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UNDERSTANDING OF RECURRENT RESPIRATORY INFECTIONS IN CHILDREN AT THE PRESENT STAGE. REVIEW.

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Abstract

Introduction. Recurrent respiratory infections represent a significant burden on both individuals and healthcare systems worldwide. These infections, characterized by repeated episodes of upper and lower respiratory tract infections, are a common cause of morbidity and mortality in all age groups. The impact of recurrent respiratory infections extends beyond the physical symptoms experienced by affected individuals, often resulting in impaired quality of life, increased healthcare utilization, and economic costs.

Aim. To study the features of recurrent respiratory infections in children, based on research data from the current literature in this field.

Search strategy. The study was conducted using databases such as UpToDate, PubMed, Embase, Cochrane Library, and the Google Scholar search engine. The literature search spanned 9 years, from 2015 to 2024 inclusively. Original articles, randomized controlled trials, systematic reviews, and meta-analyses were included in the study.

Results and conclusions. Understanding the underlying causes and mechanisms behind recurrent respiratory infections is crucial for effective management and prevention strategies. Managing recurrent respiratory infections is a complex task that requires a multifaceted approach. This review article has provided an overview of the various factors contributing to these infections, including host immune response, microbial pathogens, and environmental factors.

Keywords: *recurrent respiratory infections, immunity, children, pneumonia, common cold.*

Резюме

ПОНИМАНИЕ О РЕЦИДИВИРУЮЩИХ РЕСПИРАТОРНЫХ ИНФЕКЦИЯХ У ДЕТЕЙ НА СОВРЕМЕННОМ ЭТАПЕ. ОБЗОР ЛИТЕРАТУРЫ

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Введение. Рецидивирующие респираторные инфекции представляют собой значительное бремя, как для отдельных людей, так и для систем здравоохранения во всем мире. Эти инфекции, характеризующиеся повторными эпизодами инфекций верхних и нижних дыхательных путей, являются распространенной причиной заболеваемости и смертности во всех возрастных группах. Последствия рецидивирующих респираторных инфекций выходят за рамки обычных симптомов, испытываемых пациентами, и часто приводят к ухудшению качества жизни, увеличению числа обращений за медицинской помощью и несут экономические затраты.

Цель. Изучить особенности течения рецидивирующих респираторных инфекции у детей, на основании исследований данных современной литературы в этой области.

Стратегия поиска. Исследование проводилось с использованием баз данных, таких как UpToDate, PubMed, Embase, Cochrane Library и поисковой системы Google Scholar. Литературный поиск охватывал период в 9 лет, с 2015 по 2024 год включительно. В исследование были включены оригинальные статьи, рандомизированные контролируемые исследования, систематические обзоры и мета-анализы.

Результат и заключение. Понимание причин и механизмов, лежащих в основе рецидивирующих респираторных инфекций, имеет решающее значение для разработки эффективных стратегий лечения и профилактики. Лечение рецидивирующих респираторных инфекций - сложная задача, требующая многогранного подхода. В данном обзоре были представлены различные факторы, способствующих развитию респираторных инфекций, включая иммунный, микробные патогены и факторы окружающей среды.

Ключевые слова: *рецидивирующие респираторные инфекции, иммунитет, дети, пневмония, простуда*

Түйіндеме

ҚАЗІРГІ КЕЗЕҢДЕ БАЛАЛАРДАҒЫ ҚАЙТАЛАНАТЫН РЕСПИРАТОРЛЫҚ ИНФЕКЦИЯЛАР ТУРАЛЫ ТҮСІНІК. ӘДЕБИЕТТІК ШОЛУ.

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Кіріспе. Қайталанатын респираторлық инфекциялар бүкіл әлем бойынша жеке адамдарға да, денсаулық сақтау жүйесіне де айтарлықтай салмақ түсіреді. Жоғарғы және төменгі тыныс жолдарының инфекцияларының қайталанатын эпизодтарымен сипатталатын бұл инфекциялар барлық жас топтарындағы аурушаңдық пен өлімнің жалпы себебі болып табылады. Қайталанатын респираторлық инфекциялардың әсері зардап шеккен адамдарда кездесетін физикалық белгілерден асып түседі, бұл көбінесе өмір сапасының нашарлауына, денсаулық сақтауды пайдаланудың жоғарылауына және экономикалық шығындарға әкеледі.

Мақсат. Осы саладағы заманауи әдебиеттердің деректерін зерттеу негізінде балалардағы қайталанатын респираторлық инфекциялардың ерекшеліктерін зерттеу.

Іздеу стратегиясы. Зерттеу UpToDate, PubMed, Embase, Cochrane Library және Google Scholar іздеу жүйесі сияқты мәліметтер базасын қолдана отырып жүргізілді. Әдеби іздеу 2015 жылдан 2024 жылға дейінгі 9 жылдық кезеңді қамтыды. Зерттеуге түпнұсқа мақалалар, рандомизацияланған бақыланатын зерттеулер, жүйелі шолулар және мета-талдаулар енгізілді.

Нәтиже және қорытынды. Қайталанатын респираторлық инфекциялардың себептері мен механизмдерін түсіну тиімді емдеу және алдын алу стратегияларын әзірлеу үшін өте маңызды. Қайталанатын респираторлық инфекцияларды емдеу көп қырлы тәсілді қажет ететін күрделі міндет. Бұл шолуда респираторлық инфекциялардың дамуына ықпал ететін әртүрлі факторлар, соның ішінде иммундық, микробтық қоздырғыштар және қоршаған орта факторлары ұсынылды.

Түйін сөздер: *қайталанатын респираторлық инфекциялар, иммунитет, балалар, пневмония, тұмау*

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Introduction

Recurrent respiratory infections (RRI), the condition characterized by recurrent infections in children, more commonly seen in children before school age. Depending on the pathogen, it can affect both the upper and lower respiratory tract. RRI can significantly impact an individual's health and quality of life [10,58,65,14].

Due to delayed treatment of respiratory diseases, various complications may arise, leading to chronic infections and fatal outcomes among young children, a phenomenon more prevalent in developing countries [35,61,20]. In many developed nations, upper respiratory tract infections account for over 20% of pediatrician visits, increasing to 70% during epidemic periods. Recurrent infections in children have emerged as the most common pathology in recent years, constituting approximately 90% of all outpatient visits to physicians. RRI is widespread across various countries worldwide, irrespective of economic development levels and climates. Consequently, over 75% of the global demand is for antibacterial agents [21,67], utilized in treating infectious diseases. Microbial resistance to antibacterial agents develops due to frequent and inappropriate administration of these medications [37, 42].

According to various studies, the highest frequency of Recurrent Respiratory Infections (RRI) occurs between 6 months and 1 year of age. This is because breastfeeding typically ceases during this period, leading to the development of the child's own antibodies. Various factors, such as the immaturity of the immune system, environmental influences, having many siblings, and early socialization where a child comes into contact with pathogens from other children in daycare settings, contribute to the frequency of respiratory infections. Children who start attending daycare, the frequency of RRI is around 40-50%, decreasing to 15-20% by the second year, and further dropping to 5-10% by the third year [41, 3].

Literature lacks a clear definition regarding the frequency of respiratory infections and how often a child should fall ill within a year, what constitutes a normal occurrence. Different scientific studies provide varying definitions for the frequency of respiratory infections. The definition of recurrent respiratory infections is characterized by a child falling ill more than 6 times a year [60] or experiencing pneumonia either as a standalone condition or because of respiratory infection complications - with a frequency of 2 or more episodes within a year [43, 5]. Acute rhinitis is considered recurrent if episodes occur more than 5 times a year [10,52], while acute otitis media is recurrent if there are 3 episodes within 6 months or 4 episodes per year [4, 28].

In a study by *Chiappini E. et al.,* the determination of RRI used various criteria such as illness duration, hospitalizations, the severity of the child's condition, and how often they visited the pediatrician. Points were assigned to each criterion, and if the total exceeded 30 within 6 months, the child was classified as having RRI [10].

Therefore, RRI has always been a pertinent topic in pediatric and family medicine practice. Timely diagnosis of RRI can enhance the quality of life for children and serve as a preventive measure against chronic illnesses.

Aim. To study the features of recurrent respiratory infections in children, based on research data from the current literature in this field.

Search strategy. The study was conducted using databases such as UpToDate, PubMed, Embase, Cochrane Library, and the Google Scholar search engine. The literature search spanned 9 years, from 2015 to 2024 inclusively. This depth of search was maintained, as the previously utilized literature remains relevant to this day. Original articles, randomized controlled trials, systematic reviews, and meta-analyses were included in the study. The literature review specifically focused on full-text articles. A total of 152 articles were analyzed, with 70 included in the review. After gathering the material, a critical analysis of the literature was conducted, and a plan for further research was developed in line with the required tasks and objectives.

The search strategy employed for the study encompassed a combination of terms including keywords such as «recurrent respiratory infections» OR («respiratory tract infections in children») OR («respiratory» AND «infection»), OR («recurrent» AND «respiratory» AND «infections»). Furthermore, the search included keywords such as secondary immune deficiency, immunity in children, upper respiratory tract infections and lower, children, risk factors for recurrent respiratory infections, treatment modalities, and recovery of children with immune deficiencies, along with their respective synonyms.

Results and discussion.

During the research of scientific literature using the search strategies mentioned above, it was discovered that the primary etiological factor in children with RRI can be both pathogens from the external environment and the child's own conditionally pathogenic flora, due to the decrease in immune resistance, which we will discuss later.

In a study conducted by *Li L. et al.* in 2019, a significant difference in the composition of the microbiome in children with RRI was discovered [31]. The respiratory microbiome plays a protective role against respiratory infections of viral origin, preventing various complications. The mechanisms of this protection continue to be actively studied. Symbiotic bacteria such as Dolosigranulum and Corynebacterium play an important role in protecting the mucous membranes of the upper respiratory system in early age. On the other hand, elevated levels of Haemophilus influenzae, Streptococcus and Moraxella catarrhalis are linked to a heightened susceptibility to respiratory infections and inflammatory complications in children. A study by *Teo S.M. et al.* showed that these microorganisms, in addition to frequent recurrent respiratory infections, may contribute to allergic sensitization and asthma at a later age [57].

In a cohort study conducted by researchers under the guidance of *Bosch A.A. et al*., it was found that children who experienced frequent respiratory infections during infancy demonstrated a different path of respiratory tract microbiome development compared to children who were less ill. These patients showed a decrease in the presence of Dolosigranulum and Corynebacterium bacteria, as well as a rapid increase in the amount of Moraxella catarrhalis from a very early age [6].

In a study conducted by researchers under the guidance of *Robinson P.F.M. et al*., it was noted that

children with recurrent wheezing most commonly had the following bacteria: Streptococcus pneumoniae, Staphylococcus aureus, Moraxella catarrhalis, and Haemophilus influenzae [51].

The main risk factors for children that can lead to RRI [2] are presented in the table below. Conditionally, they can be divided into exogenous and endogenous. All of these risk factors combine to form a group of children with RRI.

Table 1.

RRI risk factors.

RRI risk factors	
Exogenous	**Endogenous**
chronic diseases of the mother	early going to daycare
family allergoanamnesis	early termination of breastfeeding
prematurity and premature birth	frequent use of antibiotics
pregnancy on the background of anemia	mother's smoking during pregnancy
atopic diseases	environmental pollutants
congenital and genetic diseases	sisters and brothers of school age
	poor socio-economic conditions

The immune response of children to various pathogens can be diverse due to the maturation and functioning characteristics of their immune system. Children with RRI often exhibit changes in the immune system. The secondary post-infection nature of these changes may manifest through a combination of two or more immune system impairments. In 19% of children with RRI, abnormalities in the production of specific antibodies are noted despite normal IgG levels. It is likely that all observed nonspecific changes in the immune system may be associated with frequent respiratory infections. Various infections, especially viral ones, can influence the immune response, cytokine reactions, and phagocytosis. Respiratory infections can lead to a deeper immune dysfunction induced by the virus, as the child's immune system does not always fully recover, thereby contributing to infection relapses [50].

In the study conducted by *Raniszewska A.* and colleagues, which examined immunological abnormalities in children with RRI, a decrease in the absolute numbers of CD4+ and CD8+ T lymphocytes, B lymphocytes, and neutrophils was noted. The chemiluminescence method was used in this study to analyze the activity of granulocytes to assess the nonspecific immune response. The results showed that in children with reduced chemiluminescence, a more frequent decrease in the level of neutrophils was observed compared to children with a normal or increased chemiluminescent response ($p < 0.05$) [49].

Children experiencing RRI may exhibit an altered response of neutrophils to pathogenic microorganisms, a crucial element in triggering the nonspecific immune reaction that shields the body against harmful bacteria. Diagnostic assessments should involve determining the absolute levels of granulocytes and conducting a morphological examination. In cases of RRI, there is a reduction in leukocyte adhesion, a lack of myeloperoxidase and glucose-6-phosphate dehydrogenase, along with an increased IgE syndrome [26].

In the scientific work by *Pasternak G. et al.*, which focused on studying IgG and its subclasses in children with RRI, a deficiency of total IgG was found in 12.2%, IgA in 8.4%, and IgM in 7.4% of children ($p<0.05$). Deficiency of IgG (particularly the IgG-1 subclass) was more common in children with RRI compared to IgA and IgM deficiencies [46].

Munteanu A. and colleagues utilized immunophenotyping of T and B lymphocytes in children with RRI to assess the condition of immune cells through flow cytometry. In 70% of instances among children with RRI, immunoglobulin levels fell within the normal range, while 30% exhibited a moderate deviation either in decrease or increase of immunoglobulins. Concerning peripheral immune cells like T and B lymphocytes, as well as NK cells (natural killer cells), an immune response dysfunction was observed. RRI in children resulted in a diminished cellular immune response and a decrease in the quantity of CD8+ T cells [44].

In modern times, one of the approaches to treating RRI involves nonspecific enhancement of the immune response or reinforcement of innate defense mechanisms. As children's immune systems are not fully mature and react suboptimally to infectious agents. Immunotherapy provides an opportunity to stimulate the activity of specific components of the immune system, making the body's defense mechanisms more effective [47,19].

Immune rehabilitation for RRI encompasses the establishment of an ideal daily schedule, minimizing the chances of infection (by avoiding crowded areas during epidemics), adhering to a balanced diet, engaging in adequate physical activity and tempering practices, addressing chronic infection sites, resolving deficiencies in vitamins and micronutrients, and rectifying imbalances in gut microbiota [22,63].

Immunotherapy

In 1993, a synthetic dipeptide molecule called pidotimod (PDT) was first introduced in Italy. Research shows that PDT can influence innate and specific immune responses by increasing the expression of toll-like receptors, which helps initiate the innate immune response. PDT also stimulates the maturation of dendritic cells and natural killer cells, as well as promotes the proliferation of T-lymphocytes. These properties make PDT potentially useful for enhancing immunity and combating infections. Additionally, while the use of PDT did not lead to an increase in B-cells or antibody levels in one study, it did result in elevated production of secretory IgA. PDT has demonstrated good tolerability and a favorable safety profile, with most treatment durations ranging from 1 to 3 months in continuous use, and in some cases, administered for the initial 10 days over a span of 3-6 months [48,69].

In multicenter randomized trials involving children aged 2 to 14 years, the efficacy of PDT was evaluated based on factors such as fever duration, antibiotic usage, hospitalization length, school absenteeism, recovery time, and recurrence rates. The results suggested a reduction in these parameters among children receiving PDT. However, some studies have raised concerns regarding the reliability of these findings due to certain limitations in the research [45].

OM-85 is a blend of lysates derived from 21 bacterial strains, encompassing essential species and subspecies that are associated with numerous cases of RRI such as Moraxella catarrhalis, Haemophilus influenzae, Streptococcus pneumoniae, Klebsiella ozaenae, Klebsiella pneumoniae, Streptococcus pyogenes, Staphylococcus aureus and Streptococcus viridans. Research has indicated that OM-85 acts on both specific and nonspecific immune responses. It promotes the proliferation of T-lymphocytes, maturation of dendritic cells, and regulates the balance between Th-1 and Th-2 cytokines (an important aspect in early childhood where there is an imbalance of Th-1 and Th-2 cytokines) [12]. Furthermore, the bacterial lysate OM-85 stimulates the production of antimicrobial peptides, promotes the activation of macrophages to produce chemokines (α and β interferons) and cytokines. Levels of immunoglobulins A and G increase in the blood as cytokines stimulate B cells. OM-85 regulates inflammatory processes; for instance, it reduces the levels of anti-inflammatory Th-2 cytokines (interleukins 4,5,13), eosinophils, and macrophages, which can reduce atopic manifestations, hypersecretion of mucus in the bronchi, and other symptoms associated with asthma [30].

OM-85 has been licensed in various European countries, Asia, Central, and South America. A comprehensive clinical study was conducted in North America to evaluate the efficacy of the drug in protecting against respiratory infections. The therapy involved oral administration of OM-85 from 6 months of age, at a dosage of 3.5 mg once daily for 10 days over a period of 3 months. Positive results in favor of the drug were noted. A meta-analysis encompassing 53 studies involving OM-85 administration demonstrated a significant reduction in the frequency of recurrent respiratory infections among children receiving the treatment compared to the control group ($p < 0.05$) [12, 30, 18].

Probiotics

Currently, the effectiveness of probiotics and their impact on the immune system is crucial in various diseases. The microbiome positively influences the body's immunomodulatory role, stimulating immune cells, which contributes to reducing the frequency of recurrent respiratory illnesses [66, 70, 9, 13, 34]. Some studies have proposed using lactobacilli and bifidobacteria for 2 months to prevent RRI, with the dosage tailored to the children's age. The group of children receiving probiotic treatment showed significantly lower average rates of acute respiratory viral infections, reduced durations of fever and cough, fewer antibiotic prescriptions compared to the placebo group ($p < 0.05$) [32, 29, 33]. There are studies indicating positive results in preventing recurrent otitis in children who received Lactobacillus salivarius PS7 for 6 months [8]. However, a Cochrane review presented conflicting findings, suggesting that probiotics were not effective in cases of recurrent otitis (Relative Risk (RR) of 0.97 with a 95% Confidence Interval (CI) of 0.85-1.11) [55].

Vitamins

Research on the effectiveness of vitamins A and C in preventing respiratory infections among children is limited and conflicting. There are a number of studies on the effectiveness of vitamin C in colds, showing that it can shorten the duration of the illness and alleviate the patient's condition. The effectiveness is attributed to two main factors: firstly, the decrease in vitamin C levels in the blood during viral infections, and secondly, the role of vitamin C in the production of alpha and beta interferons. These two mechanisms account for the effectiveness of vitamin C in this context [38, 39, 11]. The use of oral vitamin C may reduce the duration of prodromal and catarrhal periods, as well as the length of hospital stay. While clinical effectiveness has been demonstrated, further high-quality research is needed to confirm this hypothesis [54]. Studies indicate a low level of vitamin A in the majority of individuals with chronic infectious diseases. A low level of vitamin A increases the risk of recurrent respiratory infections [68, 1, 64, 59, 56]. Regarding studies on vitamin D, it has been shown that besides its role in bone tissue mineralization and metabolic processes, it can modulate specific and nonspecific immune responses. One important aspect is the enhancement of immune defense efficiency against various infectious agents [24,62]. Vitamin D contributes to reducing the risk of lower respiratory tract infections in newborns and is recommended for use [27]. Some authors have not observed an effect of vitamin D in pneumonia cases [25]. It is possible that low doses of vitamin D (400 IU) did not have a significant effect on pneumonia prevention, which in turn calls for research on higher doses of vitamin D [15,23]. In 2019, *Martineu A. and co-authors* conducted a systematic review and meta-analysis using various methods, including prospective, randomized, double-blind, placebo-controlled trials on vitamin D supplements. Subgroup assessments were also conducted to reduce data errors. It was concluded that the addition of vitamin D during acute respiratory infections had a positive impact on patients with vitamin D levels below 10 ng/mL ($p = 0.002$). No significant changes were observed in patients with normal vitamin D levels ($p = 0.15$) [40]. Children with RRI often have low levels of vitamin D [7, 16, 36, 53]. Based on the studies mentioned, it is evident that vitamin D has beneficial properties in respiratory infections.

Conclusion

The study of recurrent respiratory infections (RRI) in children is crucial in pediatrics. Timely diagnosis can enhance children's quality of life and prevent chronic illnesses. Factors influencing RRI development and immune system changes were identified. Immunotherapy like OM-85 boosts immunity, while probiotics and vitamin D help prevent infections. A comprehensive approach including immunotherapy, probiotics, and vitamin D can significantly improve children's health. Further research is needed to enhance treatment and prevention methods for RRI.

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