Respiratory Syncytial Virus Infections

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Abstract

Respiratory syncytial virus (RSV) is one of the most common respiratory pathogens in infants and young children worldwide. Almost all children are infected at least once by the age of 2 years. The clinical manifestations vary depending on age, health status, and whether the infection is primary or reinfection. Most RSV-infected children experience upper respiratory tract symptoms and 20% to 30% develop lower respiratory tract disease (e.g., bronchiolitis and/or pneumonia). RSV is the most common cause of lower respiratory tract infection in children younger than 1 year of age. Most children who have been previously healthy have mild lower respiratory tract infections. However, prematurity, chronic lung disease, congenital heart disease, and primary or secondary immunodeficiencies are risk factors for severe RSV infections. Diagnosis can often be clinical. Diagnostic testing is not routinely recommended. The treatment of upper and lower respiratory tract infections is generally supportive. Ribavirin can be used in patients with immunodeficiency but is not routinely recommended. There is not a routine vaccine for RSV. The RSV-specific humanized mouse monoclonal antibody "palivizumab" is particularly safe and effective for prophylaxis in high-risk groups. *(J Pediatr Inf 2016; 10: 60-7)*

Keywords: Respiratory syncytial virus, RSV, bronchiolitis

Introduction

The respiratory syncytial virus (RSV) that can cause diseases in all age groups is one of the the most frequent infection agents in the childhood period. Despite the antibodies transmitted from their mothers, almost all children get infected by the RSV in the first two years of life (1). The first infections are almost always symptomatic and reinfections can also be symptomatic. Even though RSV is common in children in the form of upper respiratory tract infections, it also causes 20-30% lower respiratory tract infections as well. The most frequent cause of lower respiratory tract infections in infants is RSV (2). The World Health Organization states that RSV is responsible for 60% of acute lower respiratory tract infections in children. This particular rate is over 80% in infants (3). In a study carried out in a big center in Turkey,

RSV positivity was found in 37.9 % of children who are under two years of age and hospitalized due to acute lower respiratory tract infections (4). Across the world, 33 million RSV-related lower respiratory tract infections were seen in children in 2005. It was calculated that RSV-related hospitalization was 16.9/1000 in infants aged 0-5 months and 5.1/1000 in infants aged 6-11 months. The annual RSV-related mortality rate in children under five years of age varies between 66.000/year-199.000/year (5).

Etiology

Respiratory syncytial virus is a *Pneumovirus* type virus within the *Pneumovirinae sub-family of the Paramyxoviridae* family. Within the *Pneumovirinae* sub-family, there is also the *Metapneumovirus* type that also includes human Metapneumovirus (hMPV) identified in 2011 (6).

The RSV genome, which is single strand of negative-sense RNA is located in a helical nucleocapsid. This helical nucleocapsid is surrounded by a viral envelope derived from the plasma membrane of the host cell. The RSV genome encodes 10 structural and non-structural proteins. The non-structural NS1 and NS2 proteins prolong the survival of infected cell by preventing the interferon response and enhance the formation of new viruses. The structural proteins N (nucleoprotein), P (phosphoprotein), and L (polymerase) constitute the nucleocapsid structure. The non-glycosylated M and M2 structural proteins are also the matrix proteins. F (fusion), G (attachment) and SH (non-glycosylated hydrophobic) structural proteins on the envelop are the surface proteins. SH protein is not mandatory. for the disease, but with its deficiency, virus replication in the upper respiratory tract is reduced ten times. F and G proteins, on the other hand, are primarily responsible for the infection. The G protein is responsible for attachment to the host cell. Unlike the viruses in the *Paramyxoviridae* family, it does not contain neuraminidase and hemagglutinin. F protein is responsible for the fusion of the virus with the cell membrane and transmission of the virus from cell to cell as well as syncytial formation, characteristic of RVS. RSV has a serotype, but is majorly divided into groups of A and B according to the G protein. In both groups, there are different strains depending on the variations in the F, G, N and P proteins (7).

Epidemiology

The only source for RSV is humans. Transmission occurs through the arrival of contaminated secretions onto the nasopharyngeal mucosa, eye mucosa and at a less degree onto the oral mucosa. It occurs due to the large particulate droplets (≤0.9 m) within a short range that spread during frequent breathing, sneezing, coughing or fomites. RSV can persist on environmental surfaces for several hours and for a half-hour or more on hands. Therefore, hand washing and contact precautions are important in the prevention of transmission (8). Numerous studies concluded that infants in a household were infected by their elder siblings. The process of viral replication is usually 3-8 days. However, in small infants and immunocompromised cases, it can last as long as 3-4 weeks. The incubation period in RSV infections is 2-8 days and the frequency is 4-6 days (8).

Respiratory syncytial virus has seasonal characteristics. In both hemispheres where there are warm climates, RSV frequency reaches its peak level in winter months. Around the Equator region, RSV is prevalent throughout most of the year. In the Northern hemisphere where Turkey is located, the RSV season stares in the months of November-December, reaches its peak between January-February and ends in March-April (9). A complex process including daily average temperatures, humidity and precipitation rates and ultraviolet rays are responsible for the seasonal activity changes of RSV (10).

Results from several epidemiologic studies suggest that vitamin D may be protective against RSV lower respiratory tract infection. These studies linked the frequency of infections increasing in winter months with decreasing vitamin D serum concentrations (7).

Pathogenesis

RSV is replicated in the nasopharynx and causes upper respiratory tract infection. The lower respiratory tract infection develops by the infection of bronchial epithelium and then type 1-2 alveolar pneumocytes. This particular picture emerges 1-3 days after the symptoms of upper respiratory tract infection (11, 12). Aspiration of the secretions or spread of the virus from cell to cell might be responsible for it. Infection of monocytes and macrophages may also cause respiratory tract spread. Apart from some immunocompromised patients, RSV causes infections only in the respiratory tracts. In two studies, although RSV was demonstrated by polymerase chain reaction (PCR) in serum, no virus was grown; therefore, infected monocytes and macrophages are held responsible for the systemic spread in immunocompromised patients (13, 14).

Early pathologic findings is RSV bronchiolitis include lymphocytic peribronchiolar infiltration with edema, progressing to proliferation and necrosis of bronchiolar epithelium. Mucus and necrotic materials block the small bronchiolar lumens, increase resistance to pulmonary airflow especially during expiration and cause atelectasis. Simultaneously with bronchiolitis, pneumonia characterized by interstitial mononuclear cell infiltration may develop (7).

In RSV pathogenesis, besides direct cytotoxic effect of the virus, the immune response of the host also plays a role. In the infant lung tissues examined after fatal RSV infections, it was found that antigenemia was high; however, lymphocyte and natural killer cells were fewer (15). Similarly, in experimental human studies, it was shown that clinical course was directly proportional to the viral load. Furthermore, when it is compared with influenza, the fact that there is less cytokine response in the RSV makes us think that it is the direct cytokine effect of the virus in the pathogenesis (7).

The importance of the immune response of the host in the pathogenesis was understood with a study in which RSV vaccines inactivated with formalin were administered between 1966 and 1967. RSV infection that required hospitalization was seen in 80% of the children aged between

2 months and 9 years vaccinated following the natural RSV infection. Two children died due to severe RSV infection. The vaccine strain inactivated with formalin induced T cell response, but there was no protective antibody response (6, 16, 17).

Clinical Manifestations

The clinical manifestations vary depending on age, health status, and whether the infection is primary or re-infection. When the RSV frequency in the first weeks after birth is compared with the second month, it is clearly low (in the rate of 1/3) (18). The low level in the RSV frequency in neonetes can be explicated thanks to the fact that neonetes are kept in a protective environment and thus there is less exposure, and the antibodies or some other immunological mechanisms transmitted from the mother (19). The symptoms in the neonates especially in the first three weeks accompanying the mild upper respiratory tract infection might be feeding difficulty and failure to gain weight, which are the non-specific symptoms (20). After the third week, symptoms in the form of lower respiratory tract infections start to emerge. The neonates and especially the preterms are under risk in terms of severe RSV infections and hospitalization rate in this group has increased (19). Although RSV is not an established cause of sudden infant death syndrome, evidence of RSV infection has been found in some infants with this syndrome (21). Lethargy, irritability, and poor feeding, sometimes accompanied by apneic episodes, may be the presenting manifestations in preterm infants.

On the other hand, in infants, unlike the neonates, the symptoms of primer RSV infections are more distinctive. They mostly emerge with bronchiolitis and/or pneumonia. Fever accompanies the symptoms in less than half of the cases. The clinical picture starting as an upper respiratory tract infection may develop into a lower respiratory tract infection within few days. Clinical-radiologic distinction of RSV pneumonia and bronchiolitis is not easy and these two conditions frequently co-exist. Most of the cases have a mild course and can be treated on outpatient basis (6, 7). Children with underlying conditions have a high risk for severe RSV disease. These include children with chronic lung disease or prematurity, and congenital heart disease (22). Table 1 illustrates the risk groups for the RSV infections.

Neurological complications of RSV bronchiolitis include seizures and acute encephalopathy. When compared with non-RSV viral infections, these complications in RSV bronchiolitis are not more frequent. Meningitis, encephalitis, myelitis, myocarditis, arrhythmia and exanthema are among the rare complications (6).

It is commonly accepted that apart from the acute otitis media, the risk of secondary bacterial infection does not increase. The risk of bacteremia or meningitis is low (<1-2%) in children who have RSV bronchiolitis and fever. There is no need for advanced sepsis examination in these cases. Although frequency of urinary tract infection, on the other hand, is less in comparison to the patients without bronchiolitis, it cannot be ignored (1-5%) (6, 23).

Upper respiratory tract symptoms are the most common manifestations of RSV infection in older children and adults. Nasal congestion, cough and mild fever may accompany. While the otitis media that can be seen both in infants and adults may directly be linked to RSV, second-

Table 1. Patients at risk for RSV related lower respiratory tract disease (22)

Risk groups
Infants younger than six months of age, particularly those who are born during the first half of the RSV season, those attending daycare, and those with older siblings (who may have asymptomatic RSV infection).
Infants and children with an underlying chronic lung disease such as bronchopulmonary dysplasia
Infants born before 35 weeks' gestation
Infants and children with congenital heart disease
Infants exposed to secondhand smoke
Patients with Down syndrome
Immunocompromised patients (eg, severe combined immunodeficiency, leukemia, or bone marrow or lung transplant)
Patients of any age group with significant asthma
Adults with cardiopulmonary disease
Residence at altitude >2500 m
Older adult patients with chronic pulmonary disease or functional disability
RSV: Respiratory Syncytial Virus
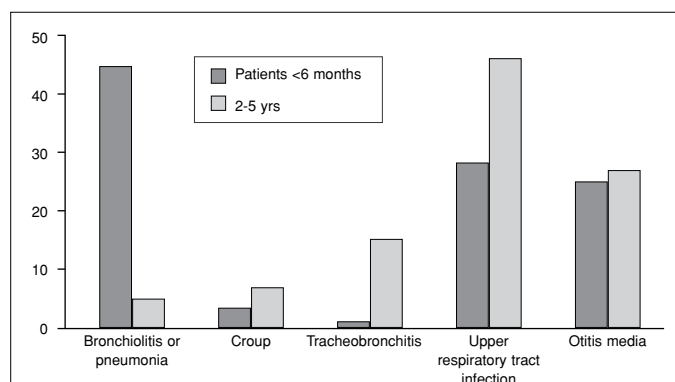
Figure 1. Clinical diagnoses of children with RSV infection according to age (7)

ary bacterial infections may also be the cause. Figure 1 illustrates the clinical diagnoses of children with RSV infection according to age (7).

Respiratory syncytial virus-related lower respiratory tract infections may cause morbidity in the long term. Numerous studies demonstrated that hospitalizations due to viral lower respiratory tract infections were related to increasing asthma and respiratory disorders in the first decade of life. It was concluded in a meta-analysis that the risk of asthma and wheezing in children hospitalized before the age of 3 increased (22%) (24). In the Tucson study, more than 1200 children were examined between 1980 and 1984 and more than 900 of them were followed up until the age of 13 years. This study revealed that RSV-related lower respiratory tract infections increased the risk of wheezing until the age of six, but as the child got older, the risk decreased and it eventually disappeared at the age of 13 (25). In an adult study, on the other hand, it was found that the respiratory function test anomalies in patients (44%) aged 18-20 who were hospitalized due to RSV in the first two years of life were significantly higher in comparison to the control group (11%) (26). However, it is not clear whether RSV is an independent risk factor for asthma and recurrent wheezing. Although it is commonly known that the severity of the symptoms in recurring RSV infections decreased, it was found in a study involving 211 cases that the recurrent infections in adults were 84% symptomatic. Although majority of them were in the form of upper respiratory tract infections, there were also cases with tracheobronchitis and wheezing (27). RSV can cause severe disease in the elderly and in adults with chronic heart or lung disease. In a study done with this patient group, RSV was responsible for the 10% of hospitalizations due to chronic obstructive lung disease and pneumonia, and 5% of hospitalizations due to asthma and hearth failure (28).

Diagnosis

A presumptive diagnosis of RSV lower respiratory tract disease often is made on the basis of the age of the child, the clinical syndrome, especially bronchiolitis, and the usual period of peak RSV seasonal activity. In children younger than 2 years of age with complaints of bronchiolitis in the winter months, especially in the periods when similar cases increase, the RSV infection should be taken into consideration. Mild clinical symptoms with tachypnea, wheezing, common sibilan rhoncus, sometimes crepitations are the typical symptoms for the diagnosis. Hyperinflation can be seen on chest X-ray, if taken. A complete blood count is not specific, but is compatible with viral infection; no significant elevation is expected in the C-reac-

tive protein. Apart from the excess aeration in the chest X-ray, peribronchial thickening, atelectasis and consolidation may be seen (29).

Diagnosis can mostly be made clinically; diagnostic tests are not recommended routinely. However, these tests may be useful in epidemiological studies in the diagnosis of atypical cases. Definitive RSV diagnosis is important with regards to the prevention of unnecessary antibiotic use. A specific diagnosis of RSV infection may be made by viral culture, antigen-antibody detection or PCR. The samples can be taken in the form of nasal wash, nasopharyngeal swab or throat swab. Great performance can be achieved through the nasal wash method. If the patient is intubated or bronchoscopy is to performed, it will be more appropriate to work with the samples from tracheal aspirates or bronchoalveolar lavage (8, 22). While the growth of the virus from the culture was the golden standard diagnosis method for RSV in the past, this particular method today has become more limited. The need for considerable technical expertise and time, and the need for reliably sensitive tissue culture are the disadvantages of viral culture (30). The antigen tests produce faster results in comparison to culture tests and have 90% specificity. Since the antibody tests, on the other hand, can also reveal the antibodies transmitted from the mother, they are not helpful for the diagnosis in young children. Since the diagnosis of RSV through PCR is cheaper and faster in comparison to the culture method and more reliable in comparison to antigen and antibody tests, it is the most frequently used diagnosis method. The use of Multiplex PCR that enables to detect the other viral agents accompanying RSV with a single test becomes more widespread (31).

Treatment

In upper and lower respiratory tract infections, the treatment is usually supportive. If they do not have a respiratory distress or oral intake disorder, most of the patients can be followed up on outpatient basis. In the case

Table 2. Hospitalization indications in RSV infections (32)

Toxic appearance, poor feeding, lethargy, dehydration
Moderate to severe respiratory distress, manifested by one or more of the following signs: nasal flaring; intercostal, subcostal, or suprasternal retractions; respiratory rate >70 breaths per minute; dyspnea; or cyanosis
Apnea
Regardless of hypercarbia, oxygen saturation <92 percent
Social indication (The family is unable to look after the baby)
RSV: Respiratory Syncytial Virus

of the presence of risk factors specified in the clinic section, there is a high possibility of hospitalization. If this high risk groups is followed up on outpatient basis, first couple days of watchful waiting will be required. Table 2 illustrates the hospitalization indications in RSV infections (32).

Supportive treatment is essential in inpatients. Nutritional support as well as hydration should be provided. Nasal congestion should be unblocked by nasal saline. Deep pharyngeal or tracheal aspiration is not recommended. Percussion or vibration has no place in the treatment. If oxygen saturation ≤90%, oxygen should be given. There will be a need for mechanical ventilation in 5% of the inpatients. However, in the group of adult patients with bone marrow suppression, this rate can be as high as 50% (33).

If the patient responds to the beta adrenergic therapy which is frequently used in practice, they may be continued. However, its routine use in not recommended in the RSV treatment (8).

Numerous randomize-controlled studies demonstrated that systemic steroid therapy had no role in the treatment of bronchiolitis (34). Although it was shown in a placebo-controlled study that hospitalization rates of patients admitted to emergency decreased after oral steroid treatment, this finding was not supported by the following studies (35). Children older than two years of age with a previous wheezing or asthma history, on the other hand, may benefit from the systemic steroids (8, 36).

Montelukast which is the antagonist of leukotriene receptor has no role in the treatment.

Apart from otitis media, the coexistence of bacterial infections and RSV is not frequently common. Unnecessary long-term intravenous antibiotic use, on the other hand, may result in secondary bacterial infections. Therefore, antibiotherapy has no place in the treatment of RSV (8).

Ribavirin is a nucleoside analogue with in vitro activity against RSV. Ribavirin generally is not indicated for treatment of RSV bronchiolitis in immunocompetent patients because of high drug cost, cumbersome administration apparatus, and concern regarding toxicity to healthcare providers. It may especially be used in some cases with immunodeficiency (8).

It was shown that the nebulizer hypertonic saline accelerated the improvement of symptoms and decreased the length of hospitalization in children with longer than three days hospitalization. There is no data available for patients hospitalized in the intensive care units. It is stated that high-flow nasal cannula (HFNC) treatment can be used in the infants with respiratory distress, and also nasal continuous positive airway pressure (nCPAP) application can be used as an alternative for the HFNC treatment. Helium therapy can also be used in infants with severe respiratory distress (8).

Protection

Supporting the breast milk, eliminating exposure to tobacco smoke, standard infection control measures, identifying the risk groups, keeping away from crowds, complying with the routine vaccination schedules and recommending the annual influenza vaccines, identifying the new cases at the hospitals and contact isolation are essential protection procedures against RVS. There is no routine vaccine to be used against RSV. Immunoprophylaxis, on the other hand, was started after it was shown that the severity of the disease decreased following the monthly application of intravenous immunoglobulin. Intravenous application was abandoned because of high cost and potential for interference with childhood vaccinations. Intravenous immunoglobulin was replaced by intramuscularly applied 'palivizumab', the RSV-specific humanized mouse monoclonal antibody (6). It was proven that palivizumab was efficient and reliable to use in the preterm with a chronic lung disease and in the congenital heart patients with hemodynamic disorder. In the Cochrane 2013 meta-analysis, three randomized studies where 2831 children were evaluated, it was shown that palivizumab decreased the RSV-related hospitalizations from 101/1000 to 50/1000 (with a relative risk of 0.49), and the intensive care hospitalizations from 34/1000 to 17/1000 (with a relative risk of 0.5) (37). During the RSV season (November-April for the Northern Hemisphere), palivizumab is administered monthly 15 mg/kg intramuscularly as much as 5 doses maximum (one in a month, for 5 months maximum).

The recent studies that revealed that hospitalization rate of the older preterm due to RSV were no different from the babies born in time and since the profits from the short-term hospitalizations due to RSV infections especially in the older preterm failed to meet the high costs, palivizumab prophylaxis has been limited by the American Academy of Pediatrics (AAP). Since the previous studies failed to prove the short and long-term effects of palivizumab sufficiently and the risk group of infants would be neglected when prophylaxis was recommended in the large groups, the AAP introduced the limitation, independent of the idea of costs (38). The decrees of the committee dated 2014 were published in the 30th edition of the Redbook as of February 2015. Even when the preterm between 32 weeks, 0 days of gestation and 34 weeks, 6 days of gestation that met some conditions in 2012 were recommended the prophylaxis, it was limited in the preterm patients without the underlying chronic lung disease or congenital heart disease to 29 weeks, 0 days of gestation. The limit of prophylaxis for the patients with chronic lung disease was 32 weeks, 0 days of gestation. The decision for prophylaxis in cyanotic congenital

heart disease infant patients recommended to take prophylaxis was taken together with pediatric cardiologists. If the prophylaxis was continued in the second year, it was limited to the preterm that were born only before 32 weeks, 0 days of gestation, took at least 28 days of oxygen treatment and were given steroids, bronchodilators, and oxygen at the onset of the second RSV season. Furthermore, different from 2012, it was decided that the infants who were required to be hospitalized while they took RSV prophylaxis due to RSV hospitalization would be discontinued the prophylaxis (8). The Turkish Neonatal Society (TNS) published their recommendations for palivizumab prophylaxis in 2007 and updated in 2012. New limitations were introduced for the last time in 2014. The TNS recommendations have great similarities with the last AAP recommendations. The 2014 palivizumab prophylaxis recommendations of TNS are given below and summarized in Table 3 (39).

Who are recommended to be administered palivizumab prophylaxis:

1. Preterm babies:

Prophylaxis is given to preterm babies who are under the gestational age of 29 weeks, 0 days or who have the birth weight under 1000 g without considering the gestational age and to those preterm infants who are younger than 12 months (chronologically) at the onset of the RSV season.

2. The preterm babies with a chronic lung disease:

Prophylaxis is given to preterm babies who are under the gestational age of 32 weeks, 0 days or who took oxygen treatment at least for 28 days of have the birth weight under 1000 g without considering the gestational age and to those preterm infants who are younger than 12 months (chronologically) at the onset of the RSV season.

Prophylaxis is given to preterm babies in the second year of their lives that were given steroids, bronchodilators, and oxygen 6 months before the onset of the RSV season.

3. The infants with congenital heart disease that causes haemodynamic impairment:

Palivizumab prophylaxis is given to the infants under one year of age who received medical treatment for congestive heart failure and who had cyanotic congenital heart disease that needed surgery as well as moderate or severe pulmonary hypertension at the end of the RSV season.

In cases that were operated for cardiopulmonary bypass in the presence of palivizumab prophylaxis indication, it is recommended to give an additional postoperative dose (15 mg/kg).

Table 3. TNS recommendations for palivizumab prophlaxis, 2014 (39)

Status	Chronologic age on the onset of RSV season	
	<12 months	12-24 months
Preterm <29 weeks' gestation	Apply prophylaxis	No
Birth weight <1000 g	Apply prophylaxis	No
CLD**	Apply prophylaxis	No
CLD treatment in the last 6 months***	Apply prophylaxis	Apply prophylaxis
CHD with hemodynamic instability*	Apply prophylaxis	No

*CHD (Congenital Heart Disease) with hemodynamic instability, pulmonary hypertension, cardiomyopathy.

**CLD (Chronic Lung Disease) <32 weeks' gestation, longer than 28 days O2 requirement

***Infants with chronic lung disease who receive steroids, oxygen, bronchodilators and diuretic therapy for the last 6 months should be given prophylaxis in the second season as well.

Candidates who have had RSV infection, the continued doses are not administered in the season.

The infant identified as prophylaxis candidate completes the 5 doses even if it exceeds the age criteria within the season.

It is optional to administer prophylaxis to the neonates in the risk group hospitalized in the neonatal intensive care unit during an epidemic.

TNS: Turkish Neonatal Society; RSV: Respiratory Syncytial Virus

The decision of prophylaxis to be given to the babies with congenital heart disease should be taken in consultation with pediatric cardiologists.

Those who are not recommended the palivizumab prophylaxis as they are not in the high risk group regarding RSV infection are:

1. Cardiac patients with no hemodynamic impairment (eg, secundum ASD, small VSD, pulmonic stenosis, uncomplicated aortic stenosis, mild coarctation of aorta and PDA) are not given prophylaxis.
2. If congestive heart failure treatment is not needed in the surgically corrected cases, they are not given prophylaxis.
3. The mild cardiomyopathy cases not requiring medical treatment are not given prophylaxis.
4. The babies with congenital heart disease who are given prophylaxis within one year of age.
5. Since the babies who need to be hospitalized due to RSV while they are still receiving RSV prophylaxis have a low possibility (<0.5%) of hospitalization due to more than one RSV infection within the same season, prophylaxis is discontinued.

It was stated that in addition to the babies with congenital respiratory tract abnormalities or neuromuscular disease, the babies with severe combined immunodeficiency or advanced stage AIDS diagnosis could benefit

from immunoprophylaxis. There is contraversial recommedations for cystic fibrosis. Although AAP does not recommend prophylaxis for the Down syndrome without any extra disease, these patients take increasing amounts of prophylaxis and benefit from it (8, 40).

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