, 4-8.6% in Switzerland, 9.6% in the UK, 8.7% in Germany). Recent US figures have suggested a 20% cumulative prevalence rate (i.e. approximately 40 million people in the USA). Scandinavian studies indicate prevalence rate of 15% in men and 14% in women.

An increasing AR prevalence in the last three decades has been reported by a number of studies. The studies from Switzerland, England and Sweden reported that prevalence of AR doubled in the period of a decade.

AR occurs in subjects of all races. In childhood, AR is more common in boys than in girls, but in adulthood the prevalence is approximately equal between men and women. In 80% of cases, the symptoms of AR occur before the age of 25. The prevalence of AR has been reported to be as high as 40% in children, subsequently decreasing with age. In the geriatric population, rhinitis is less common allergic in nature.

AR often coexists with other disorders, such as asthma, and may be associated with asthma exacerbations. It is also associated with allergic conjunctivitis, otitis media, eustachian tube dysfunction, sinusitis, nasal polyps, and atopic dermatitis.

2.7.1. Results from our epidemiological study of allergic rhinitis in R. Macedonia

Epidemiological observations of AR and aeropalinological measurements in R. Macedonia have started in the early 1990s. During 1993, 556 cases of SAR and 127 cases of PAR (ratio 4.4 / 1.0) at the Institute of Occupational Health Skopje were registered.

In the middle 1990s the first epidemiological survey of AR on a cohort of 113 randomly selected subjects aged over 18, was carried out. Evaluation of the examined children included completion of a questionnaire and SPT to common aeroallergens. The prevalence of AR was found to be 11.5%. In that period a survey of occupational AR had also been conducted.

The Project “Epidemiological characteristics of allergic rhinitis in R. Macedonia in correlation to pollen microflora” started in the late 1990s. AR was detected in a group of 1121 randomly selected subjects (722 adults and 399 children) from six centers in R. Macedonia. Evaluation of the examined adults for AR included completion of a questionnaire and SPT to common aeroallergens, while the diagnosis of AR in the examined children was questionnaire-based.

Prevalence of chronic rhinitis, AR and nonallergic rhinitis (NAR) was 30.2%, 20.8%, and 9.3%, respectively (Figure 88).
Prevalence of chronic rhinitis, AR, and NAR in all examined subjects was 30.2%, 20.8%, and 9.5%, respectively (Figure 88).

Figure 88. Prevalence of chronic rhinitis, AR, and NAR in all examined subjects

Prevalence of SAR and PAR in all examined subjects was 13.5% and 7.3%, respectively (Figure 89).

Figure 89. Prevalence of AR, SAR, and PAR in all examined subjects

2.7.2. Prevalence of rhinitis in examined adults

Prevalence of rhinitis in examined adults was 34.4%. Prevalence of AR and NAR was 23.1% and 11.3%, respectively. Prevalence of SAR and PAR in examined adults was 16.5% and 6.7%, respectively (Figure 90).
The increasing trend of AR prevalence in the last decades, reported by many authors, was also confirmed in the actual study. The prevalence of AR in adults in the period 1995-2003 has doubled, particularly due to the increase of the prevalence of SAR (Figure 91).

Prevalence of AR was slightly higher in women than in men (24.4% vs. 21.2%). (Figure 92). Prevalence of both SAR and PAR was slightly higher in women (17.1% vs. 15.2% and 7.2% vs. 6.0%, respectively). Non-significant sex distribution of AR was obtained in our previous study, as well as in the many studies carried out worldwide.
The highest prevalence of AR in examined adults was registered in the age group 31-40 (29.5%) (Figure 93). Data from the reviewed studies indicate higher prevalence of AR in younger age groups. The highest prevalence of SAR in England and Wales was registered in the age group 5-15, in Denmark in the age group 10-19, and in the USA in the age of 24. Prevalence of SAR in the European countries is lower than in the USA and Australia. This could be a result of the higher allergic potential of the allergens in these countries.

2.7.2.1. Prevalence of allergic rhinitis in examined adults from certain centers

The highest AR prevalence in examined adults was registered in Prilep (35.4%) and the lowest in Ohrid and Skopje (20.0% and 16.5%, respectively). The highest SAR prevalence in examined adults was also registered in Prilep (29.7%) and the lowest one in Debar and Skopje (9.7% and 8.5%, respectively). The highest prevalence of PAR was registered among examined adults from Debar (13.6%) and the lowest one among examined adults from Ohrid (1.0%) (Figure 94).
The highest prevalence of SAR was registered among examined adults from Prilep (29.7%), that is one of the highest SAR frequencies reported in the literature. Aeropalinological measurements showed the highest concentrations of airborne grass and weed pollens in Prilep. The highest prevalence of allergic sensitization to tree, grass, and weed pollens among examined adults was registered also in Prilep (25.4%, 41.5%, and 43.2%, respectively). The period in which the skin prick tests were performed (April-May), that is a period of the highest pollination of the most grass species, also play a role for the obtained results.
2.7.2.2. Distribution by sensitization to common aeroallergens

The importance of mite sensitization as a risk factor for AR and asthma has been indicated in many reviewed studies and was confirmed in our study. The highest sensitization to common aeroallergens among subjects with AR was registered for goosefoot pollen, *Dermatophagoides pteronyssinus*, mugwort pollen, and cat fur (Table 13).

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Positive SPT in the examined adults (%)</th>
<th>Positive SPT in the examined adults with AR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tree pollens</td>
<td>10.8</td>
<td>25.4</td>
</tr>
<tr>
<td>Grass pollens</td>
<td>17.9</td>
<td>41.5</td>
</tr>
<tr>
<td>Weed pollens</td>
<td>19.4</td>
<td>43.2</td>
</tr>
<tr>
<td>Goosefoot</td>
<td>13.6</td>
<td>30.5</td>
</tr>
<tr>
<td>Mugwort</td>
<td>11.9</td>
<td>26.3</td>
</tr>
<tr>
<td>Nettle</td>
<td>7.5</td>
<td>18.6</td>
</tr>
<tr>
<td>Plantain</td>
<td>5.1</td>
<td>12.7</td>
</tr>
<tr>
<td><em>Ambrosia</em></td>
<td>4.4</td>
<td>11.0</td>
</tr>
<tr>
<td><em>Penicillium</em></td>
<td>3.9</td>
<td>4.2</td>
</tr>
<tr>
<td><em>Alternaria</em></td>
<td>3.6</td>
<td>4.2</td>
</tr>
<tr>
<td>Cat</td>
<td>5.5</td>
<td>10.2</td>
</tr>
<tr>
<td>Dog</td>
<td>2.8</td>
<td>6.8</td>
</tr>
<tr>
<td>Feathers</td>
<td>3.9</td>
<td>6.8</td>
</tr>
<tr>
<td><em>Dermatophagoides pteronyssinus</em></td>
<td>13.9</td>
<td>26.3</td>
</tr>
<tr>
<td>Cockroach</td>
<td>3.2</td>
<td>3.4</td>
</tr>
</tbody>
</table>

Table 13. Distribution of the adults with AR by sensitization to common aeroallergens

2.7.2.3. Sex distribution

The non-significant role of the gender in AR development has been reported by many studies that is in agreement with the results of our study. The prevalence of AR in adults was non-significantly higher in women, whereas in children it was non-significantly higher in boys.

2.7.2.4. Allergic rhinitis and respiratory symptoms

Many studies indicated strong link between AR and respiratory symptoms that was confirmed by results of our study. AR was significantly associated with respiratory symptoms in both examined adults \((P < 0.01)\) and examined children \((P < 0.01)\).
2.7.2.5. Allergic rhinitis and atopy

Atopy is defined as a predisposition for production of IgE antibodies following the exposure to extrinsic allergens. Prevalence of atopy worldwide varies from 10 to 50% of the general population. Atopy may be demonstrated by in vivo or in vitro tests, as well as by positive personal or family history of allergic diseases. Prevalence of atopy in our study was 34.8% and it was non-significantly higher in males (38.7% vs. 31.6%).

We found significant association between AR and positive family history of allergic diseases in examined children. In examined adults this association was statistically non-significant.

2.7.2.6. Allergic rhinitis and environmental factors

Although the significant association between AR and any individual environmental factor was not registered it could be noted that the frequency of AR and SAR is higher among examined adults exposed to traffic pollutants, and the frequency of PAR is higher among examined adults who own pets (Figure 95).

![Figure 95. Prevalence of AR, SAR, and PAR in examined adults exposed to certain environmental factors](image)

According to data from the population-based study carried out in the UK including 2000 subjects, exposure to dust and pets ownership were considered to be the most important triggers of respiratory allergic diseases. The role of exposure to pets allergens as a risk factor for respiratory allergies was also reported in the Turkish study carried out in 2003. According to the results of actual study, the avoidance of exposure to pets should be recommended.

Many studies have indicated increasing trend of AR incidence and prevalence in industrialized countries in the last three decades. An increased concentration of traffic pollutants is considered as one of the most important factors for such changes in AR frequency. The urban-type pollutants, such as ozone and nitric oxides, may also play a
role in the development and severity of rhinitis symptoms. Data from the Italian study, carried out in the period 1998-2000 which included 18,873 examined subjects aged 20-44 from continental and Mediterranean region, showed that exposure to nitric dioxide in subjects living in warm climate regions increased the risk for AR. Data from the English study revealed that exposure to sulfur dioxide and ozone may worsen the rhinitis symptoms.

2.7.3. Prevalence of allergic rhinitis in examined children

The present study was the first epidemiological observation of AR in children in R. Macedonia. The epidemiological diagnosis of AR was questionnaire-based.

![Figure 96. Prevalence of rhinitis symptoms, AR, SAR, and PAR in examined children](image)

Rhinitis symptoms were reported by 22.6% of the examined children. Prevalence of AR, SAR, and PAR was 16.5%, 8.3%, and 8.3%, respectively (Figure 96). Data of the actual study indicated higher prevalence of AR in adults than in children. In the reviewed studies higher AR prevalence in children is reported. The English study indicated the highest AR prevalence in the age group 5-15. The study from Denmark reported the highest AR prevalence in the age group 10-19 affecting 15-20% of the school-children with higher prevalence in boys.

The AR prevalence in children was higher in the girls than in the boys (17.3% vs. 15.8%) (Figure 97).
The highest AR prevalence in examined children was registered in Skopje and Prilep (21.1% and 20.4%, respectively) and the lowest one in Debar (8.4%). The highest and the lowest prevalence of SAR was registered in Skopje and Debar (10.6% and 3.6%, respectively). The highest and the lowest prevalence of PAR was also registered in Skopje and Debar (10.6% and 4.8%, respectively) (Figure 98).

We found significant association between AR in examined children and respiratory symptoms ($P < 0.01$). Significant association between AR in examined children and endogenous factors was registered for family history of allergic diseases ($P < 0.01$), whereas the association with other endogenous factors was not statistically significant.
2.7.3.1. **Association between allergic rhinitis in examined children and environmental factors**

Statistical significance between AR, SAR, and PAR in examined children was not registered with any individual environmental factor. However, more frequent occurrence of these diseases was noted in children with certain exposure (Figure 99). AR occurred more frequently among children that reported exposure to environmental air pollutants and cat ownership. According to our findings exposure to traffic pollutants and cat ownership may play a role in PAR development, whereas housing in environment rich with plants and trees may be important for development of SAR.

![Figure 99. Prevalence of AR, SAR, and PAR in children exposed to certain environmental factors](image)

Results from the studies that investigate the effect of environmental factors to respiratory allergies are controversial. The study carried out in the United Arab Emirates that included 2,200 children aged 6-12 years had indicated pets ownership as a risk factor for allergic sensitization and AR. On the contrary, Swedish follow-up study carried out on a sample of 3,000 children aged 7-9 and 12-13 years had showed that exposure to pets allergens in the first year of life led to lower prevalence of AR and asthma. The Dutch contribution to ISAAC, carried out on a sample of 3,000 children, reported non-significantly lower risk of sensitization to pollens in children exposed to pets allergens in the first two years of life.

The study from Austria indicated lower prevalence of allergic sensitization, SAR, and asthma in children with farming exposure. The German study, carried out on a sample of 317 children at the age of 9, showed significant association between pollens sensitization and the air level of nitric dioxide. Similar findings (i.e. significant association between AR and level of traffic air pollutants) were reported by the study carried out among teenagers in Taiwan.

Many studies indicate that AR prevalence in developing countries in both children and adults is recently increasing following the urbanisation and industrialisation. Possible explanations, beside the exposure to pollution from industrial and motor vehicle exhaust
emission, may be the changes in diet that cause a loss of protection against allergic diseases caused by *Lactobacillus*, contained in fermented milk usually drunk in African rural areas, as well as the decrease in worm infections (e.g. *Ascaris lumbricoides*), considered responsible for protection against development of allergies by some authors.

Furthermore, some authors report an adverse effect of childhood immunisations, as well as the use of antibiotics on the allergic diseases development. Some authors also report that sibship size is inversely related to the prevalence of childhood allergic diseases. A potential explanation may be that having more siblings contribute to a higher infectious burden, thereby directing the development of the immune system in a nonatopic (Th1) direction.

The hygienic hypothesis, being on the scene long time ago, assumes all these elements. John Bostock, the doctor who first identified hay fever, noted that it was a condition of the educated and he could not report any case among poor people.

### 2.7.4. Occupational allergic rhinitis

A significant association between AR, SAR, and PAR and any individual workplace factor was not found in our study. However, higher prevalence of AR and SAR was registered in subjects with workplace exposure to dusts. The prevalence of AR, SAR, and PAR was non-significantly higher in subjects that reported higher level of humidity at the workplace (Figure 100).

![Bar chart showing prevalence of AR, SAR, and PAR](image)

**Figure 100.** Prevalence of AR, SAR and PAR in examined adults with harmful work environment

Workplace-associated worsening of the rhinitis symptoms was reported by 33.3% of the adults with AR. Despite the fact that our the questionnaire was not designed for detection...
of the occupational AR, the prevalence of occupational AR in the examined adults may be estimated to 7.6%. That was consistent with the published data. The prevalence of occupational AR in published literature varies from 1.7 to 20%. It seems that the prevalence of occupational AR is quite underdiagnosed since in many cases the workplace relatedness of rhinitis symptoms is not registered by both patients and doctors.

The findings of our previous study, carried on a sample of 198 subjects and based on the completion of a questionnaire (Appendix 6), SPT, and lung function tests, showed prevalence of occupational AR of 10.1%. The highest prevalence of occupational AR was registered in the tea and spice processors (15.5%). Occupational AR was significantly associated with respiratory symptoms (P < 0.001), whereas the age over 45, high dust level, and physical exercise were considered as contributing factors in its development.

2.7.5. Conclusions

1. The prevalence of AR in all examined subjects was 20.8%.
2. The prevalence of AR in examined adults was 23.1%, being slightly higher in women (24.4%) than in men (21.2%). The prevalence of SAR in examined adults was 16.5% (15.2% in men and 17.1% in women), while the prevalence of PAR was 6.7% (6.0% in men and 7.2% in women).
3. The prevalence of AR showed trend of increase that was more expressed for SAR than for PAR.
4. The highest AR prevalence among examined adults was registered in Prilep (35.4%). The highest prevalence of SAR was registered also in Prilep (29.7%), whereas the highest prevalence of PAR was registered in Debar (13.6%). In respect to the age, the highest AR prevalence was registered in the age group 31-40.
5. The weed pollens were the most important aeroallergens in the adults with SAR. The goosefoot and the mugwort pollen were the most important individual aeroallergens.
6. Significant association was found between AR in adults and respiratory symptoms. The association between AR and other endogenous and exogenous factors was not statistically significant.
7. Although no significant association was found, exposure to traffic pollution and pets ownership could play a role in AR development.
8. The prevalence of occupational AR was estimated to be 7.6%. Although no significant association between AR and any workplace factor was registered, workplace exposure to dusts and humidity could play a role in AR development.
9. The prevalence of AR in examined children was 16.5%, being slightly higher in the boys (17.3%) than in the girls (15.8%). The prevalence of both SAR and PAR in examined children was 8.3%.
10. AR in examined children was closely related to positive family history of allergic diseases and to respiratory symptoms. Association between AR and other endogenous and exogenous factors was not statistically significant.
2.7.6. References:


3.0. **Allergic conjunctivitis - ICD - 10; H 10.8**

Conjunctivitis is one of the most common nontraumatic eye complaints. The term describes any inflammatory process that involves the conjunctiva. Classification usually is based on cause, including viral, bacterial, fungal, parasitic, chlamydial, chemical, and allergic agents.

3.1. **Classification and definition**

According to the actual classification there are five types of allergic ocular diseases, including allergic conjunctivitis (that may be seasonal or perennial), atopic keratoconjunctivitis, vernal keratoconjunctivitis, and giant papillary conjunctivitis.

Allergic conjunctivitis (AC) is conjunctival inflammation caused by IgE-mediated mechanism and manifested by redness, pruritus, tearing, discharge, and photophobia.

AC is the most common type of allergic ocular disease that often accompanies allergic rhinitis (allergic rhinoconjunctivitis). It may be divided into seasonal and perennial AC (intermittent and persistent AC) as in the subdivision of allergic rhinitis. Seasonal AC (SAC) occurs during certain season (spring and/or summer), whereas the symptoms of perennial AC (PAC) persist during the whole year. Seasonal rhinoconjunctivitis (hay fever) is the most common allergic disease worldwide, affecting 15-20% of the general population.

Atopic keratoconjunctivitis (H 10.1; H 16.2) involves associated corneal affection, typically occurring in male teenagers who have a history of childhood atopic dermatitis. The condition resembles vernal keratoconjunctivitis but is not seasonal.

Vernal keratoconjunctivitis (H 16.2) is presumed to be a hypersensitivity to exogenous antigens and usually affects young boys. The condition occurs during the warm months of the year, particularly in hot climates. Characteristic laboratory finding is blood eosinophilia and increased total IgE level. In 75% of the cases vernal keratoconjunctivitis is accompanied with other allergic diseases, whereas the family history of allergic diseases is positive in 60% of these subjects.

Giant papillary conjunctivitis (H 10.8) occurs mainly in soft contact lens wearers who develop a syndrome of excessive pruritus, mucous production, and increasing intolerance to contact use.

3.2. **Pathogenesis**

Type I immunological reaction according to Gell and Coombs is the underlying mechanism of AC.
Complexes of the aeroallergens and specific IgE antibodies cause degranulation of the mast cells from conjunctival substantia propria and inflammatory mediators (histamine, prostaglandines, leukotrienes) release. The multiple effects of inflammatory mediators, including plasma exudation, eosinophils and neutrophils migration, and sensory nerve activation, lead to clinical manifestations of the disease.

### 3.3. Clinical manifestations

Redness, itching and burning or a foreign-body sensation, tearing, discharge, and photophobia are manifestations of both allergic and nonallergic conjunctivitis.

The symptoms of SAC usually occur in spring or summer, during certain types of pollen domination. The symptoms of PAC persist throughout the whole year. *Dermatophagoides pteronyssinus*, pets, and moulds allergens are the most important allergens in subjects with PAC.

### 3.4. Diagnosis

Diagnosis of AC is based on history, physical examination, and allergologic evaluation. In addition, measurement of IgE level in tears, as well as conjunctival biopsy can be performed.

History of acute or subacute episodes of redness, itching, discharge, tearing, and sensitivity to light, that may be seasonal or persistent, suggests AC. Furthermore, positive personal and/or family history of allergic diseases is reported by a number of subjects with AC.

Physical examination of the eye usually shows palpebral edema and moderate conjunctival injection. Clear, watery discharge with or without a moderate amount of mucous production is typical. In subjects with AC there is no associated corneal involvement (Figure 101). The visual acuity is not affected.

![Image of eye](image)

**Figure 101.** Typical signs of AC

Allergologic evaluation includes identification of the allergen by skin prick tests or laboratory methods. Specific IgE antibodies may also be detected in the tears of the subjects with AC.

3.5. Treatment

The treatment of AC includes nonpharmacological measures and medication use.

Non-pharmacological treatment includes measures for control of the environment but in most cases these measures have a limited effect.

Pharmacological treatment includes use of antihistamines and anti-inflammatory drugs.

Antihistamines are basic medications in the pharmacological treatment of AC. These medications reduce symptoms of AC by blockage of the histamine receptors (H1 receptors), but they have no effect on the other inflammatory mediators. Local and systemic preparations of antihistamines may be used in the AC treatment. Local decongestants may also be used for reduction of the symptoms of AC.

Cromones, such as disodium cromoglycate and nedocromil sodium, are the most important anti-inflammatory agents in the AC treatment. By stabilizing the mast cell membrane these medications inhibit mast cell degranulation and mediators release. The mast cell stabilizers are recommended for prevention of the symptoms following allergen exposure. Non-steroidal anti-inflammatory agents (NSAIDs) also exhibit anti-inflammatory effect by inhibition of the prostaglandine synthesis. Corticosteroids are recommended only in treatment of severe symptoms that failed to respond to conventional therapy. The medications used in the AC treatment are shown in Appendix 4.

3.6. Environmental control

Measures of the environmental control, i.e. avoidance of allergens and irritants, are effective in treatment of both allergic rhinitis and AC.

3.7. Frequency of allergic conjunctivitis

Epidemiological characteristics of AC are usually investigated within the epidemiological observations of allergic rhinitis. The results of numerous studies have shown that allergic rhinitis is accompanied by AC in approximately 70% of the cases.

Prevalence of AC in the general population of the USA and the UK is estimated to 5-22%. Approximately 15% of the population in the USA (more than 22,000 000 individuals) will have an AC episode at some time.
AC prevalence is usually higher in females than in males. The disease occurs in all ages and no racial predilection exists. Its occurrence is more frequent in hot climate areas. It seems that air pollution, particularly traffic pollution, contributes to development of AC.

### 3.8. Results of our epidemiological study of AC in R. Macedonia

Until today no previous epidemiological study of AC in R. Macedonia has been carried out. The diagnosis of AC in the actual study was based on the presence of one or more conjunctivitis symptoms and positive skin prick tests to common aeroallergens. Since in the examined children skin prick tests was not performed and completion of the questionnaire was not sufficient to confirm allergic background of the disease, AC was observed in the examined adults.

Conjunctivitis symptoms in the last 12 months were reported by 30.1% of the examined adults. Prevalence of AC and nonallergic conjunctivitis (NAC) was 12.9% and 17.2%, respectively (Figure 102) that is within the range of the published data.

![Figure 102. Prevalence of conjunctivitis symptoms, NAC and AC in examined adults](image)

The prevalence of perennial AC was higher than the prevalence of seasonal AC (7.8% vs. 5.3%). (Figure 103).
3.8.1. Sex and age distribution

The allergic conjunctivitis prevalence was slightly higher in females than in males (13.0% vs. 12.0%) (Figure 104).

Results from the reviewed studies indicated higher AC prevalence in the younger age groups. Our data showed the highest AC prevalence in the age group 21-30 (19.6%) and decreasing prevalence in the older age groups (Figure 105).
3.8.2. Prevalence of allergic conjunctivitis among examined adults in certain centers

Similarly to allergic rhinitis, the highest and the lowest AC prevalence was registered in Prilep and Pehchevo (26.0% and 8.3%, respectively). The AC prevalence in Skopje was 8.5% (Figure 106).

3.8.3. Distribution by sensitization to common aeroallergens

The highest prevalence of sensitization to common aeroallergens in the subjects with AC was registered for pollens, *Dermatophagoides pteronysinus*, and pets (87.2%, 31.9%, and 19.1%, respectively) (Figure 107). The most important individual pollen allergens were goosefoot and mugwort pollens (47.8% and 31.1%, respectively).
Sensitization to common aeroallergens in the subjects with AC

Allergic rhinitis was registered in 76.1% of the subjects with AC that is complementary to published data. The prevalence of allergic rhinoconjunctivitis in the examined adults was 7.3% (Figure 108).

3.8.4. Association with allergic rhinitis and asthma

Allergic rhinitis was registered in 76.1% of the subjects with AC that is complementary to published data. The prevalence of allergic rhinoconjunctivitis in the examined adults was 7.3% (Figure 108).

The published data suggest no close relation of AC to asthma that was confirmed by findings in our study. The prevalence of AC with asthma in the examined adults was 1.5% (Figure 109).
3.8.5. Allergic conjunctivitis and endogenous factors

The importance of endogenous factors in the AC development was confirmed by its close relation to positive family history of allergic rhinitis (P < 0.05). Positive family history of allergic rhinitis was reported by 62.5% of the subjects with AC (Figure 110).

3.8.6. Allergic conjunctivitis and environmental factors

The increasing prevalence of allergic diseases in the last decades may be due to the environmental changes. According to the results from published studies, traffic pollution and workplace air pollutants, may play a role in the AC development, contributing to the processes of allergic sensitization and conjunctival inflammation. Air pollutants can also worsen the symptoms of manifested AC. In present study exposure to dusts was reported by 68.1% of the subjects with AC, to smoke in 36.9%, and to workplace pollutants in 17.3% (Figure 111).
According to many studies, urban residence is a risk factor for development of allergic diseases. In our study the AC prevalence was significantly higher in the subjects living in urban areas than in rural ones (14.8% vs. 7.2%, P < 0.05). (Figure 112).

Association between AC and other exogenous factors, such as active smoking, exposure to environmental tobacco smoke (ETS), exposure to traffic pollutants, pets ownership, and green plants outdoors, was not statistically significant.

3.8.8. Conclusions

1. Prevalence of AC in the examined adults was 12.9%, slightly higher in females than in males, that was in agreement with the results in the literature.
2. Prevalence of SAC was nonsignificantly lower than prevalence of PAC.
3. The highest prevalence of AC was registered in the age group 21-30.
4. Similarly to allergic rhinitis, the highest prevalence of AC was registered in the examined adults from Prilep.

5. Sensitization to pollens, Dermatophagoides pteronyssinus and pets was the most important aeroallergens in the subjects with AC. The most important individual pollens were goosefoot and mugwort pollen.

6. There was a strong link between AC and allergic rhinitis. Association between AC and other allergic diseases was nonsignificant.

7. AC was closely related to positive family history of allergic rhinitis. Association between AC and other endogenous factors was nonsignificant.

8. AC was significantly associated with urban residence. Association between AC and other exogenous factors was nonsignificant.

3.8.9. References:

4.0. Asthma - ICD - 10; J. 45

4.1. Definition

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation causes an associated increase in airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment (Global Initiative for Asthma – GINA Updated 2004).

4.2. Risk factors

Asthma develops as a result of the interplay between host and environmental factors. It is still not completely possible to distinguish which factors are true causes of the development of asthma and which are triggers of asthma attacks. The major risk factors for asthma according to Sheffer are shown on Scheme 3.

![Scheme 3. Asthma risk factors](image)

**Figure 113.** Risk factors for asthma

Sex, atopy, family history of asthma, ethnic group, early life risk factors like prematurity and bottle feeding in the first 4-6 months, and childhood and adulthood respiratory trouble, are considered as endogenous risk factors for asthma. On the other hand, exposure to allergens, active and passive smoking, indoor and outdoor air pollution, workplace exposure, lifestyle, and diet and alcohol consumption are the main environmental risk factors for asthma.
4.2.1. Genetics of asthma

Despite intensive effort and the advances of molecular biology over the last few years, no genes involved in asthma pathogenesis have been clearly identified. According to the actual knowledge several genes or gene groups, which expression is variable, may be involved in the asthma pathogenesis. Recent studies indicate that separate genetic factors for bronchial hyperresponsiveness and for tendency to over-produce IgE exist, but they are linked by a phenomenon of coheredity. A locus which regulates the IgE production has been found in the chromosome 5q31-q33. The results of other studies indicate that certain asthma phenotype characteristics are associated with other chromosomal regions, such as 6r21.3 and 14q11.

4.2.2. Atopy

Atopy, defined as a personal or familial tendency to produce IgE antibodies in response to low doses of allergens, usually proteins, and to develop typical symptoms such as asthma, rhinoconjunctivitis, or eczema/dermatitis, is considered as a major risk factor for asthma. The prevalence of atopy worldwide varies from 10 to 45%, depending upon race, gender, age, and environmental factors. The results of the multicentric study in R. Macedonia carried out in 1995 by Institute of Occupational Health showed prevalence of atopy among adults of 38%.

4.2.3. Allergens

The inhalant allergens, causative factors of the respiratory allergic disorders, are usually classified as common and occupational allergens. The common inhalant allergens are presented in the outdoor and indoor atmosphere of certain geographic area, while the occupational allergens are associated with certain workplace. Tree, grass, and weed pollen, as well as some types of moulds are the main outdoor allergens. House dust mite (Dermatophagoides pteronyssinus), pet, and mold allergens are considered as the most important indoor allergens.

4.2.4. Air pollution

Air pollution may cause adverse respiratory effects by mechanisms of sensitization and irritation. Nitrogen dioxide (NO2), sulphur dioxide (SO2), ozone, diesel exhaust particles, and outdoor allergens are considered as the most important outdoor air pollutants. A number of compounds and mixtures, such as tobacco smoke, combustion products (carbon monoxide, nitrogen dioxide, sulphur dioxide), cleansing agents, volatile organic compounds (formaldehyde, alkanes, aldehydes), and indoor allergens are identified as relevant indoor pollutants that may cause respiratory impairment. A large group of air pollutants associated with the workplace has a special importance as an occupational asthma has become the most important work-related respiratory disorder in developed countries.
There are suggestions that a substantial increase of incidence and prevalence of respiratory allergic disorders in the last three decades is partially due to the increased levels of air pollution in an urban environment. Anyway, the role of air pollution in the determination of asthma still remains unclear. Adjuvant effect of the pollutants in the process of allergic sensitization and its role in maintenance of the chronic airway inflammation are possible proasthmogenic effects of the air pollutants.

4.3. Pathogenesis and classification of asthma

It is now widely accepted that chronic inflammation including both central and peripheral airways (chronic eosinophil bronchitis) plays a key role in asthma. It is characterized by epithelial desquamation, infiltration of the airway wall by inflammatory cells with predomination of T helper 2 lymphocytes (Th2 ly), eosinophils and mast cells, increased smooth muscle mass, hypertrophy of mucous glands and goblet-cell hyperplasia, as well as subepithelial fibrosis. Structural changes of the airway wall (also referred to as airway wall remodeling) lead to a thickened airway wall and a markedly reduced airway caliber (Figure 114).

Figure 114. Normal and asthmatic bronchiole
Adapted from: Asthma. Available at www.nlm.nih.gov/medlineplus/

Airway inflammation in asthma, extremely complex in origin, regulation and outcomes, involves a cascade (“allergic cascade”) of events including many different kind of cells, cytokines, as well as over 100 inflammatory mediators. Inflammation, remodeling and altered neural control of the airways are responsible for variable airflow obstruction and increased airway responsiveness. The recurrent episodes of symptoms and reversible airflow limitation that characterize asthma represent an acute inflammatory response acting upon structurally and functionally altered airways.

It seems that the mast cells play a key role in development of the acute symptoms (early asthmatic reaction) (Figure 115), while eosinophils and Th2 ly are involved in the chronic inflammation that is associated with bronchial hyperresponsiveness (late asthmatic reaction).
In about 80% of childhood asthma and about 40-50% of the adult form the allergic cascade is initiated by inhalation of detectable common allergen and IgE-mediated activation of the inflammatory cells, followed by increased level of specific IgE antibodies directed against common allergens. This subgroup of asthma is defined as allergic asthma (J 45.0). In the other cases, defined as nonallergic asthma (J 45.1), the cascade is not initiated by inhalation of detectable allergen and there is no evidence of specific IgE antibodies directed against common allergens. There are several theories about initiation of the cascade in nonallergic asthma, such as inhalation of as-yet undetected allergen, local IgE production, triggering by infection, etc. Occupational asthma presents variant form of asthma caused by specific agent from the workplace.

4.4. Clinical manifestations

Asthma is a chronic disease characterized by recurrent acute or subacute episodes (asthma exacerbations) of wheezing, breathlessness, chest tightness, and coughing, with symptom-free intervals in the majority of the patients. In small amount of patients there are persistent asthma symptoms with episodes of worsening. Asthma symptoms usually occur at night or in the early morning with variable frequency and severity. Asthma, both allergic and nonallergic, is frequently accompanied by upper airways diseases, such as rhinitis, sinusitis, and sinonasal polyposis.
Triggers that precipitate asthma exacerbations include respiratory viral infections, allergen exposure, air pollutants, physical exercise, cold air, weather changes, drugs such as nonsteroid anti-inflammatory drugs (NSAIDs) and β blockers, gastroesophageal reflux disease (GERD), and extreme emotional expression. Usually, asthma exacerbations are precipitated by several triggers that vary from person to person and from time to time. However, there are variants with predomination of one trigger such as seasonal (pollen) asthma, Candida asthma, exercise-induced asthma (EIA), and aspirin-induced asthma. Work-related asthma (WRA) is a variant of asthma that includes two subtypes, occupational asthma (OA) and work-aggravated asthma.

On the basis of severity (the level of airflow limitation and its variability), asthma is subdivided into four grades: Intermittent, Mild Persistent, Moderate Persistent, and Severe Persistent.

4.5. Diagnosis and assessment

The diagnosis of asthma is focused on the history of asthma symptoms and on lung function testing that confirms reversible airflow limitation and increased airway responsiveness. Diagnostic procedure also includes determining of allergic status and measuring of the markers of airflow inflammation.

4.5.1. The characteristic symptoms of asthma are recurrent episodes of wheezing and breathlessness, often associated with chest tightness and cough, which are partially or completely reversible, either spontaneously or after bronchodilator administration.

4.5.2. Lung function testing includes tests which confirm the presence of reversible airflow limitation, such as bronchodilator test, serial spirometry, and serial peak expiratory flow rate (PEFR) measurement. For patients with symptoms consistent with asthma, but normal lung function, measurement of airway responsiveness to non-specific stimuli, such as metacholine, histamine, exercise, or cold air, may help establish asthma diagnosis. Specific challenge with agent to whom the patient is sensitized is a gold standard for diagnosis of allergic and occupational asthma, that is not performed in every day practice due to the complex protocol and possibility of adverse effects.

4.5.3. Atopic status is evaluated by in vivo (skin prick tests) and in vitro tests (total and specific IgE measurement). These tests add little to the asthma diagnosis, but they can help in risk factors or triggers identification so that adequate environmental control measures can be recommended.

4.5.4. Markers of the chronic airway inflammation, i.e. measurement of the level of nitric oxide (NO) in exhaled breath, of the eosinophil count in the blood and sputum, and of the level of eosinophil cationic protein (ECP) in the blood and sputum, may help in establish asthma diagnosis.
4.6. Management

The goals for successful management of asthma are to achieve and maintain control of symptoms; to prevent asthma exacerbations; to maintain pulmonary function as close to normal levels as possible; to maintain normal activity levels, including exercise; to avoid adverse effects from asthma medications; to prevent development of irreversible airflow limitation; and to prevent asthma mortality.

Asthma management includes non-pharmacological and pharmacological treatment.

4.6.1. Patients education to control their own condition is the basic non-pharmacological measure in asthma management. Measures for reducing exposure to environmental and occupational allergens, air pollutants, foods and drugs, improve the control of asthma and reduce medication needs. Allergen-specific immunotherapy, used in selected patients with allergic asthma, also presents a type of non-pharmacological treatment of asthma.

4.6.2. Pharmacological treatment includes chronic treatment of asthma and treatment of the acute exacerbations.

Chronic treatment of asthma should be tailored according to the severity of disease with a stepwise approach that means increasing the number, dosing and frequency of medications with increasing asthma severity, considering the presence or absence of control of the disease. The mainstay of the chronic asthma therapy consists of using agents that induce bronchodilatation (bronchodilators or relievers) and that control chronic inflammatory process (anti-inflammatory agents or controllers).

4.6.2.1. Bronchodilators. The group of bronchodilators includes short- and long-acting β2-agonists, anticholinergics, and theophylline. Short-acting β2-agonists are the best relievers, while long-acting β2-agonists and slow-release theophylline are best used in conjunction with inhaled corticosteroids in the treatment of moderate and severe persistent asthma.

4.6.2.2. Anti-inflammatory agents. The group of anti-inflammatory agents includes corticosteroids, cromolines and antileukotrienes. Inhaled corticosteroids (ICS) by inhibiting eosinophilic inflammation and mediator/cytokine expression remain the basic controller in the chronic asthma treatment.

Currently available pharmacological agents when taken regularly enable achieving good control of the disease in most patients with asthma.

The treatment of acute exacerbations of asthma also rests on the use of bronchodilators (short-acting β2-agonists) and anti-inflammatory agents (corticosteroids) administered orally or parenterally.

The present asthma medications, the doses of ICS, and the actual combined asthma medications are shown in Appendices 7, 8, and 9.
4.7. Prevention of asthma

4.7.1. Primary prevention includes measures of prenatal prophylaxis such as maternal smoking during pregnancy, as well as of measures in infancy and childhood such as reduction of the exposure to indoor pollutants (indoor allergens, passive smoking), and adulthood (smoking cessation, environmental and workplace control).

4.7.2. Secondary prevention could be used to prevent development of symptomatic disease in sensitized, but still asymptomatic subjects including measures for environmental and workplace control, treatment of allergic rhinitis and atopic dermatitis, and orientation to occupations with reduced exposure to allergens.

4.7.3. Tertiary prevention is used in the subjects with symptomatic disease and includes nonpharmacological and pharmacological treatment of asthma.

4.8. Multinational, national, and regional epidemiological studies of asthma

The prevalence of asthma showed increasing trend in both developed and developing countries in the last three decades. The largest increase has been detected in the younger age group and in Anglo-Saxon countries. A World Health Organization (WHO) estimate, published on the Internet in January 2000, showed that 100 –150 million individuals all over the world suffered from asthma. The yearly direct and indirect medical costs associated with asthma in the European Union countries was estimated to 2,000-3,000 euros per patient.

The social and economic burden of this condition is heavy. Asthma costs of the society may be largely reduced through national and international concerted actions. In 1995, the Global Initiative on Asthma (GINA) was implemented by the WHO, and it was revised in 1998, 2002, and 2004, according to the actual knowledge. In the same period several national guidelines were developed. The Macedonian National Consensus for Asthma and Chronic Obstructive Pulmonary Disease was developed in 1999.

In the 1980s and 1990s a number of regional, national, and multinational epidemiological studies of asthma were carried out. The studies which have contributed with standardized definitions to improve the knowledge in the epidemiology of asthma include the European Community Respiratory Health Survey (ECRHS), the International Study of Asthma and Allergies in the Childhood (ISAAC), the Swiss Studies on Air Pollution and Lung Diseases in Adults (SAPALDIA), the Italian Studies on Respiratory Diseases (the Po Delta study, the Pisa and Cascina study), the Obstructive Lung Disease in Northern Sweden Study (OLIN), etc.

The ECRHS was a cross-sectional study carried out in the first half of the 1990s. The database of the ECRHS included about 140,000 participants aged 20-44 from 48 centers from 22 countries (Europe, North America, and Australia). The reason for undertaking
the ECRHS was a rapid increase in the prevalence of asthma that had been reported from many different countries. The increase was over a too short time period to be explained by genetic factors and therefore, was related to environmental changes.

In stage I subjects were sent the ECRHS screening questionnaire asking about symptoms suggestive of asthma, use of medication for asthma, and presence of hay fever and nasal allergies. In stage II, a smaller random sample of subjects who had completed the screening questionnaire were invited to attend a more detailed interviewer-led questionnaire, skin prick tests, blood tests for measurement of total and specific IgE, spirometry, and metacholine challenge. The symptomatic subjects with positive metacholine challenge and/or subjects using asthma medications were considering having asthma.

Over 100 papers written in English, as well as a large number of papers in languages other than English, have been published by the ECRHS. About 20 papers have been based on analyses of the complete data set (central analyses) and the rest from analyses of data from one or several of the centers (local analyses).

According to the ECRHS protocol several national (Bulgaria, Chile) and regional surveys (St. Petersburg, Manisa) were carried out.

The ISAAC is a cross-sectional study of childhood asthma started in the first half of the 1990s including children aged 6-7 and adolescents aged 13-14 years in 56 countries all over the world, including R. Macedonia. The ISAAC consisted of three phases. In phase I subjects completed a questionnaire on asthma symptoms, as well as nasal and skin disorders. In phase II clinical evaluation which included lung functional testing, carbachole challenge, and allergologic evaluation by in vivo and in vitro tests was performed. Phase III started in 2001 with an ecologic evaluation as a basic field of research.

The Global Allergy and Asthma European Network (GA2LEN) is a consortium of leading European research centers committed to establish a European research area of excellence in the field of allergy and asthma. The network intends to harmonize diagnostic and therapeutic procedures, accelerate the application of research results to clinical practice, patients’ needs and policy development, as well as to promote training and integration between public and private sectors. One of the work packages within GA2LEN project was designed to identify all European birth cohorts (started between 1985 and 2004) on asthma and atopic diseases, to create a common database of the different study characteristics which would allow comparison of study methods including design and assessment of outcome as well as exposure parameters.

4.9. Epidemiological studies of asthma in R. Macedonia

An epidemiological survey of adult asthma in R. Macedonia was carried out in 1995 by the Institute of Occupational Health, Skopje in collaboration with Occupational Health Services in R. Macedonia. The polycentric study including 556 randomly selected adults (302 men and 254 women, aged 18-74) from 11 centers (Skopje, Kumanovo, Tetovo,
Shtip, Veles, Kichevo, Kavadarcı, Prilep, Struga, Ohrid, and Bitola) was performed. Evaluation of the examined subjects included a questionnaire for respiratory and allergic symptoms, lung function testing, skin prick tests to 11 common aeroallergens, and acetyl choline challenge by indications.

The most important data obtained from the survey included:

- Prevalence of asthma – 3.2%;
- Non-significant sex distribution of the disease;
- Higher asthma prevalence in the older age groups;
- Atopy detected in 72.2% of the subjects with asthma;
- Mite sensitization was the most important allergen in the subjects with allergic asthma (61.1%);
- Prevalence of active smokers in the subjects with asthma – 38.8%.

Several surveys of occupational asthma in certain industries in R. Macedonia were also carried out by the Institute of Occupational Health, Skopje. The data obtained indicated prevalence of occupational asthma of 1.6% among herbal tea processors, 5.2% among grain workers, 5.7% among rice workers, and 6.2% among tanners.

Epidemiological survey of asthma including school children (aged 7 to 18) from Skopje, carried out in 1993, showed prevalence of asthma of 2.75%. The data obtained in the Macedonian part of the third phase of the ISAAC (December 2001-March 2002) with school children from Skopje aged 13-14, showed prevalence of asthma ever and wheezing in the last 12 months of 1.7% and 8.8%, respectively.

4.10. Results from our epidemiological survey of asthma in R. Macedonia

The present survey of adult asthma was carried out as a continuum of its epidemiological evaluation in R. Macedonia. The survey was performed according to the ECRHS protocol.

A cross-sectional survey included subjects aged 20-44 (368 subjects, 138 men and 230 women) that was about one third from the subjects included in the Project (1121 subjects) (Figure 116).
In the first phase (February - June 2002) all examined subjects underwent completion of a questionnaire and skin prick tests (SPT) to common aeroallergens. An interviewer-led questionnaire included the questions from the ECRHS screening questionnaire, as well as the questions about family history of asthma and allergic diseases, current smoking and smoking history, environmental and workplace exposure, and medication use. The battery of allergens for the SPT contained 13 commercial allergen extracts (tree pollen, grass pollen, mugwort, goosefoot, plantain, ragweed, Penicillium notatum, Alternaria alternata, Dermatophagoides pteronyssinus, cockroach, cat fur, dog hair, and feathers mixed) selected as a result of a 3-year aeropalinological follow-up.

In the second phase (October - November 2003) the examinees with symptoms suggestive for asthma underwent spirometry, including vital capacity (VC), forced expiratory volume in one second (FEV1), and mean expiratory flow at 75%, 50%, and 25% of VC (MEF75, MEF50, and MEF25, respectively), and histamine challenge. Histamine challenge was considered positive if provocative concentration equal or less than 4 mg/mL caused a 20% fall of FEV1 (PC20 ≤ 4 mg/mL). In the subjects with asthma-suggested symptoms and reduced lung function bronchodilator test with inhaled salbutamol was performed. The bronchodilator test was considered positive if the increase of FEV1 15 minutes after salbutamol application was equal or more than 12% of the baseline value. The symptomatic subjects with positive histamine challenge or positive bronchodilator test were considered having asthma.

The data obtained were statistically processed using the Statistical Package for the Social Sciences (SPSS) Release 11.0.

4.10.1. Prevalence of respiratory symptoms and asthma

The prevalence of respiratory symptoms in the last 12 months, wheezing, wheezing with dyspnea (W/D 12), asthma attacks, and use of asthma medications was 22%, 12.2%,
6.8%, 4.1%, and 2.2%, respectively. Positive histamine challenge was obtained in 4.9%, positive bronchodilator test in the subjects with reduced lung function in 0.5%. The prevalence of asthma was 5.4% (Figure 117 and 118).

**Figure 117.** Prevalence of asthma symptoms, asthma medications use, and asthma in examined subjects

The prevalence of asthma was within the range of its prevalence in the Central and South Europe countries. It was higher than the asthma prevalence in Asia and Africa, and lower than in English speaking (Anglo-Saxon) countries (Table 14).
<table>
<thead>
<tr>
<th>Country</th>
<th>Asthma prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Algeria</td>
<td>3.0%</td>
</tr>
<tr>
<td>India</td>
<td>3.5%</td>
</tr>
<tr>
<td>Greece</td>
<td>2.0 - 4.5%</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>4.7%</td>
</tr>
<tr>
<td>Italy</td>
<td>3.3 - 5.1%</td>
</tr>
<tr>
<td>Macedonia</td>
<td>5.4%</td>
</tr>
<tr>
<td>Portugal</td>
<td>4.3 - 6.0%</td>
</tr>
<tr>
<td>Spain</td>
<td>2.1 - 6.3%</td>
</tr>
<tr>
<td>USA</td>
<td>6.1 - 10.2%</td>
</tr>
<tr>
<td>Sweden</td>
<td>5.8 - 10.8%</td>
</tr>
<tr>
<td>New Zealand</td>
<td>8.0 - 12.5%</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>7.5 - 15.0%</td>
</tr>
</tbody>
</table>

**Table 14.** Asthma prevalence in the age group 20-44 in the certain countries

The prevalence of wheezing, wheezing with dyspnea, asthma attacks, and asthma medication use in the last 12 months was also similar to its prevalence in the Central and South Europe countries, two to threefold lower than in the Anglo-Saxon countries.

The use of asthma medications (relievers and/or controllers) in the last 12 months was reported by 2.2% of the examined subjects (39% of the subjects with asthma). The asthma medications use among subjects with asthma varied from 30% in Estonia to 85% in the United Kingdom (Figure 119).

The ICS use was reported by 20% of the subjects with asthma. Its use in the European countries varied from 17% in Italy to 49% in the United Kingdom. The use of the inhaled bronchodilators (salbutamol) was reported by 33.3% of the subjects with asthma, whereas the use of the oral bronchodilators (theophylline) by 14.8%. Data obtained suggested insufficient use of the ICS that was confirmed by high frequency of asthma symptoms reported by patients with asthma (Figure 120).
The asthma prevalence in our study was higher than its prevalence in the study carried out in 1995 (5.4% vs. 3.2%) (Figure 106). It has to be mentioned that the survey carried out in 1995 included subjects aged 18 to 74 (Figure 121).

The increasing prevalence of asthma has been reported by a number of regional and national studies in the last decades. The prevalence of asthma in the USA has increased for over 60% in the last 20 years. According to the UCB data, the prevalence of asthma in the West European countries doubles every 10 years. Increasing prevalence of asthma is also registered in the countries of Asia, Africa, Central and South America. Such increase, registered in a too short time period could not be explained by genetic factors and must, therefore, be related to environmental factors such as outdoor and indoor air pollution, diet, lifestyle, etc.
4.10.2. Sex distribution

We found non-significantly higher asthma prevalence of asthma in males (6.4 vs. 4.9%) (Figure 122).

Figure 122. Sex distribution of asthma

Data from a number of studies indicate sex difference of the prevalence of asthma and bronchial hyperresponsiveness. The prevalence of bronchial hyperresponsiveness in childhood is higher in boys, in the middle age it is higher in women, while in the elderly it is similar in both sexes. On the other hand, according to data from the ECRHS the prevalence of sensitization to common aeroallergens is higher in men that is consistent with the results of our study.

4.10.3. Prevalence of asthma in certain centers

Asthma prevalence varied from 3.3% in Dojran, 4% in Pehchevo, 4.8% in Prilep, 5.9% in Ohrid and Debar to 6.3% in Skopje (Figure 123).

Figure 123. Prevalence of asthma in certain centers
The highest asthma prevalence among examined subjects in Skopje, the capital of R. Macedonia, could be explained by characteristics of the lifestyle and high concentrations of air pollutants from industry and traffic. Table 15 shows data from the Republic Institute for Health Protection, Skopje about concentration of the air pollutants in the area of Skopje in 2003.

<table>
<thead>
<tr>
<th>Air pollutant</th>
<th>Number of checking points</th>
<th>Number of samples</th>
<th>Mean conc.</th>
<th>Min - max concentration</th>
<th>MPL*</th>
<th>Number of samples with level over MPL*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air sediment (mg/m²)</td>
<td>30</td>
<td>338</td>
<td>182,1</td>
<td>32,1 - 707,2</td>
<td>300,0</td>
<td>42</td>
</tr>
<tr>
<td>CO (mg/m³)</td>
<td>4</td>
<td>168</td>
<td>3,5</td>
<td>0,2-13,8</td>
<td>3</td>
<td>56</td>
</tr>
<tr>
<td>SO₂ (mg/m³)</td>
<td>7</td>
<td>2485</td>
<td>0,0166</td>
<td>0 - 0,2649</td>
<td>0,150</td>
<td>4</td>
</tr>
<tr>
<td>Smoke (mg/m³)</td>
<td>7</td>
<td>2506</td>
<td>0,0205</td>
<td>0,0006-0,2550</td>
<td>0,050</td>
<td>219</td>
</tr>
</tbody>
</table>

*MPL: Maximal Permitted Level

Table 15. Concentration of the air pollutants in the area of Skopje in 2003

The prevalence of asthma in Skopje was within the range of its prevalence in the centers of Central and South Europe (Table 16).

<table>
<thead>
<tr>
<th>Center</th>
<th>Prevalence of asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Algeria</td>
<td>3.0%</td>
</tr>
<tr>
<td>Bombay</td>
<td>3.5%</td>
</tr>
<tr>
<td>Turin</td>
<td>4.5%</td>
</tr>
<tr>
<td>Basel</td>
<td>5.4%</td>
</tr>
<tr>
<td>Bordeaux</td>
<td>5.5%</td>
</tr>
<tr>
<td>Coimbra</td>
<td>6.0%</td>
</tr>
<tr>
<td>Skopje</td>
<td>6.3%</td>
</tr>
<tr>
<td>Huelva</td>
<td>6.3%</td>
</tr>
<tr>
<td>Portland</td>
<td>7.1%</td>
</tr>
<tr>
<td>Stockholm</td>
<td>7.6%</td>
</tr>
<tr>
<td>Cambridge</td>
<td>8.4%</td>
</tr>
<tr>
<td>Auckland</td>
<td>10.1%</td>
</tr>
<tr>
<td>Wellington</td>
<td>11.3%</td>
</tr>
<tr>
<td>Melbourne</td>
<td>11.9%</td>
</tr>
</tbody>
</table>

Table 16. Prevalence of asthma in certain cities
4.10.4. Distribution by atopic status and sensitization to common aeroallergens

Allergic asthma was registered in 60% and nonallergic asthma was registered in 40% of the subjects with asthma (Figure 124). The results obtained are in agreement with the results from the ECRHS, as well as to the results from our previous study (1995). The prevalence of atopy was higher in men, in all examined subjects, as well as in subjects with asthma.

![Distribution of the subjects with asthma by atopic status](image1)

**Figure 124.** Distribution of the subjects with asthma by atopic status

*Dermatophagoides pteronyssinus* and goosefoot (58.3%), followed by mugwort (50%), plantain (33.3%) and *Alternaria* (25%) were the most important individual air allergens in the subjects with allergic asthma (Figure 125).

![Prevalence of the sensitization to individual air allergens](image2)

**Figure 125.** Prevalence of the sensitization to individual air allergens in the subjects with allergic asthma

Similar prevalence of mite sensitization (61.1%) was registered in our previous study (1995), as well as in 16 centers where the ECRHS was carried out. Our data confirmed the role of weed pollen and *Alternaria* as potent allergens. We found lower prevalence of the subjects sensitized to pet allergens compared to the ECRHS data that was probably due to the lower frequency of pet ownership in R. Macedonia than in the West European countries.
4.10.5. Allergic Rhinitis and its Impact to Asthma (ARIA)

In the majority of the subjects with asthma (70.4%), concurrent rhinitis was registered. Rhinitis accompanied both allergic and nonallergic asthma. The prevalence of asthma with rhinitis was 3.8% (Figure 126).

Data from our study showed that in the majority of the subjects with asthma (71.0%) rhinitis preceded asthma, in 21.0% occurrence of asthma and rhinitis at the same time was registered, and in 8.0% rhinitis developed after the asthma occurrence (Figure 127).

Data from our study that had investigated the same association carried out in 2002 indicated prevalence of rhinitis in patients with allergic and nonallergic asthma of 73.1% and 63.4%, respectively. Results reported in the consulted studies showed prevalence of rhinitis in patients with asthma of 50 to 90%, and prevalence of asthma in patients with rhinitis of 20 to 40%.

The association between upper and lower respiratory airways has been confirmed by numerous epidemiological studies. Cross-sectional studies have shown that the coexistence
of rhinitis and asthma is quite common and longitudinal studies have shown that subjects with both allergic and nonallergic rhinitis frequently develop asthma, and that rhinitis usually precedes asthma. Many clinical observations have also shown the occurrence of BHR in rhinitics as well as the comorbid role of sinusitis in asthma. Furthermore, it has been repeatedly shown, that an effective treatment of rhinitis have a beneficial effect on bronchial symptoms as well as on the occurrence of respiratory infections.

The WHO experts team in 2001 published an extensive position paper devoted to the relationship between rhinitis and asthma and its therapeutic implications, called Allergic Rhinitis and its Impact on Asthma (ARIA). On the other hand, the acronym CARAS (Combined Allergic Rhinitis and Asthma Syndrome) has been used by World Allergy Organization (WAO) for indicating the concept “one airway, one disease”. At present, the hypothesis of the unity of the airways is supported by many data and new therapeutic rationales are put forth.

4.10.6. Association with endogenous factors

We found significant association between asthma and positive family history of asthma and atopy. The prevalence of asthma among atopics was 13.2%, whereas atopy was detected in 60% of the patients with asthma. Presence of asthma in the first degree relatives (parents and siblings) was reported in 54.8% of the subjects with asthma (Figure 128).

Data from the ECRHS indicate close relation between asthma and parental asthma, and even more so if both parents have asthma. The odds ratios for asthma in subjects with maternal and paternal asthma were 3.2 and 2.9, respectively. If both parents had asthma, the odds ratio for asthma increased to 7.0.

We found no significant association between asthma and sex, family history of allergic diseases, and family history of allergic rhinitis. Association between asthma and ethnic group was also nonsignificant. On the other hand, the study carried out in Israel as a part
of the ISAAC showed that in school-children aged 13-14, the prevalence of “current asthma” and “ever asthma” was higher among Jews than among Arabs. Epidemiological investigations of childhood asthma in the USA showed higher prevalence of asthma in blacks than in whites (9.1% vs. 6.4%). Possible explanation for ethnic differences in asthma prevalence might be a genetic predisposition, poor access to the care system, difference in family structures, and associated social risk factors.

### 4.10.7. Association with environmental factors

We found no significant association between asthma and urban residence, active smoking, exposure to traffic pollution, as well as with housing conditions such as heating conditions (exposure to combustion products), high indoor humidity, green plants outdoors (exposure to pollens), and pets ownership (Figure 129). We found significant joint effect of urban residence, active smoking, exposure to traffic pollution, and green plants outdoors ($P < 0.05$).

![Figure 129](image.png)

**Figure 129.** Prevalence of asthma in the subjects living in urban zone, active smokers, subjects exposed to traffic pollution, pet owners, and subjects having green plants outdoors.

The role of outdoor and indoor air pollution in asthma development is complex and still unclear. The highest increase of asthma prevalence in the West European countries occurred in the period characterized by reduced levels of the conventional outdoor air pollutants (carbon monoxide, sulfur dioxide) and increased levels of nitric oxides, diesel exhaust, and ozone. At the same time, a number of studies emphasize the importance of indoor air pollutants in asthma development. However, future prospective studies will further clarify the role of certain exposures for individuals with different genetic predisposition.

### 4.10.8. Association with workplace exposure

Worsening of the symptoms at the workplace was reported by 24.7% of the subjects with asthma. The prevalence of work-related asthma (WRA) was 1.4% (Figure 130).
We found nonsignificant association between asthma and certain workplace hazards, such as exposure to dusts, chemical agents, high air humidity and temperature. The joint effect of these factors on asthma development was also nonsignificant (Figure 131).

Prevalence of asthma in office workers was 4.8%, whereas its prevalence in workers with specific exposure at the workplace was 5.8% (Figure 132).
The highest prevalence of asthma among exposed workers was detected in pharmaceutical industry workers (8.7%), textile workers (7.2%), and chemical industry workers (6.2%) (Figure 133).

Many studies have shown the relationship between workplace exposure and asthma. WRA, that includes occupational asthma (OA) and work-aggravated asthma, is a growing problem, becoming the most common work-related respiratory disease in many countries. The prevalence of WRA ranges from 10 to 25% of the cases with adult asthma. In the Norwegian general population, the prevalence was 0.9%, and it increased to 28.0% considering only subjects with asthma that is similar to the results of our study. The risk of asthma attributable to occupational exposure was studied in analyses of the Spanish ECRHS data set and the data set from New Zealand. The proportion of asthma attributed to occupational exposure was estimated to be 5-7% in Spain and 2-3% in New Zealand. In both these investigations, a higher risk for asthma was found in farmers, painters, plastic...
workers, cleaners, and agricultural workers. After creating a job exposure matrix, asthma found to be associated with high dose exposure to biological and mineral dust, as well as exposure to gases and fumes.

4.10.9. Conclusions

1. Prevalence of asthma in the age group 20-44 was 5.4%, 6.4% in males and 4.9% in females, which translated to approximately 100,000 subjects with asthma in R. Macedonia. The asthma prevalence in R. Macedonia was within the range of the South European countries, such as Italy, Greece, Bulgaria, Spain, and Portugal.
2. The highest asthma prevalence was registered in Skopje (6.3%), and the lowest one in Dojrjan (3.3%). The asthma prevalence in Skopje was within the range of South and Central European centers, such as Turin, Basel, Bordeaux, Coimbra, and Huelva.
3. This study has indicated higher asthma prevalence than it has been detected in our study carried out in 1995 (5.4% vs. 3.2%). Increasing prevalence of asthma is a global problem, and it is registered in a number of studies undertaken all over the world.
4. We noted relatively low use of anti-inflammatory medications among asthma patients, approximately threefold lower than its use among subjects with asthma in the United Kingdom.
5. Allergic asthma was detected in 60%, and nonallergic asthma in 40% of the subjects with asthma.
6. Sensitization to *Dermatophagoides pteronyssinus* and goosefoot pollen were the most important common allergens in the subjects with allergic asthma. Mite sensitization was the most important common allergen in our previous study (1995), as well as in a number of studies from different countries.
7. We found asthma / rhinitis association in 70% of the subjects with asthma that confirmed “the united airway disease” concept. In the majority of subjects with asthma accompanied by rhinitis, asthma development was preceded by rhinitis.
8. We found significant association of asthma with atopy and family history of asthma. Allergic rhinitis was detected in about half of the atopic subjects and asthma was detected in about 15% of the atopic subjects. Paternal asthma was reported by half of the subjects with asthma. Association between asthma and other endogenous factors, such as sex, ethnic group, and family history of allergic diseases, was nonsignificant.
9. Association between asthma and individual exogenous factors was nonsignificant. We found significant joint effect of some environmental factors (urban residence, active smoking, exposure to traffic pollution, and green plants outdoors) on asthma development.
10. Prevalence of WRA was 1.4%, (24.7% of the subjects with asthma). Asthma prevalence was higher in exposed workers than in office workers. The highest prevalence among workers with specific exposure at the workplace was found in pharmaceutical, textile and chemical industry workers.
4.10.10. References:


5.0. Atopic dermatitis - ICD 10; L20.8-L20.9

5.1. Definition

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by dry skin, recurrent intense pruritus and a typically age-related distribution and skin morphology. AD, allergic rhinoconjunctivitis, and asthma are referred to as atopic diseases.

According to the revised nomenclature of the allergic disease 2001, the current term for eczematous hypersensitivity reactions in the skin is atopic eczema/dermatitis syndrome (AEDS). Other synonyms, such as exudative eczematoïd, endogenous eczema, eczema flexuratum, diathetic prurigo, prurigo Besnier, neurodermatitis, asthma-eczema, hay fever-eczema, and many others that reflect insufficient knowledge about the disease pathogenesis were considered as not suitable for international use. However, during a transition period, it may be useful to highlight the well-accepted view that AD is not one, single disease but rather a group of several diseases with certain clinical characteristics in common.

5.2. Pathogenesis

AD is a genetic predisposed disease caused by immunological mechanisms in which many other factors play a role with intensity that varies in certain individuals, as well as in the same individual in different periods of life. However, the importance of the immunological mechanisms in AD pathogenesis remains still unclear.

Allergic AD (AEDS) is a form of AD caused by immunological mechanisms that can be demonstrated. IgE-associated AD is the only immunologically well-defined subgroup of allergic AD, in which the clinical selection is based on Hanifin & Rajka criterion, “family history of or simultaneous occurrence of symptoms of atopy”. Since less is known about the precise role of IgE antibodies initiating the disease in comparison with other allergic disease, the term associated is used instead of the term mediated. Another subgroup of allergic AD, named T-cell-associated AD, seems to include cell-mediated forms. This form is characterized by positive atopy patch test to aero- and food allergens or allergen-specific T cells in the peripheral blood or in skin biopsies, but in absence of IgE sensitization.

The form of AD in which immunological mechanisms can not be demonstrated is referred to as nonallergic AD. This term should replace the term intrinsic/cryptogenic AD.

Genetic predisposition seems to be the main individual risk factor for AD development. Results from the studies indicate significantly higher risk (OD varies from 3.0 to 6.0) for AD in children with positive parental history of AD. Exposure to aero- and food allergens, bacterial and viral superinfections, climate factors (fall-winter season, pollen season), and emotional factors are considered as environmental factors that could play a role in AD development and severity.
The role of AD as the first step of the allergic march, i.e. its role as a predictor of development of the other allergic diseases such as allergic rhinoconjunctivitis and asthma, has a special importance. Results of the studies that investigated the efficacy of the treatment of AD in the prevention of the other allergic diseases are controversial.

5.3. Clinical manifestations

Atopic dermatitis usually occurs in the early childhood. In about 60% of the cases it occurs in infancy, and in about 85% in the first five years. In about 70% of the children with AD symptoms of the disease improve at the age of puberty.

The disease is characterized by chronic course with exacerbations of variable severity. A key feature of AD is severe dryness of the skin typically accompanied by intense pruritus and inflammation that is triggered by a number of factors and conditions.

The morphology of the skin lesions and its distribution is variable in different periods of the life. In infancy predominate exudative eczematous lesions localized on the face, gluteal region, and on the extremities. (Figure 134).

Figure 134. AD in an infant – exudative eczematous lesions with typical distribution


Lichenified papules usually localized on the antecubital and popliteal fossae, accompanied by severe pruritus, are typical skin lesions in the period of childhood. Dominant skin lesion in adults is a prurigo-papule with similar distribution (Figure 135).
5.4. Diagnosis

As there is a lack of the specific clinical or laboratory markers of the disease, the diagnosis of AD is based on a combination of clinical features. Rajka & Hanifin determined major and minor features for the diagnosis of AD. The diagnosis of AD is confirmed in cases where at least positive three major and three minor features exist.

The major features of AD include:

- **intense itching**,  
- **characteristic skin rash in locations typical for the disease**,  
- **chronic or repeatedly occuring symptoms**,  
- **personal or family history of atopic disorders (eczema, hay fever, asthma)**.

The minor diagnostic features of AD include: **early age of onset**, **dry skin that may also have patchy scales or rough bumps**, **positive skin prick tests to aero- and food allergens**, **increased total IgE**, **hand or foot involvement**, **inflammation around the lips**, **nipple eczema**, and **susceptibility to skin infections**.

The diagnostic work-up includes assessment of the disease severity and investigation of exacerbating factors. On the basis of severity, AD is subdivided into mild, moderate and severe. The investigation of exacerbating factors involves specific skin and blood tests, and challenge tests. Both SPT and measurement of specific IgE can be used for sensitization to a food. However, standardized food challenges provide the most accurate diagnostic tool. Sensitization to inhalant allergens can be detected by means of SPT (if the skin is free from eczema) or by measurement of specific IgE. Skin biopsies are not essential for the diagnosis of AD but might be needed to exclude other diagnoses, particularly in adults.
Atopy patch test (APT), an epicutaneous patch test with type 1 allergens known to elicit IgE-mediated reactions and the evaluation of eczematous skin lesions after 24-72 h can be used as a diagnostic tool in characterizing patients with aeroallergen- and food-triggered AD. Allergen specific T cells cloned from the APT biopsies showed a characteristic Th 2 secretion pattern initially, whereas after 48 h a Th 1 pattern was predominant. The same pattern is also found in the chronic lesions of AD. It has also been shown that APT reactions to aeroallergens are associated with specific T-cell responses to the corresponding allergen in the circulation. In the EAACI/GA2LEN Position paper 2006 entitled “Present status of the atopy patch test”, indications for testing with APT, choice of allergens, test material and technique, and present knowledge on sensitivity and specificity are reviewed on the basis of available literature.

5.5. Management

The atopic dermatitis management includes non-pharmacological measures and medications use.

5.5.1. Non-pharmacological treatment

Non-pharmacological treatment should comprise optimal skin care, addressing the skin barrier defect with regular use of emollients and skin hydration, along with identification and avoidance of specific and nonspecific trigger factors. The main nonspecific triggers include contacts, such as clothing made from occluding or irritating synthetic or wool material, as well as inadequate soaps and hot water temperature during showering and bathing.

There is no universally recommended diet for patients with AD. Dietary restrictions should be recommended in cases of established diagnosis of food hypersensitivity. The positive effect of avoidance measures regarding inhalant allergens (dust mite, animal dander, and pollens) has been shown in various studies.

For optimal disease management, education of the patient and appropriate psychosocial support is needed. Orientation to occupations with lower exposure to allergens and irritants is also recommended.

5.5.2. Pharmacological treatment

Pharmacological treatment includes use of topical and systemic medications. Topical corticosteroids (TCS), topical calcineurin inhibitors (TCI), and topical antimicrobial therapy are the basis of the local AD treatment. Systemic treatment includes use of antihistamines, systemic corticosteroids, systemic antibiotics, cyclosporine A (CyA), azathioprine, and phototherapy (UV therapy). Until today, immunotherapy is not an established instrument for the treatment of AD.
The pharmacological AD treatment, on the basis of disease severity, includes multiple therapeutic agents in a step-wise fashion. According to the actual guidelines, mild to moderate AD should be treated with low-mid potency TCS and/or TCI, whereas the use of mid-high potency TCS and/or TCI is recommended in the treatment of moderate to severe AD. In cases of severe AD that cannot be controlled with topical treatment, systemic treatment options should be considered (i.e. CyA or UV therapy).

5.6. Epidemiological studies of atopic dermatitis

As there is no single marker of the disease, it is difficult to carry out epidemiological survey of AD. According to Schäfer “opinion of the experienced dermatologist is a gold standard in AD diagnosis”. Usually, children or children of certain age group are the target population of epidemiological observations of AD. The studies commonly are based on questionnaire that includes items about type and distribution of the skin lesions and duration and course of the disease, as well as about personal and family history of allergic diseases. A few studies are based on questionnaire with additional allergologic evaluation or reports of dermatologists.

The prevalence of AD in children, reported by epidemiological observations carried out in the 1990s, varies from 0.7% in Tanzania, 4% in Turkey, 5.8% in Italy, 3.9-6.3% in Czech Republic, 2.5-8.3% in Germany, up to 7% in Denmark, 9% in the USA, 10.4% in Australia and 20.2% in the UK. The studies carried out in the USA, the UK, Sweden and Swiss indicate increasing prevalence of AD in the last decades. The AD prevalence in children in the UK increased from 4.1% in 1964 to 10.2% in 1989.

Epidemiological studies emphasize higher AD prevalence in girls, in children from the urban areas with higher socioeconomic status, as well as the association between AD and family history of AD and other allergic diseases (allergic rhinoconjunctivitis and asthma).

Seasonal variations of the disease (worsening of the symptoms in the pollen season and in the fall-winter period) are also reported by many epidemiological studies of AD. Results of the studies that investigate association between AD and exposure to outdoor and indoor pollutants are controversial. Some studies indicate higher risk of AD in children with maternal smoking during pregnancy and exposure to environmental tobacco smoke (ETS) in childhood.

5.6.1. Results of our epidemiological study of AD in R. Macedonia

Epidemiological observation of AD in R. Macedonia was not conducted previously. The study we carried out included children aged 0 to 15 years. A questionnaire designed similar to the model of questionnaires used in the studies of AD performed in the West European countries.
The prevalence of AD among examined children was 3.8% (Figure 136). Similar prevalence of AD was detected in Mediterranean (Turkey, Italy) and Central European countries (Czech Republic, Germany). Higher prevalence of AD is registered in Scandinavian and English speaking countries that could be due to the interaction of genetic and environmental factors (lifestyle, diet, high proportion of childhood immunizations, low proportion of children with intestinal infections and infestations, and effects of the outdoor and indoor air pollutants in the urban areas).

**Figure 136.** Prevalence of AD in examined children

The prevalence of AD was nonsignificantly higher in girls (Figure 137) that is in compliance with the results of many epidemiological studies of AD. Schäfer has indicated that female sex is an independent risk factor for AD.

**Figure 137.** Sex distribution of AD in examined children

Results from many studies of AD reported that in about 70% of the cases the disease occurred in the first year of life. Our results showed higher prevalence of AD in the children aged less than 7 years (Figure 138).
5.6.2. Prevalence of AD in certain centers

The prevalence of AD among examined children varied from 1.8% in Dojran, 2.4% in Pehchevo, 2.9% in Debar, 3.1% in Ohrid, 3.3% in Skopje to 6.2% in Prilep (Figure 139).

5.6.3. Association between atopic dermatitis and other allergic entities

Seasonal worsening of the symptoms was reported by 60.0% of the children with AD (Figure 140).
Figure 10. Prevalence of AD in examined children with seasonal variations of the disease

We registered significant association between AD and allergic rhinitis \((P < 0.01)\) (Figure 124). Allergic rhinitis was present in 53.3% of the cases with AD. Association with other allergic entities was statistically nonsignificant.

Figure 11. Association between AD and allergic rhinitis

Results of our study confirm the role of heredity in AD development. Positive family history of allergic diseases was reported by 73.0% of the cases with AD \((P < 0.001)\) (Figure 142).

Figure 12. Association between AD and family history of allergic diseases
### 5.6.4. Association between AD and lifestyle

Results of the actual study indicated significantly higher prevalence of AD among children from urban in respect to children from rural areas ($P < 0.05$) (Figure 143) that is complementary to the results from many studies carried out in the West European countries and in the USA.

**Figure 143.** Association between AD and living in urban area

Statistical analyses showed no statistically significant association between AD and birth weight and type of feeding in infancy. However, AD is more frequent among children with birth weight less than 3000 g and bottle fed children (Figure 144).

**Figure 144.** Presence of AD among children with low birth weight, complementary feeding in the period of infancy, and breast-feeding shorter than 6 months

### 5.6.5. Association with air pollution

Results from several studies indicated significant association between AD and maternal smoking during pregnancy and exposure to ETS during childhood. Such associations were not confirmed in our study (Figure 145).
5.7. Conclusions

1. Prevalence of AD among examined children was 3.8%. AD was detected more frequently among examined girls (4.1%) than among examined boys (3.4%). The highest prevalence was detected in Prilep and the lowest one in Dojran.
2. Seasonal worsening of the disease was registered in 60.0% of the children with AD.
3. AD was significantly associated with family history of allergic diseases. In over half of the cases with AD, the disease was accompanied by allergic rhinitis.
4. Association between AD and hypersensitivity to drug and food hypersensitivity and insect sting allergy was not statistically significant.
5. Prevalence of AD was significantly higher in the children with urban residence than in the children from rural areas.
6. AD was not significantly associated with low birth weight and type of feeding in infancy. AD was also nonsignificantly associated with maternal smoking during pregnancy and exposure to ETS.

5.8. References:


6.0. Drug hypersensitivity - ICD - 10; T 88.7

6.1. Definition

Drug hypersensitivity is defined as an occurrence of objective and reproducible symptoms and/or signs initiated by exposure to a drug at dose tolerated by other subjects (T 88.7). When immunological mechanisms are shown, either antibody or cell mediated, the adverse reaction to drug should be referred to as drug allergy. By adding the adjective immediate, late or delayed, we can both describe the onset of symptoms and indicate probable mediating mechanisms. If we wish to highlight the role of IgE antibody in the drug allergy, it may be called IgE-mediated drug allergy. All other reactions to drugs, caused by identifiable or unknown mechanisms, should be referred to as nonallergic drug hypersensitivity.

6.2. Pathogenesis

The underlying immunological mechanisms that cause drug allergy include all four types described by Gell and Coombs (Table 17). Some allergic reactions to drugs may include mechanisms of two types (e.g. β-lactames, sulphonamides). On the other hand, the same drug in certain subjects may cause immunological reactions of different types (e.g. benzylpenicillin may cause reaction type I, II, and IV) or may cause immunological and non-immunological reactions (e.g. angiotensin-converting enzyme inhibitors).

<table>
<thead>
<tr>
<th>Type</th>
<th>Effector mechanism</th>
<th>Clinical manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>IgE, mast cells and basophils</td>
<td>Anaphylactic shock, Urticaria/angioedema, Bronchospasm</td>
</tr>
<tr>
<td>II</td>
<td>IgG, IgM, Complement and/or phagocytosis</td>
<td>Cytopenia, Glomerulonephritis</td>
</tr>
<tr>
<td>III</td>
<td>Precipitins, IgG, IgM and Complement</td>
<td>Serum sickness, Glomerulonephritis, Vasculitis</td>
</tr>
<tr>
<td>IV</td>
<td>T-lymphocytes</td>
<td>Contact dermatitis, Maculopapular rash</td>
</tr>
</tbody>
</table>

Table 17. Immunological reactions according to Gell and Coombs

Nonallergic hypersensitive reactions mimic allergic symptoms but they do not have an immunological mechanism. The etiologies of these reactions include different mechanisms (Table 18).
Mechanism | Drug
---|---
Nonspecific histamine release | Opiates, Radiocontrast media, Vancomycin
Bradykinin accumulation | Angiotensin-converting enzyme (ACE) inhibitors
Complement activation | Radiocontrast media, Protamine
Induction of leukotriene synthesis | Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs)
Bronchospasm | Sulfur dioxide released by drugs containing sulfites

Table 18. Mechanisms of nonallergic drug hypersensitivity

6.3. Clinical manifestations

Drug hypersensitivity is a common and complicated problem in clinical practice. The clinical picture of drug hypersensitivity is very heterogeneous, encompassing such distinct diseases as morbilliform or bullous exanthema, urticaria, anaphylaxis, blood cell dyscrasia, fever, interstitial lung disease, hepatitis, nephritis, and various forms of autoimmune diseases.

6.4. Diagnosis

Diagnosis of the drug allergy is based on history, clinical manifestations, *in vivo* and *in vitro* allergological evaluation, and provocation tests. The available clinical and laboratory tools at our disposal are few and have not all been fully evaluated.

Under the aegis of the European Academy of Allergy and Clinical Immunology (EAACI), the European Network of Drug Allergy (ENDA) is working for the establishment of pragmatic and standardized clinical tools for daily practice. Members of ENDA have developed a questionnaire that enables a uniform format for data collection and harmonization of the drug hypersensitivity diagnostic procedures. It also includes some procedures such as skin tests, provocation tests, and biological tests.

6.4.1 Clinical history

Clinical history includes symptomatology, chronology of the symptoms (previous exposure, delay between the last dose and onset of the symptoms, effect of stopping treatment), use of other medications (at the time of reaction and other affiliated drugs
used since), as well as the medical background of the subject (information about previous allergies associated with medications or not).

6.4.2. Skin prick tests and intradermal tests

Skin prick tests and intradermal tests are particularly important in order to demonstrate an IgE-mediated reactions. The diagnostic value of skin tests is not fully evaluated. In general, there are no reliable skin tests procedures for the diagnosis of drug hypersensitivity and test concentrations are poorly validated for most drugs.

Skin tests should be performed 4-6 weeks after the reaction. The sensitivity of skin tests varies depending on the drug - from excellent (penicillins, myorelaxants, heterologous sera, and enzymes), through satisfactory (vaccines, hormones, protamine, and opiates) to poor or unknown (local anesthetics, paracetamol, sulfonamides, iodine radiocontrast media, aspirin and other nonsteroidal anti-inflammatory drugs - NSAIDs, etc).

6.4.3. Dose-provocation tests (DPT)

**Dose-provocation tests (DPT)** have the highest sensitivity, but can only be performed under the most rigorous conditions and therefore are restricted to certain specialist centers. These tests are particularly needed for aspirin and other NSAIDs, local anesthetics, antibiotics other than penicillins or penicillins when skin tests are negative.

6.4.4. In vitro tests

Laboratory tests are useful in the diagnosis of drug hypersensitivity but, similar to skin tests, these tests are not fully validated.

The demonstration of drug-specific IgE (by UniCap or RAST method) to penicillins, myorelaxants or tetanus toxoid, in conjunction with positive anamnesis suggests the IgE-mediated reaction.

Increased concentration of histamine in the blood while receiving certain drug correlates with skin tests and specific IgE for myorelaxants.

The test of basophil degranulation in the presence of incriminated drug is not recommended due to the low sensitivity.

For drug-induced type II and III reactions, a Coomb’s test, in vitro hemolysis test, determination of complement factors and circulating immune complexes can be performed.
6.5. Prevention

6.5.1. Primary prevention

Measures of primary prevention include identification of the risk factors for development of drug hypersensitivity, such as presence of other allergic diseases, liver disorders, and chronic disease that requires use of several drugs. Primary prevention also includes knowledge about adverse effects of the administered drug/drugs and avoidance of polypharmacy.

6.5.2. Secondary prevention

Secondary prevention includes measures in the subjects with registered drug hypersensitivity, such as discontinuation of drug, as well as avoidance of the administration of medications with known cross-reactivity with incriminated drug. Registration of the hypersensitive reaction to certain drug is recommended in all subjects in which drug hypersensitivity has occured.

6.6. Epidemiological studies of drug hypersensitivity

A number of studies of drug hypersensitivity in the USA and the West European countries in the last decades has been conducted. The majority of these studies has been based on a questionnaire that included items about hypersensitive reaction to certain drug and its clinical manifestations. Only in a few studies allergological evaluation has been added to the completion of the questionnaire.

It is estimated that adverse reactions to drugs occur in about 25% of the treated subjects. The prevalence of drug allergy is estimated to 5-10% and skin changes are the most frequent clinical manifestations (70-80%). The prevalence of drug hypersensitivity in hospitalized patients in the USA and France was found to be 5% and 2-3%, respectively. The prevalence of self-reported drug hypersensitivity that is not confirmed by allergological testing is about 15%, being more frequent among women.

6.6.1. Penicillins

Hypersensitivity to penicillins is the most frequent type of drug hypersensitivity. It occurs in about 2.5% of the hospitalized patients in the USA. Hypersensitivity to penicillins is responsible for 400 deaths from anaphylactic shock per year in the USA. The studies carried out in the USA reported that in only 10-20% of the subjects with history for penicillins hypersensitivity it was demonstrated by in vivo or in vitro tests.
6.6.2. Antibiotics other than penicillins and sulphonamides

Prevalence of the reactions of hypersensitivity to other antibiotics is much lower in respect to penicillins. Hypersensitivity to sulphonamides occurs in 3-6%, to tetracyclines in 0.1 - 0.5%, to macrolydes in 0.5%, and to gentamicin in 0.1 - 2% of the treated subjects. Different immunological and nonimmunological mechanisms could be involved in the pathogenesis of hypersensitive reactions to these medications.

6.6.3. Aspirin and other NSAIDs

Aspirin causes hypersensitive reactions, commonly manifested by skin rash, angioedema and/or bronchospasm, in 0.3 -0.5% of the general population, in 1.4% of the subjects with allergic rhinitis, in about 4% of the subjects with asthma, in 10-15% of the subjects with sinonasal polyposis, as well as in about 20% of the subjects with chronic urticaria. Similar reactions could occur in the course of use of other NSAIDs affecting usually middle aged women. The mechanism of aspirin-induced hypersensitivity is non-immunological and may involve increased leukotriene synthesis, higher sensitivity of the leukotriene receptors, disturbances in synthesis of the platelet mediators, etc.

In some subjects that have used aspirin, antibodies to aspirin may be detected in the blood, but their appearance and titre do not correlate with clinical manifestations of aspirin-induced hypersensitivity.

6.6.4. Myorelaxants

Myorelaxants may cause IgE-mediated reaction that usually occurs in women. The prevalence of allergic reactions to myorelaxants is about 1/4,500 general anesthesias. Fatal reactions occur in about 6% of the subjects with myorelaxants-induced allergy.

6.6.5. Local anesthetics

Local anesthetics may cause hypersensitive reactions, usually manifested by dizziness or collapse, in 2 - 3% of the subjects in which they are administered. The mechanism of these reactions is unknown.

6.6.6. ACE inhibitors

ACE inhibitors (usually enalapril) cause nonproductive cough (enalapril-induced cough) in about 10% of the treated subjects by bradykinin accumulation as underlying mechanism. ACE inhibitors may also cause IgE-mediated reaction manifested by angioedema.
6.7. Results of the actual study of drug hypersensitivity in R. Macedonia

The actual study is the first epidemiological observation of drug hypersensitivity in R. Macedonia. The study was based on a questionnaire designed according to the ENDA recommendations.

6.7.1. Prevalence of drug hypersensitivity

Prevalence of drug hypersensitivity in all examined subjects (both adults and children) was 10.5%, that is within range of the published data for self-reported drug hypersensitivity (Figure 146).

![Figure 146. Drug hypersensitivity in all examined subjects](image)

Similarly to the other allergic entities, the prevalence of drug hypersensitivity was not significantly higher in females (12.4% vs. 8.9%) (Figure 147).

![Figure 147. Sex distribution of drug hypersensitivity in all examined subjects](image)
6.7.2. Prevalence among examined subjects in certain centers

The highest prevalence of drug hypersensitivity was registered in Skopje (17.8%) and the lowest one in Dojran (3.1%). The prevalence of drug hypersensitivity in Prilep, Debar, Ohrid, and Pehchevo was 13.7%, 9.6%, 4.9%, and 4.2%, respectively (Figure 148).

![Figure 148. Prevalence of drug hypersensitivity among examined subjects in certain centers](image)

6.7.3. Age distribution

6.7.3.1. Prevalence of drug hypersensitivity in adults

Prevalence of drug hypersensitivity in adults was 11.2%. It was higher in women than in men (13.4% vs. 7.8%), but there was no statistical significance (Figure 149).

![Figure 149. Sex distribution of drug hypersensitivity in examined adults](image)

The highest prevalence of drug hypersensitivity in examined adults was registered in the age group 51-60 (14.7%), and the lowest one in the age group 21-30 (9.3%) (Figure 150).
6.7.3.1.1. Prevalence among examined adults in certain centers

The highest prevalence of drug hypersensitivity in adults was registered in Prilep (16.9%), and the lowest one in Dojran (4.3%). The prevalence of drug hypersensitivity in adults in Skopje was 8.0% (Figure 151).

6.7.3.1.2. Prevalence of hypersensitivity to certain drugs

Hypersensitivity to antibiotics was the most common type of drug hypersensitivity in the examined adults (73.9% of the adults with self-reported drug hypersensitivity). It was followed by hypersensitivity to NSAIDs (17.4%), to anesthetics (4.3%), and to other drugs (4.3%) (Figure 152).
Hypersensitivity to natural and synthetic penicillins was the most frequent type of drug hypersensitivity in the examined adults (6.8%). Literature data indicate prevalence of the self-reported hypersensitivity to penicillins of approximately 10%, but allergic background was demonstrated in only 10-20% of these subjects. Hypersensitivity to aspirin and affiliated drugs was reported by 0.6% of the examined adults (Figure 153). Consulted studies indicate prevalence of hypersensitivity to aspirin in the general population of 0.3–0.5%.

6.7.3.1.3. Clinical manifestations in the adults with drug hypersensitivity

As many studies have indicated, skin changes are the most common clinical manifestations of drug hypersensitivity. Our data also showed skin manifestations as the most common type of drug hypersensitivity in adults (skin rash was reported by 41.0% and angioedema by 23.0% of the adults with self-reported drug hypersensitivity), followed by dyspnea (18.7%) and collapse (15.6%) (Figure 154).
Figure 154. The most frequent clinical manifestations in the adults with drug hypersensitivity

6.7.3.2. Prevalence of drug hypersensitivity in children

The prevalence of drug hypersensitivity in children was 9.8%. It was slightly higher in boys (10.7%) than in girls (8.9%) (Figure 155).

Figure 155. Prevalence and sex distribution of drug hypersensitivity in examined children

Similarly to the food hypersensitivity, prevalence of drug hypersensitivity in examined children was higher in the age group 0-6 than in the age group 7-15 years (11.6% vs. 6.7%) (Figure 156).
6.7.3.2.1. Prevalence among examined children in certain centers

The highest prevalence of drug hypersensitivity in the examined children was registered in Skopje (23.5%). Drug hypersensitivity was not registered in the examined children in Pehchevo (Figure 157).

6.7.3.2.2. Hypersensitivity to certain drugs

The most common type of drug hypersensitivity in the examined children was hypersensitivity to antibiotics. Hypersensitivity to natural penicillins was reported by 48.2%, semisynthetic penicillins by 37.9%, and sulphonamides by 13.7% of the children with drug hypersensitivity (Figure 158). Prevalence of hypersensitivity to penicillins in the examined children was 8.4%.
6.7.3.2.3. Most common clinical manifestations

The most common clinical manifestations in the children with drug hypersensitivity were skin manifestations (70%), followed by diarrhea (18.3%) and other manifestations (11.7%) (Figure 159).

6.7.3.2.4. Association of drug hypersensitivity with other allergic diseases

Drug hypersensitivity in the examined adults was closely related to food hypersensitivity ($P < 0.05$). Drug hypersensitivity was reported by 11.1% of the examined adults with food hypersensitivity, whereas it was present in 4.1% of the examined adults that did not report food hypersensitivity (Figure 160). Association between drug hypersensitivity with other allergic entities was nonsignificant. Nonsignificant association was also detected between drug hypersensitivity and other endogenous and exogenous factors of interest.
Drug hypersensitivity in the examined children was significantly associated with allergic rhinitis (P < 0.05) and family history of allergic diseases (P < 0.05) (Figure 161). There was no significant association between drug hypersensitivity in the examined children and other endogenous and exogenous factors.

**Figure 160.** Prevalence of drug hypersensitivity in the examined adults with and without food hypersensitivity (FH)

**Figure 161.** Prevalence of drug hypersensitivity in the examined children with allergic rhinitis and positive family history of allergic diseases

### 6.8. Conclusions

1. Drug hypersensitivity was reported by 10.5% of all examined subjects that suggested that more than 200,000 subjects in R. Macedonia had history of hypersensitivity to one or more medications. The prevalence of drug hypersensitivity was higher in the examined adults (11.2%) than in the examined children (9.8%), as well as in the females (12.4%) than in the males (8.9%).
2. Drug hypersensitivity in the examined adults was commonly caused by penicillins and NSAID and in the examined children by penicillins and sulphonamides.
3. Hypersensitivity to penicillins was the most frequent type of drug hypersensitivity. It was reported by 6.8% of the examined adults and 8.4% of the examined children.
4. Hypersensitivity to aspirin and affiliated drugs was reported by 0.6% of the examined adults.
5. Skin manifestations was the most frequent clinical manifestation of drug hypersensitivity in both adults and children.
6. Drug hypersensitivity in the examined adults was closely related to food hypersensitivity. In the examined children, significant association of drug hypersensitivity with allergic rhinitis and family history of allergic diseases was registered.

6.9. References:

7.0. Food hypersensitivity - ICD 10; L 23.6; L 25.4; L 27.2; T 78.0

7.1. Definition

Similar to drug hypersensitivity, food hypersensitivity is defined as an occurrence of objective and reproducible symptoms and/or signs initiated by exposure to food tolerated by other subjects. When immunologic mechanisms are demonstrated, the appropriate term is food allergy. Food allergy, depending upon underlying mechanism, may be IgE-mediated and Non-IgE-mediated. All other reactions, previously sometimes referred to as “food intolerance”, should be referred to as nonallergic food hypersensitivity.

7.2. Pathogenesis

Everyday consumed food includes a number of allergens which may cause allergic reactions in sensitized subjects. The allergenicity of the consumed food may change in the process of its preparing, as well as in the process of its digestion in the GI tract. Allergic reactions in sensitized subjects may occur following the consumption of certain food; in some cases as little as one five-thousandth of a teaspoon of an allergenic food can cause death. Reactions can also occur simply by touching or inhaling a food allergen. The most important products that may cause allergic reaction in sensitized subjects include cow milk, egg, soy, fish, shellfish, wheat, peanut, and tree nut.

Everyday consumed food also includes numerous substances which may cause nonallergic hypersensitive reactions in some individuals. These reactions may be caused by high histamine content of certain food or by nonspecific histamine release (e.g. tuna, mackerel, strawberry, and citrus). The other mechanism of nonallergic reactions to food is an enzyme deficit, such as hypersensitivity to cow milk in the subjects with lactase deficit. Reactions of hypersensitivity to food may also be caused by a number of food additives, such as benzoate, glutamates, sulfites, tartrazine, etc.

The underlying mechanisms of the allergic and nonallergic reactions to food are shown in Table 19.

<table>
<thead>
<tr>
<th><strong>Allergic reactions</strong></th>
<th><strong>Clinical manifestations</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>IgE-mediated</td>
<td>Anaphylactic shock, urticaria/angioedema, atopic dermatitis, asthma, dyspepsia, diarrhea</td>
</tr>
<tr>
<td>IgG/IgM-mediated</td>
<td>Serum sickness, vasculitis</td>
</tr>
<tr>
<td>IgA-mediated</td>
<td>Gluten enteropathy</td>
</tr>
<tr>
<td>Cell mediated</td>
<td>Contact dermatitis</td>
</tr>
<tr>
<td><strong>Nonallergic reactions</strong></td>
<td><strong>Clinical manifestations</strong></td>
</tr>
<tr>
<td>Mediators release</td>
<td>Anaphylactic shock, urticaria/angioedema</td>
</tr>
<tr>
<td>Enzyme deficits (lactase, galactocinase, uridyl transferase)</td>
<td>Diarrhea, syndrome of malabsorption</td>
</tr>
</tbody>
</table>

*Table 19. Mechanisms of food hypersensitivity*
7.3. Clinical manifestations

Skin manifestations are the most frequent reactions of food hypersensitivity (about half of the cases), followed by respiratory and gastrointestinal manifestations (about 20%) and cardiovascular disturbances (10-15%). The skin reactions involve a maculopapular exanthema, urticaria, angioedema, atopic dermatitis, and contact dermatitis. The respiratory manifestations include rhinitis symptoms and asthma attacks, whereas the GI affection may be manifested by dyspepsia and/or diarrhea. The life-threatening anaphylactic shock is the most serious manifestation of food allergy. A case of anaphylactic shock in a school child following the consumption of sesame was published in our literature, as well. The risk of anaphylactic shock in the subjects with food allergy, if they consume the food to which they are sensitized, is estimated to be 40-50%. Every food allergy reaction has the possibility of developing into a life-threatening and potentially fatal anaphylactic reaction. This can occur within minutes of exposure to an allergen.

Special consideration is the cross-reactivity between food and air allergens (i.e. pollen-food syndromes). Subjects suffering from pollinosis often display adverse reactions after ingestion of a wide variety of plant-derived foods as a consequence of IgE cross-reactive structures shared by pollen and food allergen sources. There are a number of documented pollen-food syndromes, such as birch-apple syndrome, birch-carrot syndrome, mugwort-peach association, goosefoot-fruit association, plantain – melon association, ragweed-melon-banana association, etc.

The natural course of food allergy is of special importance since its frequency is higher in children than in adults. The outcome of food allergy in childhood is variable. Egg and cow’s milk allergy usually resolve early in life, while peanut and tree nut, along with fish and shellfish, are often considered to be lifelong allergies.

7.4. Diagnosis

The diagnostic modalities currently available to clinicians for the diagnosis of food allergy include clinical history, physical examination, SPT, specific IgE assays, and oral food challenge (OFC).

7.4.1. Clinical history

Clinical history includes symptomatology, chronology of the symptoms (previous consumption, delay between the last consumption and onset of the symptoms, effect of stopping consumption), and allergic background of the affected subject (personal and family history of food allergy or other allergic diseases).

7.4.2. Oral food challenge (OFC)

At present, the double-blind placebo-controlled food challenge (DBPCFC) represents the only way to establish or rule out an allergy to food in older children and adults,
whereas an open challenge controlled by trained personnel is sufficient in infants and young children.

The clinical history is important when making the diagnosis of food allergy, but its relation to OFC may not be optimal. In general, studies that make use of the OFC to establish a diagnosis of food allergy reveal that a comprehensive clinical history may only be validated in less than 50% of patients. The reasons for negative OFC in the face of a suggestive history include confusing histories, misidentification of food in the history, and non-allergic causes of symptoms.

On the other hand, the challenge procedure is not fully developed and no standardized procedure has so far been agreed upon.

7.4.3. Skin prick tests

Results of the skin prick tests are of limited value in the diagnosis of food allergy due to the high prevalence of false positive and negative results. There is a general consensus that negative SPT or negative specific IgE to some foods (egg, milk, and peanut), in the presence of negative history, have a high negative predictive value. However, no negative predicted value is sufficiently high if it does not reach 100%, and any discrepancy between a positive history and negative SPT or specific IgE must be adjudicated by an OFC.

7.4.4. Laboratory tests

In vitro tests, such as measurement of specific IgE, circulating immune complexes and complement, are not sufficient in the diagnosis of food allergy due to reasons mentioned above.

7.5. Prevention

The primary prevention measures in infancy include exclusively breast-feeding in the first 4-6 months and avoidance of the potent food allergens, such as egg or fish, in the first year.

Secondary prevention includes avoidance of the known food the subject is sensitized to. Use of oral disodium cromoglycate is indicated as sufficient preventive measure by some authors. Some authors indicated that treatment with humanized anti-IgE antibodies may protect at least a subset of patients by increasing their threshold dose for allergenic responses. Consumption of hypoallergenic foods (e.g. hypoallergenic milk) may also help in the prevention of allergic reactions to food.

A couple of case reports and a few studies on a limited number of patients suggested that specific oral tolerance can be induced by oral administration of the offending food, starting with very low dosages, gradually increasing the daily dosage up to an amount
equivalent to a usually relevant dose for daily intake. However, the body of scientific evidence concerning specific oral tolerance induction (SOTI) is still rather poor and SOTI is not recommended for daily practice. The efficacy of anti-IgE antibodies or pollen immunotherapy as preventive measures for food allergy is still unknown.

**Treatment** of the allergic reaction to food is based on the principles of the treatment of the certain type of reaction (urticaria, bronchospasm, anaphylactic shock) in the event of accidental ingestion.

### 7.6. Epidemiological studies of food hypersensitivity

Results from the published studies indicate the food allergy as a cause of considerable morbidity and mortality in the USA and in the West European countries. It is estimated that approximately 2.5% of the US population have food allergies, which translates to approximately 6 to 7 million Americans, the majority being children. Food allergy prevalence in the USA has increased 55% in the last five years. Anaphylaxis is estimated to cause about 2,500 emergency room visits annually and believed to be responsible for up to 125 deaths each year. Eight foods (peanut, tree nut, milk, egg, soy, wheat flour, fish and shellfish) account for 90% of total food allergies in the USA, although any food has the potential to cause an allergic reaction. Peanut and tree nuts account for 92% of severe and fatal reactions.

The prevalence of food allergy in the French general population is estimated to 3.5%, being more frequent among children. Fish, egg, soy, and cow milk are most important in the allergic adults, whereas the reactions to cow milk, peanut, egg, and fish are most frequent in the allergic children.

The German study indicated prevalence of food allergy in Berlin general population sample of 3.6%, being more frequent in females (60.6%) than in males (39.4%). The prevalence of IgE-mediated and non-IgE-mediated food allergy was found to be 2.5% and 1.1%, respectively.

The prevalence of food allergy in the UK and Scandinavian countries is estimated to approximately 5% in children and 2% in adults.

Anaphylaxis due to food allergy is estimated to cause about 200 deaths each year in the West European countries.

### 7.7. Results of our study of food hypersensitivity in R. Macedonia

The present study represents the first epidemiologic observation of food hypersensitivity in R. Macedonia. Evaluation of examined adults and children included completion of a questionnaire. Food hypersensitivity was reported by 4.2% of all examined subjects (Figure 162).
The prevalence of food hypersensitivity in all examined subjects was significantly higher in females than in males (5.1% vs. 2.3%, P < 0.05) that is comparable to data from the published studies (Figure 163).

The highest prevalence of food hypersensitivity was reported by examined subjects in Dojran (8.9%). There was no reported any case of food hypersensitivity by examined subjects in Ohrid (Figure 164).

### 7.7.1. Prevalence of food hypersensitivity in certain centers

The highest prevalence of food hypersensitivity was reported by examined subjects in Dojran (8.9%). There was no reported any case of food hypersensitivity by examined subjects in Ohrid (Figure 164).
7.7.2. Prevalence of food hypersensitivity in adults

Prevalence of food hypersensitivity in adults was 3.3%. The difference in the food hypersensitivity prevalence between males and females was statistically significant (1.8% vs. 4.3%, $P < 0.05$) (Figure 165).

The highest prevalence of food hypersensitivity in examined adults was registered in the age group 21-30, and the lowest one was reported by the subjects aged over 60 (Figure 166).
Figure 166. Age distribution of food hypersensitivity in examined adults

The highest prevalence of food hypersensitivity was registered among examined adults in Prilep (7.6%). There was no reported food hypersensitivity among examined adults in Ohrid (Figure 167).

Figure 167. Prevalence of food hypersensitivity among examined adults in certain centers

7.7.3. Prevalence of food hypersensitivity in children

Prevalence of food hypersensitivity in examined children was 5.0%. As in the examined adults, the difference in its prevalence between boys and girls was significant (6.8% vs. 3.1%, $P < 0.05$) (Figure 168).
The prevalence of food hypersensitivity was significantly higher in the examined children aged less than 7 years than in the examined children aged over 7 years (9.0% vs. 4.4%, P < 0.05) (Figure 169).

The highest prevalence of food hypersensitivity among examined children was registered in Dojran (11.5%). There was no reported food hypersensitivity among examined children in Ohrid (Figure 170).
The most frequent clinical manifestations of food hypersensitivity in both adults and children were skin changes. The skin manifestations following consumption of certain food were reported by approximately 50% of the subjects with food hypersensitivity (Figure 171).

There was a significant association between food and drug hypersensitivity in the examined adults. History of drug hypersensitivity was reported by 56.3% of the adults who experienced reaction of food hypersensitivity (Figure 172).
There was no positive association between food hypersensitivity in the examined adults and any other endogenous and exogenous factor.

Significant relation of food hypersensitivity in the examined children was registered with positive family history of allergic diseases. Food hypersensitivity was reported by 20.0% of children with positive family history of allergic diseases and by only 3.1% of children with no allergic diseases in their blood relatives ($P < 0.001$) (Figure 173).

There was no positive association between food hypersensitivity in the examined adults and any other endogenous and exogenous factor.
7.8. Conclusions

1. Prevalence of reported food hypersensitivity in examined subjects was 4.2% which meant over 80,000 subjects in R. Macedonia that experienced an adverse reaction to food. As in the other allergic diseases, the higher prevalence of food hypersensitivity was registered in females than in males.

2. Prevalence of food hypersensitivity was higher among children than among adults. The higher prevalence was registered in the age group 0-7 years and the lowest prevalence of food hypersensitivity was reported by subjects aged over 60 years.

3. The highest prevalence of food hypersensitivity was registered among examined adults in Prilep and among examined children in Dojran.

4. Skin manifestations were the most frequent clinical manifestations in both adults and children, occurring in approximately half of the subjects with reported food hypersensitivity.

5. Food hypersensitivity was closely related to the allergic background of examined subjects, being significantly associated with drug hypersensitivity in examined adults and with positive family history of allergic diseases in examined children.

7.9. References:

4. The UCB Institute of Allergy. Allergies. c/o UCB Center 1999; 40-45.


8.0. Insect sting allergy - ICD 10 (T 63.4 X 23)

8.1. Definition and classification

Insect allergy can be categorized into the following main subtypes: **stinging and biting insect allergy** (*Hymenoptera*, fleas, horseflies, etc.) and **inhalant insect allergy** (cockroaches). Mosquitoes fit into both categories. Not only allergic reactions can be expected with insect stings or bites, but toxic reactions are quite common too and many infectious diseases are transmitted by insects as well.

Allergic reactions caused by *Hymenoptera* sting are the most important subtype of the insect stinging allergy due to their frequency and severity. Biting insect allergy, i.e. allergic reactions which occur in the subjects sensitized to salivary proteins of the insects that bit, such as fleas, horseflies, and mosquitoes, are characterized by lower frequency (commonly occur in children) and severity (commonly limited to skin reactions).

Respiratory allergies may occur in individuals sensitized to inhalant particles of cockroaches (inhalant insect allergy). The prevalence of sensitization to cockroach in the subjects with asthma in the USA is estimated to approximately 40%. The results of the actual study indicated the prevalence of cockroach sensitization in 10% of the subjects with asthma.

8.2. Insects from *Hymenoptera* order and allergens from *Hymenoptera* venoms.

The order *Hymenoptera* includes the Apids, or bees, and the Vespids, represented by wasps and hornets. The most important species in R. Macedonia include the Honeybee (*Apis mellifera*), the Common wasp (*Vespula spp.*), the Paper wasp (*Polites spp.*), and the Hornet (*Vespa spp.*) (Figure 174).

![Figure 174](www.intelihealth.com)

A. A. Honeybee (*Apis mellifera*), B. Wasp (*Vespula spp.*), and C. Hornet (*Vespa spp.*)
Adapted from: *Insect Venom Allergy. Available at: www.intelihealth.com*
Honeybees, the most common of these stinging insects, are not aggressive unless provoked. They can be easily recognized by their hairy bodies and bright yellow or black markings. The honeybees are typically found around flowers or clover. Once they sting, they die. They often leave their stinger behind. Wasps are hairless with narrow “waists” that separate their chests from their long, slim, lower bodies. They can be black, brown or red. Wasps build nests in the caves of buildings and under rafters. They sting repeatedly.

Hornets have short black bodies with yellow or white markings. They nest in trees or bushes and sting repeatedly.

Venoms from these insects contain several vasoactive substances, which are hemolytic and neurotoxic. They are also highly potent sensitizing agents which may cause mild to life-threatening allergic reactions in the sensitized subjects. Hymenoptera venoms were defined in the late 1980s. Honeybee and wasp venom are different, while wasp and hornet venom are similar by their allergens content. The honeybee venom includes melitine and fosfolipase 2, and the antigen 5 is the major wasp venom allergen (Figure 175). Wasp venom may cross-react with hornet venom, while the cross-reactivity between honeybee and wasp venom is quite weak.

Figure 175. Tertiary structure of the wasp venom antigen 5

The subjects stung by a Hymenoptera insect are exposed to large quantities (i.e. several micrograms) of the major allergens per sting, an amount similar to the annual dose of inhaled pollen allergen. This is probably the reason for almost the same prevalence of atopy among patients with IgE sensitization to Hymenoptera venoms as in the normal population. There is a different multisystem response pattern when a subject is exposed to very high allergen dosage via mucosal membrane, as by food and drugs, or by inoculation, as by Hymenoptera venoms and drugs. Moreover, subjects with a less obvious tendency to mount an IgE antibody response will do this after a large dose of allergen stimulation.
8.3. Clinical manifestations

Manifestations in the stung individual include a local reaction with pain, swelling (up to 1 cm diameter), and redness confined at the sting site that usually resolves in a few hours. The clinical reaction in the allergic individual covers a wide range of symptoms, often starting locally and sometimes developing into a general reaction.

8.3.1. Local allergic reactions

Local allergic reactions include intense redness, swelling spanning two joints, itching and pain; these reactions occur within minutes and last for more than 24 hours (Figure 176).

![Local reactions due to wasp sting](Adapted from: Ewan PW. Venom allergy. Available at: http://bmj.bmjjournals.com/cgi/)

8.3.2. Systemic allergic reactions

Such a reaction is characterized by hives, itching, and swelling in areas other than the sting site, difficulty in breathing, dizziness or a sharp drop in blood pressure, nausea, cramps or diarrhea, unconsciousness and cardiac arrest. According to Müller the severe allergic reactions to *Hymenoptera* venoms are classified in four stadiums:

I. Large local reaction at the sting site;
II. Large local reaction associated with generalized skin reaction;
III. Generalized skin reaction associated with affection of other systems (laryngeal edema, asthma attack and/or abdominal pain);
IV. Shock associated with loss of consciousness.
8.3.3. Course and prognosis

A substantial proportion of patients (20-80% in different studies) with a history of a generalized reaction to a sting have no such reaction to a subsequent sting. Less or more severe generalized reactions may also occur. However, the course can be variable, a series of stings may result in a generalized reaction, no reaction, and then another generalized reaction. Children do particularly well, one study showed that 95% of those with a history of mild generalized reactions had no reaction to a re-sting. The next sting will not necessarily cause a more severe reaction, but patients in accident and emergency departments are often told that it will.

Reasons for the variable outcome are not well understood but include the interval from the last sting (the longer the interval the lower the risk of another generalized reaction), the patient’s immune response at the time of the sting (this will change with time), the dose of venom injected, and the site of the sting.

8.4. Diagnosis

The diagnosis of insect sting allergy rests on the history, because positive test results can occur in persons who do not react to insect stings. Positive in vivo and/or in vitro tests are used to confirm the presence of allergy in a patient who has reacted to an insect sting and to identify the specific insect to which the patient is allergic.

There is no correlation between the severity of the insect sting reaction and the level of specific IgE. In fact, the strongest reactions on skin tests often occur in patients who have had only large local reactions to insect stings and have a low risk of anaphylaxis, whereas weak sensitivity on skin or laboratory test may be demonstrated in some patients who have experienced life-threatening anaphylactic shock.

8.5. Prevention

Preventive measures regarding re-sting include:

- To avoid wearing sandals or walking barefoot in the grass;
- To avoid wearing bright-colored clothing;
- To avoid sweet-smelling perfumes, hair sprays, colognes and deodorants;
- Not to drink from open beverage cans since the stinging insects may crawl inside a can attracted by the sweet beverage;
- To keep food covered at all times when eating outdoors;
- To avoid insects nests since the stinging insects are most dangerous in the vicinity of their nests;
- Yard work and gardening should be done with caution;
- To keep doors and windows of the house and car shut as much as possible;
- To keep prescribed medications handy at all times and to follow the attached instructions in the case of re-sting. These medications are for immediate emergency use while en route to a hospital emergency room for observation and further treatment.
8.6.   Treatment

The treatment depends on the severity of the reaction. The local reaction should subside uneventfully over 48 hours, but on occasion will require the application of ice or a cold compress, elevation of affected arm or leg, antihistamines, and, rarely, oral corticosteroids.

The mild and moderate systemic reactions should be treated by oral or parenteral antihistamines and corticosteroids. Severe systemic reaction requires parenteral administration of adrenaline (epinephrine), antihistamines, and corticosteroids. In some cases, further therapy with intravenous fluids, oxygen and medications will be necessary.

With the potential for repeated reactions hovering menacingly overhead prevention is paramount. Epinephrine kits are available by prescription for self-administering epinephrine immediately after a second sting. Using this as directed will delay a reaction that otherwise may have progressed. ASIT is the treatment of choice for children with a history of anaphylaxis and adults with hives or anaphylaxis following a sting.

8.7.   Specific immunotherapy

ASIT towards insect sting allergy has been available since the pioneer works of Hunt et al. 1978. These studies demonstrated an almost complete protection by treatment with specific insect venom in contrast to earlier studies using whole body extract which turned out to be equivalent to placebo. Since then many therapy modalities have been developed.

In double-blind, placebo controlled clinical studies, venom immunotherapy has been shown to be 97% effective in eliminating a reoccurrence of a systemic reaction to an insect re-sting. Numerous other studies evaluating the frequency of anaphylaxis after re-sting in immunotherapy treated patients and in untreated patients confirm these results.

The venom immunotherapy is recommended in subjects with history of Müller III and IV reaction associated with positive SPT or in vitro tests to venom allergens. Injections of gradually increasing concentrations of venom are given on a weekly basis for 6-8 weeks to confer immunity. Maintenance injections of full-strength venom are then given every 4-6 weeks. Clinical improvement (i.e. protection of the re-sting) occurs earlier than serologic improvement. The prevalence of the systemic adverse effects is approximately 10%.

In the Appendices 10 and 11 the protocols for rush and conventional venom immunotherapy according to Döring et al., by which over 600 subjects with systemic reaction was...
successfully desensitized, are presented.

8.8. Epidemiological studies of insect sting allergy

The published data indicate the prevalence of *Hymenoptera* venom allergy of 9%-13%. As many as two million people in the USA are allergic to the venom of stinging insects. Many of these individuals are at risk for life-threatening anaphylactic reactions, resulting in curtailment of outdoor activities. More than 500,000 people enter hospital emergency rooms every year suffering from insect stings. Mortality attributed to these stings is estimated to 50 deaths per year. Data from the UK suggest an annual average of four deaths from bee or wasp stings, but this is almost certainly an underestimate because venom anaphylaxis is not always recognized as the cause of death.

Insect sting allergy can occur in persons of any age, especially after multiple stings. Systemic reactions to insect stings are estimated to occur in 3% of adults, while approximately 1% of children have a medical history of severe sting reactions. Large local reactions are more common than systemic reactions and are mediated by IgE in up to 85% of cases. IgE antibodies to *Hymenoptera* venom, measured by SPT or *in vitro* test, are present in 20 to 30% of normal adults who had an insect sting in the previous two to three years.

8.9. Results of our study of insect sting allergy in R. Macedonia

There has been no epidemiological observation of insect sting allergy in R. Macedonia previous to this study. The diagnosis of insect sting allergy in adults and children was questionnaire-based.

Insect sting allergy was reported by 3.1% of all examined subjects indicating over 60,000 subjects in R. Macedonia with reaction following the *Hymenoptera* insect sting (Figure 177).

![Figure 177. Prevalence of insect sting allergy in all examined subjects](image)

8.9.1. Prevalence of insect sting allergy in adults
Insect sting allergy was reported by 2.5% of examined adults. Its prevalence was significantly higher in women than in men (3.8% vs. 1.1%, \( P < 0.05 \)) (Figure 178).

**Figure 178.** Prevalence of insect sting allergy in examined adults

The highest prevalence of insect sting allergy was registered in the age group 41-50 (3.2%), and the lowest one in the age group over 60 years (1.7%) (Figure 179).

**Figure 179.** Age distribution of insect sting allergy in examined adults

### 8.9.1.1. Prevalence of insect sting allergy in certain centers

The highest prevalence of insect sting allergy was registered among examined adults in Dojran (8.5%). No reaction after Hymenoptera insects sting was reported by examined adults in Ohrid and Prilep (Figure 180).
8.9.2. Prevalence of insect sting allergy in children

Insect sting allergy was reported by 3.8% of examined children. Its prevalence was not significantly higher in girls than in boys (4.4% vs. 3.1%) (Figure 181).

Figure 181. Prevalence of insect sting allergy in examined children

Non-significantly higher prevalence of insect sting allergy was registered in children aged over 7 years (Figure 182).

Figure 182. Age distribution of insect sting allergy in examined children
8.9.2.1. Prevalence of insect sting allergy in certain centers

The highest prevalence of insect sting allergy was registered among children in Dojran (9.1%), while among examined children in Ohrid insect sting allergy was not reported (Figure 183).

Figure 183. Prevalence of insect sting allergy among children in certain centers

8.9.3. Clinical manifestations of insect sting allergy

Systemic allergic reactions following the insect sting were reported more frequently by examined adults with insect sting allergy that can be compared with the published data.

The prevalence of skin and systemic reactions among allergic adults was 24.7% and 75.3%, respectively. In the allergic children local reactions following the insect sting were reported by 45.5%, while the prevalence of systemic reactions was 54.5% (Figure 184).

Figure 184. Prevalence of skin and systemic reactions in the subjects with insect sting allergy
### 8.9.4. Association between insect sting allergy and other allergic diseases

Association between insect sting allergy and positive family history of insect sting allergy was not significant in both adults and children with reported allergic reaction to Hymenoptera venom.

In allergic adults significant association was registered between insect sting allergy and food hypersensitivity. Insect sting allergy was reported by 22.2% of the adults who experienced food hypersensitivity reaction and by only 2.2% of the adults who had no such reaction ($P < 0.05$) (Figure 185). Association between insect sting allergy in examined adults with family history of allergic diseases and atopy was statistically non-significant.

![Figure 185. Prevalence of the subjects with insect sting allergy with and without food hypersensitivity](image)

On the contrary, insect sting allergy in examined children was significantly associated with positive family history of allergic diseases (Figure 186). Association between insect sting allergy and other allergic diseases in examined children was not statistically significant.

![Figure 186. Prevalence of insect sting allergy in children with positive and negative family history of allergic diseases](image)
8.10. Conclusions

1. The prevalence of insect sting allergy in all examined adults was 3.1%, being more frequent in females (3.9%) than in males (1.9%).
2. The prevalence of insect sting allergy in examined adults was 2.5%, being significantly higher in women (3.8%) than in men (1.1%).
3. The prevalence of insect sting allergy in examined children was 3.8%, being more frequent in girls (4.4%) than in boys (3.1%).
4. The high prevalence of Hymenoptera insects sting allergy among examined subjects in Dojran may be due to higher exposure to these insects in the area characterized by warm climate. On the other hand, the prevalence of insect sting allergy may be overreported or underreported (e.g. no reported insect sting allergy among examined subjects in Ohrid) that can not be excluded in the questionnaire-based studies.
5. Systemic reactions following the Hymenoptera insect sting were more frequent in allergic adults than in allergic children.
6. There was no positive association between insect sting allergy and positive family history of insect sting allergy in both adults and children.
7. Insect sting allergy in examined adults was significantly related to food hypersensitivity. Association with other endogenous and exogenous factors was not significant.
8. Insect sting allergy in examined children was closely related to positive family history of allergic diseases. There was no positive association between insect sting allergy in examined children and other endogenous and exogenous factors.

8.11. References:

4. Ewan PW. Venom allergy. Available at: http://bmj.bmjjournals.com/cgi/.


Part IV
Economic burden of certain allergic diseases in R. Macedonia
1.0. Economic burden of allergic rhinitis and asthma

At the turn of the new millenium, allergic diseases represent considerable cause of morbidity and mortality and a further increase in morbidity is expected in the future. Substantial limitations to the patients’ well being and quality of life, as well as the financial impact of allergic diseases on the society are considered to be significant.

A number of studies were performed to quantify the cost attributed to allergic diseases. The burden associated with allergic diseases include both direct and indirect costs. Direct costs comprise the costs of hospitalization, rehabilitation and drugs, physician visits and diagnostic tests. Indirect costs involve the adverse effect of allergic diseases at personal and society level, i.e. the effect of the disease on life and work activities.

1.1. Allergic rhinitis (AR)

AR is extremely common condition, affecting approximately 20% of the population. While it is not a life-threatening condition, complication can occur and the disease can significantly impair quality of life, which leads to a number of direct and indirect costs.

The total direct and indirect cost of AR in the USA was estimated to be $ 2.7 billion in 1995. It is estimated that in 1995 there was 10 millions lost work and school days and 28 million days with reduced work and school activities. This expenditure underestimated the true economic burden associated with AR since the costs due to the accompanying diseases, such as sinusitis and asthma, were not included. The total direct and indirect costs attributed to AR were estimated to be $ 5.3 billion in 1996. According to the public health experts the doubled cost was due to the increase of the indirect costs, especially to the extensive use of systemic antihistamines which may seriously affect psychomotor and cognitive functions. Due to this, some allergologists indicated the ASIT as a more eligible AR treatment modality.

1.1.1. Seasonal allergic rhinitis in R. Macedonia

Although seasonal allergic rhinitis (SAR) is the most frequent allergic disease in R. Macedonia there is no evidence about the economic burden attributed to this condition.

Although seasonal allergic rhinitis (SAR) is the most frequent allergic disease in R. Macedonia there is no evidence about the economic burden attributed to this condition.

Table 20. and Table 21. show the direct costs associated with medical treatment of SAR in adults and in children aged 4-12 years. The monthly costs were calculated taking into account the costs of the medications registered in R. Macedonia following the treatment modalities recommended by the Allergic Rhinitis and its Impact on Asthma guidelines.
Table 20. Monthly costs for treatment of SAR in adults

<table>
<thead>
<tr>
<th>SAR</th>
<th>Treatment modality</th>
<th>Monthly cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Tablets Cetirizin</td>
<td>300,00 MKD (5 €)</td>
</tr>
<tr>
<td>Moderate/severe</td>
<td>Spray Fluticasone 50 mcg  +  Tablets Cetirizin</td>
<td>1,100,00 MKD (19 €)</td>
</tr>
</tbody>
</table>

Table 21. Monthly costs for treatment of SAR in children aged 4-12 years

<table>
<thead>
<tr>
<th>SAR</th>
<th>Treatment modality</th>
<th>Monthly cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Syrup Cetirizin</td>
<td>200,00 MKD (3,5 €)</td>
</tr>
<tr>
<td>Moderate/severe</td>
<td>Spray Fluticasone 50 mcg</td>
<td>1,000,00 MKD (17 €)</td>
</tr>
</tbody>
</table>

Data obtained suggest that monthly cost for medical treatment of SAR in adults varied from 5 to 19 euros depending on the severity of the disease. The monthly cost for medical treatment of SAR in children aged 4-12 varied from 3.5 to 17 euros. The monthly amount did not include the costs for medications required in the treatment of conjunctivitis which was often associated with AR, as well as the costs for additional medications which may be required in the SAR treatment (e.g. short-term course of oral corticosteroids).

1.1.2. Perennial allergic rhinitis in R. Macedonia

Table 22. and Table 23. present the direct costs associated with medical treatment of PAR in adults and in children aged 4-12. As with SAR, the monthly costs were calculated taking into account the costs of the medications registered in R. Macedonia following the treatment modalities recommended by the Allergic Rhinitis and its Impact on Asthma guidelines.
### Table 22. Monthly costs for treatment of PAR in adults

<table>
<thead>
<tr>
<th>PAR</th>
<th>Treatment modality</th>
<th>Monthly cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Tablets Cetirizin or Spray Fluticasone 50 mcg</td>
<td>300,00 MKD (5 €) or 780,00 MKD (13 €)</td>
</tr>
<tr>
<td>Moderate / severe</td>
<td>Spray Fluticasone 50 mcg + Tablets Cetirizin (1,5 sk)</td>
<td>1.900,00 MKD (30 €)</td>
</tr>
</tbody>
</table>

### Table 23. Monthly costs for treatment of PAR in children aged 4-12 years

<table>
<thead>
<tr>
<th>PAR</th>
<th>Treatment modality</th>
<th>Monthly cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Syrup Cetirizin or Spray Fluticasone 50 mcg</td>
<td>200,00 MKD (3,5 €) or 780,00 MKD (13 €)</td>
</tr>
<tr>
<td>Moderate / severe</td>
<td>Spray Fluticasone 50 mcg + Syrup Cetirizin</td>
<td>1.000,00 MKD (17 €)</td>
</tr>
</tbody>
</table>

Data obtained suggest that monthly cost for medical treatment of PAR in adults varied from 5 to 30 euros depending on the severity of the disease. The monthly cost for medical treatment of SAR in children aged 4-12 varied from 3.5 to 17 euros. The monthly amount did not include the costs for medications required in the treatment of accompanied conditions, such as allergic conjunctivitis, sinusitis, and sinonasal polyposis.

### 1.2. Asthma

Asthma is a common life-long chronic inflammatory disease that affects adults and children of all ages placing a considerable burden on society. As there is an evidence of increasing asthma prevalence in some European countries, such as France and Finland, asthma has been officially recognized by their respective public health authorities as a priority area for action.

According to data from the European Lung White Book the total cost of asthma in the European Union countries, Norway, and Switzerland in 2000 was 17.7 billion euros (Table 24).

<table>
<thead>
<tr>
<th>Type of costs</th>
<th>Amount (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambulatory care</td>
<td>3.765 millions</td>
</tr>
<tr>
<td>Inpatient care</td>
<td>507 millions</td>
</tr>
<tr>
<td>Drugs</td>
<td>3.641 millions</td>
</tr>
<tr>
<td>Lost work days</td>
<td>9.754 millions</td>
</tr>
<tr>
<td>Total cost</td>
<td>17.7 billions</td>
</tr>
</tbody>
</table>

According to the WHO reports from 2000, the estimate of economic costs associated to asthma exceeds the combination of those for tuberculosis and human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS).

Current costs attributed to asthma in the UK are estimated to approximately 1.8 billion dollars for medical treatment and for sick leave due to the disease. In Australia direct and indirect costs associated with asthma are close to 460 million dollars. In the UK, the data indicate that asthma is a significant cause of absence from work, with 2.7 million days of sickness benefit paid in 1991/1992. It seems that the lost work days attributed to asthma exacerbations are markedly underreported as the patients present their disease as respiratory infection afraid of the workplace loss.

The costs attributed to asthma in the USA in the late 1990s were estimated to 12.6 billion dollars in total costs, 1.9 billion dollars in indirect morbidity costs, and 0.9 billion dollars in indirect mortality costs. In these reports the costs of the adults and children with private health insurance were not taken into account. Data from the USA indicate 10 million lost school days, as well as limited physical activities in approximately 30% of the children with asthma.

In both France and the UK, the number of prescriptions for asthma medications doubled in the period from 1980 to 1990. In the UK the number of prescriptions for inhaled corticosteroids was approximately 1.2 million in 1980, increasing to 7 million in 1992.

1.2.1. Asthma in R. Macedonia

As with AR, there is no evidence about economic burden of asthma in R. Macedonia.

Table 25. shows the direct costs associated with chronic treatment of asthma in adults and children aged over 5 years. Table 26. shows the direct costs attributed to the chronic
treatment of asthma in children aged less than 5 years. The monthly costs were calculated taking into account the costs of the medications registered in R. Macedonia following the treatment modalities recommended by the GINA Updated 2004.

<table>
<thead>
<tr>
<th>Asthma</th>
<th>Treatment modality</th>
<th>Monthly cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild persistent</td>
<td>Spray Fluticasone 125 mcg</td>
<td>1.800,00 MKD (30 €)</td>
</tr>
<tr>
<td>Moderate persistent</td>
<td>Spray Fluticasone 125 mcg + Spray Salmeterol</td>
<td>5.200,00 MKD (85 €)</td>
</tr>
<tr>
<td>Severe persistent</td>
<td>Spray Fluticasone 125 mcg + Spray Salmeterol</td>
<td>7.000,00 MKD (110 €)</td>
</tr>
</tbody>
</table>

Table 25. Monthly cost for chronic treatment of asthma in adults and children aged over 5 years

<table>
<thead>
<tr>
<th>Asthma</th>
<th>Treatment modality</th>
<th>Monthly cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild persistent</td>
<td>Spray Fluticasone 50 mcg</td>
<td>950,00 MKD (15 €)</td>
</tr>
<tr>
<td>Moderate persistent</td>
<td>Spray Fluticasone 125 mcg</td>
<td>1800,00 MKD (30 €)</td>
</tr>
<tr>
<td>Severe persistent</td>
<td>Spray Fluticasone 125 mcg + Spray Salmeterol</td>
<td>5.200,00 MKD (85 €)</td>
</tr>
</tbody>
</table>

Table 26. Monthly cost for chronic treatment of asthma in children aged less than 5 years

Data obtained suggest that monthly cost for chronic treatment of asthma in adults and children aged over 5 years varied from 30 to 110 euros depending on the severity of the disease. The monthly cost for chronic treatment of asthma in children aged less than 4 years varied from 15 to 85 euros. The monthly amount did not include the costs for medications required in the treatment of acute exacerbations of asthma (antibiotics, bronchodilators, such as short-acting β2 agonists and theophylline, and systemic corticosteroids).
1.3. Conclusions

1. Despite the need of estimated costs, there is no evidence of economic burden attributable to allergic diseases in R. Macedonia.

2. The direct costs for medical treatment of SAR in adults varied from 5 to 19 euros per month, depending on the disease severity. The direct costs for medical treatment of SAR in children aged 4-12 varied from 3.5 to 17 euros per month.

3. The direct costs for medical treatment of PAR in adults varied from 5 to 30 euros per month, depending on the disease severity. The direct costs for medical treatment of PAR in children aged 4-12 varied from 3.5 to 17 euros per month.

4. The direct costs for chronic treatment of asthma in adults and children aged over 5 years varied from 30 to 110 euros per month, depending on the disease severity. The direct costs for chronic treatment of asthma in children aged less than 5 years varied from 15 to 85 euros per month.

Data obtained suggest considerable economic burden attributable to AR and asthma in R. Macedonia.

1.4. References:

Part V
Appendices
Appendix 1:
Appearance and spread of some plants and their pollen grains

I. TREE POLLENS

SILVER BIRCH (Betula pendula)

The birch is a deciduous tree of 25 - 30 m height.
It is widely spread in Europe as well as in our country. It is found along the south border of R. Macedonia as well as in beech region.

Birch pollen grains were numerously present in the air of examined cities.
The beech is a deciduous tree, up to 30 m high and a crown rich in leaves. It is spread in Central and Western Europe. In the R. Macedonia it is present in all mountains at the height of 800 to 2000 m above the sea level.

Beech pollen grains were registered in the air of all examined cities. These pollen grains are characterized by their largeness (diameter 40 - 50 mcm).
COMMON OAK (*Quercus petraea*)

The oak-common is a deciduous tree, 25 - 30 m high. It is widespread in Europe as well as in our country. It is found along the south border of R. Macedonia as well as in beech region.

Oak pollen grains were numerously present in the air of examined cities.
BLACK PINE (*Pinus nigra*)

Pine black is an evergreen (periwinkle) tree, up to 40 m high. The crown in young stalk is piramidal and later becomes egg-shaped, widely branched with a horizontal top.

It is spread in Southern Europe. In R. Macedonia it is present at the height of 1000 to 1800 m above the sea level.

Pine black pollen grains were numerously present in the air of examined cities. These pollen grains are characterized by their air balloons.
Mountain juniper is an evergreen (periwinkle) bush or short tree, up to 6 m high.

It is particularly specific for the North America areas. It is found on limestones and rocks in the western part of R. Macedonia.

Cypress-juniper pollen grains were numerously present in the air of examined cities.
II. WEED POLLENS

DOCK (SORREL) (Rumex sp.)

Dock - Sorrel

Dock pollen grain

Dock - Sorrel is one-year plant of 10 to 40 cm height. It is widely spread plant both in the world and in our country. In R. Macedonia it is found in all valleys.

Dock-Sorrel pollen grains were numerously present in the air of examined cities.
NETTLE (*Urtica dioica*)

Nettle

Nettle pollen grains

Nettle is a many-years plant of 2 m height. It is a widely spread plant both in the world and in our country. In R. Macedonia it is present in all valleys.

Nettle pollen grains were numerous found in the air of examined cities. These pollen grains are significantly smaller in size than others.
PIGWEED (*Amarantus sp.*)

Pigweed is a one-year plant of 30 to 130 cm height. It is a widely spread plant both in the world and in our country. In R. Macedonia, it is present in all valleys.

Pigweed pollen grains were numerously found in the air of examined cities.
DANDELION (Taraxacum officinale)

Dandelion is one-year plant of 10 to 40 cm height. It is widely spread plant both in the world and in our country. It is found in all valleys in R. Macedonia.

Dandelion pollen grains were present in the air of examined cities for a short period of time.
III. GRASS POLLENS (*fam. Poaceae*)

Smooth-Stalked meadowgrass (Poa pratensis) | Timothy (Phleum pretense)

*Poaceae* pollen grain

Grasses (*Fam. Poaceae*) is a wide group of plants, comprising one-year and many-year grasses.
# Questionnaire for Allergic and Respiratory Symptoms in Adults

**Name:** ______________________________

**Sex:**
- 1. male
- 2. female

**Birth date:** _____________________________

**Place of living:** __________________________

**Address:** ______________________________

**Tel:** ___________ **Education level:** ___________

**Are you:**
- 1. employed (where?__________)
- 2. unemployed
- 3. renter

**Duration of the employment:** _________________

**Tel. (office):** _______________________________

**Ethnicity:**
- 1. 1. urban
- 2. rural

**1. Residence**
- 1. urban
- 2. rural

**2. Heating conditions:**
- 1. central heating
- 2. wood heating
- 3. electric heating
- 4. other_______

**3. Green plants:**
- a) indoors:
- 1. no
- 2. yes
- b) outdoors:
- 1. no
- 2. yes

**4. Environmental air pollution:**
if “no” go to question 6, if “yes”:
- 1. no
- 2. yes

**5. Type of air pollutants:**
- 1. manure
- 2. industrial air pollutants
- 3. traffic air pollutants
- 4. other_______

**6. Pets ownership:**
if “no” go to question 8, if “yes”:
- 1. no
- 2. yes

**7. Which pet do you own?**
- 1. dog
- 2. cat
- 3. parrot
- 4. other.___________

**8. Do you smoke?**
if you are unemployed go to question
- 1. no
- 2. yes

**9. Actual workplace:**
Duration of employment at the actual workplace: _________________

**10. Workplce hazards:**
- a) dust
- 1. no
- 2. yes

- b) high air humidity
- 1. no
- 2. yes
c) high air temperature  
y 1. no 2. yes

d) other (chemical agents, ionising radiation, etc): __________________________

 1. no  2. yes
11. Have you any nose symptom?
if “no” go to the item 22

 1. no  2. yes
12. Type of symptom:

a) nasal blockage  
y 1. no  2. yes

b) sneezing  
y 1. no  2. yes

c) itching  
y 1. no  2. yes

d) runny nose  
y 1. no  2. yes

13. At what age did nose symptoms occur _____________________________

14. Are there seasonal occurrence of the nose symptoms (spring/summer)?
if “no” go to question 18, if “yes”:

 1. no  2. yes

15. Season of the occurrence of the nose symptoms (month): _________________
Duration: _____________________________

16. Do the symptoms occur year by year subsequently?

 1. no  2. yes

17. Is there worsening of the nose symptoms in the environment rich with:

a) trees  
y 1. no  2. yes

b) grasses  
y 1. no  2. yes

18. Do the nose symptoms persist year-round?

 1. no  2. yes

19. Is there worsening of the symptoms by exposure to:

a) dust  
y 1. no  2. yes

b) smoke  
y 1. no  2. yes

c) workplace air pollutants  
y 1. no  2. yes

d) other: __________________

 1. no  2. yes

20. Is there worsening of the symptoms by exposure to cold air?

 1. no  2. yes

21. Are the nose symptoms associated with:

a) respiratory problems  
y 1. no  2. yes

b) ocular symptoms  
y 1. no  2. yes

c) skin changes  
y 1. no  2. yes

22. Have you any respiratory symptom?
if “no” go to question 29, if “yes”:

 1. no  2. yes

23. Type of symptoms:

a) shortness of breath  
y 1. no  2. yes

b) wheezing or whistling  
y 1. no  2. yes

c) cough  
y 1. no  2. yes

d) phlegm  
y 1. no  2. yes
24. At what age did the respiratory symptoms occur? ______________________

25. Have you any asthma attack? | 1. no  | 2. yes |
   if “no” go to question 28, if “yes”:

26. Are the respiratory problems: | 1. seasonal | 2. persistent |

27. How frequent do the respiratory symptoms occur: | 1. daily | 2. weekly | 3. monthly | 4. rarely |

28. Triggers of the respiratory symptoms:
   a) exercise | 1. no  | 2. yes |
   b) cold air | 1. no  | 2. yes |
   c) wind | 1. no  | 2. yes |
   d) other________ | 1. no  | 2. yes |

29. Have you any ocular symptom? | 1. no  | 2. yes |
   if “no” go to question 33, if “yes”:

30. Type of the ocular symptoms:
   a) tearing | 1. no  | 2. yes |
   b) redness | 1. no  | 2. yes |
   c) itching | 1. no  | 2. yes |
   d) eyelids swelling | 1. no  | 2. yes |

31. At what age did the ocular symptoms occur? ________________________

32. Is there seasonal occurrence (spring and/or summer) of the ocular symptoms? | 1. no  | 2. yes |

33. Have you any skin changes? | 1. no  | 2. yes |
   if “no” go to question 38, if “yes”:

34. Type of the skin changes:
   a) rash | 1. no  | 2. yes |
   b) itching | 1. no  | 2. yes |
   c) angioedema | 1. no  | 2. yes |
   d) other________ | 1. no  | 2. yes |

35. At what age did the skin changes occur? ____________________________

36. Is there seasonal occurrence of the skin changes? | 1. no  | 2. yes |

37. Are the skin changes associated with:
   a) food consumption:__________ | 1. no  | 2. yes |
   b) insect sting______________ | 1. no  | 2. yes |
   c) workplace exposure___________ | 1. no  | 2. yes |
   d) other________________________ | 1. no  | 2. yes |

38. Have you any adverse reaction after drug intake, such as:
1. rash                              2. angioedema             3. shortness of breath
        4. diarrhea                       5. collapse                     6. other___________
by which drug the adverse reaction was caused?

39. Do you actually use any medication?  1. no  2. yes
    which medication if “yes”:

40. Have you positive family history of allergic diseases such as:
    1. asthma                         2. hay fever                3. skin changes
    4. insect sting allergy      5. drug allergy           6. other_______
### QUESTIONNAIRE FOR ALLERGIC AND RESPIRATORY SYMPTOMS IN CHILDREN

<table>
<thead>
<tr>
<th>Name ____________________________________________</th>
<th>Sex: 1. male 2. female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth date______________________________________</td>
<td>Place of living_________</td>
</tr>
<tr>
<td>Address:________________________________________</td>
<td>Tel: ____________________</td>
</tr>
</tbody>
</table>

**Education level:**
1. mother_______ 2. father_______

**Workplace:**
1. mother_______ 2. father_______

**Ethnicity:**
1. mother_______ 2. father_______

1. During the pregnancy did the mother:
   a) smoke
   b) take medications
   c) experience stress
   d) have any kind of health problems

<table>
<thead>
<tr>
<th>1. no</th>
<th>2. yes</th>
</tr>
</thead>
</table>

2. Was the child born:
   1. at time 2. premature
   1. normal 2. forceps 3. vacuum 4. Sectio Caesarea

<table>
<thead>
<tr>
<th>1. no</th>
<th>2. yes</th>
</tr>
</thead>
</table>

3. Apgar index_____________________________________

4. Birth weight ___________________birth length_________

5. Has the child been breastfed during the first 4-6 months?
   if “no” go to question 7, if “yes”:

<table>
<thead>
<tr>
<th>1. no</th>
<th>2. yes</th>
</tr>
</thead>
</table>

6. Duration of the breastfeeding:________________________

7. Was there any nutritional problem in infancy with:
   a) milk
   b) other food

   (which food?______________________________________)

<table>
<thead>
<tr>
<th>1. no</th>
<th>2. yes</th>
</tr>
</thead>
</table>

8. During the first year of life was the child affected by:
   1. cough 2. pneumonia 3. nasal symptoms
   4. diarrhea 5. skin changes 6. something else

<table>
<thead>
<tr>
<th>1. no</th>
<th>2. yes</th>
</tr>
</thead>
</table>

9. Sibship:

<table>
<thead>
<tr>
<th>1. no</th>
<th>2. yes</th>
</tr>
</thead>
</table>

10. Day-care attendance:

<table>
<thead>
<tr>
<th>1. no</th>
<th>2. yes</th>
</tr>
</thead>
</table>
11. Residence and housing conditions?
   1. urban                 2. rural
   1. house                  2. flat

12. High humidity at the home:  
   1. no  2. yes

13. Heating conditions:  
   1. central heating  2. wood heating  3. electric heating  4. other_______

14. Green plants:  
   a) indoors  
   1. no  2. yes
   b) outdoors  
   1. no  2. yes

15. Environmental air pollution:  
   if “no” go to question 17, if “yes”:  
   1. no  2. yes

16. Type of air pollution:  
   1. manure  2. industrial pollutants  3. traffic pollutants  4. other_______

17. Pets ownership:  
   if “no” go to question 19, if “yes”:  
   1. no  2. yes

18. Which pets do you own?  
   1. dog                     2. cat                       3. parrot                   4. other_________

19. Daily smoking:  
   a) mother:  
   1. no  2. yes
   b) father:  
   1. no  2. yes
   c) other  
   1. no  2. yes

20. Is there a family manufacture at the home?  
   if “no” go to question 22, if “yes”:  
   1. no  2. yes

21. Is the family manufacture associated with exposure to:  
   a) dust  
   1. no  2. yes
   b) high humidity  
   1. no  2. yes
   c) chemical agents  
   1. no  2. yes
   d) high temperature  
   1. no  2. yes
   e) noise  
   1. no  2. yes
   f) other:____________________  
   1. no  2. yes

22. Has the child any nose problem?  
   if “no” go to question 33, if “yes”:  
   1. no  2. yes

23. Type of nose problems:  
   a) nasal blockage  
   1. no  2. yes
   b) sneezing  
   1. no  2. yes
   c) itching  
   1. no  2. yes
   d) runny nose  
   1. no  2. yes

24. At what age did the nose problems occur? ___________________________
25. Is there a seasonal occurrence (spring/summer) of the nasal symptoms?  
   1. no  2. yes  
   if “no” go to question 29, if “yes”:

26. Season of the occurrence of the nose symptoms (month): ____________
   Duration: ______________________________________________________

27. Do the nose symptoms occur year by year?  
   1. no  2. yes

28. Is there worsening of the nose symptoms in the environment rich with:
   a) trees  1. no  2. yes
   b) grasses  1. no  2. yes

29. Do the nose problems persist year-round  
   1. no  2. yes

30. Is there worsening of the nose symptoms by exposure to:
   a) dust  1. no  2. yes
   b) smoke  1. no  2. yes
   c) other: ____________________________  1. no  2. yes

31. Is there worsening of the nose symptoms by exposure to cold air?  
   1. no  2. yes

32. Are the nose symptoms associated with:
   a) respiratory symptoms  1. no  2. yes
   b) ocular symptoms  1. no  2. yes
   c) skin changes  1. no  2. yes

33. Has the child any respiratory symptom?  
   if “no” go to question 40, if “yes”:
   1. no  2. yes

34. Type of the respiratory symptoms:
   a) shortness of breath  1. no  2. yes
   b) wheezing or whistling  1. no  2. yes
   c) cough  1. no  2. yes
   d) phlegm  1. no  2. yes
   g) chest tightness  1. no  2. yes

35. At what age did the respiratory symptoms occur?  _________________

36. Has the child had any asthma attack?  
   if “no” go to question 40, if “yes”:
   1. no  2. yes

37. Are the respiratory symptoms:
   1. seasonal  2. persistent

38. How frequent do the respiratory symptoms occur?  
   1. daily  2. weekly  3. monthly  4. rarely

39. Triggers of the respiratory symptoms:
   a) exercise  1. no  2. yes
   b) cold air  1. no  2. yes
   c) wind  1. no  2. yes
   d) other_________  1. no  2. yes
40. Has the child any ocular symptom?  
   if “no” go to question 44, if “yes”:  
   1. no  2. yes

41. Type of the ocular symptoms:  
   a) tearing  
   b) redness  
   c) itching  
   d) eyelids swelling  
   1. no  2. yes

42. At what age did the ocular symptoms occur___________________________

43. Is there seasonal occurrence (spring and/or summer) of the ocular symptoms?  
   1. no  2. yes

44. Has the child any skin change?  
   if “no” go to question 49, if “yes”:  
   1. no  2. yes

45. Type of the skin changes:  
   a) rash  
   b) itching  
   c) angioedema  
   d) other________________________________________________________  
   1. no  2. yes

46. At what age did the skin changes occur? _____________________________

47. Is there seasonal occurrence (spring and/or summer) of the skin changes?  
   1. no  2. yes

48. Are the skin changes associated with  
   a) food consumption:______________________________________________  
   b) insect swing ___________________________________________________  
   c) other _________________________________________________________  
   1. no  2. yes

49. Has the child experienced any adverse drug reaction such as:  
   1. skin rash                     2. angioedema              3. shortness of breath  
   4. diarrhea                     5. collapse                     6. other _________________  
   by which drug was the adverse reaction caused _______________________

50. Do the child actually use any medication?  
   which medication if “yes”: _________________________________________  
   1. no  2. yes

51. Has the child positive family history of allergic diseases such as:  
   1. asthma                         2. hay fever                  3. skin changes  
   4. insect sting allergy 5. drug allergy       6. other__________________
Appendix 4.

*Prizes should be corrected due to WAT decrease (11-13%)

**Glossary of rhinoconjunctivitis medications**

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Commercial name</th>
<th>Mode of administration</th>
<th>Cost [MKD (€)]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systemic antihistamines</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sedating ( H_1 ) blockers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloropyramine</td>
<td>Synopen* (Pliva)</td>
<td>Injections</td>
<td></td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>Dimidril** (Pliva)</td>
<td>Tablets, Syrup</td>
<td>179.00 (3.0), 161.00 (2.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Non-sedating ( H_1 ) blockers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cetirizin</td>
<td>Cetirizin* (Replekfarm)</td>
<td>Tablets, Syrup, Letizen* *</td>
<td>183.00 (3.0), 196.00 (3.2), 384.00 (6.3), 183.00 (3.0)</td>
</tr>
<tr>
<td>Loratadine</td>
<td>Loratadin** (Alkaloid)</td>
<td>Tablets, Syrup</td>
<td>242.00 (4.0), 169.00 (2.8), 120.00 (2.0), 68.00 (1.1)</td>
</tr>
<tr>
<td></td>
<td>Loratadin** (Lek)</td>
<td>Tablets, Syrup</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Loratadin* (Replekfarm)</td>
<td>Tablets, Syrup</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rinolan** (Pliva)</td>
<td>Tablets, Syrup</td>
<td></td>
</tr>
<tr>
<td>Desloratadine</td>
<td><em>Aerius</em>**</td>
<td>Tablets</td>
<td></td>
</tr>
<tr>
<td>Levocetirizine</td>
<td><em>Xysal</em>**</td>
<td>Tablets</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Local preparations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cromones</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

239
<table>
<thead>
<tr>
<th><strong>Sodium cromoglycate</strong></th>
<th><strong>Asmatal</strong>** (Replekfarm)**</th>
<th>Nasal spray</th>
<th>385.00 (6.3)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disodium cromoglycate</strong></td>
<td><strong>Lomudal</strong>***</td>
<td>Nasal spray</td>
<td>Eye-drops</td>
</tr>
<tr>
<td></td>
<td><strong>Cromohexal</strong>***</td>
<td>Nasal spray</td>
<td>Eye-drops</td>
</tr>
<tr>
<td></td>
<td><strong>Cromoglicin</strong>***</td>
<td>Nasal spray</td>
<td>Eye-drops</td>
</tr>
<tr>
<td><strong>Nedocromil sodium</strong></td>
<td><strong>Vividrin</strong>***</td>
<td>Nasal spray</td>
<td>Eye-drops</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>α agonists</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Oxymethasoline</strong></td>
<td><strong>Operil</strong>** (Lek)**</td>
<td>Nasal spray</td>
<td>85.00 (1.4)</td>
</tr>
<tr>
<td></td>
<td><strong>Operil P</strong>** (Lek)**</td>
<td>Nose-drops</td>
<td>82.00 (1.4)</td>
</tr>
<tr>
<td></td>
<td><strong>Edil</strong>** (JAKA 80)**</td>
<td>Nose-drops</td>
<td>38.00 (0.7)</td>
</tr>
<tr>
<td></td>
<td><strong>Edil P</strong>** (JAKA 80)**</td>
<td>Nose-drops</td>
<td>33.00 (0.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antihistamines</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Levocabastine</strong></td>
<td><strong>Livostin</strong>**</td>
<td>Nasal spray</td>
<td>Eye-drops</td>
</tr>
<tr>
<td><strong>Azelastine</strong></td>
<td><strong>Allergodil</strong>***</td>
<td>Nasal spray</td>
<td>Eye-drops</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antiholinergics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ipratropium</strong></td>
<td><strong>Atrovent</strong>***</td>
<td>Nasal spray</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intranasal corticosteroids</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Beclometasone</strong></td>
<td><strong>Beconase</strong>* (GlaxoSmithKline Pharmaceuticals) <strong>Gnadion</strong>** (Pliva)**</td>
<td>Nasal spray</td>
<td></td>
</tr>
<tr>
<td><strong>Budesonide</strong></td>
<td><strong>Tafen nazal</strong>* (Lek)</td>
<td>Nasal spray</td>
<td>413.00 (6.9)</td>
</tr>
<tr>
<td></td>
<td><strong>Alerzin</strong>* (Replekfarm)</td>
<td>Nasal spray</td>
<td>427.00 (7.0)</td>
</tr>
<tr>
<td><strong>Fluticasone</strong></td>
<td><strong>Flixonase</strong>* (GlaxoSmithKline Pharmaceuticals)</td>
<td>Nasal spray</td>
<td>785.00 (13.0)</td>
</tr>
</tbody>
</table>

* The drug is included in the Essential Drug List, covered by the Health Insurance Fund of Macedonia
** The drug is not included in the Essential Drug List, covered by the Health Insurance Fund of Macedonia
*** The drug is not registered in R. Macedonia
Available 2007, May 31
Appendix 5.

Effect of therapies on rhinitis symptoms

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Sneezing and nasal itch</th>
<th>Rhinorrhea</th>
<th>Nasal obstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>H₁</em> antihistamines</td>
<td>+++</td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
<td>Cromones</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Oral decongestants</td>
<td>-</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>-</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Intranasal corticosteroids</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
</tbody>
</table>

Appendix 6.

OCCUPATIONAL ALLERGIC RHINITIS QUESTIONNAIRE

Name________________________________ Sex: 1. male 2. female □
Age__________________________ Address ____________________________
Ethnicity ___________________________________________________________
Actual employment:___________________ Actual workplace: ___________________________
Duration of the actual employment: ____________________________________________

1. Classification of the actual workplace: □
   1. administrative worker
   2. industry worker
   3. service worker
   4. other ________________________

2. Is your work: □
   1) dominantly in a sitting posture when arm muscles are slightly engaged
   2) in a sitting posture when arm muscles are increasingly engaged
   3) in a standing posture when arm muscles are slightly engaged
   4) in a standing posture when arm muscles are increasingly engaged
   5) in a standing posture when arm muscles and body are increasingly engaged
   6) standing, walking, intensive engagement of whole body muscles
   7) other:__________________________________________________________________

3. Actual workplace hazards: □
   1. none  2. high temperature  3. low temperature  4. draught  5. high humidity
   11. physical exercise  12. long-term standing or sitting  13. chemical agents
   14. atmospheric pressure changes 15. other)

4. Is your working engagement 1. full time 2. part time □

5. Is your work: □
   1) night work  2) shift work  3) related to travelling
   4) outdoors  5) in water  6) individual  7) team work
   8) other specific characteristics of your work __________________

6. To which chemical agents are you exposed at the actual workplace:
   _______________________________________________________________________

7. Type of the agent:
1. gas  2. fume  3. dust  4. smoke  5. liquid

8. Have you, at the workplace, contact with:
   a) animal and animal products
   b) herb and herbal products
   v) subjects with contagious diseases or contagious material

9. Do you use your voice at the workplace (singing, loud speaking)
   1. no   2. yes

10. Have you any nose symptom?
    1. no   2. yes

11. Type of symptom:
    a) nasal congestion
    b) sneezing
    v) nasal itching
    g) runny nose
    d) other

12. Have the symptoms occurred after entering the actual workplace?
    1. no   2. yes

13. Are the symptoms provoked by the actual workplace?
    1. no   2. yes

14. By which agent

15. In what period after beginning the work shift the symptoms occur? _____

16. Do the symptoms worse during the work shift?
    1. no   2. yes

17. Do the symptoms improve during
   1. weekends
   2. vacations
   3. other work off periods

18. At what age did you first notice the nose symptoms? ______________

19. How long had you been employed at the actual workplace before the nose symptoms have occurred? ______________

20. How often the symptoms occur:
   1. daily   2. weekly   3. monthly   4. a few times per year
   5. rarely   6. just in certain circumstances

21. Are the nose symptoms accompanied by respiratory symptoms (cough, phlegm, shortness of breath, wheezing or whistling, and/or chest tightness)?
   1. no   2. yes   3. from time to time

22. Have you even been treated for disease of the nose and/or sinuses?
    1. no   2. yes

23. Have you ever had some other chronic disorder?_____________________

24. Do you feel exhausted during the workshift?
    1. no   2. yes   3. sometimes
25. Smoking status:
   1. active smoker  2. ex-smoker  3. non-smoker

26. Daily mean of cigarettes smoked _________  Smoking experience _________

27. Do you consume alcohol more than bottle of beer or glass of wine daily?  1. no  2. yes

28. How long?  __________________________________________________________

29. Have you any blood relative with:
   a) nasal disorder (rhinitis, sinusitis, polyposis)  1. no  2. yes
   b) lung disorder (asthma, chronic bronchitis)  1. no  2. yes
   c) allergic disorder  1. no  2. yes

30. Duration of employment________________________________________________

31. Previous employments:
   1_________________________years: _______ hazards: 
   2_________________________years: _______ hazards: 
   3_________________________years: _______ hazards: 
   4_________________________years: _______ hazards: 
   5_________________________years: _______ hazards: 

32. Do you use any personal protective during the work shift?  1. no  2. yes

33. Do you have regular periodical check-ups?  1. no  2. yes

34. When the last periodical check-up was performed?  ____________________
Appendix 7.

*Prizes should be corrected due to WAT decrease (11-13%)

**Glossary for asthma medications**

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Commercial name</th>
<th>Mode of administration</th>
<th>Cost [MKD (€)]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Controllers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(antiinflammatory) drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium cromoglycate</td>
<td>Intal***, Bicromat***</td>
<td>inhaled</td>
<td>250.00 (4.0)</td>
</tr>
<tr>
<td>Nedocromil sodium</td>
<td>Tilade**</td>
<td>inhaled</td>
<td>950.00 (15.0)</td>
</tr>
<tr>
<td><strong>Cromones</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Inhaled corticosteroids</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beclomethasone dipropionate</td>
<td>Becotide 50 mcg*</td>
<td>inhaled</td>
<td>250.00 (4.0)</td>
</tr>
<tr>
<td></td>
<td>(GlaxoSmithKline Pharmaceuticals)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Becloforte 250 mcg**</td>
<td>inhaled</td>
<td>950.00 (15.0)</td>
</tr>
<tr>
<td></td>
<td>(GlaxoSmithKline Pharmaceuticals)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>Flixotide 50 mcg*</td>
<td>inhaled</td>
<td>1800.00 (30.0)</td>
</tr>
<tr>
<td></td>
<td>(GlaxoSmithKline Pharmaceuticals)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Flixotide 125 mcg*</td>
<td>inhaled</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(GlaxoSmithKline Pharmaceuticals)</td>
<td></td>
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</tr>
<tr>
<td>Mometasone furoate**</td>
<td>Asmanex***</td>
<td>inhaled</td>
<td>1800.00 (30.0)</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>Inhacort**</td>
<td>inhaled</td>
<td></td>
</tr>
<tr>
<td>Budesonide</td>
<td>Tafen *(Lek)</td>
<td>inhaled</td>
<td>1800.00 (30.0)</td>
</tr>
<tr>
<td>Cyclosonide**</td>
<td>Pulmicort**</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alvesco***</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Sistemic corticosteroids

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Formulation</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone</td>
<td>Prednizon 5 mg** (JAKA 20)</td>
<td>oral</td>
<td>68.00 (1.1)</td>
</tr>
<tr>
<td></td>
<td>Prednizon 20 mg** (JAKA 20)</td>
<td>oral</td>
<td>103.00 (1.6)</td>
</tr>
<tr>
<td></td>
<td>Pronizone 5 mg** (Galenika)</td>
<td>oral</td>
<td>107.00 (1.6)</td>
</tr>
<tr>
<td></td>
<td>Pronizone 20 mg** (Galenika)</td>
<td>oral</td>
<td>119.00 (2.0)</td>
</tr>
<tr>
<td></td>
<td>Nizon 5 mg** (Bosnalijek)</td>
<td>oral</td>
<td>68.00 (1.1)</td>
</tr>
<tr>
<td></td>
<td>Solu-decortin H 25 1 mL</td>
<td>parenteral</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Solu-decortin H 25 5 mL</td>
<td>parenteral</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Merek kGaA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisolone</td>
<td>Decortin 5 mg*</td>
<td>oral</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decortin 20 mg*</td>
<td>oral</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decortin 50 mg*</td>
<td>oral</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Merek kGaA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>Lemod Solu 20 mg</td>
<td>parenteral</td>
<td>195.00 (3.0)</td>
</tr>
<tr>
<td></td>
<td>Lemod Solu 40 mg</td>
<td>parenteral</td>
<td>802.00 (13.0)</td>
</tr>
<tr>
<td></td>
<td>Lemod Solu 500 mg</td>
<td>parenteral</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lemod depo 40 mg</td>
<td>parenteral</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lemod 4 mg* (Hemofarm)</td>
<td>oral</td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Dexametazon 4 mg/mL</td>
<td>parenteral</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dexametazon 0,5 mg* (Krka)</td>
<td>oral</td>
<td>179.00 (3.0)</td>
</tr>
<tr>
<td></td>
<td>Dexsazon 4 mg/mL</td>
<td>parenteral</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dexazon 0,5 mg (Galenika)</td>
<td>oral</td>
<td>40.00 (0.8)</td>
</tr>
<tr>
<td></td>
<td>Maxidex 5 ml (Alkon)</td>
<td>parenteral</td>
<td></td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>Kenalog 40 mg/mL (Krka)</td>
<td>parenteral</td>
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</table>

## Leukotriene modifiers

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
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<tbody>
<tr>
<td>Zafirlukast</td>
<td>Accolate***</td>
<td>oral</td>
</tr>
<tr>
<td>Montelukast</td>
<td>Singulair***</td>
<td>oral</td>
</tr>
<tr>
<td>5-lipoxygenase inhibitors</td>
<td>Zileuton***</td>
<td>oral</td>
</tr>
</tbody>
</table>

## Drugs with possible, but still unproved antiinflammatory effect

### Long-acting $\beta_2$ agonists (LABA)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhaled LABA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salmeterol</td>
<td>Serevent**</td>
<td>inhaled</td>
</tr>
<tr>
<td>Formoterol</td>
<td>Foradyl***</td>
<td>inhaled</td>
</tr>
<tr>
<td>Oral LABA</td>
<td>Bambec***</td>
<td>oral</td>
</tr>
<tr>
<td>Bambeterol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylxanthines</td>
<td>Theophylline</td>
<td>oral</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>--------------</td>
<td>------</td>
</tr>
<tr>
<td><strong>Sustained-release</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>theophylline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teotard retard 200 mg** (Krka)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teotard retard 350 mg** (Krka)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Durofilin retard 125 mg** (Zdravlje)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Durofilin retard 250 mg** (Zdravlje)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminofilin R 350 mg* (JAKA 80)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminofilinum retard 350 mg (Lek)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Relievers** *(Bronchodilators)*

<table>
<thead>
<tr>
<th>Short-acting β₂ agonists</th>
<th>Salbutamol</th>
<th>oral</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ventolin 2 mg**</td>
<td>oral</td>
</tr>
<tr>
<td></td>
<td>(GlaxoSmithKline GmbH&amp;Co.)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ventolin 2 mg/5 mL*</td>
<td>oral</td>
</tr>
<tr>
<td></td>
<td>(GlaxoSmithKline Production)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ventolin 100 mcg*</td>
<td>inhaled</td>
</tr>
<tr>
<td></td>
<td>(GlaxoSmithKline Pharmaceuticals)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Salmo 2 mg** (Pliva)</td>
<td>oral</td>
</tr>
<tr>
<td></td>
<td>Salmo 2 mg/5 mL** (Pliva)</td>
<td>oral</td>
</tr>
<tr>
<td></td>
<td>Salmo 100 mcg** (Pliva)</td>
<td>inhaled</td>
</tr>
<tr>
<td></td>
<td>Salbutamol 2 mg** (Alkaloid)</td>
<td>oral</td>
</tr>
<tr>
<td></td>
<td>Salbutamol 2 mg/5 mL** (Alkaloid)</td>
<td>oral</td>
</tr>
<tr>
<td></td>
<td>Aloprol 2 mg* (Replekfarm)</td>
<td>oral</td>
</tr>
<tr>
<td></td>
<td>Aloprol 2 mg/5 mL* (Replekfarm)</td>
<td>oral</td>
</tr>
</tbody>
</table>

| Terbutaline              | Terbutalin*** | parenteral |
|                         | Bricanyl***   | inhaled    |

| Fenoterol                | Berotec***    | inhaled    |

**Methylxanthines**

<table>
<thead>
<tr>
<th>Theophylline</th>
<th>Aminofilinum 500 mg/2 mL (Pliva)</th>
<th>parenteral</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aminofilinum 250 mg/10 mL (Pliva)</td>
<td>parenteral</td>
</tr>
<tr>
<td></td>
<td>Aminofilin 250 mg/10 mL (Alkaloid)</td>
<td>parenteral</td>
</tr>
<tr>
<td></td>
<td>Aminofilin 350 mg* (Alkaloid)</td>
<td>oral</td>
</tr>
<tr>
<td></td>
<td>Aminofilin 100 mg* (Alkaloid)</td>
<td>oral</td>
</tr>
<tr>
<td></td>
<td>Aminofilin 100mg** (JAKA 80)</td>
<td>oral</td>
</tr>
<tr>
<td></td>
<td>Odinal 100 mg** (Replekfarm)</td>
<td>oral</td>
</tr>
<tr>
<td></td>
<td>Aminofilinum 100 mg** (Lek)</td>
<td>oral</td>
</tr>
<tr>
<td></td>
<td>Tbl. Aminofilin 100 mg** (Famfarm)</td>
<td>oral</td>
</tr>
</tbody>
</table>

* The drug is included in the Essential Drug List, covered by the Health Insurance Fund of Macedonia

** The drug is not included in the Essential Drug List, covered by the Health Insurance Fund of Macedonia

*** The drug is not registered in R. Macedonia

Available 2007, May 31
### Appendix 8.

#### Estimated comparative daily dosage for inhaled corticosteroids (ICS)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Low daily dose (mcg)</th>
<th>Medium daily dose (mcg)</th>
<th>High daily dose (mcg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adults</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beclomethasone dipropionate</td>
<td>200-500</td>
<td>500-1000</td>
<td>&gt; 1000</td>
</tr>
<tr>
<td>Budesonide</td>
<td>200-400</td>
<td>400-800</td>
<td>&gt; 800</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>500-1000</td>
<td>1000-2000</td>
<td>&gt; 2000</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>100-250</td>
<td>250-500</td>
<td>&gt; 500</td>
</tr>
<tr>
<td><strong>Children</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beclomethasone dipropionate</td>
<td>100-400</td>
<td>400-800</td>
<td>&gt; 800</td>
</tr>
<tr>
<td>Budesonide</td>
<td>100-200</td>
<td>200-400</td>
<td>&gt; 400</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>500-750</td>
<td>1000-1250</td>
<td>&gt; 1250</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>100-200</td>
<td>200-500</td>
<td>&gt; 500</td>
</tr>
</tbody>
</table>

Appendix 9.

*Actual combined inhaled medications used in asthma treatment*

<table>
<thead>
<tr>
<th>Medication</th>
<th>Content</th>
<th>Form of application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seretide</td>
<td>Salmeterol + Fluticasone</td>
<td>Metered-dosed inhaler</td>
</tr>
<tr>
<td>Seretide</td>
<td>Salmeterol + Fluticasone</td>
<td>Diskhaler</td>
</tr>
<tr>
<td>Symbicort</td>
<td>Formoterol + Budesonide</td>
<td>Turbuhaler</td>
</tr>
</tbody>
</table>
Appendix 10.

Rush (hospital) immunotherapy

*Venomil bee / Venomil wasp*

**Initial immunotherapy**

*Initial immunotherapy in extremely sensitive patients*

<table>
<thead>
<tr>
<th>Day</th>
<th>Conc. (µg insect venom/mL)</th>
<th>Volume (mL)</th>
<th>Conc. (µg insect venom/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (1)</td>
<td>0.0001</td>
<td>0.1</td>
<td>0.00001</td>
</tr>
<tr>
<td></td>
<td>0.0001</td>
<td>0.1</td>
<td>0.00002</td>
</tr>
<tr>
<td></td>
<td>0.0001</td>
<td>0.4</td>
<td>0.00004</td>
</tr>
<tr>
<td></td>
<td>0.0001</td>
<td>0.8</td>
<td>0.00008</td>
</tr>
<tr>
<td>2 (2)</td>
<td>0.001</td>
<td>0.1</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>0.001</td>
<td>0.2</td>
<td>0.0002</td>
</tr>
<tr>
<td></td>
<td>0.001</td>
<td>0.4</td>
<td>0.0004</td>
</tr>
<tr>
<td></td>
<td>0.001</td>
<td>0.8</td>
<td>0.0008</td>
</tr>
</tbody>
</table>

*Initial immunotherapy in commonly sensitive patients*

<table>
<thead>
<tr>
<th>Day</th>
<th>Conc. (µg insect venom/mL)</th>
<th>Volume (mL)</th>
<th>Conc. (µg insect venom/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (3)</td>
<td>0.01</td>
<td>0.1</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>0.01</td>
<td>0.2</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>0.01</td>
<td>0.4</td>
<td>0.004</td>
</tr>
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<td></td>
<td>0.01</td>
<td>0.8</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td>0.1</td>
<td>0.1</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>0.1</td>
<td>0.2</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>0.1</td>
<td>0.4</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>0.1</td>
<td>0.8</td>
<td>0.08</td>
</tr>
<tr>
<td>2 (4)</td>
<td>1</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>0.1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>0.2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>0.4</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>0.8</td>
<td>8</td>
</tr>
<tr>
<td>3 (5)</td>
<td>100</td>
<td>0.1</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>0.2</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>0.4</td>
<td>40</td>
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<td>4 (6)</td>
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<td>50</td>
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<td>100</td>
<td>0.6</td>
<td>60</td>
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<td>100</td>
<td>0.8</td>
<td>80</td>
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<td>5 (7)</td>
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<td>0.9</td>
<td>90</td>
</tr>
<tr>
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<td>100</td>
<td>1.0</td>
<td>100</td>
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</tbody>
</table>
Maintenance therapy

Concentration of 100 µg insect venom should be injected in:

1. 7 days-interval
2. 14 days-interval
3. 21 days-interval
4. 28 days-interval

The shots should be applied in a 4 week-intervals in a period of 3 years.

* The sensitivity has to be determined prior to immunotherapy initiation by history of systemic insect sting reaction and positive SPT to concentration of 1µg/mL of the insect venom extract.
Appendix 11.

Conventional (ambulatory) immunotherapy  *Venomil bee / Venomil wasp*

**Initial immunotherapy**

**Initial immunotherapy in extremely sensitive patients** *

<table>
<thead>
<tr>
<th>Day</th>
<th>Conc. (µg insect venom/mL)</th>
<th>Volume (mL)</th>
<th>Conc. (µg insect venom/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1)</td>
<td>0.00001</td>
<td>0.1</td>
<td>0.00001</td>
</tr>
<tr>
<td>(8)</td>
<td>0.0001</td>
<td>0.1</td>
<td>0.00001</td>
</tr>
<tr>
<td>(15)</td>
<td>0.001</td>
<td>0.1</td>
<td>0.0001</td>
</tr>
<tr>
<td>(22)</td>
<td>0.01</td>
<td>0.1</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**Initial immunotherapy in commonly sensitive patients**

<table>
<thead>
<tr>
<th>Day</th>
<th>Conc. (µg insect venom/mL)</th>
<th>Volume (mL)</th>
<th>Conc. (µg insect venom/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (29)</td>
<td>0.1</td>
<td>0.1</td>
<td>0.01</td>
</tr>
<tr>
<td>8 (36)</td>
<td>0.1</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>15 (43)</td>
<td>1</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>22 (50)</td>
<td>1</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>29 (57)</td>
<td>1</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>36 (64)</td>
<td>1</td>
<td>0.05</td>
<td>0.5</td>
</tr>
<tr>
<td>43 (71)</td>
<td>10</td>
<td>0.1</td>
<td>1</td>
</tr>
<tr>
<td>50 (78)</td>
<td>10</td>
<td>0.2</td>
<td>2</td>
</tr>
<tr>
<td>57 (85)</td>
<td>10</td>
<td>0.4</td>
<td>4</td>
</tr>
<tr>
<td>64 (92)</td>
<td>10</td>
<td>0.05</td>
<td>5</td>
</tr>
<tr>
<td>71 (99)</td>
<td>100</td>
<td>0.1</td>
<td>10</td>
</tr>
<tr>
<td>78 (106)</td>
<td>100</td>
<td>0.2</td>
<td>20</td>
</tr>
<tr>
<td>85 (113)</td>
<td>100</td>
<td>0.4</td>
<td>40</td>
</tr>
<tr>
<td>92 (120)</td>
<td>100</td>
<td>0.6</td>
<td>60</td>
</tr>
<tr>
<td>99 (127)</td>
<td>100</td>
<td>0.8</td>
<td>80</td>
</tr>
<tr>
<td>106 (134)</td>
<td>100</td>
<td>1.0</td>
<td>100</td>
</tr>
</tbody>
</table>

**Maintenance therapy**

Concentration of 100 µg insect venom should be injected in:

5. 7 days-interval
6. 14 days-interval
7. 21 days-interval
8. 28 days-interval

The shots should be applied in a 4 week-intervals in a period of 3 years.

* The sensitivity has to be determined prior to immunotherapy initiation by history and positive SPT to concentration of 1µg/mL of the insect venom extract.
List of abbreviations

AC - allergic conjunctivitis
ACE - angiotensin-converting enzyme
AD - atopic dermatitis
AEDS - atopic eczema/dermatitis syndrome
APC – antigen-presenting cell
APT – atopy patch test
AR – allergic rhinitis
ARIA - Allergic Rhinitis and Its Impact to Asthma
ASIT - allergen-specific immunotherapy
ATS - American Thoracic Society
AV – allergy vaccination
B-ly - B lymphocyte
BTS - British Thoracic Society
C - Celsius grade
Can - canis (dog)
CARAS - Combined Allergic Rhinitis and Asthma Syndrome
CD - cluster of differentiation
CFC – chlorofluorocarbons
CIC – circulating immune complexes
CNS - central nervous system
cm – centimeter
CT – computed tomography
CyA – cyclosporine A
DBPCFC - double-blind placebo-controlled food challenge test
De - Debar
Do - Dojran
DPT – dose-provocative test
EAACI - European Academy for Allergology and Clinical Immunology
EAWP - European Allergy White Paper
ECRHS - European Community Respiratory Health Survey
ECSC - European Community for Steel and Coal
EIA - exercise-induced asthma
ECP – eosinophil cationic protein
ENDA - European Network of Drug Allergy
ENT -
EPI - European Pollen Information
ERS - European Respiratory Society
Fel - felix (cat)
FEV1 - forced expiratory volume in 1 second
GA²LEN – Global Allergy and Asthma European Network
GI tract – gastrointestinal tract
GINA - Global Initiative for Asthma
GERD – gastroesophageal reflux disease
gr – gram
h - hour
**ICD-10 – International Statistical Classification of Diseases and Related Health Problems Tenth Revision**
ICS - inhaled corticosteroids
IFN - interferon
IgA - immunoglobulin A
IgG - immunoglobulin G
IgE - immunoglobulin E
IgM - immunoglobulin M
IL - interleukin
ISAAC - International Study of Asthma and Allergies in Childhood
kg. – kilogram
L – litre
LABA – long-acting \( \beta_2 \) agonists
LT – leukotriene
m - meter
MBP - major basic protein
mcg - microgram
mcm - micrometer
MEF - maximal expiratory flow
mg - miligram
MHC – major histocompatibility complex
mL - millilitre
mm – millimeter
MRI – magnetic resonance imaging
NAC – nonallergic conjunctivitis
NAR - nonallergic rhinitis
NSAIDs - nonsteroid anti-inflammatory drugs
OA – occupational asthma
OFC – oral food challenge
Oh – Ohrid
PAC – perennial allergic conjunctivitis
PAR – perennial allergic rhinitis
PC20 - provocative concentration 20
Pe – Pehcevo
PEFR – peak expiratory flow rate
PG - prostaglandin
PG - pollen grains
Pr – Prilep
QAU - quality assurance units
QLQ – quality of life questionnaire
RAST – radioallergosorbent test
SAC – seasonal allergic conjunctivitis
SAR - seasonal allergic rhinitis
SCIT - subcutaneous immunotherapy
Sk – Skopje
SLIT - sublingual immunotherapy
SOTI – specific oral tolerance induction
SPT – skin prick tests
TCI – topical calcineurin inhibitors
TCS – topical corticosteroids
Th - T helper (lymphocyte)
T-ly - T lymphocyte
Tregs - regulatory T cells
UV therapy – ultraviolet therapy
VC - vital capacity
WAO – World Allergy Organization
W/D 12 – wheezing with dyspnea in the last 12 months
WHO – World Health Organization
WRA - work-related asthma
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