

ABSTRACT

for the dissertation work by Zhamankulov Adil Abusalimovich on the topic: «Improving the effectiveness of immune rehabilitation in children with recurrent respiratory infections» submitted for the degree of Doctor of Philosophy (PhD) in the specialty 8D10102- «Medicine»

Relevance.

The frequency of respiratory tract diseases occupies one of the leading places among the morbidity of children of different age groups. Every year around the world in developing countries from respiratory infections, in particular, pneumonia, about 150 million cases are registered, of which 920,000 thousand deaths among children under 5 years old (Perin J., 2022). Recurrent respiratory infections (RRI) in children are one of the most common causes of hospitalization in hospitals and frequent visits to pediatricians (Toivonen L., 2016).

RRI in children is defined as the incidence of respiratory infections more than six times a year or two or more episodes of respiratory infection of the lower respiratory tract, as well as otitis media with a frequency of four or more, tonsillopharyngitis from three or more times and bronchitis more than three episodes during the year (Woicka-Kolejwa K., 2016, De Benedictis F.M., 2018, Venekamp R.P., 2018). RRI requires a serious diagnostic approach and identification of the causes, since there is a problem of unjustified prescription of antibacterial drugs all over the world. For example, in the United States of America, about 10 million prescriptions of antibacterial drugs are prescribed annually on an outpatient basis for the treatment of diseases of the respiratory system, which is ultimately ineffective, since respiratory diseases are more often of viral origin (Hersh A. L., 2011). Such irrational use of antibacterial drugs leads to undesirable side effects, resistance of microorganisms, and also incur large economic losses (Cohen A.L., 2008, Piovani D., 2013).

According to the latest research data, the main risk factors for RRI are: excessively early attendance of preschool institutions, early socialization, a large number of family members, environmental pollution, smoking in the family and during pregnancy, anemia, atopic diseases of the child, vitamin D deficiency, early termination of breastfeeding and poor socio-economic situation, etc. (Ikramova S. H., 2018, Bloomberg G.R., 2011, Schaad U.B., 2015).

Constant contact with a variety of pathogens causes a recurrence of respiratory infections, the immune system "does not have time" to recover. The pathological chain of recurrent respiratory infections leads to a decrease in the response functions of the immune system, resistance of the body, adaptive and immunobiological protective barriers and the formation of chronic foci of infections. Subsequently, this leads to the fact that children with RRI become more susceptible to various infectious diseases (Bossuyt X., 2007).

At the end of December 2019, 41 cases of pneumonia of unknown origin with an atypical course were registered in Wuhan, Hubei Province (China). On

January 10, 2020, a new type of coronavirus infection was identified during the study, which quickly spread throughout China and beyond (Lu H., 2020). In February 2020, the research team of the International Committee on the Taxonomy of Viruses identified this pathogen as a new type of coronavirus infection-2, leading to acute severe respiratory syndrome, as SARS-CoV-2. Since this type of coronavirus infection was recorded in 2019, the World Health Organization (WHO) gave the name coronavirus infection-2019 (COVID-19) (Gorbalenya A. E., 2020). On March 11, 2020, WHO announced a pandemic, as the rapid spread of COVID-19 took on a large scale (Cucinotta D., 2015). The onset of COVID-19 disease in the Republic of Kazakhstan was registered on March 13, 2020. On March 22, 2020, the government adopted strict quarantine measures and major cities of Kazakhstan were closed (Zhalmagambetov B., 2020).

The first cases of COVID-19 infection among children were described in January 2020 in Shenzhen, China (Chan J. F. W., 2020). Data from numerous scientific publications have shown that the course of SARS-CoV-2 infection in children was less severe than in adults. Fever and cough were the most frequently observed clinical symptoms in children (She J., 2020). As for adult patients, the most common clinical signs were fever (98.6%), fatigue (69.6%), dry cough (59.4%) and shortness of breath (31%) (Wang D., 2020).

Lymphopenia is the most commonly described prognostic marker of COVID-19, which indicates immune dysfunction (Huang W., 2020). In patients hospitalized in China, the decrease in lymphocytes was 83.2% of cases, and in another study, in Wuhan, lymphopenia was also noted in 85% of patients (Wang D., 2020, Guan W. J., 2020). There is evidence that after the asymptomatic course of coronavirus infection, patients had a decrease in the number of lymphocytes, and in some cases, the function of lymphocytes was low, even after complete clinical improvement (Yang X., 2020). In the United States, patients in severe and critical condition were found to have a critical decrease in lymphocytes (Arentz M., 2020). Tan L. and co-author. A prognostic model of lymphocyte count was proposed, where patients with a lymphocyte count of less than 20% (10-12 days) from the onset of symptoms and less than 5% (17-19 days) had poor prognoses for COVID-19 (Tan L., 2020).

Thus, after a coronavirus infection, most patients need immune rehabilitation, regardless of the severity of the disease. The COVID-19 outbreak has significantly increased attention to RRI and their prevention. Therefore, any preventive approach capable of modulating and enhancing the immune response will have an important prognostic value. Given the urgency of this problem and the current course of coronavirus infection, the methods of immune rehabilitation developed to date do not take into account the individual characteristics of the immune response of children. Therefore, it is necessary to develop effective methods of immune rehabilitation of children with RRI, since this group of children is more susceptible to various infectious diseases, including coronavirus infection.

The purpose of the study.

Improving the effectiveness of immune rehabilitation of children with recurrent respiratory infections based on the identification of the main leading phenotypes and their course in the pre- and post-coronavirus period.

The object of the study.

The study examined a group of patients with recurrent respiratory infections before and during coronavirus infection, as well as a group of healthy (occasionally ill) children who had a coronavirus infection.

The subject of the study.

Based on the study of clinical and immunological features of the course of recurrent respiratory infections, to evaluate the effectiveness of the method of increasing immune rehabilitation in children.

Research objectives:

1. To study the clinical and anamnestic features of the formation and course of recurrent respiratory infections in children in the period before the onset of the coronavirus pandemic;
2. To compare the features of the course of coronavirus infection in children with recurrent respiratory infections and in healthy (occasionally ill) children;
3. To study the distribution of immune phenotypes in children with recurrent respiratory infections who have not been ill and have had a coronavirus infection;
4. To evaluate the effectiveness of immune rehabilitation in children with recurrent respiratory infections who have not been ill and have had a coronavirus infection.

Research methods:

1. General clinical research;
2. Analysis of medical histories;
3. Laboratory testing;
4. Methods of statistical analysis;
5. Survey of patients and their parents.

Scientific novelty of the research results:

1. For the first time, clinical and immunological phenotypes were compared in children with recurrent respiratory infections in the pre- and post-ovoid periods;
2. Clinical and laboratory changes in children with recurrent respiratory infections who have had a coronavirus infection were studied for the first time;
3. For the first time, the course of coronavirus infection was compared in children with recurrent respiratory infections and in healthy (occasionally ill) children;
4. For the first time, the effectiveness of immune rehabilitation methods was evaluated in children with recurrent respiratory infections and healthy (occasionally ill) children who had a coronavirus infection.

Practical significance:

1. Analysis of etiological factors and established clinical and diagnostic criteria allow timely identification of the leading phenotype in children with recurrent respiratory infections at all stages of medical care;
2. The prognostic algorithm of diagnostics of identification of risk groups of children with recurrent respiratory infections depending on the leading clinical and immunological phenotype with their further immune rehabilitation has been developed and put into practice;

3. The developed scheme of immune rehabilitation made it possible to increase the efficiency of management of patients with recurrent respiratory infections, including after a coronavirus infection;

4. The results of the research work have been introduced into the pedagogical process of the Department of Children's Diseases with courses in allergology, hematology and endocrinology in the form of materials for creating situational tasks and practical classes for students.

The main provisions submitted for protection:

1. The selected clinical and immunological phenotypes make it possible to distribute children with recurrent respiratory infections according to the corresponding phenotypes (anemic, D-deficient and atopic), which requires an individual approach in the implementation of rehabilitation programs;

2. To increase the effectiveness of immune rehabilitation methods, correction of the leading phenotype of recurrent respiratory infections (anemic, D-deficient, atopic) is necessary;

3. The results of the studies obtained suggest that the use of combination therapy reduces the frequency of acute respiratory infections, reduces the use of antibacterial drugs, positively affects the immunological indicators of the immune status in a group of children with recurrent respiratory infections;

4. The safety profile and good tolerability of OM-85 and vitamin D3 preparations, according to the IMOS (by the researcher) and IMPSS (by the parents / guardians of children) scales, allow us to recommend this combination for the prevention of recurrent respiratory infections, as well as for the immune rehabilitation of children after a coronavirus infection.

Conclusions:

1. The main features of the formation of groups of children with RRI can be divided into exogenous and endogenous risk factors. The clinical course of RRI in children is characterized by longer febrile and catarrhal periods, frequent formation of bacterial complications and the need for prescribing antibacterial drugs for relief ($p < 0.001$). In children who have had a coronavirus infection, these patterns deepen.

2. In children with RRI, a more severe course of coronavirus infection was noted, which consisted in the frequent need for hospitalization, the duration of stay in the hospital. In the period after the coronavirus infection, postcovid syndrome was more often formed in children with RRI (51.6%), as well as laboratory changes indicating a secondary immunodeficiency state, compared with episodically ill children ($p < 0.05$).

3. The frequency of occurrence of the main phenotypes of RRI in children who were not ill and had COVID-19 was the same ($p = 0.317$). However, it is worth noting that children with atopic phenotype were clinically more likely to have skin manifestations (32.8%) in the postcovid period and a long residual cough after recovery (34.7%).

4. It was revealed that the elimination of the leading clinical and immunological phenotypes (anemic, atopic and D-deficient), as well as the use of a combination of OM-85+D3 reduces the frequency of acute respiratory infections by 2.4 and 2.24

times ($p < 0.001$), the duration of catarrhal and febrile periods ($p < 0.001$), reduces the frequency of VDP diseases ($p = 0.001$) and NDP ($p < 0.001$), reduces the use of antibacterial drugs by more than 2 times ($p < 0.001$), increases the number of lymphocytes, the concentration of serum immunoglobulins A, M, G ($p < 0.001$), it also promotes recovery and clinical improvement in the post-ovoid period.

Publications on the topic of the dissertation:

16 scientific papers have been published on the topic of the dissertation, including 6 articles in periodicals of Kazakhstan recommended by the Committee for Supervision and Certification in the Field of Education and Science of the Ministry of Education and Science of the Republic of Kazakhstan; 2 articles in publications indexed in the Scopus information base: Russian Open Medical Journal, World Journal of Experimental Medicine; 8 publications in the materials of international scientific-Practical conferences (Kazakhstan, Kyrgyzstan, Uzbekistan, Russia, China, Estonia). There is 1 author's certificate No. 20946 dated 10/18/2021 and 3 acts of implementation in practical healthcare in the GKP on the PCV "City Polyclinic № 8", the allergological center "Umit", the medical center "Family".

The author's contribution to the research:

During the research, the author took part in determining the subject of the dissertation work, forming its methodological structure, formulating goals and objectives, collecting research materials, independently conducted statistical analysis and generalization of the results obtained, carried out clinical and laboratory interpretation of patient data, compiling and questioning patients, analyzing literary data on the topic of the dissertation work. The author has prepared and published research results in journals recommended by the Committee for Control in the Field of Education and Science of the Ministry of Education and Science of the Republic of Kazakhstan, at international scientific conferences and foreign publications.

Approbation of dissertation materials

The main provisions of the dissertation work are reported on:

- XXII International Scientific and Practical Conference "European Scientific Conference" (Penza, Russia – October 7, 2020);
- Republican scientific and practical conference of young scientists with international participation "Science and Health" (Semey, Kazakhstan – November 20, 2020). Scientific and practical journal "Science and Health" No. 6(1);
- International Scientific and Practical Conference "Scientific research of the SCO countries: synergy and integration" (Beijing, China - December 8, 2020);
- International Scientific Conference Days of Science - 2021 "COVID-19: Prevention, diagnosis and treatment", (Kyrgyzstan, Bishkek – April 14, 2021). Bulletin of the I.K.Akhunbayev KSMU Journal;
- 75th International Scientific and Practical Conference of Medical Students and Young Scientists (Samarkand, Uzbekistan - May 18, 2021). Journal of Hepato-Gastroenterological Research No. 2(1);
- Republican scientific and practical conference with international participation "Modern pediatrics. Achievements and prospects. Modern perinatal medical

technologies in solving demographic security problems" (Semey, Kazakhstan – May 21, 2021). Scientific and practical journal "Science and Healthcare", collection of abstracts;

- IV International Scientific and Practical Conference Science, Education, Innovation: Topical Issues and Modern Aspects (Tallinn, Estonia – October 4-5, 2021);

- III Congress of Immunologists of the Republic of Kazakhstan "Topical issues of clinical immunology", (Nur-Sultan, Kazakhstan – October 8-9, 2021);

- IV International Project "The best young scientists – 2021", among scientific and educational institutions of the CIS countries. IV International Book Edition (Volume V) (Nur-Sultan, Kazakhstan - 2021).

Structure and scope of work:

The dissertation work is presented on 126 pages of typewritten text and includes the following sections: introduction, literature review, sections describing materials and research methods, 2 chapters of own research, conclusions, practical recommendations, a list of references and appendices. The text is illustrated with 22 tables, 33 figures. The list of references includes 288 sources.