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RESPIRATORY COMPLICATIONS FOLLOWING RSV INFECTION IN CHILDREN: FROM ACUTE INFECTION TO PERSISTENT STRUCTURAL SEQUELAE – A LITERATURE REVIEW

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ABSTRACT

Respiratory syncytial virus (RSV) infections are a significant health burden worldwide, being the leading cause of hospitalization in infants and an important factor affecting long-term lung function. The aim of this review is to provide a summary of current data on the pathophysiological mechanisms, clinical consequences and modern strategies for the prevention of respiratory complications following RSV infection in children. Analysis of the literature indicates that RSV leaves a specific 'molecular footprint' in the airways, including both structural changes and activation of ICL2 cells and epigenetic modifications. These phenomena constitute the biological basis for recurrent obstruction and the development of asthma, and the risk of their occurrence is particularly high after a severe course of infection in early infancy. Acute complications such as bronchiolitis, atelectasis or respiratory failure may be associated with a permanent reduction in lung function parameters, persisting even into adulthood. The introduction of modern passive immunoprophylaxis (nirsevimab) and vaccination of pregnant women offers the possibility of protection during the critical developmental window and favorable shaping of the respiratory system development trajectory. RSV remains one of the strongest modifiable risk factors for chronic lung disease, and effective prevention and early identification of risk biomarkers are crucial for protecting the lung function of future generations.

Methodology: This article provides a narrative review of the current literature on acute and chronic respiratory complications following RSV infection in children, based on a systematic search and qualitative analysis of available clinical, observational and review studies.

KEYWORDS

RSV, Respiratory Syncytial Virus, Children, Respiratory Complications, Bronchial Asthma, Bronchiolitis, Pathophysiology, Immunoprophylaxis, Nirsevimab

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1. Introduction

One of the main causes of acute lower respiratory tract infections in children, especially in the first two years of life, are infections associated with respiratory syncytial virus (RSV). The course of RSV infection varies greatly, ranging from mild symptoms to severe forms of bronchiolitis and pneumonia, which may require hospitalization, sometimes with the need for treatment in an intensive care unit. In the vast majority of cases, RSV infection is mild and self-limiting, but there are certain groups of patients, especially infants and children with comorbidities, who are at significantly increased risk of severe infection (1,2,3).

The high incidence of RSV infections places a significant burden on the healthcare system and generates considerable economic costs. It is estimated that each year there are over 33 million cases of acute lower respiratory tract infection associated with RSV in children under 5 years of age worldwide, of which approximately 3 million require hospitalization and over 100,000 result in death, generating significant direct and indirect costs for healthcare systems and patients' families. Importantly, the vast majority of hospitalizations involve healthy, full-term infants (4). RSV infections show a clear seasonal pattern, with the highest incidence in winter, which further increases the burden on the healthcare system (1,4).

The RSV virus occurs in two main variants, A and B. Both types cause similar symptoms, but infection with type A is more often associated with a more severe course of the disease and a higher number of hospitalizations. A thorough understanding of the differences between RSV types plays an important role in assessing the risk of infection and selecting preventive strategies such as vaccination and administration of monoclonal antibodies (1,2).

Respiratory complications following RSV infection include both acute conditions such as respiratory failure and chronic disorders including recurrent obstructions, asthma and lung function disorders. They are

one of the most significant clinical problems in modern paediatrics. The highest risk of their occurrence is in infants in the first months of life, premature babies and children with heart disease or chronic lung disease. High-risk patients may experience a more severe course of the disease, which in the long term may predispose them to chronic respiratory disorders (1,2,3,4). It should be noted that the mechanisms leading to pulmonary complications after RSV infection are very complex and are not only related to the direct action of the virus, but also largely result from disorders of the child's innate immune response (5). In addition, there is growing evidence that early exposure to the virus may permanently affect the development of the respiratory system, impacting lung development in later childhood and even in adulthood (3).

The aim of this paper is to present the current state of knowledge on respiratory complications following RSV infection in children. It discusses both pathophysiological and immunological mechanisms, as well as the long-term effects of early childhood infections, with particular emphasis on changes in lung structure and function. The review also covers risk factors and the impact of genetic and environmental predispositions on the development of chronic obstructive symptoms. In addition, the latest diagnostic strategies, lung function monitoring, and prospects for prevention and treatment are analysed, which may in the future reduce the risk of chronic complications and improve the quality of life of children affected by this condition.

2. Characteristics of RSV infection

RSV is an RNA virus belonging to the Paramyxoviridae family. It mainly attacks the respiratory epithelium of children, leading to ciliary dysfunction and disruption of the mucociliary clearance mechanism (5,6). The virus replication process begins mainly in the superficial ciliated epithelial cells of the upper respiratory tract and can then spread down to the bronchioles and lungs, which is particularly important in infants and children with immature immune systems. Damage to the epithelium causes local inflammation, swelling and overproduction of mucus, which mechanically impedes airflow and leads to typical clinical symptoms such as wheezing and shortness of breath (1,5). Two surface glycoproteins of the virus play a key role in RSV infection: the G protein, responsible for binding the virus to host cells, and the F protein, which enables the virus to fuse with the cell membrane (1,2). One of the distinguishing features of RSV infection, from which the virus takes its name, is the formation of syncytia, i.e. multinucleated cells formed as a result of the fusion of neighbouring infected cells under the influence of the F protein (2). The pathogenesis of acute RSV infection results from both direct damage to epithelial cells by the virus and the host's immune response. The virus produces NS1 and NS2 proteins, which inhibit interferon signalling, allowing the virus to replicate effectively and prolonging the duration of infection (6). The host's immune system responds to RSV infection in a complex manner. In the initial phase, the innate immune response activates PRRs (pattern recognition receptors) such as RIG-I and TLR, inducing the production of pro-inflammatory cytokines (5,6). Excessive activation of the Th2 and Th17 responses can exacerbate local inflammation, especially in the small bronchioles of infants, increasing the risk of severe infection (6,7).

Factors increasing the risk of severe RSV infection include: age below 6 months, prematurity and comorbidities, including congenital heart defects, bronchopulmonary dysplasia and immunodeficiency (1, 3, 4, 6). In the youngest patients, RSV infection is usually more severe, with symptoms such as tachypnoea, wheezing, cyanosis, and sometimes requires hospitalisation and respiratory support. Older children usually have a milder course of the disease, with symptoms most often limited to a runny nose, cough, and mild shortness of breath (1,5).

3. Acute pulmonary complications following RSV infection

Acute pulmonary complications in the course of RSV infection are a serious clinical problem, especially in the youngest children, in whom the virus can cause rapidly progressive respiratory failure, often requiring hospitalisation (8). In infants and high-risk patients, the course of RSV is usually more severe, and complications such as bronchiolitis, pneumonia and bronchial obstruction occur more frequently and increase the risk of death and long-term complications (9). The acute phase of RSV infection plays a key role in the subsequent functioning of the respiratory system, as confirmed by many studies analyzing both the biological mechanisms of airway damage and long-term clinical effects (1, 2, 3).

3.1 Bronchiolitis

Bronchiolitis, most commonly caused by the RSV virus, is one of the main reasons for hospitalisation of infants in their first year of life (10,11). The mechanism of disease development is associated with infection of the small bronchiolar epithelium, leading to mucosal oedema, epithelial cell damage and excessive mucus production, which forms characteristic mucus plugs that obstruct airflow (10). This leads to obstruction of the small airways, increased respiratory resistance and hypoxia, which explains the typical clinical symptoms of the disease (10,11). The clinical picture of bronchiolitis is dominated by cough, wheezing, tachypnoea, increased respiratory effort and difficulty in breathing, especially in infants (11). Hospitalisation is indicated in severe cases, based on the severity of symptoms such as hypoxia ($SpO2 < 90–92\%$), dehydration, severe shortness of breath and inability to eat orally (11,12). Multicentre analyses confirm that the most important risk factors for severe disease include prematurity, congenital heart defects, chronic lung disease and age below 6 months (12). Severe bronchiolitis is associated with the risk of more serious pulmonary complications such as hypoxia requiring oxygen therapy, bronchiolar obstruction leading to atelectasis and, in the most severe cases, acute respiratory failure requiring assisted ventilation (10,11,12). Significant clinical problems in the course of RSV infection include an increased risk of secondary bacterial infections and exacerbation of comorbidities, which in some patients requires intensive hospital care (12). Current research suggests that not only direct damage to cells by the virus, but above all an abnormal immune response by the host, including, among other things, disturbances in the ubiquitinisation mechanisms of proteins modulating innate immunity, plays a key role in the severity of pathophysiological changes during RSV infection (5,7). Active recruitment of inflammatory cells and release of pro-inflammatory mediators in the small airways promote early remodelling of these structures, which may predispose to obstructive complications later on (3,6). The results of multicentre studies emphasise that severe bronchiolitis is a significant clinical and economic burden, often requiring intensive respiratory support such as high-flow nasal oxygen therapy or non-invasive pressure support (CPAP) (4, 11). The degree of epithelial damage and the severity of inflammation in the acute phase of infection are crucial for the development of long-term respiratory sequelae, including recurrent wheezing later in life (2,8).

3.2 RSV-associated pneumonia

The RSV virus causes pneumonia mainly through direct invasion of the respiratory tract epithelium, which, combined with a violent immune response from the host, generates a cascade of pathological changes. Viral replication in epithelial cells leads to their apoptosis and necrosis, accompanied by severe oedema and accumulation of very thick mucus, which mechanically blocks the small bronchioles, contributing to the formation of infiltrates in the lung parenchyma (13). RSV is also able to deactivate some of the immune mechanisms by blocking interferon signalling (among other things, thanks to the NS1 and NS2 proteins), which weakens the early antiviral response and results in the virus spreading more freely. This leads to greater tissue damage and increased inflammation in the respiratory tract. The interaction of the virus with the immune response, and in particular the excessive activation of certain inflammatory pathways, largely determines the degree of damage to the respiratory tract and the severity of clinical symptoms (5,13). Clinically, RSV pneumonia usually begins with upper respiratory symptoms such as a runny nose and cough. In younger children, the infection can quickly progress to lower respiratory tract symptoms, such as tachypnoea, wheezing, rapid breathing, and feeding difficulties (3,11,13). Physical examination reveals crackles, and imaging studies show signs of pulmonary parenchymal consolidation (8,13). Compared to isolated bronchiolitis, patients with pneumonia more often present with high fever and profound hypoxemia, reflecting the extent of pulmonary parenchymal involvement and the severity of the inflammatory response (8,9). The severity of symptoms in this group of patients significantly increases the likelihood of requiring passive oxygen therapy or ventilatory support, which is one of the key elements of the acute phase of the disease (4,13). In radiological images, RSV-induced pneumonia usually presents with non-specific but fairly characteristic changes. These include patchy consolidation, peribronchial oedema, excessive lung hyperinflation and areas of atelectasis, most often in the lower parts of the lungs or within obstructed bronchioles. In the youngest children, changes of this type may be subtle and difficult to assess, so the interpretation of the radiograph should always take into account the patient's clinical picture. (8,13). It is worth noting that although radiological changes in the form of parenchymal infiltrates appear in many hospitalised infants, their severity does not always directly translate into the severity of respiratory failure. Therefore, it seems important to monitor blood gas parameters and assess the patient's condition clinically (8,9). At the same time, literature data show that persistent areas of atelectasis visible on X-rays can lead to secondary bacterial infections, which often prolongs hospitalisation

and significantly increases the cost of medical care (4,13). In cases with an ambiguous course, the literature suggests extending the diagnosis to include chest ultrasound, which allows for more accurate detection of small subpleural consolidations typical of more severe RSV infections (6,11). Differentiating between isolated RSV infection and bacterial superinfections, such as S. pneumoniae infection, is therapeutically important because the presence of co-infection significantly increases the risk of severe disease and the need for intensive care (14). Although the presence of parenchymal infiltrates on X-ray, sudden high fever and an increase in inflammatory markers may suggest a bacterial aetiology, the same radiological examination rarely allows for an unambiguous diagnosis (13,14). In clinical practice, the decision to initiate antibiotic therapy is based on the overall clinical picture and assessment of the risk of complications (12,13). The prognosis for RSV pneumonia varies. In most children, the disease is self-limiting and the short-term prognosis is favourable, especially when radiological changes are mild and there is no hypoxia. In infants with severe infection, comorbidities or bacterial co-infection, the risk of complications such as respiratory failure, prolonged hospitalisation and, in rare cases, death is significantly higher. In addition, severe pneumonia in early childhood may increase the risk of long-term respiratory problems such as recurrent wheezing or bronchial hyperresponsiveness (2,3,13,14).

3.3 Atelectasis

Atelectasis following RSV infection occurs primarily as a result of mechanical obstruction of the small bronchioles by swollen epithelium, cell necrosis and mucus plugs. Combined with inflammation and reduced elasticity of the bronchiolar walls, this leads to a ‘ball valve’ effect, in which air enters the alveoli during inspiration but cannot escape freely during expiration. As a result, resorptive atelectasis and local alveolar collapse develop (15). The changes most often involve the lower lung fields, bronchopulmonary segments and subsegments, and peripheral bronchioles, where the airways are narrow and highly susceptible to obstruction (16). The formation of areas of atelectasis leads to ventilation/perfusion mismatch (V/Q mismatch), which may manifest itself in increased oxygen demand and the need for increased respiratory support (15). The loss of aerated lung parenchyma forces the remaining segments to work harder, which may reduce chest compliance and exacerbate restrictive symptoms (16,17). Prolonged recurrent episodes of atelectasis may contribute to airway remodelling and reduce the patient's respiratory reserve, which increases the risk of developing bronchial hyperresponsiveness later in life (2,3). Recent studies suggest that atelectatic areas may promote colonisation of the lower airways by Streptococcus pneumoniae. In this case, we are dealing with a synergistic effect: RSV, by impairing mucociliary clearance and facilitating bacterial adhesion in collapsed lung segments, exacerbates inflammation and increases the risk of the primary viral infection progressing to severe bacterial pneumonia (1,14). It should be noted that lung ultrasound is playing an increasingly important role in bedside diagnostics, often surpassing X-ray in terms of sensitivity in detecting small subpleural atelectasis and dynamic changes in lung aeration. This test allows for the rapid identification of patients requiring intensive respiratory physiotherapy, even before full-blown respiratory failure develops (16).

3.4 Acute respiratory failure

Acute respiratory failure is one of the most serious consequences of RSV infection and develops in situations of significant airway narrowing accompanied by increasing gas exchange impairment (1,2,17). The mechanism leading to acute respiratory failure in the course of RSV infection is the result of processes more complex than the cytopathic effect of the virus itself. Dysregulation of the immune response, especially at the level of mechanisms controlling the innate response, also plays an important role (5,6). This results in the intensive recruitment of inflammatory cells, which damage the alveolar-capillary barrier by releasing proteases and reactive oxygen species (6,12). In the course of severe RSV infection, type II pneumocyte damage is also added to the pathophysiological picture of acute respiratory failure. This leads to secondary deficiency and dysfunction of surfactant, and consequently to alveolar instability, collapse and further exacerbation of hypoxaemia. This mechanism is one of the pathophysiological justifications for therapeutic trials using exogenous surfactant in the most severe cases (1,15). Children with severe disease present with hypoxaemia, hypercapnia, rapid breathing and uneven ventilation. Some patients may develop multiple organ failure. In newborns and young infants, the first sign of acute respiratory failure may be apnoea, which sometimes precedes the appearance of classic auscultatory changes. This mechanism involves both airway obstruction and the direct effect of the virus on central respiratory regulation, which necessitates immediate observation and support in an intensive care unit (10,13). In clinical practice, escalation of respiratory support depends primarily on the severity of respiratory effort and signs of exhaustion of compensatory reserves. Rapid use of

HFNC or CPAP in high-risk children significantly improves prognosis and reduces the need for invasive ventilation (12,17). The group at highest risk of acute respiratory failure includes infants with congenital heart defects, bronchopulmonary dysplasia and children under 6 months of age. In addition, the coexistence of a bacterial infection, e.g. pneumococcal, may accelerate respiratory decompensation (14). Contemporary cohort analyses show that acute respiratory failure associated with RSV in infancy may be a significant risk factor for long-term reduction in lung function and may contribute to the development of chronic respiratory diseases in adulthood. Early identification of the first signs of increasing respiratory failure and rapid implementation of treatment are therefore crucial not only for controlling the acute phase of infection, but also for the further development and maturation of the child's respiratory system (2,3,6,17).

3.5 Complications in children with comorbidities

Children with comorbidities are at particularly high risk of severe RSV infection and the development of respiratory complications. In this population, premature infants are at the forefront, as the immaturity of both their respiratory system and immune mechanisms significantly increases the frequency of hospitalisation and the need for respiratory support during infection, and the course of infection itself is often significantly more complicated than in full-term newborns. The limited efficiency of the respiratory tract's defence mechanisms, including impaired ciliary function and an immature immune response, promotes the accumulation of thick secretions and obstruction of the small bronchioles. This, in turn, directly increases the risk of developing acute respiratory failure (1,2,15,17). The high susceptibility of preterm infants to severe RSV infection is therefore the result of overlapping anatomical and immunological factors and the developmental immaturity of the lung parenchyma, rather than a single pathophysiological mechanism. Due to the small calibre of the airways, even slight swelling of the mucous membrane can lead to a rapid increase in respiratory resistance. According to Poiseuille's law, a 50% reduction in the radius of the bronchial lumen translates into a 16-fold increase in airflow resistance (10,15). The situation is further complicated by the immaturity of the collateral ventilation channels, including poorly developed Kohn's pores, which limits the ability to compensate for mucosal obstruction and promotes the development of extensive areas of atelectasis, especially in the lower parts of the lungs (13,16). At the immunological level, premature infants have limited concentrations of specific IgG antibodies against RSV, as the most intensive transport of immunoglobulins through the placenta occurs only in the third trimester of pregnancy (1,6). In addition, their immune system has a limited ability to produce an effective interferon response. In practice, this results in high viral titres in the respiratory tract and a prolonged and more severe course of infection (6,19). Importantly, severe RSV infection during the critical period of early lung development can disrupt the process of alveolarisation. This results in a permanent reduction in gas exchange surface area and decreased respiratory capacity in later childhood (3,20).

In high-risk groups such as children with congenital heart defects, RSV infection is associated with a significantly more severe course of the disease, extending beyond typical respiratory symptoms. In patients with haemodynamically significant heart defects, especially those with left-to-right shunting or concomitant pulmonary hypertension, infection can lead to an acute increase in pulmonary vascular resistance, causing secondary cardiopulmonary decompensation. This mechanism involves both hypoxemic pulmonary vasoconstriction and an exacerbated inflammatory process involving mediators acting on the endothelium. This leads to longer hospitalisation, more frequent treatment in intensive care units and a higher risk of death in this group of patients (18,20).

An increased risk of complications also applies to children with chronic lung diseases, especially bronchopulmonary dysplasia (BPD). In these patients, permanent structural changes in the airways and alveolar development disorders limit the effectiveness of ventilation and promote the retention of secretions. As a result, susceptibility to recurrent infections and the formation of areas of atelectasis increases. RSV infection overlaps with existing lung maturation disorders, exacerbating inflammatory processes and airway remodelling. In clinical practice, this results in a permanent reduction in lung function parameters such as FEV1 and increases the risk of developing a chronic obstructive pulmonary disease phenotype later in life (1,2,3,6).

Patients with neuromuscular diseases constitute another group particularly vulnerable to severe RSV infection. Weakened respiratory muscles and impaired coughing efficiency make it difficult to clear the airways, which promotes the accumulation of secretions, secondary infections and increasing respiratory failure (12,17).

A particularly severe course of RSV is observed in children with immunodeficiencies, including those who have undergone haematopoietic cell transplantation or are undergoing cancer treatment. In such patients, the virus is eliminated much more slowly, resulting in prolonged excretion of the virus from the respiratory tract. In practice, this means a higher risk of infection progression, the emergence of opportunistic co-infections and poorer treatment outcomes, including increased mortality (19,20). All of the above-mentioned groups require early diagnosis of infection symptoms, constant monitoring of lung function and rapid implementation of appropriate respiratory support. Optimal care combines prevention (including vaccination and immunoprophylaxis) with individually tailored treatment of acute respiratory failure and careful monitoring for possible long-term complications (1,2,18,19,20).

4. Chronic respiratory complications following RSV infection

RSV infection in the first years of life, i.e. during the period of intensive lung maturation, may have consequences that extend far beyond the acute phase of the disease and significantly affect the subsequent functioning of the respiratory system (2,21). A growing body of evidence suggests that severe RSV infection is not limited to transient damage to the lung parenchyma. Such an episode may permanently disrupt the trajectory of lung function development, which in clinical practice translates into lower flow parameters such as FEV1, observed even in adulthood (3,21). The pathomechanism of this phenomenon involves a complex relationship between airway remodelling and persistent immune dysregulation. Particular importance is attached to the shift in the response profile towards Th2, which promotes the development of bronchial hyperresponsiveness and asthmatic phenotypes (6,21). Therefore, RSV infection is increasingly recognised as an important and potentially modifiable risk factor for the development of chronic lung disease throughout life, necessitating long-term monitoring of children after hospitalisation (2,21).

4.1 Recurrent airway obstruction and hyperresponsiveness

Recurrent wheezing is the most common clinical manifestation of persistent bronchial hyperresponsiveness in children after RSV infection. Depending on the study, it affects between 20% and 50% of infants hospitalised for infection, and the risk is particularly high in premature babies and children with bronchopulmonary dysplasia. In these patients, respiratory immaturity overlaps with post-infectious lung parenchymal damage, increasing susceptibility to recurrent episodes of obstruction (2,3,21,22). Recurrent obstruction after RSV infection is mainly due to permanent changes in the structure of the airways. Unlike classic atopic asthma, both structural changes and bronchial epithelial dysfunction play a key role here. The literature highlights the phenomenon of dysanapsis, i.e. the disproportionate rate of lung volume growth in relation to bronchial diameter, as a pathophysiological concept that may increase the susceptibility of the airways to obstruction (3,21). Post-infectious epithelial remodelling and increased extracellular matrix deposition perpetuate these changes. As a result, the airways become more susceptible to collapse, even with minor inflammatory stimuli (21,24). RSV may affect the development of the neuroimmunological axis of the lungs, promoting airway hyperresponsiveness. Experimental studies show that infection induces changes in the functioning of afferent nerve fibres and alters the expression of certain neuropeptides such as substance P, VIP, and nerve growth factors (NGF), which may lower the bronchial excitability threshold (22,25). This is accompanied by a persistent tendency towards a Th2 response, eosinophil infiltration, and increased epithelial sensitivity to subsequent viral infections. Together, these processes promote the persistence of low-grade inflammation and airway hyperresponsiveness (1,3,26). However, it should be emphasised that most of the data on the neurogenic mechanism comes from experimental studies, and the full clinical significance of these mechanisms still needs to be confirmed in further analyses. Increasing evidence suggests that respiratory tract dysbiosis plays a role in perpetuating the wheezing phenotype. Colonisation of the nasopharynx by bacteria such as Moraxella catarrhalis or Haemophilus influenzae during the acute phase of RSV infection may exacerbate inflammation and promote the development of persistent obstruction in later years (14,23,26). These factors, combined with exposure to tobacco smoke, further modify the maturation of the immune system and perpetuate airway hyperresponsiveness. In some patients, this may predispose them to the later development of bronchial asthma (23,24). The diagnosis of chronic hyperresponsiveness after RSV infection requires careful differentiation from classic atopic asthma, as structural and neuroimmunological mechanisms often predominate in these cases, rather than allergic ones. The therapeutic approach should be comprehensive: it should include strict environmental control (elimination of tobacco smoke), regular monitoring of lung function (e.g. FEV1 in older children) and targeted pharmacotherapy to reduce hyperresponsiveness and protect the airway epithelium (2,21,25).

4.2 Increased risk of developing asthma

The results of multicentre cohort studies and the latest meta-analyses indicate that early RSV infection is one of the strongest independent risk factors for developing asthma in later childhood (2,3,27). A meta-analysis published by Jia et al. (2025), covering several large population cohorts from different regions of the world, showed that RSV infection in infancy is associated with an average 2/3-fold increase in the risk of developing asthma in later life (27). The most important factor determining the risk of developing asthma after RSV infection is the age at the time of first exposure. The greatest susceptibility is observed in children infected in the first six months of life, which is associated with the existence of a so-called critical developmental window of the immune system, in which RSV infection can disrupt the maturation of the immune response, including by disrupting Treg lymphocyte function and promoting a persistent pro-allergic phenotype, which ultimately increases the risk of developing asthma in later childhood (24,27). There has been a long-standing debate in the medical literature as to whether RSV infection is a direct cause of bronchial asthma or rather reveals a child's innate genetic and immunological predisposition (24). Epidemiological data and clinical observations show that children with a positive family history of atopy or previous bronchial hyperresponsiveness have a significantly higher risk of developing asthma after severe RSV. These results support the hypothesis that the virus acts more often as a factor revealing the host's congenital susceptibility than directly causing the disease (23,24). At the same time, more and more data indicate that the observed relationship between severe RSV infection and the subsequent development of asthma is of a gene-environment interaction nature. It has been shown that early, severe infection can interact synergistically with specific genetic variants, particularly within the 17q21 locus (including ORMDL3 and GSDMB), which are strongly associated with the risk of developing asthma in childhood (3,21). In this context, RSV may act as an initiating or modulating factor in the maturation of the immune system and the development of the respiratory tract in predisposed children, contributing to the consolidation of the asthmatic phenotype (3,22). An important argument supporting the hypothesis of RSV involvement in the pathogenesis of later asthma comes from observations from immunoprophylaxis studies. The data indicate that effective prevention of severe infections, for example through the administration of monoclonal antibodies, is associated with a reduced frequency of recurrent wheezing and obstructive symptoms at school age. Some analyses even suggest that this may translate into a lower risk of developing asthma. These results emphasise that modifying the course of acute infection can have a real impact on the long-term trajectory of a child's respiratory health (3,24). The mechanism of action of RV goes beyond short-term inflammation – the virus can permanently modulate the host's immune response. Studies show that infection promotes long-term activation of type II innate lymphoid cells (ILC2) and impaired function of regulatory lymphocytes (Treg), which in turn may shift the balance of the immune system towards a Th2 response (6,22). The concept of the so-called ‘innate memory’ of the epithelium and ILC2 cells may be a potential biological basis for a persistent pro-allergic phenotype after severe RSV infection and is considered one of the mechanisms promoting the development of allergic diseases later in life (22,24). Susceptibility to the development of asthma after RSV infection largely depends on the maturity of the newborn. Premature infants, especially those with low birth weight and coexisting bronchopulmonary dysplasia, are clearly more at risk of progression to bronchial asthma (3,22). In these children, two mechanisms overlap – structural immaturity of the lungs and viral dysregulation of the inflammatory response, which promotes the consolidation of changes in the airways. Clinically, this may manifest not only as recurrent wheezing, but in some patients may lead to the development of a bronchial asthma phenotype requiring anti-inflammatory treatment (22,23,27). In summary, current data suggest that early RSV infection may act as an initiating or modulating factor for both the structure and immune response of the airways. In genetically and developmentally susceptible children, this interaction may be the starting point for the development of a chronic asthmatic phenotype (3,24,27).

4.3 Permanent changes in the structure and function of the respiratory tract

In some patients, severe RSV infection during infancy is associated with permanent structural and functional abnormalities of the respiratory tract that may extend beyond transient inflammation. Histopathological studies and experimental models show that infection can lead to damage to the respiratory epithelium, impaired ciliary function and activation of inflammatory processes that promote remodelling of the airways (2,3,25,28). The described consequences include, among others, thickening of the basement membrane, metaplasia of goblet cells and increased mucus production. These changes are often accompanied by features of chronic bronchitis and bronchiolitis, which in some studies are associated with the subsequent development of bronchial hyperresponsiveness and persistent symptoms of obstruction (2,3,28). In extremely

severe cases, most often after bronchiolitis requiring hospitalisation, post-infectious damage to the small airways can lead to bronchiolitis obliterans, characterised by permanent, often irreversible narrowing of the bronchioles (29). However, it should be noted that this is a rare complication, observed almost exclusively in children after an exceptionally severe course of infection. Long-term cohort studies suggest that some children who have had a severe RSV infection may continue to have functional lung deficits into school age, adolescence and, in some analyses, even early adulthood (18–20 years of age). Spirometry studies more frequently find:

- a decrease in forced expiratory volume in one second (FEV1) and FEV1/FVC ratio,
- a decrease in small airway flow (FEF25-75), considered a relatively sensitive marker of subtle post-infectious ventilation disorders (29),
- increased variability in respiratory flow and air trapping (28).

Importantly, in some children these abnormalities may persist despite the resolution of overt clinical symptoms. This suggests that subclinical lung impairment may occur after RSV infection (29). A growing body of evidence suggests that severe RSV infection may result not so much in accelerated loss of lung function as in a permanent modification of its development trajectory. According to the concept described in recent studies (e.g. Zar et al.), children who have had severe RSV infection in early life may not reach their peak lung function in early adulthood (3,21). Such a reduced baseline lung function may promote the earlier onset of chronic obstructive symptoms in subsequent decades of life, especially when additional risk factors are present (3,21,29). The severity and persistence of functional deficits may vary between patients. More pronounced disorders are observed in premature infants, children with atopic predisposition and those exposed to harmful environmental factors such as passive smoking, air pollution or recurrent viral infections in the first years of life (2,3,28). These factors may exacerbate inflammatory reactions and perpetuate structural changes in the airways. Structural changes are reflected in imaging studies, particularly high-resolution computed tomography (HRCT). In patients with persistent ventilation disorders, bronchial wall thickening, areas of mosaic perfusion and features of chronic obstruction are described (29). It is worth noting that some of these changes may also occur in children without obvious clinical symptoms, during periods of stabilisation, suggesting the existence of 'silent' structural changes (28,29). From a clinical point of view, it is crucial to diagnose children at risk early and to monitor their lung function in the long term, e.g. through spirometry, limiting exposure to environmental factors and, in selected cases, immunoprophylaxis and respiratory support (28,29).

5. Pathophysiological mechanisms of complications: from acute infection to permanent sequelae

A complete understanding of the pathophysiology of RSV infection requires viewing this process as a two-phase phenomenon. It includes both the acute phase of infection and its long-term consequences for the respiratory tract. The acute phase is characterised by direct tissue damage and mechanical obstruction of the bronchioles, while the chronic phase results from molecular and immunological reprogramming of the respiratory system, leading to permanent structural and functional changes.

5.1 Acute phase: barrier destruction and mechanical obstruction

Direct replication of the virus in respiratory epithelial cells is the starting point for the development of clinical manifestations of severe infection. The key phenomenon is massive damage and desquamation of ciliated cells, which, combined with mucus overproduction and fibrin exudate, leads to the formation of characteristic mucus plugs in the lumen of small bronchioles (11,15). This process is responsible for the most commonly observed acute complications, such as atelectasis or air trapping, which are the result of mechanical obstruction of the lower airways. At the same time, intensive neutrophil recruitment and the release of inflammatory mediators cause submucosal oedema, which significantly reduces ventilatory reserve and may contribute to the development of acute respiratory failure (10,13). During this critical period, mucociliary clearance is also impaired, which hinders the removal of secretions. This creates favourable conditions for secondary and recurrent infections and may exacerbate the primary damage to the epithelium (28,31).

5.2 Impaired regeneration and neurogenic remodelling of the bronchi

The transition from acute inflammation to permanent lung dysfunction is associated with impaired natural repair mechanisms. Studies show that RSV can permanently affect the dynamics of the actin cytoskeleton, inhibiting epithelial cell migration and slowing down the reconstruction of the protective barrier (31). This phenomenon, known as 'stalled repair', leads to the replacement of normal tissue with fibrous changes and the formation of permanent structural scars. A key pathophysiological element that may explain

persistent airway hyperresponsiveness is the activation of the NODAL pathway. The virus can stimulate the differentiation of epithelial cells towards a neuroendocrine phenotype, resulting in the release of neuropeptides that irritate nerve endings and potentially exacerbate hyperresponsiveness (25). This mechanism may be the biological basis for the neurogenic component of chronic obstructive symptoms that persist in patients long after the virus has been eliminated.

5.3 Immunological programming of the airways

From a mechanistic perspective, RSV infection is not limited to causing transient inflammation, but can lead to long-term modulation of immune responses. Damage to the respiratory epithelium activates innate type 2 lymphoid cells (ILC2), which can act as a specific innate memory 'sensor' (6,22). Their long-term activation and sustained production of interleukin 5 (IL-5) and 13 (IL-13) promote airway remodelling, including smooth muscle proliferation and goblet cell metaplasia. Importantly, these processes can occur even without the clear involvement of classic allergic factors (25,28,29,30). At the same time, RSV infection can lead to permanent impairment of the suppressive function of regulatory T cells (Treg). Such a deficit promotes the consolidation of a pro-allergic phenotype of the immune response and increases susceptibility to eosinophilic inflammation in the airways (24,30).

5.4 Interaction with atopic predisposition and environmental factors

Medical literature emphasises that in children with genetic predisposition and atopic features, RSV infection may play a significant role in modulating the immune response towards the Th2 phenotype. This mechanism explains the observed increase in the risk of recurrent wheezing and the development of bronchial asthma in later years (3,24). A growing body of evidence indicates that the pathogenesis of long-term respiratory sequelae after RSV infection is multifactorial. In children without clear features of atopy, persistent lung function impairment in later years may be the result of a synergy between the severity of the primary infection and exposure to environmental factors. Particular importance is attached to passive exposure to tobacco smoke and air pollution, including fine particulate matter PM2.5, which exacerbate the inflammatory response and promote airway remodelling processes (3,27). The current view of the pathophysiology of RSV infections increasingly takes into account the importance of the respiratory microbiome and the concept of the so-called 'second hit'. Available data suggest that a previous RSV infection may increase the susceptibility of the respiratory epithelium to secondary bacterial colonisation. This mechanism is associated, among other things, with changes in the expression of adhesion receptors, such as the platelet-activating factor receptor (PAF-R), which facilitates the adhesion and multiplication of potentially pathogenic bacteria, in particular Streptococcus pneumoniae (14,26). This type of interaction between viral and bacterial pathogens can lead to increased damage to the extracellular matrix and physiological disorders of respiratory epithelial regeneration processes. As a consequence, especially in the most severe cases, this promotes the consolidation of obstructive changes in the small airways and, in rare cases, may be one of the mechanisms leading to the development of changes described as bronchiolitis obliterans (14,26). Less tangible, long-term molecular mechanisms are also increasingly being postulated. These include, among others, RSV-induced epigenetic changes and mitochondrial dysfunction leading to oxidative stress. These processes may contribute to permanent dysregulation of lung tissue homeostasis. These phenomena are increasingly interpreted as a possible biological basis for functional changes resembling accelerated 'ageing' of the respiratory system. This perspective may partly explain why individuals who have had severe RSV infection in infancy continue to experience persistent lung function deficits in adulthood (2,3,22,32).

In summary, complications following RSV infection result from both direct tissue damage and long-term dysregulation of repair and immune processes. Early infection can permanently modify the airways through structural, neurogenic and epigenetic changes, highlighting the importance of preventive strategies in high-risk children.

6. Prevention of RSV complications

In light of the mechanisms described above that lead to permanent structural and immunological changes, the prevention of RSV infections is no longer solely focused on preventing acute disease. It is increasingly seen as an important part of protecting the long-term health of a child's respiratory system. The current approach involves a multi-level strategy combining passive immunoprophylaxis, protective vaccination and limiting exposure to adverse environmental factors.

6.1 Immunoprophylaxis with Paliwizumab and Nirsevimab

The basis of the current RSV prevention strategy, especially in high-risk children, remains the use of monoclonal antibodies. They work by specifically neutralising the virus by binding to conserved epitopes of the F fusion protein, which blocks the fusion of the virus with respiratory epithelial cells and limits its replication (33,34). Traditionally used palivizumab, despite its documented effectiveness in reducing the incidence of hospitalisation in premature infants, children with congenital heart defects and bronchopulmonary dysplasia, has a short half-life, which necessitates monthly administration during the RSV season (34,35). A significant step forward was the introduction of nirsevimab, a monoclonal antibody with prolonged duration of action, which, thanks to modification of the Fc fragment, provides protection throughout the season after a single administration (33,36). Currently, this preparation is recommended primarily for high-risk children. Data from clinical trials and real-world evidence indicate that its use is associated not only with a significant reduction in the incidence of severe bronchiolitis, but also with a reduction in episodes of wheezing in subsequent years of life (34,36).

6.2 RSV vaccination

Alongside the development of monoclonal antibodies, medical literature increasingly documents the potential of protective vaccination as a tool influencing the epidemiology of RSV infections. The strategy of vaccinating pregnant women is currently attracting considerable interest. Thanks to the production of specific antibodies in the mother and their transfer through the placenta, the newborn receives protection from the first days of life, i.e. during the period of greatest susceptibility to severe RSV infection (35). This is particularly important in the context of the aforementioned ‘critical developmental window’. Providing protection to infants in the first months of life reduces the risk of severe epithelial damage, which may later contribute to the development of asthma (27,34). Advanced research on vaccines for children is currently underway. Their future introduction may not only protect vaccinated children, but also reduce the transmission of the virus in the population, which would ultimately reduce the burden on the healthcare system associated with the treatment of obstructive complications (36).

6.3 Non-pharmacological methods

Effective protection against RSV requires not only medical interventions, but also daily non-pharmacological practices that support the child's immunity. Breastfeeding is particularly important – in addition to providing IgA antibodies, breast milk contains immunomodulators and oligosaccharides (HMOs) that hinder the virus's adhesion to the respiratory tract epithelium (32,35). Eliminating exposure to tobacco smoke is also an important part of prevention. As shown in the chapter on pathophysiology, smoke exacerbates oxidative stress and epigenetic changes induced by RSV, which may worsen long-term prognosis (32). Combined with basic hygiene rules – frequent hand washing and avoiding contact with sick people – these measures support the effectiveness of modern protective methods. Combining pharmacological strategies with environmental measures provides children with multidirectional protection. The most effective way to prevent permanent changes in the respiratory system and loss of lung function in adulthood remains the reduction of the severity of RSV infection in early childhood (3,34,36).

7. Summary and conclusions

An analysis of contemporary literature clearly shows that RSV infection in early childhood is not just a single infectious episode, but an important factor shaping the development of the respiratory system. Complications following infection range widely, from acute obstructive syndromes and atelectasis to permanent structural and immunological changes that can affect lung function even in adulthood. The key conclusion from this review is that RSV infection leaves a specific molecular signature in the epithelium and stem cells of the lungs. Phenomena such as neurogenic remodelling of the airways and epigenetic programming of the inflammatory response create the biological basis for recurrent wheezing and the development of asthma, often independently of classic atopic predispositions. It is worth emphasising that the development of distant respiratory complications is multifactorial. It results from the severity of the primary infection, genetic predisposition, and the influence of environmental factors such as exposure to tobacco smoke or respiratory tract microbiome disorders. In this context, the introduction of modern immunoprophylaxis methods and the development of prenatal vaccinations are changing the approach to child health protection. Ensuring respiratory tract protection during the so-called critical developmental window offers a real opportunity to reduce hospitalisations and limit long-term obstructive complications in the paediatric population. In summary, RSV remains one of the strongest modifiable risk factors for chronic lung disease. Effective protective strategies should combine the search for precise biomarkers, the implementation of modern prevention measures and education, creating the foundation for long-term protection of the ventilatory reserve of future generations.

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