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EDITORIAL OFFICE

Institute of Immunophysiology
4, Ostrovityanova Street 117513 Moscow, Russia
Phone: +7(495) 735-1414; fax: +7(495) 735-1441; E-mail: info@wipocis.org
Web site: www.isir.ru

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World Immunopathology Organization (WIPO)

General Information

The World Immunopathology Organization (WIPO) is a professional, non-profit organization. WIPO was created in December 2002, at the I World Congress on Immunopathology in Singapore. During these years, WIPO successfully organized many international congresses and regional and national meetings throughout the world all promoting basic and clinical research and giving an opportunity for exchanging ideas. WIPO is aimed at collecting and disseminating scientific information and providing training and continuous education in various fields of immunopathology.

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Nowadays, immunopathology has become a multidisciplinary problem. The WIPO global mission is to *promote* through education and research activities worldwide:

- basic and clinical research in experimental and clinical immunology, allergy and asthma, autoimmunity, immunodeficiency, AIDS, immunobiotechnology,
- prevention and treatment of different manifestations of immunopathology—immune-associated disorders,
- excellence in patient care in this very important area of medicine

and to establish communication between specialists in various fields of medical science and practice.

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June 15–19, 2018, Tbilisi, Georgia	VI European Congress on Asthma, COPD & Respiratory Allergy
October 18–21, 2018, Moscow, Russia	XII World Congress on Asthma, COPD & Immunopathology

World Immunopathology Organization (WIPO)
Phone: (+7-495) 735-1414; Fax: (+7-495) 735-1441
E-mail: info@wipocis.org **Web site: www.wipocis.org**

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POLLEN ALLERGY, ASTHMA AND CLIMATE CHANGE

Maria D'Amato[1], Carolina Vitale[2], Antonio Molino[1], Mauro Mormile[1], Alessandro Vatrella[2], Alessandro Sanduzzi[1], Gennaro D'Amato[3]

[1]First Division of Pneumology, High Speciality Hospital 'V. Monaldi'
and University 'Federico II'Medical School Naples, Napoli, Italy
[2]Department of Medicine and Surgery, University of Salerno, Salerno, Italy
[3]Division of Respiratory and Allergic Diseases, Department of Chest Diseases,
High Speciality A. Cardarelli Hospital, Napoli, Italy

It is now widely accepted that the earth's temperature is increasing, as confirmed by warming of the oceans, rising sea levels, glaciers melting, sea ice retreating in the Arctic and diminished snow cover in the Northern Hemisphere. Moreover, changes are also occurring in the amount, intensity, frequency and type of precipitation as well as the increase of extreme weather events, like heat waves, droughts, floods and hurricanes; [1–2]. The recent Working Group I Report of the Intergovernmental Panel on Climate Change (IPCC) states "most of the observed increase in globally averaged temperatures since the mid-20th century is very likely due to the observed increase in anthropogenic greenhouse gas concentrations" [1].

Key words: *climate change and pollen allergy, meteorological factors and asthma, pollen calendars, pollen allergy, allergic asthma.*

Address for correspondence: *Professor Gennaro D'Amato MD*
Rione Sirignano, 10-80121 Napoli Italy
E-mail: gdamatomail@gmail.com

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Observational evidence indicates that recent regional changes in climate, particularly temperature increases, have already affected a diverse set of physical and biological systems in many parts of the world [1–2]. A rapid rise has been observed in the number of hot days and severe meteorological events such as the 2003 heat wave where temperatures of 35°C and greater were reached resulting in around forty thousand excess deaths across Europe [3]. Sea levels have also started to rise as an effect of a regression of the polar ice packs. Both events have led to water deprivation in certain areas, often associated with water degradation which potentially could result in population migration and the effects on health that result from mass population movement.

Migration studies provide useful information on the role of environmental factors, including climate changes, on the development of atopy and asthma [5–8]. Migration involves exposure to a new set of pollutants and allergens as well as changes in housing conditions, diet and accessibility to medical services, all of which are likely to affect migrants' health. Atopy and asthma are more prevalent in developed and industrialized countries as compared with undeveloped and less affluent countries, and the effect of migration is age and time-dependent: early age and longer time spent in the new environment increase the likelihood of developing allergenic symptoms such as asthma, rhinoconjunctivitis, or eczema. Migrants should, therefore, be aware of the potential for developing allergies and/or asthma. Strategies for primary prevention in high risk atopic individuals and secondary prevention guidelines should be developed both for populations in developing countries and for immigrants from such countries to atopy-prevalent developed countries.

Climate changes will influence the development of allergic respiratory diseases [5–19]. Climate affects local and national food supplies, air and water quality, weather, economics and many other critical health determinants. Climate change thus represents a massive threat to global health that could affect many disease factors in the 21st century.

There is also a link between climate changes and air pollution, and an individual's response to air pollution depends on the source and components of the pollution, as well as on climatic agents [9–10]. Some air pollution-related episodes of rhinitis and asthma exacerbation are due to climatic factors that favour the accumulation of air pollutants, such as ozone, at ground level. Studies have demonstrated some effects of ozone over respiratory symptoms, acute decreases in lung function, increased airway responsiveness, airway injury and inflammation and systemic oxidative stress. Gent et al. [11] examined the simultaneous effects of ozone and PM2.5 at levels below EPA standards on daily respiratory symptoms and rescue medication use among children with asthma. Daily respiratory symptoms and medication use were examined prospectively for children with physician-diagnosed asthma. Ozone level (but not PM2.5) was significantly associated with respiratory symptoms and rescue medication use among children using maintenance medication. A 50-ppb increase in 1-hour ozone was associated with increased likelihood of wheeze (by 35%) and chest tightness (by 47%). The highest levels of ozone (1-hour or 8-hour

Table 1

Potential health effects of climate change

Climate events	*Agriculture, forestry*	*Human health impact*
Heavy precipitation events: frequency increases over most areas	Damage to crops; soil erosion, inability to cultivate land, water logging of soils; Adverse effects on quality of surface and groundwater; contamination of water supply	Deaths, injuries, infectious diseases, allergies and dermatitis from floods and landslides
Area affected by drought	Land degradation, lower yields/crop damage and failure; livestock deaths; land degradation; More widespread water stress	Increased risk of food and water shortage; increased risk of water and cardiovascular disorders
Number of intense tropical cyclones	Damage to crops; wind throw of trees; Power outages causedisruption of public water supply	Increased risk of water- and food-borne diseases; asthma
Incidence of extreme high sea level	Salinization of irrigation and well water; Decreased freshwater availability due to saltwater intrusion	Increase in stress-related disease; other allergic conditions

averages) were associated with increased shortness of breath and rescue medication use. No significant exposure-dependent associations were observed for any outcome by any pollutant among children who did not use maintenance medication (a marker of asthma severity).

The key determinants of greenhouse gas emissions are energy production, transportation, agriculture, food production and waste management, and attempts at mitigating climate change will need to address each of these. However, while there is some uncertainty about predicting future meteorological trends, whatever interventions may be put in place to ameliorate climate change, it more periods of heavy rain and consequent flooding [12]. Paradoxically it is likely that there will be more periods of drought. A huge increase in CO2 concentrations during the last two decades has been experienced (figure 1). However, it is important to consider that after CO2 emissions are reduced and atmospheric concentrations stabilize, surface air temperature continues to rise slowly for a century or more.

The effect of climate changes on allergic and respiratory diseases

A body of evidence suggests that major changes involving the atmosphere and the climate, including global warming induced by human activity, have an impact on the biosphere and human environment [3, 18, 43–45]. A synthesis of the health effects due to climate change is presented in table 1.

Studies on the effects of climate changes on respiratory allergy are still lacking and current knowledge is provided by epidemiological and experimental studies on the relationship between asthma and environmental factors, e.g., meteorological variables, airborne allergens and air pollution. Climate change is correlated with allergens for several reasons:

(i) increase and faster plant growth;

(ii) increase in the amount of pollen produced by each plant;

(iii) increase in the amount of allergenic proteins contained in pollen;

(iv) increase in the start time of plant growth and therefore the start of pollen production and

(v) earlier and longer pollen seasons.

Climate changes affect allergenic plants and pollen distribution worldwide [13, 17–20].

There is also considerable evidence that subjects affected by asthma are at increased risk of developing obstructive airway exacerbations with exposure to gaseous and particulate components of air pollution [11]. Climate change coupled with air pollutant exposures may have potentially serious adverse consequences for human health in urban and polluted regions. Data also suggest that air pollution can lead to the development of asthma [14–16].

It is not easy to evaluate the impact of climate changes and air pollution on the prevalence of asthma in general and on the timing of asthma exacerbations, but the global rise in asthma prevalence and severity indicates that air pollution and climate changes could be contributing.

Effect of climate change on pollen allergy

Pollen allergy is frequently used to study the interrelationship between air pollution and allergic respiratory diseases (rhinitis and asthma). Epidemiologic studies have demonstrated that urbanization, high levels of vehicle emissions and westernized lifestyle are correlated with an increase in the frequency of pollen-induced respiratory allergy in people who live in urban areas compared to those who live in rural areas [18].

Studies on plant responses to elevated CO2 concentrations indicate that plants exhibit enhanced photosynthesis and reproductive effects and produce more pollen [13, 17–19]. An earlier start and peak of the pollen season is more pronounced in species that start flowering early in the year. Moreover, plants flower earlier in urban areas than in the corresponding rural areas with earlier pollination of about 2–4 days. Meteorological factors (temperature, wind speed, humidity, thunderstorms etc) along with their climatic regimes (warm or cold anomalies and dry or wet periods etc), can affect both biological and chemical components of this interaction. In addition, by inducing airway inflammation, air pollution overcomes the mucosal barrier, leading to the priming of allergen-induced responses.

Climate changes might induce negative effects on respiratory allergic diseases favouring the increased length and severity of the pollen season, the higher occurrence of heavy precipitation events and the increasing frequency of urban air pollution episodes.

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The main diseases of concern are asthma, rhinosinusitis, COPD and respiratory tract infections, but the extent to which these are affected will vary according to the proportion of susceptible individuals in a given population. Areas of greater poverty with limited access to medical care will suffer more as will those areas with less well developed medical services which are likely to include migrating populations and those with the greatest population growth.

With warming over the longer term, changing patterns of plant habitat and species density are likely, with gradual movement northward in the Northern Hemisphere, and further south in the Southern Hemisphere. The change in land use might also play a relevant role, especially for some important allergenic species, such as grasses. Since most data come from the analysis of distribution of airborne pollen, these findings are potentially biased by the occurrence of long and medium distance transport episodes of allergenic pollen [21–22].

Climatic factors (temperature, wind speed, humidity, thunderstorms etc) can affect both components (biological and chemical) of this interaction [23–29). By attaching to the surface of pollen grains and of plant-derived particles of paucimicronic size, pollutants could modify not only the morphology of these antigen-carrying agents but also their allergenic potential. In addition, by inducing airway inflammation, which increases airway permeability, pollutants overcome the mucosal barrier and could be responsible for "priming" the allergen-induced responses of pollinosis in allergic and atopic individuals. However, the relationship between air pollution, pollen exposure and respiratory allergy is based on an individual's response to air pollution, which depends on the source and components of the pollution, as well as on climatic agents.

Interaction between climate change and urban air pollution

Some air pollution-related episodes of asthma exacerbations are due to climatic factors that favour the accumulation of air pollutants at ground level, and some cities are continuously affected by pollution caused by motor vehicles [19, 26–27]. Air pollution can interact with allergen-carrying paucimicronic particles derived from plants [28]. The paucimicronic particles, pollen-originated or not, are able to reach peripheral airways with inhaled air, inducing asthma in sensitized subjects. Air pollution – in particular PM, DEP, ozone, nitrogen dioxide and sulfur dioxide – have been shown to have an inflammatory effect on the airways of susceptible subjects, causing increased permeability, easier penetration of allergens into the mucus membranes, and easier interaction with cells of the immune system [30]. There is also evidence that predisposed subjects have increased airway reactivity induced by air pollution and increased bronchial responsiveness to inhaled allergens.

Some pollutants seem to have an adjuvant immunologic effect on IgE synthesis in atopic subjects – in particular, DEPs, which can interact in atmosphere with pollens or paucimicronic particles [27]. It is also important to consider that in the Mediterranean area (Greece, Spain, Italy etc), in California and other areas, hundreds of thousands of hectares of woods are destroyed each year by fire. Moreover, fire produces millions of tons of CO2 which play a role in the greenhouse effect [24–26].

Thunderstorm-related allergic respiratory diseases and bronchial asthma in pollinosis subjects

Thunderstorms occurring during the pollen season have been observed to induce severe asthma attacks in pollinosis patients [29–40].

Associations between thunderstorms and asthma morbidity have been identified in multiple locations around the world [32-47). The most prominent hypotheses for thunderstorm-related asthma are linked with bioaerosols, and involve the role of rainwater in promoting the release of respirable particulate matter.

After hydratation and rupture by osmotic shock during the beginning of a thunderstorm, pollen grains release part of their cytoplasmic content into the atmosphere, including inhalable, allergen-carrying paucimicronic particles such as starch granules and other cytoplasmic components [28–29].

In summary, the occurrence of these epidemics is closely linked to thunderstorms; the thunderstorm-related epidemics are limited to late spring and summer when there are high levels of airborne pollen grains; there is a close temporal association between the arrival of a thunderstorm, a major rise in concentration of pollen grains and the onset of asthma epidemics. As a consequence, subjects affected by pollen allergy should be alert to the danger of being outdoors during a thunderstorm in the pollen season.

Changes in the profile of local allergens

We urgently need to monitor changes in vegetation and airborne allergens arising from climate change so that new allergen vaccines can be available for immunotherapy. Allergists should also be alert to changes in insect, mite, fish and animal populations that could give rise to new environmental allergen exposures, with the potential for new allergic sensitizations and a concomitant increase

Conclusions

Climate changes affect many physical and biological systems including the immunologic and respiratory systems that are critical to human health, and it is foreseeable that environmental risk factors will have a stronger effect in the coming decades [40–47]. Climate changes interact with and affect air pollution and pollinosis, which in turn increases the frequency and severity of asthma, and affects the clinical expression of allergic disease. Climate change affects the timing, dispersion, quantity, and quality of aeroallergens and the distribution and severity of allergic disease. Climate change alters local weather patterns including minimum and maximum temperature, rain precipitation, and storms, all of which affect the burden of allergic disease.

A combined approach comprises primary prevention by greenhouse gas mitigation to stabilize the climate, and secondary prevention by clinical intervention to minimize climate change–related increases in asthma and allergic disease [40].

Climate changes in the future may depend on how rapidly and successfully global mitigation and adaptation strategies are deployed. The effect of human intervention and efforts to minimize changes in vegetation and aeroallergen exposure remains to be seen.

Reducing air pollution might contribute to lessening of the impact of climate change on pollen and thus directly on patients, while recognizing that ozone, the key pollutant associated with climate change, may be the major driver of pollutant/pollen interactions.

What can we do to decrease the effects of environmental factors affecting respiratory allergic diseases? Suggested measures are as follows: encouraging policies to promote access to non-polluting sources of energy; reducing the private traffic in towns and improving public transport; decreasing the use of fossil fuels and controlling vehicle emissions; planting non-allergenic trees in cities, and in this context the proposed implantation of new trees should be evaluated by allergy specialists in order to avoid high allergenic species.

Many measures to reduce greenhouse gas emissions may have positive benefits for health. These co-benefits will offset at least some of the costs of climate change mitigation and should be taken into account in international negotiations.

In conclusion, strategies to reduce climatic changes and air pollution are political in nature, but citizens, and in particular health professionals and societies, must raise their voices in the decision process to give strong support for clean air policies at both national and international levels.

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Meeting Calendar

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March 2–5, 2018 Orlando, USA

WAO–AAAAI JOINT CONGRESS

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EXTREME METEOROLOGICAL EVENTS (THUNDERSTORMS DURING POLLEN SEASONS), CLIMATE CHANGE AND ASTHMA ATTACKS

Maria D'Amato[1], Carolina Vitale[2], Antonio Molino[1], Alessandro Sanduzzi[1], Mauro Mormile[1], Giovanna Calabrese[1], Giorgio Emanuele Polistina[1], Alessandro Vatrella[2], Gennaro D'Amato[3]

[1]First Division of Pneumology, High Speciality Hospital 'V. Monaldi' and University 'Federico II' Medical School Naples, Napoli, Italy
[2]Department of Medicine and Surgery, University of Salerno, Salerno, Italy
[3]Division of Respiratory and Allergic Diseases, Department of Chest Diseases, High Speciality A. Cardarelli Hospital, Napoli, Italy

There are observations that thunderstorms occurring during pollen seasons can induce severe asthma attacks in pollinosis patients [1]. According to current climate change scenarios, there will be an increase in intensity and frequency of heavy rainfall episodes, including thunderstorms, over the next few decades, which can be expected to be associated with an increase in the number and severity of asthma attacks both in adults and in children [2–3]. Associations between thunderstorms and asthma attacks have been identified in multiple locations around the world [4]. So, called "thunderstorm asthma" is characterized by asthma outbreaks possibly caused by the dispersion of more respirable allergenic particles derived from pollen and spores [1, 5–6].

Keywords: *climate change and thunderstorms, climate change and pollen allergy, bronchial asthma, severe asthma, near fatal asthma, thunderstorm-related asthma, meteorological factors and asthma, prevention of thunderstorm-related asthma*

Address for correspondence: *Professor Gennaro D'Amato MD*
Rione Sirignano, 10-80121 Napoli Italy
E-mail: gdamatomail@gmail.com

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Thunderstorms have been linked to asthma epidemics, especially during the pollen seasons, and there are descriptions of asthma outbreaks associated with thunderstorms, which occurred in several cities, prevalently in Europe (Birmingham and London in the UK and Napoli in Italy) and Australia (Melbourne and Wagga Wagga) [1, 4, 7] (Table 1). The thunderstorm-asthma outbreaks are characterized, at the beginning of thunderstorms, by a rapid increase of visits for asthma in general practitioner or hospital emergency departments. Subjects without asthma symptoms, but affected by seasonal rhinitis can experience an asthma attack.

No unusual levels of air pollution were noted at the time of the epidemics, but there was a strong association with high atmospheric concentrations of pollen grains such as grasses or other allergenic plant species. However, subjects affected by pollen allergy should be informed about a possible risk of asthma attack at the beginning of a thunderstorm during pollen season.

On 21 November 2016 in Melbourne there was a dramatic event with 8 deaths and 8500 patients who needed medical treatments in Emergency departments of Melbourne Hospital for asthma attacks [7]. This in Melbourne has been the worst event of thunderstorm-asthma.

One of the first observations regarding thunderstorms and asthma outbreaks was provided by Packe and Ayres at the East Birmingham Hospital (Birmingham, UK) on July 6 and 7, 1983. These authors described a remarkable increase in the number of asthma emergency department admissions during the hours of a thunderstorm. In a 36-h period, 26 asthma cases were treated in the emergency department, compared with a daily average of two or three cases in the days preceding the outbreak.

Another asthma outbreak occurred in London, UK, coinciding with a heavy thunderstorm on June 24, 1994, when a large increase in the number of visits for asthma at the emergency departments of London and the southwest of England was observed. Several patients who were examined, who were not known to be asthmatics or were affected only by seasonal rhinitis, experienced an asthma attack. During a 30-h period from 6 p.m. on June 24, 1994, 640 patients with asthma or other airways disease (283 of whom

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Table 1

Epidemics of thunderstorm-associated asthma outbreaks [1, 4, 7]

Year	*Country*	*Observations*
1983	UK	26 sudden cases of asthma attacks in relation to thunderstorms.
1992	Australia	Late spring thunderstorms in Melbourne can trigger epidemics of asthma attacks (five to 10-fold rise).
1997	UK	Asthma or other airways disease hospital visits. 640 cases who attended during a 30-h period on June 1994, nearly 10 times expected number.
1992–2000	Canada	18 970 hospital ED asthma visits among children 2–15 years of age. Summer thunderstorm activity was associated with an OR of 1.35 (95% CI 1.02–1.77) relative to summer periods with no activity.
1993–2004	USA	215 832 asthma ED visits; 24 350 of these visits occurred on days following thunderstorms. Significant association between daily counts of asthma ED visits and thunderstorm occurrence. Asthma visits were 3% higher on days following thunderstorms.
2000	Australia	Asthma visits during thunderstorms. History of hayfever and allergy to ryegrass are strong predictors for asthma exacerbation during thunderstorms in spring.
2001	Australia	The incidence of excess hospital attendances for asthma during late spring and summer was strongly linked to the occurrence of thunderstorm outflows.
2002	UK	A case-control study of 26 patients presenting to Cambridge University Hospital with asthma after the thunderstorm Alternaria alternata sensitivity is a compelling predictor of epidemic asthma in patients with seasonal asthma and grass pollen allergy and is likely to be the important factor in thunderstorm-related asthma.
2004	Italy	Six cases of thunderstorm-related asthma because of pollen (Paretaria).
2010	Italy	20 cases of thunderstorm-related asthma because of pollen (olive tree).
2010	Australia	Epidemics of 'thunderstorm asthma' that occurred in Melbourne during spring 2010. The approach of spring, together with high winter rainfall in and around Melbourne that heralds another severe pollen season, raises the risk of allergic rhinitis and asthma in pollen-sensitive individuals.
2016	Australia	Epidemics of thunderstorm asthma in Melbourne with 8 deaths and 8500 in emergency department.

were not known to be asthmatic and 403 were affected only by seasonal rhinitis) attended several emergency departments, nearly 10 times the expected number of 66 patients. In total, 104 patients were admitted (including five to an intensive care unit) (574 patients attributable to the thunderstorm).

Other asthma outbreaks during thunderstorms have been described in Australia. In Melbourne, other than the dramatic outbreak of 21 November 2016, two large asthma outbreaks (rapid increase in hospital or general practitioner visits for asthma) coincided with thunderstorms. In Wagga Wagga, 215 asthmatic subjects attended the local emergency department, 41 of whom required admission to hospital.

In south eastern Australia, Marks et al. [8] observed that the incidence of excess hospital attendances for asthma during late spring and summer was strongly linked to the occurrence of thunderstorm outflows and demonstrated that the arrival of a thunderstorm outflow was accompanied by a large increase in the concentration of ruptured pollen grains in ambient air.

2004, when five adults and one child received treatment in emergency departments. One patient was admitted to an intensive care unit for a very severe bronchial obstruction and acute respiratory insufficiency following a sudden thunderstorm. All individuals were outdoors when the thunderstorm struck. In one severe case, a female sensitized only to Parietaria pollen allergen, soon began to show symptoms of intense dyspnoea, which gradually worsened. She was taken to hospital where she was intubated and given high intravenous doses of corticosteroids. She was discharged a few days later. This patient had previously suffered from seasonal asthma but had been asthma-free for the past few years and did not need continuous therapy. None of the other five subjects took anti-allergic and/or anti-asthma drugs regularly.

All six patients were sensitized with allergic respiratory symptoms upon exposure to Parietaria pollen, but were not sensitized to grasses. Parietaria is an Urticacea that is widespread in the Naples area of Italy with a spring and summer pollen season that is, in part, coexistent with that of grasses.

During the thunderstorm, the concentration of airborne Parietaria pollen grains was particularly high, with a peak of 144 grains/m^3 being recorded on June 3, 2004. Air pollution levels for both gaseous and particulate components based on the hourly concentrations of nitric dioxide, ozone and respirable particulate matter were not particularly high in Naples on June 3 and 4, 2004.

Subjects with sensitization to Parietaria who were indoors in Naples with the windows closed during the night between June 3 and 4, 2004, did not experience asthma attacks. No moulds or viruses were involved in the Naples epidemics. Other outbreaks and/or case reports have been described in Barletta, Cartagena, Atlanta.

A similar phenomenon has been suggested for moulds after the observation of a possible key role of sensitization to Alternaria species in thunderstorm-related asthma.

Characteristics of described epidemics of thunderstorm-associated asthma
• The occurrence of epidemics is closely linked to thunderstorm • The thunderstorm-related epidemics are limited to late spring and summer when there are high levels of airborne pollen grains. • There is a close temporal association between the arrival of the thunderstorm, a major rise in the concentration of pollen grains and the onset of epidemics. • Patients with pollen allergy, who stay indoors with windows closed during thunderstorm, are not involved. • There are no high levels of gaseous and particulate components of air pollution There is a major risk for patients who are not under antiasthma correct treatment.

Although much remains to be discovered about the relationship between an increase in the number of asthma attacks and thunderstorms, reasonable evidence exists in favour of a causal link between them in patients suffering from pollen allergy. The most prominent hypotheses for thunderstormrelated asthma are linked with bioaerosols, and involve the role of rainwater in promoting the release of respirable particulate matter [1]. Pollen grains can be carried by thunderstorm at ground level, where pollen rupture would be increased with release of allergenic biological aerosols of paucimicronic size, derived from the cytoplasm and which can penetrate deep into lower airways. In other words, there is evidence that under wet conditions or during thunderstorms, pollen grains may, after rupture by osmotic shock, release into the atmosphere part of their content, including respirable, allergen-carrying cytoplasmic starch granules (0.5–2.5 lm) or other paucimicronic components that can reach lower airways inducing asthma reactions in pollinosis patients.

These allergens can likely penetrate deeper into the lung, provoking more severe symptoms. It has been suggested that grass pollen starch granules are the most likely cause of associations between thunderstorms and asthma [8]. Suphioglu et al. [9] showed that ryegrass pollen grains contain a large amount of starch granules coated with allergens. After being ruptured in rainwater by osmotic shock, each grain can release 700 starch granules, which are small enough to penetrate the airways and trigger asthma attacks in previously sensitized subjects. Later Taylor et al. [10] hypothesized that the turbulent front of the advancing outflow releases more pollen from flowering grasses and grass pollen may release large amounts of paucimicronic allergenic particles, that is cytoplasmatic starch granules containing grass allergens (allergenbearing starch granules), after rupture by osmotic shock during thunderstorms. Even though thunderstorms can induce severe asthma attacks or exacerbations, they are neither frequent nor responsible for a high amount of disease exacerbation. This constitutes a major concern nowadays as the possibility of thunderstorm-associated asthma outbreaks have become of dramatic actuality due to the "highly likely" increase in frequency of heavy precipitation events, including thunderstorms, projected by the climate change scenarios for the future decades [2–3].

In summary, the occurrence of these epidemics is closely linked to thunderstorm and they are limited to late spring and summer when there are high levels of airborne pollen grains. There is a close temporal association between the arrival of the thunderstorm, a major rise in the concentration of pollen grains and the onset of epidemics. As a consequence, subjects affected by pollen allergy should be alert to the danger of being outdoors during a thunderstorm in the pollen season.

Authors declare they haven't conflict of interest.

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ADVANCES IN SEVERE ASTHMA TREATMENT

Diego Bagnasco, Matteo Ferrando, Giovanni Passalacqua

Allergy and Respiratory Diseases, Policlinico San Martino,
University of Genoa, Italy

Bronchial asthma remains a major health problem in all age groups for patients, their families and the community. In the majority of patients, asthma can be adequately treated with the standard of care therapy, and most patients achieve a satisfactory control of the disease. Nonetheless, a subgroup of subjects remains "difficult-to treat" or "uncontrolled" despite adequate therapy. Severe asthma accounts for only 5–10% of all cases, but it is responsible for the majority of direct and indirect costs. Thus, severe asthma poses, therefore, a relevant health care burden. In the report, various therapies for severe asthma are discussed: biological treatment with monoclonal antibodies towards sensible targets of the immune inflammation, and allergen specific immunotherapy. Only uncontrolled asthma is now recognized as an absolute contraindication to the use of allergen specific immunotherapy.

Key words: *homogeneous phenotypes, allergen sensitization, immune inflammation, monoclonal antibodies.*

Address for correspondence: *Professor Giovanni Passalacqua*
Allergy and Respiratory Diseases
IRCCS San Martino-IST, University of Genoa
Genoa 16132, Italy
E-mail: assalacqua@unige.it

UDC 616.211-002:616.248

Bronchial asthma, which prevalence is 5–10% worldwide [1–2], remains a major health problem in all age groups for patients, their families and the community. The asthma-related symptoms cause limitations in everyday activity with consequent additional indirect costs. Exacerbations may require extra visits, emergency room admissions, and hospitalizations. Of note, fatalities continue to be reported [3]. Indeed, in the majority of patients, asthma can be adequately treated with the standard of care therapy [4], and most patients achieve a satisfactory control of the disease. Nonetheless, a subgroup of subjects remains "difficult-to treat" or "uncontrolled" despite adequate therapy. "Severe" asthma, that remains uncontrolled and needs frequent systemic steroids, is a heterogeneous condition that encompasses different phenotypes/endotypes, such as eosinophilic, obesity-related, neutrophilic, late onset asthma, and remains a major unmet need [5–6]. Severe asthma accounts for only 5–10% of all cases, but it is responsible for the majority of direct and indirect costs. Thus, severe asthma poses, therefore, a relevant health care burden.

The heterogeneity of asthma is well known. There were numerous attempts to identify homogeneous phenotypes, but these attempts always faced the large overlap among clinical presentations. To date the only, although gross, acceptable phenotyping distinguishes the Th2-high (*e.g.*, allergic asthma with allergen sensitization, early onset and eosinophilic inflammation) and the Th2-low phenotype (*e.g.,* asthma with obesity ore late onset asthma with poor inflammation) [5]. The more detailed knowledge on the pathogenic mechanisms of asthma, especially in its severe form, lead to the development of biological treatments, in particular monoclonal antibodies towards sensible targets of the immune inflammation.

For historical and cultural reasons, the antagonism towards IgE was the first approach attempted, and the monoclonal anti IgE antibody (Omalizumab) was commercialized more than 10 years ago. Its efficacy and safety in severe allergic asthma is now well established [6], and some effects on the bronchial remodeling have also been suggested [7]. IL-5, that is specific for eosinophil activation, proliferation and survival, immediately appeared as a suitable target for biological treatments.

In fact, anti-IL-5 monoclonal antibodies (mepolizumab, reslizumab) were synthesized and rapidly tested in clinical settings with very favourable results. Mepolizumab (Nucala TM) and Reslizumab (Cinquaero TM) are now approved and commercialized [8]. Another possible choice is to antagonize the IL-5 receptor alpha subunit, as done with the monoclonal antibody benralizumab. This latter approach, in addition to a significant clinical improvement, lead to an enhanced apoptosis of eosinophil cells [9]. IL-4 and IL-13 are other targets of interest for specific antagonism. IL-4 enhances IgE production, whereas IL-13 is deeply involved in bronchial inflammation, mucus secretion and smooth muscle contraction. IL-13 AND IL-4 share in part the same receptor, thus a monoclonal antibody directed towards the common subunit was synthesized (Dupilumab). This monoclonal antibody displayed a remarkable effect on asthma symptoms and exacerbations, and it is expected to be commercialized soon for asthma, whereas now accepted for atopic dermatitis [10].

Finally, allergen specific immunotherapy (AIT) has been now recognized as a valuable adjunct in asthma treatment, and only uncontrolled asthma is now recognized as an absolute contraindication to the use of AIT, provided that the causal allergen is clearly identified.

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Meeting Calendar

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April 20–23, 2018 Barcelona, Spain

XI WORLD *ASTHMA, ALLERGY & COPD* FORUM

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Phone: (+7-495) 735-1414; Fax: (+7-495) 735-1441
E-mail: info@wipocis.org

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ALLERGEN IMMUNOTHERAPY: WAYS FORWARD

Giovanni Passalacqua

Allergy and Respiratory Diseases, Policlinico San Martino, University of Genoa, Italy

Allergen specific immunotherapy was introduced in clinical practice more than one century ago and due to its clinical efficacy it is widely spread now. There are two modes of administration: SCIT (subcutaneous injections) and SLIT (sublingual administration). The clinical efficacy of SLIT and SCIT are equivalent, although SLIT has a more favorable safety profile. New modalities of administration are also discussed in this report, namely intralymphatic and epicutaneous. Those routes of administration seem to achieve a clinical efficacy similar to the traditional SLIT and SCIT routes, with lower doses of allergen(s) and/or reduced side effects.

Key words: *immune response, subcutaneous injections, SLIT, asthma, atopic dermatitis, allergic disorders.*

Address for correspondence: *Professor Giovanni Passalacqua*
Address: Allergy and Respiratory Diseases
IRCCS San Martino-IST-University of Genoa
Genoa 16132, Italy
E-mail: assalacqua@unige.it

UDC 615.234

Allergen specific immunotherapy (AIT) was introduced in clinical practice more than one century ago, with the supposed aim of "vaccinating" against hypothetical "aerogenic toxins". Despite the rationale was wrong, the procedure resulted to be clinically effective and therefore rapidly spread. Subcutaneous injections (SCIT) remained the only mode of administration for more than 70 years, when new modalities were proposed, with the aim of improving the safety and convenience. Among the various routes proposed, the sublingual one (SLIT) rapidly gained credibility, so that it was accepted as a viable alternative to SCIT in all official documents and guidelines [1]. In general, the clinical efficacy of SLIT and SCIT are equivalent, although SLIT has a more favorable safety profile [2].

To date, the practice of SCIT is sufficiently standardized, as testified by position papers and practice parameters [3–6]. On the other hand, SLIT can be administered as drops, monodose vials or tablets, with variable timings and doses depending on the manufacturer. In the last decade, highly standardized products in tablets (grass, mite, ragweed) have been approved as drugs by EMA and FDA. The aim of AIT is of interfering with the immune response to the offending allergen, thus inducing a tolerance that results in a reduction of symptoms and medication intake upon natural exposure to the allergen itself. SCIT usually consists of an updosing phase (with gradually increasing doses of the allergen) followed by a maintenance phase, were the maximum dose is given at regular intervals (usually monthly) for 3–5 years. With SLIT, due to the favorable safety profile, the updosing phase is absent or very short, and the maintenance is given on daily basis.

It is true that SLIT represented an important step forward in AIT, but also it probably prompted more detailed investigations, leading to novel possible therapeutic approaches. Of note, some randomized controlled trials specifically designed for asthma were performed with AIT [7–9]. Asthma ever remained an uncertainty for the use of AIT, since the majority of the studies had been conducted in rhinitis, without objective assessments for asthma, and asthma was considered a risk factor for adverse events by AIT. The new trials, indeed, showed that AIT is clinically effective also on asthma symptoms and can reduce the exacerbation rate and the consumption of controller medications. In addition, an extensive review of literature suggested that asthma is not an absolute contraindication to the use of AIT [10]. For this reasons, SLIT have been recently accepted as an adjunct treatment in the GINA document [11].

The more and more detailed immunological and clinical knowledge on allergic disorders [12] provided the opportunity for new approaches. For instance, new modalities of administration were proposed, namely intralymphatic and epicutaneous. Those routes of administration seem to achieve a clinical efficacy similar to the traditional SLIT and SCIT routes, with lower doses of allergen(s) and/or reduced side effects [13–14]. The use of AIT was also proposed for other atopic disorders such as atopic dermatitis, although the results in such condition are promising, but not conclusive [15].

The other relevant and promising aspect of AIT (in this case "oral desensitization") is food allergy. In fact, numerous controlled trials showed that the administration of gradually ascending doses of the offending food (milk, egg, peanut), can achieve a full tolerance to the food itself [16]. It is still not clear if this procedure can induce a permanent desensitization, or if the achieved tolerance must be maintained with a regular assumption of the food. The use of desensitization (either oral or sublingual) is nonetheless confined to research, and it is recommended that this practice must be performed only under medical supervision, due to the occurrence (about 20%) of severe adverse reactions [17].

Finally, the introduction of molecular diagnosis instruments allowed to better refines the prescription of AIT [18]. In this regard, the use of a "tailored" AIT, considering only

the relevant allergenic molecules still remains a new horizon, despite the high costs.

AIT, in any field of application (e.g. when the pathogenic mechanism is well known) recognized surprising advancements in the last decade. The use of the component resolved diagnosis model, the bio-engineering techniques and, especially the enterprise of large-population based (often with a dose-finding design) trials, allowed to better define the indications and limitations of this therapeutic approach.

This keeps true in particular for SLIT that still remains the most investigated route of administration, also due the introduction of the tablet formulation. The use of SLIT or "oral desensitization", in its various forms and procedures, also remain an intriguing field of research for food allergy. Finally, it must be highlighted, that it is currently not possible, and not scientifically correct, to consider the clinical effects of AIT as a general "class effect", but the efficacy needs to be clearly demonstrated and documented for each single product, with a well-defined dose.

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Meeting Calendar

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May 26–30, 2018 Munich, Germany

EUROPEAN ACADEMY OF ALLERGOLOGY AND CLINICAL IMMUNOLOGY(EAACI) CONGRESS

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NEW INSIGHTS INTO THE MECHANISMS OF ACTION OF MECHANICAL BACTERIAL LYSATES IN THE TREATMENT OF RESPIRATORY TRACT DISEASES

Giacomo Sidoti Migliore, Stefania Campana, Chiara Barberi, Claudia De Pasquale, Paolo Carrega, Giovanni Melioli, Guido Ferlazzo

Laboratory of Immunology and Biotherapy, Department of Human Pathology, University of Messina, Mesina, Italy

Bacterial lysates are widely employed in the treatment of respiratory tract infections. In this paper we show that human airway epithelial cells can directly recognize bacterial lysates obtained by mechanical lysis and, as a consequence, undergo a significant cell proliferation and up-regulation and *de novo* expression of different adhesion molecules involved in cell-cell junctions and cell-matrix adhesions, which represents critical structures for maintaining the epithelial barrier.

Key words: *respiratory tract diseases, treatment, bacterial lysates, mechanism of action.*

Address for correspondence: *Professor Guido Ferlazzo*
Piazza Pugliatti, 1, 98122 Messina ME, Italy
Laboratory of Immunology and Biotherapy, Deptartment of Human Pathology, University of Messina
E-mail: guido.ferlazzo@unime.it

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Bacterial lysates have been introduced in the prevention of common human infections since the beginning of the past century. The original aim of a therapeutic approach based on bacterial-derived antigens was the induction of a specific adaptive immune response against pathogens invading different organs, in particular upper and lower respiratory tract infections.

Despite the wide use of this prophylactic approach and several evidences of efficacy [1] few information are yet available regarding the fine mechanisms of action of bacterial lysates. It is conceivable that bacterial antigen-based drugs should be able to mediate the maturation of dendritic cells (DCs) because of the presence, in the bacterial lysate, of a suitable amount of structures acting as ligands of the Pattern Recognition Receptor system expressed on circulating monocyte and immature DCs [2]. Indeed, it has been shown that the oral administration of chemically lysed bacteria of the respiratory tract was able to mediate the maturation of dendritic cells [3].

Likewise, we have previously shown similar results employing polyvalent mechanical bacterial lysate (PMBL), a commercial drug containing a mixture of microbial bodies obtained from mechanically killed bacteria, which included *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Hemophilus influenzae*, *Moraxella catarrhalis* and *Klebsiella pneumoniae*. In particular, we demonstrated a higher capacity of the bacterial strain mixture versus single bacterial strains to induce DC maturation, both in terms of expression of an activating phenotype and secretion of relevant cytokines and chemokines on different DC subsets, including monocyte-derived DC, circulating myeloid DCs and plasmacytoid DCs [4].

Remarkably, we have previously demonstrated that the weak naturally induced IgA secretion at salivary level could be significantly increased by the stimulation of mouth mucosa immunity with a Polyvalent Mechanical Bacterial Lysate (PMBL) [5].

Nevertheless, despite the clear evidence of DC activation and of a *de novo* secretion of anti-bacterial body IgA, the mechanisms of action of bacterial lysates appears to mainly rely on innate immune response [6] and, at present, still appears only partially clarified.

Because bacterial lysates are mainly employed in the treatment of respiratory tract infections, we should start to consider the complexity of the innate response in the airway epithelium, which represents the first point of contact for inhaled foreign organisms. The protective arsenal of the airway epithelium is provided in the form of physical barriers and a vast array of receptors and antimicrobial compounds that constitute the innate immune system. Many of the known innate immune receptors, including the Toll-like receptors and nucleotide oligomerization domain-like receptors, are expressed by the airway epithelium, which leads to the production of proinflammatory cytokines and chemokines that affect microorganisms directly and recruit immune cells, such as neutrophils and T cells, to the site of infection. The release of soluble factors by the airway epithelium activated by pathogens, and presumably by bacteri-

al lysates, can also affect the mucosal physical barrier, which itself represents part of the airways innate immunity.

In this paper we show that human airway epithelial cells can directly recognize bacterial lysates obtained by mechanical lysis and, as a consequence, undergo a significant cell proliferation and up-regulation and *de novo* expression of different adhesion molecules involved in cell-cell junctions and cell-matrix adhesions, which represents critical structures for maintaining the epithelial barrier.

Material and Methods

Bacterial Lysates. As bacterial lysates, the PMBL Ismigen® (Lallemand Pharma) was employed. Ismigen® represents a mixture of 13 lyophilized bacterial strains: *S. aureus, S. viridans, S. pneumoniae* (6 strains), *S. pyogenes, K. pneumoniae, K. ozaenae, M. catarrhalis* and *H. influenzae*. For our experiments, the bacterial lysate was resuspended in PBS at 5mg/ml, then added to the cell cultures at the final concentration of 100 µg/ml.

Cell cultures. The human NSCLC cell line A549 was purchased from Interlab Cell Line Collection of IRCCS AOU San Martino-IST-Istituto Nazionale per la Ricerca sul Cancro and cultured in RPMI medium supplemented with FBS 10% and penicillin/streptomycin. Human normal bronchial epithelial cells (HBEpiCs, Cat. No. 3210) were purchased from Sciencell and cultured in Human Bronchial Epithelial Cell Medium (HBEpiCM, Cat. No. 3211) supplemented with Bronchial Epithelial Cell Growth Supplements (HBEpiCGS, Cat. No. 3262) and penicillin/streptomycin solution (P/S, Cat. No. 0503).

Flow Cytometry. The following monoclonal antibodies to human proteins were used. From Miltenyi: APC-conjugated anti-EpCAM (dil: 1:100). From BD Biosciences: PE-conjugated anti-CD54 (ICAM-1, dil: 1:100), APC-conjugated anti-CD54 (ICAM-1, dil: 1:100), PE-conjugated anti-EpCAM (dil: 1:100), BV421-conjugated anti-CD324 (E-Cadherin, dil 1:50), BV421-conjugated anti-Ki67 (dil: 1:100). Intranuclear staining with BV421-conjugated anti-Ki67 was performed using the Fix/Perm buffer set by Miltenyi according to manufacturer's indications. Samples were then acquired using FACSCanto II cytometer (Becton Dickinson, Mountain View, CA) and data analyzed by FlowJo software.

Multispectral-imaging flow cytometry. For each experiment, cell lines (A549 and HBECs) were stained with relevant surface (EpCAM, ICAM-1) and intranuclear markers (Ki67) and suspended in 100 µl cold PBS in 1.5 ml Eppendorf tubes. Then, cells were analyzed by ImageStreamx (Amnis, Seattle, WA), a multispectral flow cytometer combining standard microscopy with flow cytometry. Up to 100 cells/s were acquired, with simultaneously acquisition of six images of each cell, including bright field, scatter and multiple fluorescent images. We used the integrated software INSPIRE to run the ImageStreamx. Before running the samples, the ImageStreamx was calibrated using SpeedBeads. Samples were acquired in the following order: unlabeled, single-color fluorescence controls, and finally, the experimental samples. Samples were always left on ice.

At least 10.000 cells/experimental sample and 2.000 cells/single-color control were acquired for each sample. Images were analyzed using IDEAS image-analysis software (Amnis).

Results and Discussion

Pathogens at a variety of mucosal surfaces enter epithelial cells to invade underlying tissues. This pathogenic mechanism is counteracted by epithelial exfoliation. In the distal mammalian gut that is continuously exposed to microbes, the epithelium is short-lived (turnover time 5 days). In the lungs that are only intermittently exposed to microbes, the epithelium is long-lived (turnover time 180 days) and epithelial shedding only occurs during infection or injury [7]. Thus, epithelial cells proliferation in the airways should be important for both prevention of pathogen invasion and for regeneration and maintenance of mucosal barrier integrity. Either NSCLC cell line A549 or the normal human bronchial epithelial cells (HBEpiCs) were cultured in the presence of bacterial lysates (Ismigen®, Lallemand Pharma) at the concentration of 100 µg/ml. After 24 h cells were harvested and analyzed for the expression of the

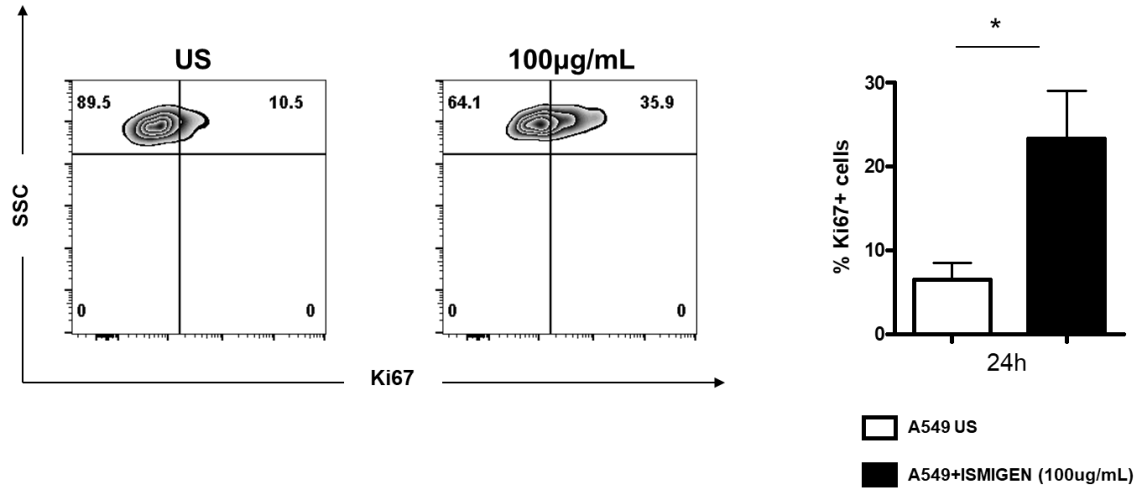

Fig. 1. **Lung epithelial cells proliferate in the presence of mechanical bacterial lysates.** Both normal and neoplastic epithelial cells express Ki67 upon contact with bacterial lysates. Data obtained with A549 cells are shown. US: unstimulated cells.

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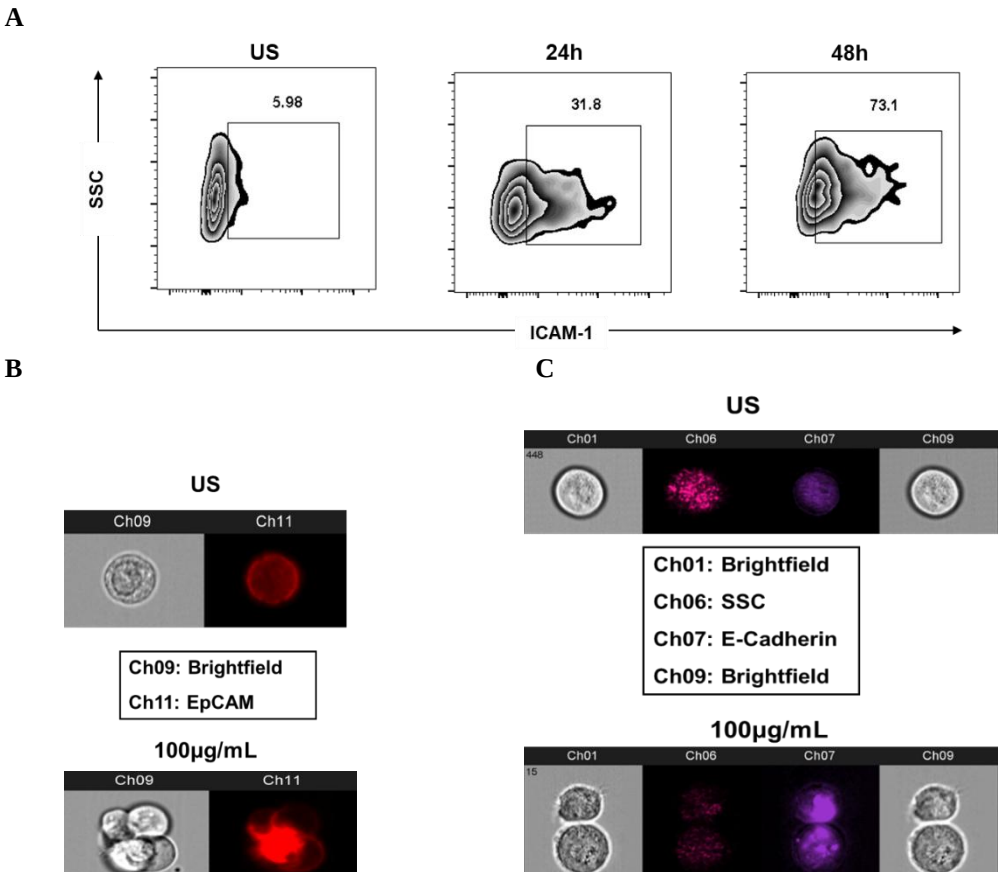

Fig. 2. **Bacterial lysates induce on human normal bronchial epithelial cells the expression of molecules involved in cell-cell junctions.** Up-regulation of ICAM-1 on bronchial epithelial cells is time-dependent; flow cytometry dot plot shows cell side scatter (SSC) versus ICAM-1 expression at two different intervals of time (A). Multispectral imaging flow cytometry shows that polyvalent mechanical bacterial lysates (PMBL) induces cellular aggregates and polarization of EpCAM (B) and E-Cadherin (adherens junctions) (C) on human bronchial epithelial cells.

proliferation marker Ki67 and of different adhesion molecules. Both in neoplastic and normal lung epithelial cells Ki67 was upregulated in the presence of bacterial lysates (Fig. 1).

Airway mucosal cells serve also as mechanical barriers to microbial entry. However, microbes have developed numerous strategies for crossing this barrier by passing between cells, entering and passing through cells. Conversely, since it is comprised of living cells, the epithelial barrier is capable of plasticity in its ability to resist microbial penetration. Indeed, epithelial barrier functions are modulated both by pathogens and as part of the host response, presenting a dynamic situation during infection. Clearly, a similar scenario can be envisaged when administered bacterial components come in contact with airway epithelial cells.

With the aim of investigating whether mechanical bacterial lysates contained in Ismigen® can improve inducible barrier function, we analyzed the expression of adhesion molecules involved in cell-cell junctions. Following culture of HBEpiCs in the presence of bacterial lysates, we observed up-regulation of ICAM-1, EPCAM and E-Cadherin on epithelial cells (Fig. 2). Remarkably, bacterial lysates induced and stronger physical association among epithelial cells (Fig. 2, panel B, C).

The efficacy of the lung epithelium in contrasting pathogen invasion has been often neglected relative to its roles in signaling to leukocytes and acting as a mechanical barrier. Similarly, the role of airway epithelium in mediating the beneficial effects of bacterial lysates-based drugs has been so far underestimated. This neglect is due in part to the requirement for stimulation before the antimicrobial capabilities of the lung epithelium become apparent, which would be overcome by the administration of bacterial lysates, and in part to being overshadowed by the dazzling array of antimicrobial activities displayed by the wide variety of human leukocytes.

Better understanding of inducible lung epithelial innate resistance in the presence of bacterial lysates is likely to lead to insight into the mechanisms of action of PMBL, in particular if loco-regionally administered, and on their ability to manipulate resistance therapeutically, not only to infections but also in the control of other inflammatory respiratory tract diseases, such as asthma and chronic obstructive pulmonary disease.

In these latter pathological conditions, the ability of PMBL to maintain the integrity of epithelial barrier and, at the same time, boost mucosal tissue regeneration could play a fundamental role in the control of the diseases.

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Meeting Calendar

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June 15–19, 2018 Tbilisi, Georgia

VI EUROPEAN CONGRESS ON ASTHMA, COPD AND RESPIRATORY ALLERGY

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CONGRESS SECRETARIAT
World Immunopathology Organization (WIPO)
Phone: (+7-495) 735-1414; Fax: (+7-495) 735-1441
E-mail: info@wipocis.org

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PULMONARY REHABILITATION IN COPD

Bülent Tutluoğlu

Acıbadem International Hospital, Pulmonology & Allergy Department, Istanbul, Turkey

The primary goal of rehabilitation programs for chronic obstructive pulmonary disease (COPD) is to restore the patient to the highest possible level of independent function. Pulmonary rehabilitation is a behavioral intervention for patients with COPD that improves symptoms control and quality of life, reduces hospital admissions and teaches self-management skills. There are a variety of pulmonary rehabilitation programs available, all of which offer supervised exercise and education to motivate patients and promote sustainable behavior change.

Key words: *COPD, rehabilitation programs, symptoms, quality of life.*

Address for correspondence: *Prof. Dr. Bülent Tutluoğlu*
Yeşilköy Mahallesi, İstanbul Caddesi No.82,
34149 Bakırköy, Istanbul, Turkey
E-mail: bulent.tutluoglu@internationalhospital.com.tr

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Rehabilitation programs for patients with chronic lung diseases are well-established as means of enhancing standard therapy in order to control and alleviate symptoms and optimize functional capacity. The primary goal is to restore the patient to the highest possible level of independent function. This goal is accomplished by helping patients to become more physically active, and to learn more about their disease, treatment options, and how to cope. Patients are encouraged to become actively involved in providing their own health care, more independent in daily activities, and less dependent on health professionals and expensive medical resources. Rather than focusing solely on reversing the disease process, rehabilitation attempts to reduce symptoms and reduce disability from the disease.

Many rehabilitation strategies have been developed for patients with disabling COPD. Programs typically include components such as patient assessment, exercise training, education, nutritional intervention, and psychosocial support.

Pulmonary rehabilitation has also been applied successfully to patients with other chronic lung conditions such as interstitial diseases, cystic fibrosis, bronchiectasis, and thoracic cage abnormalities. In addition it has been used successfully as part of the evaluation and preparation for surgical treatments such as lung transplantation and lung volume reduction sur surgery.

Pulmonary rehabilitation is appropriate for any stable patient with a chronic lung disease who is disabled by respiratory symptoms. Patients with advanced disease can benefit if they are selected appropriately and if realistic goals are set.

Pulmonary rehabilitation is a behavioral intervention for patients with chronic obstructive pulmonary disease (COPD) that improves symptoms control and quality of life, reduces hospital admissions and teaches self-management skills. There are a variety of pulmonary rehabilitation programs available, all of which offer supervised exercise and education to motivate patients and promote sustainable behavior change.

People with chronic obstructive pulmonary disease (COPD) undergo a variable but progressive functional decline that causes muscle de-conditioning, reduces their quality of life and increases their risk of hospitalization and death. Pulmonary rehabilitation refers to the use of non-pharmacological interventions to improve the physical and psychological health of these patients by encouraging sustainable self-management skills. The interventions are part of a structured program which is typically delivered by a physiotherapist in an outpatient setting over eight weeks. Physical exercise is always included in pulmonary rehabilitation programs to improve strength and endurance of limbs and respiratory muscles. Education, smoking cessation, breathing exercises, nutritional advice, energy conservation strategies and psychological support can also be included. Following completion of a program, patients should be encouraged to continue to exercise regularly in order to maintain the health benefits they have gained.

A systematic review of 65 randomized controlled trials revealed overwhelming evidence that pulmonary rehabilitation programs benefit patients. Patients who complete these programs are likely to have: an increased sense of control and reduced breathlessness, improved fitness and energy levels, increased quality of life. A reduced risk of hospitalization due to exacerbations and a reduced risk of admission to hospital following an exacerbation. Compared to the use of inhaled medicines alone, pulmonary rehabilitation results in greater improvements in quality of life and functional exercise capacity for patients with COPD. Many patients with COPD have co-morbidities, *e.g.* cardiovascular disease, depression, diabetes, which are also likely to improve following participation in pulmonary rehabilitation programs. Exercise is known to decrease dyspnea by increasing respiratory volume and reducing dynamic hyperinflation. Muscle function and exercise tolerance are also increased

with regular physical activity, while fatigue is delayed. The education component of a pulmonary rehabilitation program aims to improve decision-making and help patients better manage their condition.

Outcomes of comprehensive pulmonary rehabilitation programs:

- lower extremity exercise training; dyspnea;
- health-related quality of life (HRQOL);
- health-care utilization and economic analysis;
- survival;
- psychosocial outcomes;
- long-term benefits from pulmonary rehabilitation:
  • Duration of pulmonary rehabilitation;
  • Post rehabilitation maintenance strategies;
  • Intensity of aerobic exercise training;
  • Strength training in pulmonary rehabilitation;
  • Anabolic drugs;
  • Upper extremity training;
  • Inspiratory muscle training (IMT);
  • Education;
  • Psychosocial and behavioral components of pulmonary rehabilitation;
  • Oxygen supplementation as an adjunct to pulmonary rehabilitation;
  • Noninvasive ventilation;
  • Nutritional supplementation in pulmonary rehabilitation.

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Meeting Calendar

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September 2–5, 2018 Amsterdam, The Netherlands

EUROPEAN CONGRESS ON IMMUNOLOGY (EFIS)

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COPD: NEW GUIDELINES AND FUTURE THERAPIES

Kamal M. Hanna, Amir K.M. Hanna

Faculty of Medicine, Cairo University, Cairo, Egypt
Marie Lannelongue Pulmonology Hospital, Paris, France

Chronic obstructive lung disease (COPD) is a leading cause of death and a major cause of mortality and morbidity around the world. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) released a new "2017 Report" with modified recommendations for the diagnosis, management, and prevention of COPD. The report contains several changes from the previous one.

Key words: *COPD, symptom severity exacerbations, prevention, management*

Address for correspondence: *Kamal Maurice Hanna, MD, PhD, Dr A.I.*
Faculty of Medicine,
Cairo University, Cairo, Egypt
E-mail: keem4@hotmail.com

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Definition of COPD has been changed in the new report: "COPD is a common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airflow limitations that are due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases." The report points out that "COPD may be punctuated by periods of acute worsening of respiratory symptoms, called exacerbations." The description of the pathophysiology of COPD is more elaborate and more detailed and the terms "emphysema" and "chronic bronchitis" have been removed.

The previously accepted statement that cough and sputum production for at least 3 months in each of 2 consecutive years, is a diagnostic criterion has been now found to be present in only a minority of patients.

The new guidelines include symptom severity and exacerbation risk to classify COPD. Two symptom measurement tools, The Modified British Medical Research Council (mMRC) questionnaire and COPD Assessment Test (CAT), are used. Low risk of exacerbation is defined as no more than one exacerbation not resulting in hospital admission in the last 12 months; high risk of exacerbation is defined as at least two exacerbations or any exacerbations resulting in hospital admission in the last 12 months. Symptom severity and exacerbation risk is divided into four quadrants: GOLD group A, group B, group C, and group D.

As regards prevention and management of stable COPD, smoking cessation remains of great importance and strongly recommended. Influenza and pneumococcal vaccinations are also recommended.

COPD medications are extensively discussed in the 2017 Report which recommends escalation strategies. Preference is given to LABA/LAMA (long-acting beta-agonist/long-acting muscarinic antagonists) combinations over LABA/ICS (long-acting beta-agonist/inhaled corticosteroid) combinations as a mainstay of treatment. The rationale for this change is that LABA/LAMAs give greater bronchodilation compared with LABA/ICS. In addition, patients with COPD who receive ICS appear to have a higher risk of developing pneumonia. GOLD recommendations are:

• Group A: Start with single bronchodilator (short- or long-acting), escalate to alternative class of bronchodilator if necessary.

• Group B: Start with LABA or LAMA, escalate to LABA/LAMA if symptoms persist.

• Group C: Start with LAMA, escalate to LABA/LAMA (preferred) or LABA/ICS if exacerbations continue.

• Group D: Start with LABA/LAMA (preferred) or LAMA monotherapy, escalate to LABA/LAMA/ICS (preferred) or try LABA/ICS before escalating to LAMA/LABA/ICS if symptoms persist or exacerbations continue; roflumilast and/or a macrolide may be considered if further exacerbations occur with LABA/LAMA/ICS.

Future COPD therapies which are under trial include p38 MAP kinase inhibitors, CXCR2 antagonists, soluble epoxide hydrolase inhibitor, and mesenchymal stem cells therapies.

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BRONCHIAL ASTHMA IN PATIENTS WITH SEVERE PLAQUE PSORIASIS: A RETROSPECTIVE DERMATOLOGICAL CLINIC-BASED STUDY

Nadezhda Batkaeva, Edgem Batkaev

Peoples' Friendship University of Russia (RUDN University),
Moscow, Russia

Psoriasis is a chronic inflammatory systemic disease. Evidence shows an association of psoriasis with Chronic Obstructive Pulmonary Disease, including bronchial asthma (BA). No studies have been conducted in Russian population of Psoriasis patients. PsO pts with BA were identify in hospital Database reporting and coding by International Statistical Classification of Disease and Related Health Problems (ICD-10) between 2010–2015 years. This study included 889 psoriasis patients. 145 out of 889 pts (16.3%) had BA. In PsA pts BA was found in the same number of cases as in PsO pts ($p<0.05$). BA was found in significantly more cases in old F. pts compare to young F. pts ($p<0.05$). BA was found in significantly more cases in old M. pts compare to young M. pts ($p<0.05$). BA are common for hospital-treated cohort pts with severe plaque PsO. Old M. pts with severe plaque PsO significantly often suffer from BA compared to Young M. pts. Old F. pts with severe plaque PsO significantly often suffer from BA compared to Young F. pts.

Keywords: *psoriasis, bronchial asthma, psoriatic arthritis, comorbidities.*

UDC: 616.517+616.521]-056.7-036.

E-mail: nbatkaeva.derm@yandex.ru

Psoriasis is a chronic inflammatory skin disease affecting 2–3% of worldwide population. Chronic plaque psoriasis, the most common form of psoriasis vulgaris, is characterized by sharply demarcated erythematous papules and plaques with scales and with various distribution, severity and course.

Psoriasis results from interaction between an individual's genetic susceptibility, specific environmental factors, and immune mechanisms. Today there is increasing evidence to substantiate that psoriasis is not just a disease of the skin but a systemic inflammatory disease. The systemic inflammation in psoriasis generates elevation of C-reactive protein, homocysteine, and inflammatory cytokines such as TNF-α, IL-6, IL-17, IL-20, IL-22, and IL-23, which may contribute to the overall morbidity and mortality in these patients [1].

Numerous studies have evaluated the increased prevalence of comorbid diseases and risk factors in psoriatic patients, including obesity, metabolic syndrome, cardiovascular disease, psoriatic arthritis, autoimmune disease, psychiatric illness, liver disease, smoking, malignancy, chronic obstructive pulmonary disease, sleep apnea, and alcohol abuse. Insight into the overlapping pathogenesis of these comorbidities of psoriasis highlights the importance of immune-mediated mechanisms in these disease states [2–3]. Comorbidities tend to increase with age.

Moderate to severe psoriasis (>10% of body surface area) is frequently associated with psoriatic arthritis and metabolic diseases, like abdominal obesity, diabetes, non-alcoholic fatty liver disease, dyslipidemia, metabolic syndrome, chronic kidney disease and Chronic Obstructive Pulmonary Disease [4].

Chronic Obstructive Pulmonary Disease (COPD) is a lung disease that includes chronic bronchitis, emphysema and asthma.

Asthma is a chronic disease involving the airways in the lungs. These airways, or bronchial tubes, allow air to come in and out of the lungs. Asthma is a common chronic disease worldwide and affects approximately 26 million persons in the United States. The pathophysiology of asthma is complex and involves airway inflammation, intermittent airflow obstruction, and bronchial hyperresponsiveness. In bronchial asthma, airway inflammation is characterized in most cases by an increased number of activated T-lymphocytes, particularly $CD4^+$ Th2 cells, and sometimes eosinophils and mast cells. The most notable difference of chronic severe asthma compared with mild to moderate asthma is an increased number of neutrophils [5].

Previous studies have reported a positive correlation between psoriasis and chronic obstructive pulmonary disease (COPD); however, no studies have been conducted on Russian population of Psoriasis patients [6–7]. Psoriasis, as well as other skin diseases, can affect the patient's self-esteem, interfering with all aspects of quality of life.

Psoriasis is a chronic inflammatory skin disease and the patients require long-term systemic basic anti-inflammatory and/or anti-cytokine targeted therapies. According to modern concepts [2–3], the choice of treatment for PsA and Ps depends not only on the clinical manifestations and disease activity, but also on the presence of a patient of a comorbid disease.

Comorbidity diseases influence on the PsO and the PsA results of treatment.

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These results have practical value. So, at the PsA existence of an atherosclerosis, obesity, fat hepatosis indicates not achievement of remission or the minimum activity of a disease in 1 year of therapy by inhibitors of tumor necrosis factor-α. It is shown that depression of an index of body weight at sick PsO improves the response to treatment by systemic drugs on PASI on average for 30% [1]. No studies have been conducted for a research of prevalence of comorbidity disease in patients with severe plaque psoriasis. Studying of prevalence of bronchial asthma at patients with a psoriasis is a new and urgent task. Objectives: to evaluate the prevalence of BA comorbidity in a hospital-based cohort of patients (pts) with severe PsO.

Methods

All potential study subjects have a diagnosis of psoriasis confirmed by a dermatologist. The sources of recruitment are varied and include patients with a range of psoriasis types (primarily chronic plaque psoriasis) and severity. Patients are mainly recruited from dermatology clinic in Moscow. The severity of skin symptoms was assessed by the Psoriasis Area and Severity Index (PASI). 889 pts (Male (M) –516, Female (F) – 329) with moderate-to-severe plaque PsO, mean age 50.4±17.6 years, mean PASI 49.4±0.56, PsO duration 21.5±14,7 years were included. 302 out of 889 pts (33.9%) had PsA and 587 out of 889 pts (66.1%) had PsO alone. PsA pts were older then PsO pts – 55.3±13.7 and 50.4±17.6 ($p<0.001$). PsO pts with BA were identify in hospital Database reporting and coding by International Statistical Classification of Disease and Related Health Problems (ICD-10) between 2010–2015 years.

When was created the initial database used spreadsheet software MS Excel 2010. Statistical data processing performed using the software packages Statistica 10.

Statistical significance of the differences of the characteristic values in the two groups were determined using nonparametric Mann–Whitney test, and in 3 and more using the nonparametric Kruskall–Wallace criterion. To understand the relationships between variables was used the Spearman rank correlation coefficient. For comparison, the indicators used non-parametric Wilcoxon test. To describe quantitative and ordinal data were used mean and standard deviation (M±S). All $p<0.05$ were considered to indicate statistical significance.

Results

We identified 889 patients with severe psoriasis. 145 out of 889 pts PsO (16.3%) had BA. In PsA pts BA coding as J45 was found in the same number of cases as in PsO pts – in 48 out of 302 pts (15.9%), in 97 out of 587 pts (16.5%) accordingly ($p<0.05$). BA coding as J45 was found in significantly more cases in old F. pts as compared with young F. pts – in 48 out of 261 pts (18.4%) and in 15 out of 113 pts (13.3%) accordingly ($p<0.05$). BA was found in significantly more cases in old M. pts compared to young M. pts – in 41 out of 212 pts (19.3%) and in 41 out of 305 pts (13.5%) accordingly ($p<0.05$).

Conclusion

BA are common for hospital-treated cohort pts with severe plaque PsO. Old M. pts with severe plaque PsO significantly often suffer from BA compared to Young M. pts. Old F. pts with severe plaque PsO significantly often suffer from BA compared to Young F. pts. Screening and accurate management of bronchial asthma and other Chronic Obstructive Pulmonary Disease are needed [8–9].

Dermatologists caring for patients with psoriasis should be aware of this association, consult a general practitioner or pulmonologist, and advise the patients to stop smoking and reduce additional risk factors for asthma [5].

The main factor associated with asthma is smoking, followed by lung inflammation, which is responsible for small airways thickening and alveolar destruction. There is evidence that COPD seems to be a more complex disorder than only airways obstruction. The inflammation appears to be the link between COPD, BA and various other diseases such as metabolic syndrome and psoriasis [6–7, 10].

Ungprasert P. and Srivali N. conducted a systematic review and meta-analysis of case-control and cross-sectional studies that compared the risk of COPD in patients with psoriasis versus non-psoriasis participants. Authors have analyzed seven studies met our inclusion criteria and were included in the data analysis. The pooled odds ratio of COPD in patients with psoriasis versus control was 1.45 (95% CI, 1.21–1.73). The statistical heterogeneity was high with an I (2) of 91%.

Therefore, our study provided evidence to support the increased risk of COPD among patients with psoriasis [9].

The presence of comorbidities has important implications in the approach to patients with psoriasis. The integral approach of psoriasis should include the identification of cardiovascular risk factors and metabolic diseases, the adaption of treatments to the existing comorbidities, as well as the evaluation of existing psychological/psychiatric disorders, in order to achieve a long-term control of the disease and improve the cumulative quality of life.

Early and aggressive treatment of severe psoriasis, PsA and associated comorbidities may influence the well-being and probably the longevity of patients [11].

Our findings support the view of the high frequency of comorbid disease in PsO. The high incidence of comorbidities such as cardiovascular disease, gastrointestinal damage, liver, affect the choice of therapy Ps and PsA and results of treatment with systemic drugs and genetically engineered biological agents.

Comorbid pathology contributes to a more severe course of the underlying disease and as a result the development of functional disorders, deterioration in the quality and life expectancy of patients with Ps and PsA. Now in dermatologic and rheumatologic clinics not enough attention is attached to questions of detection of comorbidities in PsO and PsA. For the decision of this problem will be promoted as development of multidisciplinary approach to maintaining such patients, and development at the national level of references on identification and prevention of comorbidities diseases in PsO and PsA patients.

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CLINICAL-IMMUNOLOGICAL FEATURES OF HEMORRHAGIC FEVER WITH RENAL SYNDROME

I.P. Balmasova[1,2], M.F. Ivanov[3], E.S. Malova[1], R.I. Sepiashvili[1]

[1]Peoples' Friendship University of Russia (RUDN University),
[2]A.I. Evdokimov Moscow University of Medicine & Dentistry, Moscow, Russia
[3]Samara State Medical University, Samara, Russia

Hemorrhagic fever with renal syndrome (HFRS) is a feral herd disease caused by hantaviruses which manifestations include hemorrhages and renal disorder. HFRS may be severe. Disease severity is generally tailored to immune mechanisms. The role of innate lymphocytes, i.e., NK cells and NKT, still remains elusive. Our study demonstrated that T helper cell blood count decreases in HFRS while the number of NKT and regulatory T cells increases. Severe HFRS develops under functional predomination of regulatory T cells, cytotoxic T cells plays the key role while B cells and innate immune cells are less important.

Key words: *hemorrhagic fever, renal disorder, immune mechanisms.*

Address for correspondence: *Professor Irina Balmasova*
Moscow State University of Medicine and Dentistry
20/1 Delegatskaya Str., 127473 Moscow, Russia
E-mail: immunolab@mail.ru

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In Russia, hemorrhagic fever with renal syndrome (HFRS) ranks first among zoonotic viral infections and feral herd human infections.

The sources of infection are mainly wild rodents, the carriers of Hantaan, Puumala, Seoul, and Dobrava viruses. Clinical manifestations of human disease include intoxication, pain, and hemorrhagic syndromes. The disease is characterized by cyclic course with early, oliguric, polyuric, and convalescence periods [1].

Several data suggest that hantaviruses, causative agents of HFRS, significantly impact the nature of immune response to this disorder. The most typical changes are the leading role of $CD8^+$ cells in virus eradication [2] and the effect of $CD4^+$ type 1 helper T cells (Th1) [3] and regulatory T cells [4] on disease severity. Immunological abnormalities may result from the virus itself or renal disorder as it was demonstrated for other viral infections [5]. Less data on the role of innate lymphocytes (i.e., NK cells and NKT) are available; however, modern scientific literature comprises some evidence on NK cells cytokine regulation in HFRS [6].

Considering this, the aim of our study was to reveal the association between blood levels of NK cells and NKT and other immune cells in HFRS depending on disease severity.

Materials and Methods

Peripheral blood was collected from 54 patients with HFRS admitted to Samara Hospital of the Samara State Medical University (Russia) between October 2013 and December 2016. Clinical diagnosis of HFRS was verified by serum detection of IgM and IgG antibodies against HTNV nucleocapsid protein (NP). Disease severity was assessed using clinical and laboratory diagnostic criteria of HFRS in Russia as follows: (i) renal failure without classic oliguric stage; (ii) symptoms of uremia, hemorrhage (skin and mucous membranes), and renal failure with classic oliguric stage; (iii) severe uremia, effusion, hemorrhage (skin and mucous membranes), and renal failure with oliguria (urine output 50 to 500 ml/day) for ≤5 days or anuria (urine output <50 ml/day) for ≤2 days. 16 healthy volunteers matched on age and gender were controls.

Fresh PBMCs were isolated from whole blood by density gradient centrifugation using standard procedures. For surface-expressed antigens, PBMCs (approximately 2×10^6 cells/ml) were incubated with antibodies for 30 min at 4°C in the dark. For intracellular staining, cells were permeabilized using BD FACS-Perm2 (BD Biosciences) according to the manufacturer's instructions. After an additional wash, PBMCs were analyzed with four-color fluorescent-antibody staining.

Statistical analysis was performed using SPSS Statistic 21.0. For parameter comparisons between subject groups, a Mann–Whitney U test was used. The data in dot plots represent the median, minimum, and maximum. Spearman's test was used for correlations. P values of less than 0.05 were considered significant.

Results

Blood levels of various lymphocyte phenotypes in patients with HFRS as compared with controls are represented in Table 1.

Table 1

Immunological parameters in the blood of HFRS patients compared with controls

Immune cells	*Phenotype*	*Median [minimum; maximum] (%)*		*p*
		Patients with HFRS (n=40)	*Healthy controls (n=16)*	
T lymphocytes	$CD3^+$	68.0 [44.4; 86.0]	75 [62; 87]	0.008*
T helper cells	$CD3^+CD4^+$	36.1 [5.5; 58.7]	41 [14; 57]	0.038*
Cytotoxic T cells (CTL)	$CD3^+CD8^+$	31.8 [10.4; 78.0]	28 [16; 71]	0.173
NKT cells	$CD3^+CD56^+$	5.4 [2.5; 8.1]	3.4 [2.3; 5]	0.041*
NK cells	$CD16^+CD56^+$	16.6 [11.0; 33.8]	12.9 [9.5; 28]	0.123
B lymphocytes	$CD19^+$	12.6 [5.0; 25.0]	10.5 [2.5; 16]	0.159
Activated T cells	$CD3^+CD25^+$	4.2 [2.1; 9.6]	7.4 [2.6; 7.8]	0.108
Regulatory T cells	$CD3^+CD4^+FoxP3^+$	10.7 [4.0; 27.0]	3.0 [2.3; 8.1]	<0.001*
	$CD3^+CD8^+FoxP3^+$	12.5 [3.5; 26.1]	0.4 [0.1; 4.4]	<0.001*
Cells expressing activated lectin receptor	$CD16^+CD56^+$ $NKG2D^+$	48.6 [23.4; 71.6]	12.6 [9.6; 27]	<0.001*

Note: n, the number of patients in each group; p, the probability of the difference between the data at baseline and after 1 year; * – the significance of the difference by Mann–Whitney test (p<0.05).

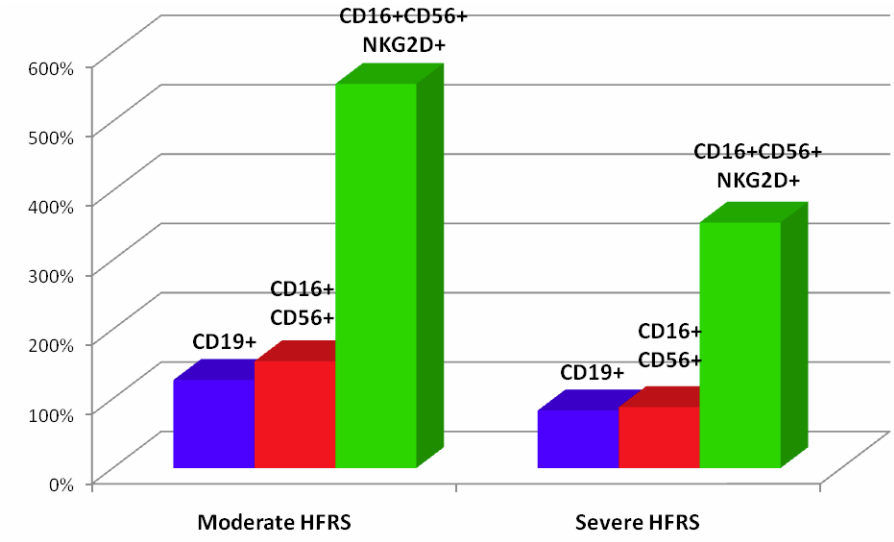

Fig. 1. The ratio of informative lymphocyte phenotypes in moderate and severe HFRS

As shown in Table 1, immunological changes in HFRS predominantly affect various types of T cells. The number of T cells reduces mainly through the decrease of T helper cells. It might be associated with significant increase of regulatory T cells since these lymphocytes negatively correlate with T helpers (p<0.05).

NKT cell count increases moderately while the number of cells expressing activated lectin receptor NKG2D rises significantly. The latter includes cytotoxic cells (NK) and, to a lesser extent, CTL.

We attempted to identify cell populations and subpopulations associated with HFRS severity and revealed differences between moderate and severe disease course in three lymphocyte types, i.e., B cells, NK cells, and $NKG2D^+$ cells (Fig. 1).

In severe HFRS, B cell count decreases by 1.5 times, i.e., statistically significantly but not too much. The number of NK cells as well as the number of cells expressing NKG2D decrease by 1.7 times in severe HFRS. The results of the analysis of correlations are represented in Table 2. As shown in Table 2, only regulatory T cells, NK cells, and cells expressing NKG2D demonstrate significant differences in correlations in the different severity of HFRS.

In moderate HFRS, regulatory T cells did not generate any correlations positive correlations with the number of cytotoxic T cells, NK T cells, and NK cells and negative correlations with the number of T helper cells and activated T cells.

In severe HFRS, negative correlations imply that the targets of immunosuppressive effect of regulatory T cells are predominantly T helper cells and NK T cells. NK cells were not involved into these correlations while NKG2D expression demonstrated positive correlation with cytotoxic T cells only.

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Conclusion

Our study has shown that immune mechanisms of hemorrhagic fever with renal syndrome are mediated by T cells as well as innate immune cells, i.e., NK cells and NK T cells. Severe HFRS develops under functional predomination of regulatory T cells, cytotoxic T cells plays the key role while B cells and innate immune cells are less important.

Table 2

Correlation coefficients between lymphocyte phenotypes in HFRS

Lymphocyte phenotype	*$CD3^+CD4^+$*	*$CD3^+CD8^+$*	*$CD3^+CD56^+$*	*$CD16^+CD56^+$*	*$CD19^+$*	*$CD3^+CD25^+$*	*$CD3^+CD4^+$ FoxP3$^+$*	*$CD3^+CD8^+$ FoxP3$^+$*	*$NKG2D^+$*
Moderate HFRS									
$CD3^+$	0.278	0.478	0.298	0.087	-0.073	-0.407	-0.218	-0.142	0.280
$CD3^+CD4^+$		-0.526	-0.197	-0.136	0.125	0.227	-0.304	0.071	-0.686
$CD3^+CD8^+$			0.229	0.142	-0.186	-0.651	0.032	-0.045	0.768
$CD3^+CD56^+$				0.680	0.076	-0.027	-0.087	-0.253	0.323
$CD16^+$ $CD56^+$					0.378	-0.002	-0.359	-0.165	0.389
$CD19^+$						0.076	-0.280	0.047	-0.006
$CD3^+CD25^+$							0.088	0.144	-0.542
$CD3^+CD4^+FoxP3^+$								0.082	0.005
$CD3^+CD8^+FoxP3^+$									-0.111
Severe HFRS									
$CD3^+$	0.256	0.496	0.298	0.129	-0.011	-0.408	-0.248	-0.148	0.337
$CD3^+CD4^+$		-0.525	-0.181	-0.065	0.237	0.240	-0.377	0.152	-0.682
$CD3^+CD8^+$			0.192	0.099	-0.239	-0.644	0.058	-0.092	0.776
$CD3^+CD56^+$				0.685	0.054	0.015	-0.033	-0.376	0.295
$CD16^+CD56^+$					0.337	0.028	-0.302	-0.271	0.342
$CD19^+$						0.092	-0.259	-0.029	-0.080
$CD3^+CD25^+$							0.091	0.182	-0.537
$CD3^+CD4^+FoxP3^+$								0.154	0.061
$CD3^+CD8^+FoxP3^+$									-0.180

Note: significant negative correlations are represented in blue, significant positive correlations are represented in dark blue.

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ONTOGENETIC FEATURES OF REACTION OF C3 COMPLEMENT IN RESPONSE TO ACUTE SOMATIC PAIN IN RATS

I.M. Bykov[1], V.V. Alekseev[2], R.I. Sepiashvili[3]

[1]Kuban State Medical University, Krasnodar, Russia
[2]Rostov State Medical University, Rostov-on-Don, Russia
Peoples' Friendship University of Russia (RUDN University), Moscow, Russia

Painful syndrome has an effect on the reactivity of the body. The data on the effect of pain on the immune system, in particular on the C3 complement component, have not been found in the available literature. The article presents the results of studies of the level of C3 complement before and after acute pain during 180 min in ontogenesis. The initial level of complement in different age groups of animals is different and the response to acute pain also varies with age

Key words: *acute pain, C3, complement, ontogenesis*.

Address for correspondence: *Associate Professor V.V. Alekseev*
Department of Pathological Physiology,Rostov State Medical University
29, Nakhichevansky Per., 344022 Rostov-on-Don, Russia
E-mail: alexeev911@gmail.com

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Complement is a system of serum proteins and several proteins of cell membranes that perform 3 important functions: opsonization of microorganisms for their further phagocytosis, initiation of vascular inflammation reactions and perforation of membranes of bacterial and other cells. [9]. The C3 protein in the complement system plays a central role, since it closes the cascade of all three activation paths. C3 is split into active fragments (C3a and C3b), which subsequently leads to the formation of a membrane-attacking complex (C5b-9) [2]. It was proved that the complement system reacts not only to specific factors such as antigen-antibody complex (classical pathway), microbial cell surface (alternative pathway), mannose-binding lectin (lectin path), but also not specific effects on the body: stress, pain, hypoxia [4, 10, 12, 14, 16–17].

Pain has been proved to be a factor leading to the mobilization of reserves that provide resistance of the organism to unfavorable factors [3, 5, 7]. AbramovYu.B. believes that both the pain system and the immune system objectively resist damage being functionally connected [1]. The recognized commonality of the two systems suggests the possibility of an inverse order, that is, pain can influence immunological reactivity.

We have not found the information on the influence of pain in general or acute somatic in particular in the available literature. The peculiarities of the change in the content of the compliment in connection with the age have been studied [11, 13, 15], but there is no information on the reaction of the system of the complement to acute somatic pain (ASP) in ontogenesis.

The aim of the study was to evaluate the effect of short-term ASP on the change in the C3 complement component level in rats of different ages: newborns, rats of the 14th day of life, monthly age rats, sexually mature and old rats.

Materials and methods

Study design: Non-randomized controlled crossover study.

Compliance Criteria: The healthy rats living in the conditions appropriate to the experiment requirements were included in the study. Newborns and rats of the 14th day of life received breastfeeding. Monthly age rats, mature and old rats were fed with mixed fodder, balanced according to the needs in proteins, fats, carbohydrates, vitamins, minerals, substances and microelements, in rational doses.

Terms and conditions: All experiments were carried out under standard conditions of animal keeping, temperature regime, illumination, time of day, preset parameters of stimulation in the laboratory for studying the mechanisms of somatic pain formation at the Department of Pathological Physiology of the Rostov State Medical University. ASP of the 3rd-4th degree of intensity was modeled by the electro cutaneous stimulation of the receptor zone of the rat tail with the help of the electrostimulator (ESU-2, State Register 4515-74, USSR) with the following parameters: current frequency – 100 Hz; the voltage is 30 V; the pulse duration is 500 m/sec; pulse delay – 2 m/sec; stimulation time – 2 min. The animals were decapitated in 2 min, 30–60 min and 120–180 min after pain in each series of experiments and blood was taken. It was then centrifuged for 20 min at 1500 rpm.

Duration of the study: The duration of the study was 1.5 years spanning gestation period (21 days), reaching animals of the given age (2–3 days, 14 days, 1 month, 3–4 months, more than 1 year) and the actual experiment time (2, 30, 60, 120 and 180 min).

Outcomes of the experiment: The outcome of the experiment was the achievement of the ASP of the 3–4th intensi-

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ty degree with the subsequent decapitation of animals at given intervals of time and blood sampling. The resulting material was used to determine the C3 compliment component level.

Methods of recording outcomes: The fact of the presence of pain and its intensity were recorded on the basis of behavioral and vegetative responses of experimental animals in accordance with generally accepted criteria proposed by A.V. Valdman, Yu.N. Vasiliev in the modification of V.G. Ovsyannikov [6].

The level of C3 complement component in the animal plasma was determined using the immune-enzyme test systems for rats from Cloud Clone Corp. (USA). The results were detected using the multiscan "Labsystem" (Finland).

Analysis in subgroups: The experiment was carried out in each group step by step. The serum lysozyme activity was evaluated in control group of intact animals (n=10), in groups of animals after 2 min of algogenic exposure (n=10), after 30–60 min (n=10) and 120–180 min (n=10).

Ethical expertise: The experimental studies were carried out in full compliance with the requirements of the International Convention on the Humane Treatment of Experimental Animals (Strasbourg, 1986), and also with the Order of the Ministry of Health and Social Development of the Russian Federation No. 708n "On Approval of the Rules of Laboratory Practice" of August 23, 2010 [8].

Statistical analysis: Statistical processing of data was carried out using software STATISTICA v. 8.0 (StatSoft Inc., USA) and Microsoft Office Excel 2010. Statistical analysis included checking the normal distribution of quantitative traits using the Kolmogorov-Smirnov test with Lillieforce's correction and the Shapiro–Wilk test; median (Me), quantiles ($Q_{0.25}$ – lower quantile, $Q_{0.75}$ – upper quantile), range of values from minimum value (Min) to maximum (Max) for data not subjected to normal distribution), data comparison based on U – Mann–Whitney test. The critical significance level (p) was assumed to be 0.05. The results of the calculations are presented as a median with quantiles and a range of Me values [$Q_{0.25}$, $Q_{0.75}$] (Min–Max).

Object of study: The objects of study were nonlinear laboratory white rats. All animals were combined into five age groups: newborns (n=218), and rats of the 14th day of life (n=40), monthly rats (n=40), sexually mature rats – 3–4 months (n=40), the old rats are older than 1 year (n=40). The body mass of newborn animals was 14–16 g, the body mass of rats of the 14th day of life was 30–35 g, for the monthly rats – 50–55 g, for the sexually mature – 160–200 g, and for the old rats – 250–300 g. Newborn and rats of the 14^{th} day of life were taken into the experiment without taking into account gender differences. Rats of monthly age, mature and old rats are males.

Main results

The control group included newborn rats, whose mothers and they themselves did not undergo painful effects.

In the animals in this series of experiments, the median (Me) of C3 complement content fraction is 71.00 ng/ml [$Q_{0.25}$=58.00 ng/ml; $Q_{0.75}$=91.50 ng/ml]. 2 min after the painful stimulation, MeC3=68.75 ng/ml [$Q_{0.25}$=66.50 ng/ml; $Q_{0.75}$=74.00 ng/ml]. Between 30 and 60 min after the algogenic effect MeC3=71.00 ng/ml [$Q_{0.25}$=66.5 ng/ml; $Q_{0.75}$=74.5 ng/ml]. The median of C3 complement component content slightly increased and accounted for 73.25 ng/ml [$Q_{0.25}$=64.5 ng/ml; $Q_{0.75}$=75.0 ng/ml] in the interval between 2 and 3 hours after the application of pain stimulation.

The statistical analysis for pairwise comparison of the series showed perpetually stable results in the dynamics during the entire experiment. In no case was a statistically significant difference between the series.

In the rats of the 14th day of life we found the content of the C3 complement protein in the control group: MeC3=59.25 ng/ml [$Q_{0.25}$=56.00 ng/ml; $Q_{0.75}$=83.50 ng/ml]. 2 min after the application of the pain to the animals, the indices practically did not change: MeC3=59.00 ng/ml [$Q_{0.25}$=57.5ng/ml; $Q_{0.75}$=64.00 ng/ml]. After 30–60 min, MeC3=59.75 ng/ml [$Q_{0.25}$=54.00 ng/ml; $Q_{0.75}$=78.00 ng/ml]. Between 2 and 3 hours of the experiment, the median of C3complement component acquired a value of 60.00 ng/ml [$Q_{0.25}$=53.5ng/ml; $Q_{0.75}$=78.00 ng/ml].

The results of statistical processing of the data in a pairwise comparison of the series showed that in no case, and under any combination, there was no statistically significant difference in the indices.

Study revealed that the median of C3 complement fraction content in the animals of monthly age in the control group is at the level of 91.50 ng/ml [$Q_{0.25}$=90.00 ng/ml; $Q_{0.75}$=92.00 ng/ml], this is higher than in the previous two age groups. 2 min after the application of pain stimulation, the C3 complement fraction dropped to MeC3=64.50 ng/ml. This decrease is statistically significant with respect to control (p=0.00028) [$Q_{0.25}$=61.50 ng/ml; $Q_{0.75}$=74.00 ng/ml]. Between the 30^{th} and 60^{th} min from the start of the experiment, the C3 complement fraction content returned to the control values MeC3=89.50 ng/ml [$Q_{0.25}$=86.00 ng/ml; $Q_{0.75}$=91.50 ng/ml]. In the interval between 2 and 3 hours from the moment of pain application, the C3 complement fraction content continued to remain at

Table 1

The level of significance (p) is the difference between the data for a pairwise comparison of groups of monthly animals

Groups	*Control*	*2 min*	*30–60 min*	*120–180 min*
Control				
2 min	**0.000280**			
30–60 min	0.104111	**0.000280**		
120–180 min	0.545350	**0.000280**	0.256840	

Table 2

The level of significance (p) of the difference in the data for pairwise comparison of groups of mature animals

Groups	*Control*	*2 min*	*30–60 min*	*120–180 min*
Control				
2 min	**0.001499**			
30–60 min	**0.002827**	0.140466		
120–180 min	0.226477	0.570751	0.273037	

Table 3

The level of significance (p) of the difference in the data for pairwise comparison of groups of old animals

Groups	*Control*	*2 min*	*30–60 min*	*120–180 min*
Control				
2 min	**0.002497**			
30–60 min	**0.001152**	0.762369		
120–180 min	**0.001008**	0.112412	0.427356	

Table 4

The level of significance (p) of the difference in the data for paired comparison of age groups before painful stimulation

Groups	*Newborn*	*Rats of the 14th day of life*	*Monthly*	*Mature*	*Old*
Newborn					
Rats of the 14th day of life	0.344705				
Monthly	**0.049367**	**0.000440**			
Mature	**0.000183**	**0.000183**	**0.000183**		
Old	**0.000183**	**0.000183**	**0.000183**	**0.00194**	

the control values MeC3=91.25 ng/ml [$Q_{0.25}$=88.50 ng/ml; $Q_{0.75}$=92.00 ng/ml].

Thus, animals of monthly age for the first time in their stages of ontogeny respond to algogenic stimulation by lowering the C3 complement fraction level. This decrease is short-term and is leveled within the first hour from the beginning of the experiment (Table 1).

In the study of the change in the C3 complement component in the control group of sexually mature animals the following parameters were measured: MeC3=147.75 ng/ml [$Q_{0.25}$=121.5 ng/ml; $Q_{0.75}$=137.2 ng/ml]. Two min after the application of pain stimulation, the C3 complement component level is decreased: MeC3=127.25 ng/ml [$Q_{0.25}$=121.5ng/ml; $Q_{0.75}$=137.3 ng/ml]. The difference in the median values with the control is highly significant. After 30–60 min, the C3 complement fraction content in the rats blood continued to decrease: MeC3=119.50 ng/ml [$Q_{0.25}$=114.50 ng/ml; $Q_{0.75}$=132.50 ng/ml]. During 2 and 3 hours, the median of the C3 complement component level changed slightly: MeC3=119.75 ng/ml [$Q_{0.25}$=117.00 ng/ml; $Q_{0.75}$=158.50 ng/ml].

Thus, after of pain stimulation to mature rats, a decrease in the C3 complement fraction level occurred after 2 min. This decrease is statistically reliably recorded at least in one hour. Between 2 and 3 hours in adult animals, within a single group, a different degree of reaction occurred from the decrease of the C3 complement component level below the control values in some animals, the approach of the level to the control values in others, and the excess of values above the median of the control values (Table 2).

For old animals that are included in the control group of experiments, a rather high level of C3 complement fraction in the blood is typical. MeC3=113.75 ng/ml [$Q_{0.25}$=110.50 ng/ml; $Q_{0.75}$=140.50 ng/ml]. 2 min after applying painful irritation after, the MeC3reduced to 105.50 ng/ml. In comparison with the control value, this decrease is significant. The boundaries of the interquantile distance are close [$Q_{0.25}$=101.50 ng/ml; $Q_{0.75}$=109.5 ng/ml]. In the period from 30 to 60 min since the moment of pain stimulation, the median of C3 component fraction remained unchanged: MeC3=105.2 ng/ml [$Q_{0.25}$=99.00 ng/ml; $Q_{0.75}$=108.50 ng/ml]. Within 2–3 hours from the moment of pain stimulation, the median values of the C3 complement fraction reached 100.75 ng/ml [$Q_{0.25}$=97.00 ng/ml; $Q_{0.75}$=102.00 ng/ml].

Thus, old animals react with a change in the content of C3 complement fraction. Its level was gradually decreasing. The peculiarity of the reaction is that the primary differences are statistically significant. Further, they acquire a statistically significant character, which remains until the end of the experiment (Table 3).

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Conclusion

Firstly, the basal level of C3 complement fraction content of intact rats in the control experimental groups is minimal in newborns and matured rats, but as they grow older, they progressively increase and reach their maximum values during puberty (Table 4). In older animals, a slight decrease in the fraction is observed. But it remains high in relation to newborn, rats of the 14th day of life and rats of monthly age.

Secondly, there are ontogenetic features of the change in the content of C3 complement fraction in response to acute somatic pain. In newborns and mature animals, there is no reaction to pain in the C3 complement fraction. In rats of monthly age, there is a short-term activation of the C3 complement protein, which is no longer detected after 30–60 min since ASP application. In mature and old animals, the activation of the C3 fraction of complement is formed in response to acute algogenic exposure after 2 min. It maintained until the end of the experiment.

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Meeting Calendar

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November 15–19, 2018 Seattle, USA

ANNUAL MEETING OF THE AMERICAN COLLEGE OF ALLERGY, ASTHMA & IMMUNOLOGY (ACAAI)

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HUMAN AIRWAY EPITHELIAL CELLS DIRECTLY RECOGNIZE MECHANICAL BACTERIAL LYSATES ELICITING TIGHT JUNCTION SEALING, ANTIMICROBIAL PEPTIDES PRODUCTION AND EPITHELIAL CELL PROLIFERATION

Giacomo Sidoti Migliore, Stefania Campana, Claudia De Pasquale, Paolo Carrega and Guido Ferlazzo
Laboratory of Immunology and Biotherapy, Dept. of Human Pathology, University of Messina, Italy

Mechanical bacterial lysates are made from a wide range of pathogenic bacteria, including all of the most commonly occurring pathogens of the upper and lower respiratory tract obtained by mechanical lysis. They are currently administered for aiding in the prevention of recurrent respiratory tract infections, their mechanism of action relying on triggering accessory cells of the innate immunity, especially mucosal dendritic cells, for a more efficient bacteria-specific immune response. More recently, they have been proposed for reducing the exacerbation episodes of both COPD and pediatric asthma but the mechanisms of action behind their protective role in these respiratory diseases are still a matter of debate. Microbes entering the bodies of multicellular eukaryotes must first cross an epithelial cell layer. Besides functioning as physical barriers to prevent infection, mammalian epithelial cells are able to sense the presence of microbes and to respond by augmenting their barrier function, signaling to leukocytes, and directly killing pathogens. While signaling to leukocytes has received considerable attention, augmented barrier function and pathogen killing have received less. Here, we show that human airway epithelial cells (HAEC) can recognize bacterial lysates obtained by mechanical lysis (Ismigen) and, in response, undergo a potent activation resulting in significant amphiregulin production, cell proliferation, and expression of different adhesion molecules including e-cadherin. In addition, culturing HAEC in the presence of bacterial lysates results in the production of the antimicrobial peptides beta defensin-2 and -3. Altogether, our current data indicate a novel protective mechanism of action for mechanical bacterial lysates by which epithelial cells can directly counteract pathogen invasion upon activation by bacterial lysates. Proliferation of damaged epithelial cells and expression of molecules involved in tight junction formation can locally contribute to provide a more efficient physical barrier but also to alleviate flogosis and regenerate damaged airway tissues, as can desirable in both COPD and asthma. On the other hand, conditional pathogen killing by epithelial cells is an important aspect of innate resistance to infection that merits further attention in understanding the homeostasis of epithelial surfaces throughout the body and in manipulating innate immunity therapeutically.

C-REACTIVE PROTEIN IN CHILDHOOD ASTHMA

Ketevan Nemsadze[1], Tamar Bakhtadze[1], Nino Kiknadze[2]
[1]David Tvildiani Medical University; [2]Clinic "CURATIO", Tbilisi, Georgia

BACKGROUND: Childhood asthma research focused on postnatal exposures, but there is recent evidence to indicate immune responses might be initiated in fetal period. Systemic Inflammatory processes during pregnancy might affect fetal lung development that could increase propensity in the child to develop lung diseases.

OBJECTIVE: To identify the association of C-reactive protein (CRP) levels in Pregnant (with stress in second trimester), newborn blood samples (cord blood) with childhood wheezing.

METHODS: Serum CRP concentrations (Turbidimetric method) were measured in maternal blood on the 13–17 weeks of gestation in 32 pregnant women and in the newborn cord blood after delivery. During1 year the frequency of wheezing diseases evaluated by the International Study on Asthma and Allergy in Childhood (ISAAC).

RESULTS: Maternal C-reactive protein was associated with the wheezing and lower respiratory tract infections r=413*; p=0.019. Compared to children with cord blood C-reactive protein high level had increased risks of wheezing, r=572; p=0.001

CONCLUSION: Our results suggest that elevated maternal and Cord blood CRP levels are associated with wheezing and lower respiratory tract infections in the first years and predictive asthma young in life.

PREVALENCE, TRIGGERS AND CLINICAL FEATURES OF ATOPIC DERMATITIS IN CHILDREN

T.A. Slavyanskaya[1], N.P. Petrova[1], V.V. Derkach[2] ***[1]Peoples' Friendship University of Russia (RUDN University), Moscow; [2]Pacific State Medical University, Vladivostok, Russia***

The aim of the study was to study the cause-significant allergenic and non-allergenic triggers, prevalence and clinical features of atopic dermatitis (AD) in Primorye Territory of Russia among young children (Ch) and adolescents.

Methods: The epidemiological studies on prevalence of AD among 3634 Ch of 6–14 years old (y.o.) were performed under the program ISAAC, Vladivostok, Russia along with definition of basic triggers affecting its development. Parents of 6–7 y.o. Ch filed 1924 forms and 13–14 y.o. Ch filed 1710 forms by themselves. Number of boys and girls in the both groups was comparable (51.4-49.5% of boys and 50.5–48.6% of girls). We used SCORAD scale to define AD severity level (SL). All Ch held general clinical and allergological examinations (AE).

Results: It was found that the percent of Ch up to 14 y.o. having the AD within allergic disease (ADs) is over 43%. The most significant symptom was a long-lasting itchy rash lasting for 6 month in 12,42±0,56% of Ch 6–7 y.o. and 9,23±0,49% of Ch 13–14 y.o. The first morbidity of AD was noticed at the age of up to 2 y.o. among 56,29±1,27%. At the age of 2–4 y.o. and older than 5 y.o. the skin ADs onset was noticed for 31,12±1,11% Ch and 12,58±0,57% accordingly. The AD SL was determined for Ch as follows: 52% – moderate (Mo), 12% – severity (S), 36% – mild (Mi) disease. The AE results displayed a high degree of sensibilization such aeroallergens as: house dust mite, domestic and library dusts. When the focalized AD they noticed a Mi disease in 100% cases, when diffuses – S AD, when extensive form: 2/3 cases – Mo, 10% Ch – S and 3% – Mi AD. Each 3rd Ch of 6–7 y.o. and each 2nd Ch of 13–14 y.o. having AD clinical symptoms of disease went with a respiratory syndrome (asthma symptoms – BA and/or allergic rhinitis – AR), AR was found twice more often among

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Ch of earlier age (76.02±0.94%), and BA and AR were of the same frequency for Ch 13–14 y.o. – 90.90±0.48% and 98.48±0.08% accordingly. The most important non-allergenic factors of AD early development are: maternally inherited predisposition (found in 63% cases); abnormal texis (found in medical history of 2/3 Ch); Ch's improper feeding on their first year of life; Ch's statical and/or functional pathology of gastro-intestinal tract; frequent virus infection (herpetic infection was found for 17% of deceased, 44% has frequent acute respiratory disease). Chronic relapsing course of the disease is common for all AD sick, itch of varying intensity, somnipathy, soreness, tiredness, tendency for long-lasting recurrent skin infection are typical for recrudescence period. 66.3% had moderate itch, 33% – intolerable. Symmetrical grouped erythematous papular rash, infiltration site of damage and lichenification, punctate and linear excoriations, barks, finely lamellar ecdysis and medium lamellar ecdysis are typical for AD sick's creeping diseases. Monotonous disease progression was noticed for 28 % Ch, developing disease progression – 67%, retrogressive disease progression – 5%.

Conclusions: Thus, the true picture of prevalence of AD in Primorye Territory of Russia among young children and adolescents was established, clinical features and the main allergenic and non-allergenic triggers that contribute to the early development of the disease were determined. The revealed peculiarities will be promoting the timely conduct of therapeutic and preventive measures among Ch.

ALLERGY IN CHILDREN

Maia Maglaperidze, Manana Chikhladze, Darejan Khachapuridze
National Institute of Allergy, Asthma and Clinical Immunology, Tskaltubo, Georgia

Background: Respiratory system diseases are global problems of public health. Especially increased the prevalence of allergic rhinitis, bronchitis and bronchial asthma in different age groups.

The aim of our trial was to study the most common respiratory diseases in children aged population.

Methods: The study was done in children from Kutaisi and Tbilisi randomly and on based of questionnaire of representative cohort. (2014–2016). The cohort was 2500 children, 1–16 years old, risk factors were studied by way of interviewing, clinical-laboratory dates. For assessing the risk factors, was used 'case control' method. The statistical processing of material was done with computer program sps/sv12. Inclusion criteria for enrolment were: collectors of dust, gender, existence of moisture and mold consuming of Tabaco, atopic dermatitis and seasonality.

Results: The groups, which we have studied, prevalence of acute respiratory viral infection was 61%, bronchitis – 29,3%, allergic rhinitis – 33.9%, atopic dermatitis – 9.1%, food allergy – 5.4%. The reliability was high ($p<0.05$) in families with bronchial asthma compared with healthy population. Bronchial asthma was detected in 5.7% of population. The hereditary load of allergic diseases in patients with bronchial asthma was 9.7% and in healthy cohort it was 5.7% ($p<0.001$).

Conclusion: Based on the results, we can conclude that, ecological factors and genetic predisposition significantly influences on prevalence of sensibilization of house dust mite, molds and formation of bronchial asthma. With early prevention program, we can avoid allergic loading. In children population determinant factor of bronchial asthma phenotype is age. The less is age, child will have the more risk having allergy and asthma.

PERIPHERAL EOSINOPHILIA AND EXACERBATION OUTCOMES IN COPD – IS THERE A RELATIONSHIP?

Angelique Megevand*, Helen Clayton*, Rajeev Ratnavadivel*#, Richard Lee*#
****Gosford District Hospital, Gosford NSW, AUSTRALIA #School of Medicine and Public Health, University of Newcastle***

Background: Eosinophilia in COPD has been proposed as a potential phenotypic biomarker for risk of exacerbation and predicting response to therapy. Prevalence of eosinophilia in an Australian COPD population has not been investigated to date.

Aims: To investigate the prevalence of elevated blood eosinophils in patients presenting with acute exacerbations of COPD requiring hospitalisation in an Australian population. To compare clinical outcomes between eosinophilic and non-eosinophilic phenotypes.

Methods: This is a retrospective observational study of patients admitted to a tertiary Australian Hospital with an (infective/non-infective) acute exacerbation of COPD (AECOPD group) from May to Dec 2015. Demographic data (age, gender, smoking status and co-existing asthma) was collected (asthma-COPD group). Subgroups were predefined as elevated eosinophil $\geqslant$200 cells/microL (elevated eos) vs low eosinophil <200 cells/microL (low eos) groups. Exclusions included pneumonia (opacification on CXR) and oral corticosteroids within 2 weeks prior to admission. Outcome variables were length of hospital stay (LOS), duration of antibiotics, need for corticosteroids (none, oral, iv + oral), 30-day readmission for AECOPD, and 30-day mortality.

Results: A total of 251 subjects were included (AECOPD group (n=222) and asthma-COPD group (n=29). Median age was 74 years (IQR 17); 46.8% were male. The majority of patients received oral/iv corticosteroids (95.9%). The prevalence of elevated blood eosinophilia was 31.5% in this cohort. Difference in LOS (days) between elevated and low eos groups did not reach significance (p=0.07), median 4 (IQR 4) and 4 (IQR 5), respectively. There was no significant difference in rates of elevated and low eos by smoking status or 30-day readmission. There was no difference in the rates of elevated eos between AECOPD (30.1%) and asthma-COPD groups (35.7%) p=0.95. There were significantly more patients in the younger age groups presenting with elevated eos (p=0.01).

Conclusion: While most patients are treated with iv or oral corticosteroids for AECOPD, the outcome for those with eosinophilic phenotype does not appear to be different in terms of outcome measures within our cohort. There was an association between rates of elevated eosinophils and younger age.

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SYNTHETIC CANNABINOID USE CAUSING ARDS

Fadime Tulucu, Ulvan Ozad, Deniz Granit *Near East University, Nicosia, Cyprus*

In the last years, synthetic cannabinoid use has significantly raised in the younger population. Similarly, cerebrovascular and psychosocial side effects have been increasingly seen as well as the other systemic complications. Use of synthetic cannabinoids is prohibited in Cyprus; therefore, its use is not routinely questioned in health consultations; even if questioned, the answer is not provided by the patient. In this case, a 21 years old male patient has presented with acute haemoptesis, alveolar haemorrhagia and acute respiratory distress syndrome (ARDS). The initial differential diagnosis was bilateral acute pneumonial however synthetic cannabinoid use was found as the real underlying cause. In addition to the antibiotics treatment, mechanical ARDS protocol for mechanical ventilation was provided as part of the treatment. The patient was successfully treated and discharged. Therefore, synthetic cannabinoid use should be questioned in hospital aldmissions of young people presenting with alveolar haemorrhagia or ARDS.

PREVALENCE OF EOSINOPHILIA AND CLINICAL CHARACTERISTICS IN A COHORT OF PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE AT A TERTIARY HOSPITAL IN PUEBLA

Herrera-García José Carlos, Arellano MontellanoEkIxel, Jaramillo Arellano Luis Enrique, Espinosa Arellano Andrea *Asthma and COPD Clinic, University Hospital Puebla, Meritorious Autonomous University of the State of Puebla, Mexico*

Objective: The prevalence of eosinophilia in Chronic Obstructive Pulmonary Disease (COPD) is of great importance for the prevention of complications and the treatment of episodes of exacerbation. The existence of a bio-marker would enable monitoring. The review of the literature demonstrates the possible eosinophilia-COPD relationship. There is little information on this area in medical studies.

Methodology: An observational descriptive study of the population attended at out-patient neumology appointments at University Hospital Puebla. The following variables were analyzed: age, gender, years since COPD diagnosis, haemogram (a diagnosis of eosinophilia was established in > 2%), severity (GOLD guide), and the number of exacerbations over the 1 year duration of the study.

Results: A diagnosis of COPD in 50 patients (30% men, 70% women), with an average age of 60±10. 24% of the patients present eosinophilia at a representative level of more than 2%, which is not associated with the severity of the disease. 70% of the patients use inhaled corticosteroids.

Conclusion: 24% of the patients with COPD have eosinophilia at a representative level of more than 2%, which has no relationship with the severity of the disease, and is only representative of the population. Eosinofilia is a determinant biomarker in the treatment of COPD with phenotypes.

USE OF OMALIZUMAB IN MEXICAN PATIENTS WITH A DIAGNOSIS OF MODERATE TO SEVERE NON-ATOPIC ASTHMA: AN OBSERVATIONAL STUDY

Herrera García J.C., Arellano Montellano E.I., Jaramillo Arellano L.E., Espinosa Arellano A., Caballero López C.G. *Asthma Clinic and EPOC University Hospital of Puebla, Benemérita Autonomous University of the State of Puebla, Mexico; Department of Education and Medical Research BUAP, Mexico*

Introduction: While up to 50% of patients with severe asthma have no evidence of allergy, IgE has been linked to asthma, regardless of the atopic state. It has been reported that omalizumab, an anti-IgE monoclonal antibody, significantly benefits a subset of patients with severe and persistent allergic asthma. Therefore, we investigated whether omalizumab has biological and clinical effects in patients with non-atopic refractory asthma.

Methods: 20 Adult patients who despite daily treatment with or without maintenance oral corticosteroids had severe, non-atopic refractory asthma according to GINA (Global Initiative for Asthma) step 4 were assigned to receive omalizumab at doses of IgE levels (150 Mg SC each month) The primary end point was the change in clinical and functional parameters of patients through ACT (Asthma Control Test).

Results: After 52 weeks of administration of Omalizumab showed an overall increase in FEV1 and clinical and functional parameters. Symptomatic improvement of patients with ACT increase of 9 to 20 points. There was also good tolerance to the drug, with no serious adverse effect and improvement in asthma exacerbation in all patients.

Conclusions: Omalizumab negatively regulates FcεRI expression in patients with severe non-atopic asthma, as in severe atopic asthma. Omalizumab has a therapeutic role in severe non-atopic asthma. Our findings support the clinical efficacy of omalizumab in Mexican non-atopic asthmatic patients.

FEATURES OF THE IMMUNE SYSTEM PERFORMANCE IN PATIENTS WITH MONO- AND MIXED HERPESVIRUS INFECTIONS

I.V. Nesterova[1], E.O. Khalturina[2] *[1]People's Friendship University of Russia (RUDN University); [2]Department of Microbiology, Virology and Immunology, I.M. Sechenov First Moscow State Medical University, Moscow, Russia*

Herpesvirus infections are a group of widespread infections caused by Herpesviridae. Most often, these infections take the form of mixed infections and co-infections and can occur asymptomatically (latently), in acute, chronic persistent form with a recurrent course, and also in the form of atypical chronic active infection (ACA), which presents the greatest problem

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in diagnosis and treatment. ***Objective:*** to identify clinical diagnostic markers of the atypical chronic active form of mono- and mixed herpes infections.

Materials and Methods: We examined 198 people aged 23 to 60 years, suffering from mono and mixed ACA EBV, CMV, HSV 1/2 type. In addition to the traditional methods (medical history intake, methods of physical examination, CBC, etc.) for the detection of herpesviral infections, methods of serodiagnosis were used (IgM VCA EBV, IgG VCA EBV, IgM CMV, IgG CMV IgM HSV1/2, IgG HSV1/2) using the ELISA test systems of the "Diagnostic Systems" SPA (Russia), as well as the PCR test system "AmpliSens" (Russia) to detect the genome of viruses in biomaterials (blood, saliva, urine, scraping from the tonsils and the posterior pharyngeal wall). To evaluate the features of the functioning of antiviral immunity (immunogram, INF-status, etc.), flow cytometry and ELISA methods were used.

Results: According to the data obtained, the most specific and sensitive laboratory markers of ACA EBV are a simultaneous increase in IgG to EBNA-95% and / or IgG to VCA – 95% along with quantitative detection of the viral genome in various biomaterials (saliva 80%, scraping from tonsils 70%, the posterior pharyngeal wall – 70%) in combination with the presence of clinical markers of the disease. The most pronounced disturbances in the IFN system are present in herpetic infections. Reduction in induced production of IFN-α and IFN-γ was present in 100% of patients and was more pronounced than in mono- infection. Infringements and an imbalance in a population structure of blood lymphocytes are revealed: deficit CD3 + CD8 + cells – 70%, NK – 80%; EKT-67%. In CBC- neutropenia and lymphocytosis in 100% of cases.

Conclusion: during the study there were developed clinical and diagnostic markers of ACA, which allowed developing questionnaires for patients and diagnostic algorithms for physicians, including the definition of diagnostic markers of herpetic infections and the features of the antiviral immunity system performance.

CLINICAL AND LABORATORY FEATURES OF THE DIAGNOSIS OF MIXED HERPES-VIRAL AND BACTERIAL CO-INFECTIONS IN IMMUNOCOMPROMISED CHILDREN

E.O. Khalturina ***Department of Microbiology, Virology and Immunology, I.M. Sechenov First Moscow State Medical University, Moscow, Russia***

Introduction: The observed tendency towards the growth of viral-viral and viral-bacterial co-infections in children of different ages is associated with a violation of an adequate immune system (IS) performance. Dysfunctions of lymphocytes, both innate and adaptive IS, may be associated with the quantitative and morpho-functional imbalance of immunocompetent cells, and with the process of accelerated shortening of the end structures of chromosomal telomeres.

Materials and Methods: Under our supervision there were 60 children, aged 4 to 7 years, suffering from chronic diseases of the respiratory tract (CDoRT). A study was made of the features of the peripheral blood cell composition, the study of the length of telomeres through the Flow-FISH method using flow cytofluorimetry; a serological profile was studied for the detection of herpesvirus and bacterial infections (IgM VCA EBV, IgG VCA EBV, IgM CMV, IgG CMV IgM HSV1/2, IgG HSV1/2, IgM and IgG for mycoplasma pneumoniae and Chlamidia trachomatis. "Diagnostic Systems" SPA (Russia).

Results: All patients were divided into 2 groups. Group 1 included 45 children with CDoRT, seropositive for co-infections: mixed herpesvirus (IIH, EBV, CMV in various combinations) and the bacterial nature of Chlamydia trachomatis and/or Mycoplasma pneumonia. The second group included 15 children suffering from CDoRT, seronegative for mixed herpes-viral and bacterial co-infections. During a comparative study was found, that telomere lymphocytes were shortened in children with CDoRT seropositive for mixed-herpesvirus infections and bacterial co-infections compared to children with CDoRT without mixed-viral and bacterial co-infections ($p \leq 0.01$). In the hemogram of children from the 1st group, there was revealed pronounced anemization (37%); neutropenia (30%), leukopenia with lymphocytopenia (38.6%), which together indicates a marked decrease in immunoreactivity.

Conclusion: Thus, it was demonstrated that in children suffering from CDoRT associated with mixed herpes-viral and intracellular bacterial co-infections, there is a marked decrease in immunoreactivity, a more pronounced shortening of telomere lymphocytes, and there are features of the serological profile of detected infections.

CLINICAL AND IMMUNOLOGICAL EFFICACY OF IMMUNOMODULATORY THERAPY IN THE REHABILITATION OF IMMUNOCOMPROMISED CHILDREN WITH CONGENITAL CLEFT LIP AND PALATE AT STAGES OF SURGICAL TREATMENT

M.N. Mitropanova, I.V. Nesterova[1] ***Kuban State Medical University, Krasnodar; [1]Peoples' Friendship University of Russia (RUDN University), Moscow, Russia***

Introduction: One of the priority direction of the treatment of immunocompromised children (ICC) with congenital cleft lip and palate (CLP) is normalization of functioning of the immune system. ICC with CLP need in plastic reconstructive surgery, but often have postoperative complications, because they are suffering from reccurrent acute viral and bacterial infections of the upper and lower respiratory tract (RAVBI). ICC with CLP need in restoration of the immune system that that w'll have allow to decrease the frequency of RAVBI of respiratory tract, postoperative complications and to increase the effectiveness of complex rehabilitation. ***The aim*** of the study was to create the program of immunomodulatory therapy for ICC with CLP by using of drug Likopid in the pre- and postoperative period.

Material and Methods: Three groups of children in the age from 4 to 6 years old both gender were comparison. The group 1 included 20 children without immunomodulatory therapy. The group 2 included 30 children who were treated by immunomodulatory drug Likopid in the pre- and postoperative period. The group 3 – control group included 20 healthy children. Different chains of the immune system were detected in group 2 and group 3.

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Results: In group 2 the different positive effects were shown: a) the clinical effects were expressed in decreasing of the frequency of acute respiratory viral infection, reducing the number of exacerbations of chronic foci of bacterial infection of the oral cavity and nasopharynx, regression of the number of postoperative complications, reducing hospital stay; b) positive restoration effects were detected on the immune system (reconstruction of functioning of neutrophilic granulocytes, nature killers reduction, increasing the level of CD3+CD8+T cells). Other positive effects: the number of courses of antibiotic therapy and the duration of antibiotic usage were decreased.

Conclusion: The inclusion of the immunomodulatory therapy in the program of stage-by-stage rehabilitation of ICC with congenital CLP allowed us to significantly optimize therapeutic tactic on the base of restoration of immune system. And as soon as it became possible for all patients of the group 2 to provide timely surgical care that to avoid negative clinical consequences during the recovery phase after surgical treatment, and at the same time increase resistance to respiratory infections.

THE EFFECTIVENESS OF THE INFLUENCE OF THE IMMUNOTROPIC SUBSTANCE OF THE SODIUM SALT OF -5-AMINO-1,2,3,4-TETRAHYDROPHTHALAZINE-1,4-DIONE ON THE FORMATION OF NEUTROPHIL EXTRACELLULAR TRAPS UNDER EXPERIMENTAL WOUND INFECTIOUS INFLAMMATORY PROCESS

A.A. Evglevsky[1], I.V. Nesterova[2], S.G. Pavlenko[3] *[1]Kuban State University, Krasnodar; [2]Peoples' Friendship University of Russia (RUDN University), Moscow; [3]Kuban Medical Institute, Krasnodar, Russia*

Neutrophilic granulocytes (NG) are full-fledged immunocompetent cells capable of expression of genes, the synthesis of de novo cytokines and the formation of neutrophil extracellular traps (NET). NGs have a powerful microbicidal and cytotoxic potential and can influence the outcome of the inflammatory reaction.

In an experiment on 20 male rats of the Wistar line, which under local anesthesia, a model of open wounds of soft tissues of the dorsum measuring 3X3 cm was created. The wound was naturally infected with the microbial flora of the airy environment of the vivarium. The animals were divided into 2 groups-experimental (EG) and comparison group (CG), in 10 animals each. In the EG, from the first day of the experiment, by applying to the wound, a pectin film was used that included the immunotropic substance of the sodium salt of 5-amino-1,2,3,4-tetrahydrophthalazine-1,4-dione (IS) at a concentration of 5 %, which was necessary to elucidate the influence of IS on the dynamics of the formation of NET in conditions of the flow of the EWIP. Observations were carried out on the 2nd, 4th, 8th and 11th days from the beginning of the experiment. To assess the dynamics of the formation of NET in slides of wound exudate (WE), a modified method for detecting DNA was used, followed by microscopic analysis.

The number of NETs per one field of view in the GS and EG, respectively, was 9.1±1.1; 15.1±1.4; 3±0.06; 2±0.04 and 16.4±1.5; 28.3±1.9; 6.1±0.5; 1.1±0.01 ($p<0.001$). The percentage of the NET number to the total number of mature NGs, respectively, was 10.5%, 16.2%, 4.2%, 3.5% and 18.2%, 33.6%, 10.2%, 2.6%. for CG and EG, respectively.

Thus, with topical application, already to the second day of the experiment, the sodium salt of -5-amino-1,2,3,4-tetrahydrophthalazine-1,4-dione significantly stimulates the formation of NET in the WE. This effect persists until the eighth day of the experiment. By the 10th day the described effect fades away, which is apparently connected with the "phase" of the EWIP flow.

THE PECULIARITIES IN SENSIBILITY OF THE PROTEIN THIOL GROUPS IN THE BLOOD PLASMA TO OXIDATIVE MODIFICATION

I.M. Bykov, I.A. Egorova, K.A. Popov, Kh.P. Berberidi, I.A. Sevostyanov, R.I. Sepiashvili
The Kuban State Medical University, Krasnodar; Peoples' Friendship University of Russia (RUDN University), Moscow, Russia

The study in the thiol link of antioxidative system of the blood plasma is widely used for evaluation of the functional state of non-specific resistance of the body. We have assumed the informativeness of the proportion determination for different types of the protein thiol groups and the evaluation of their reactionary ability to interact with various modifiers.

In the blood plasma of patients suffering from the inflammatory diseases of small pelvis (n=71) before and after treatment including the usage of antioxidative remedies the content of the total, easily accessible SH-groups as well as those difficult of access has been evaluated by means of the Ellman's reagent against the background of further calculation of their proportion ($SH_д/SH_т$).

The laboratory study has been performed on the intact biological material or after its reaction with H_2O_2 in vitro after which the portion of the oxidated SH-groups has been determined.

The performed study has presented the changes like – the increase in content of fractions of easily accessible SH-groups against the background of the decrease in those difficult of access by the development of pathological process which has manifested itself in the increased indices of their proportion by 2–4 times. It probably happens due to the conformative reconstruction of protein molecule by its oxidative damage. Besides the increase in portion of the SH-groups oxidated by H_2O_2 by 2-5 has been revealed in patients suffering from the inflammatory diseases of small pelvis which indirectly indicates the lowered antioxidative activity. The analysis of effectiveness for the performed therapy in patients suffering from the chronic endometritis with the double salpingoophoritis has revealed the highest effectiveness of injections of sodium thiosulfate as well as vitamins A and E in addition to the standard therapy. Thus, the proportion $SH_д/SH_т$ has been statistically not different from the index of the healthy patients and the portion of the SH-groups oxidated by H_2O_2 has made only 25% which has been 2,5 times less than the index before the therapy. At the same time the indices of the thiol metabolism

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after treatment have statistically not changed with no usage of antioxidants. The received results allow recommending the approach to diagnostics of the functional state of prooxidant-oxidative system based on the determination of the offered integral coefficient which takes into account the proportion of easily accessible thiol groups and those difficult of access as well as their oxidability by the implementation of hydrogen peroxide into the test system.

METHEMOGLOBINEMIA AS A RISK FACTOR FOR THE DEVELOPMENT OF PATHOLOGICAL CONDITIONS

D.V. Vasilenko, K.V. Boev, A.V. Budnewski, V.V. Alabovsky, V.N. Borisoglebskaya L.I. Popova, V.V. Hamburov, N.A. Ramazanov ***N.N. Burdenko Voronezh State Medical University, Voronezh, Russia***

Methemoglobinemia is the condition of the body for which the concentration of methemoglobin (MetHb) in the blood exceeds 2.0% of the concentration of the total hemoglobin. According to the literature, in the average individual produces up to 0.5% of MetHb a day. The physiological rate is 1% MetHb. The increase in the concentration of MetHb up to 2% is considered to be a consequence of physiological adaptation of the organism to the action of external and internal factors (medications, smoking, genetic characteristics, etc.). If in methemohlobinemia ocurrs some change in the general analysis of blood: increased level of total hemoglobin, decrease in ESR, reticulocytosis. Insignificant hyperbilirubinemia is observed. In conjunction with the oxidation of the iron atom of heme this leads to a violation of cooperative activity of subunits of hemoglobin and thus oxygen-transport function of the protein. If methemohlobinemia is a violation of the gas transport function of blood. Hypoxia is a universal pathogenic factor. The identification of methemohlobinemia is important in the diagnosis of disease and monitoring therapy. The examined contingent in the total number of 408 people (170 males and 238 females) aged 22–55 years. The concentration of MetHb was determined according to methodical recommendations (1980). Analysis of the data reveals the following: 1. In the conditions of harmful production of methemoglobinemia was diagnosed in men and women (the sample of 210 people). It was found that in men is critical for development of methemohlobinemia is the level of total hemoglobin 130 g/l. 2. The risk of developing cholesterins associated with the level of MetHb. Contingent (121 subjects) with a total cholesterol concentration of 6.0±0.71 mmol/l blood MetHb made up 2.45±0,2%. 3. Identified methods of clinical laboratory diagnostics of pathological States are accompanied by methemoglobinemia. Have primarily examined patients (40 women, 27 men) with significant level exceeding the reference interval concentrations of glucose, cholesterol, urea, total bilirubin, activity of marker enzymes of the content of MetHb was 2.4±0.1%. Therefore, the identification of methemohlobinemia is essential for early diagnosis of diseases.

SIGNIFICANCE OF HUMAN COGNITIVE FUNCTIONS IN CLINICAL MEDICINE

N.A. Ryabchikova ***Lomonosov Moscow State University, Moscow, Russia***

The informative assessment of probabilistic prognosis definition as an innovative estimation of human intelligence method is of interested for a wide range of scientific researches. The success of solving tasks in situations with varying probability of events and the structure of their relationship determines the human life quality and safety ultimately. A computer version of the new psychological original methodology “Prognosis 1, 2.5” developed for healthy adult subjects for integrative brain activity assessment as the basic research methodology was used. It is widely used to assess of psychophysiological man status in different situations and in patients with Parkinson's disease, dementia. The present research platform is based on the simultaneous registration of Transcranial dopplerogramm ("MultiDFop-P") at the base of the Middle cerebral artery, reoencefalogramm ("Mitsar"), EEG and saccadic eyes movements on the PC of Windows XP by using the ADC "PowerLab-4", using modified programs "Chart 5" и 6-11 "Canvas" and brain predictive abilities assessment by computerized method of "Prognozis-2.5" This survey was supported by “Bodiflo”, LLC (Australia) and ITAG (USA).

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PHENOTYPIC CHARACTERISTICS OF SUBPOPULATIONS OF NEUTROPHILIC GRANULOCYTES FULL-TERM NEWBORNS WITH CONGENITAL PNEUMONIA AND NEONATAL SEPSIS

G.A. Chudilova, I.V. Nesterova[1], S.V. Kovaleva, L.V. Lomtatidze, O.N. Sapun ***Kuban State Medical University, Krasnodar; [1]The Peoples' Friendship University of Russia (RUDN University), Moscow, Russia***

Background: Neutrophilic granulocytes (NG) are able to regulate the function of innate and adaptive immune systems cells. Depending on the conditions NGs exert both activating and suppressing effects on immune system cells, participating in the immunopathogenesis of many infectious and inflammatory diseases.

Materials and Methods: In study were included 32 full-term newborns 3-15 days age with congenital pneumonia (CP) (36% of cases complicated by neonatal sepsis (NS)). Control group: 22 healthy full-term newborns. In study was estimated amount of NG (%) expressing CD62L, CD63, CD11b, CD16, CD32, CD64 and fluorescence intensity level (MFI).

Results: Comparative analysis of differences between receptor expressions on $CD62L^{+}CD63^{+}$ and $CD64^{+}CD16^{+}CD32^{+}CD11b^{+}$ NG subsets indicates a transformation of activation characteristics of circulating NG. Obtained data can be a diagnostic mirror of dysfunction NGs and reflect the severity of the infectious and inflammatory process. It was revealed that in healthy term infants $CD62L^{dim}CD63^{dim}$ and $CD62L^{bright}CD63^{dim}$ NG’s subsets are in equal proportions

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(46-50%), CD62L^{dim}CD63^{mid}NG is minor subset (less than 2%). When infectious process is developing, CD62L^{dim}CD63^{mid} NG subset was increased, and was decreased CD62L^{bright}CD63^{dim}NG subset, that more pronounced in severe cases. We defined several variants CD64^{+}CD16^{+}CD32^{+}CD11b^{+} NGs phenotype in term infants with CP and NS. CD64^{bright}CD16^{bright}CD32^{dim}CD11b^{dim}NG subset in healthy term infants was minor. Amount of NGs and receptor expression density in studied phenotypes is changed dramatically: CD64^{bright}CD16^{bright}CD32^{bright}CD11b^{bright} – in patient with CP, CD64^{bright}CD16^{dim}CD32^{bright}CD11b^{dim}- in patient with NS when infectious and inflammatory processes is occurred.

Conclusion: Evaluation of the phenotypic characteristics of the NG and the density of expression (MFI) CD62L, CD63, CD11b, CD16, CD32, CD64 molecules has allowed us not only to identify the existence of different subpopulations of NG in full-term newborns suffering from CP or NS, but to evaluate the role of each of the identified subpopulations in the immunopathogenesis of CP and NS.

INFLUENCE OF OZONE THERAPY ON INDICATORS OF NONSPECIFIC ANTIMICROBIAL RESISTANCE IN ATOPIC DERMATITIS IN CHILDREN OF EARLY AGE

Y.Yu. Ileck, A.V. Galanina, E.A. Fedyaeva, L.L. Ryseva, G.V. Soloveva, M.L. Vyaznikova
Kirov State Medical University, Kirov, Russia

65 children aged 8 months to 2 years with prevalent moderate atopic dermatitis (AtD) were observed. They were divided into two groups, depending on the nature of the treatment. The first group of patients with AtD (n=33) received complex conventional therapy, the second group of patients (n=32) – complex treatment in combination with two courses of ozone therapy with three months interval between them. The course of ozony therapy consisted of lubrication with ozonized olive oil of affected skin areas (2 times a day for 15 days) and rectal insufflation of the ozone-oxygen mixture, which were conducted every other day (8 procedures in total). In patients with AtD, the timing of the onset of complete clinical remission and its duration was determined, the serum anti-alpha-staphylolysin content, phagocytosis (phagocytic activity of neutrophils, phagocytic index, nitrosine tetrazolium test), TLR-2 expression and TLR-6) on lymphocytes, monocytes and neutrophils. The results of studies in patients with atopic dermatitis were compared with those obtained in 80 practically healthy children of similar age. It was found that in the second group of patients with AtD, the onset of clinical remission was registered on average 4.5 days earlier, and its duration was 3.5 times more than in the first group. At the onset of clinical remission in the first group of patients with AtD, the increased content of anti-alpha-staphylolysin in the blood serum, reduced phagocytic activity of neutrophils, phagocytic index, nitrosinium tetrazolium test, but signs of TLR-2 and TLR-6 activation appeared. In the second group of patients with AtD, upon the onset of clinical remission, normalization of the anti-alpha-staphylolysin content in serum and phagocytosis were detected, signs of high functional activity of the pattern-recognition receptors (TLR-2 and TLR-6), which play a key role in the detection of pathogenic microorganisms and the formation of mechanisms of antimicrobial immunity. The results of studies show that the inclusion of ozone therapy in the complex treatment of young children with AtD provides a faster onset of prolonged clinical remission and contributes to the increase of nonspecific antimicrobial resistance.

THE *IN VIVO* STUDY OF ANTITUMOR ACTIVITY OF THE ACTINOMYCIN D PROTEIN-VECTOR DRUG DELIVERY

B.I. Krugliy[1], E.D. Nikolskaya[2], O.G. Tereshchenko[1], R.U. Popov[2], O.A. Zhunina[1], N.G. Yabbarov[1], V.I. Shvets[2], E.S. Severin[1] ***[1]Russian Research Center for Molecular Diagnostics and Therapy, Moscow; [2]Moscow State University of Fine Chemical Technologies (MITHT), Moscow, Russia***

One of the main directions of modern pharmacology is the target drug delivery to the specific loci of the human body. The advantage of this approach is the ability to reduce the effective dose of the drugs bypassing of passive diffusion and directionally delivery to tumor target cells. Principal for this approach is the creation of chemically or biologically designed macromolecules consisting of a vector part and a non-specific part containing an antitumor drug. To increase the effectiveness of therapy for malignant neoplasms, we previously developed a preparation of protein-vector drug delivery system based on actinomycin D and recombinant alpha-fetoprotein (Aphotide®). The results of preclinical study on the model of human colorectal cancer HCT116 line on xenografts are presented in the article. A comparative analysis of the antitumor activity of the commercial drug Acnomide D® with Afotide® was carried out. Thus, *in vivo* experiments were conducted, which determined the range of therapeutic doses and the regimen of the drug on a solid model of colorectal carcinoma HCT116 on SCID mice.

THE USAGE OF THE ORAL LIQUID IN THE LABORATORY EFFECTIVENESS MONITORING OF TREATMENT OF THE DENTAL DISEASES

I.M. Bykov, I.A. Sevostyanov, O.V. Shvets, A.A. Ovsyannikova ***The Kuban State Medical University, Krasnodar, Russia***

Recently due to the development of new technologies as well as fundamental aspects of the molecular medicine the great attention has been paid to the possible usage of the oral liquid for diagnostic purposes. The oral liquid can easily be sampled and stored and also possesses a number of advantages during the laboratory study in comparison with the other biological liquids. The saliva diagnostics is the subject of concern to the research both of the diseases of the oral cavity and the somatic diseases.

In the study 78 recipients have taken part. The first group (n=20) has included practically healthy people. The second group has been composed of patients (n=20) suffering from the adentia of 1–3 teeth before taking measures concerning the

restoration of dentition. The third group has included patients suffering from the adentia (n=13) which have undergone the restoration of dentition by means of implementation of the cermet crowns based on implants. The fourth group have been made up of 25 patients having some imperfections of dentition replaced by the solid metal non-removable bridging dentures made of the cobalt chromic alloy. In the oral liquid of the participants the content of waste products after the oxidative modification of biomolecules have been determined by means of the thiobarbituric acid as well as the calculation of the thiobarbituric number (TBN).

As the result of the performed study it has been revealed that the content of waste products after the oxidative modification of biomolecules in the oral liquid of respondents included in the third group after the dental implantation and the implementation of crowns have corresponded to the TBN level of the control group. In the patients suffering from the adentia who have undergone the restoration of the dentitions by means of the non-removable dentures the TBN level has been 3,4 times higher than the same index of the control group and 1,8 times higher than the index of respondents of the second group. Thus, it has been presented that the replacement of imperfections of the dentitions by means of the non-removable dentures can lead to the even greater intensification of the free-radical processes in patients suffering from the adentia of 1-3 teeth, therefore this category of patients should be given certain recommendations concerning the usage of oral hygiene products of the antioxidative orientation. At the same time the treatment including the dental implantation possesses the more favourable effect on the metabolic processes in the oral cavity in comparison with the other methods of prosthetics.

ANTI-HSV1 ACTIVITY OF GLYCYRRHIZIN-CONTAINING TOOTHPASTE

P.P. Nesmiyanov, M.D. Malykhin, S.V. Korkach-Romanov, N.N. Nosik, D.N. Nosik
SPLAT Cosmetics, Moscow, Russia

More than 50% of the population are affected by HSV-1. Common oral symptom of HSV-infection is gingivostomatitis which substantially affects quality of life [1–2]. Prevention and treatment options are limited, but hygiene remains an important measure [3]. The aim of this study was to explore anti-HSV properties of Splat toothpaste, containing 0.3% dipotassium glycyrrhizinate which was shown to have antiviral properties [4]. We used Splat Special Love® as a reference product.

Materials and methods: We used HSV L2 strain with a stock titer of 6.0 log10 TCD50/1 mL. Virucidal properties were studied in a suspension test with susceptible VERO cells in Eagle medium supplemented with 10% FCS and in a surface test (artificial leather). The antiviral activity was expressed as the virus titer reduction. Results: Virus titer reduction was at 2.0 log10 in the suspension test. The surface test showed compete HSV-1 inactivation. Thus, Splat Special Love® toothpaste exerts significant anti-HSV-1 activity. This is explained by the presence of dipotassium glycyrrhizinate and supports the idea of the use of such toothpastes as an additional hygienic practice to prevent recurrence of oral HSV-1 clinical symptoms.

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THE PATHOGENETIC SUBSTANTIATION OF THERAPY FOR THE CHRONIC GENERALIZED PERIODONTITIS IN PATIENTS SUFFERING FROM THE GLUCOCORTICOID OSTEOPOROSIS

N.I. Bykova[1], S.V. Sirak[2], R.I. Sepiashvili[3], A.A. Ovsyannikova[1]
[1]The Kuban State Medical University, Krasnodar; [2]The Stavropol State Medical University, Stavropol; [3]Peoples' Friendship University of Russia (RUDN University), Moscow, Russia

As the result of the performed multi-aspect clinical, roentgenological and biochemical studies in 235 patients suffering from the generalized periodontitis against the background of the steroid-dependent bronchial asthma it has been proved that the severity of clinical manifestation of the pathological process in the periodontium of the patients is mainly determined by the intensity of the osteoporosis and in a less degree – by the inflammatory reaction in the gum tissues.

It has been revealed that the glucocorticoid therapy by means of both the inhalation and the systemic remedies leads to the disturbance of the metabolic processes of the bone remodeling in the alveolar bone. By usage of the inhalation glucocorticoid remedies the resorption processes intensify while the processes of the bone formation suffer by a less degree. By the combined intake of the inhalation systemic steroid remedies the intensification of the resorption processes in the bone structures occurs against the background of the weakening of the bone synthesis.

On the basis of the revealed regularities in the bone metabolic disorders under the influence of the inhalation remedies and the combination of the inhalation and the systemic glucocorticoids the pathogenetic formation mechanisms of the osteoporosis focuses of different intensity have been revealed in the alveolar bone, notably those of low, moderate and high activity. In consideration of the bone metabolic disorders and the manifestation activity of the osteoporotic process in the alveolar processes the individual regimen of the osteotropic therapy have been developed within the complex treatment of the generalized periodontitis.

In addition to the traditional complex treatment of the generalized periodontitis the patients suffering from the osteoporotic process of low activity have been given certain recommendations concerning the usage of the Theraflex® remedy, Sagmel, Inc., USA; those suffering from the osteoporotic process of moderate activity – the combination of Theraflex® and

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osteogenon; those suffering from the osteoporotic process of high activity – the combination of Theraflex® and Vitrum as the osteotropic therapy.

Their usage has contributed to the decrease of the inflammatory relapses in periodontium by 28.9% and to the persistent clinical and roentgenological long-term stabilization in 82.5% of patients suffering from the generalized periodontitis and associated glucocorticoid osteoporosis.

THE IMMUNE RESPONSE OF HEALTHY PERSONS' BLOOD LEUKOCYTES ON XENOGENEIC PARODONTS' ANTIGEN *IN VITRO*

A.S. Orazaliev, S.A. Pleskanovskaja
Turkmenistan State Medical University, Ashkhabad, Turkmenistan

The global burden of the parodont illnesses does necessary the decision of a question a cart is possible of earlier revealing of the given pathology, finding-out of degree and character of its interconditionality with the general condition of an organism (Petersen P.E, Ogawa H., 2012). Does not raise the doubts that the first the immune system reacts to the most insignificant pathological changes in the bodies' tissues and cells. Hence, the immunological approach to the decision the questions of early prediction diagnostics of the parodont illnesses are optimal. We investigate migration activity of the practically healthy persons' (PHP) and children' sick of caries (CHSC) blood leukocytes in the presence of soluble tissues' allogenic (AAG) and xenogenic (XAG) antigens of parodont *in vitro*. It is surveyed 75 (PHP) at the age from 10 till 25 years which were not addressing to the stemmatologist and 45 CHSC at the age from 9 till 15 years. Migration activity of leukocytes were studied in the modified reaction of the leucocytes' braking migration (S. Pleskanovskaja, 1982). Results expressed as the leukocytes' migration index (LMI). Soluble tissues' antigens were prepared from monthly BALB/c mice and the parodont tissues from newborn children who were lost in birth. Antigens were prepared by the method water-salt extraction taking into account G. Frimel's recommendations (1987). Blood for research received from a ring finger of surveyed persons with observance aseptic rules. The received data's were mathematically processed by the SPSS program help. It has been established that on the average on group PHP both antigens brake migration of leukocytes in vitro, but LMI in the presence of AAG a little above, in comparison with XAG ($p > 0,05$). In group of CHSC the LMI in the presence of AAG has made 89 c.u. in the presence of XAG – 110.6 ($p<0.05$). Besides, in the CHSC group the value of LMI in the presence of AAG authentically exceed average values in 60%of cases, and in the presence of XAG – in 69%. In other words, xenogeneic antigen *in vitro* almost equally influences on the migration activity of leukocytes of both PHP and KCH blood. In our opinion obtained data allows to use the parodontal XAG in immunological diagnostics of parodonts' illnesses.

IMMUNOSENESCENCE: HEALTHY AGING AND CANCER

Tinatin Chikovani[1], Nia Sharikadze[2], Ana Mikaberidze[1,3], Rusudan Tskitishvili[1,3], Levan Iashvili[1,3], Ia Pantsulaia[1], Nino Kikodze[1]
[1]Immunology Department, Tbilisi State Medical University, Tbilisi Georgia; [2]MediClubGeorgia, Tbilisi, Georgia; [3]MedGuide 101, Tbilisi, Georgia

Introduction: Age is the most important risk factor for cancer. The immune surveillance successfully avoids cancer development in individuals with apparently normally regulated immune system. The changes in the immune status with aging contribute to the higher incidence of cancer, but data on this important topic are few and not well clarified.

Immunosenescence is not accompanied by an unavoidable and progressive deterioration but is the result of a remodeling of the immune function. It is known that changes in the adaptive immune system, especially in the frequency and phenotype of T lymphocytes, are more important than changes in innate immunity. Age-related changes of the immune system are directly or indirectly involved in increased susceptibility to infectious diseases, autoimmunity and cancer as well as decreased responsiveness to vaccination.

Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have recently been considered as two new inflammatory markers in tumor. It is reported that NLR and PLR could be predictive of the prognoses of patients with diverse conditions. Just recently was shown that these indices change with age: individuals aged 18 to 50 years had significantly lower NLR and PLR than older individuals aged >51 years.

Objectives: The aim of the presented project was to study whether the NLR or the PLR predict the clinical outcomes in colorectal cancer (CRC) patients.

Methods: Medical records from a total of 68 patients with CRC at MediClub Georgia, Tbilisi were retrospectively reviewed. All blood samples were taken at the time of admission. NLR and PLR were calculated by dividing the absolute neutrophil/platelet count by the absolute lymphocyte count.

Results: Difference between the cancer outcomes of patients with high NLR (≥ 3.0) and high PLR (≥ 160) (group 1) and normal NLR (0.78–3.0) and normal PLR (75–160) (group 2) were evaluated. It was shown that in group 1 – 54.5% of patients live up to 5 months, 27.3% – from 5 months to 1 year and 18.2% – from 1 to 2 years. In group 2 – 26.7% of patients live from 5 months to 1 year, 40% – from 1 to 2 years and 33,3% – at least years after admission.

Conclusion: High NLR and high PLR are independent risk factors predicting poor outcomes in CRC patients. Most of CRC patients with high NLR have a rectosigmoid cancer, high PLR was found in the patients with II and III stages of CRC.

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ADHERENCE TO TREATMENT IN OBSTRUCTIVE RESPIRATORY DISEASES: STEPS FORWARD

Matteo Ferrando[1,3], Enrico Heffler[2,3], Francesca Racca[2], Luca Malvezzi[4], Giovanni Passalacqua[1], Giorgio Walter Canonica[1,2,3], Francesca Puggioni[2,3]
[1]Allergy & Respiratory Diseases, DIMI Dept of Internal Medicine, University of Genoa, IRCCS AOU San Martino-IST, Genoa, Italy; [2]Personalized Medicine, Asthma and Allergy Clinic, Humanitas Research Hospital, Milano, Italy; [3]Department of Biomedical Sciences, Humanitas University, Milano, Italy; [4]Department of Otolaringology, Humanitas Research Hospital, Milano, Italy

The problem of adherence to treatment of obstructive respiratory diseases in well-known since decades but no significant improvements have been made so far in order to solve this problem. In fact, among all pathologies, those affecting the respiratory system probably have the lowest adherence to treatments. Respiratory drugs are carried by a huge variety of devices, some of which are not easy to be used without a proper training. A step forward in increasing patients' adherence to their treatments should be the assessment conduced by the respiratory physicians, the general practitioners and especially-trained nurses. This should be done at each visit, even for reminding the patients the correct inhalation technique, especially when a patient reports respiratory symptoms despite the prescription of an adequate therapy.

Furthermore, the latest technologies introduced in monitoring patients' compliance to respiratory therapeutic regimen will be of interest. Smartphone applications are noticeable: easy to use and fast to be completed, they are very useful in reminding to patients the need of inhaling their drugs and permit also the completion of several questionnaire that are helpful for the clinicians to better understand the way their patients live with their disease.

NETWORKING IN SEVERE ASTHMA MANAGEMENT

Matteo Ferrando[1,3], Enrico Heffler[2,3], Francesca Racca[2], Luca Malvezzi[4], Giovanni Passalacqua[1], Giorgio Walter Canonica[1,2,3], Francesca Puggioni[2,3]
[1]Allergy & Respiratory Diseases, DIMI Dept of Internal Medicine, University of Genoa, IRCCS AOU San Martino-IST, Genoa, Italy; [2]Personalized Medicine, Asthma and Allergy Clinic, Humanitas Research Hospital, Milano, Italy; [3]Department of Biomedical Sciences, Humanitas University, Milano, Italy; [4]Department of Otolaringology, Humanitas Research Hospital, Milano, Italy

Networking is a fundamental intervention to increase the capabilities of respiratory physicians to manage severe asthma. Referring to highly specialized centers in severe asthma management is important for those patients whose asthma is inadequately controlled despite the utilization of the maximal therapies as stated by international guidelines.

Several examples of academic health education and counseling programs have been set up for these reasons. One example of severe asthma management network is the Severe Asthma Network Italy (SANI) program, which is part of the international programs Staying Healthy-Asthma Responsible & Prepared™ (SHARP) and ISAR (International Severe Asthma Registry).

Several respiratory centers from all Italian regions are taking part in SANI with the goal of sharing current knowledge on severe asthma and helping minor centers to deal with severe asthmatic patients.

Hopefully, from the efforts of all these principal centers, there will be not only a huge amount of data but a spirit of tangible cooperation among all these centers will rise.

IS PRECISION MEDICINE THE WAY TO TREAT ASTHMA?

Matteo Ferrando[1,3], Enrico Heffler[2,3], Francesca Racca[2], Francesca Puggioni[2,3], Luca Malvezzi[4], Giovanni Passalacqua[1], Giorgio Walter Canonica[1,2,3]
[1]Allergy & Respiratory Diseases, DIMI Dept of Internal Medicine, University of Genoa, IRCCS AOU San Martino-IST, Genoa, Italy; [2]Personalized Medicine, Asthma and Allergy Clinic, Humanitas Research Hospital, Milano, Italy; [3]Department of Biomedical Sciences, Humanitas University, Milano, Italy; [4]Department of Otolaringology, Humanitas Research Hospital, Milano, Italy

The archetypal asthma therapy is composed by inhaled corticosteroids and long acting beta agonists for baseline treatment plus short acting bronchodilators as needed. These drugs are to be considered nonspecific in their mechanisms of action and they do not always guarantee the complete control of the disease, requiring alternative strategies. To this previous era, the so-called 'blockbuster era', based on symptomatic and nonspecific drugs, is getting closer the 'one-size does not fit all' era of the precision medicine which reckons on the use of molecularly targeted drugs acting directly on specific targets. We are talking about precision medicine with a closer look to molecular pathogenetic mechanisms. Precision medicine should not be compared with personalized medicine, which has a slightly different meaning since it is based on the individual patients not on the pathogenesis of the disease, but sometimes both terms are used as synonyms.

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ALLERGEN IMMUNOTHERAPY IN ASTHMA: STATE OF THE ART

Matteo Ferrando[1,3], Enrico Heffler[2,3], Francesca Racca[2], Francesca Puggioni[2,3], Luca Malvezzi[4], Giovanni Passalacqua[1], Giorgio Walter Canonica[1,2,3]
[1]Allergy & Respiratory Diseases, DIMI Dept of Internal Medicine, University of Genoa, IRCCS AOU San Martino-IST, Genoa, Italy; [2]Personalized Medicine, Asthma and Allergy Clinic, Humanitas Research Hospital, Milano, Italy; [3]Department of Biomedical Sciences, Humanitas University, Milano, Italy; [4]Department of Otolaringology, Humanitas Research Hospital, Milano, Italy

Allergen Immunotherapy (AIT) is the only disease-modifying treatment approved for allergic rhinitis and allergic asthma and represents a suitable therapeutic option, especially in childhood, to modify the progression of respiratory allergic diseases. AIT was empirically proposed more than one century ago in the subcutaneous form (SCIT). The sublingual administration (SLIT) was developed during the 1980ties, to achieve an improvement in safety and convenience. Since we are getting even closer to the era of the precision medicine, AIT is a good example of a personalized therapeutic intervention, in which the most important variables for an appropriate selection of the right therapeutic strategy can be identified. At variance from the previous perspective, the efficacy of AIT is no longer considered as a generic "class effect" and each AIT product is evaluated according to the scientific evidence. Furthermore, the efficacy of SLIT preparation in asthmatic patients has been demonstrated in several clinical trials and this led to the approval of single AIT preparations by EMA and FDA. Most guidelines agree that AIT is not contraindicated but also state that asthma must be fully controlled by the standard of care pharmacological treatment, when AIT is prescribed. The recent ARIA guidelines suggest both SCIT and SLIT as a conditional recommendation in allergic asthma, due to the moderate/low quality of evidence. The lack of robust evidence led to a certain grade of opposition to the use of AIT in asthmatics. Indeed, the potential benefits of AIT must be weighed against the risk of adverse effects, the inconvenience and cost of a prolonged course of therapy, considering also other factors such as poor adherence, clinically non relevant allergens, poly-sensitizations, unavoidable adverse reactions of routine medication, etc.

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