UDK 616.211-002+616.22-002+616.23
DOI: 10.56871/CmN-W.2024.36.12.002

RECURRENT RESPIRATORY INFECTIONS IN CHILDREN

© Vera L. Gritsinskaya

Saint Petersburg State Pediatric Medical University. Lithuania 2, Saint Petersburg, Russian Federation, 194100

Contact information:
Vera L. Gritsinskaya — Doctor of Medical Sciences, Leading researcher of the laboratory of medical and social problems in Pediatrics, research center; Professor of the department of general medical training.
E-mail: tryfive@mail.ru ORCID ID: 0000-0002-8290-8674 SPIN: 7966-9470

For citation: Gritsinskaya VL. Recurrent respiratory infections in children. Children's Medicine of the North-West (St. Petersburg). 2024;12(1):19-29. DOI: https://doi.org/10.56871/CmN-W.2024.36.12.002

Received: 22.11.2023 **Revised: 20.12.2023** **Accepted: 25.01.2024**

Abstract. The lecture presents the anatomical and physiological prerequisites for the occurrence, etiopathogenetic mechanisms and medical and social risk factors for the formation of recurrent respiratory pathology in children of different ages. The possibilities for the prevention of chronic diseases and rehabilitation measures in children with recurrent respiratory infections are described.

Key words*: children; acute respiratory infections; recurrent respiratory infections; risk factors.*

РЕКУРРЕНТНЫЕ РЕСПИРАТОРНЫЕ ИНФЕКЦИИ У ДЕТЕЙ

© Вера Людвиговна Грицинская

Санкт-Петербургский государственный педиатрический медицинский университет. 194100, г. Санкт-Петербург, ул. Литовская, 2

Контактная информация:
Вера Людвиговна Грицинская — д.м.н., ведущий научный сотрудник лаборатории медико-социальных проблем в педиатрии, научно-исследовательский центр; профессор кафедры общей медицинской практики.
E-mail: tryfive@mail.ru ORCID ID: 0000-0002-8290-8674 SPIN: 7966-9470

Для цитирования: Грицинская В.Л. Рекуррентные респираторные инфекции у детей // Children's Medicine of the North-West. 2024. Т. 12. № 1. С. 19–29. DOI: https://doi.org/10.56871/CmN-W.2024.36.12.002

Поступила: 22.11.2023 **Одобрена: 20.12.2023** **Принята к печати: 25.01.2024**

Резюме. В лекции представлены анатомо-физиологические предпосылки возникновения, этиопатогенетические механизмы и медико-социальные факторы риска формирования рекуррентной респираторной патологии у детей разного возраста. Описаны возможности профилактики хронических заболеваний и реабилитационных мероприятий у детей с рекуррентными респираторными инфекциями.

Ключевые слова*: дети; острые респираторные инфекции; рекуррентные респираторные инфекции; факторы риска.*

INTRODUCTION

The widespread of acute respiratory infections (ARIs) is an urgent medical and socio-economic problem. The medical science is extremelly intrested in ARI due to its high incidence rate and risks of complications. ARI invloves all age groups in the epidemic process, as well as causes the most significant economic damage in the structure of all infectious pathology [1, 2]. Recurrent acute respiratory infections in children deserve special attention, as they create significant discomfort for patients' the families and pose serious challenges for physicians. It seems expedient to separate children with reccurent respiratory tract infections into a separate group of dispensary observation in order to develop a set of health-improving measures for reducing morbidity [3]. However, developed rehabilitation programs did not show expected results. The analysis showed that health-improving measures for children with recurrent respiratory tract infections are often insufficiently effective as they miss an individual approach in therapy and prevention [4].

 ISSN 2221-2582

GENERAL INFORMATION AND TERMINOLOGY

Acute respiratory infections are diseases manifested by catarrhal inflammation of the upper respiratory tract and occurring with fever, runny nose, cough, sore throat, and general impairment of varying severity. In most cases, ARIs are self-limiting diseases that end with complete recovery of a patient [1].

Frequently ill children (FIC) is a group of dispensary observation that includes children susceptible to frequent infections of the upper and lower respiratory tract due to transient, correctable disfunctions of imune systems without persistent organic disorders [3].

In 1986 V.Y. Albitsky and A.A. Baranov [5] proposed to include patients into FIC group if the following criteria are met:

Age	Recurrent RTI during one year
Children under 1 year old	4 times and more
Children from 1 to 3 years old	6 times and more
Children from 4 to 5 years old	5 times and more
Choldren older than 5years old	4 times and more
Chronically ill children — RTI lasts longer than 14 days	

Infection index (II) and resistance index (J) was also proposed as a criterion for inclusion:

- II is defined as the ratio of the sum of all cases of ARI during one year to the age of a child. The II in the group of children with FIC varies from 1.1 to 3.5; among rarely ill peers it ranges from 0.2 to 0.3;
- J is defined as the ratio of the number of all cases of ARI to the number of months of follow-up. Infants under 1 year of age can be referred to FIC group if J is ≥ 0.33; however, according to other authors, it must be at least 0.5 [6].

According to the World Health Organization (WHO) and a number of foreign pediatric schools, healthy toddlers tolerate up to 8 episodes of ARI per year. If the incidence is higher, recurrent respiratory tract infections (RRTIs) are considered. RRTIs are repeated, recurrent upper respiratory tract infections in the absence of any underlying pathologic condition [7, 8]. It is proposed to classify a child into RRTI group if the following criteria are present:

Age	Recurrent RTI during one year
Children under 1 year old	7 times and more
Children from 1 to 3 years old	8 times and more
Children over 3 years old	6 times and more
Recurrent acute otitis media, rhinosinusitis — three episodes within 6 months or four episodes within 12 months	
Recurrent pharyngotonsillitis — six episodes within 12 months	

According to Russian authors, FIC make up 14–18% of the total child population, although there might be higher (up to 50%) rates. Preschoolers amount up to 50% of FIC; younger schoolchildren — 15%; adolescents — 10% [9–11].

In 2021, leading specialists of Italian Medical Associations — pediatricians, pediatric infectious disease specialists, allergists, immunologists, hematologists, oncologists, geneticists and otorhinolaryngologists published the Intercommunity Consensus [12]. The paper is based on the results of 213 clinical studies published on PubMed and Embase electronic resources between 2009 and 2019. The authors estimate that about 25% of infants under 1 year and 6% of children under 6 years suffer from RRTIs. Harmonized criteria for defining patients with RRTIs vary by age and cannot be applied to infants under 1 year.

Age	Frecuency of polytopic respiratory infections
1–3 years	≥ 6 respiratory tract infections (1 of which may be pneumonia, including severe pneumonia) within a year, or
	2 mild cases of pneumonia, confirmed by clinical criteria and/or radiologically within a year
3–6 years	≥ 5 и5 respiratory tract infections (1 of which may be pneumonia, including severe pneumonia) within a year, or
	2 mild cases of pneumonia confirmed by clinical criteria and/or radiologically within a year
6–12 yaers	≥ 3 respiratory tract infections (1 of which may be pneumonia, including severe pneumonia) within a year, or
	2 mild cases of pneumonia confirmed by clinical criteria and/or radiologically within a year

Age	Frecuency of polytopic respiratory infections	
Frequency of specific respiratory diseases	> 3 episodes of acute pharyngotonsillitis within a year	
	> 3 episodes of acute otitis media in 6 months and > 4 within a year	
	≥ 2 2 episodes of severe pneumonia confirmed by clinical criteria and/or radiographically within a year	
	> 4 episodes of acute sinusitis (probably bacterial) within a year	
Pneumonia severity indicators	Mild and moderate-severe : temperature < 38.5 °C; • respiratory rate < 50 breaths/ min • light respiratory distress; • no vomiting	Severe: • temperature > 38,5 °C; • respiratory rate > 50 breaths/ min; • severe respiratory distress; • tension of the nose wings; • cyanosis; • grunting; • signs of dehydration; • tachycardia; • capillary refill time > 2

The consensus authors emphasize that RRTI is a diagnosis of exclusion of other chronic conditions such as genetic disorders, cystic fibrosis and CFTR-pathies, primary immunodeficiencies, malformations of the cardiac and respiratory systems, neuromuscular disorders, etc. The Commission also prepared first, second and third level research designs recommended on the basis of clinical and anamnestic picture and practical algorithm.

PREREQUISITES FOR THE RECURRENT RESPIRATORY PATHOLOGY

Numerous factors of various genesis may influence on RRTI formation [13, 14]. The majority of authors mention following most common exogenous factors:

- low level of hygiene and sanitary culture in the family;
- low level of material well-being and unfavorable social and living conditions;
- early socialization of the child (attendance of preschool institutions, mass events, developmental activities, etc.);
- unfavorable environmental conditions (extreme climatic factors, air pollution, passive smoking, etc.);
- irrational use of medicines (antipyretic drugs, antibiotics, etc.);
- malnutrition (early formula feeding, failure to introduce complementary foods at the right time, restrictive diets, etc.)..

Endogenous unfavorable factors include:

- unfavorable ante-, intra- and early postnatal periods (prematurity, morphofunctional immaturity, perinatal pathology, etc.);
- background conditions (rickets, iron deficiency anemia, lymphatic-hypoplastic type of constitution, hyperplasia of lymphoid organs, etc.);
- aggravated family history of allergic pathology;
- deficiency of vitamins (A, D, E, C, etc.), micronutrientst (iron, iodine, selenium, zinc, etc.), polyunsaturated fatty acids;
- malabsorption syndrome;
- disorders of the microbiocenosis.

Morphological features of respiratory tarct organs deserve special attention among other endogenous factors. They intensively grow and differentiate during the first years of life. By the age of 7 years, the formation of respiratory tarct organs ends, and thereafter there is only an increase in their size [13, 14].

Morphologic structure of the respiratory tract organs in young children have following peculiarities:

- thin, easy-to-remove mucous membrane;
- underdeveloped mucus-producing glands;
- reduced production of immunoglobulin A and surfactant;
- capillary-rich submucosa layer, consisting mainly of loose fiber;
- soft, pliable cartilaginous framework of the lower respiratory tract;
- insufficient amount of elastic tissue in the airways and parenchyma.

Most frequently RRTI in children develops due physiologic immaturity of their immune system. The development of the immune system continues throughout childhood. During active growth and development, "critical" periods may be distinguished, which are characterized by high risks of inadequate or paradoxical reactions of the immune system when interacting with antigens [15, 16].

The first critical period lasts from the moment of birth to the end of the first month (the neonatal period). The immune system of a newborn is suppressed, although passive immunity is provided by maternal antibodies; the phagocytosis system has not been developed yet. Newborns show

 ISSN 2221-2582

weak resistance to opportunistic, Gram-negative flora, so they have a tendency to generalization of microbial-inflammatory processes, and high sensitivity to viral infections.

The second critical period (4–6th month of life) is characterized by the loss of passive immunity due to catabolism of maternal antibodies. The primary immune response after a penetrated infection develops with the help of IgM antubodies and leaves no immunological memory. The same type of immune response develops after vaccination, and only revaccination forms a secondary immune response with the production of IgG antibodies. Later accumulation of secretory IgA leads to insufficient local defense of mucous membranes. Incompleteness of local immunity system is manifested by repeated ARI, intestinal dysbiosis, skin diseases. Such children are highly susceptible to parainfluenza viruses, respiratory syncytial viruses, rotaviruses and adenoviruses. Many hereditary diseases, including primary immunodeficiencies, make their debut. The incidence of food allergies increases dramatically.

The third critical period (2nd year of life) coincides with a significant expansion of child's contacts with the outside world. An incomplete primary immune response to many antigens persists: IgM synthesis predominates, and IgG synthesis suffers from insufficient production of one of the most important subclasses — G2 (antibacterial defense). The system of local immunity remains imperfect due to low levels of secretory IgA. Many primary immunodeficiencies, autoimmune and immunocomplex diseases are manifested for the first time; high sensitivity of children to recurrent viral and microbial-inflammatory diseases of respiratory and otorhinolaryngological organs remains. Manifestations of food allergy gradually weaken.

A characteristic feature of the fourth critical period (6th–7th years of life) is that the average concentration of IgG and IgM in the blood is close to the level of adults; the level of IgA is still lower, which is associated with insufficient local protection of mucous membranes. The content of IgE in blood plasma reaches the maximum level compared to other age periods, which is obviously associated with the high prevalence of parasitic infections — giardiasis, helminthiasis. High level of IgE and low level of IgA is a risk factor for the formation of many chronic diseases of polygenic nature, including allergic diseases. Sensitivity to infectious diseases remains high as well.

The fifth critical period is adolescence (12–15 y. o.); it takes place during active hormonal cahnges. Pubertal growth spurt is combined with a decrease in the volume of lymphoid organs, and the beginning of the secretion of sex hormones (including androgens) is the cause of suppression of cellular mechanisms of immunity; the content of IgE decreases. There is a high sensitivity to viral infections, mycobacterium tuberculosis.

ETIOPATHOGENETIC MECHANISMS OF RECURRENT RESPIRATORY PATHOLOGY

Up to 90% of ARI cases are caused by RNA- and DNA-containing viruses (more than 300 species), but the etiologic structure of pathogens is inconstant and can change even during one epidemic season. 55–60% cases of ARIs remain unidentified. Studies doveted to ARI etiology determined following agents: rhinoviruses (30–50%), coronaviruses (10–15%), influenza pathogens (5–15%) which privailed, and entero-, adeno-, respiratory syncytial and parainfluenza viruses which were detected less frequently (from 2 to 5% in each group) [3, 16–18].

Herpes-virus infections play a major role in the etiology of RRTIs. Cytomegalovirus (CMV), Epstein-Barr virus (EBV) and human herpes virus type VI predominate. Due to the complex strategy of antagonizing and eluding the host immune system, it becomes possible for herpetic viruses to remain in the human body for a long period of time. Herpes simplex virus is a weak inducer of interferon (IFN), so inactivation of viral DNA inside cells does not occur and the virus persists in the cell for a long time. CMV causes destruction of macrophages, sharply suppresses the activity of killer cells, inhibits IFN production and persists in leukocytes and phagocytes for a long time, causing immunodeficient states. The EBV genome is encapsulated in a nucleocapsid, which is covered with the glycoprotein tagument gp350, which is a receptor interaction factor. The virus penetrates into B-lymphocytes through these receptors. EBV is also able to evade immune surveillance during acute infection and reactivation, resulting in viral persistence. In addition, the immunosuppressive effect of EBV contributes to activation of secondary flora, involving the digestive system and nasopharynx in the pathological process. Herpes viruses and adenoviruses persist in 20–30% of children with RRTI during the period of clinical recovery [19, 20].

In recent years, new subtypes of coronavirus (SARS-CoV, HCoV-NKU1, HCoV-NL63, MERS-CoV, SARS-CoV-2) have taken a special place among severe infections with respiratory tract involvement. Severe epidemics of coronavirus infection in 2002 and 2012, and the pandemic of 2019 have placed them on the leading position among all infections with respiratory system involvement [12].

The current etiology of acute respiratory infections often includes several pathogens, namely mix infections (10 to 70%) of respiratory and herpes viruses, followed by bacterial infection. Bacteria (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, etc.), chlamydia (*Chlamydia psittaci*, *Chlamydia pneumoniae*) and mycoplasmas (*Micoplasma pneumoniae*, *Micoplasma hominis*) can also be causative agents of ARI. In children aged 3–6 years, associations with streptococcal (16%), mycoplasma (10%) and chlamydia (4%) infections were noted, the course of which is accompanied by pathologic proliferation of lymphoid tissue (in 84%) and abundant growth of opportunistic bacterial pathogens in half of the patients. In 5–10% of cases there is a development of bacterial or viral-bacterial respiratory infections due to changes in the microbiota of the respiratory tract, impaired mucosal defense (mucociliary clearance, MALT) and superinfection with bacterial pathogens [21, 22].

The organism responds to an ARI pathogen with complex defense-adaptive reactions aimed at limiting its reproduction and subsequent elimination, and finally — at complete restoration of resulting structural and functional disorders. Repeated attacks of viruses and bacteria lead to stress, further exhaustion of the immune system, disorders of compensatory-adaptation mechanisms and reduction of immunity resistance, which contributes to the chronicization of the process. Thus, the developped immunologic insufficiency is a pathologic background that forms a group of children with RRTI [1, 10, 11].

Children with RRTIs have increased susceptibility to pathogens due to a shift of the immune response towards the Th2-type, simultaneously local immunity of respiratory mucous membranes is suppressed as evidenced by lower level of IgA in saliva. Spontaneous hyperproduction of proinflammatory interleukins (IL-2, IL-4), including interleukins involved in inflammation chronization (IL-6 and IL-8), is accompanied by an increase in their concentrations in serum, a deficiency of immunoglobulins, a decrease in cellular cytotoxicity (a decrease in the number of activated CD8DR + cells), as well as an increase in the number of cells expressing apoptosis-inducing receptors. In addition, the overwhelming majority of children with RRTI show abnormalities in their interferon system. It was found that an adequate content of IFN in serum is accompamnied by a decrease in induced production of alpha- and gamma-interferons, which reflects the insufficiency of reserve capabilities. Children with RRTI also have dysfunction in the phagocytosis system, characterized by lower levels of phagocytosing neutrophils and cells expressing adhesion molecules (CD 11b), which largely explains their high susceptibility to reccurent respiratory infections and propensity to bacterial complications [23, 24].

The epithelial structures of airway mucosa perform one of the main protective functions. Viral infections damage the cilia that covers the nasal and pharyngeal mucosa, forming areas of "baldness". A single exposure to viral agents is reversible, whereas frequent exposures violate regenerative processes of the mucosa which forms a transitional type of epithelium and facilitate further infiltration by phagocytes and lymphocytes. The damaged basal membrane and the lamina propria of the mucosa provoke the release of transforming growth factor β by fibroblasts, which leads to hyperplasia of lymphoid tissue. Some viruses with tropism to lymphoid tissue (adenoviruses, herpes viruses) inhibit the apoptosis of lymphocytes; as a result, there is a marked hypertrophy of tonsils and lymph nodes. Persistent inflammatory process during RRTIs predisposes to the development of secondary bacterial microflora on the nasal and nasopharyngeal mucosa, forming a combined viral-bacterial pathogenic flora, which also causes hypertrophy of lymphoid tissue [25]. The lymphatic pharyngeal Waldeyer's ring perform a barrier function and participate in the formation of local and systemic immunity. Hypertrophy of nasopharyngeal lymphoid organs in children is a response to respiratory antigenic viral-bacterial load and is currently considered as a physiological process of immune system formation in preschool children. However, when the resistance of lymphoid organs is reduced, pathogenic microorganisms are able to persist for a long time, forming bacterial biofilms [1, 16, 26].

Recurrent respiratory infections, especially in early childhood (before the beginning of active socialization), require the exclusion of various

 ISSN 2221-2582

hereditary, congenital or acquired pathologies (cystic fibrosis, malformations of bronchopulmonary and cardiovascular systems, otorhinolaryngological organs, gastroesophageal reflux disease, primary immunodeficiencies, etc.) [10, 27].

The conducted examinations revealed that children with RRTIs did not have persistent immunologic changes, however primary immunodeficiencies were verified in 74% of patients with a combination of recurrent viral and recurrent bacterial infections . In most cases, there were non-critical (small) B-cell defects of the immune system (selective IgA deficiency, IgG subclass deficiency, selective antibody formation defect, transient lower levels of immunoglobulins in children). In isolated cases such severe primary immunodeficiency conditions as agammaglobulinemia, hyper IgM syndrome have been detected in children with RRTIs [10, 18]. It was also shown that 40% of patients with isolated recurrent viral infections and 23% of children with a combination of recurrent viral and bacterial infections had bronchial asthma under the mask of RRTI [28]. It should be taken into account that children with RRTIs often have anxiety and general emotional tension, which cause overstrain of the body's psychophysiological systems, the early signs of which manifest in the form of psychosomatic syndromes, including decreased reactivity and increased frequency of illness [6].

POSSIBILITIES OF REHABILITATION FOR CHILDREN WITH RECURRENT RESPIRATORY PATHOLOGY

When treating a patient with RRTI, it is necessary to detail a family history, identify features of intrauterine and early postnatal development, clinical manifestations of diseases, epidemiological and social conditions, which allows to choose the right vector searching for the provoking factors [29].

Rehabilitation of patients with RRTI should include:

- optimal daily and nutritional regimen;
- a full age-appropriate diet;
- regular cold exposure trainings and physical exercises;
- sufficient stay in the fresh air;
- normalization of psychological and social conditions;
- individualized drug therapy,
- scheduled vaccination and non-specific immunological prophylaxis.

Specific immunization helps to reduce the risk of frequent and/or severe diseases in toddlers and preschool children. Vaccination against influenza and the most significant bacterial infections (Pneumococcus and Haemophilus influenzae type B) has shown high effectiveness in reducing the incidence in children [30].

The data accumulated indicates that the colonization of host biotopes by microflora represents a complex ecosystem of metabolic homeostasis and immune tolerance in humans. There is no doubt about an obvious relationship between health status and a gut microbiota, as it plays a crucial role in maintaining metabolic and immunobiologic functions and homeostasis of the organism as a whole [31]. Topical application of antiseptics and local or systemic antibiotic therapy negatively affect the microbiome of children with RRTIs, as it disrupts the qualitative composition and diversity of the child's intestinal microbiota for a long time [32]. It is recommended to prescribe patients with RRTIs:

- probiotics (eubiotics) — live microorganisms, their use in the required amount has a therapeutic and preventive effect; the basic mechanisms of interaction between probiotic bacteria and a host immune system are currently considered in the context of influenting on the balance of Th1/Th2/Th17/Treg-subpopulations. The interaction of ligand-receptor systems are also considered as it provides immune tolerance and anti-infective response of the macroorganism;
- prebiotics, which selectively stimulate the growth of symbiotic microorganisms in the large intestine;
- synbiotics (a combined drug containing several strains of obligate microflora, vitamins, lysozyme, complex multivalent immunoglobulins).

It is recommended to prescribe patients with RRTI immunostimulating agents — drugs that enhance immune response in conditions of weakened immune system [9, 15, 33]. Following drugs are more often used in pediatric practice:

- bacterial lysates;
- herbal preparations;
- interferons;
- inducers of interferon production.

Since there is no vaccination against the majority of ARI pathogens, bacterial lysates (a mixture of antigens of various inactivated bacteria that are the most common ARI pathogens) have been pro-

posed for the prevention of upper respiratory tract diseases. Bacterial lysates have a dual purpose: specific (forming a selective immune response against specific pathogens) and nonspecific (immunostimulatory — activation of key mechanisms of innate and adaptive immunity). Bacterial lysates can be prescribed both in the acute period and for prevention. In the acute period of respiratory infections, it is more effective to prescribe bacterial lysates in combination with appropriate etiotropic therapy [34]. The most well-known bacterial lysate preparations on Russian drug market are IRS-19, Ismigen®, Imudon, OM-85 (Broncho-Munal, Broncho-Vaxom).

Herbal preparations (ginseng, eleutherococcus, thyme, echinacea, honey, rhodiola rosea, milk thistle, chicory, ginger root, birch buds, etc.) contain natural immunomodulators. They should be recommended for use in pediatric practice with a certain degree of caution, since these drugs may cause allergic reactions, especially in sensitized children with RRTI [35].

The modern program of RRTI prevention and treatment of FIC may include pathogenetically justified therapeutic measures with immunotropic effects. Preparations containing interferon α2b (Viferon®, Kipferon®, Grippferon), prevent the attachment and multiplication of pathogens on the airway mucosa as it suppresses viral nucleic acid replication and, at the same time, increases the formation of IgA-antibodies. Moreover, phagocytic activity of macrophages rise along with specific cytotoxicity to target cells of lymphocytes [36].

The use of interferon production inducers is promising concerning RRTI prevention. Interferon production inducers include heterogeneous natural and synthetic compounds with high and low molecular weight united by their ability to activate the production of α-, β- and γ-classes of endogenous IFNs. At the same time, their synthesis is under control of interleukins and repressor proteins and does not reach the level that can have a damaging effect on the body. Moreover, each inducer stimulates IFN synthesis in certain cells that have appropriate receptors [9, 13, 15]. IFN inducers with immunotherapeutic effect include natural low molecular weight polyphenols — gossypol derivatives (megasin, kagocel, savraz, rogasin, gosalidone), and polymers — double-helical RNA (larifan, ridostin). The group of synthetic compounds includes fluorenones and acridanones (amyxin, cycloferon, neovir), and polymers (semidan, ampligen, polyagucil).

A certain tactic of RRTI treatment has developed, which consists in the sequential use of drugs with antiviral activity, IFN and IFN inducers. Drugs capable of inhibiting viral replication should be prescribed during the acute period of viral infections. After acute symptoms and viremia have gone (a subacute period or a recovery period) it is advisable to use IFN inducers in combination with recombinant IFNs to stimulate the processes of immune activation [36].

In a number of cases, the effectiveness of such recovery measures will be insufficient if RRTIs are associated with primary immunodeficiencies, cytopenic conditions, allergies and gastropathology, lack of micronutrients, etc., since special therapy is required in these cases [10, 37].

Clinical and diagnostic examination of patients with RRI should include:

- examination for latent allergies;
- examination for opportunistic infections (herpes viruses);
- examination of interferon status;
- examination of local cytokine status.

The minimum examination complex for children with RRTI should include consultations of otorhinolaryngologists, allergologists, gastroenterologists.

PREVENTIVE HEALTH CHECK-UPS FOR CHILDREN WITH RECURRENT RESPIRATORY PATHOLOGY

Children with recurrent respiratory diseases require a paediatric check-up in health group II (Russian system of classification according to child's health grounds). Accordingly, a prevention program is developed for such kids:

- after recovering from ARI, the child is exempted from physical education lessons for 10 days, then a physical education class with reduced exercise load is recommended;
- a pediatrician examines the child four times a year;
- examination by an otorhinolaryngologist and a dentist — 2 times a year, other specialists — as indicated;
- clinical blood tests and common urine tests — 2 times a year;
- a biochemical blood test and an immunogram — as indicated.

A child is removed from the regular medical check-up list when the frequency of ARIs at the age of up to 3 years is up to 4 times; 3–5 years — up to 3 times; 5–7 years — up to 3 times in a year

and the duration of one episode of illness decreases to 8 days or less [35].

ADDITIONAL INFORMATION

The author read and approved the final version before publication.

Funding source. This study was not supported by any external sources of funding.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Автор прочитал и одобрил финальную версию перед публикацией.

Источник финансирования. Автор заявляет об отсутствии внешнего финансирования при проведении исследования.

REFERENCES

1. Ostrye infekcii dyhatel'nyh putej u detej. Diagnostika, lechenie, profilaktika: klinicheskoe rukovodstvo. Pod red. Geppe N.A. [Acute respiratory infections in children. Diagnosis, treatment, prevention: a clinical guide]. Moskva: MedKom-Pro Publ.; 2018. (in Russian).
2. Kimberlin D.W., Brady M.T., Jackson M.A., Long S.S. Red Book: 2018. Report of the Committee on Infection Diseases: American Academy of Pediatrics; 2018.
3. Samsygina G.A. Problema chasto boleyushchih detej v pediatrii. [The issue of frequently ill children in paediatrics]. Pediatriya. 2015; 94(1):167–9. (in Russian).
4. Zaplatnikov A.L., Girina A.A. K diskussii o "chasto boleyushchih detyah". [To the discussion about "frequently ill children"]. Pediatriya. 2015; 4: 215–21. (in Russian).
5. Al'bickij V.Yu., Baranov A.A. Chasto boleyushchie deti. Kliniko-social'nye aspekty. Puti ozdorovleniya. [Often sick children. Clinical and social aspects. Ways to improve your health]. Saratov; 1986. (in Russian).
6. Romancov M.G., Mel'nikova I.Yu. Respiratornye zabolevaniya u chasto boleyushchih detej: nastol'nyj spravochnik dlya vracha. [Respiratory diseases in frequently ill children: a reference book for doctors]. Moskva: GEOTAR-Media Publ.; 2015. (in Russian).
7. Toivonen L., Karppinen S., Schuez-Havupalo L. et al. Burden of recurrent respiratory tract infections in children: a prospective cohort study. Pediatr Infect Dis J. 2016; 35(12): e362–9. DOI: 10.1097/INF.0000000000001304.
8. Trandafir L.M., Boiculese M.L., Moscalu M. Recurrent respiratory tract infections in children. 2017 E-Health and Bioengineering Conference (EHB). IEEE; 2017: 741–4.
9. Kosenko I.M. Rekkurentnye respiratornye infekcii u detej: sovremennye podhody k racional'noj farmakoterapii. [Recurrent respiratory infections in children: modern approaches to rational pharmacotherapy]. Pediatriya. 2018; 1: 51–6. DOI: 10.26442/2413-8460_2018/1/51-56. (in Russian).
10. Zaplatnikov A.L., Girina A.A., Lokshina E.E. Chasto boleyushchie deti: vsyo li resheno? [Frequently ill children: is everything resolved?]. Medicinskij sovet. 2018; 17: 206–12 (in Russian).
11. Zajceva O.V., Lokshina E.E. Rekurrentnye respiratornye zabolevaniya u detej. [Recurrent respiratory infections in children]. Moskva; 2015. (in Russian).
12. Chiappini E., Santamaria F., Marseglia G.L. et al. Prevention of recurrent respiratory infections. Ital J Pediatr. 2021;47(211). DOI: 10.1186/s13052-021-01150-0.
13. Nikolaeva S.V., Hlypovka Yu.N., Zavolozhin V.A. i dr. Respiratornye virusnye infekcii u detej — vozmozhnosti patogeneticheskoj terapii. [Respiratory viral infections in children — possibilities of pathogenetic therapy]. RMZH. Medicinskoe obozrenie. 2021; 5(11): 762–7. (in Russian).
14. Velikoreckaya M.D. Rekkurentnye respiratornye infekcii u detej. [Recurrent respiratory infections in children]. Medicinskij sovet. 2017; 9: 124–30. (in Russian).
15. Zaplatnikov A.L., Girina A.A., Burceva E.I. Ostrye, rekurrentnye i recidiviruyushchie infekcii respiratornogo trakta u detej: voprosy immunoprofilaktiki i immunoterapii. [Acute, recurrent and recurrent respiratory tract infections in children: issues of immunoprophylaxis and immunotherapy]. RMZH. Mat' i ditya. 2023; 6(1): 50–9. DOI: 10.32364/2618-8430-2023-6-1-50-59. (in Russian).
16. Levchin A.M, Lebedenko A.A., Porutchikova Yu.A. Prediktory razvitiya rekurrentnyh respiratornyh zabolevanij u detej doshkol'nogo vozrasta. [Predictors of the development of recurrent respiratory diseases in preschool children]. Sovremennye problemy nauki i obrazovaniya. 2016; 4: 88–93. (in Russian).
17. Levina A.S., Babachenko I.V., Skripchenko N.V., Imyanitov E.N. Etiologicheskaya struktura zabolevanij u chasto boleyushchih detej v zavisimosti ot vozrasta. [The etiological structure of diseases in frequently ill children depending on age]. Rossijskij vestnik perinatologii i pediatrii. 2017; 62(2): 72–7. DOI: 10.21508/1027-4065-2017-62-2-72-77. (in Russian).
18. Kozlovskij A.A. Rekurrentnye respiratornye infekcii. [Recurrent respiratory infections in children]. Medicinskie novosti. 2018; 17: 52–9. (in Russian).
19. Levina A.S., Babachenko I.V., Skripchenko N.V. i dr. Terapiya hronicheskoj gerpesvirusnoj infekcii u chas-

to boleyushchih detej. Vozmozhnye prichiny neeffektivnosti. [Therapy of chronic herpesvirus infection in frequently ill children. Possible reasons for ineffectiveness]. RMZH. Mat' i ditya. 2022; 5(4): 332–9. DOI: 10.32364/2618-8430-2022-5-4-332-339. (in Russian).
20. Orlova N.V., Suranova T.G. Ostrye respiratornye zabolevaniya: osobennosti techeniya, medikamentoznaya terapiya. [Acute respiratory diseases: clinical features, drug therapy]. Medicinskij sovet. 2018; 15: 82–8. DOI: 10.21518/2079-701X-2018-15-82-88. (in Russian).
21. Denisova A.R. Effektivnost' simptomaticheskoj terapii ORI u detej. [The effectiveness of symptomatic treatment of ORI in children]. Medicinskij sovet. 2021; (1): 72–7. DOI: 10.21518/2079-701X-2021-1-72-77. (in Russian).
22. Aleksandrovich Yu.S., Kozlova E.M., Novopol'ceva E.G. Ostrye respiratornye infekcii u detej. Oslozhneniya i zhizneugrozhayushchie sostoyaniya. [Acute respiratory infections in children. Complications and life-threatening conditions]. Uchebnoe posobie dlya vrachej. Sankt-Peterburg: SPbGPMU Publ.; 2021. (in Russian).
23. Haitov R.M., Il'ina N.I. Allergologiya i immunologiya. [Allergology and immunology]. Nacional'noe rukovodstvo. Moskva: GEOTAR-Media Publ.; 2014. (in Russian).
24. Zaplatnikov A.L., Girina A.A., Burceva E.I. i dr. Ostrye, rekurrentnye i recidiviruyushchie infekcii respiratornogo trakta u detej: voprosy immunoprofilaktiki i immunoterapii. [Acute, recurrent and recurrent respiratory tract infections in children: issues of immunoprophylaxis and immunotherapy]. RMZH. Mat' i ditya. 2023; 6(1): 50–9. DOI: 10.32364/2618-8430-2023-6-1-50-59. (in Russian).
25. Mahmutov R.F., Bobrovickaya A.I. Rekurrentnye respiratornye zabolevaniya verhnih dyhatel'nyh putej s limfoproliferativnym sindromom u detej: sovremennyj vzglyad na problem. [Recurrent respiratory diseases of the upper respiratory tract with lymphoproliferative syndrome in children: a modern view of the problem]. Vestnik gigieny i epidemiologii. 2020; 24(1): 5–10. (in Russian).
26. Kurdyukova T.I., Krasnoruckaya O.N. Mikrobiom verhnih dyhatel'nyh putej u detej rannego i doshkol'nogo vozrasta. [Microbiome of the upper respiratory tract in infants and preschool children]. Pediatriya im. G.N. Speranskogo. 2023; 102(1): 98–105. DOI: 10.24110/0031-403X-2023-102-1-98-105. (in Russian).
27. Kazumyan M.A., Vasilenok A.V., Teplyakova E.D. Sovremennyj vzglyad na problemu "Deti s rekurretnymi infekciyami" (chasto boleyushchie deti) i ih immunnyj status. [A modern view on the problem of "Children with recurrent infections" (frequently ill children) and their immune status]. Medicinskij vestnik Yuga Rossii. 2018; 9(3): 37–43. (in Russian).
28. Zajceva O.V., Lokshina E.E., Zajceva S.V. i dr. Virusinducirovannaya bronhial'naya astma u detej: znachenie sistemy interferona. [Virus-induced bronchial asthma in children: the significance of the interferon system]. Pediatriya. 2017; 96(2): 99–105. (in Russian).
29. Vasechkina L.I. Azarova E.K., Akinfiev A.V. Algoritmy kompleksnoj terapii chasto boleyushchih detej. [Algorithms for complex therapy of frequently ill children]. Lechashchij vrach. 2015; 1: 35. (in Russian).
30. Harit S.M. Fridman I.V. Klinicheskie rekomendacii okazaniya medicinskoj pomoshchi detyam s klinicheskoj situaciej «Vakcinoprofilaktika chasto i dlitel'no boleyushchih detej». [Clinical recommendations for providing medical care to children with the clinical situation "Vaccinal prevention of frequently and long-term ill children"]. Moskva; 2016. (in Russian).
31. Kishechnaya mikrobiota kak regulyator raboty organov i sistem cheloveka: rukovodstvo dlya vrachej. Pod red. V.P. Novikovoj, M.M. Gurovoj, A.I. Havkina [Intestinal microbiota as a regulator of the functioning of human organs and systems: a guide for doctors]. Moscow: GEOTAR-Media, 2024. DOI: 10. 33029/9704-8174-5-IMR-2024-1-352. (in Russian).
32. Safina A.I. Strategiya povysheniya kachestva lecheniya detej s ostrymi respiratornymi infekciyami. [Strategy for improving the quality of treatment of children with acute respiratory infections]. Medicinskij sovet. 2020; (18): 22–8. DOI: 10.21518/2079-701X-2020-18-22-28. (in Russian).
33. Chugunova O.L. Protivovirusnaya terapiya ostryh respiratornyh zabolevanij u detej. [Antiviral therapy of acute respiratory diseases in children]. Praktika pediatra. 2020; 4: 39–47.
34. Zaplatnikov A.L., Girina A.A., Svincickaya V.I. i dr. Bakterial'nye lizaty: tradicionnye predstavleniya i novaya paradigm. [Bacterial lysates: conventional views and a new paradigm]. RMZH. Mat' i ditya. 2021; 4(3): 284–91. DOI: 10.32364/2618-8430-2021-4-3-284-291. (in Russian).
35. Pikuza O.I., Generalova E.V., Rizvanova F.F. Opyt primeneniya fitoterapii v reabilitacii podrostkov s rekurrentnymi respiratornymi zabolevaniyami. [Experience in the phytotherapy use for rehabilitation of adolescents with recurrent respiratory diseases]. Medicinskij sovet. 2022; 16(19): 71–7. DOI: 10.21518/2079- 701X-2022-16-19-71-77. (in Russian).
36. Nesterova I.V., Harina D.V., Shuvalov A.N., Malinovskaya V.V. Lokal'naya interferonoterapiya v

immunoreabilitacii detej rannego vozrasta, chasto i dlitel'no boleyushchih respiratornymi infekciyami. [Local interferon therapy in the immunorehabilitation of young children who often suffer from respiratory infections for a long time]. Voprosy prakticheskoj pediatrii. 2018; 13(3): 66–72. DOI: 10.20953/1817-7646-2018-3-66-72. (in Russian).

37. Karimova D.Yu., Harina D.V., Karimov B.N. Puti optimizacii ozdorovitel'nyh meropriyatij sredi chasto i dlitel'no boleyushchih detej v doshkol'nyh uchrezhdeniyah. [Ways to optimize health-improving activities among frequently and long-term ill children in preschool institutions]. Voprosy prakticheskoj pediatrii. 2018; 13(4): 112–8. DOI: 10.20953/1817-7646-2018-4-112-118. (in Russian).

ЛИТЕРАТУРА

1. Острые инфекции дыхательных путей у детей. Диагностика, лечение, профилактика: клиническое руководство. Под ред. Геппе Н.А. М.: МедКом-Про; 2018.
2. Kimberlin D.W., Brady M.T., Jackson M.A., Long S.S. Red Book: 2018. Report of the Committee on Infection Diseases: American Academy of Pediatrics; 2018.
3. Самсыгина Г.А. Проблема часто болеющих детей в педиатрии. Педиатрия. 2015; 94(1): 167–9.
4. Заплатников А.Л., Гирина А.А. К дискуссии о «часто болеющих детях». Педиатрия. 2015; 4: 215–21.
5. Альбицкий В.Ю., Баранов А.А. Часто болеющие дети. Клинико-социальные аспекты. Пути оздоровления. Саратов; 1986.
6. Романцов М.Г., Мельникова И.Ю. Респираторные заболевания у часто болеющих детей: настольный справочник для врача. М.: ГЭОТАР-Медиа; 2015.
7. Toivonen L., Karppinen S., Schuez-Havupalo L. et al. Burden of recurrent respiratory tract infections in children: a prospective cohort study. Pediatr Infect Dis J. 2016; 35(12): e362–9. DOI: 10.1097/INF.0000000000001304.
8. Trandafir L.M., Boiculese M.L., Moscalu M. Recurrent respiratory tract infections in children. 2017 E-Health and Bioengineering Conference (EHB). IEEE; 2017: 741–4.
9. Косенко И.М. Реккурентные респираторные инфекции у детей: современные подходы к рациональной фармакотерапии. Педиатрия. 2018; 1: 51–6. DOI:10.26442/2413- 8460_2018/1/51-56.
10. Заплатников А.Л., Гирина А.А., Локшина Э.Э. Часто болеющие дети: все ли решено? Медицинский совет. 2018; 17: 206–12.
11. Зайцева О.В., Локшина Э.Э. Рекуррентные респираторные заболевания у детей. М.; 2015.
12. Chiappini E., Santamaria F., Marseglia G.L. et al. Prevention of recurrent respiratory infections. Ital J Pediatr. 2021;47(211). DOI: 10.1186/s13052-021-01150-0.
13. Николаева С.В., Хлыповка Ю.Н., Заволожин В.А. и др. Респираторные вирусные инфекции у детей — возможности патогенетической терапии. РМЖ. Медицинское обозрение. 2021; 5(11): 762–7.
14. Великорецкая М.Д. Реккурентные респираторные инфекции у детей. Медицинский совет. 2017; 9: 124–30.
15. Заплатников А.Л., Гирина А.А., Бурцева Е.И. Острые, рекуррентные и рецидивирующие инфекции респираторного тракта у детей: вопросы иммунопрофилактики и иммунотерапии. РМЖ. Мать и дитя. 2023; 6(1): 50–9. DOI: 10.32364/2618-8430-2023-6-1-50-59.
16. Левчин А.М., Лебеденко А.А., Порутчикова Ю.А. Предикторы развития рекуррентных респираторных заболеваний у детей дошкольного возраста. Современные проблемы науки и образования. 2016; 4: 88–93.
17. Левина А.С., Бабаченко И.В., Скрипченко Н.В., Имянитов Е.Н. Этиологическая структура заболеваний у часто болеющих детей в зависимости от возраста. Российский вестник перинатологии и педиатрии. 2017; 62(2): 72–7. DOI: 10.21508/1027-4065-2017-62-2-72-77.
18. Козловский А.А. Рекуррентные респираторные инфекции. Медицинские новости. 2018; 17: 52–9.
19. Левина А.С., Бабаченко И.В., Скрипченко Н.В. и др. Терапия хронической герпесвирусной инфекции у часто болеющих детей. Возможные причины неэффективности. РМЖ. Мать и дитя. 2022; 5(4): 332–9. DOI: 10.32364/2618-8430-2022-5-4-332-339.
20. Орлова Н.В., Суранова Т.Г. Острые респираторные заболевания: особенности течения, медикаментозная терапия. Медицинский совет. 2018; 15: 82–8. DOI: 10.21518/2079-701X-2018-15-82-88.
21. Денисова А.Р. Эффективность симптоматической терапии ОРИ у детей. Медицинский совет. 2021; (1): 72–7. DOI: 10.21518/2079-701X-2021-1-72-77.
22. Александрович Ю.С., Козлова Е.М., Новопольцева Е.Г. Острые респираторные инфекции у детей. Осложнения и жизнеугрожающие состояния. Учебное пособие для врачей. СПб.: Изд-во СПбГПМУ; 2021.
23. Хаитов Р.М., Ильина Н.И. Аллергология и иммунология. Национальное руководство. М.: ГЭОТАР-Медиа; 2014.

24. Заплатников А.Л., Гирина А.А., Бурцева Е.И. и др. Острые, рекуррентные и рецидивирующие инфекции респираторного тракта у детей: вопросы иммунопрофилактики и иммунотерапии. РМЖ. Мать и дитя. 2023; 6(1): 50–9. DOI:10.32364/2618-8430-2023-6-1-50-59.
25. Махмутов Р.Ф., Бобровицкая А.И. Рекуррентные респираторные заболевания верхних дыхательных путей с лимфопролиферативным синдромом у детей: современный взгляд на проблему. Вестник гигиены и эпидемиологии. 2020; 24(1): 5–10.
26. Курдюкова Т.И., Краснорукая О.Н. Микробиом верхних дыхательных путей у детей раннего и дошкольного возраста. Педиатрия им. Г.Н. Сперанского. 2023; 102(1): 98–105. DOI: 10.24110/0031-403X-2023-102-1-98-105.
27. Казумян М.А., Василенок А.В., Теплякова Е.Д. Современный взгляд на проблему «Дети с рекурретными инфекциями» (часто болеющие дети) и их иммунный статус. Медицинский вестник Юга России. 2018; 9(3): 37–43.
28. Зайцева О.В., Локшина Э.Э., Зайцева С.В. и др. Вирусиндуцированная бронхиальная астма у детей: значение системы интерферона. Педиатрия. 2017; 96(2): 99–105.
29. Васечкина Л.И., Азарова Е.К., Акинфиев А.В. Алгоритмы комплексной терапии часто болеющих детей. Лечащий врач. 2015; 1: 35.
30. Харит С.М., Фридман И.В. Клинические рекомендации оказания медицинской помощи детям с клинической ситуацией «Вакцинопрофилактика часто и длительно болеющих детей». М.; 2016.
31. Кишечная микробиота как регулятор работы органов и систем человека: руководство для врачей. Под ред. В.П. Новиковой, М.М. Гуровой, А.И. Хавкина. М.: ГЭОТАР-Медиа, 2024. DOI: 0.33029/9704-8174-5-IMR-2024-1-352.
32. Сафина А.И. Стратегия повышения качества лечения детей с острыми респираторными инфекциями. Медицинский совет. 2020; (18): 22–8. DOI: 10.21518/2079-701X-2020-18-22-28.
33. Чугунова О.Л. Противовирусная терапия острых респираторных заболеваний у детей. Практика педиатра. 2020; 4: 39–47.
34. Заплатников А.Л., Гирина А.А., Свинцицкая В.И. и др. Бактериальные лизаты: традиционные представления и новая парадигма. РМЖ. Мать и дитя. 2021; 4(3): 284–91. DOI: 10.32364/2618-8430-2021-4-3-284-291.
35. Пикуза О.И., Генералова Е.В., Ризванова Ф.Ф. Опыт применения фитотерапии в реабилитации подростков с рекуррентными респираторными заболеваниями. Медицинский совет. 2022; 16(19): 71–7. DOI: 10.21518/2079- 701X-2022-16-19-71-77.
36. Нестерова И.В., Харина Д.В., Шувалов А.Н., Малиновская В.В. Локальная интерферонотерапия в иммунореабилитации детей раннего возраста, часто и длительно болеющих респираторными инфекциями. Вопросы практической педиатрии. 2018; 13(3): 66–72. DOI: 10.20953/1817-7646-2018-3-66-72.
37. Каримова Д.Ю., Харина Д.В., Каримов Б.Н. Пути оптимизации оздоровительных мероприятий среди часто и длительно болеющих детей в дошкольных учреждениях. Вопросы практической педиатрии. 2018; 13(4): 112–8. DOI: 10.20953/1817-7646-2018-4-112-118.