УДК 616.921.5+616.988/_053.2_08_084

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Современные аспекты профилактики и лечения гриппа и ОРВИ у детей

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SOVREMENNAYA PEDIATRIYA.2017.4(84):82_85; doi 10.15574/SP.2017.84.82
Статья посвящена проблеме частой заболеваемости детей острыми респираторными инфекциями (ОРИ). В настоящее время имеются все возможности для эффективного предупреждения и комплексного подхода к лечению повторных ОРИ у детей. В статье представлены результаты ретроспективного неселективного анализа медицинской документации 164 детей первого года жизни, перенесших грипп и ОРВИ и находившихся под наблюдением в ГУ «Институт педиатрии, акушерства и гинекологии НАМН Украины» за период с 2012 по 2017 годы. В качестве этиотропного противовирусного препарата был использован растительный препарат — сироп Иммунофлазид®, эффективность которого определялась путем сравнения динамики клинических общетоксических симптомов, местных реакций и основных лабораторных показателей периферической крови. Оценивалась частота развития осложнений и сроки выздоровления у детей. В результате проведенного исследования доказана эффективность лечения и профилактики ОРВИ и гриппа у детей раннего возраста путем использования сиропа Иммунофлазид®.
Ключевые слова: дети, острые респираторные инфекции, профилактика, лечение, Иммунофлазид®.

Modern aspects of prevention and treatment of influenza and ARVI in children

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The article deals with the problem of frequent incidence of acute respiratory infections (ARI) in children. It is shown that at the present time there are opportunities to effectively prevent repeated ARI in children. The article presents the results of a retrospective non3selective analysis of medical documentation of 164 children of the first year of life who had influenza and ARI and were monitored by the State Institution «Institute of Pediatrics, Obstetrics and Gynecology of NAMS of Ukraine» for the period from 2012 to 2017. As an etiotropic antiviral preparation, a herbal preparation, the Immunoflazid® syrup, was used, the efficacy of which was determined by comparing the dynamics of clinical general toxicity symptoms, local reactions and the basic laboratory parameters of peripheral blood. The incidence of complications and the terms of recovery in children were assessed. As a result of the study, the efficacy of treatment and prevention of acute respiratory viral infection and influenza in young children was proved by using the Immunoflazid® syrup.
Key words: acute respiratory infections, children, prevention, treatment, Immunoflazid®.

Сучасні аспекти профілактики та лікування грипу та ГРВІ у детей

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Стаття присвячена проблемі частої захворюваності дітей гострими респіраторними інфекціями (ГРІ). Наразі є усі можливості для ефективного запобігання і комплексного підходу до лікування повторних ГРІ у дітей. У статті наведені результати ретроспективного неселективного аналізу медичної документації 164 дітей першого року життя, що перехворіли на грип і ГРІ і знаходилися під спостереженням в ДУ «Інститут педіатрії, акушерства і гінекології НАМН України» за період з 2012 по 2017 роки. У якості етіотропного противірусного препарату застосовувався рослинний препарат — сироп Імунофлазід®, ефективність якого визначалася шляхом порівняння динаміки клінічних загальнотоксичних симптомів, місцевих реакцій та основних лабораторних показників периферичної крові. Оцінювалася частота розвитку ускладнень і терміни одужання у дітей. У результаті проведеного дослідження доведена ефективність лікування і профілактики ГРВІ та грипу у дітей раннього віку шляхом застосування сиропу Імунофлазід®.
Ключові слова: діти, гостра респіраторна інфекція, профілактика, лікування, Імунофлазід®.

Introduction

According to the present epidemiological data, in the world, the share of viral diseases accounts for up to 90% of all infectious diseases [1,2,4]. The most vulnerable among the world's population are children. According to the literature, on average, each child suffers from three to six episodes of acute respiratory viral infection during the year, often with the risk of further allergic complications, delayed physical and psychomotor development, secondary immunosuppression as well as chronic diseases among which bronchopulmonary and ENT-pathology occupy the leading place [3,5].

Acute respiratory diseases (ARD) are infectious diseases of the respiratory tract similar in their epidemiological characteristics, developmental mechanisms and clinical manifestations caused by respiratory viruses of heterogeneous polyetheological groups. Among the etiological factors of ARD, the leading place is occupied by: influenza A viruses (H1N1, H2N2, H3N3); influenza B virus; influenza C virus; adenoviruses - 41 serovars; respiratory syncytial virus - 2 serovars; metapneumonic viruses - 2 types; parainfluenza virus - 5 types; rhinovirus - 113 serotypes; reovirus - 3 serotypes; enteroviruses - 30 serovars; coronaviruses (229E, OS43, and B814), SARS (mutant) [2,7,10].

The "entrance gate" for the causative agents of acute respiratory viral infection (ARVI) is the mucous membranes of the respiratory tract (nose, throat, larynx, trachea, bronchi) where active replication of respiratory viruses occurs. The penetration of viruses into epithelial cells leads to the development of a local inflammatory response. Products of the cell dissolution getting into the bloodstream cause systemic toxic effects. All this causes a symptom complex typical for ARVI: a combination of general toxic (fever, weakness, apathy, headache, myalgia), and local reactions (rhinitis, nasal congestion, sore throat, hyperemia of the mucous membranes of the oropharynx, cough) [6,9,12].

The probability of ARD, the intensity of clinical manifestations and the disease outcome in children are determined by age, susceptibility to ARVI pathogens, i.e. the state of both general and local immunity of the mucous membranes of the respiratory tract.

The physiological development of the immune system in children consists of several critical periods: the first takes place in the age of 0 to 28 days; the second in 4–6 months; the third at about 2 years; the fourth at 4–6 years, and the fifth is terminated at 12–15 years [4,12].

Immunity is a protective system of the body against genetically foreign exogenous and endogenous agents which functioning mechanisms are aimed at preserving and maintaining homeostasis, structural, functional, biochemical integrity and antigenic individuality. The operational stages of defense mechanisms are known, there are the recognition, processing and elimination of foreign structures [8,10,18].

There are two systems for the protection of immunity, non-specific (congenital, natural) and specific (acquired). Non-specific immunity acts as the first line of defense and as its final stage, and the system of acquired immunity performs the functions of specific recognition and memorization of an foreign agent and connection of powerful innate immunity at the final stage of the process [4,9].

In the development of the immune system upon birth, the first and second periods, when the child is most vulnerable and not protected from external viral aggression, are of particular importance. It should be noted that in the neonatal period, the immunity of the baby who is breastfed is, to a greater extent, is passive in nature due to maternal immunoglobulins and antibodies. At the same time, the own immune system is in a relatively suppressive state with a functionally immature cytokine profile and regulation of the balance between T-helpers of the Th1- and Th2-lymphocytes [3,11,12].

Th1/Th2_balance is important for the implementation of an adequate immune response. Th1_cells mainly specialize in the production of gamma-interferon (γ-IFN), interleukin-12 (IL-12), IL-2, and tumor necrosis factor alpha (TNF-α), and Th2-cells produce IL-4, IL-5, IL-10, and IL-13 [12]. Th1 lymphocytes potentiate the development of a cellular immune response directed against intracellular pathogens (viruses, etc.) and oncogene-transformed cells by triggering cytotoxic reactions and also stimulate the production of IgM and IgG antibodies by B lymphocytes. Th2 cells, in turn, enhance the development of the humoral immune response against extracellular pathogens (including bacteria) and multicellular parasites [2,10,12].

In the neonatal period, given the existence of the immaturity of the regulatory system and the suppressor state of its own immune system with an unformed Th1/Th2 balance, children during this period have the highest sensitivity to viral load, realization and generalization of secondary bacterial infection [4].

Then (aged from 4 to 6 months) with gradual termination of breastfeeding, maternal antibodies are destroyed, the child develops a primary immune response with the synthesis of immunoglobulins M without forming an immunological memory, and also begins the gradual formation of an immune response mechanism capable of removing one or another antigen in the form of the ability to differentiate Th0 cells. Stimulation of Th0 cells with high and low doses of antigen leads to their differentiation into Th1 cells, and with medium doses, to differentiation into Th2 lymphocytes [4,12].

According to the literature, differentiation processes of immunocompetent cells in the second critical period are among the leading causes of increased morbidity in young children. Among pediatricians, immunologists and allergologists, the prevailing role of the helper orientation of the immune response vector and the prevalence of type 1 (Th1) T-helper over type 2 (Th2) T-helper is discussed. Thereby, it is suggested that ontogenetically the tolerated ARDs are physiologically significant for the maturation of immunity (a kind of "training" of immunity), since they contribute to the normalization of the Th1/Th2 ratio and the reorientation of the primary immune response to secondary [5,11,14].

In fetus, the Th2-type immune response is predominant, so allergic sensitization can occur even in the period of prenatal development. The imbalance between Th1 and Th2 production observed in early childhood can persist for a long time. Therefore, it is believed that the very first months of life are crucial in terms of the development of allergies [12,15,18].

It is the reorientation of the immune response from Th2 to Th1 which begins at the age of 6–7 months, in the 2nd year of life causes a higher sensitivity of the child's body and a less differentiated response of the immune system to respiratory viral infections including influenza. In addition, the anatomical and physiological peculiarity and lack of local immune response in the first and second critical periods of the immunity formation play their assigned role in susceptibility to repeated ARVI, susceptibility to skin lesions, intestinal infections, etc. in young children [4,13,16].

Considering that these processes are due to the effects of certain cytokines produced in response to infection, researchers' expectations of the preventive use of various drugs that modulate the cytokine profile (interferons and their inductors, bacterial immunomodulators, peptidoglycans, muramyldipeptide, etc.) become understandable.

Thus, the peculiarities of the immune system formation and anti-infective protection from birth and during the first year of life explain the reasons for the protracted, repeated and complicated course of ARD in children which necessitates the search for effective methods of preventing and treating SARS and influenza in young children. A necessary condition for a qualified approach to the SARS treatment is the safety of drugs, high pharmacodynamic possibilities of suppressing the viral aggression, increasing immunological protection at the systemic and local level based on latest evidences [8,13,15].

In those cases when, despite ongoing preventive measures, the child still suffers from another episode of respiratory infection, it is very important to adhere to the principles of appropriate therapy. In view of the polyetiology of the causes and provoking factors of the ARD emergence, a comprehensive approach at all stages of child observation (family, organized community, clinic, sanatorium) is needed which includes:

- compliance with the day regimen;
- full balanced diet;
- correction of autonomic disorders;
- conditioning;
- massage;
- physical activity according to age;
- phytotherapy, oral detoxification (if necessary);
- rehabilitation of chronic infection nidus;
- treatment of comorbid (concomitant) diseases;
- polypragmasy control;
- immunotropic therapy [12,13,18].

Of particular note is the inadmissibility of the patterned use of antibiotics. The use of antibacterial therapy is possible only when there are sufficient grounds for this (angina, exacerbation of chronic tonsillitis, purulent otitis, pneumonia, etc.). Otherwise, the widespread and uncontrolled use of antibiotics not only contributes to the selection of resistant strains but also leads to serious dysbiotic disorders in the child [5,7,11].

The most effective means of preventing SARS and influenza is vaccination, however, because of the constant change in the antigenic abilities of the pathogen, constant monitoring with the annual development of new vaccine strains is necessary which is not always possible for the population in each specific epidemic season.

Currently, among the medical treatment and prevention of SARS and influenza, various groups of antiviral drugs with a direct mechanism of action are offered: M2 channel blockers, RNA synthesis inhibitors, neuraminidase inhibitors. These drugs have a number of significant drawbacks - a narrow spectrum of action (inefficiency against type B influenza), age restrictions, the presence of significant contraindications.

According to the literature, the long-term and widespread use of M2-channel inhibitors (cyclic amines - adamantane and its derivative rimantadine hydrochloride) leads to the emergence of an increasing number of resistant strains of influenza viruses [9]. It should also be noted that many strains of influenza viruses are already resistant to rimantadine hydrochloride preparations. The rarer use of drugs of this group in recent years is explained by the fact that their effect is limited only by the forms of influenza infection that are caused by the influenza A virus (especially A2).

Unlike rimantadine hydrochloride preparations, oseltamivir derivatives inhibit all types of influenza virus epidemic strains (a group of neuraminidase inhibitors). Thereby, over a period of years, the frequency of the oseltamivir-resistant strains of the influenza virus was extremely low which allowed the World Health Organization to recommend to national authorities to create strategic stocks of the drug in case of a new pandemic. At the same time, preparations of neuraminidase inhibitors are not used for the prevention and treatment of other ARVI, they have a pronounced selective effect exclusively on neuraminidase of influenza type A virus and influenza type B virus [6]. The disadvantage of taking these drugs is frequent gastrointestinal tract and blood system disorders [9].

In addition, in the clinical manifestations of ARVI, interferons or their inducers can be used - a group of glycopeptides, regulators of immunogenesis with pronounced antiviral activity [12,14].

In recent years, the topic of the efficacy and safety of herbal medicines has been brought up in the medical community. These include adaptogens and biogenic drugs. Generally, they have a general tonic effect, increase the adaptive reactions of the body, contribute to the restoration and normalization of the immune system.

However, there are also such herbal preparations that exhibit a direct antiviral effect due to the inhibition of virus-specific enzymes which leads to a decrease or cessation of the virus reproduction. These herbal preparations inhibit viral neuraminidase, stimulate the production of endogenous interferon, and also have an immunomodulatory action.

The medical information field published the results of experimental and clinical studies on the use of the Immunoflazid® syrup (LLC NPK EKOFARM) for the treatment and prevention of SARS and influenza in children of different ages which contains the extract of Proteflazid from turfy hair grass (Herba Deschampsia caespitosa L.) and bush grass (Herba Calamagrostis epigeios L.) (1: 1) [4,16,17,19].

The flavonoids that make up the syrup have the ability to inhibit the replication of DNA and RNA viruses, both in vitro and in vivo. When conducting preclinical and clinical studies, the inhibitory activity of the drug was found relative to influenza viruses and acute respiratory infections, herpes viruses. It is proved that the mechanism of direct antiviral action consists in inhibiting the synthesis of virus-specific enzymes - DNA and RNA polymerases, thymidine kinase, reverse transcriptase, neuraminidase, and induction of the synthesis of endogenous interferon.

In addition to the direct antiviral effect, Immunoflazid® syrup protects the mucous membranes of the upper respiratory tract normalizing the indices of local immunity (lactoferrin, sIgA and lysozyme). During the research, it was found that the drug normalizes the synthesis of endogenous α- and γ-interferons to a physiologically active level which increases the non-specific resistance of the organism to viral and bacterial infections.

Clinical studies have shown that with daily administration of Immunoflazid in the age-related doses and in accordance with the dosage schemes, refractoriness of the immune system does not occur: no further inhibition of the synthesis of α- and γ-interferons is observed.

Table

Dynamics of indicators of the SARS and influenza course in children, absolute number (M ± m)

Indicator	Study group		p
	Main, Immunoflazid (n=98)	Control (n=66)	
Duration of symptoms (days): • general toxic • local	 3.2±0.9 2.9±1.4	 10.3±2.4 11.5±1.8	 p<0.01 p<0.01
Changes in laboratory parameters: • lymphocytosis (absolute number) • recovery of indicators (days)	 72 4.7±1.4	 51 12.6±2.7	 p<0.01
Recovery to the 5th day (absolute number)	88	12	
Duration of treatment (days)	3.7±1.3	9.7±2.6	p<0.01
Duration of the bronchitis clinical symptoms (days)	6.8±1.9	11.5±2.4	p<0.05

This property of Immunoflazid® syrup helps to maintain the level of interferons which is sufficient for an adequate body immune response, regarding the time and strength, to an infectious pathogen. In turn, this makes it possible, if necessary, to use the drug for a long time.

The drug has antioxidant activity, inhibits the free radical processes, thereby preventing the accumulation of lipid peroxidation products, enhancing the antioxidant status of cells, reduces intoxication, contributes to the restoration of the body after infection and adaptation to adverse environmental conditions.

Immunoflazid® is a modulator of apoptosis: it enhances the action of apoptosis-inducing factors activating caspase-9 which contributes to a more rapid elimination of virus-infected cells and primary prevention of the onset of chronic diseases against the latent viral infections.

The complex properties of the syrup and its safety led to the choice of this drug for the treatment and prevention of recurrent respiratory infections in children of the first year of life.

Objective of the research***:*** to increase the effectiveness of treatment and prevention of SARS and influenza in young children through the use of Immunoflazid® syrup (LLC NPK EKOFARM).

Material and methods of research

Medical documentation of 164 children of the first year of life who have had influenza and ARVI and were under observation in the State Institution "Institute of Pediatrics, Obstetrics and Gynecology of the National Academy of Medical Sciences of Ukraine" during the period from 2012 to 2017 was retrospectively non-selectively analyzed. The main study group consisted of 98 children who received an etiotropic antiviral drug - Immunoflazid® syrup as a treatment for SARS and influenza. The control group included 66 children of the first year of life who received traditional therapy without the herbal preparation Immunoflazid.

For treatment of influenza and ARVI with uncomplicated course, Immunoflazid® syrup was used in an age-related dosage for five days, according to the instructions for the preparation. Depending on the course of the disease, the course of treatment was extended to two weeks, and in children with recurrent diseases, the administration of the drug was extended to 4-6 weeks.

The efficacy of Immunoflazid® syrup was determined by comparing the dynamics of clinical symptoms and the main laboratory parameters of peripheral blood (general detailed blood test, CRP). The intensity of clinical symptoms in all children was accompanied by a combination of general toxic (increased body temperature from subfebrile to febrile levels, weakness, apathy, headache, myalgia) and local reactions (rhinitis, nasal congestion, sore throat, hyperemia of the mucous membranes of the oropharynx, cough). The incidence of complications and recovery time in children of both groups was assessed.

Research results and discussion thereof

In general, 5-day therapy with Immunoflazid positively influenced all stages of the course of SARS and influenza in children (see table). By the fifth day of observation, complete recovery occurred in 89.7% of children in the main group, while in the control group - only in 18.2%. Thereby, it was noted that the use of the Immunoflazid® syrup made it possible to shorten the course of treatment by almost three times. Administration of an antiviral drug was supplemented with regimen, adequate diet and symptomatic therapy. In addition, the need for nasal decongestants was two times less than in the control group ($p < 0.01$). It was also shown that in the control group a need for mucolytics and antipyretics was up to 2.5 times more often.

A detailed analysis of the characteristics of the course of respiratory infections in children of the main group showed a positive effect of the Immunoflazid on the dynamics of regression of individual clinical manifestations. In general, it was found that when prescribing the etiotropic antiviral drug Immunoflazid®, arresting the symptoms of ARVI occurred more quickly. Thus, the regression of general toxic symptoms (fever from subfebrile to febrile levels, weakness, apathy, headache, myalgia) and local reactions (rhinitis, nasal congestion, sore throat, hyperemia of the mucous membranes of the oropharynx, cough) were more significant in the main group and 2.5 times different from the control group. Thereby, the maximum differences in the intensity and regression rate of these symptoms were noted already by the 3-5th day of treatment.

Bronchitis, as a frequent complication of influenza and ARVI, was observed in 18.4% of children in the main group, and in children who did not receive syrup, it was diagnosed more often in 28.8%. In view of the complication of the disease, the course of treatment with the Immunoflazid was extended to 2 weeks. Thereby, the dynamics of the cough intensity during syrup therapy was characterized by a more rapid recovery. It was noted that in the main group, auscultatory changes which by the 7th day of observation in children who received Immunoflazid® were detected two times less frequently than in the control group, were arrested more quickly.

It should be noted that there was no recurrence of the disease in 85.7% of children who received Immunoflazid® for three months after the treatment and the good tolerability of the drug was observed as well as its high therapeutic and prophylactic potential which was noted in the treatment of 100% of children with uncomplicated ARVI.

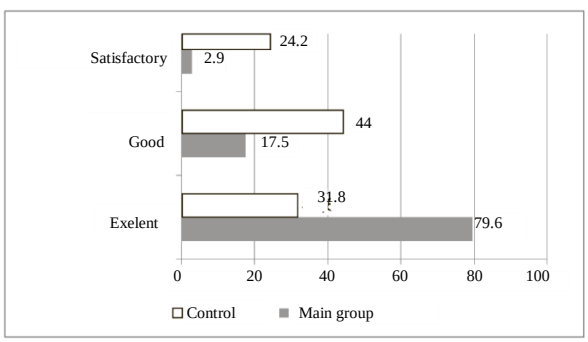

Fig. *The character of complex treatment tolerance in children, %*

To confirm cases of SARS and influenza in children of both groups, standard peripheral blood parameters were monitored before the start of therapy and in the dynamics of observation. Among the changes confirming the viral nature of the disease, leukopenia with lymphocytosis was noted in 73.5% of the children in the main group and in 77.3% of the control group. The normalization of indicators against the therapy with Immunoflazid took place by 3-5 days of the disease, whereas in children of the control group - only by 10-14 days.

The tolerance to Immunoflazid® in the examined children was separately studied. It should be emphasized that the excellent and good tolerance to the drug was noted in the vast majority of children (97.1%). Thereby, excellent tolerance to the complex therapy with the inclusion of the etiotropic antiviral drug Immunoflazid® was established in 79.6% of cases, while a similar assessment of basic therapy occurred in only 31.8% of children ($p < 0.01$). Satisfactory tolerance to the therapy with the inclusion of immunoflazid was only in isolated cases (2 patients). At the same time, the satisfactory tolerance to the traditional treatment (control group) was in 24.2% of children ($p < 0.01$) (see Fig.). Of particular interest is the fact that, if re-use of the drug in subsequent periods of observation is necessary, the high clinical efficacy and good tolerance thereof remain.

Thus, the presented data indicate a high therapeutic efficacy and good tolerance of the etiotropic antiviral drug Immunoflazid® in the treatment of SARS and influenza in children of the first year of life.

Conclusions

1. At the present stage of development of pharmaceuticals and medicine, there are all possibilities for the effective prevention and treatment of recurrent infections in young children. The basis of all preventive work aimed at rehabilitation lies in finding out the causes and provoking factors of recurrent ARVI and their elimination, normalization of the day regimen and diet, sanitation of chronic inflammatory nidus, general conditioning measures, and immunoprophylaxis of respiratory infections. For specific immunoprophylaxis in children, both immunization against pneumococcal, rhino-syncytial, rotavirus and CIB infections at the decree age, and anti-influenza vaccination should be used. Non-specific prophylaxis of respiratory infections is carried out using immunomodulators selected according to the individual characteristics of the child [12–17].

2. In the rehabilitation of children, reasonable treatment during the period of ARD or in the case of recrudescence of chronic infectious and inflammatory diseases of the respiratory tract,

taking into account the characteristics of the immune age-related status, is of great importance. At the same time, Immunoflazid® syrup can be recommended for effective and safe antiviral therapy.

3. As a part of the study, it was found that the use of the antiviral drug Immunoflazid® contributed to a rapid clinical improvement - the average recovery time was five days, the regression dynamics was 2.5 times faster. There was also a significant reduction in the frequency of respiratory infections in children who received syrup in subsequent periods of observation (during the year).

Authors declare no conflict of the interest.

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