

Perinatal respiratory infections and long term consequences

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From the womb to the adult

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Abstract

Respiratory syncytial virus (RSV) is the most important pathogen in the etiology of respiratory infections in early life. 50% of children are affected by RSV within the first year of age, and almost all children become infected within two years. Numerous retrospective and prospective studies linking RSV and chronic respiratory morbidity show that RSV bronchiolitis in infancy is followed by recurrent wheezing after the acute episod. According to some authors a greater risk of wheezing in children with a history of RSV bronchiolitis would be limited to childhood, while according to others this risk would be extended into adolescence and adulthood. To explain the relationship between RSV infection and the development of bronchial asthma or the clinical pathogenetic patterns related to a state of bronchial hyperreactivity, it has been suggested that RSV may cause alterations in the response of the immune system (immunogenic hypothesis), activating directly mast cells and basophils and changing the pattern of differentiation of immune cells present in the bronchial tree as receptors and inflammatory cytokines. It was also suggested that RSV infection can cause bronchial hyperreactivity altering nervous airway modulation, acting on nerve fibers present in the airways (neurogenic hypothesis).

The benefits of passive immunoprophylaxis with palivizumab, which seems to represent an effective approach in reducing the sequelae of RSV infection

in the short- and long-term period, strengthen the implementation of prevention programs with this drug, as recommended by the national guidelines of the Italian Society of Neonatology.

Keywords

Respiratory syncytial virus, bronchiolitis, immune reactivity, lung, long term consequences, palivizumab.

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Introduction

Respiratory syncytial virus (RSV) is the most important pathogen in the etiology of respiratory infections in early life. 50% of children are affected by RSV within the first year of age, and almost all children become infected within two years [1]. Furthermore, after the first contact with the virus, about 40% of children develop an infection of the lower airways (Low Respiratory Tract Infection, LRTI), usually bronchiolitis or pneumonia, clinically characterized by cough, tachypnea, hyperventilation, inspiratory retractions, crackles and wheezing. In 0.5-2% of cases these infections result in hospitalization, with a mortality of 0.5-1% in industrialized countries. In Italy, RSV causes 42.6% of hospitalizations for severe respiratory infection in term infants and up to 71.4% in preterm infants.

Evidence shows that, in addition to the substantial direct health impact, RSV infection has an impact on children's health in later years.

Children affected by RSV have an increased risk of LRTIs and request medical examinations and new hospitalizations. An increasing number of epidemiological data also supports the existence of a connection between RSV infection in childhood and chronic respiratory morbidity, recurrent wheezing (RW), reactive airway syndrome and asthma, which extends in adolescence and early adult age.

Epidemiological data

Numerous retrospective and prospective studies linking RSV and chronic respiratory morbidity show that RSV bronchiolitis in infancy is followed by RW after the acute episode in a variable percentage from 42% to 71% [1]. According to some authors a greater risk of wheezing in children with a history of RSV bronchiolitis would be limited to childhood, while according to others this risk would be extended into adolescence and adulthood.

Sigurs N. and colleagues [2] followed prospectively a cohort of 47 children hospitalized in the first year of life for RSV bronchiolitis, comparing them with a control group of 93 children. They evaluated the frequency of RW/asthma at the age of 3, 7, 13 and 18 years. RW was defined as ≥ 3 episodes of bronchial obstruction in one year not verified by a doctor and asthma as ≥ 3 episodes of bronchial obstruction in one year verified by a doctor.

With a median follow-up of three years starting from the infection, it was found an increased risk of bronchial hyperresponsiveness (RW/asthma) in children with RSV bronchiolitis compared with controls (23% versus 1%, $p < 0.001$). At the second follow-up at 7 years, the cumulative prevalence of asthma was 30% in the RSV and 3% in controls ($p < 0.001$) and the prevalence of RW of 28% and 11%, respectively ($p < 0.015$); allergic sensitization was observed in 41% of children with bronchiolitis and 22% of controls ($p = 0.039$). At thirteen years of age the cumulative prevalence of asthma in the RSV group was 37% compared to 5.4% in the control group ($p < 0.001$). Similarly, the cumulative prevalence of RW was 30% in the RSV group compared to 16.3% in the control group ($p = 0.093$) [3].

The follow-up at age 18 years showed current asthma/RW in 18 of 46 (39%) subjects with RSV and in 8 of 92 (9%) controls ($p = 0.001$). The prevalence of sensitisation determined by SPT was significantly increased in the RSV cohort compared with controls (41% vs 14%; $p = 0.001$). Reduced spirometric airway function was documented in the RSV cohort compared with controls. Bronchodilator response and blood eosinophil cell counts were greater in the RSV cohort than in the controls, but FeNO was not. A history of hospitalisation for RSV bronchiolitis was the only significant risk factor identified at age 18 for current asthma/wheezing [4].

The correlation between RSV infection and RW has also been reported by Pullan and Hey, that in their study enrolled 130 patients with a diagnosis

of bronchiolitis and 111 controls: after 48 months from the initial infection, 55/130 (42%) children with a history of bronchiolitis experienced episodes of wheezing compared with 21/111 (19%) in the control group, with a statistically significant difference [5]. After 10 years of follow-up asthma was diagnosed in only 6.2% of subjects who presented bronchiolitis compared with 4.5% of controls. It was not found any significant difference between the two populations in terms of allergic sensitization (19% in the RSV and 15% in the control group).

Conversely, in a Finnish study the risk of bronchial asthma and respiratory hyperreactivity increased in children who presented an episode of bronchiolitis in the first year of life. A cohort of 127 children hospitalized before 2 years of age for bronchiolitis or pneumonia has been followed up to 18-21 years of age and has been compared to a control group of similar age, followed from birth. The prevalence of asthma between 8 and 10 years of age was 15% in the group with bronchiolitis and 7% in the group with pneumonia, compared to 2% in the control group [6].

At 18-21 years of age, asthma was present in the 30-41% of subjects in the group with bronchiolitis, in the 15-24% of subjects in the group with pneumonia and 11% in the control group. Multivariate analysis indicated bronchiolitis as independent risk factor for the development of asthma [7].

Signs suggestive of a pathogenic correlation cause-effect between RSV infection and asthma are reported by different sources. It remains to be determined if a serious RSV infection in infancy may be responsible for lung function abnormalities that predispose to the development of asthmatic disease or if there are congenital or acquired abnormalities that predispose children to the development of severe LRTIs and to the onset of bronchial hyperreactivity.

Pathogenesis

To explain the relationship between RSV infection and the development of bronchial asthma or clinical pathogenetic patterns related to a state of bronchial hyperreactivity, it has been suggested that RSV may cause alterations in the response of the immune system (immunogenic hypothesis), activating directly mast cells and basophils and changing the pattern of differentiation of immune cells present in the bronchial tree as receptors and inflammatory cytokines. However we stress that the available evidences can also be read in a different way: a personal predisposition to allergic-

type immune response may determine the recurrent bronchial hyperreactivity in months and years following RSV infection.

Altering the immune reactivity of the lung, the virus may predispose to the development of a chronic respiratory disease in young and adult age.

It is now known that the prevalence of differentiation of CD4 + T lymphocytes in the sense Th2 (T helper 2) than that in Th1 (T-helper 1) causes an increased susceptibility to atopic diseases and bronchial asthma. The Th2 response physiologically prevails over the Th1 in the fetus and newborn, and then move towards the synthesis of IgA (stimulation of Th1 and downregulation of Th2) following the first contact with antigens. The RSV, instead, is able to activate directly mast cells and basophils, inducing the synthesis of cytokines that stimulate Th2 sense in increasing the synthesis of IgE and promoting the recruitment of eosinophils in the respiratory mucosa. So, the virus determines a response similar to that which occurs in the atopic response [8-10].

Since it has been demonstrated a genetic predisposition for a Th2 persistent response (ie., particular HLA haplotypes), the intervention of environmental factors (such as stimuli on the immune system in the critical postnatal period) may represent a possible mechanism that influences the susceptibility to the development of asthma or bronchial hyperresponsiveness in response to RSV infection.

The RSV replication in the epithelial cells represents a powerful biological stimulus inducing the expression of inflammatory genes that regulate the release cascade of proinflammatory cytokines and chemokines (interleukins 1, 6, 8 and 11, GM-CSF, TNF alpha, RANTES, etc.), responsible for the inflammatory and immune response against the host and the recruitment of inflammatory mononuclear cells in peribronchial mucosa. In this way the virus could alter the immune reactivity of the bronchial lung and predispose to the development of respiratory disease in young and adult.

It was also suggested that RSV infection can cause bronchial hyperreactivity altering nervous airway modulation, acting on nerve fibers present in the airways (neurogenic hypothesis) [11].

These fibers are of three types: adrenergic (that cause bronchodilation), cholinergic (that cause bronchoconstriction) and non-adrenergic non-cholinergic (NANC). The excitatory portion of NANC fibers cause bronchoconstriction by the release of substance P, a proinflammatory metabolite known for its function of hinge between

nervous and immune and inflammatory systems; substance P could be a key in mediating the effects of RSV infection. The substance P, in fact, is released also at a distance from the RSV infection after different stimuli, such as other viruses or respiratory allergens. This is due to the high affinity of the RSV towards the NK-1 receptor of substance P. The virus significantly boosts the expression of NK-1 in the epithelium and endothelium of the lung [12], as well as boosts some subpopulations of T cells belonging to lymphoid tissue associated with the bronchioles. The up-regulation of NK-1 receptors may explain the abnormal inflammatory response and airway hyperresponsiveness shown by children after RSV bronchiolitis: in experimental animals, in fact, the phenomenon can persist for a long time after the virus elimination.

In addition to the effects on the receptors NK-1, the RSV is able to act also through other mechanisms on the airways nerve fibers, as demonstrated by several experimental evidence in animals [13]: reducing the bronchodilator activity of the NANC fibers and inducing the synthesis and the release of high amounts of NGF (Nerve Growth Factor). NGF, together with other neurotrophins, has an important role in allergic diseases, that is evidenced by the high rate of neuromodulators present in subjects with allergic asthma or rhinoconjunctivitis [14].

A recent study investigated a potential immunological mechanism for the association between RSV and the development of allergic inflammation. The results showed for the first time that RSV can induce the expression and bioactivity of the enzyme indoleamine 2,3-dioxygenase (IDO) in human dendritic cells (moDC), in vitro. IDO has been reported to induce selective apoptosis of Th1 cells and contributed to Th2-biased immune responses. The authors suggested that RSV activation of IDO could be a potential mechanism for the development of allergic diseases [15].

Palivizumab prophylaxis

The relevance of the sequelae of RSV infection and their potential impact in the subsequent stages of life, emphasize even more the need for an effective prophylaxis. Some data show a positive impact on the short and long term sequelae of the passive immunoprophylaxis with the monoclonal antibody palivizumab. With regard to the immediate consequences of RSV infection, it has been shown that prophylaxis with palivizumab reduces the severity of the disease. Within the IMPact-RSV [16] and Cardiac

[17] studies, children treated with palivizumab presented a significantly shorter duration of hospitalization, required less oxygen supplementation and spent fewer days with moderate or severe LRTI.

For the long-term outcomes, a recent international multicentric study evaluated the relationship between LRTI caused by RSV in early childhood and the rates of wheezing occurred later, with the assumption that prevent the RSV LRTIs through prophylaxis with palivizumab may be useful to reduce the rate of RW in later life [18].

The study included 191 premature infants (GA < 35 weeks) who received palivizumab before 6 months of age and 230 children who had never received palivizumab (76 had been hospitalized for RSV and 154 had not). The incidence of RW and RW documented by the physician was significantly lower among those children who received palivizumab (respectively 13% and 8%) compared to all children who did not receive prophylaxis (respectively 26%, $p = 0.001$ and 16%, $p = 0.011$) and to the subgroup who had not received palivizumab and had not been hospitalized (respectively 23% $p = 0.022$ and 16%, $p = 0.027$). These results suggest that the prevention of RSV infection with palivizumab can reduce RW in later life in premature babies.

In a recent double-blind, placebo-controlled trial, Blanken M.O. et al. randomly assigned 429 otherwise healthy preterm infants born at a gestational age of 33 to 35 weeks to receive either monthly palivizumab injections (214 infants) or placebo (215 infants) during the RSV season. In the first year of life the number of days with parent-reported wheeze was lower in the RSV-prevention group than in the placebo group. This result was consistent for all 3 study years and independent of the number of injections of palivizumab or placebo. It has been observed an absolute reduction of 2.7 percentage points in rates of wheezing in the RSV-prevention group versus the placebo group (930 of 53,075 days [1.8%] and 2,309 of 51,726 days [4.5%], respectively), for a relative reduction of 61% (95% confidence interval [CI], 56 to 65). The proportion of infants with RW was lower in the RSV-prevention group if compared with the placebo group (11.2% vs. 20.9%, $p = 0.005$) (**Tab. 1**). Similarly, the proportion of infants receiving bronchodilators was lower in the RSV-prevention group than in the placebo group (13% vs. 23%, $p < 0.001$) [19].

The authors hypothesize that RSV primarily causes direct pulmonary epithelial damage and local immunologic alterations in the lungs, leading to long term airway hyperresponsiveness and wheezing.

Table 1. Infants with wheezing.

Variable	Palivizumab (N = 214)	Placebo (N = 215)	Absolute reduction	Relative risk reduction (95% CI)
Any wheezing ^a , no. of infants (%)	66 (30.8)	101 (47.0)	16.2	34 (14-53)
Wheezing episodes ^b , no.	137	266	129	48 (32-62)
Recurrent wheezing (RW) ^c , no. of infants (%)	24 (11.2)	45 (20.9)	9.7	47 (14-80)

^aAny wheezing was defined as at least one episode of wheezing during the first year of life; ^ba wheezing episode was defined as a respiratory episode with wheezing on more than 1 day; ^cRW was defined as three or more episodes of wheezing during the first year of life. P < 0.001 for the between-group comparisons for any wheezing and wheezing episodes and p = 0.005 for RW.

The benefits of passive immunoprophylaxis with palivizumab, which seems to represent an effective approach in reducing the sequelae of RSV infection in the short and long term, strengthen the implementation of prevention programs with this drug, as recommended by the national guidelines of the Italian Society of Neonatology.

Declaration of interest

The Authors declare that there is no conflict of interest.

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