

ALLERGOLOGY IMMUNOLOGY DERMATOLOGY



New Approaches

Collection of Research Papers

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Collection of Research Papers on application of Enterosgel. 1st English edition: Allergology, Immunology, Dermatology, June 2013, Prague

Extensive clinical experience on the use of the innovative intestinal adsorbent Enterosgel has been accumulated over the past 20 years. Enterosgel provides a wide range of the therapeutic effectiveness due to its ability to bind toxins, harmful substances, pathogens and allergens in the gastrointestinal tract and eliminate these from the body.

This collection of research papers presents study results of the application of Enterosgel in allergology, immunology and dermatology. Enterosgel was shown to be an effective treatment for asthma, dermal-respiratory syndrome, food allergy, urticaria, atopic dermatitis, acne vulgaris.

It is our hope that this collection of papers will serve both for education and as a tool for students, physicians and practitioners in this field and as for discussion. The key issues of gastrointestinal adsorption (enterosorption) in clinical practise addressed in this book can be relevant to all physicians, regardless of specialty or practice setting.

All the clinical studies were conducted in compliance with the Declaration of Helsinki.

Originals of the research papers have been adapted for translation into English.

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According to the data published by the World Allergy Organization, the prevalence of allergic diseases worldwide is rising. This increase is particularly sharp in children. Due to ever more severe clinical course, the impact on concomitant conditions and a significant decrease in patients' quality of life, allergic diseases are becoming a serious health issue.

We discussed the methods for fighting allergies with a specialist in this field, doc. MUDr. Jaromir Bystron, CSc. Dr. Jaromir Bystron is a member of the Czech Allergy and Clinical Immunology Society committee (CSAKI) and held the

position of Vice President for two terms. In 2012 he was awarded Honorary CSAKI Membership. He has authored or co-authored 6 monographs and more than 150 publications in foreign and national press.

Dr. Bystron, please tell a few words about yourself. You are an allergologist – what made you chose this specialization? What, or who, inspired you to do so?

My choice was very prosaic. After graduating from the Faculty of Medicine of Palacký University I started working at the Pediatric Department at Havířov Hospital, where, after a time, the Senior Physician of the department decided that I should broaden my knowledge of allergology and sent me to Prague for an internship with Professor Špičák. Under his guidance I spent a wonderful 6 weeks in Prague, I got to like the specialization and dedicated myself to it ever since. That was in 1980. A few years later I worked as a fellow at the Allergology Department of the Olomouc University Hospital under Associate Professor Malota; this was another milestone in my professional life, and the field of allergology and clinical immunology has been a part of my life ever since.

Do you specialize in any particular type of allergic pathology?

I do not strictly specialize in one type of allergy. I practice and teach allergology and clinical immunology in its full scope, although I am rather interested in the possibilities of immunomodulation therapy, especially in the use of immunomodulators of bacterial origin.

Every country provides guidance to physicians in the form of national guidelines for the management of allergies. Have you been involved in the drafting of the document?

“Indications for physicians” (now called guidelines in the modern terminology, and usually based on international consensus – such as GINA – Global Initiative for Asthma, or ARIA – recommendations for diagnosis and management of allergic rhinitis) are a relatively recent development; previously we relied mostly on publications and

books by leading specialists in the field which provided certain guidance in treatment. In 1997 I published a book titled ALLERGIES – a Guide to Allergic Diseases for Physicians and Patients (Mirago publishing, Ostrava), with 4 000 copies, which became very popular both with allergologists and with physicians of other specializations because it was written in a very straightforward way, and for quite some time it was used as a textbook by physicians preparing for postgraduate certification in allergology and clinical immunology. Then, in 2004, the first comprehensive Czech textbook by a group of authors titled ALLERGOLOGY was published (Galén publishing, Prague). I contributed to its content by writing several chapters.

A growing number of allergologists agree today that a food allergy may provide an impulse towards the development of atopic march and anaphylaxis. Can you briefly tell us about your approach in the treatment of food allergies?

Food allergies are no different from other types of allergies. The main therapeutic strategy is to identify the causal allergen and then try to eliminate it. If it cannot be entirely eliminated, then we should seek a treatment that would significantly alleviate the allergic inflammation triggered by the causal allergen, or induce tolerance to that allergen.

Is it possible to intervene at the very beginning of the disease and mitigate the discomfort or even prevent food allergy from developing?

Yes, it is possible, mainly by early introduction of different types of food to an

infant's diet. If the baby gets to try various kinds of food at the right time, it will develop tolerance to it and allergic inflammation is prevented. Later in life emphasis should be placed on the care for proper functioning of the digestive system.

Now allergologists are considering experimental treatment of food allergies with the use of Oral Immunotherapy Treatment (OIT). We would be interested in knowing your opinion on this issue.

Yes, but again, this is extinguishing a burning fire that did not have to start in the first place. For that reason we prefer to place the emphasis on prevention of food allergies, consisting in the introduction of complementary foods (almost all common types of food) in children 4 to 6 months old to complement full breastfeeding. This helps the infant to build immune tolerance to such food. If the food is first introduced when the child is older, it is more likely to develop an allergy. Simply put, we are going back to our grandmothers' wisdom.

In Ayurvedic medicine, asthma does not start in the lungs but in the digestive system. How much do you share that opinion?

In the human body, all systems are equal and, in terms of immunity, delicately balanced. This is true in particular of the digestive and the respiratory system which represent a natural barrier between the external and the internal environment. This barrier (mucosa and submucosal connective tissue) is densely populated with immune system cells which recognize risks coming from the external environment

and are able to respond to those risks with the defensive action of an inflammatory response or by developing tolerance. Where those mechanisms fail (for various reasons), a harmful inflammation develops, together with symptoms of the disease. In this perspective, bronchial asthma is caused mainly by interaction between congenital properties of the bronchial and lung tissue and the external environment. Bearing in mind the vast changes in the external environment that have occurred in the last decades, we must admit that this is a very complex phenomenon which is not primarily caused by just one impairment of one system. Industrialization accompanied by pollution of the environment, increase in combustion engine emissions, smoking at home, children lacking physical activity in the fresh air, time spent in large groups of people where viral and bacterial infections are easily spread and which we then power through and do not treat properly, excessive use of antibiotics and other medications, increased content of chemical substances in food and in our homes and a number of other factors damage the protective barriers in the respiratory and the digestive system, impairing control of the defence mechanisms, which contributes to the development of allergic diseases.

Dr. Bystron, in your opinion, can the application of intestinal adsorbents (enterosorption) be useful in maintaining the internal ecology?

In the comprehensive treatment of various allergic diseases it is highly desirable to detoxify the intestinal tract and norma-

lise the intestinal microflora. Reduction of intoxication, restoration of mucosal barrier function and re-establishing of the natural intestinal microflora are the main goals of enterosorption treatment. Enterosorbents are medical products that can irreversibly bind toxic substances in the intestines, prevent or alleviate irritation of the intestinal mucous membrane, and prevent passing of toxic substances through intestinal mucosa into the bloodstream, thereby reducing the overall concentration of such substances in the body. The intensity of adsorption of toxic substances and thus their level in the body is directly dependent on the functional state of the intestinal mucous membrane. The success of enterosorption is dependent on the ability of the enterosorbent to renew the role of the intestinal mucous membrane as a protective barrier.

You have carried out a clinical study in order to evaluate the efficacy of gastro-intestinal adsorption (enterosorption) in the treatment of patients with allergic diseases. Your choice of Enterosgel adsorbent was not random in this case?

No, the choice was not random. I was approached by representatives of the company distributing Enterosgel in the Czech Republic who asked me whether I would be interested in trying its effects, which were being verified in the country where Enterosgel had been developed – Russia, in patients with allergies. I proposed an open pilot study which was performed at our department and we were pleasantly surprised with the results. We verified that these comprehensive requirements are met by Enterosgel. It is a next-generation adsorbent

with a high sorption capacity, a protective effect on the intestinal mucous membrane and a positive influence on the intestinal microflora. I then shared those findings with other professionals by publishing the study results in our specialized journals and at professional events.

It is a known fact that effective allergy treatment regimens include 3 or 4 preparations from different medication classes, creating a medication / toxic burden for the body. In addition to that, the treatment course can be rather expensive. What other aspects of allergy management are being overlooked by the physicians? Other than medications?

As I have already mentioned, the basis of allergy management consists first and foremost of the identification of the causal allergen and the effort aimed at its elimination. Only where this not possible we turn to medication therapy which should be based on the principle of using the lowest possible number of medications and administered amounts, while ensuring optimal effect. Furthermore, the treatment should be comprehensive, i.e. it should include appropriate diet and nutrition, ample regeneration, sleep, exercise. A failure to adhere to these principles will limit the effects of any treatment (including phytotherapy, acupuncture, homeopathy). In case of alternative treatments and dietary supplements it is important to see whether they in fact have a proven effect, confirmed by independent clinical studies, whether preparations sold under a certain name do indeed have the right composition and

dosage, possibly confirmed by studies. Not every dietary supplement is suitable for every patient (e.g. some herbal preparations in phytotherapy can cause substantial harm to some allergy patients while helping others).

What are, in your opinion, the most valuable and the most promising advances in allergology in the recent years?

The most important success in allergology was the discovery and subsequent refining and introduction of corticosteroids in the treatment of allergic diseases. These are life-saving drugs for severe allergic conditions, while their systemic use substantially mitigates severe allergies. Their local administration (for inhalation in the respiratory tract or as skin ointments or creams) has completely changed the severe manifestations of bronchial asthma or eczema. Bronchial asthma has become an out-patient condition with minimal need for in-patient treatment of patients who can fully dedicate themselves to work or leisure activities. Another major success was the introduction of standardized allergen immunotherapy for certain allergic diseases, and the development of biological treatment (monoclonal antibodies against specifically defined targets in the impaired process of immune response) also seems promising. Hopefully, we are also starting to see efforts to preserve and improve the environment and to maintain a healthy lifestyle which could put a stop to the growing number of the diseases of civilization – but that goal is still a way off. Most people still prefer to simply pop a pill to get better, instead of making an effort themselves.

What do you like to do in your leisure time? Do you have any hobbies?

I have many hobbies. I love sports, trekking, gardening, I like music, theatre, I enjoy spending time with my family and friends and, naturally, I love my profession of physician and teacher.

Do you have a lesson or a piece of advice for students and young specialists?

In my life, a couple of catchphrases proved to be valid:

1. Frequent things are the ones that happen most frequently.

2. All complicated things are in fact simple – it is just complicated to find out.

Is there a rule or a motto that you follow in your profession and which helps you in your work? If so, would you be so kind to share it with the readers?

It may seem naïve or outdated today, but I still believe that success comes through hard and honest work, or at least personal satisfaction does.

The Interview was prepared by Olga Volovik

MINI REVIEW

The Detoxifying Potential and Clinical Effectiveness of the Enterosorbent Enterosgel in the Combination Therapy of Various Diseases in Children and Adults

N. V. Nagornaya, A. V. Dubovaya

Donetsk National Medical University named after M. Gorky, Ukraine

Zdorove rebenka [Child health]. 2010;3:65–70 (in Russian)

Abstract

The article describes different types of intoxication, presents a method of intracorporeal detoxification, and includes a classification of gastrointestinal adsorbents (enterosorbents). It summarizes the experience that has been gained with the intestinal adsorbent Enterosgel in the combination therapy of children and adults suffering from allergic diseases, gastrointestinal disorders, burn disease, chronic pyelonephritis, and recurrent non-specific vaginitis.

Keywords: adsorbent, allergy, asthma, atopic dermatitis, detoxification, diarrhea, intoxication, burn disease, endotoxin, enterosorbent, Enterosgel

The development and progression of intoxication is an integral process accompanied by accumulation of toxic substances of exogenous and / or endogenous origin in the bloodstream [5, 8]. Toxins are substances that damage cells [25].

Exogenous compounds that are foreign to the human body (heavy metals, pesticides, household chemicals, preservatives, etc.) and may cause harm to human health when digested are termed xenobiotics [24]. Nature and severity of exogenous intoxication depends on the properties and concentration of the xenobiotic entering the body [7]. Xenobiotics are included in metabolic processes and cause metabolic disorders, which in their turn lead to membrane damage, dystrophy, apoptosis, and cell necrosis [25].

Endogenous intoxication is caused by endogenous toxic substances, i.e. excessive products of normal metabolism and abnormal products of metabolism and cell response. Depending on the mechanism underlying their accumulation, four types of endogenous intoxication are distinguished [1, 7]:

- productive intoxication (excessive production of endogenous toxins);
- retentive intoxication (retarded elimination of endogenous toxins);
- resorptive intoxication (increased resorption of endogenous toxins from a certain site, such as in parietic gut);
- infectious intoxication.

According to G. P. Kozinets et al., toxins accumulating in the blood may have differently sized molecules, depending on the

etiological and pathogenetic mechanisms of the disease [8]. As a result of metabolic disorders, toxins with molecules < 10 nm accumulate. Bacterial and exogenous toxins have molecules measuring 10–200 nm. Toxins with molecules > 200 nm in diameter accumulate as a result of resorptive disturbances. Apart from the direct damage inflicted on the cells, toxins can have mediated effects resulting from their ability to trigger autoimmune reactions [25].

The functional system of detoxification (FSD) is composed of the lungs, liver, intestines, kidneys, and other organs responsible for dilution and mobilization of toxins, as well as their biotransformation and elimination [7]. An acute impact of endogenous toxins always results in a specific response at the organ and system levels, acute endotoxicosis [8].

The development of endotoxemia is associated with FSD failure, generalized impairment of blood rheology, and altered immune responsiveness, which necessitates maintenance and replacement of suffering FSD elements by means of active detoxification [25].

There are two groups of active detoxification methods [25]:

1. *Intracorporeal methods* that augment the elimination effects of the FSD (forced diuresis, gastrointestinal adsorption, device-assisted or monitoring large intestinal purification, peritoneal dialysis, intestinal lavage, etc.).
2. *Extracorporeal methods* are capable of ensuring dilution and immobilization of toxic substances, their biotransformation, and intensified excretion through mass exchange devices (adsorption of

blood, plasma, lymph, and cerebrospinal fluid, blood oxygenation, blood ozonation, plasmapheresis, haemodialysis, blood filtration, etc.).

Gastrointestinal sorption (enterosorption) means therapeutic or prophylactic use of sorbents capable of binding metabolites, toxins, and other deleterious substances in the gastrointestinal tract and eliminating them from the body [24]. Sorbents may bind toxic substances by way of adsorption, absorption, ion exchange, and complex formation.

V. G. Nikolaev distinguished the following principal mechanisms of action of gastrointestinal sorbents [14, 15]:

- adsorption of toxic substances entering the gastrointestinal tract from outside the body;
- adsorption of toxins entering the intestinal lumen from the blood by diffusion;
- binding of toxic substances secreted with the digestive juices;
- adsorption of toxic substances produced in the gastrointestinal tract (indole, skatole, etc.);
- sorptive modification of diet through selective adsorption of amino acids and free bile acids;
- fixation and transfer of physiologically active substances (enzymes, bile acids, etc.);
- change in the volume of undigested dietary fibers;
- catalytic action.

Additional mechanisms of action of gastrointestinal sorbents are [14]:

- obducing and cytoprotective effects;

- improvement in the structure of intestinal contents;
- formation of aggregates and flocculates containing microorganisms and viruses;
- direct bactericidal activity;
- complex formation and chelation;
- modification of the chemical composition of intestinal contents (creating an environment unfavourable for proliferation of pathogenic flora).

No conventional classification of oral sorbents is currently available. V. G. Nikolaev divided oral sorbents into a number of groups by chemical structure [14, 15]:

- carbon sorbents of generations I–IV;
- sorbents based on natural and synthetic resins, synthetic polymers, and indigestible lipids;
- silicon-containing sorbents, including silicone sorbents, aerosils, and clays;
- natural organic sorbents based on dietary fibers, hydrolysis lignin, chitin, pectin, and alginates;
- combined sorbents, which may include two or more types of the above enterosorbents.

A widely preferred gastrointestinal sorbent option is Enterosgel [polymethylsiloxane polyhydrate (methylsilicic acid hydrogel)], which has a number of advantages over other sorbents. Numerous studies have demonstrated its high efficacy and effectiveness, selectivity of adsorption (as it binds and eliminates only toxic metabolites and pathogenic microflora), and safety [3, 4, 6, 10–12, 14–19, 22, 23].

Enterosgel is an organosilicon adsorbent designed to eliminate toxic substances from

the body, correct intestinal microbiota, and restore epithelium in the gastrointestinal mucous membrane [1]. The drug demonstrates a high biocompatibility profile.

The sorptive and detoxifying properties of Enterosgel are a result of its porous globular structure that predominantly includes medium-sized pores (mesopores), which allows to bind and eliminate toxins with a molecular weight of 70–1000 Da, toxic products of proteins, bilirubin, cholesterol, urea, and creatinine [21]. It has been proven that Enterosgel does not bind or eliminate micronutrients and other essential substances [3, 12, 13, 16, 22, 23].

The bactericidal properties of the adsorbent Enterosgel are due to its ability to bind and eliminate pathogenic microorganisms and their products or debris from the gastrointestinal tract and other ecological niches (when the product is administered). Adhesion involves Gram-positive and Gram-negative microorganisms, *Candida* fungi, and viruses (rotaviruses and some others) [6, 12]. Enterosgel does not inhibit intestinal saprophytic microflora (lactobacilli, bifidobacteria, etc.) [4, 11, 17, 19].

As a result of adsorption of substances that irritate the mucous membrane (exogenous and endogenous pathogenic microflora, toxic metabolites), as well as the obducing and regenerative effects, Enterosgel helps recover mucous membranes [11, 19]. Enterosgel augments the immune protection provided by the epithelial barrier of the intestinal mucous membrane, which is manifested by elevated concentrations of IgA responsible for local immunity and preventing mucous lining from being invaded by microorganisms [4, 12, 17].

Enterosgel suppresses endotoxin aggression through binding endotoxins of Gram-negative bacteria [13, 16]. Endotoxin excesses present in the human body are known to complicate the course of many pathological processes [3].

A number of studies that have been conducted in recent years in Ukraine and other CIS member countries have demonstrated that Enterosgel can be successfully used in the combination treatment of various diseases, both in adults and in children.

A study by O. I. Lasycja et al. assessed the effectiveness of Enterosgel therapy in the treatment of allergic diseases given together with conventional therapy. The study included 99 children aged from 4 months to 14 years who suffered from bronchial asthma, atopic dermatitis, recurrent urticaria, and angioneurotic oedema [9]. The administration of Enterosgel resulted in faster reduction of dermal-respiratory syndrome: rash elements were improved by the 3rd or 4th day of therapy and angioneurotic oedema was relieved by the 2nd or 3rd day in 75% of the patients. At the same time, the improvements observed in dermal-respiratory syndrome in control group patients were less significant and were only observed in 22% of these patients.

A. A. Baranov et al. evaluated the efficacy of Enterosgel in the treatment of bronchial asthma and atopic dermatitis in children aged from 2.5 to 13 years [2]. All study subjects were administered broncholytic therapy. The children with severe bronchial asthma received inhaled corticosteroids, while the others were given cromoglicic acid. The experimental group subjects were given Enterosgel for 14 days as part of their combi-

nation treatment programme. An improvement occurred as soon as on the 3rd day of Enterosgel therapy: there were no more episodes of choking sensations, manifestations of the skin syndrome had been reduced, and gastrointestinal function had improved. The obstructive syndrome was eliminated by the 5th day of treatment in 50% of the patients, whereas respiratory function recovered by the 14th day of treatment. The children with atopic dermatitis presented with considerable improvements in the skin syndrome by the 5th day of treatment, while a complete remission was observed on treatment day 10 in 85% of subjects. Adolescent patients presented with significantly improved acne vulgaris rash. A clinical improvement was generally achieved in the Enterosgel group 7 to 10 days earlier than in the control group. No adverse drug reactions were observed in the patients on Enterosgel therapy.

A publication by O. Yu. Poberezhnik et al. presented data on the use of Enterosgel in the treatment of allergic skin diseases [20]. The authors recruited 140 patients with acute eczema and acute allergic dermatitis. Rash was generalized in 60% of the patients and localized in 40% of them. All patients were divided into two groups: an experimental group (standard therapy + Enterosgel) and a control one (standard therapy). The patients in the experimental group had faster elimination of fresh skin rash elements, immune status normalization, and blood chemistry improvement, as compared with controls.

I. V. Maev et al. investigated the effectiveness of Enterosgel in the treatment of gastrointestinal diseases accompanied by

a chronic diarrhea syndrome in the adult patients [11]. They established a high clinical effectiveness of the intestinal adsorbent Enterosgel in this patient population, its favourable effects on the intestinal mucous membrane, digestion and adsorption, as well as intestinal microbiota. An immunomodulating effect was detected. No adverse drug reactions were observed.

V. N. Chernobrovyi and I. G. Paliy evaluated the potential of Enterosgel therapy in the treatment of large intestinal dysbiosis in the adult patients [4]. Fecal microbiology revealed intestinal dysbiosis in all study subjects: increased counts of *E. coli haemolyticus* and cocci, as well as positive tests for *Klebsiella pneumoniae*, *S. aureus*, and *P. vulgaris*. Clinical manifestations of large intestinal dysbiosis included abdominal flatulence, constipation, diarrhea, alternation of constipation and diarrhea, and periodic abdominal pain. The experimental group patients received conventional basic therapy (diet therapy, vitamin therapy, probiotics) and the intestinal adsorbent Enterosgel. Improvement and elimination of clinical symptoms occurred by the 4th or 5th day of therapy in 98% of the experimental group patients. Intestinal microbiota returned to normal in 100% of the patients after the treatment course, as demonstrated by microbiological examination.

A. B. Petukhov et al. investigated the effectiveness of Enterosgel in the treatment of gastrointestinal diseases associated with indigestion and impaired absorption [19]. This trial enrolled adult patients with malabsorption syndrome, post-gastric resection syndrome, disorders following small intestinal resection and right-side hemicolectomy,

as well as patients with irritable bowel syndrome. In the experimental group, patients were given Enterosgel for 21 days along with conventional treatment. Controls received conventional therapy only. The experimental group patients reported a subjective improvement as early as in 3 days in 85.7% of cases. In 10 to 12 days, all patients administered Enterosgel had normalized stool frequency, a trend towards better formed feces, and no more pain or dyspepsia; there were also coprogram improvements and favourable changes in the large intestinal microflora composition. In the control group, improvements began after 18 to 20 days of treatment. Additionally, the experimental group patients had decreased total bilirubin, cholesterol, urea, and uric acid concentrations; as well as normalized antioxidant index as a result of elimination of free radical oxidation products. Endoscopic and morphological-functional examinations conducted in the patients given Enterosgel revealed increased mucous membrane thickness and longer intestinal villi along with more shallow intestinal crypts, less oedema, less pronounced microscopic haemorrhages and lymphocytic infiltration of the epithelium, as well as increased amounts of plasmacytes in the lamina propria of the mucous membrane. No adverse drug reactions were observed in the patients treated with Enterosgel.

A. I. Mosunov et al. investigated the effectiveness of Enterosgel in the treatment of liver diseases [12]. The duration of Enterosgel therapy ranged from 12 days (in acute toxic hepatitis) to 3 months (in active viral liver cirrhosis). The study results demonstrated that the inclusion of the intestinal adsorbent

Enterosgel in the treatment programme promoted acceleration of clinical improvement and favourable effects on lipid, enzymatic, and nitrogen metabolism, on the state of cytolysis, and on mesenchymal inflammation. According to these authors, gastrointestinal sorption achieved with Enterosgel helps accelerate liver tissue repair thanks to elimination of toxic metabolites from the body and alleviating toxic and metabolic burden on hepatocytes.

A. M. Boyarskaya et al. assessed the effectiveness of Enterosgel in the treatment of intestinal dysbiosis in children with burn disease [3]. They examined 68 children aged from 1 year to 7 years. All subjects had suffered extensive burns associated with increased risk of wound contamination with pathogenic microflora, including Gram-negative microorganisms. The rich vascular network of the skin and soft tissues was responsible for the early manifestations of burn-associated toxemia. Enterosgel was administered to the experimental group patients as part of a combination therapy programme. Detoxification therapy with Enterosgel allowed to restore anaerobic resident intestinal microflora in 20–40% patients and aerobic and facultative aerobic in 40–60% patients. Antagonism was regained against a whole range of intestinal infection pathogens and viruses. Use of Enterosgel in the patients with burn-associated intoxication significantly decreases cytolytic activity of autologous serum and the content of middle-molecular-weight compounds, helping preserve function of phagocytosing cells at a subcompensated level, and relieves toxic burden on immunocompetent cells. Intestinal sorption decreases the

content of auto-aggression factors: activity of autoimmune reactions becomes decreased both because of antagonism of the stimulating activity of the autologous serum and due to auto-sensitization of lymphocytes [16].

B. S. Sheiman et al. demonstrated the effectiveness of Enterosgel in the treatment of children with pyelonephritis. They established that the inclusion of Enterosgel in a conventional treatment programme promoted normalization of plasma toxicometry parameters. Patients treated with Enterosgel presented with a significant reduction in the number of middle-weight molecules and decreased toxicity of these molecules (free and protein-bound in the blood circulation), as compared with the control group. The marked detoxifying activity of Enterosgel implies that it should be used in the combination therapy of inflammatory and suppurative-septic conditions [21].

L. N. Ilenko and E. V. Ivanova conducted the study of the efficacy of oral and topical application of Enterosgel in the treatment of recurrent non-specific vaginitis [6]. Use of the intestinal adsorbent Enterosgel was demonstrated to significantly boost the efficacy of administered therapy of non-specific vaginitis: the clinical effect and recovery of normal vaginal and intestinal microflora were achieved more rapidly, while the risk of disease recurrence was considerably reduced. The most effective approach is the combination treatment of this condition: administration of oral and intravaginal Enterosgel therapy combined with probiotics and immunomodulators, alongside conventional antibacterial therapy.

CONCLUSIONS

In conclusion, gastrointestinal detoxification (enterosorption) has to be included in the combination therapy of allergic diseases, gastrointestinal disorders, burn disease, chronic pyelonephritis, and recurrent forms of non-specific vaginitis. The adsorbent Enterosgel is an effective and safe detoxifying agent. As a result of the selective adsorption of toxic metabolites and pathogenic microflora exerted by Enterosgel, the patients proceed to have a significantly improved intestinal mucosa state; normalized digestion, intestinal microbiota, gastrointestinal tract and immune system functions; thus benefiting from faster elimination of clinical symptoms and improved prognosis.

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Correction of Systemic Endotoxemia in Children with Atopic Dermatitis

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Abstract

This controlled study has demonstrated that the plasma endotoxin levels in the children with atopic dermatitis is statistically significantly greater (up to 0.140 ± 0.071 EU/ml) than in the healthy children (0.0024 ± 0.001 EU/ml, $p < 0.001$). The plasma endotoxin level depends on the stage of disease, severity and activity of skin process. The presence of systemic endotoxemia upon atopic dermatitis is the indication for performing detoxification by method of gastrointestinal adsorption (enterosorption). Combination therapy with application of intestinal adsorbent Enterosgel results in 1.6-fold reduction of the exacerbation time (from 20 to 12 days), 5-fold decrease in the SCORAD index and decrease in the plasma endotoxin level.

Keywords: adsorbent, atopic dermatitis, endotoxemia, endotoxin, enterosorption, Enterosgel

INTRODUCTION

The endotoxin is a biologically active compound containing the cell membrane lipopolysaccharide from Gram-negative bacteria. The endotoxin is released when Gram-negative bacteria are destroyed inside the human gut. In physiological conditions, most of the endotoxin is eliminated from the intestines with feces, while the remaining part crosses the blood-gut barrier and reaches the systemic bloodstream. The endotoxin is detoxified in the liver. Its presence in the systemic bloodstream is called “systemic endotoxemia”, which is one of the factors of antigenic stimulation of the immune system. As healthy individuals have been shown to have detectable endotoxin levels, endotoxemia may be physiological.

Systemic endotoxemia develops as a result of the function of intestinal microbiota, impaired permeability of the small intestinal mucous membrane, pancreatic and biliary insufficiency, depression of the hepatic barrier, decreased portal blood flow intensity, etc. [5].

Normally, anti-endotoxin antibodies are produced in response to endotoxemia. Children with significant endotoxemia have decreased levels of anti-endotoxin antibodies, which reflects deteriorating adaptive capacity and body resistance [1, 3, 4]. It has also been demonstrated that this condition is accompanied by cell hypoxia, abnormal metabolic processes, activation of the sympathetic nervous system and the complement system, thus resulting in leukocyte lysis and platelet

aggregation with subsequent release of biologically active substances (kinins, histamine, serotonin).

Endotoxin aggression results from the massive release of endotoxins into the bloodstream against a background of deficient eliminating systems. Endotoxin excesses released into the bloodstream over a long time lead to mobilization, and then breakdown, of the reserves of the adaptive systems and may also result in transient insufficiency of multiple organs regardless of age. Endotoxin aggression is regarded as a universal mechanism participating in the pathogenesis of the majority of infectious and non-infectious diseases [6].

All of the above led us to presume a possible presence of systemic endotoxemia and endotoxin aggression in children with atopic dermatitis.

The presence of systemic endotoxemia syndrome is an indication for use of intestinal adsorption and inclusion of drugs with sorptive, detoxifying, and cytoprotective activities, as well as those with a favourable effect on intestinal microflora, in combination anti-allergy treatment regimens for patients with atopic dermatitis [2]. Enterosgel is such a medicinal product that exhibits a complex mechanism of action.

This study was conducted with the aim to determine the effect of plasma endotoxin concentrations on immune status markers in children with atopic dermatitis, as well as to evaluate the clinical effectiveness of the new-generation intestinal adsorbent Enterosgel in the treatment of atopic dermatitis.

MATERIALS AND METHODS

We followed up 50 children aged from 10 to 17 years. To determine both plasma endotoxin concentrations and their relationship with immune status markers, the children were divided into two groups: Group 1 comprised 30 children suffering from atopic dermatitis, while Group 2 composed 20 healthy children.

Group 1 (n = 30) had 43% of boys (n = 13) and 57% of girls (n = 17); 50% of the children (n = 15) were aged from 10 to 12 years and 50% (n = 15) were aged from 13 to 17 years. The children with erythematous-squamous atopic dermatitis with lichenification comprised 40% of the patients (n = 12), and those with the lichenoid form of atopic dermatitis 60% (n = 18). The skin process was in the second grade of activity in 40% (n = 12) of the children, and in the third grade in 60% (n = 18) of them.

Moderate atopic dermatitis was observed in 67% (n = 20) of the patients, and severe dermatitis in 33% (n = 10). All children complained of pruritus, rash, and skin dryness. Elevated total serum IgE concentrations were observed in 67% of the children (n = 20). 50% of the children had total serum IgE levels that were many times above normal, and 16% presented with insignificant elevations.

Among the children with increased total serum IgE levels (n = 20), levels up to 300 IU/ml were found in 15% (n = 3), and those above 500 IU/ml in 85% (n = 17) of them.

Specific serum IgE to food allergens was detected in 60% of the children (n = 18), that to indoor allergens in 13% (n = 4), and that to pollen allergens in 16% (n = 5).

70% (n = 21) of the patients were sensitized to all the three allergen groups.

Group 2 consisted of 40% of boys (n = 8) and 60% of girls (n = 12); 50% of the children (n = 10) were aged from 10 to 12 years and 50% (n = 10) were aged from 13 to 17 years.

To evaluate the effectiveness of method of gastrointestinal adsorption (enterosorption) with Enterosgel, the patients with atopic dermatitis (n = 30) were divided into two groups. The experimental group consisted of 16 children who received the oral adsorbent Enterosgel along with conventional anti-allergy therapy. Enterosgel was administered at the age-matched doses: 2 teaspoons 3 times a day (30 g/day) for the children aged under 14 years and 1 tablespoon 3 times a day (45 g/day) for the children aged over 14 years of age – over a 2-week course. The reference (control) group included 14 children who were administered conventional anti-allergy therapy alone (hypoallergenic diet, antihistamine medication, topical anti-

-inflammatory treatment, and therapeutic and cosmetic skin care).

Endotoxin was determined according to Levin J. and Bang F. B in an LAL (Limulus Amebocyte Lysate) test according to the instructions of the manufacturer, Sigma (USA). Results were expressed in international endotoxin units (EU/ml).

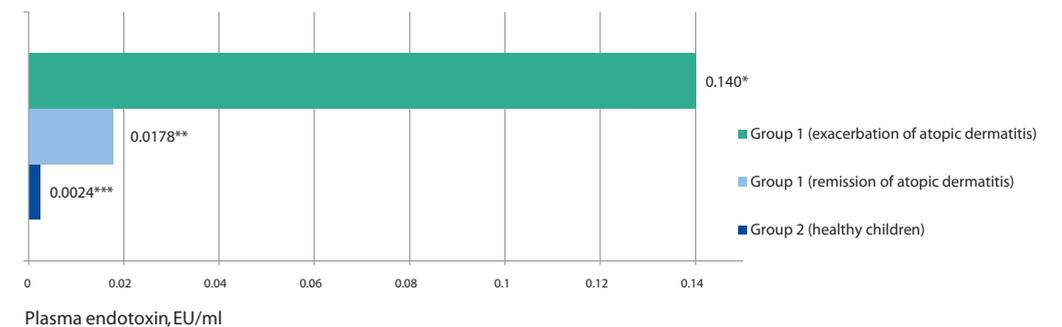
Severity of atopic dermatitis was assessed using the SCORAD scale. Statistical analyses included Student's t-test (t) and correlation analysis (r).

RESULTS

Our data analysis demonstrated that Group 1 children evaluated during an exacerbation of atopic dermatitis had a mean plasma endotoxin concentration of 0.140 ± 0.071 EU/ml, whereas the respective Group 2 value was 0.0024 ± 0.001 EU/ml. During the remission, the mean plasma endotoxin concentration fell to 0.0178 ± 0.0138 EU/ml, but the endotoxin levels still exceeded the Group 2 value ($p < 0.001$) (Fig. 1).

Figure 1.

Plasma endotoxin concentrations in the healthy children and in the children suffering from atopic dermatitis



Note: * $p < 0.05$, ** $p < 0.05$, *** $p < 0.001$.

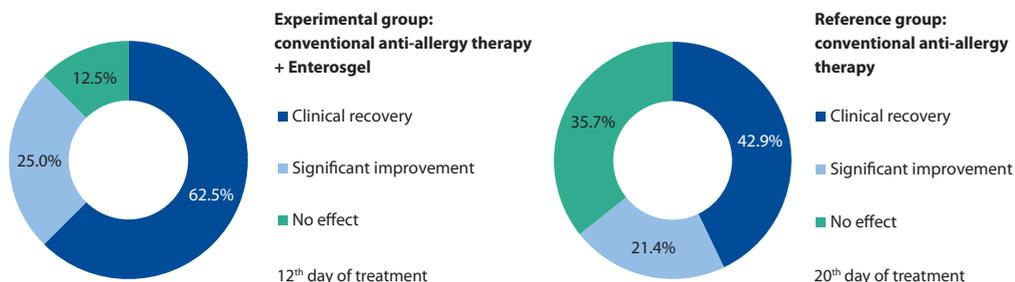
In severe atopic dermatitis, the mean plasma endotoxin concentration was 0.168 ± 0.079 EU/ml, significantly exceeding the moderate disease arm level of 0.076 ± 0.023 EU/ml ($p < 0.05$). The children with erythematous-squamous atopic dermatitis with lichenification and those with lichenoid atopic dermatitis had practically the same endotoxin concentrations, the means being 0.123 ± 0.118 EU/ml and 0.124 ± 0.077 EU/ml, respectively. In the children with the second activity grade of the skin process, the mean plasma endotoxin concentration (0.143 ± 0.092 EU/ml) was statistically significantly higher than in those with the third grade activity (0.112 ± 0.061 EU/ml), $p < 0.05$.

Therefore, the plasma endotoxin concentration in exacerbated atopic dermatitis exceeded respective Group 2 (healthy children) values almost 60 times ($p < 0.001$), decreasing 8-fold during the remission ($p < 0.05$), but failing, however, to reach the healthy children levels ($p < 0.001$).

The overall proportion of therapeutic effect in the experimental group was found to be 87.5% ($n = 14$). A clinical recovery was observed in 62.5% of the patients ($n = 10$).

Figure 2.

Treatment outcomes in the children with atopic dermatitis in the experimental group and in the reference group

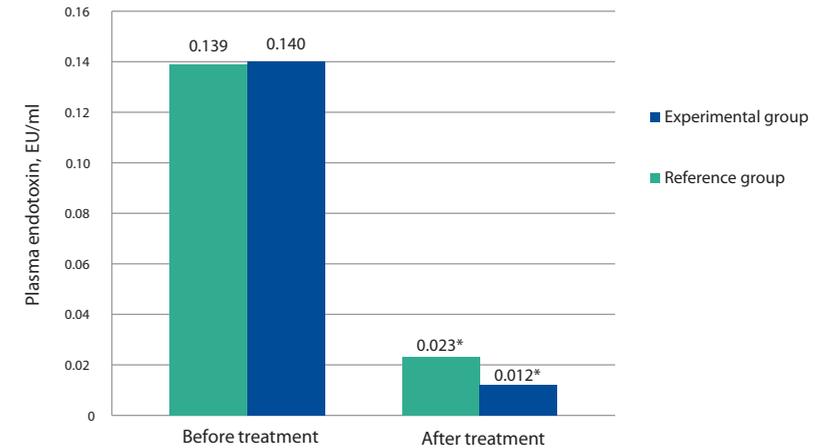


Significant improvement of the skin process and reductions greater than 2.5-fold in the SCORAD index, as well as decreased intensity of pruritus and recovered night sleep, were observed in 25% ($n = 4$) of the patients. No effect was seen in 12.5% ($n = 2$) of subjects (Fig. 2). With the administered treatment, the time of exacerbation was reduced, while a complete elimination of morphological elements on the skin and achievement of a clinical remission of the disease occurred on the 12th day of treatment on the average. The SCORAD index decreased 5-fold in this group on the average, from 50 to 10 points. There was also a 12-fold decrease in the plasma endotoxin level, from 0.140 EU/ml to 0.012 EU/ml.

In the reference group, the overall proportion of therapeutic effect was 64.3% ($n = 9$). A clinical recovery was observed in 42.9% of subjects ($n = 6$). A significant improvement of the skin process was obtained in 21.4% of the patients ($n = 3$). No effect was achieved in 35.7% of subjects ($n = 5$) (Fig. 2). Against the background of the described treatment, the SCORAD index decreased 3.3-fold on the average, from 50 to 15 points.

Figure 3.

Pre- and post-treatment plasma endotoxin concentrations in the children suffering from atopic dermatitis



Note: * $p < 0.05$.

A clinical remission of the disease was achieved by the 20th day of treatment. The plasma endotoxin reduction was half that observed in the experimental group, just 6-fold, from 0.139 EU/ml to 0.023 EU/ml, $p < 0.05$ (Fig. 3).

Enterosgel is very well tolerated and safe. No adverse effects were noted.

CONCLUSIONS

1. Systemic Endotoxemia was demonstrated in children with atopic dermatitis.
2. The plasma endotoxin concentration during an exacerbation of atopic dermatitis exceeded the respective levels in the healthy children group almost 60 times.
3. The plasma endotoxin concentration decreases during a remission of atopic dermatitis, but does not reach the physiological endotoxemia level.

4. The plasma endotoxin concentration depends on the severity and activity of the skin process.
5. Enterosgel coupled with conventional anti-allergy therapy results in a 1.6-fold reduction in the duration of the exacerbation period (from 20 to 12 days) and a 5-fold decrease in the SCORAD index against a background of decreased plasma endotoxin. Therefore, the clinical effectiveness of Enterosgel in the treatment of atopic dermatitis was defined.
6. Endotoxemia is an indication for use of gastrointestinal adsorbents.

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A Clinical and Immuno-Allergological Study of the Efficacy of Enterosgel in Food Allergy

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Abstract

This article demonstrates the clinical efficacy of Enterosgel in the treatment of food allergy. Enterosgel was shown to have beneficial effect on the allergy status and promote normalization of total serum IgE levels, early interferon, and pro-allergic cytokine (interleukin-5) concentrations in patients with food allergy manifesting by angioedema. The reported studies the benefits of gastrointestinal sorption (enterosorption) achieved with Enterosgel during the combination treatment in patients with food allergy manifesting by angioedema.

Keywords: adsorbent, angioedema, circulating immune complexes, food allergy, enterosorbent, Enterosgel

INTRODUCTION

The incidence of food allergy varies, according to different literature sources, from 1% to 20%, and males are more predisposed to it [4, 5]. Food allergy is manifested by classical symptoms of allergy, including erythema and urticaria, as well as by gastrointestinal disturbances.

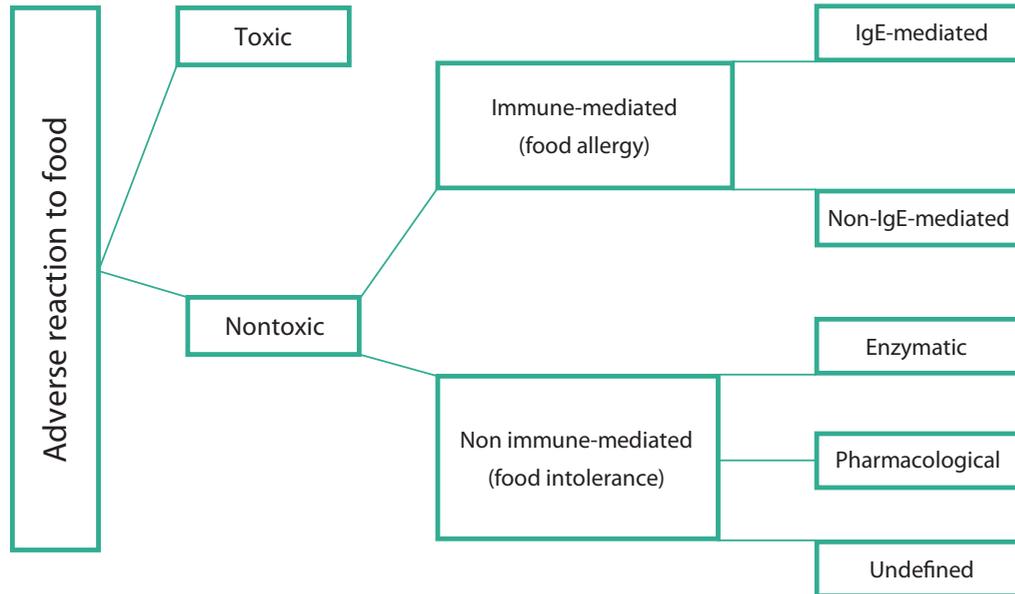
The most severe forms of food allergy are angioedema (Quincke’s edema) and anaphylactic shock. Food allergy is most commonly manifested by reactions to one or two foods, while polyvalent food allergy (caused by multiple foods) is less frequent. It is presumed that a significant proportion of food reactions are pseudo-allergic or even toxic [9].

The diagnosis of food allergy is made in patients with any adverse reactions developing after a food is taken. According to the international classification adopted by the European Academy of Allergology and Clinical Immunology (EAACI), all kinds of adverse reactions to food can be subdivided into two groups as demonstrated in the Figure [10].

A true (immune-mediated) food allergy is either delayed-type or immediate-type hypersensitivity. Non-dietary histamine liberators (dyes, preservatives, flavours, thickeners, etc.), as well as microbial antigens, play an important role in food intolerances.

Adsorption therapy methods are employed for binding toxic products of food-stuffs, some components of food additives, and, particularly so, in patients with im-

Figure.
Adverse reactions to food EAACI classification (2001)



paired protective mechanism of IgA-secretion required for oral food resistance. These methods include haemosorption, plasmapheresis, and enterosorption (binding and removal of toxic substances from the gastrointestinal tract) [4]. It should be mentioned that clinical practices most frequently utilize intestinal adsorption (enterosorption) as a simple and rather effective method of detoxification [3]. One of the most effective enterosorbents is Enterosgel, which exhibits selective sorptive activity towards middle-molecular-weight toxic metabolites [7, 8]. Some data are available that demonstrate the favourable effect of Enterosgel on immunological parameters in patients with various diseases [1, 2]. Our study was

directed to evaluate the clinical efficacy of Enterosgel in patients with food allergy manifested by angioedema.

MATERIALS AND METHODS

The experimental group included 67 patients aged from 12 to 50 years who had food allergy and a history of various manifestations thereof ranging from mild erythema to angioedema. All study subjects underwent immunological testing for presence of the inhibitor of the first component of the complement system (C₁-inhibitor) to allow identification of the cause of the angioedema. Patients with any evidence of a possible familial history of the disease were excluded from the study.

The control group included 10 practically healthy volunteers aged from 17 to 45 years who were recruited to evaluate the effects of Enterosgel on immunological parameters.

The experimental group patients were administered conventional treatment in combination with the adsorbent Enterosgel: exclusion of allergenic foods from the diet, as well as desloratadine, calcium gluconate, and Enterosgel 15 g 2 times a day for 10 days.

Healthy subjects were given a course of Enterosgel, 15 g 2 times a day for 10 days.

All patients with food allergy underwent a clinical-immunological work-up for allergy: their allergic history was collected, a prick test for individual food allergens was staged, and serum concentrations of circulating immune complexes (CIC), immunoglobulins (Ig), interleukins (IL-5 and IL-6), and alpha- and gamma-interferons (IFN- α and IFN- γ) concentrations were determined. CIC were determined by sedimentation, using 3.75% polyethylene glycol solution (Serva, Germany), with subsequent spectrophotometry (Specord, Hungary), overall CIC levels were expressed in conventional optical density units.

Statistical analyses of study results were performed using the parametric Student's t-test.

RESULTS AND DISCUSSION

33 patients presented with skin manifestations of food allergy, which developed 10 to 50 minutes after a meal and ranged from perioral erythema to generalized urticaria and subsequent angioedema.

Apart from some of the aforementioned manifestations of food allergy, 24 patients

also complained of facial angioedema, which had begun with swelling of the lips, soft tissues under the eyes, and the tip of the nose. Angioedema usually lasted 2 to 3 days and was eliminated within 10 to 20 hours in the patients administered antihistamine medication and the adsorbent Enterosgel.

10 patients had gastrointestinal complaints, including reactions to foods, which started with the events described above and were then accompanied by a single episode of vomiting, epigastric pain, or rapidly developing diarrhea. Skin manifestations of food allergy developed at a later time in these patients.

Subsequently, for the purpose of this study we selected the patients with angioedema, who had laboratory tests. Allergological tests (prick test) performed for 20 food allergens in these patients demonstrated that the most common reactions were those to citrus fruits (n = 10), chocolate (n = 6), dairy products (n = 5), chicken egg allergens (n = 5), sea food (n = 3), and tomato-containing foods (n = 3). Simultaneous reactions to two allergens were detected in 12 study subjects, and reactions to three allergens in 5.

Outcomes of the treatment programme including the intestinal adsorbent Enterosgel in the patients with food allergy included improvement of skin reactions (in the prick test) to allergens: decreased dimensions of the hyperaemic area, pallor of spots that were first observed and then rapidly resolved.

The state of humoral immunity in the patients from the experimental group (with food allergy) and healthy subjects observed before and after treatment is presented in Table 1.

Table 1.

Humoral immunity factors in patients with food allergy and in practically healthy subjects before and after Enterosgel treatment

Parameters	Groups			
	Healthy subjects (n = 10) (average value)		Patients with food allergy (n = 67) (average value)	
	Before treatment	After treatment	Before treatment	After treatment
IgE (IU/ml)	67.0	64.0	166.6	92.5*
IgM (g/l)	2.1	2.0	1.9	2.2
IgG (g/l)	9.3	9.4	9.6	10.0
IgA (g/l)	2.3	2.0	2.4	2.2
IgG ₄ (g/l)	0.45	0.46	0.66	0.62
CIC (optical density units)	34.9	22.6	116.6	50.0*

Note: * $p < 0.05$.

The data shown imply that patients with food allergy had elevated total serum IgE concentrations (reference interval, 85–120 IU/ml) and CIC content. Enterosgel treatment was followed by normalization of these parameters in patients with food allergy (92.5 IU/ml),

while no significant changes were observed in these parameters in the group of healthy subjects.

The cytokine profile studies revealed 3.8-fold and 2.5-fold elevations in IFN- γ and IL-5, respectively, in patients with food allergy, in contrast to controls (Table 2).

Table 2.

Serum cytokine concentrations in patients with food allergy and in practically healthy subjects before and after Enterosgel treatment

Cytokine concentration (pg/ml)	Groups			
	Healthy subjects (n = 10) (average value)		Patients with food allergy (n = 67) (average value)	
	Before treatment	After treatment	Before treatment	After treatment
IFN- α	2.8	2.6	3.5	6.2*
IFN- γ	68.0	74.5	258.8*	206.6*
IL-5	2.5	2.7	6.6*	1.4*
IL-6	42.6	41.7	107.2*	72.5

Note: * $p < 0.05$.

As a result of treatment, patients with food allergy had a statistically significant reduction in the content of the pro-allergic cytokine IL-5; however, the IFN- γ level did not change significantly, although a trend towards lower concentrations was observed in 55% of patients. A significant increment in early IFN- α concentrations was demonstrated in patients with food allergy who took the adsorbent Enterosgel.

CONCLUSIONS

1. The increased total serum IgE concentrations in study subjects demonstrated a reagin-dependent type of food allergy and allowed to classify this condition as a true allergy [6].
2. Apart from the increased IgE concentrations, patients with food allergy had increased circulating immune complexes, IFN- γ , IL-5, and IL-6 concentrations. No such deviations were observed in healthy controls.
3. Inclusion of the intestinal adsorbent (enterosorbent) Enterosgel in the treatment programme for patients with food allergy significantly improves their allergy status and promotes normalization of the total serum IgE levels, early IFN- α and the pro-allergic cytokine IL-5.
4. The reported study demonstrates the value of intestinal adsorption, in particular with Enterosgel, as part of treatment for patients with food allergy manifested by angioedema.

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Enterosorption in the Treatment of Pediatric Atopic Dermatitis Complicated by Fungal Infection

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Abstract

Patients with atopic dermatitis (AD) are highly susceptible to certain cutaneous bacterial, fungal and viral infections. This study has shown the clinical effectiveness of intestinal adsorption (enterosorption) with modern adsorbent Enterosgel in 40 children with secondarily infected AD. The overall clinical effectiveness rate was 87.5% for the children who received Enterosgel. That fact was manifested by the exacerbation reduced down by 1.8 times to 14 days (from former 26 days), and obtaining 4.5 times lower value for the SCORAD index (reduced down from 54 to 12). The remission duration was 3 times prolonged by delaying the time of next onset from 3.2 to 9.6 months during the therapy. The number of exacerbations in a year was brought down 3.3 times (from 4 to 1.2 times a year). The total serum IgE levels were decreased almost threefold from 350 to 120 IU/ml. The specific IgE levels to cow milk proteins and casein was decreased twice, whereas that to egg albumin was decreased thrice. Thus, administering Enterosgel in the treatment of AD complicated by fungal infection brings positive outcomes, decreasing the sensitization and serum levels of *Candida* antigen.

Keywords: adsorbent, atopic dermatitis, fungal infection, enterosorbent, enterosorption, Enterosgel

INTRODUCTION

Patients with atopic dermatitis (AD) have a tendency to develop complications. 25% of cases get accompanied by a secondary infection during the course of AD. That makes reconsideration of the treatment vital in order to improve it. On the background of present-day poor environmental conditions, irrational use of antibiotics, and wide use of topical corticosteroids, one of the factors causing increased severity of AD is fungal infection [3, 5, 8, 10]. The prevailing causative agents for fungal infection in toddlers and

younger children are yeast: *Malassezia furfur* and *Candida albicans*. Whereas in older children the causative fungal agents are *Candida* and *Rhodotorula rubra* as well as dermatophytes. Fungal infections exacerbate severity of the inflammatory skin process because they participate in AD pathogenesis by inducing specific serum IgE, sensitizing and activating dermal lymphocytes [1, 2, 6].

Inflammatory diseases of gastrointestinal (GI) tract play a significant role in the development of secondarily infected AD. The reason behind this is the GI tract being the main reservoir of *Candida* [11]. In addition to

that, increased intestinal yeast colonization exerts a sensitizing effect on the body. All this indicates to recommend sorbents that have detoxifying and cytoprotective actions for the treatment of secondarily infected AD, leaving no adverse effects on the intestinal flora [7]. Enterosgel with its complex adsorbing mechanism of action can be considered as such medicinal product.

The main objective of this study was to investigate the clinical effectiveness of intestinal adsorbent (enterosorbent) Enterosgel as a part of anti-allergic and anti-fungal therapy of pediatric AD complicated by fungal infection.

MATERIALS AND METHODS

192 children with AD were included in the study. All of them had continuous type of development of their disease with resistance to the anti-allergic therapy. Among them, 72 were infants and toddlers aged between 8 months and 3 years, whereas rest 120 were aged between 3 years and 15 years. 68% of the examined children had moderately severe course of the disease, whereas 32%

of them showed severe course. 47% of the children had food allergen sensitization, 25% had indoor allergen sensitization, and 28% had polyvalent sensitization.

Different methods of investigation were used while performing the study. They are as follows:

- physical examination and SCORing AD (SCORAD) index to estimate severity of the disease;
- total and specific serum IgE levels test;
- mycological examination (direct microscopic and fungal culture) of the skin scrapings of affected areas with antifungal susceptibility testing [9];
- serum levels of circulating *Candida* antigen (CAG) test with the help of amperometric immunoenzyme sensor. CAG represents *Candida albicans* cell wall mannoprotein complexes [4].

Fungal colonisation was detected on the skin in 70.8% of the children with continuous type of the AD development and resistance to the standard anti-allergic therapy (Fig. 1, 2).

Figure 1.

Pattern of fungal colonization of the skin in the children aged between 8 months and 3 years

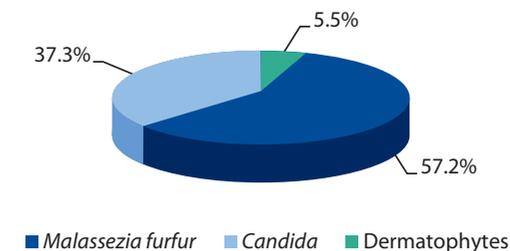
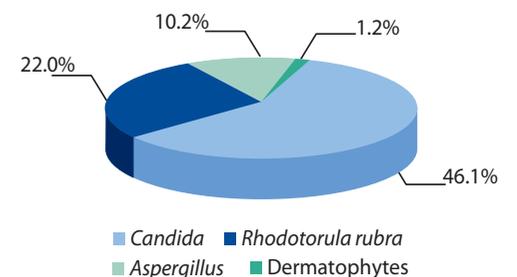


Figure 2.

Pattern of fungal colonization of the skin in the children aged between 3 years and 15 years



Candida colonization on the skin. Highly elevated serum levels (10^5 – 10^4 mg/ml) of circulating CAg were detected in 30.8% of the cases, 50.8% showed moderate levels (10^7 – 10^6 mg/ml), whereas the rest 18.4% showed low levels (10^9 – 10^8 mg/ml). There exists a correlation between serum levels of circulating CAg and the severity of disease ($r = 0.74$; $p < 0.05$), as well as the overall duration of the disease from its onset ($r = 0.78$; $p < 0.05$). Identification circulating CAg in the serum indicates transition from benign fungal colonization of the skin lesions to deep fungal inflammation (invasion). As opposed to antibodies against *Candida*, CAg is rapidly cleared from circulation, thus being regarded as marker of the candidal invasion [8].

For assessment of the effectiveness of therapy that includes the use of adsorbent Enterosgel, the patients were separated into two groups. The experimental group included 40 children with complicated forms of AD with fungal infection. They received Enterosgel combined with the standard conventional treatment. Enterosgel was administered for 2–3 weeks according to the age-related dosing. The children under 5 years of age were administered 1 teaspoon

3 times a day (15 g/day). Those between 5 years and 14 years of age were administered 2 teaspoons 3 times a day (30 g/day). Whereas, the adolescents (over 14 years of age) were administered 1 tablespoon 3 times a day (45 g/day). The control group included 20 children who received the conventional treatment alone.

The generally accepted standard treatment between both of the compared groups remained the same. It included:

- elimination diet (hypoallergenic diet), esp. eliminating food products that include yeasts during their production (cultured dairy products, yeast dough, cheese, etc.);
- antihistamines;
- combined anti-inflammatory and anti-fungal topical medications;
- good daily skin care with special hypoallergenic skin cleansers and moisturizers;
- systemic antifungal drugs when indicated (in severe or refractory cases).

The assessment of the clinical effectiveness was carried out by taking into consideration the overall therapeutic effect (total percentage of the patients who showed positive clinical outcomes of the treatment), average duration of exacerbations, ob-

Table 1. The resulting estimate of the effectiveness of the proposed treatment in the children with AD complicated by secondary fungal infection

Groups	Overall therapeutic effectiveness (%)	SCORAD index	Average duration of exacerbation (days)	Low effectiveness (%)
Experimental (n = 40)	87.5	4.5 times reduced	14.2 ± 1.7	12.5
Control (n = 20)	65.0	3 times reduced	26.3 ± 1.8	35.0

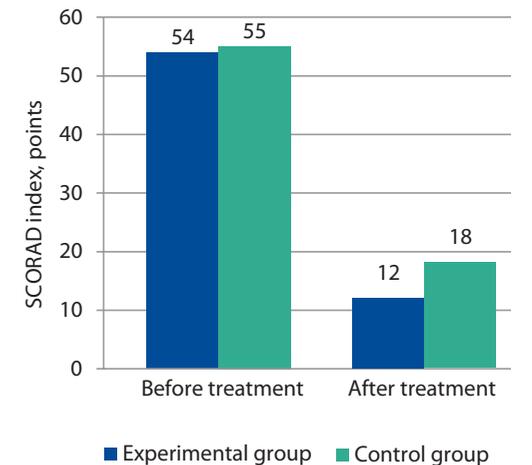
taining of lower values of SCORAD index, prolongation of remission duration, reduction in the incidence of acute exacerbations, and lowering of levels of atopic sensitization.

RESULTS AND DISCUSSION

It was shown that overall therapeutic effectiveness reached 87.5% in the experimental group and 65% in the control group (Table 1).

There was marked reduction in exacerbation in relation with the experimental treatment. In 85% of the patients, hyperemia and pruritus (skin itch) disappeared by 3rd day of the treatment. In 90% of the patients infiltrations, lichenoid papules, vesicles, and oozing lesions disappeared by 5th day. Complete remission with disappearance of manifestations on skin was achieved around day 12–16 of the treatment. Whereas in the control group, complete remission with disappearance of manifestations on skin was observed around day 24–28 of the treatment. On an average, SCORAD index showed 4.5 times lower value (from former 54 to 12 points) in the experimental group, whereas 3 times in the case of the control group (from former 55 to 18), (Fig. 3).

Figure 3. SCORAD dynamics depending on the treatments given in the children with AD complicated by secondary fungal infection



Information regarding long-term outcomes based on the clinical observation data for the period of 18 months is provided in Table 2.

Those exacerbations which were observed after the treatment with combination therapy using adsorbent

Table 2. The resulting estimate of long-term outcomes of the proposed treatment based on the observation data for the period of 18 months in the children with AD complicated by secondary fungal infection

Groups	Remission duration (months)		Exacerbations (years)	
	Before treatment	After treatment	Before treatment	After treatment
Experimental (n = 40)	3.2 ± 1.2	9.6 ± 1.3*	4.0 ± 0.6	1.2 ± 0.2*
Control (n = 20)	3.3 ± 1.4	6.2 ± 1.4	3.8 ± 0.6	2.0 ± 0.4

Note: * $p < 0.05$.

Enterosgel characterized by lesser severity of the clinical manifestations on skin. They showed smaller area covering the lesions, decrease in pruritus (skin itch) and inflammatory activity, reduce the duration of relapse. In addition to that, 32% of the patients from the experimental group had a stable clinical remission. There was no exacerbation of disease noticed in them during the entire period of the observation. On the other hand, the control group showed just 20% of such ($p < 0.05$).

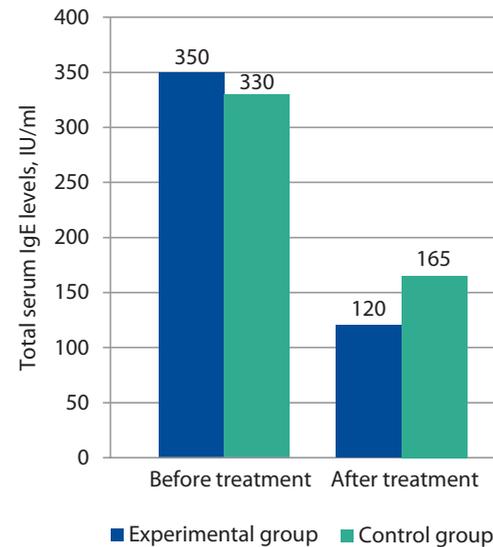
Thus in the children with complicated forms of AD with fungal infection in regards with the treatment given, there were noticed not only positive short-term outcomes, such as reduction in exacerbation by 1.8 times to 14 days (from former 26) and obtaining of 4.5 times lower values of SCORAD index, but also favourable long-term effects, such as prolongation of remission duration as well as reduction in the incidence and severity of exacerbations.

Serum levels of circulating CAg in the 85% of the children from the experimental group went down to traces, and in the rest 15% cases were achieved low levels. Whereas in 55% of the children from the control group, the serum levels of circulating CAg went down to traces, in 30% of the patients the levels were moderately reduced, and the rest 15% cases showed no changes in the levels.

Total serum IgE levels and specific serum IgE levels revealed that the children who received Enterosgel displayed well-expressed fall in the total serum IgE levels than the patients from the control group (Fig. 4).

Probably, this result is connected not only with the adsorbing effect of the

Figure 4. Changes in total serum IgE levels in complicated forms of AD in the children with fungal infection before and after treatment



Enterosgel, but also with the cytoprotective effect of it, which reduces down the food allergens that pass through mucous membrane of the GI tract, thus reducing the sensitization in children.

Changes in specific serum IgE levels to cow milk proteins and casein were elevated in the experimental group before the treatment in 72.5% of the cases, whereas that to egg albumin in 47.5% of the cases. In the control group, these values were 70% and 45%, respectively. The resulting estimate in specific serum IgE levels for three months after the treatment showed that the decrease rate for the sensitization for food allergens is higher in the experimental group than in the control group (Table 3).

Table 3. Changes in specific serum IgE levels (expressed in different classes*) in the children with AD complicated by fungal infection

Allergens	Experimental group (n = 40)		Control group (n = 20)	
	Before treatment	After treatment	Before treatment	After treatment
Cow milk proteins	4 ± 1	2 ± 1	4 ± 1	3 ± 1
Casein	4 ± 1	2 ± 1	4 ± 1	3 ± 1
Egg albumin	3 ± 1	1 ± 1	3 ± 1	2 ± 1

Note: * Class 1/0: very low level of specific IgE.
 Class 1: low level of specific IgE.
 Class 2: moderate level of specific IgE.
 Class 3: high level of specific IgE.
 Class 4: very high level of specific IgE.

CONCLUSIONS

- Administration of intestinal adsorbent Enterosgel for 2–3 weeks as a part of anti-allergic and anti-fungal combination therapy used in the treatment of pediatric AD complicated by fungal infection has a favourable short- and long-term results:
 - achievement of complete clinical remission by day 14 (when calculated from the initiation of the treatment);
 - prolongation of remission duration and reduction in the number of relapses.
- Inclusion of Enterosgel into the treatment of pediatric AD helps reduce atopic sensitization, which is confirmed by decrease in total serum IgE levels as well as in specific serum IgE levels to food allergens.

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STUDY REPORT

The Efficacy of Enterosgel in the Treatment of Children with Bronchial Asthma and Atopic Dermatitis

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Abstract

The article presents efficacy results obtained for the intestinal adsorbent (enterosorbent) Enterosgel in the treatment of bronchial asthma combined with atopic dermatitis in children aged from 2.5 to 13 years. 40 patients were administered Enterosgel at an age-related dose for 14 days. 20 patients in the control group were not given Enterosgel. All children were administered bronchodilator therapy. A clinical improvement in the Enterosgel group was achieved 7 to 10 days earlier than in the control group. No adverse effects were seen during use of the drug. Enterosgel was shown to be an effective treatment for the bronchial obstruction and skin syndrome in patients with atopic bronchial asthma and dermatitis.

Keywords: adsorbent, allergen, atopic dermatitis, bronchial asthma, enterosorbent, Enterosgel

INTRODUCTION

The growth of allergic diseases throughout the world forces to search new approaches for their prophylaxis and treatment. From this point of view, multifaceted action of gastrointestinal sorption may be very perspective [4].

Enterosgel is an organosilicon polymeric compound that can selectively adsorb toxins, pathogens and allergens from the intestinal contents and the blood, prevent absorption of these substances, and eliminate them from the body [1, 2, 3]. Enterosgel is chemically inert; it is not absorbed in the gut, undergoes no biotransformation, and activates propulsive bowel movements. The properties of this medicine permit its use in the treatment of bronchial

asthma and atopic dermatitis with concomitant gastrointestinal diseases in children.

The principal objective of this open-label comparative controlled study was to evaluate the efficacy and tolerability of the intestinal adsorbent (enterosorbent) Enterosgel in patients with bronchial asthma and atopic dermatitis.

MATERIALS AND METHODS

This study enrolled 60 children diagnosed with bronchial asthma.

Inclusion criteria

Male or female gender, age from 2.5 to 13 years, bronchial asthma of various severity, including the combination with atopic dermatitis. Bronchial asthma types: atopic, combined.

Exclusion criteria: none.

Groups

The experimental group was composed of 40 children who were administered Enterosgel in accordance with the algorithm that we had designed.

The control (reference) group consisted of 20 children. The two groups were comparable with regard to gender, age, and severity of clinical manifestations of asthma.

All patients were given bronchodilators (methylxanthines and beta-agonists); 7 patients suffering from severe bronchial asthma received inhaled corticosteroids while the rest were administered cromoglicic acid.

Dosing and administration of Enterosgel

The children aged between 2.5 and 5 years were administered 1 teaspoon of Enterosgel 3 times a day (15 g/day), the children aged over 5 years were given 1 tablespoon 3 times a day (45 g/day) 2 hours before or after a meal.

Course of the study

The first stage of the study consisted of two periods:

- a 7-day control period, when the experimental group patients (n = 40) were followed up and did not receive Enterosgel;
- Enterosgel treatment period that lasted 10 to 14 days on the average.

In the second stage of the study, we compared treatment outcomes obtained in the experimental group (before Enterosgel treatment and during / after Enterosgel treatment), and also compared results obtained in the control group and in the experimental group.

Clinical observation and examination

A "Subject Diary" was kept for each patient to register the following parameters: general clinical condition, complaints, state of the skin, chest auscultation data, gastrointestinal tract status (abdominal tenderness on palpation, appetite, stool characteristics), and blood test results. Records were made in the "Subject Diary" prior to and during treatment with Enterosgel (on day 5 and day 10).

Additionally, all children underwent a complete laboratory and instrumental investigation, which included the following:

- routine blood and urine tests;
- blood chemistry tests;
- immunological blood tests (total and specific IgE);
- respiratory function test (RFT);
- abdominal ultrasonography;
- gastroscopy (when indicated);
- fecal analysis for intestinal dysbiosis (when indicated).

An individual Case Report Form was kept for each subject to reflect adverse events associated with the use of Enterosgel.

RESULTS AND DISCUSSION

Prior to the study, all patients in the experimental group (n = 40) suffered from choking sensations whose frequency and severity corresponded to the progression of the disease. Severe bronchial asthma was observed in 8 patients (20%), and moderate asthma in 32 (80%). By the time of Enterosgel treatment initiation, most patients were in a satisfactory clinical condition.

All study subjects presented with various disease manifestations revealed by auscultation (dry and moist rales, diminished breath sounds).

Immunological examination revealed that all subjects had elevated total and specific IgE concentrations, as well as polyvalent sensitization to dietary and indoor allergens. The majority of the patients (80%) had eosinophilia (relative count, up to 12%).

All patients included in the study presented with bronchial obstruction: respiratory function test results were reduced to 70–60% of respective reference values.

More than half the patients in the experimental group (n = 22) had atopic dermatitis as a concomitant disease. In the majority of the patients, this disease was exacerbated and manifested by skin maceration with purulent crusting, excoriation, and lichenification. Many patients had taken antihistamine medications to relieve the skin syndrome but had had no improvement before admission to the clinic.

Gastrointestinal diseases were detected in all patients (n = 60) enrolled in the clinical study:

- clinically relevant exacerbated gastroduodenitis verified by gastroscopy in 60% of the patients;
- gastrointestinal and biliary dyskinesia in 65% of subjects;
- intestinal dysbiosis in 20% of the patients.

Concomitant gastrointestinal disorders were controlled by antacids and enzymatic preparations.

The first stage of the study

The study proper was preceded (in the experimental group) by a 7-day control period, when the patients were followed up without receiving Enterosgel. Improvements were first observed on the 3rd day of Enterosgel treatment: choking sensations

had ceased, the skin syndrome manifestations were not observed anymore, and gastrointestinal function had improved.

The obstructive syndrome was clinically eliminated in 50% of study subjects by the 5th day of Enterosgel treatment. Normalization of respiratory function occurred by the 14th day of treatment, while the patients with severe bronchial asthma experienced this normalization by the third week of Enterosgel treatment. Along with the improvement of the main symptoms of bronchial asthma, the patients had their abdominal pain relieved and stools normalized.

In the children with atopic dermatitis, the skin syndrome became significantly improved after a mean of five days on Enterosgel treatment. A complete remission was achieved by the 10th day in 85% of subjects. Complete blood counts of these patients revealed decreased eosinophil counts.

The second stage of the study

Our analysis of study results demonstrated a significant improvement in the clinical course of bronchial asthma and concomitant conditions in the patients treated with Enterosgel, as compared with controls. In particular, the obstructive syndrome was relieved in the experimental group 7 to 10 days earlier than in the standard therapy group. As a result of Enterosgel treatment, all patients had their dyspepsia relieved and gastrointestinal function improved.

All sorts of skin inflammation were alleviated:

- allergic rash resulting from inappropriate diet was eliminated within 6 hours after initiation of Enterosgel;
- acne vulgaris was significantly improved in adolescents.

No adverse effects were observed during Enterosgel treatment. Enterosgel is easy to take and well tolerated by children.

CONCLUSIONS

1. Administration of the intestinal adsorbent Enterosgel in the patients with bronchial asthma and atopic dermatitis allows rapid relief of the bronchial obstruction and the skin syndrome.
2. Use of Enterosgel allows a reduction in the dosage of antihistamines, shorten duration of bronchodilator therapy and reduce their potential side effects.
3. Enterosgel has demonstrated the high clinical efficacy in the treatment of concomitant gastrointestinal diseases.

Therefore, Enterosgel can be successfully added to conventional therapy of children with allergic and gastrointestinal diseases to raise effectiveness of treatment.

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STUDY REPORT

Application of Enterosorption Method with Organosilicon Enterosorbent Enterosgel in the Integrated Treatment of Allergic Diseases

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Abstract

This pilot, randomized, controlled study was carried out for evaluation of the safety and efficacy of Enterosgel application, concomitantly with standard therapy of patients with skin allergies (atopic dermatitis and chronic urticaria) and respiratory allergic diseases (atopic asthma and allergic rhinitis) in the exacerbation stage. Effect of Enterosgel was assessed in 24 patients during 21 days of treatment. A control group was composed of the same patients before the Enterosgel application. Combination therapy with Enterosgel has shown to have a very good effect: statistically significant improvement for bronchial asthma, chronic urticaria and other examined immune pathological conditions (polyvalent and food allergy, chronic fatigue syndrome).

Keywords: adsorbent, allergic diseases, atopic dermatitis, asthma, enterosorbent, Enterosgel, urticaria

INTRODUCTION

The Gastrointestinal (GI) tract plays an essential role in pathogenesis of allergic diseases. Decreased enzyme activity, disruption of intestinal motility, improper digestion and malabsorption lead to increased intestinal permeability to toxic compounds and macromolecules, which can lead to sensitization of the immune system. For this reason as part of a comprehensive treatment of various allergic diseases, it is highly desirable to protect the GI tract and normalize the intestinal microflora. These requirements are met by Enterosgel – an innovative intestinal adsorbent with a high sorption capacity and a protective effect on the intestinal mucous

membrane and a positive influence on the intestinal microflora [1, 2]. The main objective of this study was to evaluate the safety and clinical efficacy of intestinal adsorbent Enterosgel in patients suffering from allergic diseases.

MATERIALS AND METHODS

This study involved 24 patients (10 men and 14 women aged from 2 to 80 years, average age is 43,1) diagnosed with: mild to moderate stable bronchial asthma (6 patients), chronic urticaria (7 patients), stable atopic dermatitis (6 patients) and 5 patients with a different diagnosis (1 patient with polyvalent allergy and indigestion, 1 patient with food allergy, 2 patients with chronic

fatigue syndrome and 1 patient suffering from chronic uveitis, chronic keratitis and recurrent stomatitis). The patients arrived at the allergological outpatient department due to deterioration of their disorders or in relation to the regular control over their medical condition. A point-based assessment was carried out during 21 days prior to the commencement of Enterosgel application (control group), and further during 21 days of regular taking of Enterosgel (experimental group). Patients were randomized to groups according inclusion and exclusion criteria.

Basic inclusion criteria:

1. Patients over 2 years with an allergic disease (see above patient samples).
2. Patients with the prerequisite to cooperate properly in the course of study, who gave a written informed consent to participate in the study.

Basic exclusion criteria:

1. Hypersensitivity to the medical product Enterosgel in their medical anamnesis.
2. Patients from whom proper cooperation cannot be expected.
3. Absence of a written consent to participate in the study.
4. Participation in any other research within the previous 3 months.
5. Patients treated with enterosorbents, probiotics and prebiotics within the last 30 days.

After signing the written informed consent, patients were given a Patient's Diary to record their point-based assessments of disorders, according to their individual diseases.

Dosage of Enterosgel

For adults and children over 6 years of age: 1 tablespoon (15 g) 3 times a day (45 g/day) stirred in a glass of water, taken 2 hours after meals or 1–2 hours before meals. An adequate water intake was recommended over the course of Enterosgel application, i.e. not less than 1.5–2 litres of liquids per day.

For children under 6 years of age: 1 teaspoon (5 g) 3 times a day (15 g/day) in the same regimen as above. Daily intake of liquids should not be less than 0.5 litres.

The following medicines and products were forbidden for use over the course of the study:

any enterosorbents, prebiotics and probiotics.

The following drugs were allowed to be used:

all drugs previously taken by the patients as well as such drugs which are officially accepted by modern standards for treatment of the specified diseases.

Point-based symptom assessment

The patient's symptom severity was assessed by the point-based symptom score regarding individual diseases:

- 1 point – significant deterioration;
- 2 points – deterioration;
- 3 points – current condition;
- 4 points – improvement;
- 5 points – significant improvement.

The clinical parameters which were monitored for the individual diseases:

- *bronchial asthma (8 items):* general well-being, dyspnea, wheezing, difficulty in

breathing (chest tightness), cough, nocturnal dyspnea, quality of sleep, everyday activities;

- *atopic dermatitis (9 items):* general well-being, erythema (redness), new lesions, weeping, scratching / excoriations, xerosis (dryness of skin), itching, quality of sleep, everyday activities;
- *chronic urticaria (8 items):* general well-being, new lesions, mean wheal diameter, itching, scratching, facial edema, quality of sleep, everyday activities;
- *other diseases (8 items):* general well-being, headache, abdominal pain, joint pain, muscle pain, regularity of bowel movements, quality of sleep, everyday activities.

The initial value was equal to 3 points that correspond to the symptoms as of the monitoring commencement date. During the following days, the patients assessed their symptoms in the range of 1–5 points.

The 21-day period prior to the application of Enterosgel was used as a control. The 21-day period of Enterosgel use was used as experimental.

Laboratory and functional tests

Laboratory investigations were performed for all patients on following dates:

- first examination (day 0);
- second examination (day 21) prior to the commencement of Enterosgel treatment;
- third examination (day 42) that is integrally 21 days after start of the Enterosgel treatment.

The following tests were performed:

- total serum IgE levels and specific IgE, especially as a response to the causative

allergens (according to the medical anamnesis or to previous skin prick tests);

- blood chemistry tests: urea, creatinine, bilirubin, cholesterol, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and amylase (AMS).

A Spirometria was performed on patients with bronchial asthma.

Statistical estimation

Statistical analysis was performed at the Department of Medical Biophysics Faculty of Medicine and Dentistry Palacký University (Mgr. Langrová). The comparison of outcomes before and after Enterosgel application, was used for each and every patient. The paired Student's t-test, Wilcoxon signed-rank test and linear regression analysis were used for statistical calculations. The paired samples t-test was applied when sample data was normally distributed. If the sample data was not normally distributed we used Wilcoxon test.

RESULTS AND DISCUSSION

Assessment of symptoms in the patients with bronchial asthma

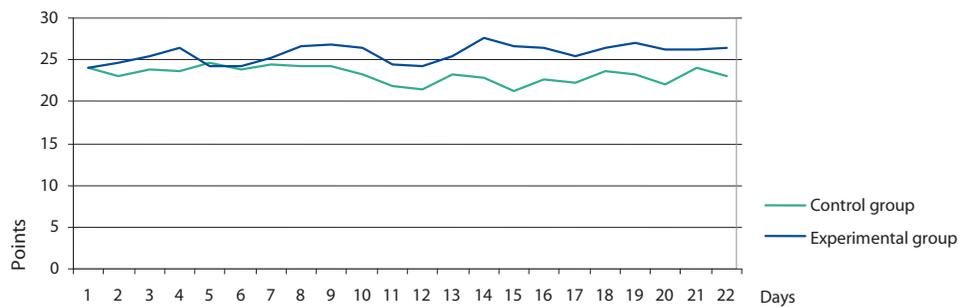
Table 1 shows the values of the point-based assessment of symptoms by individual patients, within the period before the commencement of Enterosgel application, as well as during the subsequent 21-day period of its application. With respect to the initial point-based value, the current status makes 24 points.

The average values of the point-based assessment of symptoms for individual days of monitoring is shown in the Figure 1.

Table 1. Symptom scores of individual patients with bronchial asthma during the control and experimental periods (from day 0 to day 21)

Control group (n = 6)																					
0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
24	22	22	22	23	23	24	24	24	24	24	22	22	20	20	20	21	21	20	19	24	24
24	24	24	24	24	22	22	22	20	20	20	20	21	21	21	23	23	24	24	24	24	24
24	24	24	24	24	24	24	24	24	24	20	20	20	20	23	24	24	24	24	24	24	24
24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24
24	19	19	19	29	29	29	29	29	29	19	19	29	29	24	24	24	24	24	24	24	24
24	25	30	29	24	21	24	22	25	19	24	24	23	23	16	21	18	25	24	17	24	18
Experimental group (n = 6)																					
0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
24	24	25	28	28	28	31	31	32	30	30	32	32	30	30	30	26	26	30	30	30	30
24	24	24	22	24	24	24	25	25	26	25	25	29	30	25	23	25	25	25	27	26	27
24	24	26	27	25	26	28	25	25	24	20	19	20	20	25	25	27	27	27	27	28	28
24	24	24	24	25	25	25	25	26	26	26	26	26	27	27	27	27	27	27	27	27	27
24	29	29	29	19	19	19	29	29	29	29	19	21	29	29	29	23	29	29	22	22	24
24	23	25	29	24	24	24	25	24	23	17	24	24	22	24	24	24	24	24	24	24	23

Figure 1. Enterosgel application: influence on the symptom score in the patients with bronchial asthma (n = 6; p = 0.024)



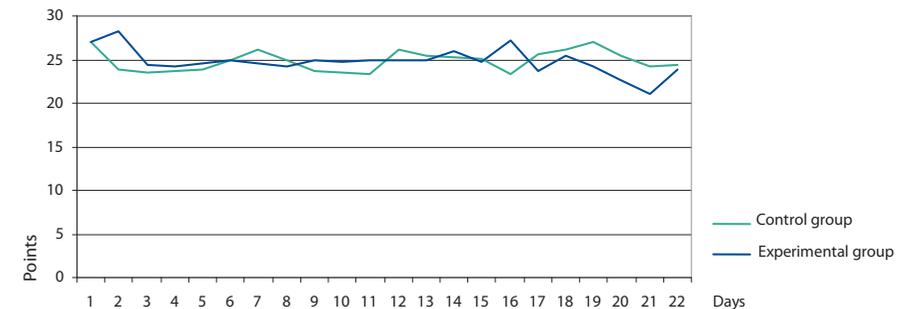
Assessment of symptoms in patients with atopic dermatitis as well as during the subsequent 21-day period of its application (Table 2). With respect to the initial point-based value, the current status makes 27 points. Below are the values of the point-based assessment of symptoms by patients during the period before Enterosgel application,

Table 2. Symptom scores of individual patients with atopic dermatitis during the control and experimental periods (from day 0 to day 21)

Control group (n = 6)																					
0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
27	27	27	24	24	27	27	27	27	27	27	27	27	27	27	27	27	27	27	27	27	27
27	24	27	23	25	23	26	27	27	28	25	25	26	27	27	27	27	27	27	27	27	27
27	17	17	22	20	21	24	22	22	23	26	26	25	25	26	16	20	22	27	18	18	18
27	21	20	21	21	22	23	24	20	22	21	23	22	21	24	24	26	27	27	27	27	27
27	27	23	28	28	30	30	22	19	15	15	29	26	25	20	19	27	27	27	27	19	20
27	27	27	24	25	27	27	27	27	26	26	27	27	27	27	27	27	27	27	27	27	27
Experimental group (n = 6)																					
0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
27	38	38	38	37	33	33	33	32	30	35	34	33	32	32	30	28	27	25	22	21	21
27	24	22	23	23	25	28	31	29	28	28	28	26	27	28	31	26	24	27	22	22	32
27	26	12	12	14	16	19	14	17	18	16	16	16	19	21	22	25	23	24	23	23	24
27	27	27	27	21	21	21	21	21	27	27	27	26	26	25	21	21	21	18	18	18	21
27	27	21	21	28	30	22	22	26	21	19	20	24	26	18	32	18	32	27	28	21	21
27	27	26																			

The average values of the point-based assessment of symptoms for individual days of monitoring is shown in the Figure 2.

Figure 2. Enterosgel application: influence on the symptom score in the patients with atopic dermatitis (n = 6; p = 0.049)



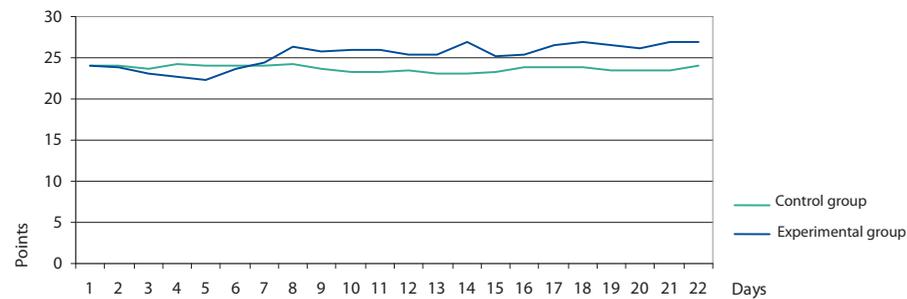
Assessment of symptoms in patients with chronic urticaria commencement of Enterosgel application, as well as during the subsequent 21-day period of its application. With respect to the initial point-based value, the current status makes 24 points. Table 3 shows the values of the point-based assessment of symptoms by individual patients during the period before the

Table 3. Symptom scores of individual patients with chronic urticaria during the control and experimental periods (from day 0 to day 21)

Control group (n = 7)																					
0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
24	24	24	24	24	24	24	25	25	22	22	22	20	20	20	24	24	24	24	24	24	24
24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24
24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24
24	24	24	24	24	24	24	24	24	22	22	22	22	22	24	24	24	24	20	20	20	24
24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24
24	24	22	25	24	24	24	24	22	23	23	24	23	23	23	23	23	23	24	24	24	24
24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24
Experimental group (n = 7)																					
0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
24	24	24	24	24	24	24	24	24	26	26	26	24	26	26	27	27	26	26	28	28	28
24	22	22	20	20	20	22	22	20	20	20	20	22	22	23	22	23	22	23	23	22	21
24	24	22	24	22	18	19	24	24	24	24	18	20	25	25	24	24	21	19	25	25	23
24	23	23	23	22	23	23	24	23	22	22	24	24	26	27	26	29	30	28	28	28	29
24	26	18	21	23	23	27	30	30	30	30	30	28	29	30	30	31	31	31	31	31	31
24	23	23	23	20	20	20	23	23	23	23	23	23	23	23	22	22	23	23	23	23	24
24	25	30	24	25	37	36	37	37	37	37	37	37	38	22	27	30	36	36	25	31	32

The average values of the point-based assessment of symptoms for individual days of monitoring is shown in the Figure 3.

Figure 3. Enterosgel application: influence on the symptom score in the patients with chronic urticaria (n = 7; p = 0.027)



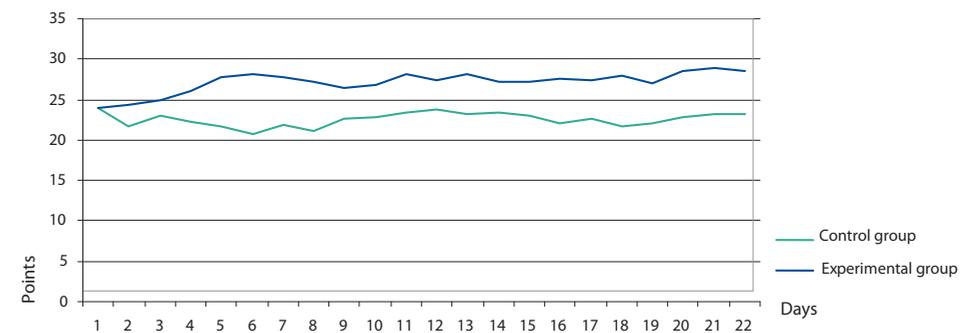
Assessment of symptoms in patients with other diseases commencement of Enterosgel application, as well as during the subsequent 21-day period of its application. With respect to the initial point-based value, the current status makes 24 points.

Table 4. Symptom scores of individual patients with other diseases during the control and experimental periods (from day 0 to day 21)

Control group (n = 5)																					
0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
24	24	24	20	19	19	21	21	24	26	30	30	30	29	27	24	24	24	24	24	24	24
24	18	19	19	19	17	18	16	17	20	20	18	16	20	20	18	20	18	20	20	21	20
24	18	24	24	22	20	22	21	24	20	19	23	22	20	20	20	21	18	18	22	23	24
24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24
24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24
Experimental group (n = 5)																					
0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
24	24	28	31	31	27	25	26	24	24	24	24	27	28	28	28	28	31	31	31	33	33
24	24	22	22	22	22	22	20	20	24	28	28	28	28	27	28	23	23	20	24	24	24
24	24	24	26	28	30	30	28	28	26	29	25	24	18	19	20	24	24	22	26	26	24
24	24	24	24	28	30	30	30	28	28	28	28	28	28	28	28	28	28	28	28	28	28
24	26	27	27	30	32	32	32	32	32	32	32	32	34	34	34	34	34	34	34	34	34

The average values of the point-based assessment of symptoms for individual days of monitoring is shown in the Figure 4.

Figure 4. Enterosgel application: influence on the symptom score in the patients with other diseases (n = 5; p = 0.004)

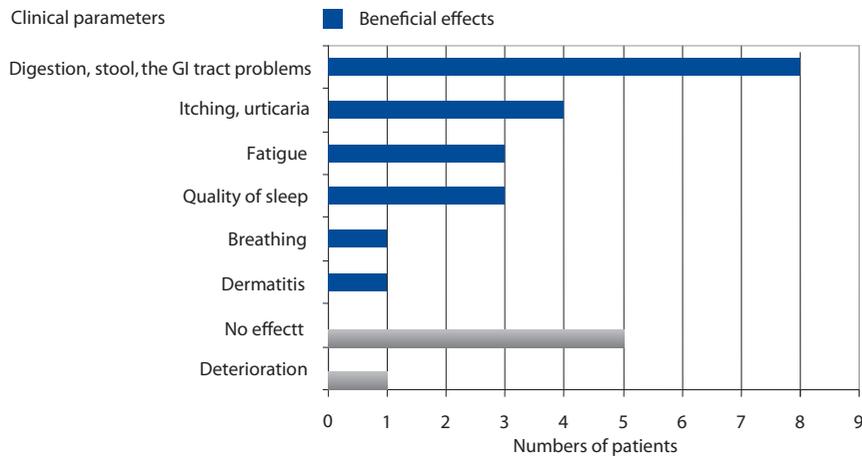


Subjective evaluation of the therapeutic effect on the part of the patients a questionnaire regarding their general impression of taking the medical product. After the application of Enterosgel came to an end, the patients were provided with It contained questions on whether the application had deteriorated the basic disease,

whether the condition was left unchanged, whether there was any improvement in the basic manifestations of the main disease, and whether there was a significant improvement in health condition. Furthermore the patients stated their subjective feelings, which they were most strongly aware of over the course of treatment.

There was only 1 patient who demonstrated a refusal to take Enterosgel, which also persisted after the dosage and taste of the drug had been changed, and therefore the treatment was stopped. 5 patients did not report any changes in their health condition. 17 patients (74%) evaluated the Enterosgel treatment as beneficial (Figure 5).

Figure 5.
Subjective evaluation of effects of Enterosgel by patients (n = 23)



Observed improvement in health apart from the basic disease:

- improvement of digestion, relieving symptoms of indigestion, normalization of stool – 35%;
- improvement in the itching condition – 17%;
- alleviation or reduction of fatigue – 13%;
- improvement in sleep quality – 13%;
- improvement in breathing – 4%;
- relieving symptoms of allergic rhinitis – 4%;
- reduction symptoms of food allergies – 4%;
- improvement in atopic dermatitis – 4%.

Deterioration or adverse events:

- vomiting, in 1 patient the Enterosgel treatment was stopped prematurely after 3 days of application (no improvement after reduction of dosage and change of the taste);
- sensation of abdominal bloating in 1 patient;
- occasional myalgia and arthralgia in 1 patient.

Data of laboratory and functional tests

A statistical analysis of the laboratory data did not show any statistically significant

changes in the test results. Neither were statistically significant changes recorded in the spirometric values of the patients with bronchial asthma.

The absence of statistically significant changes in the monitored parameters can be explained by the fact that basic biochemical values in all the patients were within the reference values. As regarding the values of total and specific IgE, the 21-day duration of treatment is evidently too short a period to reflect (to influence them) the dynamics of their changes.

CONCLUSIONS

This study provides evidence of the superiority of combination therapy with adsorbent Enterosgel in the treatment of allergic diseases. It was determined that:

1. Enterosgel has demonstrated safety and high tolerability. The treatment was stopped prematurely after 3 days of taking in 1 patient only (due to nausea and vomiting). One 7-year-old girl did not like the taste of Enterosgel, but there were no reasons for suspending or stopping the treatment.
2. No statistically significant influence on the patients with atopic dermatitis was determined.
3. No statistically significant changes in the laboratory parameters (total and specific

IgE, IgE, urea, creatinin, bilirubin, cholesterol, AST, ALT, and AMS) were recorded.

4. 74% of the patients observed improvement of their health, apart from the basic disease, which was manifested as an improvement of digestion, relieving symptoms of indigestion, normalization of stool, improvement in the itching condition, alleviation or reduction of fatigue, improvement in sleep quality, improvement in breathing, relieving symptoms of allergic rhinitis, reduction of food allergy symptoms.
5. Statistically significant improvement in the clinical scores, according to point-based assessment, proves the clinical efficacy of Enterosgel, concomitantly with standard treatment in patients, with bronchial asthma, chronic urticaria and other examined immune pathological conditions (polyvalent and food allergy, chronic fatigue syndrome).

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Asthma Prevention in Children with Recurrent Wheezing Bronchitis Who Have Elevated Levels of Heavy Metals and Aldehydes in the Body

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Abstract

A state-of-the-art approach to the prevention of asthma in children suffering from recurrent wheezing bronchitis is discussed. Results are presented from an open-label, prospective controlled study that included 217 children aged from 3 to 7 years who had recurrent wheezing bronchitis and resided in ecologically unfavorable regions. This study was conducted with the aim to evaluate the effectiveness of an optimized combination therapy regimen that included the following agents: the leukotriene receptor antagonist montelukast sodium, the new-generation intestinal adsorbent Enterosgel, and the immunomodulator azoximer bromide. The proposed method was demonstrated to be capable of enhancing effectiveness of primary prophylaxis in asthma through reducing exacerbation rates and severity of recurrent wheezing bronchitis, prolongation of remissions, and decreased bronchial hyperreactivity.

Keywords: adsorbent, azoximer bromide, atopic dermatitis, asthma, Enterosgel, heavy metals, montelukast, toxicant, wheezing bronchitis

INTRODUCTION

Despite the considerable advancement in the diagnosis and treatment of bronchopulmonary diseases, asthma in children is still one of the most pressing problems in pediatric practice due to its prevalence, severity, and clinical particulars, particularly in territories unfavourable from a sanitary-hygienic and ecological point of view. The connection between air pollution and

acute respiratory disease, for example and, more recently, the observation linking poor indoor air quality to increases in the incidence of childhood asthma has been widely publicized [4]. Chemical toxicants of hazard Classes I–II¹, both inorganic and organic, exert a direct systemic toxic impact in children with allergic respiratory disorders [1]. Long-term irritation exerted on the barrier tissues maintains non-specific inflammation in the bronchopulmonary system, thus promot-

¹ According to Russian Waste Classification System chemical toxicants are divided into four classes from I (extremely hazardous) to IV (practically non-hazardous).

ing development of immunopathological reactions that underlie the development of asthma [2, 9]. After binding to plasma proteins, heavy metals become true allergens themselves and cause additional specific sensitization in children and potentiate the auto-immune processes in the bronchial mucosa, with subsequent development of resistance to standard therapy [7]. Besides, industrial toxicants increase the immunological aggressiveness of natural allergens.

The standard method of asthma prevention in children with recurrent wheezing bronchitis includes measures: creating hypoallergenic indoor environment, elimination of obligatory and causative allergens, and timely and efficient treatment of acute respiratory viral infection (ARVI) and exacerbations of recurrent wheezing bronchitis. Conventional treatment choices during an exacerbation include antiviral therapy, bronchodilators, mucolytics, second-generation antihistamines, and, if necessary, antibiotics and inhalational glucocorticosteroids.

Quality of life of patients with recurrent wheezing bronchitis and residents of chemically contaminated, unfavorable territories depends on whether or not these patients take during their remissions regular, long-term treatment with drugs decreasing bronchial hyperreactivity and reducing the content of environmental toxicants in the human body. We believed it was appropriate to propose a combination asthma prevention regimen during a remission of recurrent wheezing bronchitis including:

- montelukast sodium (Singulair). Montelukast sodium is a selective leukotriene receptor antagonist with pronounced anti-inflammatory activity [5];

- polymethylsiloxane polyhydrate (Enterosgel). Enterosgel is an intestinal adsorbent that exhibits high detoxifying effects and safety [6, 8];
- azoximer bromide (Polyoxidonium). Azoximer bromide is a water-soluble high-molecular synthetic immunomodulator [3].

Our study was directed to assess the effectiveness of combination treatment with montelukast sodium, Enterosgel, and azoximer bromide with the aim to prevent asthma in children with recurrent wheezing bronchitis who have elevated levels of heavy metals and aldehydes in the body.

MATERIALS AND METHODS

The study included 217 children aged from 3 to 7 years who suffered from recurrent wheezing bronchitis. All of these children resided in ecologically unfavourable regions. Inclusion criteria:

- recurrent wheezing bronchitis at the stage of remission;
- concurrent allergic rhinitis;
- concurrent atopic dermatitis – total SCORAD score above 30, SCORAD index above 52 points;
- a familial history of allergy (complicated allergic history);
- a history of frequent ARVI triggering bronchitis relapses.

All study subjects were divided into two groups: 167 children with environmental toxicant contamination above the reference level (experimental group) and 50 children whose blood concentrations of technogenic chemical substances did not exceed the reference value (control group). Both groups were representative with regard to age and gender.

The children in both groups received conventional treatment (antibacterial, drugs, mucolytics, bronchodilators) during an exacerbation of recurrent wheezing bronchitis.

The experimental group children who were in a remission were administered prophylactic treatment according to the optimized regimen:

- montelukast sodium orally, as chewable tablets, 1 time a day, at bedtime, at the following doses: 4 mg for children aged from 3 to 5 years and 5 mg for children aged from 5 to 7 years, in a course of 3 to 4 months;
- Enterosgel orally, 1.5 to 2 hours before or 2 hours after a meal, at the following doses: 5 g (one teaspoon) for children aged from 3 to 5 years and 10 g (two teaspoons) for children aged above 5 years, 3 times per day, in a course of 7 to 14 days;
- azoximer bromide, intramuscularly, at a dose of 0.1 to 0.15 mg/kg body weight, once every other day, over a course of 10 injections in total.

A combination therapy course with these drugs was prescribed (administered) at least twice a year.

In the control group, children received conventional treatment only during an exacerbation of recurrent wheezing bronchitis, and they did not receive any prophylactic treatment in remission stage.

The effectiveness assessment for the proposed prophylactic method was based on analysis of complaints at different time points of the study, physical examination data, and results of laboratory and functional investigations:

- at the *first stage*: after 4 month of post-hospital, out-patient pharmacological support;

- at the *second stage*: after 1 year of follow-up and two therapeutic-prophylactic courses conducted according to the proposed regimen.

The clinical and laboratory evaluation included the following:

- physical examination;
- complete blood count;
- blood chemistry tests:
 - aspartate aminotransferase (AST);
 - antioxidant activity (AOA);
 - malondialdehyde (MDA);
- immunological and allergological tests:
 - phagocytic activity: neutrophils' ability to phagocytose and reduce nitro blue tetrazolium (HCT test) and phagocytic index;
 - determination of CD³⁺, CD⁴⁺ lymphocytes;
 - total serum IgE, IgA, IgG;
- cytokine profile: interleukins (IL-6, IL-10), interferon-gamma (IFN- γ);
- leukotrienes (LTC₄/LTD₄/LTE₄);
- allergen-specific antibodies to indoor, epidermal, and pollen allergens;
- rhinomanometry;
- spirometry: forced expiratory volume in one second (FEV₁) and peak expiratory flow (PEF);
- determination of blood concentrations of heavy metals by means of atomic absorption spectrophotometry;
- determination of formaldehyde by means of paraphasic analysis with different variants of sample preparation.

Lymphocyte phenotyping was performed with an FACS Calibur flow cytometer manufactured by Becton Dickinson, using the CellQuestPro universal application package on a Macintosh PC.

Lymphocyte populations and subpopulation (CD³⁺, CD⁴⁺) were determined by membrane immunofluorescence, using labeled monoclonal antibodies to CD receptors (Becton Dickinson, USA).

Total serum IgE level was determined by EIA on an ELx808 photometer using Chema kits, while IgA and IgG were determined by radial immunodiffusion according to Mancini.

Phagocytic activity of blood cells was investigated using formalin-treated sheep erythrocytes.

Allergen-specific antibodies to domestic, epidermal, and pollen allergens were determined by EIA on a Tekan analyzer, using Immunotex kits.

IL-6, IL-10, and IFN- γ levels were determined by EIA on an ELx808 device, using Vektor-Best kits.

Plasma LTC₄/LTD₄/LTE₄ levels were determined by EIA on an ELx808 device, using Neogen kits (USA), following preliminary extraction on "C18Sep-pak" / ELx808 columns.

Respiratory function tests were performed on a Schiller SP-10 computer spirometer, in the forced-expiration spirometry test. Reference values of the principal bronchial patency parameters on the "volume-flow" curve were represented in the application package of the device with the Knudson calculations, by age, gender, body weight and length. Degree of bronchial patency impairment was assessed with FEV₁ and PEF values by means of comparison of relative "volume-flow" parameters (% of normal) with currently adopted bronchial patency grades.

Additionally, we performed multiple assessments of the state of the nose by

measuring transnasal pressure and one-second breathing flow volume during rhinomanometry on an RhinoStream SRE2000 instrument manufactured by RhinoMetrics.

Mathematical analyses of effectiveness endpoints adopted for the recommended asthma prevention method were carried out by means of non-parametric statistical tests, by obtaining and analysis of two-way contingency tables, using single-factor analysis of variance and linear and non-linear regression analyses. We utilized Fisher's test (for model adequacy testing), Student's t-test (quantitative comparison of groups), and Pearson's (chi-squared) test (statistical structure comparison) to test obtained results for reliability. Comparative assessment of probable relationships between groups of datavalues was obtained using the odds ratio (OR) with confidence interval analysis. Differences between obtained results were viewed as statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

Prior to initiation of prophylactic treatment, all children in the experimental group were shown to have higher blood concentrations of technogenic chemical substances, above reference levels (Table 1):

- lead (Pb⁸²) – 1.1-fold;
- hexavalent chromium (Cr⁶⁺) – 1.2-fold;
- nickel (Ni²⁸) – 1.3-fold;
- manganese (Mn²⁵) – 1.3-fold;
- formaldehyde – 1.2-fold.

In the control group, levels of contamination with heavy metals and formaldehyde of industrial origin were shown to be within the reference interval (Table 1).

Table 1.

Blood concentrations of industrial chemical toxicants in study subjects with recurrent wheezing bronchitis (mg/dm³, M ± m)

Tested substance	Experimental group (n = 167)	Control group (n = 50)	Reference interval	p value
Cr ⁶⁺	0.041 ± 0.003*	0.024 ± 0.001	0.007–0.028	0.01
Pb ⁸²	0.143 ± 0.003**	0.110 ± 0.005	0.1	0.001
Mn ²⁵	0.031 ± 0.001*	0.019 ± 0.008	0.0109	0.03
Ni ²⁸	0.040 ± 0.002**	0.015 ± 0.008*	0.03	0.001
Formaldehyde	0.035 ± 0.0005**	0.007 ± 0.0008*	0.005	0.001

Note: * $p < 0.05$, ** $p < 0.01$.

Elevated levels of heavy metals and aldehydes in children from the experimental group was accompanied by characteristic deviations of laboratory test results from normal physiological levels:

- leukocyte count decreased by more than 10–20%;
- eosinophil count increased more than 1.5- to 2-fold;
- lymphocyte count increased more than 1.3-fold;
- blood AST concentration increased by more than 15%;
- plasma AOA decreased by 15% to 20%;
- plasma MDA increased by 15% to 20% or more;
- total serum IgE concentration increased more than 2.0- to 2.5-fold;
- IgA concentration decreased by more than 20%;
- phagocytic index decreased more than 1.2-fold;
- 1.3-fold reduction in phagocytosis activity and intensity.

Functional tests (spirometry) demonstrated FEV₁ and PEF reductions to a 75% level.

The following favourable effects were observed in the experimental group after the first stage (at 4 months) of prophylactic treatment provided according to the described regimen:

- the frequency of ARVI decreased with statistical significance: 34% of the children did not have a single infection episode within one year, 45% of them had one or two infection episodes during that year that were mild and did not result in bronchitis exacerbation, and 19% had ARVI with bronchitis but without obstruction;
- practically greater part of patients (79%) had relieved symptoms of chronic intoxication, improved appetite and overall health;
- an improvement in nasal breathing was observed as well;
- the state of the skin improved dramatically, the symptoms of co-existing atopic dermatitis regressed: the skin lesion area shrank,

- pruritus was relieved, dryness and scratching diminished in 75% of patients. The total SCORAD score and the SCORAD index value were reduced more than 2.0-fold;
- leukocyte counts returned to normal and average group lymphocyte counts decreased with statistical significance, thus indicating decreased of immunity stress;
- the proportion of the patients with normal AOA increased from 24.1% to 39.1% ($p < 0.05$);
- the plasma MDA level decreased with statistical significance (from $2.8 \pm 0.15 \mu\text{mol}/\text{cm}^3$ to $2.3 \pm 0.04 \mu\text{mol}/\text{cm}^3$, $p = 0.037$). Whereas the control group MDA level went up (from $2.8 \pm 0.15 \mu\text{mol}/\text{cm}^3$ to $3.10 \pm 0.1 \mu\text{mol}/\text{cm}^3$, $p < 0.05$);

- total serum IgE concentrations decreased (from $176.3 \pm 18.3 \text{ IU}/\text{ml}$ to $128.74 \pm 15.23 \text{ IU}/\text{ml}$, $p = 0.025$). No improvement in this parameter was seen in the control group;
- levels of CD³⁺-lymphocytes and CD⁴⁺-lymphocytes returned to normal;
- the cytokine profile was normalized: the mean IFN- γ concentration increased from $5.30 \pm 0.23 \text{ pg}/\text{ml}$ to $8.30 \pm 0.35 \text{ pg}/\text{ml}$ in 100% of the experimental group patients.

The favourable changes observed in the markers of biochemical, metabolic, and immunological homeostasis in the experimental group children took place against a background of statistically reliable reduction in the body's contamination (Table 2).

Table 2.

Changes in blood concentrations of industrial chemical contaminants in the children with recurrent wheezing bronchitis treated according to the described asthma prevention regimen

Tested substance	Samples with above-normal results (%)				Concentration, mg/dm ³				p value	
	Experimental group (n = 167, M ± m)		Control group (n = 50, M ± m)		Experimental group (n = 167, M ± m)		Control group (n = 50, M ± m)			
	b. tr.	a. tr.	b. tr.	a. tr.	b. tr.	a. tr.	b. tr.	a. tr.	p ₁	p ₂
Cr ⁶⁺	78.0	43.0	68.0	52.0	0.041 ± 0.003	0.024 ± 0.002	0.024 ± 0.001	0.030 ± 0.001	0.004	0.08
Pb ⁸²	47.0	21.0	43.0	35.0	0.143 ± 0.003	0.110 ± 0.005	0.110 ± 0.005	0.133 ± 0.004	0.005	0.06
Mn ²⁵	31.0	15.0	31.0	28.0	0.031 ± 0.001	0.022 ± 0.001	0.019 ± 0.008	0.038 ± 0.001	< 0.05	0.58
Ni ²⁸	28.0	10.5	27.0	18.0	0.040 ± 0.002	0.014 ± 0.001	0.015 ± 0.008	0.035 ± 0.0001	0.001	0.05
Formaldehyde	63.0	32.0	58.0	47.0	0.035 ± 0.0005	0.01 ± 0.0005	0.007 ± 0.0008	0.022 ± 0.0003	< 0.001	0.06

Note: b. tr. – values before treatment;

a. tr. – values after treatment;

p₁ – significance of differences between pre- and post-treatment values in the experimental group;

p₂ – significance of differences between pre- and post-treatment values in the control group.

Table 3.
Clinical effectiveness of asthma prevention regimens with various medicinal product combinations during follow-up (one year)

Pharmacotherapy regimen	Number of children without bronchitis exacerbation (%)	Number of children with 1–2 episodes bronchitis exacerbations per year (%)	Number of children with more than 2 bronchitis exacerbations per year (%)	Number of children developing asthma (%)
Enterosgel + Azoximer bromide	12.0	25.0	63.0	37.0
Montelukast sodium + azoximer bromide	27.0	36.0	37.0	17.0
Enterosgel + Montelukast sodium	23.0	37.0	40.0	22.0
Enterosgel + Montelukast sodium + Azoximer bromide	34.0	64.0*	2.0*	0.0*

Note: * $p < 0.05$. vs. other groups.

The average group blood Pb⁸² concentration was brought to the reference level with the optimized treatment regimen, while the number of the children with high individual values decreased from 35% to 5% ($p = 0.05$, $\chi^2 = 3.98$).

After the *first stage* that included use of montelukast sodium, Enterosgel, and azoximer bromide given according to the proposed regimen, the average formaldehyde concentrations decreased 3.5-fold, which was not observed in the control group children. In the control group, on the whole, no definite reduction in the blood concentrations of chemical substances was observed against a background of conventional treatment for recurrent wheezing bronchitis.

After the *second stage* of prophylactic treatment in the experimental group,

children had no more exacerbation of bronchitis, their results of respiratory function tests returned to normal, signs of atopic dermatitis and allergic rhinitis were eliminated, and no child with recurrent wheezing bronchitis had this disease transformed into asthma. The clinical effectiveness of various prophylactic pharmacotherapy combinations administered during the follow-up period (one year) is demonstrated in Table 3.

The presented data provide a clear demonstration of additive activity of the three medicinal products as part of the proposed prophylactic method.

CONCLUSIONS

1. The combined use of montelukast sodium, Enterosgel, and azoximer bromide is more effective treatment option for asthma prevention in children with

recurrent wheezing bronchitis than monotherapy or application of two medicines.

2. The proposed, scientifically substantiated method of combination therapy with montelukast sodium, Enterosgel, and azoximer bromide in children with recurrent wheezing bronchitis and contaminated with industrial toxicants is a valuable supplementation to standard treatment for recurrent wheezing bronchitis.

3. This treatment regimen may be recommended for the prevention of asthma and the treatment of atopic dermatitis and allergic rhinitis in children residing in industrially developed territories with increased contamination with toxicants that promote the development and progression of the atopic march.

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Enterosgel in the Combination Treatment of Atopic Bronchial Asthma

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Keywords: adsorbent, bronchial asthma, circulating immune complexes, enterosorbent, Enterosgel

INTRODUCTION

The method of gastrointestinal adsorption (enterosorption) is pathogenetically justified in view of the increasing antigenic overload, particularly with unfavorable environmental ecological factors. The new-generation intestinal adsorbent Enterosgel (polymethylsiloxane polyhydrate) exhibits potent adsorptive activity and positive effects on intestinal microbiota [1, 2]. The objective of this study was to evaluate the effectiveness and safety of the intestinal adsorbent Enterosgel in the treatment of patients with atopic bronchial asthma.

MATERIALS AND METHODS

The experimental group of the study included 57 patients with atopic asthma aged from 17 to 69 years who received conventional asthma therapy and Enterosgel. The control group was composed of 53 patients who received conventional therapy alone.

All patients were admitted to the hospital in a marked exacerbation of their

moderate to severe disease, which was hormone-dependent in 15 subjects. In 22 patients, the asthma exacerbation had been triggered by a concurrent respiratory infection or activation of concomitant nidus of chronic infection. Atopic dermatitis was associated with asthma in 12 subjects from the experimental group, and 8 patients presented with manifestations of food allergy.

The patients' clinical condition was monitored by standard physical examination, laboratory, X-ray, functional and immunological studies and tests.

Enterosgel was administered according to the standard regimen: 1 tablespoon 3 times a day, 2 hours before or 2 hours after a meal.

RESULTS AND DISCUSSION

The experimental group (Enterosgel treated) has shown appreciably earlier reduction of the number of acute asthma attacks versus the control group. And besides, the nocturnal asthma equivalents were disappeared and insomnia eliminated.

Respiratory function monitoring by means of a respirometer demonstrated a 24.4% improvement in test results in the experimental group and a 17.1% increment in the control group ($p < 0.005$).

The inclusion of the Enterosgel in the treatment programme allowed significant improvement in the manifestations of atopic dermatitis, such as pruritus, infiltration, and lichenification. Another finding was marked limitation of the skin lesion.

The dyspepsia associated with food allergy was eliminated with Enterosgel treatment.

The administration of Enterosgel also led to significant improvements in the clinical and laboratory manifestations of intoxication in patients with asthma exacerbations caused by an infection. In particular, the experimental group patients had earlier, as compared with controls, normalization of body temperature, heart rate, as well as improvement or elimination of dyspnea and sweating. The patients on Enterosgel treatment had their subjective symptoms of intoxication, including general weakness, easy weariness on physical exertion, decreased appetite, impaired power of concentration, and irritability, decreased as early as by the 5th or 6th day of treatment. These patients also had a significantly shorter time to recovery of laboratory test results: ESR, band neutrophil count, and leukocyte index of intoxication according to Ya. Ya. Kalf-Kalif (2-fold reduction).

Eosinophilia levels did not differ significantly between the experimental and control groups. The experimental group patients attained faster normalization of middle molecular weight substance content and liver

function test results (bilirubin, cholesterol, ALT, AST, GGT, alkaline phosphatase, thymol).

The patients who received Enterosgel as part of their combination treatment also had the following immunological improvements:

- there was a reduction from an elevated baseline circulating immune complexes level (approximately in half compared with the control group);
- the following phagocytosis parameters returned to normal:
 - phagocyte number;
 - phagocytosis percentage;
 - neutrophils' ability to phagocytose and reduce nitro blue tetrazolium (HCT test);
- a 23.4% reduction ($p < 0.005$) was achieved in total serum IgE in relation to controls.

Enterosgel was well tolerated, no complications were observed during its use.

CONCLUSIONS

The inclusion of the intestinal adsorbent Enterosgel in the standard (conventional) treatment programme for atopic asthma allows to achieve the following:

1. Considerably less intoxication and antigenic aggression.
2. Mitigated immunosuppressive activity of endogenous toxins.
3. Decreased pharmacological burden of conventional therapy.

Application Enterosgel simultaneously with conventional therapy has proven effectiveness in the treatment of patients with atopic bronchial asthma.

The results obtained in this study lead us to recommend Enterosgel for wider application in the combination treatment of atopic bronchial asthma.

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EXTENDED ABSTRACT

On the Issue of the Treatment of Children with Allergic Diseases

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Keywords: adsorbent, allergic diseases, dermal-respiratory syndrome, enterosorbent, Enterosgel

INTRODUCTION

A gradual growth in the incidence of allergic diseases has been observed in children since the second half of the 20th century [1]. According to epidemiological studies, 20% of the world population suffer from allergic diseases [2]. This is largely due to the impaired ecological balance, wide use of domestic and agricultural chemicals, common (and frequently uncontrolled) use of antibiotic therapy, vaccine prophylaxis of pediatric infections, and early discontinuation of breastfeeding. Furthermore, allergic diseases have been becoming considerably “younger” in the last decade, i.e. they have their onset at an earlier age and tend to more frequently have severe clinical forms. Therefore, allergy in children is one of the most topical problems in modern clinical medicine. Lability and functional immaturity of many

organs and systems are characteristic of young children, being responsible for the specifics of the immune regulation processes. This often results in sensitization, resistance to conventional, standard pharmacological therapy, and difficulties in choosing the optimal treatment strategy for the disease.

Therefore, the search for novel drugs and treatments for diseases associated with immune status impairment is a topical issue. Normalization of gastrointestinal function is an essential element in the pathogenetic treatment. Inclusion of intestinal adsorbents (enterosorbents), in particular Enterosgel, in the combination therapy of allergic diseases is one of the promising approaches. This study was carried out with the aim to evaluate the effectiveness, tolerability, and safety of Enterosgel therapy in the treatment of children with dermal-respiratory syndrome.

MATERIALS AND METHODS

We examined a total of 56 children aged from 3 to 17 years and suffering from dermal-respiratory syndrome in the period from 2006 to 2008. Among them, 27 children were given Enterosgel as part of their combination therapy (experimental group), while the other 29 patients were administered conventional therapy alone (control group).

All children aged over 5 years underwent allergological examination. The dermal-respiratory syndrome had become exacerbated because of domestic allergens, plant pollen, house dust, or use of medicines (most commonly antibiotics). Food allergy was observed in more than one-third of all evaluated children, and the overwhelming majority of them had multiple allergies, which was probably indicative of a pseudo-allergic mechanism of development underlying their disease. This reflected a need to undertake a comprehensive complex of therapeutic measures with the aim to correct all elements and stages in the development of allergic diseases.

RESULTS AND DISCUSSION

Results obtained in the study groups demonstrated that the inclusion of the intestinal adsorbent Enterosgel in the combination treatment programme promoted fast regression of the manifestations of dermal-respiratory syndrome:

- reduction of rash and skin edema (85%) by the 5th day of the combination therapy;
- improvement of dyspepsia: normalization of stools, elimination of nausea and vomiting.

At the same time, the children in the control group had less pronounced improvement in the dermal-respiratory syndrome; any improvement was achieved only in 27.6% of these subjects. Relief of the symptoms of dermal-respiratory syndrome, abdominal syndrome, and dyspepsia was achieved as late as on the 7th or 8th day of the combination therapy.

All children tolerated Enterosgel therapy well. No patients experienced adverse drug reactions or refused to have this treatment.

CONCLUSIONS

Therefore, the reported study confirmed the pathogenetic justification for and benefits of Enterosgel therapy in the combination therapy of allergic diseases in children.

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ANNEX

Enterosgel® in Allergology and Dermatology: Posology and Method of Administration*

Enterosgel® (polymethylsiloxane polyhydrate) Oral suspension						
Age range	Single dosage	Frequency	Daily dose	Method of administration	Duration of treatment	Specific recommendation
Adults ≥ 14 years	15 g (1 sachet or 1 tablespoon)	3 times per day	45 g /day	Oral administration at 1–2 hours before or after a meal	2–3 weeks	For children under 1 year the single dose is taken before feeding
Children 5 years to < 14 years	10–15 g (2–3 teaspoons)	3 times per day	30–45 g /day	When Enterosgel is taken it is recommended to wash down the single dose with sufficient quantity of water or dilute it in half a glass of water prior to administration	No restrictions on repeat of courses of Enterosgel application	For children under 1 year the single dose may be mixed with milk, infant formula, juice or a semi-liquid baby food (in the ratio 1:3) before administration
Children 1 year to < 5 years	5–10 g (1–2 teaspoons)	3 times per day	15–30 g /day			
Children < 1 year	1,7 g (1/3 teaspoon)	Up to 6 times per day	Up to 10 g /day			

*Based on the Patient Information Leaflet (revised January 2013).

Enterosgel has been approved as a medicinal product in CIS and as a Class IIa medical device in Europa.

