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Congress Proceedings

Congress Abstracts

XII WORLD CONGRESS ON COPD, ASTHMA & RESPIRATORY ALLERGY

Dubai, UAE **February 2–5, 2018**

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Abstract Submission before NOVEMBER 30, 2017

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Congress Proceedings will be published by the FILODIRITTO International Proceedings Division.
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A MODERN APPROACH TO THE CHOICE OF TACTICS OF TREATMENT OF CHILDREN WITH ATOPIC DERMATITIS

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The study considers advantages of differential approach to the treatment of children (Ch) with different immunopathogenetic phenotypes (IPGF) of atopic dermatitis (AD). It has been found that patients with non-IgE-mediated type of AtD was not sensitization to IgE to house dust mite allergens (HDMA) and was observed a decline in macrophage-phagocytic component of immune system (MPCIS). It was shown, that the IgE-mediated phenotype includes 3 forms of AtD: allergic form; mixed form (in combination with allergic rhinitis, asthma); immunocompromised form (ICF). Allergic and mixed have a proven sensitivity to non-eliminated HDMA, which promoted allergization and provoked the development of symptoms in the course of AtD, and in Ch with ICF of AtD a decrease in parameters of MPCIS (such as phagocytic number, phagocytic index). On the basis of immune system disorders (ISD), has been developed a different complex of immunotherapy (CIT). The developed algorithm of examination and diagnosis of patients with AtD allows the choice of an adequate CIT in accordance with IPGF based on detected of immune system disorders (ISD). Implementation of individual treatment allowed to reduce the risk of developing severe and chronic AD and to improve the quality of life of patients.

Key words: *Atopic dermatitis, children, immunopathogenetic phenotypes, subcutaneous allergen specific immunotherapy, cytokines, comprehensive programs of immunotherapy*.

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Atopic dermatitis (AtD) is a chronic inflammatory allergic disease (ADs) of the skin with multifactorial pathogenesis. Its development proceeds against the background of various and interdependent genetical, ecological, immunological, psychological, biochemical and other pathological processes, the most important of which is dysfunction of skin barrier. The skin barrier protective dysfunction causes the acceleration of secondary infection overlay and extraneous antigens penetration through damaged corneal layer.

The prevalence of adults' and children's AtD is steadily increasing all over the world and now reaches over 1-20% (approximately 20% for children and 1% -3% for adults). Two principal strategies for resolving of unsolved problems in management of ADs under consideration at present include application of allergic-specific immunotherapy (AIT) [1, 2], which is aimed at long-term specific modulation of immune response towards immune tolerance to cause significant allergens, and use of biological response modifiers for minimization of pathological immune reactions. The combined strategies [3-10] involving both approaches can ensure successful management of AD [11–13]. It is of great importance to carefully screen the patients with AtD [14, 15] who should be placed on patient-specific combined therapy according to revealed immune and or/non-immune disorders and phenotype of the disease.

Immunopathogenetic phenotype (IPGP) determined in accordance with the results of complete medical assessment becomes a key factor for selection of optimal therapy for AtD, allows to provide for case-specific combined therapy regimens for this disease. In this connection, development of algorithm for assessment, diagnosis and treatment of children (Ch) with various AtD IPGP is a crucial task.

The main purpose of the study was to argue the need of a differential approach to the treatment of Ch with different IPGF of AtD.

Methods

300 Ch aged 3-17 with moderate course of AtD in the exacerbation phase were examined. The control group was comprised of 30 healthy Ch of the same age. The patients underwent general clinical assessment, clinical assessment and immunoallergological assessment (IAA) aimed at detection of clinical and laboratory signs of allergen-induced inflammation. General clinical examination included clinical blood and urine analyses and screening for parasitic and viral infections. IAA consisted of: immunogram (cellular, humoral and phagocytic component of immune system), determination of levels of pro and anti-inflammatory cytokines (by fluorescence immunoassay); skin testing, challenge or elimination testing (if indicated), total and specific IgE blood testing. House dust mite allergens (HDMA) were used as a cause-significant allergen. Clinical assessment was aimed at collection of allergic anamnesis and evaluation of severity of clinical symptoms according to Scoring of Atopic Dermatitis (SCORAD) scale (Table 1).

Table 1

Detection of clinical and laboratory signs of allergen-induced inflammation

General Clinical Assessment	
Clinical analyses of blood and urine	
Screening on parasitic and viral infections	
Clinical Assessment	
Collection of allergic anamnesis	
Evaluation of severity of clinical symptoms according on a SCORAD scale	
Immuno-Allergological Assessment	
Immunogram	Evaluation of cellular, humoral and phagocytic components of immune system
Pro- and anti-inflammatory cytokines	IL-4, IL-13, INF-y
Allergological assessment	skin tests, provocation or an elimination tests (if indicated), the definition of general and specific of IgE (sensitization to the definition of cause-significant allergens)
Allergological assessment	skin tests, provocation or an elimination tests (if indicated), the definition of general and specific of IgE (sensitization to the definition of cause-significant allergens)

On the basis of the revealed disorders, several comprehensive programs of immunotherapy (CIT) were developed. For IgE-mediated forms of AtD were proposed CIT, including basic therapy (BT) and subcutaneous allergen-specific immunotherapy (SCIT) on an accelerated regimen. In cases when reduced functional activity of macrophage-phagocytic component of immune system (MPCIS) was detected, an immunomodulator (IM) was added. Selection of IM was based on its capacity to affect the cells of monocytic-macrophagal nature, increase of macrophages' cytotoxicity toward bacterial antigens and virus-infected cells, as well as correction of imbalance in cytokine profile Th1 and Th2 and intensifying the production of IFNγ, which eventually contributed to lower rate of infectious complications of AtD. For non-allergic form of AtD, the BT+IM were used (Fig. 1). BT included: elimination of cause significant allergens, application of anti-inflammatory (topical and systemic) therapy (cetirizine-based medications in age-specific dosage variances, topical glucocorticosteroids, such as Advantan, Elocom, Tri-derm, Pimafucort, emollients – series Mustela, Avene, Dardia), correction of gastrointestinal dysfunction (enzymes: Kreon 10,000, Linex – according to age).

Results

The examination divided patients into two main EPGF-groups: the first group (1G) with IgE-mediated and the second group (2G) with non-IgEmediated forms of AtD (Table 2).

The patients with non-IgE-mediated type of AtD (2G) showed no IgEsensitization to HDMA (Fig. 2) and observed a decline in MPCIS [16]: phagocytic index down to 44.2±2.4%, phagocytic number down to 2.7±0.2 microbial bodies (Fig. 3).

The IgE-mediated phenotype includes three forms of AtD: allergic form; mixed form (in combination with allergic rhinitis, asthma); immunocompromised form (ICF). Allergic and mixed have a proven sensitivity to non-eliminated

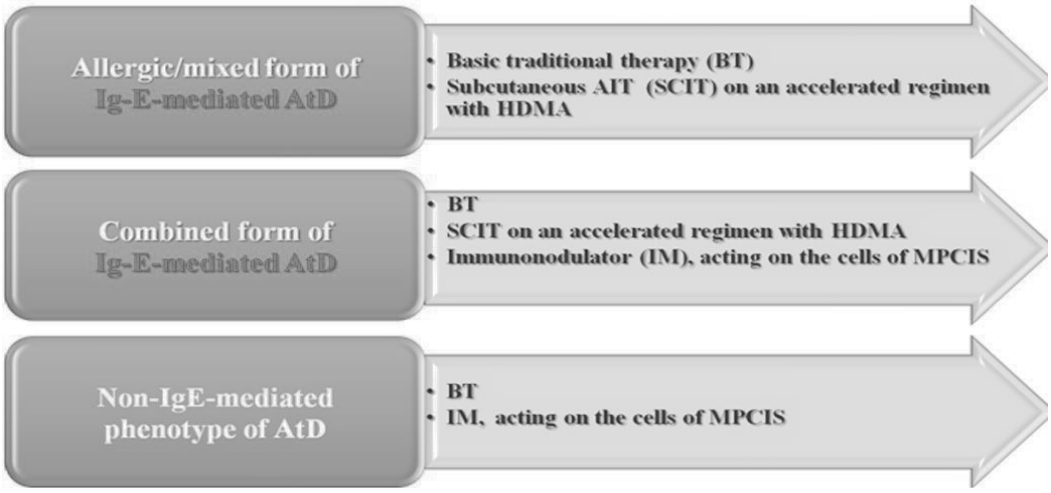

Fig. 1. Integrated multimodal immunotherapy programs for various phenotypes of atopic dermatitis.

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Table 2

Characteristics of immunopathogenetic phenotypes of atopic dermatitis and revealed immune disorders

Parameters	IgE-mediated phenotype of AtD (forms)			Non-IgE-mediated phenotype of AtD
	Allergic	Mixed***	ICF ****	
Sensitization to HDMA*	Present	Present	Present	Not present
Reduction in parameters of MPCIS** (phagocyte number, phagocyte index, NCT-test)	Within the expected range for age	Within the expected range for age	Statistically significant reduction	Statistically significant reduction

Note:
* HDMA - house dust mite antigens
** MPCIS - macrophage-phagocytic component of the immune system
*** Mixed form - the combination of AtD with allergic rhinitis and/or allergic bronchial asthma
**** ICF (immunocompromised) form - allergic AtD in combination with immune disorders in macrophage-phagocytic component of immune system

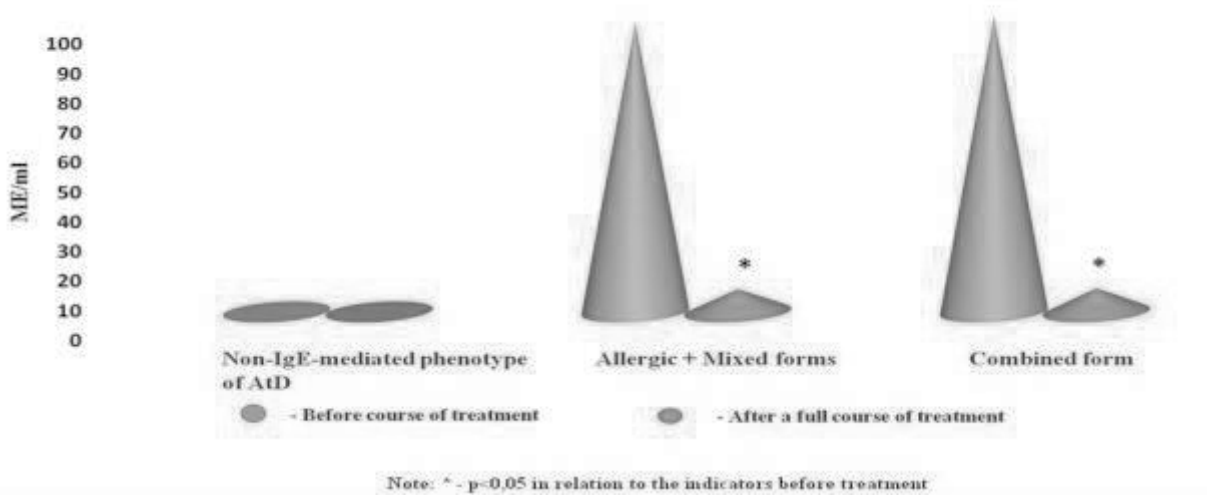

Fig. 2. Changes in blood serum level of specific IgE in children with various phenotype forms of atopic dermatitis.

HDMA, which promote allergization and provoke the development of symptoms in the course of AtD, and in Ch with ICF of AtD a decrease in parameters of MPCIS (such as phagocytic number, phagocytic index) was also found (Fig. 2, 3).

Application of pathogenetically substantiated therapy contributed to intensification of IFNγ synthesis and decrease in both serom and saliva levels of anti-inflammatory cytokines IL-4 and IL-13 (Fig. 3, 4), which stimulate secretion of IgE and participate in Th2-type immune reactions [17]. On the basis of immune system disorders (ISD), we developed a different complex of immunotherapy (CIT). For 1G it has been suggested to conduct a regimen of comprehensive IT, consisting of BT and SCIT in an accelerated scheme. CIT with IM allows to provide SCIT on an accelerated regimen and to increase effectiveness of treatment significantly. In 2G we have used BT and IM. Comparative study of changes in citykine status (levels of cytokines IL-4, IL-13 and IFNγ in blood serum and saliva) in Ch with AtD has allowed to determining the advantages of including CIT in a multimodality therapy program. Application of CIT as a part of multimodality therapy helped to reduce the level of specific IgE, IL-4 from 55.2±4.2 pg/ml to 38.1±3.4 pg/ml ($p \leq 0.05$), to increase production of IFNγ from 21.1±2.0 pg/ml to 44.6±3.5 pg/ml ($p \leq 0.05$). After a course of treatment the level of cytokines in biological fluids of patients from group which received both BT and CIT were approaching the same in healthy persons (Fig. 3, 4).

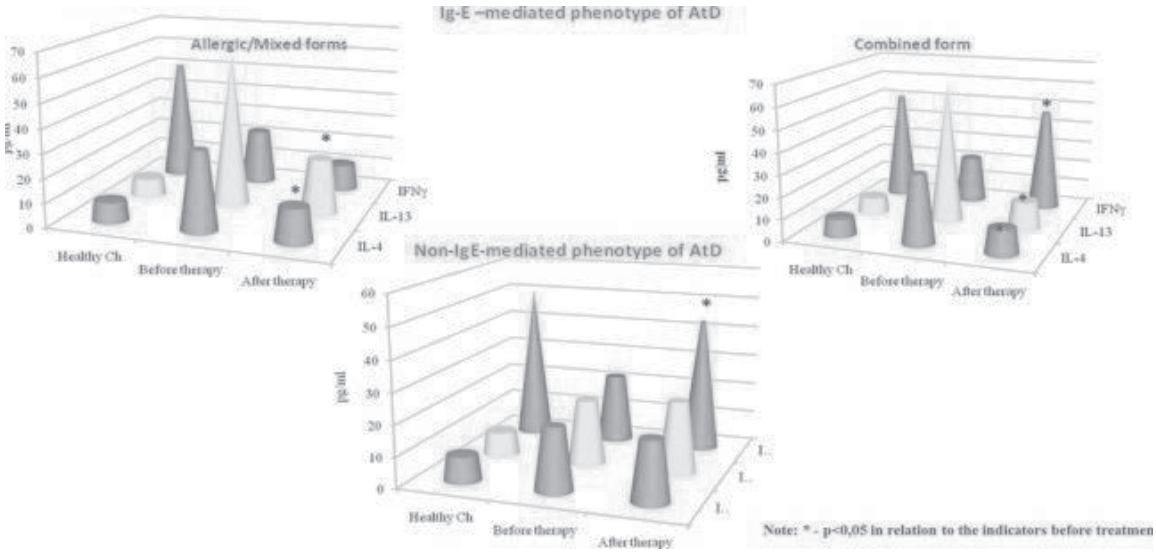

Fig. 3. Changes in blood serum levels of pro- and anti-inflammatory cytokines in children with various phenotype forms of atopic dermatitis.

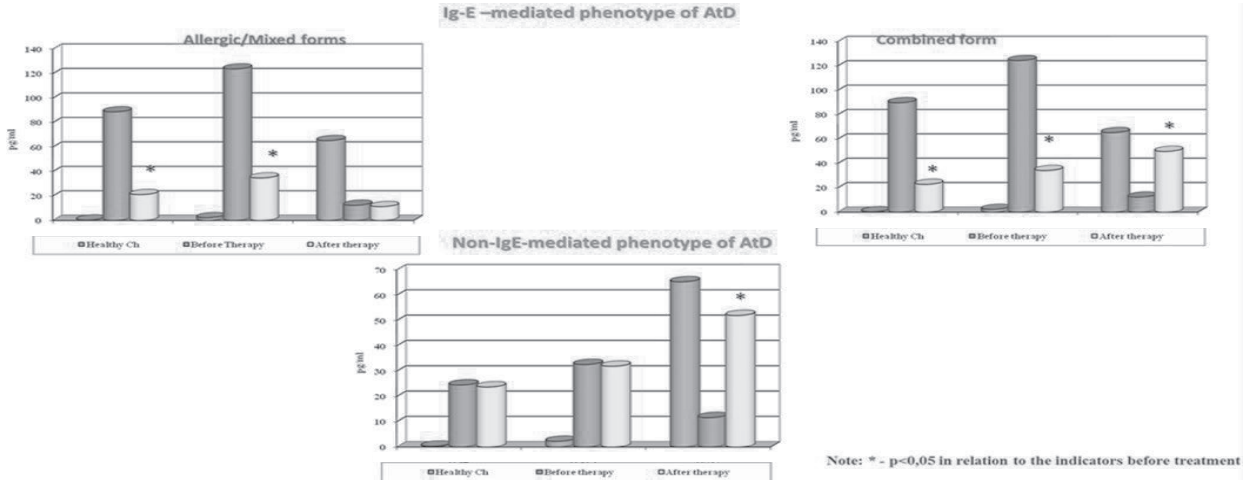

Fig. 4. Changes saliva levels of pro- and anti-inflammatory cytokines in children with various phenotype forms of atopic dermatitis.

Conclusion

The developed algorithm of examination and diagnosis of patients with AtD allows the choice of an adequate CIT in accordance with IPGF based on detected ISD. The above improves the treatment of Ch, increases the duration of remission, reduces the risk of the developing severe and chronic AD, it improves their quality of life [18, 19], provides pharmacotherapy and medical services costs reduction, and it is more cost-effective [20–25].

References

1. Slavyanskaya T., Derkach V. *Allergen-specific immunotherapy, as a pathogenetically justified method of treatment of children with atopic dermatitis* // Ed. R. Sepiashvili. MEDIMOND Int. Proc. 2013. P. 39–41.
2. Slavyanskaya T., Derkach V., Sepiashvili R. WAO Dialectics in Allergy Medicine: Specific immunotherapy efficiency in children with atopic dermatitis // *World Allergy Organization J.* 2016. Vol. 9. P.15.
3. Derkach V., Slavyanskaya T. Combined immunotherapy in children with atopic dermatitis: rationale for application // *Allergy. Asthma & Immunophysiology: from Genes to Clinical Management.* Ed. R. Sepiashvili. Medimond Int. Proc. 2014. P. 63–67.
4. Derkach V., Slavyanskaya T. Comparative characteristic of effectiveness of immunotherapy of children with atopic dermatitis // *Allergy, Asthma & Immunophysiology: Recent Advances in understanding and Management*. Ed. R. Sepiashvili. Medimond Int. Proc. 2015. P. 45–49.
5. Slavyanskaya T., Derkach V. Clinical and immunologic characteristics of allergen-specific immunotherapy in children with atopic dermatitis // *World Allergy Organization J.* 2013. Vol. 6. Suppl. 1. P. 94.
6. Slavyanskaya T.A., Derkach V.V. Immunotherapy rationale in children with exacerbation of moderate atopic dermatitis // *Allergy*. 2013. Vol. 68. Suppl. 97. P. 161.

ISSN 1562-3629

7. Slavyanskaya T.A., Derkach V.V. Clinical and immunological substantiation of immunotropic therapy in the complex treatment of atopic dermatitis in children // *World Allergy Organization J.* 2014. Vol. 7. Suppl. 1. P. 21.
8. Slavyanskaya T.A., Derkach V.V. Clinical substantiation of immunocorrective therapy in children with atopic dermatitis // *World Allergy Organization J.* 2014. Vol. 7. Suppl. 1. P. 7.
9. Slavyanskaya T.A., Derkach V.V. Rationale for the use of multiagent immunotherapy in children with atopic dermatitis // *Allergy*. 2014. Vol. 69. Suppl. S99. P. 190.
10. Slavyanskaya T.A., Derkach V.V. Combined immunotherapy in children with atopic dermatitis: rationale for application // *Allergy. Asthma & Immunophysiology: from Genes to Clinical Management.* Ed. R. Sepiashvili. Medimond Int. Proc., 2014. P. 63–67.
11. Slavyanskaya T.A., Derkach V.V. Targeted Therapy in Children with Atopic Dermatitis. *// J Allergy Clin. Immun*. 2016. Vol. 137. # 2. P. AB148. ref.485.
12. Slavyanskaya T.A, Derkach V.V. New strategies of atopic dermatitis treatment in children. // *European Journal of Immunology*. 2016. Vol. 46. Suppl. 1. P.1124. ref. 1119.
13. Slavyanskaya T. Targeted therapy as a basic issue of atopic dermatitis' management in patients. // Allergy. 2016. Vol. 71 Suppl. 102. P.399. Ref. 1494.
14. Slavyanskaya T.A., Derkach V.V. Procedure for Diagnostic and Selection of Immunotherapy Method for Children with Different Immunopathogenetic Phenotypes of Atopic Dermatitis // *World Allergy Organization J.* 2016. Vol. 9. Suppl. 1. P. 70. Ref. A226.
15. Slavyanskaya T.A. Differential-Diagnostic Criteria of Patient's Selection and Modern Treatment Strategies for Children with Atopic Dermatitis // *Annals of Allergy, Asthma & Immunology*. 2016. Vol. 117. #5. Suppl. P. S119–S120.
16. Slavyanskaya T.A., Sepiashvili R.I. Prediction of Infectious Complications in Children with Atopic Dermatitis // J. Allergy Clin. Immunol. 2017. Vol. 139. #2. Suppl. P. AB243. Ref. 761.
17. Derkach V.V., Slavyanskaya T.A. Role of cytokine profile monitoring in children with atopic dermatitis // *Allergy.* 2013. Vol. 68. Suppl. 97. P.159.
18. Derkach V., Slavyanskaya T. Severe atopic dermatitis and quality of life in children during background therapy // *J. Allergy Clin Immunol.* 2013. Vol. 131. #2. Suppl. Ref. 129.
19. Slavyanskaya T., Derkach V. Severe Atopic Dermatitis (SAD) and Quality of Life (QOL) in Children during Background Therapy (BT) // *J Allergy Clin Immunol.* 2013. Vol. 131. #2. AB35.
20. Derkach V., Slavyanskaya T. Comparative analysis of pharmacoeffectiveness of various programs of immunotropic therapy of children with atopic dermatitis // *Allergy, Asthma & Immunophysiology: from basic sciences to clinical management*. Ed. R. Sepiashvili. MEDIMOND Int. Proc. 2013. P. 43–45.
21. Slavyanskaya T., Derkach V., Sangidorj B. Atopic dermatitis in children: cost-effectiveness comparative estimation of various immunotropic therapy programmes // *Ann. Allergy, Asthma & Immunol.* 2014. Vol. 113. # 5. Suppl.1. P. A113.
22. Derkach V., Slavyanskaya T. Cost-effectiveness of immunotropic therapy for children with atopic dermatitis // *World Allergy Organization J.* 2013. Vol. 6. Suppl. 1. P. 228.
23. Slavyanskaya T.A., Derkach V.V., Sangidorj B. Atopic dermatitis in children: cost-effectiveness comparative estimation of various immunotropic therapy programmes // *Annals of Allergy, Asthma & Immunology.* 2014. Vol. 113. #5. Suppl. 1. P. A113.
24. Derkach V., Slavyanskaya T., Sangidorj B.Combination Immunotropic Therapy of Atopic Dermatitis in Children: Cost-Benefit Analysis // *J. Allergy Clin. Immunol*. 2015. Vol. 135. # 2. P. AB265. Ref. 862.
25. Derkach V.V., Slavyanskaya T.A. Comparative characteristic of effectiveness of immunotherapy of children with atopic dermatitis // Allergy, Asthma & Immunophysiology: *Recent Advances in understanding and Management.* Ed. R. Sepiashvili. Medimond Int. Proc. 2015. P. 45–49.

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Meeting Calendar

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March 3–7, 2018 Orlando, USA

WORLD ALLERGY CONGRESS

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POTENTIALLY FATAL DRUG RASHES

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Skin rashes are common manifestations of adverse drug reactions. Most drug eruptions are benign, non-specific rashes that usually resolve within a few days after discontinuation of the drug. Certain drug rashes reflect serious reactions that should be recognized early and managed promptly. Identification and discontinuation of the culprit drug can be difficult in patients receiving multiple medications. To minimize the risks of morbidity and mortality, comprehensive management requires a team collaboration by various medical specialists. Confirmation by challenge testing or attempts for desensitization can be prohibitively risky.

Key words: *drug rashes, adverse drug reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms, multiple drug hypersensitivity, acute generalized exanthematous pustulosis, drug-induced pemphigus*.

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Skin rashes are common manifestations of adverse drug reactions. Most drug eruptions are benign, non-specific rashes that usually resolve within a few days after discontinuation of the drug. However, some rashes are serious and carry substantial risk. We briefly describe here five selected drug-induced non-anaphylactic exanthematous disorders that can be potentially fatal (Table 1).

Table 1

Potentially fatal drug rashes

• Stevens-Johnson syndrome (SJS) and Toxic epidermal necrolysis (TEN)
• Drug reaction with eosinophilia and systemic symptoms (DRESS)
• Multiple drug hypersensitivity (MDH) syndrome
• Acute generalized exanthematous pustulosis (AGEP)
• Drug-induced pemphigoid

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

TEN can be at the top of the list of the potentially fatal drug rashes. The prodromal stage is erythema multiforme (EM) that may progress to SJS and then to TEN. The difference between SJS and TEN is based on the percentage of body surface area with epidermal detachment: SJS involves less than 10 percent, TEN involves greater than 30 percent, and SJS/TEN overlap involves 10 to 30 percent. In severe cases, the affected area can reach close to 100%. TEN develops in 1 out of 3 patients with SJS.

CLINICAL PRESENTATION: The initial rash is in the form of EM that appears within days after initiation of the drug. It starts as erythematous or violaceous patches with dark brown necrotic center (target-like) that can form bullae. Passing the finger over the inflamed skin causes separation of the upper layer (Nikolsky sign). When the mucous membranes become affected, the disease reaches the stage of SJS. Within days, the skin lesions progress to sloughing of the epidermal layer. In addition to the painful skin and mucous membranes, constitutional systemic symptoms are common. Warning signs for progression from EM to SJS to TEN are early onset after starting the drug, bullae formation, and rapid involvement of the mucous membranes.

COMMON OFFENDING AGENTS: Practically any drug may cause SJS/TEN, but by far anti-epileptics are the most notorious, followed by anti-bacterials/antibiotics and non-steroidal anti-inflammatory drugs. Certain drugs have strong genetic predisposition such as allopurinol and certain anti-epileptics in Chinese subjects. Certain genetic alleles have been associated with reactions to carbamazepine, including HLA-B*15:08, HLA-B*15:11, HLA-B*15:18, HLA-A*31:01. HLA-B*15:02 has also been implicated in reactions to carbamazepine, lamotrigine, oxcarbazepine, and phenytoin. Oxicams (e.g., meloxicam) and sulfonamides have been implicated in Europeans with HLA-B*12, HLA-A*29, and HLA-DR7. Allopurinol reactions have been related to HLA-B*58:01 and phenobarbital reactions to HLA-B*51:01.

PATHOGENESIS: SJS/TEN is primarily mediated by T-cells. The drug or a drug-peptide complex is recognized by T-cell receptors, leading to cytotoxic T-cell and NK-cell-mediated cytotoxicity. Possible mechanisms include granulysin, Fas–Fas ligand interaction, perforin, granzyme B, and cytokine expression, including tumor necrosis factor alpha and interferon gamma.

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DIAGNOSIS: The diagnosis of SJS/TEN is clinical. Biopsy findings can be supportive in revealing non-specific perivascular mononuclear inflammatory infiltrate and sparse lymphocytic infiltrate at the dermo-epidermal junction, with clusters around apoptotic basal keratinocytes. As the lesions progress, subepidermal vesiculation develops with epidermal necrosis. Fully developed SJS is distinguished by full-thickness epidermal detachment with splitting above the basement membrane. The underlying sweat ducts may show lymphocytic infiltrate, basal cell hyperplasia & necrosis.

RISK FACTORS: In addition to the genetic predisposition mentioned above, risk factors for developing SJS/TEN include concomitant viral infections, particularly HIV, autoimmune disorders, malignancies, and the drug's profile.

MANAGEMENT: In addition to immediate withdrawal of the suspected drug(s), supportive care is the mainstay of treatment and may be sufficient in most cases limited to EM. Once SJS starts, attention should be paid to alleviation of pain, care of skin and mucous membranes, nutrition, monitoring the fluid and electrolytes, and prevention of infection. The management of such patients is ideally provided in a burn unit or even in an intensive care unit. Comprehensive care requires collaboration of a multispecialty medical team, including specialists in wound care, ophthalmology, and urogenital tract.

Regarding specific treatments, systemic corticosteroid therapy was used in the past but has been gradually abandoned because of contradictory outcomes and the availability of more effective agents. Intravenous human immunoglobulin (IVIg) has been used in doses 0.5–2 g/kg daily for up to 4 doses, with varying degrees of success. Multiple factors are responsible for the inconsistent results, including the dose, frequency, time of starting therapy, severity of illness, patient's age, and comorbid conditions. Alternate therapies include plasma exchange, cyclosporine, and tumor necrosis factor (TNF) inhibitors.

PROGNOSIS AND MORTALITY: The overall mortality rate in SJS is 1–5% but rises in TEN to 25–50%, most commonly from sepsis. Risk factors for death are older age, extent and severity of lesions, delay in treatment, pre-existing disease (hepatic, renal, HIV, post-BMT, autoimmune disease, malignancy), and complications (infection, electrolyte imbalance, renal insufficiency).

In survivors, long-term sequelae can be disabling, particularly ocular complications, oral mucosa sicca syndrome or synechiae, esophageal strictures, urogenital adhesions or strictures, and bronchiolitis obliterans. Cutaneous complications include hyper- or hypopigmentation (especially in children), hypertrophic and keloid scars, shedding of nails, chronic pruritus, photosensitivity, hyperhidrosis, and heterotopic ossification. Corneal involvement requires amniotic membrane graft.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

In addition to skin rash, DRESS syndrome is comprised of multi-organ dysfunction, eosinophilia, and often reactivation of human herpesviruses (HHV) 6.

CLINICAL PRESENTATION: The first sign is typically high fever followed by widespread skin lesions and internal organ involvement appearing after a latent period of 2–8 weeks after introduction of the offending drug. The rash is pruritic and typically involves more than half of the body surface area. There is facial edema in about three-quarters of patients. The rash is usually polymorphous and maculopapular, but can be urticarial, exfoliative, lichenoid, pustular, bullous, target-like, and eczema-like. In some cases, the mucous membranes may be involved, usually the mouth. Desquamation will occur when the skin is healing. Half of patients have lymphadenopathy and hepatomegaly.

Hematologic abnormalities include eosinophilia (>1.500/μL) in 95%. Most patients have neutrophilia early in the illness and monocytosis later. Lymphocytosis often occurs, with atypical lymphocytes in about 30–60% of cases. Cytopenias occur in some patients.

Liver injury occurs in more than three-fourths of cases, and may be manifest prior to the rash. It is usually cholestatic (alkaline phosphatase is relatively elevated) or mixed cholestatic and hepatocellular (both alkaline phosphatase and alanine aminotransferase are elevated). Kidney injury occurs in 12–40% of patients and is more common when allopurinol is the causative drug. Lung involvement occurs in about one-third of patients and is more common with minocycline and acabavir. Patients may have impaired pulmonary function, interstitial pneumonitis, pleuritis, or acute respiratory distress syndrome. Pericarditis and myocarditis are rare; minocycline, ampicillin, and sulfonamides have been incriminated. Involvement of the central nervous system, pancreas, gastrointestinal tract, and spleen has also been reported. The clinical course of DRESS is usually prolonged and may include reactivation of various human herpes viruses, particularly HHV-6.

COMMON OFFENDING AGENTS: The most frequently associated drugs include carbamazepine, allopurinol, phenytoin, sulfamethoxazole/trimethoprim, sulfasalazine, dapsone, penicillin, nonsteroidal anti-inflammatory drugs, lamotrigine, vancomycin, minocycline, and antituberculous drugs.

PATHOGENESIS: DRESS consists of a delayed immunologic reaction to a drug in susceptible patients. Reduced activity of certain metabolizing enzymes may lead to accumulation of the drug or its metabolites, which then elicit an immune response. Another possibility is that the drug or its metabolites bind to major histocompatibility complex proteins or T-cell receptors independent of peptides.

DRESS appears to be a type IV hypersensitivity reaction. Interleukin-5, perforin, granzyme B, fatty acid synthase ligand, and interferon-gamma have been found in skin biopsies. Viral reactivation may be a direct effect of the drug (or its metabolite) or from an immunocompromised status in the initial stages of the illness. Allopurinol-induced DRESS has been associated with HLA-B*58:01 in Han Chinese patients.

MANAGEMENT: Discontinuation of the inciting drug and supportive therapy might be sufficient in mild cases. Systemic corticosteroid therapy with gradual tapering over 2–3 months is the principle treatment for moderate to severe cases. The typical starting dose of prednisolone is 0.5–1.0 mg/kg/day. Successful treatments with cyclosporine, cyclophosphamide, mycophenolate mofetil, and rituximab have been reported. Trials of IVIg yielded mixed results.

PROGNOSIS AND MORTALITY: DRESS generally has a prolonged course and the illness may continue to peak for a few weeks after discontinuation of the causative drug.

The course tends to be waxing-and-waning, with multiple flares. About 20% of patients may still have signs and symptoms three months after the disease onset. Recovery is achieved in the majority of patients without sequelae, but some patients required liver transplantation or hemodialysis. Mortality is up to 10%, mostly secondary to multi-organ failure.

Long-term sequelae include autoimmune diseases that may be due to dysfunction of regulatory T cells or HHV-6 reactivation, particularly in patients with HLA-B*62. Reported manifestations are thyroiditis, type 1 diabetes mellitus, systemic lupus erythematous, rheumatoid arthritis, alopecia, and vitiligo.

Multiple Drug Hypersensitivity (MDH) Syndrome

MDH is a syndrome of long-lasting hypersensitivity reactions to multiple structurally-unrelated drugs with different clinical manifestations over the course of weeks, months, or even years.

CLINICAL PRESENTATION: The initial manifestation is usually in the form of DRESS, although many patients may have an exanthem or erythroderma only. With the subsequent administration of other drugs, relapse or different manifestations develop. SJS/TEN typically is not the first drug reaction, but may be the second or third.

COMMON OFFENDING AGENTS: The initial culprit drug is commonly an antibiotic followed by anti-epileptics and anti-tuberculous drugs. Simultaneous reactivity to two drugs in a combination therapy is common, for example, sulfamethoxazole and trimethoprim, piperacillin and tazobactam, and amoxicillin and clavulanic acid.

PATHOGENESIS: MDH reactions are mostly T-cell-mediated, but IgE-mediated reactions, including anaphylaxis, have been reported. The drug non-covalently binds directly to an HLA protein or T-cell receptor and massive polyclonal T-cell proliferation follows. Such specifically-activated T-cells can be still detectable months to years later.

MANAGEMENT: Identification and discontinuation of the offending drugs can be a difficult task. Therapy is primarily immunosuppression with a corticosteroid such as prednisolone 0.3-0.5 mg/kg/day for a few days followed by a gradual taper titrated based on the amount of circulating lymphoblasts.

A strategy to reduce the risk of MDH in patients with severe T-cell activation is to minimize the administration of multiple drugs, even antipyretics. When a drug treatment is necessary, dosing below average seems less likely to precipitate a reaction. A drug-free period of days to weeks may be beneficial.

PROGNOSIS AND MORTALITY: MDH has only been described relatively recently; prognosis and mortality data are scarce. Mortality can be high in patients with severe reactions involving vital organs.

Acute Generalized Exanthematous Pustulosis (AGEP)

AGEP is a severe cutaneous adverse drug reaction characterized by the acute formation of sterile pustules and occasional systemic involvement.

CLINICAL PRESENTATION: Typically, within 48 hours of drug administration, acute pinhead-sized pustules on erythematous and edematous bases appear in the axillary, inguinal, and submammary regions. Within a few hours, the rash spreads to the trunk and extremities. Patients usually complain of itching, and sometimes burning sensation. Mucosal involvement, usually oral, is present in about one-quarter of patients. They may also have fever. The pustules progress to desquamation with a narrow rim off loosened keratin overhanging the periphery of the lesion (collarette-shape). Eosinophilia is present in about 30% of patients, and 75% have hypocalcemia, possibly related to decreased albumin.

Multi-organ involvement occurs in less than one-fifth of patients and may include lymphadenopathy, hepatocellular dysfunction, cholestasis, nephritis, respiratory failure, and neutropenia due to bone marrow involvement.

COMMON OFFENDING AGENTS: The most frequent causative drugs are antibiotics, sulfonamides, and antifungals. AGEP may also be triggered by infections, primarily certain viruses, mycoplasma, and chlamydia.

PATHOGENESIS: AGEP is a T cell-related sterile neutrophilic inflammatory response in which drug-specific cytotoxic T cells and proteins such as granzyme B and perforin induce keratinocyte apoptosis, leading to subcorneal vesicles. Granulolysin may also be involved. Neutrophil recruitment to form pustules may be mediated by certain chemokines.

MANAGEMENT: Topical steroids and disinfectant solutions are useful during the pustular phase. Rehydrating lotions are used during the desquamative phase. Systemic corticosteroids may be used in severe cases, but there is no evidence that they reduce the disease duration. If there are multiple suspected medications, patch testing after resolution often elicits small localized pustules in response to the culprit drug.

PROGNOSIS AND MORTALITY: Skin lesions usually spontaneously resolve within two weeks. Estimated mortality is under 5%. Death is usually due to superinfection and occurs in patients in poor general condition.

Drug-Induced Pemphigoid

Bullous pemphigoid is an autoimmune disease and can be drug-induced.

CLINICAL PRESENTATION: Drug-induced bullous pemphigoid generally occurs in younger patients than those affected by spontaneously-occurring disease. The lesions are usually pruritic and may appear up to three months after initiating the offending drug. The bullae are usually located on the trunk and limbs, particularly the lower legs, and face. They are usually tense on a base of normal-appearing skin, or, rarely, on erythematous or urticarial lesions. Target lesions may appear on the palms and soles. Mucosal involvement is mild and not always present. Eosinophilia may be present. Biopsy shows subepidermal blisters, intraepidermal vesicles, and necrotic keratinocytes. Characteristically, 90% of cases show IgG and C3 linear deposits along basement membrane zone.

COMMON OFFENDING AGENTS: Drugs implicated in drug-induced bullous pemphigoid are numerous. Frequently cited culprits are anti-epileptics, antibiotics, pyrazo-

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lon derivatives, and non-steroidal anti-inflammatory drugs. Interestingly, tumor necrosis factor alpha inhibitors have been used to treat bullous pemphigoid, yet have also been reported to induce some cases.

PATHOGENESIS: Theories on the pathogenesis of drug-induced bullous pemphigoid vary, including inactivation of endogenous regulatory processes, molecular mimicry, and the possibility that drugs directly interact with the basement membrane and change its antigenic properties.

MANAGEMENT: No specific guidelines exist, but good outcomes can be achieved by using potent topical corticosteroids and oral prednisone 0.5 mg/kg/day until improvement, then tapered gradually depending on the clinical course of the patient.

PROGNOSIS AND MORTALITY: Most cases achieve complete remissions within 6 weeks of starting treatment. Unlike classic bullous pemphigoid, the drug-induced variety rarely relapses.

Conclusion

Certain drug rashes reflect serious reactions that should be recognized early and managed promptly. Identification and discontinuation of the culprit drug can be difficult in patients receiving multiple medications. To minimize the risks of morbidity and mortality, comprehensive management requires a team collaboration by various medical specialists. Confirmation by challenge testing or attempts for desensitization can be prohibitively risky.

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References

FOR STEVENS-JOHNSON SYNDROME/TOXIC EPIDERMAL NECROLYSIS

1. Lee H.Y., Walsh S.A., Creamer D. Long term complications of Stevens-Johnson syndrome /Toxic epidermal necrolysis: The spectrum of chronic problems in patients who survive an episode of SJS/TEN necessitates multi-disciplinary follow up. *Br J Dermatol* .2017. doi: 10.1111/bjd.15734
2. Schneider JA, and Cohen PR. Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: A Concise Review with a Comprehensive Summary of Therapeutic Interventions Emphasizing Supportive Measures // *Adv Ther*. 2017. P. 1235–1244.
3. Miliszewski MA, Kirchhof MG, Sikora S, et al. Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: An Analysis of Triggers and Implications for Improving Prevention // *Am J Med.* 2016. Vol. 129. P. 1221–1225.
4. Godhwani N., and Bahna S.L. Antiepilepsy drugs and the immune system // *Ann Allergy Asthma Immunol* 2016. Vol. 117. P. 634–640.
5. Kirchhof MG, Miliszewski MA, Sikora S, et al. Retrospective review of Stevens-Johnson syndrome/toxic epidermal necrolysis treatment comparing intravenous immunoglobulin with cyclosporine // *J Am Acad Dermatol.* 2014. Vol. 71. P. 941–947.
6. Lee H.Y., Lim Y.L., Thirumoorthy T., et al. The role of intravenous immunoglobulin in toxic epidermal necrolysis: a retrospective analysis of 64 patients managed in a specialized centre // *Br J Dermatol.* 2013. Vol. 169. P. 1304–-1309.
7. Creamer D., Walsh S.A., Dziewulski P., et al. UK guidelines for the management of Stevens-Johnson syndrome/toxic epidermal necrolysis in adults 2016 // *J Plast Reconstr Aesthet Surg* .2016. Vol. 69. e119–153.

FOR DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS

8. Kardaun S.H., Sekula P., Valeyrie-Allanore L., et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study // *Br J Dermatol.* 2013. Vol. 169. P. 1071–1080.
9. Cho Y.T., Yang C.W., Chu C.Y. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): An Interplay among Drugs, Viruses, and Immune System // *Int J Mol Sci*. 2017. Vol. 18. doi: 10.3390/ijms18061243.
10. Chen Y.C., Chiu H.C., Chu CY. Drug reaction with eosinophilia and systemic symptoms: a retrospective study of 60 cases // *Arch Dermatol.* 2010. Vol. 146. P. 1373–1379.
11. Kano Y., Tohyama M., Aihara M., et al. Sequelae in 145 patients with drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms: survey conducted by the Asian Research Committee on Severe Cutaneous Adverse Reactions (ASCAR) // *J Dermatol* .2015. Vol. 42. P. 276–282.
12. Descamps V. Drug reaction with eosinophilia and systemic symptoms and thyroiditis: human herpesvirus-6, the possible common link // *Br J Dermatol.* 2013. Vol. 169. P. 952.
13. Peyrière H., Dereure O., Breton H., et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? // *Br J Dermatol.* 2006. Vol. 155. P. 422–-428.

FOR MULTIPLE DRUG HYPERSENSITIVITY

14. Pichler W.J., Srinoulprasert Y., Yun J., et al. Multiple Drug Hypersensitivity // *Int Arch Allergy Immunol.* 2017. Vol. 172. 129–138.
15. Blumenthal K.G., Saff R.R., and Banerji A. Evaluation and management of a patient with multiple drug allergies // *Allergy Asthma Proc.* 2014. Vol. 35. P. 197–203.
16. Onuma H., Tohyama M., Imagawa A., et al. High frequency of HLA B62 in fulminant type 1 diabetes with the drug-induced hypersensitivity syndrome // *J Clin Endocrinol Metab.* 2012. Vol. 97. E2277–2281.

FOR ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS

17. Feldmeyer L., Heidemeyer K., Yawalkar N. Acute Generalized Exanthematous Pustulosis: Pathogenesis, Genetic Background, Clinical Variants and Therapy *// Int J Mol Sci*. 2016. Vol. 17. # 8. doi: 10.3390/ijms17081214
18. Sidoroff A., Dunant A., Viboud C, et al. Risk factors for acute generalized exanthematous pustulosis (AGEP)-results of a multinational case-control study (EuroSCAR) // *Br J Dermatol* 2007. Vol. 157. P. 989–996.

FOR DRUG-INDUCED PEMPHIGOID

19. Stavropoulos P.G., Soura E., Antoniou C. Drug-induced pemphigoid: a review of the literature //*J Eur Acad Dermatol Venereol.* 2014. Vol. 28. P. 1133–1140.

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SYSTEMIC HYPERSENSITIVITY TO CORTICOSTEROIDS

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Systemic hypersensitivity reactions to corticosteroids (CS) are rare but can be severe and are often missed. This presentation focuses on systemic reactions regarding prevalence, manifestations, causative CS preparations, diagnostic tests, and management.

Key words: *drug allergy, adverse drug reactions, allergy to corticosteroids.*

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Unlike other drugs, corticosteroids (CS) are rarely thought of as a cause of hypersensitivity reactions because they are used in various forms as anti-allergy medications. The reactions are more commonly by dermatologic preparations causing allergic contact dermatitis and can be easier to recognize. On the other hand, systemic hypersensitivity reactions to CS are rare but can be severe and are often missed. This presentation focuses on systemic reactions regarding prevalence, manifestations, causative CS preparations, diagnostic tests, and management.

Prevalence

According to a review of the English literature over an 11-year period (2004-2014), 1 the prevalence of type I (immediate) hypersensitivity reactions to CS is estimated at 0.1 to 0.3% in the general population. The reactions in general affected all ages without significant differences by ethnicity or gender.

Manifestations

Systemic reactions to CS can manifest in any body system or in multiple systems simultaneously (anaphylaxis). Considering immediate-type hypersensitivity reactions as occurring within less than 24 hours after exposure, the most common manifestation was by far anaphylaxis (60.8%) followed by urticaria/angioedema (26.7%), and bronchospasm (5%) [1]. However, this is markedly affected by the fact that severe reactions are much more likely to be reported than the milder ones. Also, some physicians tend not to suspect a drug that was previously tolerated on multiple occasions.

ANAPHYLAXIS Though reported CS hypersensitivity in general did not show significant differences by age or gender, reported anaphylaxis was more in children under 10 years of age compared to adults over 50 years [1]. Also there was males preponderance (1.5:1) and the most common route was intravenously followed by intraarticular.

URTICARIA AND/OR ANGIOEDEMA Urticaria and /or angioedema were the second most common reported immediate hypersensitivity to CS and showed females preponderance (2:1). The more common culprit was methylprednisolone followed by prednisolone, and the most common route was oral followed by IV.

SHORTNESS OF BREATH A small number of patients were reported as developing shortness of breath due to bronchospasm or dyspnea. This reaction might be underdiagnosed because corticosteroids are unlikely to be suspected as the cause for exacerbated bronchospasm during treatment of asthma.

NONSPECIFIC RASH, FLUSHING, OR PRURITUS Probably because of their benign nature, nonspecific rashes, flushing, and pruritus are rarely reported. Delayed facial flushing has been reported in 10–15% after intraarticular triamcinolone acetonide [2–4]. Dexamethasone epidural injection was immediately followed by pruritus in 4.4% of cases [5]. Such symptoms are self-limited and are usually prevented by antihistamine premedication.

The route of administration

In addition to the most commonly used oral, intravenous, and intramuscular routes, CS hypersensitivity occurred after intra-articular, intralesional, epidural, epicutaneous, and inhalation exposures [1]. The most frequent route of exposure was intravenous injection in 44.2%, followed by oral in 25.8%, and intraarticular in 11% of cases [1]. Of interest is that all 14 reported cases after intraarticular injection were anaphylaxis. There was a report on a child who developed pruritic rash on two occasions after budesonide inhalation but not after fluticasone [6].

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Corticosteroid preparations

Although almost any preparation may cause hypersensitivity, methylprednisolone was the most common culprit for immediate hypersensitivity reaction (40.8% of reported cases) followed by prednisolone (20%) and triamcinolone (14.2%) [1]. The least common corticosteroids causing reaction are dexamethasone and prednisone (each 4.2%).

Cross-reactivity among corticosteroids

Based on their structure, CS are categorized into four reactivity groups A, B, C and D. Intragroup cross reactivity has been demonstrated in cases of cutaneous delayed-type (T-cell mediated) reactions such as allergic contact dermatitis.7 On the other hand, the majority of patients with immediate-type (IgE mediated) reactions, could tolerate other preparations from a different or from the same group [1].

Although in the majority of cases the reaction was to the CS molecule itself, in 20–30% of cases the culprit was a pharmacologically-inactive ingredient [1, 4, 7, 9]. The most implicated were the succinate or phosphate esters, followed by lactose (in highly sensitive milk-allergic subjects), carboxymethylcellulose, polyethylene glycol, and hexylene glycol. This should be taken into consideration in the diagnostic evaluation and in selecting alternative preparations.

It is worth noting that an additive may be present in a CS preparation of a certain formulation but not of the same preparation in a different formulation. Several milk-allergic children reacted to "Solu-Medrol 40 mg/mL" that contains lactose but not to "Solu-Medrol 125 mg/mL" that does not contain lactose [10–11]. The contamination with an excipient may be present in a certain batch but not in other batches of the same CS product [12].

Diagnosis

Because of the common use of CS therapy for a large variety of disorders, awareness of CS hypersensitivity and its verification are of great importance. A thorough medical history should inquire about the onset and course of symptoms, preceding events, and concomitant medications or procedures. If the patient had an immediate-type hypersensitivity reaction and the CS preparation is the prime suspect, allergy skin testing can be helpful [1, 7]. Skin prick testing using the preparation's usual strength should be done first and if negative, intradermal tests are done starting with 1:1,000 dilution and may proceed to 1:100 then 1:10. Confirmation requires incremental drug challenge test, unless the risk is very high. The reliability of skin testing is higher in cases of anaphylaxis than for other symptoms [13]. Testing with multiple preparations, including some without excipients, would identify at least one that can be tolerated.

Management

Immediate management of the reaction should be discontinuation of the suspected drug(s) plus symptomatic treatment. In the very rare instances of not identifying a safe CS alternative, desensitization may be considered using safe protocols [14–16].

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References

1. Patel A., Bahna S.L. Immediate hypersensitivity reactions to corticosteroids // *Ann Allergy Asthma Immunol.* 2015. Vol. 115. P. 178–182. e173.
2. Baeck M., Goossens A. Immediate and delayed allergic hypersensitivity to corticosteroids: practical guidelines // *Contact Dermatitis.* 2012. Vol. 66. P. 38–45.
3. Freire V., Bureau N.J. Injectable Corticosteroids: Take Precautions and Use Caution // *Semin Musculoskelet Radiol*. 2016. Vol. 20. P. 401–408.
4. Barbaud A., Waton J. Systemic Allergy to Corticosteroids: Clinical Features and Cross Reactivity // *Curr Pharm Des.* 2016. Vol. 22. P. 6825–6831.
5. El Abd O., Amadera J., Pimentel D.C., Gomba L. Immediate and acute adverse effects following transforaminal epidural steroid injections with dexamethasone // *Pain Physician*. 2015. Vol. 18. P. 277–286.
6. Sharma P.K., Gupta N., Hasan N., Krishnamurthy B, Singh S. Hypersensitivity with Inhalational Budesonide: An Under Recognised Entity. // *J Clin Diagn Res.* 2016. Vol. 10. Fd01–fd02.
7. Otani I.M., Banerji A. Immediate and Delayed Hypersensitivity Reactions to Corticosteroids: Evaluation and Management // *Curr Allergy Asthma Rep*. 2016. Vol. 16. P. 18.
8. Rachid R., Leslie D., Schneider L., Twarog F. Hypersensitivity to systemic corticosteroids: an infrequent but potentially life-threatening condition // *J Allergy Clin Immunol.* 2011. Vol. 127. P. 524–528.
9. Brandt N., Garvey L.H., Bindslev-Jensen U., Kjaer H.F., Bindslev-Jensen C., Mortz C.G. Three cases of anaphylaxis following injection of a depot corticosteroid with evidence of IgE sensitization to macrogols rather than the active steroid // *Clin Transl Allergy.* 2017. Vol. 7 P. 2.
10. Aranda A., Mayorga C., Ariza A., et al. IgE-mediated hypersensitivity reactions to methylprednisolone // *Allergy.* 2010. 65:1376-1380.
11. Ben Said B., Leray V., Nicolas J.F., Rozieres A., Berard F. Methylprednisolone-induced anaphylaxis: diagnosis by skin test and basophil activation test // Allergy. 2010. Vol. 65. P. 531–532.
12. Nowak-Wegrzyn A., Shapiro G.G., Beyer K., Bardina L., Sampson H.A. Contamination of dry powder inhalers for asthma with milk proteins containing lactose // *J Allergy Clin Immunol.* 2004. Vol. 113. P. 558–560.
13. Baker A., Empson M., The R, Fitzharris P. Skin testing for immediate hypersensitivity to corticosteroids: a case series and literature review. Clin Exp Allergy. 2015. Vol. 45. P. 669–676.
14. Lee-Wong M., McClelland S., Chong K., Fernandez E. A case of hydrocortisone desensitization in a patient with radiocontrast-induced anaphylactoid reaction and corticosteroid allergy // *Allergy and Asthma Proceedings.* 2006. Vol. 27. P. 265–268.
15. Angel-Pereira D., Berges-Gimeno M.P., Madrigal-Burgaleta R., Urena-Tavera M.A., Zamora-Verduga M., Alvarez-Cuesta E. Successful rapid desensitization to methylprednisolone sodium hemisuccinate: A case report. *// J Allergy and Clinical Immunology in Practice.* 2014. Vol. 2. P. 346–348.
16. Guvenir H., Misirlioglu E.D., Aydin F., Ece D., Cakar N., Kocabas C.N. Successful methylprednisolone desensitization in a pediatric patient // *Pediatr Allergy Immunol.* 2017. Vol. 2. P. 305–306.

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CARDIAC ALLERGY: ALLERGIC ANGINA AND ALLERGIC MYOCARDIAL INFARCTION

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The syndrome of allergic angina and allergic myocardial infarction (first described by Kounis and Zavras in 1991) is currently known as Kounis syndrome and is defined as the occurrence of acute coronary events with conditions underlined by mast cell activation, and interacting inflammatory cells in the course of allergic, anaphylactic or anaphylactoid attacks. Although it is not a rare disease, the diagnosis of Kounis syndrome is easily overlooked. Cases, although under reported, are more often encountered in clinical practice. In any case of acute coronary syndrome, careful patient questioning may reveal an allergic mechanism preceding the event, which in turn would have important therapeutic implications.

Key words: *allergic angina, myocardial infarction, Kounis syndrome, hypersensitivity reactions, food allergy.*

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Allergic angina and allergic myocardial infarction, have been first described by Kounis and Zavras in 1991. However, the first reported case was in adjunction with Penicillin Allergy in 1950.

The syndrome is currently known as Kounis syndrome and is defined as the occurrence of acute coronary events with conditions underlined by mast cell activation, and interacting inflammatory cells in the course of allergic, anaphylactic or anaphylactoid attacks.

During allergic reaction, degranulation of mast cells leads to the release of stored and newly formed inflammatory mediators, some of which, as histamine, neutral proteases, arachidonic acid products such as leukotrienes, PAF and thromboxane have important cardiovascular actions leading to coronary vasoconstriction, platelet activation leading to plaque erosion and rupture. Tryptase exerts a dual action on the coagulation cascade with both thrombotic and fibrinolytic properties. Chymase and cathepsin-D convert angiotensin I to angiotensin II, which is a vasoconstrictor. Leukotrienes are also potent vasoconstrictors as well as thromboxane and PAF which are platelet activators

Clinical types

TYPE I includes patients with normal or nearly normal coronary arteries without predisposing factors for coronary artery disease in whom acute allergic attacks can induce either coronary artery spasm alone without raised cardiac enzymes and troponins or coronary artery spasm leading to acute myocardial infarction with raised cardiac enzymes and troponins.

TYPE II includes patients with culprit but quiescent pre-existing atheromatous disease in whom the acute allergic attacks can induce either coronary artery spasm, or plaque erosion or rupture manifesting as acute myocardial infarction.

TYPE III includes patients with hypersensitivity reactions following implantation of drug-eluting stents and stent thrombosis and in whom thrombus harvesting and staining with hematoxylin–eosin and Giemsa reveals the presence of eosinophils and mast cells respectively in the pathology specimens.

Etiological factors

ENVIRONMENTAL EXPOSURES: hymenoptera stings, latex contact, poison ivy, shellfish eating and viper venom.

CLINICAL CONDITIONS: angioedema, bronchial asthma, Churg–Strauss syndrome, exercise-induced anaphylaxis, food allergy, intracoronary stenting, nicotine, serum sickness and urticaria.

DRUGS: analgesics, anesthetics, antibiotics, antineoplastics, contrast media, nonsteroidal anti-inflammatory drugs.

Experimental and clinical evidence indicates that the human heart can be the primary site and the target of anaphylaxis, resulting in the development of Kounis syndrome. Moreover, experimental findings oppose the belief that myocardial ischemia and myocardial infarction occurring during an allergic episode manifesting as Kounis syndrome, are the result of coronary hypoperfusion due to systemic vasodilation, reduced venous return, leakage of plasma and volume loss from increased vascular permeability and depression of cardiac output.

SYMPTOMS & SIGNS of Kounis Syndrome are symptoms of the allergic reactions accompanied by cardiac symptomatology and electrocardiographic changes.

CLINICAL SYMPTOMS: acute chest pain, chest discomfort, difficulty in swallowing, dyspnea, faintness, headache, malaise, nausea, pruritis, syncope, vomiting, urticarial

CLINICAL SIGNS include: Bradycardia or tachycardia, cardiorespiratory arrest, cold extremities, diaphoresis, hypotension, pallor, palpitations, skin rash, sweating.

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ELECTROCARDIOGRAPHIC CHANGES: Atrial fibrillation, bigeminal rhythm, nodal rhythm, sinus bradycardia, sinus tachycardia, ST segment depression or elevation, T-wave flattening and/or inversion, QRS complex prolongation, QT segment prolongation, ventricular ectopics, ventricular fibrillation.

Treatment

Both cardiac and allergic symptoms should be considered together. Moreover the treatment can worsen allergy and aggravate heart function.

In Type I variant, treatment of the allergic event alone can be curative. The use of intravenous steroids and H1 and H2 antihistamines is appropriate. In addition, vasodilators such as calcium-channel blockers and nitrates can control the induced vasospasm.

In Type II variant, an acute coronary event protocol together with steroids and antihistamines should be applied. Vasodilators such as nitrates and calcium blockers are given when appropriate.

In Type III variant, mast cell stabilizers, steroids and antihistamines are recommended. Furthermore, harvesting of intrastent thrombus and histological examination of aspirated material for eosinophils and mast cells should be undertaken.

Opiates such as morphine, codeine and meperidine which are usually given to relieve acute chest pain from myocardial infarction should be administered with extreme caution as they can induce massive mast cell degranulation and aggravate allergic reaction.

Conclusion

Although it is not a rare disease, the diagnosis of Kounis syndrome is easily overlooked. Cases, although under reported, are more often encountered in clinical practice.

In any case of acute coronary syndrome, careful patient questioning may reveal an allergic mechanism preceding the event, which in turn would have important therapeutic implications.

References

1. Almpanis G. Mazarakis A., Tsigkas G., Koutsojannis C., Kounis G.N., Kounis N.G. Acute stent thrombosis and atopy: implications for Kounis syndrome // *Int. J. Cardiol.* 2010. Vol. 145. P. 398–400.
2. Arena V., Valerio L., Arena E. et al. Isolated eosinophilic coronary arteritis // *Clin. Pathol.* 2010. Vol. 63. P. 469–471.
3. Biteker M. A new classification of Kounis syndrome // *Int. J. Cardiol.* 2010. Vol. 145. P. 553.
4. Brown S.G., Blackman K.E., Stenlake V., Heddle R.J. Insect sting anaphylaxis; prospective evaluation of treatment with intravenous adrenaline and volume resuscitation // *Emerg. Med. J.* 2004. Vol. 21. P. 149–154.
5. Buhaescu I., Williams A., Yood R. Rare manifestations of Churg–Strauss syndrome: coronary artery vasospasm, temporal artery vasculitis, and reversible monocular blindness-a case report // *Clin. Rheumatol.* 2009. Vol. 28. P. 231–233.
6. Dewachter P., Mouton-Faivre C., Emala C.W. Anaphylaxis and anesthesia: controversies and new insight // *Anesthesiology* 2009. Vol. 111. P. 1141–1150.
7. Jacobs J.F., Baumert J.L., Brons P.P., Joosten I., Koppelman S.J., van Pampus EC. Anaphylaxis from passive transfer of peanut allergen in a blood product // *N. Engl. J. Med.* 2011. Vol. 364. P.1981–1982.
8. Kounis N.G.G., Mazarakis A. Stent thrombosis and Kounis syndrome: who is guilty? // J. *Cardiovasc. Med. Hagerstown* 2011. Vol. 12. P. 71–72.
9. Kounis G.N, Hahalis G., Kounis N.G. Anesthetic drugs and Kounis syndrome // *J. Clin. Anesth.* 2008. Vol. 20. P. 562–563.
10. Kounis G.N., Hahalis G., Kounis N.G. Anaphylaxis, β blockade and the Kounis syndrome // *Paediatr. Anaesth.* 2008. Vol. 18. P. 904–905.
11. Kounis N.G. Mazarakis A. Tsigkas G. Giannopoulos S., Goudevenos J. Kounis Syndrome A New twist on an old disease // *Future Cardiol*. 2011. Vol. 76. P. 805–824
12. Lombardini C., Helia R.E., Boehlen F., Merlani P. Heparinization' and hyperfibrinogenolysis by wasp sting // *Am. J. Emerg. Med.* 2009. Vol. 27. 1176. e1–e3.
13. Metcalfe D.D., Schwartz L.B. Assessing anaphylactic risk? Consider mast cell clonality // *J. Allergy Clin. Immunol.* 2009. Vol. 123. P. 687–688.
14. Parent B, Wearden P., Kounis N.G., Chrysostomou C. Kounis syndrome or allergic coronary vasospasm in a two-year-old // *Congenit. Heart Dis.* 2011. Vol. 65. P. 499–503.

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PROBIOTICS AND ALLERGY

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The enormous number of controversial experimental and clinical data in the literature about the immunomodulation capacity of intestinal microbiome and its role in allergic diseases and the capacity of the *probiotics* for the primary prevention of allergies exist. The author presents contemporary information about this problem on the basis of the carried out by WAO in 2015 for the first time meta-analysis including 23 double-blind placebo-controlled studies and the resent data from Italian Society of Neonatology. The mechanisms of action of the gut microbiome as a immunomodulator which is similar of those of the *probiotics* in terms of prevention of the allergic diseases is discussed. The protective role of intestinal microbiome/*probiotics* against sensitization of human organism is to suppress the Th2 immune response by increasing the number of $CD25^+CD4^+$ regulatory T lymphocytes which release IL-10, TGF-β, FoxP3 able to stimulate Th1 Ly to synthetized IFN-γ, IL-2, IL-12, TNF-α which suppress production of IgE antibodies. By this way intestinal microbiome/*probiotics* may modulate the immunologic and the inflammatory system responses and thus to influence development of sensitization and allergy. This mechanism of action closely coincides with the "hygienic hypothesis" in allergology. Concrete recommendations – strong and conditional about the use of *probiotics*, their efficacy and side effects when they are intended for primary prevention or treatment of different allergic conditions are presented. Particular attention is given to *pregnant women at high risk for allergy in their children, breastfeeding women and infants at risk.* In conclusion, the author summarizes that are needed much more well planned and organized clinical trials, with specific design in order to allow scientifically based data about the real value of *probiotics* in clinical practice in terms of their effect on the development and prevention of allergic diseases. What is until now well known and recommended is that *probiotics* can be used in pregnant women, breastfeeding women and infants for prevention of eczema/atopic dermatitis. There are not sufficient data showing the beneficial effect of *probiotics* in the course or prevention of allergic rhinitis, bronchial asthma and any other allergies.

Key words: *probiotics, atopic dermatitis, bronchial asthma, food allergy.*

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The enormous number of controversial experimental and clinical data in the literature, many of them in a form of meta-analysis about the immunomodulation capacity of intestinal microbiome and its role in allergic diseases and the capacity of the probiotics for the primary prevention of allergies exist [1–7]. The immunomodulation activity of the Intestinal microbiome attracts the interest of the researchers and clinicians to the different probiotics which contain living microorganisms that when administered to humans in adequate doses may confer a health benefit. They have been proposed to modulate immune response and have been advocated as a therapeutic and preventive interventions for allergic diseases.

The protective role of Intestinal microbiome against sensitization of human organism is: to stimulate $CD25^+CD4^+$ regulatory T lymphocytes which release IL-10, TGF-β, FoxP3 able to stimulate Th1 Ly to synthetized IFN-γ, IL-2, IL-12 TNF-α which suppress production of IgE antibodies and to suppress Th2 immune reactivity related with IL-4 and IL-13 release. By this way intestinal mircobiome may modulate immunologic and inflammatory system responses and thus, influences development of sensitization and allergy in terms of the quality and quantity of different microorganisms (Fig. 1). This mechanism of action closely coincides with the "hygienic hypothesis" according to which the rise in the prevalence of allergic diseases could be caused by reduced exposure to micro-organisms, with consequent alteration in the balance of the immune response – the decrease of Th1 pattern of cytokine release suppressing the IgE synthesis and the predominant role of Th2 immune reactivity involved in IgE-mediated allergy.

All these above mentioned controversial issues in terms of the action of probiotics in prevention or treatment of allergic hypersensitivity stimulate the WAO via McMaster University in Canada to organize the only until now very large systematic review on randomized control trials of probiotics (21 published studies) realized by a team of 22 medical institutions from 12 countries [8] in order to assess their real role in this respect. Simultaneously with this study the Italian Society of Neonatology – a team of 12 leading pediatricians – carried out an investigation during several years on the use and clinical efficacy of probiotics in pediatric practice [9]. On the basis of these double-blind, placebo-controlled clinical

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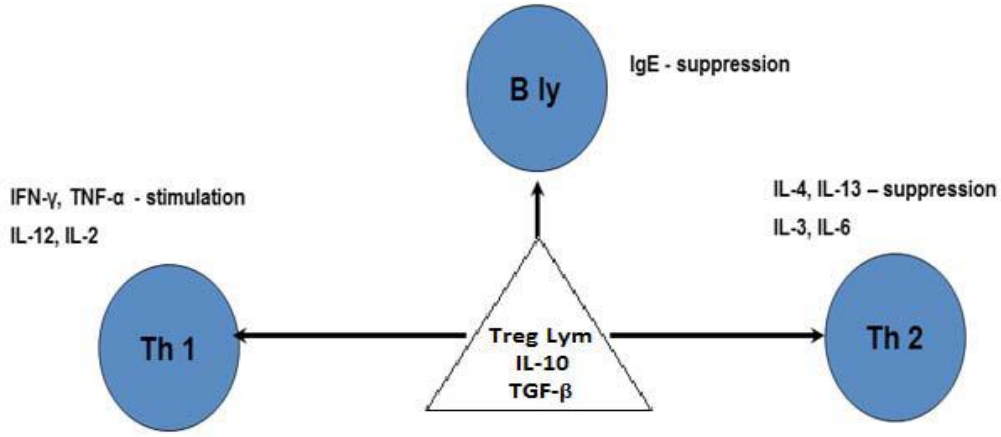

Fig. 1. Mechanism of action of microbiome/probiotics.

trials of oral probiotic supplementation the WAO presents a several recommendations concerning their efficacy and side effects when they are used for primary prevention or treatment of different allergic conditions. The recommendations are focused on three group of patients: – *pregnant women at high risk for allergy in their children* – *breastfeeding women* – *infants.* The recommendations are of two grades of strength – strong or conditional. *Strong recommendations* mean: for patients – most individuals would like the recommended course of action, and only small part of them would not; for clinicians – most individuals should receive the intervention; for policy makers – the recommendation can be adopted as a policy in most situation. *Conditional recommendations* mean: for patients – the majority of individuals would want the suggested course of action, but many would not; for clinicians – recognize that different choices will be appropriate for individual patients and to help them to make decision consistent with their values and preferences. For policy makers – policy-making will require substantial debate and involvement of different stakeholders.

Considering the results of these studies and all available data in this field *the WAO recommendations about pregnant women at high risk for allergy in their children* (*mainly in the last 3 months of pregnancy*) state that: there is high value on prevention of eczema in children when pregnant women use probiotics (*conditional recommendation*); there is relatively lower value on avoiding possible adverse effects of probiotics; there is lack of evidence that probiotics when are given to pregnant women prevent any other allergy – allergic rhinitis, asthma, food allergy. *The WAO recommendations about breastfeeding mothers are:* – to use probiotics in women who breastfeed infants at high risk of developing allergy because there is a net benefit resulting primarily from prevention of eczema (*conditional recommendation*); there is a very low certainty that there is any effect of probiotics use by breastfeeding mothers on the development of other allergies in their children; there is a lack of evidence that probiotics can prevent any other allergies when are given to breastfeeding women; the risk of any adverse effects is low. Follow-up in the included studies ranged from 4 to 36 months' infants used probiotics, *the WAO* risk of developing allergies, because there is a net benefit resulting primarily from prevention of eczema atopic dermatitis (*conditional recommendation*); the studies failed to demonstrate a statistically significant effect of probiotics on development of allergic rhinitis or asthma in children. Development of food allergy was measured in 5 randomized studies and no difference between probiotics and placebo arms was noted.

Conclusion

In conclusion we have to summarize that are needed much more well planned and organized clinical trials, with specific design in order to allow scientifically based data about the real value of probiotics in clinical practice in terms of their effect on the development and prevention of allergic diseases and to answer the following crucial questions:

Evaluation which of three discussed populations should receive probiotics? Whether there is large benefit with supplementation in one or combination of these populations? Which population is target? Evaluation whether any effect of probiotics depends on the species and the strains of microorganisms? Evaluation of the effects of different ways of administration of probiotics – as a milk or dairy supplement, stand-alone supplement? It is not clear when the administration of probiotics should be started and how long they should be used? Is the effect of natural probiotics in food different from that of supplementation?

What is until now well known and recommended is that probiotics can be used in pregnant women, breastfeeding women and infants for prevention of eczema/ atopic dermatitis. There are not sufficient data showing the beneficial effect of probiotics in the course or prevention of allergic rhinitis, bronchial asthma and any other allergies.

References

1. Garcia-Larsen V., Del Giacco S., Moreira A. et al. Dietery intake and risk of asthma ion children and adults // *Clinical and Translational Allergy* // 2016. Vol. 6. P. 17–23.
2. Kristiansen L., Rollinghoff M, Berghamans S. Gene-environment interaction in chronic diseases // *J. Allergy Clin Immunol*. 2011. Vol. 128. # 6. P. 250–310.
3. Meyer R., Fleming C., Ortega G. et al. Manifestation of food protein induced gastrointestinal allergies // *WAO Journal*. 2013. Vol. 6. P. 6–13.
4. Nembrini C., Singh A., De Castro C. et al.,Oral administration of *L paracasei* for the modulation of grass pollen allergic rhinitis // *Clinical and Translational Allergy*. 2015. Vol. 5. P. 14–17.
5. NurmatovU., Devereux G., Sheikh A. Nutrients and foods for the primary prevention of asthma and allergy // *J. Allergy Clin Immunol*. 2011. Vol. 127. P. 724–733.
6. Stein M., Hrusch C., Gozds J. et al. Farm living study confirms the Hygienic Hypothesis // *N. Engl. J. Med*. 2016. Vol. 375. P. 411–421.
7. Van Bever H., Nagarajan S., Shek L. et al. Primary prevention of allergy – Will it soon become a reality? // *Pediatric Allergy and Immunology*. 2016. Vol. 237. # 1. P. 6–12.
8. Fiocchi A., Pawankar R., Garcia C. et al. World Allergy Organization- McMaster University Guidelines for allergic disease prevention: Probiotics // *WAO Journal*. 2015. Vol. 8. P. 1–12.
9. Ziccotti G., Meneghin F., Aceti A. et al. Allergy, Probiotics for prevention of atopic diseases in infants // *Allergy*. 2015. Vol. 70. # 11. P. 1356–1371.

Meeting Calendar

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February 2–5, 2018 Dubai, UAE

XII WORLD CONGRESS ON COPD, ASTHMA & RESPIRATORY ALLERGY

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April 20–23, 2018 Barcelona, Spain

XI WORLD *ASTHMA, ALLERGY & COPD* FORUM

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CHEMICALLY MODIFIED ALLERGENS – ALLERGOIDS IN SPECIFIC IMMUNOTHERAPY OF RESPIRATORY ALLERGY

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The results from research on antigenicity and allergenicity of chemically modified preparations (allergoids) from grass pollens and house dust mites are presented in this review. The efficacy and immunological changes that occur during the course of immunotherapy with Bulgarian allergoids were assessed also. The modification of allergens to allergoids has been proved by: Determination of final amino groups; Gel-filtration on Sephadex and Isoelectric focusing. The allergenicity of the allergoids has been assessed by Skin Prick Tests. The antigenicity of the allergoids has been assessed by: Ouchterlony test – double diffusion in agar-gel. 53 patients with seasonal allergic rhinitis or bronchial asthma, sensitized to grass pollen allergen and 21 patients with bronchial asthma, sensitized to house dust mite are included for specific immunotherapy/hyposensitization with allergoids. Before the start of therapy after the first, second and third year of treatment the levels of total and allergen-specific IgE antibodies, as well as blocking IgG4 antibodies are evaluated. A scoring system of subjective reporting of the condition of patients during therapy is used. Comparing the number and size of positive skin reactions after skin prick tests with unmodified allergens and their corresponding allergoids show that allergoid possess weaker allergen activity compared to their native allergens. Antigenicity of chemically modified allergens is affected minimally. Studied Bulgarian allergoids have good therapeutic efficacy. The treatment with modified allergens causes strong immunological effects in allergic patients by forming high titers of allergen-specific IgG4 antibodies. At the same time in patients treated successfully with allergoids, there is a clear tendency to reduce the levels of total and allergen-specific IgE antibodies. All this is in favor of the broadly introducing of the allergoids in the clinical practice for the purposes of the specific hyposensitization (immunotherapy) of the atopic respiratory allergic disease.

Key words: *. allergen, chemically modified allergen, allergoid, specific immunotherapy.*

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The allergens possess two main properties:

- Allergenicity – the ability to stimulate formation of specific antibodies (mainly IgE), which sensitize human body.
- Antigenicity – connected with the formation of other kinds of antibodies, having no relation to the sensitization (mainly protective "blocking" antibodies).

Chemically modified allergens (allergoids) are allergens devoid of, or with reduced allergenicity, but with well preserved antigenicity [1, 2].

Two very important effects are achieved with the introduction of the allergoids in the clinical practice: The risk of unpleasant side reactions in the course of treatment significantly decreases and more over the possibility for introducing in the patient the higher doses of allergoid, thus obtaining better clinical results [3].

Considering all this in recent years we have developed and implemented in practice two chemically modified allergens: one from grass pollens (*Dactylis glom., Festuca sp., Lolium per., Secale cer., Phleum prat. Arrhenaterum elatius*) and other – from house dust mite *D. pteronyssinus* (D. pt.). In this review, we present the results of our research on antigenicity and allergenicity of chemically modified preparations. The efficacy and immunological changes that occur during the course of immunotherapy with Bulgarian allergoids were assessed also.

Methodology

THE MODIFICATION OF ALLERGENS TO ALLERGOIDS HAS BEEN PROVED BY:

- Determination of final amino groups – NH_2;
- Gel-filtration on Sephadex;
- Isoelectric focusing [4].

THE ALLERGENICITY OF THE ALLERGOIDS HAS BEEN ASSESSED BY: Skin Prick Tests (SPT).

THE ANTIGENICITY OF THE ALLERGOIDS HAS BEEN ASSESSED BY: Ouchterlony test – double diffusion in agar-gel [5].

PATIENTS INCLUDED FOR SPECIFIC IMMUNOTHERAPY/HYPOSENSITIZATION WITH ALLERGOIDS: 53 patients with seasonal allergic rhinitis or bronchial asthma, sensitized to grass pollen allergen and 21 patients with bronchial asthma,

Table 1

Determination of concentration of free NH_2-groups in the allergens and its respective allergoids compared with standard concentration of α-leucin

Allergens and Allergoids	*Concentration of the samples (mg/ml)*	*A340*	*LEU/mg*
Grass pollen allergen	0.25	0.720	1.0×10^{-3}
Grass pollen allergoid	1.60	0.110	2.6×10^{-5}
D. pt. allergen	0.5	0.900	5.2×10^{-2}
D. pt. allergoid	1.5	0.011	7.8×10^{-3}

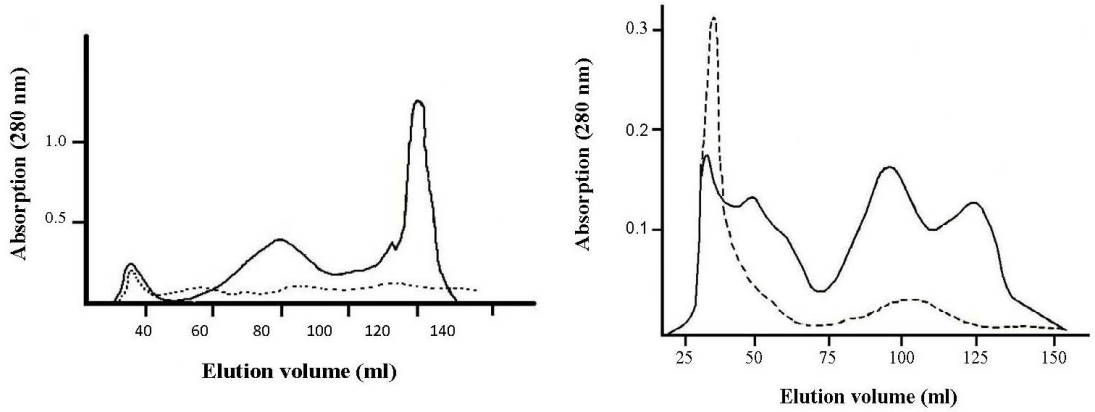

Fig. 1A. The elution profile of D. pt allergen and its respective allergoids on Sephadex G-50.

Fig. 1B. The elution profile of Grass Pollen allergen and its respective allergoids on Sephadex G-50.

Fig. 1. Gel filtration on Sephadex G-75 and G-50.

sensitized to house dust mite are enrolled in the studies. 40 from the patients are female and 34 – male. The patients are from 17 to 61 years old.

The severity of the disease was estimated as follows: 6 patients with light, 27 – with moderate and 41 with severe form.

The course of subcutaneous specific immunotherapy (SCIT) is held year around. Before the start of therapy after the first, second and third year of treatment the levels of total and allergen-specific IgE antibodies, as well as blocking IgG4 antibodies are evaluated.

A scoring system of subjective reporting of the condition of patients during therapy is used.

Results

We found that the concentration of free amino groups in chemically modified allergens is approximately 10–200 times less than that in the native allergens (Table 1).

These results confirm the thesis of Marsh [2] that an essential element of the mechanism in obtaining of allergoids is the interaction of amino groups of protein extracts with the aldehyde group of formaldehyde.

Gel filtration on Sephadex is a convenient method to assess the modification of various allergoids. By elution profiles of the native allergen and allergoid, presented in Fig. 1 A and B, we can assess that the impact of formaldehyde substantially alter the molecular mass in the modified products. In region of the elution profile, which respond to the high molecular weight of allergoid (at the elution volume 40-50 ml), occurs well defined peak, which in the native allergen is lacking.

Comparative presentation of the elution profiles of the allergen and the corresponding allergoid illustrates the mechanism of modification with formaldehyde, which is creating a numerous intermolecular bond, leading to enlarging the molecules of the modified extract.

The simultaneous isoelectric focusing of the native allergens and the corresponding allergoids, modified with formaldehyde, revealed differences in isoelectric points (pI) of proteins in extracts (Fig 2.A and B).

The data indicate that the protein profile of the unmodified allergens (Fig. 2A 1, 2, 3 and Figure 2 B 1, 2) is characterized by a evenly distribution of the proteins throughout the pH gradient of the plate (pI of proteins are from 3.5 to 9.3).

The proteins of the chemically modified allergens focus near the anode in a relatively narrow range of pH (pI 3.5 to 5.5). The observed differences in the picture of the protein profile of allergoids most likely due to the reaction of formaldehyde with a positively charged amino acid residues of the proteins in the extract.

Comparing the number and size of positive skin reactions after SPT with unmodified allergens and their corresponding allergoids show that allergoid possess weaker allergen activity compared to their native allergens.

Evidence from studies with pollen allergoid has shown that the resulting allergenicity is reduced by 90–99% against initial values. This is very clearly demonstrated by the fact that histamine release from sensitized basophils or mast cells drops a 1000-fold in the case of allergoids as compared

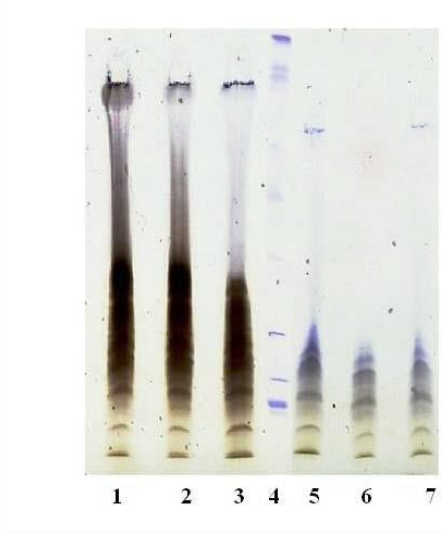

Fig. 2A. Isoelectric focusing of D. pt allergen (1, 2, 3) and its respective allergoids (5, 6, 7).

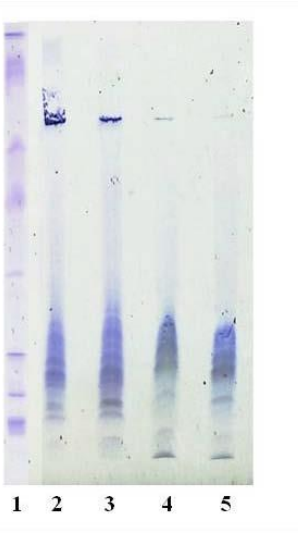

Fig. 2B. Isoelectric focusing of Grass Pollen allergen (2, 3) and its respective allergoids (4, 5).

Fig. 2. Isoelectric focusing.

Table 2

Allergy spin prick test/weal in mm/ with Grass pollen allergen and its respective allergoid in 76 patients

Skin prick test (weal in mm)	*Patients*	*Grass pollen allergen*	*Grass pollen allergoid*		
		1000 PNU/ml	*500 PNU/ml*	*2500 PNU/ml*	*1000 PNU/ml*
Mean diameter	76	7.21	4.58	3.89	<2
Median diameter	76	7.0	5.0	4.0	2.0

to the original allergen. Substantially diminishes also allergoid ability to elicit response in skin tests on allergic patients, where they have been observed to be from 200 to 2000 times less allergenic (Table 2).

Comparison between the size of the skin reaction induced by the allergen in diagnostic concentration and the reaction, elicited by allergoid in identical concentration, demonstrated that the chemically modified allergen from house dust mites had lost about 50% of a skin-sensitizing activity of the allergen.

The results from of SPT demonstrate that, even used in the highest concentration, allergoid (which is concentrated twice) - is not able to cause skin-allergic reaction, whose dimensions are comparable to those induced by the unmodified allergen (Table 3).

A comparative analysis of the antigens of the allergens and their corresponding allergoids in double diffusion in agar-gel using a rabbit hyperimmune serum obtained after immunization of experimental animals with natural allergens is shown in Fig. 4 and 5.

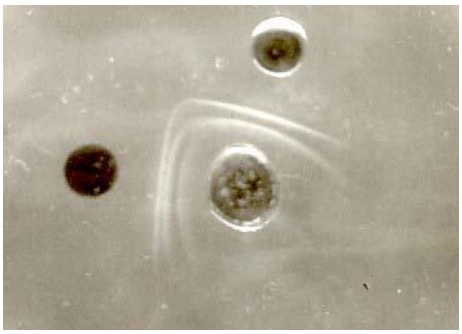

Fig. 4. Double diffusion in agar-gel of rabbit anti-D. pt. allergen serum (central well) to D. pt. allergen (left well) and to its respective allergoid (right well).

Fig. 5. Double diffusion in agar-gel of rabbit anti-Grass pollen allergen serum (central well) to Grass pollen allergen (down well) and to its respective allergoid (up well).

Table 3

Allergy skin prick test/weal in mm/with House dust mite allergen and its respective allergoid in 64 patients

Skin prick test (weal in mm)	*Patients*	*Mite allergen*	*Mite allergoid*	
		1000 BU	*3000 BU*	*1000 BU*
Mean diameter	64	6.27	4.59	3.3
Median diameter	64	6.0	4.0	4.0

Table 4

Clinical results from the specific hyposensitization, carried out with mixed Grass pollen allergoid

Term of treatment	*Treated patients*	*Clinical results from specific hyposensitization*							
		Strong effect		*Moderate effect*		*Little effect*		*Without effect*	
		number	*%*	*number*	*%*	*number*	*%*	*number*	*%*
1 year	53	20	37.5	20	37.5	6	11.3	7	13.2
2 years	53	22	41.5	22	41.5	3	5.6	6	11.3
3 years	53	36	17	9	17	3	5.6	5	9.4

Similar results are observed during assessment of clinical effect from immunotherapy with allergoid from house dust mites (Table 5.).

Table 5

Clinical results from the specific hyposensitization, carried out with D. pt. allergoid

Term of treatment	*Treated patients*	*Clinical results from specific hyposensitization*							
		Strong effect		*Moderate effect*		*Little effect*		*Without effect*	
		number	*%*	*number*	*%*	*number*	*%*	*number*	*%*
1 year	21	8	38	5	23	4	19	4	19
2 years	21	10	48	4	29	3	14	4	19
3 years	21	12	57	3	14	3	14	3	14

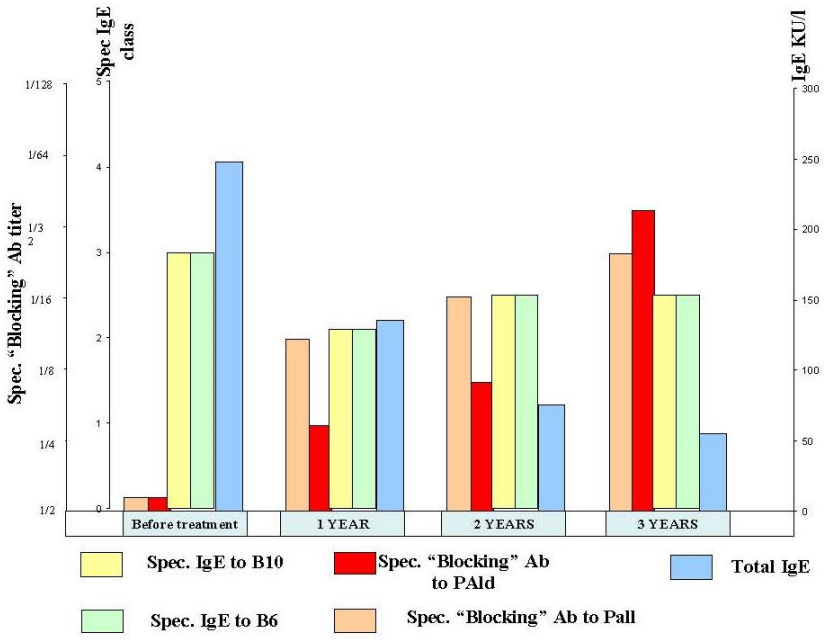

Fig. 6. The level of specific IgE and IgG4 (blocking antibodies) to grass pollen allergen and its respective allergoid in patients with respiratory allergy carried out 3 years specific immunotherapy with the latest.

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The data indicate that antigenicity of chemically modified allergens is affected minimally. Thus the allergoids after regular application are capable to stimulate the immune system for production of IgG4 "blocking" antibodies.

The slightly reduced antigenicity of modified preparation can be compensated by the application of larger amounts of allergoid during the course of specific immunotherapy without any danger of adverse allergic reactions.

After the third year of specific hyposensitization in 85% of treated patients is register strong or moderate effect from the therapy and if we add the number of patients with a little effect from SCIT, it can be concluded that 90.6% of patients obtain clinical benefits (Table 4.). No clinical effect from the SCIT with grass pollen allergoid has been observed only in 5 patients (9.4%).

In comparison to the data before treatment after three year SCIT there is a statistically significant reduction in the level of total and specific IgE antibodies and a significant increase of «blocking» IgG4 antibodies (Fig. 6.).

A correlation between the changed antibody levels and subjective evaluation of the condition has been observed also.

The data obtained give evidence that studied Bulgarian allergoids have good therapeutic efficacy, which is due to the well-preserved immunogenicity of preparations. The treatment with modified allergens causes strong immunological effects in allergic patients by forming high titers of allergen-specific IgG4 antibodies. At the same time in patients treated successfully with allergoids, there is a clear tendency to reduce the levels of total and allergenspecific IgE antibodies.

These encouraging results have even more value if one takes into mind the fact that in the course of therapy are registered single local allergic side effects and only in 4 patients (7.4%) was stopped increasing the dose of allergoid due to the strengthening of symptoms of primary allergic disease.

Conclusion

Having in mind the obtained results we are permitted to conclude that:

- The allergoids possess good therapeutic effectiveness;
- In the course of the treatment were observed in the patients single, weak local reactions only in 7-8% from them;
- It was possible to introduce in the patients twofold higher doses of allergoids in comparison with the allergens;
- Allergoid immunotherapy leads up to the formation of high titers of specific protective "blocking" IgG4 antibodies;
- After immunotherapy with allergoids decrease in the level of the total IgE and some of the specific IgE appears;

All this is in favor of the broadly introducing of the allergoids in the clinical practice for the purposes of the specific hyposensitization (immunotherapy) of the atopic respiratory allergic disease.

References

1. Marsh D.G., Lichtenstein, L.M., Campbell D.H. Studies on "Allergoids" prepared from naturally occurring allergens. I. Assay of allergenicity and antigenicity of formalized Rye group I component // *Immunology* 1970. Vol. 18, P. 705–721.
2. Marsh D.G., Norman, P.S., Roebber, M. et al. Studies on allergoids from naturally occurred allergens. III. Preparation of ragweed pollen allergoids by aldexyde modification in two steps // *J. Allergy Clin. Immunol.* 1981. Vol. 68, P. 449–459.
3. Grammer L.C., Shaughnessy M.A. Immunotherapy with modified allergens // *Immunol. Allergy Clin. North. Am*. 1992. Vol. 12. P. 95–105.
4. Overell B.G. *Modified allergens: Criteria for standartisation. Arbeiten aus dem Paul-Ehrlich Institut (Bundesamt fur Sera und Impfstoffe)*. Gustav Fischer Verlag: Stutgart-New York.1988. Bd 82. P. 233–240.
5. Maasch H.J., Marsh D.G. Standardized extracts modified allergens-allergoids // *Clin. Rev. Allergy*. 1987. Vol. 5. P. 89–106.

Meeting Calendar

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PULMONARY PHYSIOTHERAPY IN COPD AND ASTHMA

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Pulmonary rehabilitation is a behavioral intervention for patients with chronic obstructive pulmonary disease (COPD) that improves symptom 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, pulmonary rehabilitation programs, symptom control, quality of life.*

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

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 other 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 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.

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; and long-term benefits from pulmonary rehabilitation;
- duration of pulmonary rehabilitation;
- postrehabilitation maintenance strategies;
- intensity of aerobic exercise training;
- strength training in pulmonary rehabilitation;
- anabolic drugs;

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- 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;
- pulmonary rehabilitation for patients with disorders other than COPD.

People with asthma may experience recurring episodes of wheeze, dyspnoea, chest tightness and coughing, between which they may be relatively symptom free. As a result of these episodes, some individuals avoid physical activity and physical exercise due to the fear of triggering symptoms. Adults with asthma have been reported to have lower levels of physical fitness than their peers, as well as increased levels of psychological distress and reduced health-related quality of life. Chronic corticosteroid use may impact on peripheral muscle function. Some people with asthma will develop fixed airflow obstruction in adulthood, with chronic symptoms similar to those seen in COPD.

Exercise training improves physical fitness in people with asthma, without deleterious effects on asthma control. Importantly, more recent randomized controlled trials have also shown positive effects of exercise training on asthma symptoms and quality of life in adults with moderate-to-severe persistent asthma.

In addition to exercise training, pulmonary rehabilitation can include other evidence-based interventions to enhance quality of life in people with asthma. A systematic review and meta-analysis showed improvements in health-related quality of life from trials of the Buteyko breathing technique or physiotherapist-led breathing retraining and yoga breathing. The follow-up periods for these studies generally did not exceed 6 months, so the longer term benefits are not yet clear. Clinicians who offer breathing exercises to people with asthma in pulmonary rehabilitation must be aware that the physiological rationale and methods for breathing retraining differ substantially from those in COPD. In asthma, breathing retraining typically aims to eliminate overbreathing by developing a slow, shallow, controlled breathing pattern. The breathing strategies used in COPD, such as pursed lip breathing and diaphragmatic breathing, have not been tested in people with asthma and should not be routinely offered to this patient group.

References

1. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2017. Available from: http://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-COPD
2. McCarthy B., Casey D, Devane D, et al. Pulmonary rehabilitation for chronic obstructive pulmonary disease // *Cochrane Database Syst Rev*. 2015. CD003793. doi:10.1002/14651858.CD003793.pub3
3. Holland A.E., Wadell K., Spruit M.A. How to adapt the pulmonary rehabilitation programme to patients with chronic respiratory disease other than COPD // *Eur Respir Rev*. 2013. Vol. 130. P.577–586.

Meeting Calendar

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October 19–22, 2018 Moscow, Russia

XII WORLD CONGRESS ON ALLERGY, ASTHMA & COPD

♦

WORLD ALLERGY TRAINING SCHOOL (WATS)

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COUGH SYNCOPE DUE TO COPD AND ASTHMA: TWO CASE REPORTS AND REVIEW OF THE LITERATURE

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Cough syncope (CS) is a rare hemodynamic syndrome which is characterised by transient loss of consciousness after prolonged coughing episodes. In this report, we present two cases who admitted to Neurology clinic with the complaint of loss of consciousness after coughing and diagnosed with CS due to chronic obstructive pulmonary disease and asthma. Chronic obstructive pulmonary disease and asthma may be the etiologic factors that cause CS. Clinicians should be aware of this phenomenon and detailed clinical history would provide more clues for the correct diagnosis.

Key words: *cough syncope, chronic obstructive pulmonary disease, asthma*.

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Cough syncope (CS) was first described by the French neurologist Jean Martin Charcot in 1879 and labeled with the name of "laryngeal vertigo" [1]. In the 1940's and early 1950's, some authors suggested the epileptic nature and used the term of "laryngeal epilepsy" [2–3]. CS classically occurs in male patients who have a history of smoking, COPD, are obese and middle-aged [4]. However, CS due to asthma is reported primarily in the pediatric age group [5]. Herein, we present two adult patients with CS secondary to chronic obstructive pulmonary disease (COPD) and asthma.

CASE 1

A 37-year-old obese man was admitted to our clinic with recurrent loss of consciousness after coughing. He reported that each episode had a sudden onset, usually lasted between 3 seconds to 5 minutes and occurred during sleep as well as awake states. He described the dizzy spells, dyspnea, vision blackouts before coughing and noticed the bites on the tip of his tongue after the resolution. He had a variable number of coughing episodes; one or three times per month on average for the last four years. He had a 20 pack/year history of smoking. Physical and neurologic examination was unremarkable. Body mass index (BMI) was 36.1 kg /m^2 (obese, normal range: 18.5–24.9 kg/m^2). Vital signs were stable including blood pressure of 120/70 mm Hg and a regular heart rate of 73 per minute. Laboratory tests, electrocardiography (ECG), cranial magnetic resonance imaging (MRI), vertebral/carotis Doppler Ultrasonography (USG) were found to be normal. Transthoracic echocardiography (TTE) revealed a completely normal left ventricular (LV) systolic and diastolic study with a normal ejection fraction (EF). Additionally, tissue Doppler imaging (TDI) velocities for the septal and lateral walls of the LV and also the right ventricular (RV) free wall were all normal. Head-up tilt table test was performed and cardioinhibitor or vasodepressor forms of vasovagal syncope were excluded. The 24-hour Holter monitoring performed to exclude possible rhythm disturbances that would lead to syncope. In case 1, Holter monitoring showed normal sinus rhythm and did not demonstrate any dysrhythmia. We recorded a cough attack of the patient on video-electroencephalography (v-EEG). We observed loss of consciousness, speech and motor arrest resolved approximately 39 seconds after coughing episode in non-REM-2 phase of sleep. In v-EEG recording we did not detect any epileptiform discharges during this attack. (Figure 1).

Pulmonary auscultation revealed bilateral rhonchi throughout both lungs and prolonged expiratory phase of respiration were noted on chest examination. Pulmonary function test (PFT) showed post-bronchodilator FVC of 3.70 L (85% of predicted), FEV_1 was 2.60.L (70% of predicted), with an improvement of 2% and 60 ml from baseline. The FEV_1/FVC ratio was 68%. Chest X-ray (CXR) revealed minimal elevated right hemidiaphragm. He was diagnosed with COPD based on history, clinical symptoms and spirometric measures. Metilprednisolon (40 mg/day, p.o), Theophylline (400 mg/day, p.o), Ipratropium+Salbutamol (20/100 mcg, 4×1 inhaler), Fluticasone propionate (50 mcg, 2×1, spray) were used for the treatment. On follow-up 3 months later, he denied any attacks of coughing or syncopal episodes.

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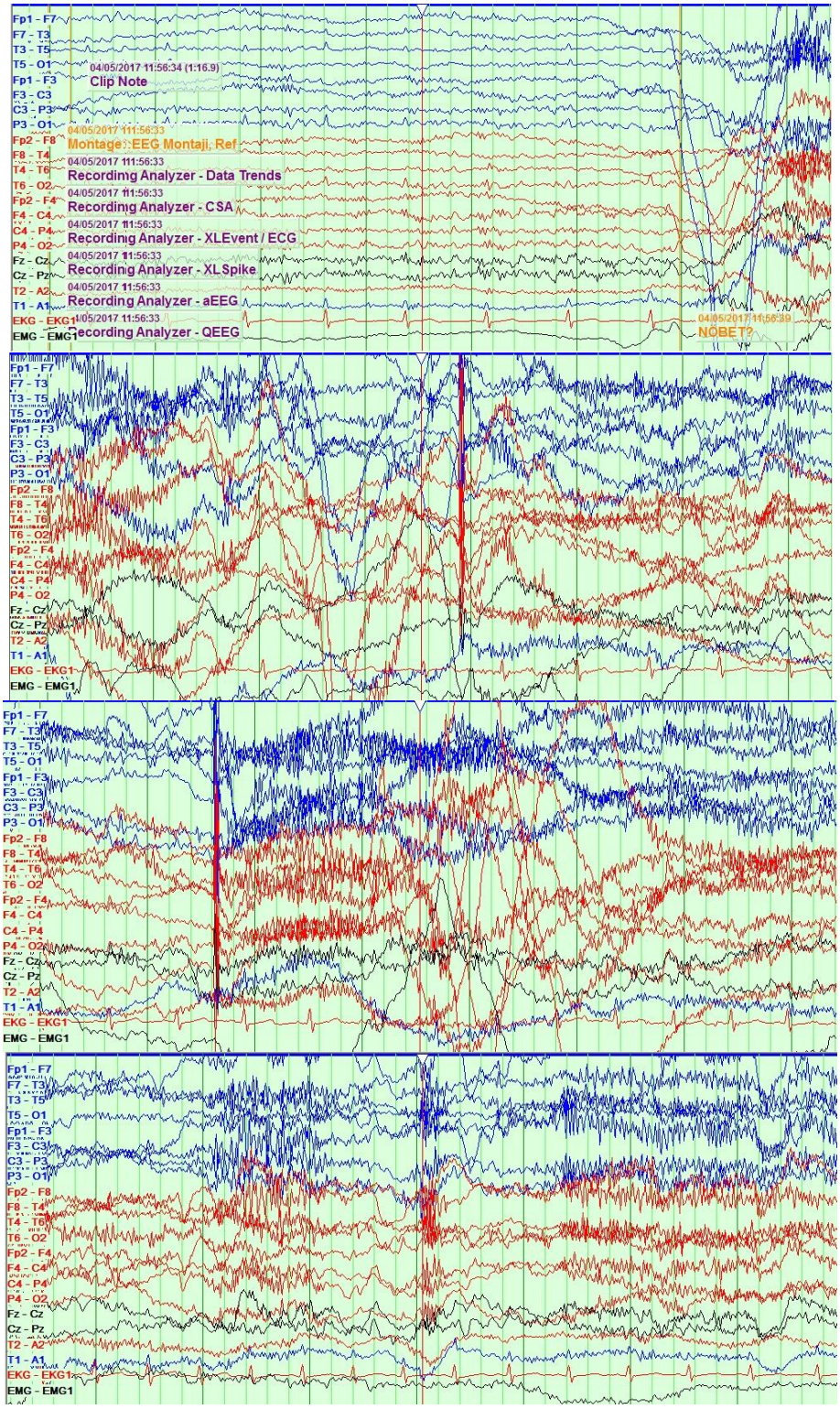

CASE 2

A 34-year-old man presented to neurology clinic with loss of consciousness after coughing episodes occurring weekly for the last several months. These attacks were sudden onset without prodrome and would last for 10–15 seconds. He reported that these symptoms usually worsen due to environmental irritants such as; cigarette smoke, perfumes, dusty conditions and cold-dry weather. He had a 10 pack/year history of smoking. His heart rate was 81beats/min with a blood pressure of 115/85 mmHg. Laboratory findings, electrocardiogram (ECG), TTE, EEG, head-up tilt table test, Cranial MRI, vertebra/carotis Doppler

USG were normal. 24-hours Holter monitoring showed normal sinus rhythm. Physical and neurologic examination was unremarkable.

Lung examination revealed prolonged expiratory phase of respiration. PFT showed a FEV_1 of 2.80 L (73% of predicted), FVC was 4.20 L (80% of predicted) with an improvement of 21% and 60 ml from baseline. FEV_1/FVC ratio was 68%. CXR was normal. Thorax computerized tomography (CT) confirms multiple small left apical subpleural cysts (max. 18 mm) and a 2 mm pulmonary nodule in the laterobasal segment of the left inferior lobe. He was diagnosed with asthma based on symptoms, clinical history and pulmonary function testing. Fluticasone furoate+ Vilanterol Trifenatate (200/25 mcg/1×1, inhaler), Omalizumab (225 mg/month), Salbutamol (100 mcg/2×1/inhaler/if needed) were used to prevent the symptoms. The patient had no any attacks of cough syncope in the past 4 months.

Discussion

CS is a rare form of reflex (synonymous with neurally-mediated) syndrome which is a sudden loss of consciousness caused by coughing [4–5]. Previous studies revealed that hemodynamic mechanisms play a major role in the pathogenesis of disease initiation and progression [6–7). Sharpey-Schafer et al. reported the loss of consciousness after the attacks are directly associated with changes in the intrathoracic pressure [8]. The increase in intrathoracic and intraabdominal pressure due to Valsalva mechanism during cough episodes cause lowered cardiac output and impaired serebral blood flow (CBF). Transient reduction of CBF can lead to syncopal or presyncopal symptoms such as dizziness, lightheadedness and weakness [4]. Other forms of loss of consciousness with reflex mechanisms are syncope due to sneezing, micturation, defecation, deglutition, laughing and weightlifting (9). The exact incidence and prevelance of CS is not known, although it is rare. CS is mostly seen in men [4–5]. Most probable reason for the gender difference is, negative intrathorasic pressure is higher and decrease in cardiac output is more distinct than women [4]. Both of the cases were male and our cases are supporting the male predominance is identified in the literature as well.

CS usually occurs in obese, middle aged, smoker men with COPD [4]. Case 1, was an obese smoker patient who diagnosed with COPD. Studies have suggested that CS related to asthma is classically seen in the pediatric population [10–11]. However, Beckman et al. reported cough syncope in an adult patient with asthma [12].

Similarly, Case 2 was diagnosed with asthma despite not being in the pediatric age limit. Other etiologic factors of CS are; cardiovascular disorders (constrictive pericarditis, atrioventricular block, pulmonary hypertension), central nervous system disorders (cerebral tumors, Arnold-Chiari malformation Type 1, hydrocephalus, carotid and vertebral arterial occlusive disease, medullary infarction), gastro esophageal reflux disease, drugs (acetyl salicylic acid, beta blockers and angiotensin converting enzyme (ACE) inhibitors) [4].

Early investigators documented rhythmic movements of the limbs and clonic jerks without any epileptiform activity during CS attacks in EEG recordings. Patients demonstrated diffuse delta and theta slowing similar to other forms of syncope according to cerebral hypoperfusion [4, 13]. CS have been reported also in the supine patients, although the exact underlying mechanism is unknown [4, 7]. In case 1, the patient performed the syncopal attack during EEG recording when he was sleeping in the supine position.

The diagnosis can be made clinically by taking a careful history. Seizure disorders, bradycardia, hypoglycaemia and cardiac dysrhythmias should be excluded for the clinical assessment. Laboratory tests, echocardiogram, TTE, 24-hour holter monitoring, tilt-table test, spirometry, EEG and neuroimaging are helpful in the evaluation and differential diagnosis [4]. Both of the cases have normal laboratory, cardiac, neurological and imaging findings including tilt table test and 24-hours Holter monitoring. However, patient's chest examination and spirometry tests revealed the diagnosis of COPD and asthma Syncope after coughing attacks due to underlying pulmonary disease usually resolves by an appropriate medical treatment [5]. Both of the patients were asymptomatic after the drug therapy for 3 months.

In conclusion, chronic obstructive pulmonary disease and asthma may be the etiologic factors that cause CS. Clinicians should be aware of this phenomenon and detailed clinical history would provide more clues for the correct diagnosis.

References

1. Charcot J.M. Statement to the Societe de Biologie // *Gaz Med de Paris* 1876.Vol. 1876. #5. P. 588e9.
2. Whitty C.W.M. On the so called "laryngeal epilepsy" // *Brain.* 1943. Vol. 66. P. 43e54.
3. O'Doherty D.S. Tussive syncope and its relation to epilepsy // *Neurology.* 1953. Vol. 3. P. 16e21.
4. Peter V., Dicpinigaitis P.V., Lim L., Farmakidis C. Cough Syncope // *Rev. Respiratory Medicine*.2014. Vol. 108. P. 244–251.
5. Beckmann T. Syncope in an adult with uncontrolled asthma // *South Med J.* 2002. Vol. 95. # 3. P. 369-370.
6. McCann W.S., Bruce R.A., Lovejoy F.W., et al. Tussive syncope; observations on the disease formerly called laryngeal epilepsy, with report of two cases // *Arch Intern Med (Chic)* 1949. Vol. 84. P. 845e56.
7. Kerr Jr. A., Derbes V.J. The syndrome of cough syncope // *Ann Intern Med.* 1953. Vol. 39. P. 1240e53.
8. Sharpey-Schafer E.P. The mechanism of syncope after coughing // *Br Med J.* 1953. Vol. 2. P. 860–863.
9. Haddad C., Haddad-Lacle J.E. Laughter-induced syncope // *BMJ Case Rep*. 2013. doi:10.1136/bcr-2013-010169
10. Katz R.M. Cough syncope in children with asthma // *J Pediatr*. 1970. Vol. 77. P. 48–51.
11. Haslam RH, Freigang B. Cough syncope mimicking epilepsy in asthmatic children // *Can J Neurol Sci.* 1985. Vol. 12. Vol. P. 45–47
12. Beckmann T. Syncope in an adult with uncontrolled asthma // *South Med J.* 2002 Vol. 95. # 3. P.369–370.
13. De Maria Jr. A.A., Westmoreland B.F., Sharbrough F.W. EEG in cough syncope // *Neurology* Vol. 1984. Vol. 34. P. 371e4.

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PREPARING THE WORKFORCE FOR THE CHANGING PRACTICE ENVIRONMENT

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The global burden of asthma continues to grow and constitutes a major healthcare challenge when preparing the next generation of providers for a redesigned healthcare system. According to the World Health Organization, it is estimated that approximately 300 million individuals suffer from asthma and the number is expected to increase by 100 million by the year 2025 (WHO, 2007). Strengthening the human resource capacity by improving training and establishing continuing education programs for healthcare providers at all level has been as a suggested plan of action to address this challenge. A "train the trainer" model has been utilized in certain fields with positive outcomes, but is less frequently employed in healthcare education (Sanders, M. Reynolds, J. Bagatelle, W, Trem, J. O Connor, E. & Katz, D, 2015). Faculty training using the "train the trainer" approach can be a key component in preparing the next generation of providers to deliver safe and effective asthma care.

Key words: *healthcare education, train the trainer model, asthma.*

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There is a strong association between symptom burden and healthcare use such as emergency room visits and hospitalization. (Fuhlbrigge, et al, 2002). In light of the growing number of people living with asthma and the shortage of healthcare professionals specializing in the disease, it is critical that providers are well prepared and willing to work on the front line to improve asthma care and self-management. Research shows that increased preparation for providers with interest and experience in a topic can strongly impact the wellbeing of patients and families (Beacham, 2016).

Changing Practice Environment

The Institute of Medicine has outlined ten important rules of performance in a re-designed healthcare system to help improve care (Finkelman, A, 2012). The first rule is that "care is based on a continuous healing relationship". In order for providers to acknowledge the client's right to self-determination and demonstrate that they value the client's beliefs values and preferences, it is recommended that patient/provider communication should be "horizontal" rather than "top- down". Goals should be short so that they can be easily achieved (Bonezzi A, Brandl, C & DeAngelis, 2011). Examining the client's health belief system to better understand different world views and offer evidence based recommendations will help to reduce conflicts. A re-designed healthcare system includes safety as a systems priority. In asthma care, safety issues include poor asthma control because of frequent symptoms, greater use of rescue medications, functional impairment or worsening function continues to be a problem for many clients. A re-organization of tasks and personnel performing those tasks may require a fundamental re-thinking. Who is currently performing the task of educating the next generation of providers and do they have the appropriate skill level?

Methodology

The purpose of faculty development is to facilitate the development of faculty skills, foster an environment in which faculty feel empowered to continually work toward improved educational scholarship. In order to address the challenge and meet the growing educational needs in asthma care, a dedicated faculty training program using a "Train the Trainer" (TTT) model is proposed. This model is one in which content is gathered from experts to educate trainers in order to allow them to instruct target audiences. They can then disseminate the information to others in a timely fashion making it cost effective and sustainable. (Sanders, et al, 2015). A structured curriculum helps to regulate the how and when the information is delivered (Slutsky, P, Bryant, Stephens, 2001).

Train the Trainer model

A train the trainer educational model established by an organization gathers content from experts to educate trainers which then enables them to instruct target audiences. The advantage of this model is its ability to be replicated and information can be easily disseminated in a timely manner. (Sanders et al, 2015; Yong, et al, 2016; Greif, et al, 2015; Mayrhofer, 2016). The expert trainer teaches the non-expert how to administer an intervention as well as trains others to do the same. It is different than traditional teaching models because it provides a cascade effect, thereby increasing the available pool of individuals with essential knowledge necessary to support learning.

Steps in the Process

The steps in the process to begin a TTT program include the following: Step 1: Obtain funding from a national foundation dedicated to supporting faculty development in asthma education Step 2: Launch a pilot program by a nurse specialist or a certified asthma educator Step 3: Begin interactive training program at a local academic center Step 4: Conduct lectures, small group discussions, workshops with asthma education experts and patient panels Step 5: complete mentored independent project benefitting education, research and patient care Step 6: Include mentorship by members of a multidisciplinary team Step 7: Attend a support or community group Step 8: Nominate scholars to advance educational scholarship and present new and innovative educational strategies to others. Share research in journals, webinars and disseminate sample curriculum on line with available resources.

Adult Learning Theory

According to adult learning theory (Knowles, M., Holton, E. Swanson, R., 2015), adult learners come to each learning event with a unique background of knowledge and experience. They are motivated to learn if they can share what they know and build on their prior experience because this will validate their expertise. Faculty are self-directed and want control over what and how they are learning. They are motivated to learn if they can make decisions not only about the content but the process in which they learn, therefore some independence is recommended.

When a train the trainer, session is in progress, it is important that participants are able to participate actively in the learning process, so that they can practice new skills or test their newly found knowledge prior to leaving the learning session.

VARK Learning Styles

A "train the trainer" model should approach teaching using a variety of strategies because it must fit the learner's style and preference. Learning preferences may include kinesthetic, visual, auditory or multimodal. Case studies/problem solving/simulation help learners anchor new skills and knowledge. Learning can be enhanced when learners have an opportunity to reflect, review or personally relate to the material presented and discuss how to apply it.

Results

Employing a pyramid model such as "train the trainer" approach for faculty development can be used to enhance the depth of knowledge about evidence based guidelines for asthma and increase the level of confidence in developing course content, lectures and clinical mentorship in the undergraduate setting. Forming an academic/practice partnership is an important bridge to build to improve care (Niederhauser, 2016).

A "train the trainer" model supports basic and ongoing collaboration of others to advance research and education. Additional goals for this model include the development of long term relationship between guest faculty, scholars and experts at nationally recognized asthma centers so that faculty can better prepare undergraduates with significantly more skills and knowledge about evidence based guidelines in asthma care.

References

1. Beacham A. et al. Meeting evolving workforce needs // *American Psychologist.* 2016. Vol 72. # 1. P. 42–54.
2. Bonezzi A., Brendl C.M., De Angelis M. Stuck in the middle: The psycho physics of goal pursuit // *Psychological Science* 2011.Vol. 22. # 5. P. 607–612.
3. Finkelman A. The movement to improve care. The Institute of medicine quality reports and implications for the advanced practice registered nurse. // *Nursing Clinics of North America* 2012. Vol. 47. # 2. P. 251–260.
4. Greif R., Becher C., Hildebrant T. Reducing eating disorder risk factors: A pilot effectiveness trial of a train the trainer approach to dissemination and implementation // *International Journal of Eating Disorders*. 2015. Vol 48. P. 1122–1131.
5. Knowles M., Holton E., Swanson R. The adult learner: The definitive classic in adult and human resource development (6th ed). Elsevier: 2015.
6. Mayrhofer A., Goodman C., Smeeton N., Handlyey M., Amador S., Davies S. The feasibility of a train the trainer approach to end of life care training in care homes: An evaluation // 2016. Vol 15. #11. doi: 10.1186/s12904-016-0081-z.
7. Niederhauser, et al. 2016. Better Together: A Win-Win Pediatric Academic Partnership // *Pediatric Nursing*. 2016. Vol 42. # 4. P. 175–179.
8. Sanders M. Reynolds J. Bagatell W. Trem J. O'Connor E., Katz D. Promoting healthy lifestyles to children at school: Using a multidisciplinarytrain the trainer approach // *Journal of Public Health Management and Practice*. 2015. Vol 21. # 4. P. 27–35.
9. Slutsky P. Bryant-Stephens T. 2001. Developing a comprehensive, community based asthma education and training program // *Pediatric Nursing*. 2001. Vol. 27. # 5. P. 449–461.
10. World Health Organization Global surveillance, prevention and control of chronic respiratory diseases: a comprehensive approach. 2007.
11. Yarber L., et al Evaluating a train the trainer approach for improving capacity for evidence based decision making in public health // *BMC Health Services Research*. 2015. Vol 15. doi: 10.1186/s12913-015-1224-2.
12. Yong W., Kua P., Soon S., Pek .P, Ong M. Dare train: The trainer pedagogy development using 2-round delphi methodology.// *Bio Medical Research Internationa*l. 2016. Vol. 2016. P. 1–9.

RISK FACTORS FOR WHEEZING IN PRESCHOOL CHILDREN: ROLE OF RHINOVIRUS AND ALLERGEN EXPOSURE

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Allergic sensitization and rhinovirus (RV) infections are the most common triggers of acute exacerbations of wheezing/asthma during early childhood. However, it is often unclear whether these exacerbations had been caused by a rhinovirus infection and/or by allergen exposure. Allergy can be diagnosed by measuring allergen-specific IgE antibodies in patient's serum, whereas diagnostic methods used to study the role of rhinoviruses in exacerbations of respiratory diseases are based on reverse transcription of viral RNA and DNA amplification by polymerase chain reaction (PCR). Hence, only the presence of the virus at the onset of exacerbation can be detected which does not necessarily prove that this particular virus detected by PCR had caused clinical symptoms in a patient. We have previously found that rhinovirus infections induce increases of IgG and IgA responses against an N-terminal portion of the rhinovirus VP1 protein and that respiratory allergen exposure induces increases in allergen-specific IgE levels. These increases of specific antibody levels can be detected several weeks after infection and allergen exposure, respectively. In this study, we analyzed IgE responses to multiple allergen components determined by the MeDALL-allergen chip and IgG antibody responses to recombinant RV-derived proteins measured by ELISA in sera from 120 preschool children obtained during an acute episode of wheeze and at follow-up several weeks after. We found that the majority of children mounted increases of IgG responses towards the rhinovirus proteins whereas in none of the children with an IgE-sensitization, increases of IgE responses to inhalant allergens were detected. Our findings thus indicate that rhinovirus infections but not respiratory allergen exposure were responsible for the elicitation of wheezing attacks among the preschool children investigated.

This study was supported by the European Commission's Seventh Framework programme under grant agreement N° 260895 (PreDicta), by a grant P29398-B30 of the Austrian Science Fund (FWF), by a research grant from Biomay AG, Vienna, Austria, by The Swedish Research Council, the Stockholm County Council and The Swedish Heart-Lung Foundation.

RHINOVIRUS DIAGNOSIS BY BLOOD TESTING WITH THE "PREDICTA" CHIP

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Rhinovirus (RV) infections are major triggers of acute exacerbations of asthma and chronic obstructive pulmonary disease (COPD) in both children and adults. The association of rhinovirus infections with exacerbations of respiratory disease is mainly based on the demonstration of the presence of virus at the onset of exacerbation. However, there are currently no serological tests available which would allow detecting specificities of antibody responses against RV epitopes as a result of infection. We, therefore, developed a high resolution antibody assay based on recombinant antigens and peptides from the most common RV strains. The optimized microarray contains in total 130 components and includes 48 recombinant RV proteins and 66 VP1-derived synthetic peptides. We demonstrated that extremely small sample volumes are sufficient to detect RV-specific IgG and IgA antibodies to a broad panel of micro-arrayed RV antigens. Moreover, using serum samples from 120 preschool children collected during an acute episode of wheeze and at follow-up visit after approximately 12 weeks, it was possible to discriminate between group- and partially strain-specific antibody responses in RV-infected patients and thus, to identify the most relevant and clinically important RV strains involved in triggering exacerbations of respiratory diseases. Furthermore, we found that the number of reactive VP1 N-terminal peptides was age-dependent. The number of peptides recognized by RV-specific IgG antibodies at the acute and the follow-up visit in the youngest group of children, 6-8 months, was significantly lower than in children above 1 year. Our results suggest that this microarray will be useful to identify the most common RV strains involved in asthma exacerbations and thus provide a rational basis for the design of a RV vaccine.

This study was supported by the European Commission's Seventh Framework programme under grant agreement N° 260895 (PreDicta), by a grant P29398-B30 of the Austrian Science Fund (FWF), by a research grant from Biomay AG, Vienna, Austria, by The Swedish Research Council, the Stockholm County Council and The Swedish Heart-Lung Foundation.

ACHIEVEMENTS AND PERSPECTIVES IN THE DIAGNOSIS AND TREATMENT OF UROTHELIAL CANCER

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Urothelial cancer (UC) takes one of the leading places among oncological diseases. An early diagnosis and prognosis determine the optimal tactics for a complex treatment of patients with UC. The improvement of methods of early diagnosis and the development of effective methods of therapy of oncological diseases is an actual problem. The work comprehensively deals with issues related to the features of the structure and localization of UC, modern and innovative methods of diagnosis and treatment of this disease. Modern classifications of UR are presented, a brief review of the investigated molecular-genetic markers of early detection and prognosis of the UC course is made, and the relationship between a gene expression

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and survival is estimated. In addition to traditional methods of treatment of UC, attention is paid to nonspecific and specific antitumor immunotherapy, the role of interleukins, Toll-like receptors, chemokines and other factors in the treatment and prognosis of the disease course is considered. In particular, the concept of an adoptive therapy of UC is given, the possibility of the using of immune checkpoints in tumor therapy is shown and innovative developments of various antitumor vaccines are described, promising directions in the diagnosis and treatment of malignant diseases, including UC, are determined. In the work the authors describe some results of their own research on the improving of the diagnosis and treatment of UC, the materials of molecular and genetic research studies with the study of both the expression of testicular antigens (PTA) and violations in the genetic code in UC.

IDENTIFICATION OF MARKERS AND CHECKPOINTS OF COPD WITH THE HELP OF MODERN APPROACHES OF SYSTEM BIOMEDICINE AND BIOINFORMATICS

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Chronic obstructive pulmonary disease (COPD) is a multifactorial, chronic, ecologically mediated inflammatory disease of the respiratory system, with predominant involvement of the distal parts of the respiratory tract and pulmonary parenchyma with the development of emphysema, manifested partly by reversible bronchial obstruction, characterized by progression and increasing events of respiratory failure. COPD takes the third place in the number of deaths in developed countries. The disease has a tendency to rapid spread, which is associated with unfavorable environmental conditions, smoking, hereditary predisposition. Exogenous and endogenous risk factors are distinguished. One of the modern approaches of systemic biomedicine and bioinformatics - the construction and application of models of biological networks - offers a holistic way to understand the biological processes associated with the disease. Chronic obstructive pulmonary disease (COPD) is a progressive inflammatory airways disease, for which there is no adequate therapy after diagnosis, even at an early stage. More than 90 models of COPD networks are important tools for better understanding of the biological components and processes underlying the initial development of the disease, the detection of genetic markers and checkpoints. Thanks to the growing literature, the use of system biology and system analysis by experts made it possible to create a comprehensive set of models relevant to COPD that can be used to identify disease markers and checkpoints, and to understand the mechanisms associated with lung pathology. The innovative approach to building biological networks that integrates literature and data mining by experts to create a comprehensive set of models appropriate to COPD can not be used to understand the mechanisms associated with lung pathology, which will lead to new opportunities for COPD therapy, as well as the creation of new ones drugs.

References

Boue S, Fields B, Hoeng J, Park J, Peitsch MC, Schlage WK1, Talikka M, Binenbaum I, Bondarenko V, Bulgakov OV, Cherkasova V, Diaz-Diaz N, Fedorova L, Guryanova S, et al. Enhancement of COPD biological networks using a web-based collaboration interface. Version 2. F1000Res. 2015

ERYTHROPOIETIN (EPO) ATTENUATES THE IMMUNOHISTOCHEMICAL EXPRESSION OF TUMOR GROWTH FACTOR-B (TGF-B) IN BLEOMYCIN (BLM)-INDUCED PULMONARY FIBROSIS (PF) IN RATS

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Aim: The enzyme TGF-β is well known to participate in the fibrotic pathway with inflammatory and apoptotic actions. Erythropoietin, on the other hand, is a multiple functional cytokine with anti-inflammatory and anti-apoptotic properties. The aim of this study was to investigate the role of EPO on the expression of TGF-β in BLM-induced PF in rats.

Methods: Fifty Wistar rats (300gr) were divided into five groups of 10 animals each: 1) control animals, 2) intratracheal (i.t) and intraperitoneal (i.p) injection of saline (0.5 ml/kg), 3) BLM hydrochloride (7.5 mg/kg) i.t injection, 4) BLM hydrochloride (7.5 mg/kg) i.t injection followed by EPO i.p injection (2000 iu/kg), 5) saline (0.5 ml/kg) i.t injection followed by EPO i.p injection (2000 iu/kg). All rats were sacrified after 14 days. The expression of TGF-β was immunohistochemically measured and a scale of four grades (A: 0–25%, B: 25–50%, C: 50–75%, D: 75–100%) was used to evaluate it.

Results: In groups 1, 2 and 5 (control groups), TGF-β was expressed only in the two lower grades of the scale (A: 90% and B: 10%). In group 3, TGF-β was expressed in the high grades (C: 20% and D: 80%). Finally, in group 4, the enzyme in question was expressed only in the low grades (A: 80% and B: 20%). The expression of TGF-β took place in the high grades for group 3 (BLM group) and in the lower grades for group 4 (BLM+EPO group) ($p<0.001$ and $p<0.05$ respectively).

***Conclusions*:** Treatment with EPO significantly ameliorated the extent and severity of the BLM-induced toxicity in lung tissue.TGF-β had a significantly lower expression in the group of animals which were administrated with EPO, compared with the group of BLM.

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ACTIVATION OF P38 KINASE MEDIATES INSPIRATORY RESISTIVE BREATHING-INDUCED PULMONARY INFLAMMATION

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Introduction: Inspiratory Resistive Breathing (IRB) is a hallmark of obstructive airway diseases, such as asthma and COPD, especially during exacerbations. IRB is associated with increased negative intrathoracic pressures, due to strenuous contractions of the inspiratory muscles. We have shown that IRB induces pulmonary inflammation in previously healthy animals. The p38 kinase is activated in the lung through phosphorylation following application of stress and mediates cellular responses. The role of p38 in IRB-induced pulmonary inflammation is unknown. We hypothesized that p38 is activated in the lung during IRB and mediates the induction of pulmonary inflammation.

Methods: Anaesthetized, tracheostomized adult rats breathed spontaneously through a 2-way non rebreathing valve. A resistance (small diameter tube) was added to the inspiratory port to provoke a peak tidal inspiratory pressure at 50% of maximum (IRB). Sham operated animals breathing spontaneously against no load, served as control. Following 6 hrs of IRB, the presence of pulmonary inflammation was evaluated by bronchoalveolar lavage (BAL) to measure total and differential cell count. Protein levels of TNFα and MIP-2α in the lung were measured by ELISA. Lung injury was detected by histology. Phosphorylated p38 (p-p38) was detected by Western blot. p38 activation was blocked by administration of the specific inhibitor SB203580 (1mg/kg, ip) 30 min prior to IRB.

Results: Following 6hrs of IRB, a significant increase of p-p38 was detected in the lung ($p=0.04$ compared to ctr), while total p38 level was not affected. Increased BAL cellularity was detected with raised numbers of neutrophils and macrophages ($p=0.009$ and $p=0.004$ to ctr, respectively). TNFα and MIP-2α increased after IRB (2-fold, $p=0.01$ and 6-fold, $p<0.001$, to control respectively). Increased lung injury score was detected by histology ($p=0.01$). Inhibition of p-38 blocked the increase of neutrophils and macrophages ($p=0.001$ and $p=0.003$ compared to 6 hrs IRB, respectively). TNFα returned to control values and MIP-2α was reduced, compared to 6 hrs IRB ($p=0.01$), but remained elevated compared to control ($p<0.001$). Lung injury score was reduced compared to 6 hrs IRB ($p=0.01$).

Conclusion: p38 activation mediates IRB-induced pulmonary inflammation.

THE KNOWLEDGE ATTITUDE AND PRACTICE OF MOTHERS OF ASTHMATIC CHILDREN TOWARD ASTHMA IN KHARTOUM ASTHMA CLINICS 2016

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Background: Prevention of asthma exacerbation is one of the major challenges of public health. Adequate knowledge and positive attitudes and right practices are crucial for prevention of exacerbations. However, there is paucity of data regarding these in Sudan.

Objectives: To assess the knowledge and to identify the attitude and practice of mothers of asthmatic children regarding their use of inhalers, compliance to preventers and to measure its effect on the severity of the disease in their children.

Materials and Methods: A total coverage of mothers of asthmatic children was enrolled. Any mother with a child diagnosed with bronchial asthma for more than 3 months, and attending the outpatient clinic of pediatric asthma in Soba or Ahmed Gasim hospitals or the ER of Ahmed Gasim or Ibrahim Malik hospital in the period from 2nd to 31st of October 2016 could be included.

Results: Asthma was believed to be infectious by 7%. 17% of the mothers thought asthma has immunization. 21% doesn't accept to use the inhaler. 50% of them didn't use the inhaler correctly. Most of the mothers (69%) don't use the inhaler in mild symptoms and 53% didn't use preventers. The severity of asthma found to be associated significantly with the attitude and practice of mothers ($p<.05$) and with the right use of inhalers and the use of preventers ($p<.05$).

Conclusion: Sincere and sustained efforts are required to disseminate knowledge about all aspects of asthma and its management among patient and to dispel their myths and misconception associated with diseases and its therapy.

ROLES OF THAI TRADITIONAL MEDICINE ON CHRONIC OBSTRUCTIVE PULMONARY DISEASE: A SYSTEMATIC SCOPING REVIEW

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Background: Patients with a chronic respiratory difficulty have been trying to seek for all possible methods to alleviate their symptoms, including alternative medicine. As current evidence has been dominated by Western medicine, this study was aimed to explore the Thai Traditional Medicine concepts, treatment approaches, and clinical outcomes.

Methods: A systematic search of 6 databases (PubMed, Thai LIS, ScienceDirect, Cochrane Library) containing article published during 2007–2016 were conducted using the search terms: COPD, asthma, chronic bronchitis, pulmonary emphysema, and pulmonary rehabilitation. Quality of the retrieved articles was then assessed.

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Results: The COPD symptoms were called "Pappasang Pikarn" or "Disabled Lung". Conceptually, the chronic respiratory symptoms are caused by (1) an imbalance of the four key body's constitutions (Din, Nahm, Lom, and Fire), (2) individual behaviors including smoking, agricultural practice, or air pollution, and (3) seasonal factors. The treatment is personalized to the individual's constitutions, especially the "Din" which was believed to be defective. Seven treatment approaches were identified: Apaisalee Recipe (oral medicine), Dok Peep (inhale medicine), Massage Therapy, Stream Therapy, Meditation Therapy, Volatile Oil Therapy, and Hermit Exercise. The clinical improvements based on different measurements were reported for Apaisalee (MMRC Dyspnea Scale increased from 56.8 to 75.00) and Dok Peep (PEFR increased from 38.72% to 68.53%). Evidence on the clinical outcomes of the other treatment approaches has been very limited.

Conclusion: Thai Traditional Medicine offers some potential treatment approaches for COPD patients.

MASSIVE PULMONARY EMBOLISM

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A case of massive pulmonary embolism which is rarely seen has been presented. A 77 years old woman had a senkop attact and was referred to our emergency after cardio respiratory arrest intubation and diagnosed as massive pulmonary embolism had a Computed Tomography (CT) showing filling defect in bilateral main pulmonary vessels. As the administration intravenously thrombolytic, Cardiology consultation wanted and because of the full blockage together decided to do embolectomy with catheter in the catheter laboratory. The main pulmonary artery bifurcation showed a 50% narrowing, and the right pulmonary artery showed a 100% narrowed thrombus. Trombus in the right pulmonary artery and main pulmonary artery aspirated several times. Right pulmonary artery flow. 15 mg of tPA (tissue thromboplastin activator) named actylise intrapulmonary was applied and the attempt was terminated. After the procedure, 85 mg actyle was applied as infusion for 6 hours. ***Control:*** Computed tomography (CT) showed thrombus, completely cleared in the main pulmonary artery and left pulmonary artery and proximal of the right pulmonary artery; continued in the distal segment of the right pulmonary artery. After low molecular weight heparin (LMWH) therapy in service called for control.

Relation between bronchial asthma and parasitic (nematodes) infection in Egyptian children

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Background: Among many factors influencing the prevalence of asthma in developing countries from the tropics are geo-helminthic infections. AIMS: This work aims were to study the relation between bronchial asthma and parasitic infection in Egyptian children. ***Patients and methods:*** A cross-section, analytical study design was chosen to perform this research on 100 school aged children. All children were interviewed and examined clinically and laboratory. ***Setting:*** Alexandria Police Hospital. ***Results:*** 86% of patients with bronchial asthma lived in urban areas, while 64% of patients with parasitic infestation lived in rural areas. Statistically significantly negative correlations were found between blood level of IgE and FEV_1% of predicted in patients with bronchial asthma as well as patients with parasitic infestation with r=-0.381, -0.325 at p=0.006, 0.021 respectively. Inverse relationship was found between blood level of IgE and FEV_1/FVC% in patients with parasitic infestation with r=-0.358 with statistical significant difference at p=0.011. ***Conclusions:*** Statistically significance higher values of IgE were found in patients with parasitic infestation compared to patients with bronchial asthma. It was noted that patients with combined bronchial asthma and parasitic infestation demonstrated statistically significance higher values of IgE which suggest a possible synergistic effect of two diseases. ***Recommendation:*** Improving personal and environmental hygiene and regular screening, treatment and health education for children as regard parasitic infections is recommended.

A CASE-CONTROL STUDY OF SEVERE LIFE THREATENING ASTHMA (SLTA)

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Background: Singapore is ranked as a country with intermediate asthma prevalence but high risk for asthma deaths. Distinct risk factors for asthma death have not been identified in Singapore. Aim: To assess risk factors for SLTA in Singapore.

Methods: Case-control study conducted in Singapore General Hospital. Cases were patients admitted to intensive care unit between 2011–2016 for "asthma exacerbation" or "status asthmatics" and requiring intubation. Controls were patients on follow up at the severe asthma clinic without prior SLTA events. Data on demographic profile, comorbidities, frequency of admission for exacerbations, severity of asthma and biomarkers were collected. Univariate and multivariate logistic regression model was used to identify risk factors, adjusted for treatment according to Global Initiative for Asthma guidelines.

Results: 57 SLTA cases and 361 controls were included. Females comprised of 64.7% of cases and 53.2% of controls. The risk factors of SLTA in comparison with controls were previous hospital admission in the past year (odds ratio (OR) 12.80, 95% CI 3.23–50.62, p<0.0001) and number of pack years (OR 1.04, 95% CI 1.01–1.07, p=0.007). There was no difference in comorbidities such as obesity, Gastro-Oesophageal Reflux disease, depression or anxiety between the two groups.

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SLTA cases had lower mean prebronchodilator Forced Expiratory Volume in 1 second (FEV_1) percent (%) predicted 64.5 vs. 72.5 (p=0.049) and lower mean Forced Expiratory Volume (FVC) % predicted 65.7 vs. 76.1 (p=0.006). Lower prebronchodilator FVC% predicted was significant for increased SLTA risk (OR 0.97, 95% CI 0.95–0.99, p=0.022). Number of admissions in the past year were significant risk factors for SLTA (OR 12.80, 95% CI 3.23–50.62, p<0.0001) while number of ED visit in the past year not leading to admission predicted a lower risk of SLTA (OR 0.043, 95% CI 0.008–0.25, p<0.0001). There was no significant difference in biomarkers such as IgE and absolute eosinophil count during the exacerbation between both groups.

Conclusion: A higher number of pack years, lower FVC % predicted and increased admissions in the past year were associated with SLTA in Singapore. Interventions to mitigate some of these factors may help to reduce incidence of SLTA.

P-GLYCOPROTEIN AND MULTIDRUG RESISTANCE-ASSOCIATED PROTEIN-1 IN STEROID RESISTANT ASTHMA

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Background: Asthma is a chronic respiratory disease. Bronchial asthma is the most common chronic diseases occurring in 300 million people and causing an estimated 250.000 deaths annually Glucocorticoid (GCs) are one of the most common and reliable therapy for asthma. In spite of the large clinical use, the benefits of these agents are often reduced by inter-individual variability, and 10–20% of patients do not respond to glucocorticoid. Over expression of P-glycoprotein (P-gp) and Multidrug resistance associated protein 1 (MRP-1) might be responsible for glucocorticoid resistance due to their ability to modulate the pharmacokinetics of glucocorticoid. We aimed to investigate the role of P-gpandMRP-1 in resistance to glucocorticoid. ***Aim:*** To evaluate the expression as well as function of P-gp and MRP-1 in steroid resistant and steroid sensitive bronchial asthma patients. ***Methods:*** After ethical approval, all asthmatic patients who matched the inclusion criteria were recruited. P-gp andMRP-1 (PE-conjugated human anti-P-gp and anti-MRP-1mAb) expression were evaluated on whole blood and functional activity on peripheral blood mononuclear cells (PBMCs) in steroid sensitive asthmatic patients (SS) (n=43, male – 29, mean age=45.19±14.32) and steroid resistant asthmatic patients (SR) (n=19, male 13, mean age=39.15±11.26) patients. SS patients were in sustained remission for at least 6 months without steroids. All definitions are as per the GINA guidelines. P-gp and MRP-1 expression were analyzed by Flow Cytometery. The absolute values were calculated using formula (% of positive cells × Relative Fluorescent Intensity (RFI)), Multi resistance activity factor (MAF) for each transporter, was calculated using formula (MAFMDR1=100× (FMDR1-F0)/FMDR1). All data are expressed as mean±s.d. ***Results***: Among 62 patients, the % of P-gp and MRP-1 positive peripheral blood mononuclear cells were significantly higher in SR as compared to SS (11.07±5.23v/s 5.70±2.97, p<0.001); (17.12±7.10 v/s 7.15±3.83, p<0.001). Absolute P-gp and MRP-1 expression were significantly high in SR (63.01±21.01 v/s 33.51±20.30, p<0.005); (67.04±22.40 v/s 40.19±19.17, p<0.005) respectively. The % of P-gp and MRP-1 positive bronchoalviolar mononuclear cells were significantly higher in SR as compared to SS (13.07±4.5

MANGIFERA INDICA A NEW POLLEN ALLERGEN

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Background: A new pollen allergen was suspected in patients who while receiving allergen immunotherapy showed recurrence of symptoms during the period Jan–March.

Methods: Fifteen patients having various allergic disorders were subjected to skin allergy testing, were found to be sensitive to various allergens and they were on immunotherapy. While on IT they developed recurrent symptoms during Jan–March. To confirm presence of the new allergen, safranin stained glycerin coated slides were exposed in the patients' surroundings with "personal volumetric air sampler". With this "sampler" pollen collection on the slide is much better than simple exposure. Mangifera pollen was recorded in abundance. Antigen of mangifera pollen was tested on all patients and strongly positive reaction was recorded. These patients were subjected to allergen immunotherapy course with mangifera pollen allergen.

Results: Patients who showed positive results with mango pollen allergen and then underwent immunotherapy course with this pollen antigens showed significant improvement in their symptoms during the next pollen season of mangifera indica.

Conclusions: 1) Mangifera Indica pollen could play an important role in nasobronchial allergy. 2) "Air sampler" makes the detection of causative allergen possible & easier when sometimes simple slide exposure may fail.

GASTROINTESTINAL DISORDERS AND PRIMARY ANTIBODY DEFICIENCIES IN ADULT PATIENTS

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Background: The actual prevalence of gastrointestinal diseases in primary immunodeficiency in adults is not defined and whether these patients were purely primary – immunodeficient is not known, but the strong association between these

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two nosology has been demonstrated. Chronic intractable diarrhea in adults can suggest common variable immunodeficiency which is characterized by a host of gastrointestinal lesions that can mimic lymphocytic colitis or other conditions.

Methods: We analyzed 7 adult patients with chronic diarrhea apparent intractable, for which it was finally established Common variable immunodeficiency, based on significant reductions in the immunoglobulins we assigned the diagnosis of common variable immunodeficiency. Colonoscopy and upper GI endoscopy with biopsy were performed.

Results: There were 3 males and 4 females, age at diagnosis ranged from 16 to 42 years. They were suffering from refractory diarrhea unknown etiology for the duration from 3 to 6 years. There were 13.5 episodes of hospital admission during this period. On average, a patient was hospitalized for median 21.3 ± 5.6 days. The main causes of hospitalizations was: prolonged diarrhea with malabsorption, fever, pneumonia. Gastrointestinal patterns in these patients was: the stomachs of 4 of patients showed lymphoid aggregates, 3 patients had a lymphocytic gastritis pattern; helicobacter pylori were found in 3 patients, in one patients was identified gastric MALT-lymphoma. Biopsy for colon showed that 4 patients had a lymphocytic colitis pattern and 2 patients had a pattern for ulcerative colitis.

Conclusion: In any patient suffering from chronic refractory diarrhea unrelated to known causes, could have common variable primary immunodeficiency with clinical manifestations in different periods of life. Lymphocytic colitis or ulcerative colitis can be suspected in patients with primary immunodeficiency.

PHENOTYPING OF EOSINOPHILS IN THE DIAGNOSIS OF ATOPIC ASTHMA

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Background: The level of eosinophils in the blood with allergies increases to 10-20%, which is called "eosinophilia". Eosinophils carry different receptors on their surface, CD23 is a low affinity receptor for IgE. Most IgE is bound to receptors, unrelated – circulates in the blood serum. The purpose of the study eosinophil level bearing $CD23^{+}IgE^{+}$ receptor as well as the possibility of using this indicator in the diagnosis of atopic asthma.

Patients and Methods: 130 children aged 6 to 18 years with atopic bronchial asthma, as well as 40 children of the control group without allergic pathology were examined. In the course of the study, the level of eosinophils bearing the CD23+IgE+ receptor was determined.

Results: The level of eosinophils carrying $CD23^{+}IgE^{+}$ receptor was 62,20% [35,40-76,60%], the absolute level of this indicator was 223,37 cells/mm 105.30-375.24 cells/mm]. The results were significantly higher than those of the control group, where the relative level was 25,45% [14,30-30,60%] ($p < 0.001$), the absolute level was 30,88 cells/mm [25,63-42,84 cells/mm] ($p<0,0001$), and also significantly exceeded the reference values (<40%). The relative level of eosinophils carrying $CD23^{+}IgE^{+}$ receptor exceeded the reference values in 92 (70,77%) children, in this group the relative index is equal to 70,60% [58,25-80,30%], the absolute level was 289.80 cells/mm [172,36-405,31 cells/mm]. Based on the results of the ROC analysis, the characteristic curve of the level of eosinophils bearing the $CD23^{+}IgE^{+}$ receptor was obtained from the presence of atopic bronchial asthma. The optimal "point of separation" for the absolute level of eosinophils carrying $CD23^{+}IgE^{+}$ receptor is 73,008 cells/mm. At this point, the sensitivity is 73,85%, and the specificity is 100%. AUC (the area under the curve) is 0,857, which indicates a high diagnostic efficiency of the model formed.

Conclusion: At the values of eosinophils carrying CD23+IgE+ receptor, 73,008 cells/mm and more are diagnosed with atopic bronchial asthma.

ACUPUNCTURE OF THE DUST SENSITIZATION OF THE ATOPIC FORM OF BRONCHIAL ASTHMA

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Research Objective: Development of new methods of treatment of a dust sensitization of an atopic form of bronchial asthma and introduction in broad out-patient and stationary clinical practice is represented very relevant.

Materials and Methods: Researches of diagnostic and medical character at group of patients with a dust sensitization of an atopic form of bronchial asthma are conducted. To all patients clinical, paraclinical examination and a reflexosodiagnostics was conducted. We have offered, successfully approved and introduced in broad clinical practice new more physiologic, highly effective and economic method of acupuncture. For knocking over of an attack of bronchial asthma and at course treatment usually used the following acupuncture points: E 36; R 5, 6, 7; RP 6; PC 3; F 1, 2; MC 6; P 1, 5, 7, 9; VG 20; R 7; VC 17; GI 4 and others; acupuncture points: AP 12, 13, 14, 15, 16, 51, 55, 71, 72, 78, 82, 95 and others. In the presence at patients of the accompanying pathology in addition included the corresponding symptomatic acupuncture points in a compounding. Sessions of inspection and treatment of patients carried out daily, generally in the morning. During one procedure used from 3 to 8 points of acupuncture. Time of an exposition of acupuncture needles averaged from 30 to 35 minutes.

Results: In the analysis of clinical, paraclinical and reflexological data it is noted that knocking over of an attack of bronchial asthma at most of patients was noted on 1-2 procedure of acupuncture. Completely disappearance of pathological symptomatology by the end of a course of treatment is noted at 78% of patients, improvement – at 20% of patients. 2% of patients had a need for carrying out 1-2 courses of treatment. At the same time regress of pathological symptomatology in control group of patients and improvement of their clinical state happened in later terms of treatment. Holding sessions of acupuncture is carried out aseptical, without serious consequences, is effective, is transferred by patients well. Complications haven't been noted.

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Conclusion: The method of acupuncture corresponds to the medical appointment. Simplicity, high efficiency, convenience in operation and competitiveness allows to use widely it in out-patient, stationary, the extreme, field conditions, emergency situations, in the conditions of medicine of accidents, at medical emergencies and rehabilitation. Further use of acupuncture in treatment of various forms of bronchial asthma is represented perspective.

REHABILITATION OF PATIENTS WITH POST-HERPETIC INTERCOSTAL NEURALGIA BY THE INNOVATIVE SVETERMOPUNKTURNOY METHOD OF REFLEXOTHERAPY

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Research Objective: Rehabilitation of patients with post-herpetic intercostal neuralgia and development of new more effective and convenient innovative methods of reflexotherapy, technical means of their providing and introduction in operation in broad out-patient and stationary clinical practice is represented relevant.

Materials and Methods: Rehabilitation 23 out-patient and inpatients (12 women and 11 men) of a neurologic profile aged from 23 up to 86 years is carried out. The first main group receiving reflexotherapy was made by 12 people (6 women and 6 men) aged from 23 up to 85 years. The second control group receiving standard all-clinical therapy was made by 11 people (5 women and 6 men) aged from 25 up to 86 years. We have offered a method of reflexotherapy the device "Sveterm-1". The device was shown and is awarded Gold and Silver medals on the Moscow international salon of innovations and investments (Russia), at the International exhibitions: in Brussels (Belgium), in Düsseldorf (Germany), in to Orlanda (USA), etc. Used acupuncture points: P 7; GI 4, 10, 11; MC 7; V 13, 40, 60; R 2, 6; F 2, 5; VB 34, 38, 40, 41; E 36, 42, etc.; acupuncture points: AP 13, 28, 29, 42, 51, 55, 78, 100, 101, 108, etc. Results. In the analysis of clinical, paraclinical data and reflexodiagnostics positive dynamics at most of patients was noted on 1-2 procedure of an innovative method of reflexotherapy by the device "Sveterm-1". Frequency of cases of recovery, considerable improvement and improvement is statistically authentically much higher, than in control group of patients and is 94,6% (11,3 + 48,4% + 34,9%). In control group respectively – 70,2% (8,3% + 38,3% + 23,6%).

Conclusion: Use of a new innovative method of reflexotherapy the device "Sveterm-1" is highly effective in rehabilitation of patients with post-herpetic intercostal neuralgia. Carrying out further domestic fundamental developments and introduction in broad practice of domestic and foreign health care of these new, highly effective, innovative and priority hardware medical technologies is advisable.

THE EFFECT OF OZONE THERAPY IN ATOPIC DERMATITIS IN CHILDREN OF DIFFERENT AGES

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We observed 333 children aged 8 months to 15 years with a common moderate (194 patients) and severe (139 patients) atopic dermatitis. The first groups of patients with infant, child and adolescent forms of atopic dermatitis (78, 68 and 31 patients) received therapy, and the second group of patients with infant, child and adolescent forms of atopic dermatitis (62, 63 and 31 patients) received standard treatment in combination with two courses of ozonotherapy. The course of ozonotherapy in patients with atopic dermatitis consisted of applying ozonized olive oil to the affected skin areas (2 times a day for 15 days) and rectal insufflation of the ozone-oxygen mixture (every other day, 8 sessions in total). The first course of ozonotherapy was started with a patient with atopic dermatitis from 1 to 2 days of observation, and the second course of ozonotherapy was performed 3 months after the completion of the first course. It was established that in the second groups of patients with infant, child and adolescent forms of atopic dermatitis who received standard treatment in combination with ozonotherapy, the onset of clinical remission occurred on average 3.7-5.5 days earlier, and the duration of clinical remission was on average in 2,4-7,0 times more than in the first groups of patients with infant, child and adolescent forms of atopic dermatitis, who received complex standard therapy. Processing of the material by the method of dispersion analysis showed that the share of the influence of the complex treatment factor in combination with ozonotherapy on the duration of clinical remission in patients with infant, child and adolescent forms of atopic dermatitis was 76.4% ($p < 0.01$), 70.2% ($p < 0.01$), 68.5% ($p < 0.01$). The results of the studies testify to the high therapeutic and anti-relapse effects of complex treatment in combination with ozonotherapy with moderate to severe atopic dermatitis in children of different ages.

REMODELING OF PHENOTYPE CD16^{+}CD11B^{+} NEUTROPHILIC GRANULOCYTES IN ACUTE EPSTEIN-BARR VIRAL INFECTION

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Neutrophilic granulocytes (NG) – the very important cells of the innate and adaptive immune system, involving in the incredibly quick implementation of antiviral defense and protection. Comparative analysis of the level of intensity of the expression of molecules CD16 and CD11b on the membrane NG revealed three distinct subpopulations in the population of CD16^{+}CD11b^{+}NG: CD16^{bright}CD11b^{dim}, CD16^{dim}CD11b^{dim}, CD16^{bright}CD11b^{dim} in healthy subjects and three distinct subpopulations – CD16^{+}CD11b^{+}NG: CD16^{bright}CD11b^{bright}, CD16^{bright}CD11b^{dim}, CD16^{bright}CD11b^{dim} in patients with severe

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acute Epstein- Barr viral (EBV) infection. It was found, that in healthy individuals prevails $CD16^{bright}CD11b^{dim}$NG subpopulation, in patients with severe acute Epstein- Barr viral infection subpopulation $CD16^{bright}$CD11bbrighNG dominates. We propose, that the high levels of expression of CD16 and CD11b was necessary for realization of antiviral activities of NG in defense against EBV infection. Remodeling of the NG phenotype $CD16^{+}CD11b^{+}$N into subpopulation $CD16^{bright}CD11b^{bright}$NG was appeared in severe acute EBV infection in comparison with healthy individuals who didn't have subpopulation $CD16^{bright}CD11b^{bright}$NG. Subpopulation $CD16^{bright}CD11b^{bright}$NG, detecting in severe acute EBV infection, had features of a high cytotoxiety ($CD16^{bright}$) and suppressive influences ($CD11b^{bright}$). Further studies are needed to determine the functional roles of the subpopulation $CD16^{bright}CD11b^{bright}$NG in severe acute EBV infection as well as to study potency of the target immunomodulating influences for positive transformation this phenotype NG with the purpose of prevention of an emergence of bacterial complications.

MONITORING THE EFFICACY OF TREATMENT IN CHILDREN WITH RISK OF ASTHMA

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Asthma is the most common chronic disease of childhood throughout the world including Georgia. The tendency of substantial increase of its prevalence and severe progression is being mentioned. Prevention of the disease, as well as effective diagnostic and treatment methods have great importance for managing this problem. The modern approaches in the prevention and treatment of asthma are delivered by GINA, "Global Strategy for Asthma Management and Prevention". The main recommendations of this initiative have already been using in different countries with consideration of national peculiarities. Using leukotriene inhibitors during obstruction of respiratory system is one of the main recommendations of the project. The cysteinyl leukotrienes, LTC4, LTD4, and LTE4, play an integral role in pathophysiology of asthma. The unique mechanism of leukotriene receptor antagonists (LTRA) action results in a combination of both bronchodilator and anti-inflammatory effects. Considering the fact that optimal place of these drugs in asthma management is still under review, our work implies the monitoring of effectiveness of treatment with Montelukast, as one of the leukotrien receptor antagonist.

AUTHOR INDEX

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