

**ALGORITHM FOR MANAGEMENT OF FREQUENTLY ILL CHILDREN OF
EARLY AND SCHOOL AGE**

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Annotation: Frequently ill children are a category of children exposed to a high incidence of acute respiratory diseases due to transient, correctable disorders in the body's defense systems. The group of frequently ill patients includes children who suffer more than 4-6 episodes of acute respiratory infections per year, which can occur in various clinical forms. Frequently ill children should be examined by a pediatrician, ENT doctor, allergist-immunologist; The diagnostic algorithm includes: CBC, culture from the mucous membranes of the pharynx and nose, detection of infections using PCR, allergy tests, immunogram studies, radiography of the paranasal sinuses and chest. Frequently ill children need sanitation of foci of chronic infection, etiopathogenetic therapy of acute respiratory infections, vaccination and nonspecific prevention. The author provides literature data on the characteristics of the biocenosis of the upper respiratory tract, the immune system, against infectious immunity, including local protection of the respiratory tract (lymphoepithelial pharyngeal system), in children of early and preschool age, causing their higher incidence of acute respiratory infections (ARI). presents a detailed description of frequently ill children (FIC), who are a heterogeneous group of patients (immaturity of the immune system, depletion of the immune system due to frequent recurrence of acute respiratory infections, partial immunodeficiencies, concomitant pathology of ENT organs and allergies, etc.). The author describes the diagnostic and treatment algorithm depending on the child's belonging to one or another group of acute respiratory syndrome, in particular, the indications and results of the effectiveness of immunostimulating therapy are given.

Key words: Immunity, epithelial cells, frequently ill children, immune system, mitogens, adenoiditis, tonsillitis, diagnostic algorithm, immunostimulating therapy.

Respiratory tract infections are a serious problem, especially in childhood; the incidence of acute respiratory infections (ARI) among children was slightly less than 50,000 cases per 100,000 children, which is more than 70% of the registered infectious pathology of childhood [1]. Moreover, the highest incidence is observed in the first 6–7 years of life and there are several reasons for this.

Firstly, in young children, the biocenosis of the upper respiratory tract (URT) is in the process of formation, and the microbial landscape is very unstable, polymorphic, dependent on the environment and approaches that of an adult only by 5–8 years of life [2].

Secondly, the immune system of young children is characterized by high proliferative activity of lymphocytes, and the fraction of undifferentiated, “naive” lymphocytes in children of this age is greater than in adults.

Thirdly, it is known that it is at the age of 1.5–3 years that a reorientation of the immune response to infectious agents occurs from the predominance of the Th2 response pathway, characteristic of fetuses, newborns and children of the first months of life, to the Th1 response, typical of the infectious process in an adult, i.e. functional maturation of the child's anti-infective immunity occurs.

Fourthly, an important feature of the immune system of children of early and preschool age is the state of the lymphoepithelial tissue of the pharyngeal ring, which provides local anti-infective protection of the respiratory tract and antigenic effects [2, 3]. LEGS has a pronounced lymphopoietic function, participates in the production and “training” of B-lymphocytes for “their region” - the mucous membrane of the respiratory tract, where they carry out local production of IgA and IgM. Epithelial cells of the mucous membrane of the nasopharynx and tonsils form a looped network where lymphocytes migrating from the general bloodstream are concentrated.

Passing between epithelial cells, lymphocytes disrupt the integrity of the epithelial cover, forming so-called “passages” that ensure contact of the lymphoid tissue of the pharynx and tonsils with the external environment. It is these intraepithelial passages that “dose” the entry of antigens into the LEGS, providing an adequate antigenic load on the lymphoid apparatus of the pharynx [2, 3]. When the integrity of the epithelium is damaged under the influence of infection, especially repeated infection, the antigenic load on the LEGS increases immeasurably. This may be accompanied by overexertion, exhaustion, or a breakdown of defense mechanisms.

The functional activity of the LEGS depends on age: in healthy children, the maximum enlargement of the palatine tonsils occurs at the age of 3–5 years, and the enlargement of the pharyngeal tonsil (adenoids) occurs at the age of 5–7 years. After these “peaks,” a gradual reduction of LEGS is observed, usually ending by the age of 18 [3].

These features of the immune system of the body of a child of early and preschool age are factors that determine their higher incidence of respiratory, especially viral infections, than in older age and in adulthood.

With respiratory infections that recur more than 6–8 times a year, adequate restoration of the functional characteristics of the immune system apparently does not occur. This characterizes the so-called group of frequently ill children (FIC). Studies of the immune status of the majority of patients have revealed nonspecific changes in anti-infective defense [4–8].

Even during the period of clinical well-being and in the absence of ARI, they showed a significantly increased content of pro-inflammatory substances. interleukins (IL2, IL4), including interleukins involved in the chronicization of inflammatory processes (IL6, IL8), and the content of interferon (IFN), especially IFN γ , is reduced.

It is known that it is in early childhood that the lymphoepithelial pharyngeal system (LEPS) is formed. Starting from the 2nd half of the first year of life, the palatine tonsils gradually form. In the 2nd year, the formation of the pharyngeal tonsil (adenoids) begins, which is localized in the so-called “strategic zone” of the upper respiratory tract, where the most intense antigenic effect is recorded [2, 3].

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According to various authors and data from general medical examination in 20022-2023. [9, 10], NPV in the general pediatric population averages 5%, although some authors cite higher figures – up to 65% [11–15]. The highest frequency of detection of NBD is observed at the age of 2–3 years – 10–15%, the lowest – at 17 years – 3% [9, 10]. Also, according to the latest scientific data, it is noted that, focusing only on officially registered episodes of ARI, one cannot judge the true frequency of respiratory infections in a child [16]. Both underdiagnosis of BBD and overdiagnosis are possible.

Some authors believe that all BBD should be divided into 3 groups [17]. Group 1 consists of children in whom ARI, as a rule, is mild and recovery usually occurs in a short time. Complications are possible, but rare. Most often, children begin to get sick at the end of the 1st or 2nd year of life. Observing in the follow-up of children of various gestational ages who suffered respiratory dysfunction syndrome in the neonatal period, for which they were given artificial ventilation, he notes that 24.7% of these children had CBD, and precisely at the age of under 3 years, mainly in the form of ARI with rapid recovery and without complications [18].

It is characteristic that these were mostly very premature babies. Only 9.5% of the NBI were full-term. In the majority of children (70%) after the age of 3 years, in a favorable environment, the frequency of ARI decreases. Under unfavorable conditions, repeated ARIs persist until 5–6 years of age, rarely longer. The physical and psychomotor development of children corresponds to the age norm. This is the main part of the acute respiratory syndrome, it accounts for about

40% of children who often suffer from ARI. Group 2—approximately 20–25% of the NBI—is characterized by the fact that their ARIs proceed with a long recovery.

After recovery, children experience malaise, loss of appetite, disruption of the sleep-wake rhythm, pallor, etc. Against the background of these changes, ARIs reappear, which turn the disease into a wave-like process without complete normalization of the condition. Sometimes the process immediately becomes severe with complications. Children get sick regardless of attending preschool institutions. As a rule, the frequency of ARI decreases after the age of 5–7 years. At 1.5–2 years of age, most children exhibit hypertrophy of the tonsils and adenoids [10, 12, 13, 15]. A history can reveal a tendency to frequent respiratory diseases in one or both parents of the child.

It is assumed that the cause of this condition is a genetically determined delay in the maturation of the immune system and unfavorable environmental factors. But we cannot exclude primary partial immunodeficiencies, about which in recent years there have been publications mainly in foreign literature [19]. Due to hereditary predisposition, the morbidity in these children is difficult to control [14]. The 3rd group of FBD is distinguished by the presence of ENT pathology, as a leading factor in the development of respiratory diseases.

These children account for 30–35% of cases. The time of onset of repeated ARIs is after 1 year of age. Children get sick regardless of attending preschool institutions.

From 2–3 years of age, during ARI, alternating exacerbations and incomplete remissions are noted, during which difficulty in nasal breathing and night cough persist. When examined by an ENT doctor, adenoiditis, tonsillitis, otitis, etc. are most often detected. Without treatment, many develop tracheitis, bronchitis, and pneumonia. Reducing the frequency of ARI depends on the adequacy of treatment of the corresponding foci of infection (adenoiditis, tonsillitis, etc.). Relatives also have pathology of the ENT organs. The physical development of children, as a rule, is not impaired [11, 15, 20].

Thus, in 40% of children, these frequent, almost monthly, ARIs are nothing more than sequential viral infections, which, apparently, is largely due to the age-related maturation of the child's immune system and the overstrain and relative depletion of the immune function of the LEGS. For these children with uncomplicated frequent incidence of ARI, general hygiene measures are recommended first of all [20]:

1) organization of a rational daily routine for the child:

Full, sufficient sleep;

Elimination of overwork and overexcitation;

Mandatory and sufficiently long walks, but without hypothermia;

Limiting visits to crowded places, etc.;

2) exclusion of passive smoking of a child in the family;

3) nutritious nutrition, taking into account the age characteristics of the child and his tendency to allergic reactions. Using foods rich in zinc and iron, because... there is no doubt that zinc and iron deficiency increase a child's susceptibility to respiratory infections [24, 22];

4) taking multivitamin preparations appropriate to the child's age and workload, prevention and treatment of iron deficiency [21] and zinc deficiency [22, 23];

5) carrying out tempering activities within reasonable limits, such as dousing with cool water, sleeping in the fresh air, baths, showers, balneotherapy, general massage, therapeutic exercises, and physical training exercises.

Luby SP et al. [24, 25], among general hygiene measures, pay great attention to washing children's hands with soap, proving in a randomized controlled study that washing hands with soap prevents the epidemiologically determined incidence of respiratory infections in children with children (see figure). It must be said that a little earlier Meadows E. and Le Saux N. [26] published a meta-analysis of 6 studies, two of which were randomized controlled trials of the use of bactericidal hand gels containing antibiotics, which were used in younger schoolchildren with frequent illnesses. This, according to the authors, also contributed to a decrease in the frequency of ARI in patients with acute respiratory infections during the epidemiological season of the year.

A completely different picture of frequent ARI develops in children suffering from allergies, which, as is known, are characterized by polarization of the immune response towards the Th2 response. Consequently, physiological Th1-dependent mechanisms to combat respiratory infections may be impaired. Children with allergic diseases (atopic dermatitis, respiratory allergies) may often suffer from ARI in infancy and early childhood and, therefore, can be classified as a group of acute respiratory infections. Ciprandi G. [27] studied the frequency and duration of respiratory infections in children with and without allergic diseases. It was shown that in children suffering from allergic diseases, the number, duration and severity of respiratory infections increased significantly compared to children without allergies.

However, this does not exclude the fact that quite often local pediatricians regard exacerbations of allergic diseases of the respiratory tract as simple ARIs and the child repeatedly receives unjustified therapy [16, 28–30]. This is probably due to the fact that there are certain difficulties in the interpretation of respiratory infections in children with allergies. It is known that in case of allergies in a child, viruses are the most common cause of exacerbation of the underlying (allergic) disease and differential diagnosis of ARI and allergic rhinitis, pharyngitis, laryngitis, tracheitis in young children suffering from allergies becomes an urgent need.

For example, with an exacerbation of allergic rhinitis associated with a viral infection, there may be a disturbance in health, nasal discharge in the form of "milk foam", swelling of the tip of the nose, maceration of the skin around the nose, even fever, which serves as the basis for the erroneous diagnosis of ARI in a frequently ill child.

In order to avoid such diagnostic errors, the first thing a pediatrician needs to do is collect or clarify the family history and allergological history of the patient himself: the connection of recurrent acute respiratory infections with causally significant allergic factors, assess recurrent broncho-obstructive syndrome, correctly assess the low effect or its complete absence when carrying out only antiviral and antibacterial therapy. Secondly, if the allergic nature of respiratory manifestations is suspected, an allergological examination is indicated for an ARI patient after recovery. An allergy examination involves testing total IgE and specific IgE in a child under 3 years of age ; after the age of 3 years - skin tests (prick test) or Phadiatop specific tests.

Phadiatop (Pharmacia differentiate atopy) is an objective test for analyzing whether a patient has allergies; the sensitivity of the test is 93% and the specificity is 89%. The test is a balanced mixture of the most common inhalant allergens [31].

In addition, it is necessary to refer the child for a consultation with an allergist, because Early diagnosis of allergic diseases of the respiratory tract is very important for prescribing adequate antiallergic therapy.

It is obvious that children suffering from allergies are mainly included in the 2nd group of FBD, because It is in these children, especially when allergic diseases of the respiratory tract are undiagnosed and the child does not receive specific antiallergic therapy, that frequent respiratory infections are more severe, the period of remission is short and occurs with changes in the patient's condition, and ARIs are often accompanied by bacterial complications. In addition, as shown mainly by foreign studies in recent years, the same 2nd group, as well as the 3rd group of CBD in combination with chronic ENT pathology, includes children with unrecognized partial primary immunodeficiencies [19].

The combination of ARI with ENT pathology is observed, as already mentioned, in 30–35% of the acute respiratory syndrome. Here, ENT pathology comes first: chronic adenoiditis, chronic and recurrent tonsillitis, recurrent otitis media, recurrent sinusitis, and also in these children recurrent bronchitis and even recurrent pneumonia are observed. The most common international definition of recurrent tonsillitis (tonsillitis) is 7 or more episodes in one year or 10 in the last 2–3 years; recurrent otitis – 3 episodes within 6 months or 4 episodes per year; recurrent sinusitis – 2 episodes per year [19].

For pneumonia, 2 episodes per year are considered recurrent pneumonia, provided that the chest x-ray was normal between episodes. As for laryngitis and bronchitis, there are no international definitions [19].

Children with a combination of ENT pathology and frequent respiratory infections require observation by an otolaryngologist and additional clarification of the child's life history and illness and examination, which is also carried out by an otolaryngologist. This is nasopharyngeal fiberoscopy for obvious adenoiditis. Its purpose is to clarify the state of adenoid vegetations and identify indirect signs of gastroesophageal reflux, if any. For sinusitis, examination includes x-rays of the paranasal sinuses, as well as the chest and a sweat test to exclude cystic fibrosis. A sinus scan may then be done to look for bony sinus defects or minimal polyposis. Finally, if the previous examination is negative and the child has persistent sinusitis, a biopsy of the nasal mucosa is indicated in order to exclude ciliary primitive dyskinesia [19, 32].

Clarifying the data on the child's life history and illness, carrying out additional examination methods make it possible to isolate from the group of primary diseases such diseases as gastroesophageal reflux, bronchopulmonary dysplasia, secondary chronic bronchitis, cystic fibrosis, bronchiectasis, congenital lung malformations, primary ciliary dyskinesia, which are often considered to be common ARI at ChBD.

If a chronic ENT pathology is confirmed in a frequently ill child, then there is a focus of chronic infection and, therefore, along with general health measures, local otorhinolaryngological treatment is indicated, the volume of which is determined by an otolaryngologist and depends on the nature, severity and topic of the lesion. Local therapy is aimed at sanitizing chronic foci of infection, restoring the integrity of the mucous membranes of the nasopharynx, and suppressing chronic inflammation [20, 32].

Local therapy includes:

- irrigation of mucous membranes with saline solutions such as Dolphin, Physiomer, Aquamaris, Salin, etc.;
- use of bactericidal lozenges such as Strepsils, Bronchikum, Faringosept, etc.; · rinsing the throat (in children over 4–5 years old) with antiseptic solutions (Hexoral, furatsilin solution, decoctions of chamomile, St. John's wort, etc.);
- rinsing the nasal passages with saline solutions (Dolphin, Physiomer, etc.);
- physiotherapeutic methods (UV irradiation on the tonsils, UHF, microwave and helium-neon laser irradiation on regional lymph nodes, inhalations with sea water, eucalyptus oil, etc.).

If these procedures do not improve the patient's condition or produce a positive effect, then an examination is necessary to identify partial primary immunodeficiencies. Over 150 primary partial immunodeficiencies are now known, some of which clinically resemble simple ARI or ARI in combination with ENT pathology.

Thus, deficiency of the IgG subclass and/or isotypes Ig is manifested by the development in children, against the background of frequent ARI, of recurrent pneumonia and recurrent sinusitis; IgA deficiency leads to the development of pneumonia, recurrent otitis media, and diarrhea against the background of frequent ARI; Mannose -binding lectin 2 (MBL2) activates the complement system and promotes the development of recurrent otitis due to frequent ARI [33–36].

Children with frequent ARIs and recurrent otitis have been described to have lower levels of antibodies to certain serotypes of pneumococcus than in healthy children of the same age [37]. The same results were described for protein P6 [38] and others.

Bossuyt X. et al. [33] provide data that when recurrent respiratory tract infections were combined with ENT pathology, only 10.9% of children did not have any immune defect, 30.3% of children had one immune defect, and 38.1% had no immune defect. two, and in 14.7% three immunity defects were identified, which may, according to the authors, be a manifestation of both immunological immaturity and primary partial immunodeficiencies. The immaturity of the child's immune system can manifest itself as temporary immunodeficiency.

It can be in the form of a quantitative and/or functional deficiency of T-lymphocytes, which is manifested by changes in subpopulations of T-lymphocytes, insufficient response to mitogens, and impaired rosette formation. There may be a temporary deficiency of immunoglobulins classes A and G; there may be a deficiency in neutrophil chemotaxis, which is thought to result from decreased production of lymphokines ; there may be a deficiency of antimicrobial activity.

A feature of the immaturity of the child's immune system is the reversibility and temporary nature of the identified changes in the immune system, in contrast to partial primary immunodeficiencies that accompany the patient throughout his entire subsequent life. Therefore, at the next stage of the examination of children from the 2nd and 3rd groups, it is necessary to determine the content of immunoglobulins (IgG and IgA), evaluate reactions to vaccine antigens (tetanus, diphtheria, Hib), and in children over 2 years of age, determine the content of IgG subclasses (IgG) and consult the child with an immunologist.

This will allow timely isolation from the group of children with partial immunodeficiencies and immunological immaturity, clinically manifested by recurrent infections of the upper and lower respiratory tract and often complicated by recurrent otitis media, recurrent rhinosinusitis, recurrent bronchitis and even recurrent pneumonia.

In the treatment of group 1 acute respiratory infections, which is characterized only by frequent acute respiratory infections, which, as a rule, occur without complications, but which, due to their frequent repetition, can lead to depletion of the child's immune system, the domestic drug Viferon, which is a recombinant drug of α -interferon in complex with antioxidants.

introduced into Viferon enhance its antiviral activity by 10–14 times, and in addition, enhance the effect of recombinant α -interferon on T- and B-lymphocytes [39].

Dosage forms of Viferon in the form of rectal suppositories (suppositories), gel and ointment provide simple, safe and painless ways to administer it. Viferon can be prescribed to all sick children, including newborns and premature babies, including patients with allergies [39].

This method of treatment (use of Viferon), according to the modern classification of immunostimulating therapy (IST), is a nonspecific active-passive IST, the main goal of which is to activate the immune system and strengthen the "general" immunity of the patient [40]. In addition, there is currently evidence of a therapeutic effect in the treatment of children with ARI with endogenous interferon inducers (Arbidol, Cycloferon, Amiksin). Interferon inducers are a heterogeneous family of high- and low-molecular synthetic and natural compounds, united by the ability to induce the formation of the body's own (endogenous) interferon. But the limitation for their use is age. Arbidol can be used in children starting from 2.5 years of age, Cycloferon is approved for use in children over 4 years of age, and Amiksin - only in children over 7 years of age.

Non-specific active IST also includes non-cytokine adjuvants - immunomodulators of microbial origin Imudon, Ribomunil, IRS19, Bronchomunal, etc., which can be used in group 1 PBD, but more appropriately - in the 2nd and 3rd group PBD. All of them have the ability to enhance the functional activity of neutrophils and macrophages, and also have a vaccine effect, which not only increases the activity of nonspecific immune defense factors, but promotes the formation of a specific immune response to the most significant pneumotropic bacterial pathogens for respiratory pathology. IRS19 and Imudon act at the "gate" of infection, while Bronchomunal influences systemic immunity [40].

Studies conducted in our country have shown that in patients with acute respiratory infections who received, in addition to symptomatic treatment of ARI, one of the immunomodulators of bacterial origin IRS19 or Imudon, at the end of the course of treatment there was an increase in IFN γ (which indicates the antiviral effect of the drug) and a decrease in IL4 and IL8. Whereas in the control group that did not receive IRS19, the content of IL8 and IL4 does not change or even continues to increase, and IFN γ decreases. Children who received IRS19 therapy became 2 times less likely to suffer from ARI, and the duration of the disease also decreased by 2 times [7, 8, 41].

For almost 2 years now, our country has been using an innovative multidirectional immunomodulator - Imunorix. Imunorix is characterized by the absence of toxic effects, rapid absorption in the gastrointestinal tract, and its bioavailability is 45%. When influencing the child's immunity, the point of application of Imunorix is macrophages, dendritic cells, B-lymphocytes at the stage of antigen presentation together with antigens of the major histocompatibility complex of the second class of T-lymphocytes. This stage is the most

important for the implementation of a complete, complete immune response of the body [42]. Imunorix reduces the expression of CD30 associated with Th2 lymphocytes, and thereby reduces the allergic nature of the immune response. This suggests that Imunorix promotes the maturation of the immune response [43].

It is also important that pidotimod enhances the phagocytic activity of human polymorphonuclear leukocytes, given the etiological role of phagocytosis deficiency in polymorphonuclear neutrophils in the development of ARI in children. In addition, pidotimod has an activating effect on various types of immunity (innate and adaptive immune response). At the same time, Imunorix exhibits its activity only in conditions of “sick” immunity and does not affect healthy immune reactions [44–47]. The immunomodulatory effect of the drug has been confirmed in more than 60 international controlled clinical studies [48]. According to domestic literature [49], after using Imunorix for a course of 1–2 months over the next 3 months of observation, relapse of ARI was recorded in 22.4% of patients only on days 68–75. Currently, pidotimod (Imunorix) is considered as an immunomodulator for the 2nd and 3rd groups of PBD, especially for children with immature immunity.

Conclusion. Thus, despite the fact that the BBD group was described back in 1986 by V.Yu. Albitsky and A.A. Baranov, until now it represents a big problem in pediatrics, both in terms of correct diagnosis and in terms of adequate therapy. The task is to correctly and timely identify in the outpatient health care setting PBD in combination with concomitant diseases and without them. An irreplaceable benefit in solving this problem comes from a survey, a complete clinical examination of the child and additional clinical, laboratory and instrumental examination, as well as timely consultations with other medical specialists. As for the use of IST in patients with acute respiratory infections, its use should be differentiated depending on the group of patients with acute respiratory infections and the severity of ARI using various immunomodulatory drugs.

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