TÜRK PEDİATRİ ARŞİVİ
TURKISH ARCHIVES of PEDİATRİCS

Review

Respiratory syncytial virüs infections in neonates and infants

Yıldız Perk, Mine Özdil

Department of Pediatrics, Division of Neonatology, İstanbul University Cerrahpaşa School of Medicine, İstanbul, Turkey

Cite this article as: Perk Y, Özdil M. Respiratory syncytial virüs infections in neonates and infants. Turk Pediatri Ars 2018; 53: 63-70.

Abstract

Respiratory syncytial virus is one of the major causes of respiratory tract infections during infancy with high rates of hospitalization and mortality during the first years of life. It is the most common cause of acute bronchiolitis and viral pneumonia in children below two years of age and second the most common cause of postneonatal infant mortality all around the world following malaria. In addition, the virus has been causally linked to recurrent wheezing and associated with pediatric asthma. The respiratory syncytial virus infections tend to be severe in high risk patients such as patients below six months of age, with prematurity, congenital heart diseases, neuromuscular diseases and immune deficiencies. No specific treatment is available for respiratory syncytial virus infections to date. Severe cases require supportive therapy, mainly oxygen supplementation and hydration, and less frequently, ventilatory support. Because there is no vaccine to prevent respiratory syncytial virus infections or clinically effective treatment to administer to children with respiratory syncytial virus infection, immunoprophylaxis with palivizumab is currently the only method for reducing morbidity associated with severe respiratory syncytial virus in high-risk infants.

Keywords: Bronchiolitis, infant, newborn, palivizumab, respiratory syncytial virus

Introduction

Respiratory syncytial virus (RSV) is the most common respiratory agent in infants and young children worldwide. Respiratory syncytial virus is the most common agent that leads to acute bronchiolitis and viral pneumoniae, and the second most common cause of infant deaths after malaria after the neonatal period (1). The clinical findings may manifest in a wide spectrum ranging from mild upper respiratory tract infection or middle ear inflammation to life-threatening lower respiratory tract infections. Among the lower respiratory tract infections, it most commonly leads to bronchiolitis and subsequently, pneumonia and croup may also be observed (2). Specific anti-RSV antibodies are positive in the majority (87%) of infants aged 18 months and in all children aged three years (3). It leads to epidemics in late autumn, winter, and early spring in areas with temperate climate (between November and April with a peak in January-February), and throughout the year in areas with tropical climates.

Respiratory syncytial virus leads to approximately 3,400,000 hospital admissions and at least 66,000 deaths each year and 99% of these deaths occur in developing countries (4). Currently, there is no effective and safe medication or vaccine for RSV infections, and infection with this virus continues to be a clinical problem worldwide. Prophylaxis with palivizumab, which is an RSV-neutralizing monoclonal antibody and administered in high-risk groups in epidemic seasons, is the only preventive method.

Virus and pathogenesis

Respiratory syncytial virus, which was isolated from a chimpanzee in 1956 for the first time was initially named as chimpanzee coryza agent. Subsequently, it

Address for Correspondence: Mine Özdil E-mail: mineozdil81@hotmail.com
Received: 09.10.2017 **Accepted:** 23.10.2017

DOI: 10.5152/TurkPediatriArs.2018.6939

was isolated from infants who had lower respiratory tract infection and labeled as a human pathogen (5).

Respiratory syncytial virus is an enveloped, single-stranded, nonsegmented, negative-strand RNA virus, which is a member of the family Pneumoviridae (previously classified as Paramyxoviridae), included in the order Mononegalevirales (6). The viral genome, which is constituted by ten genes and has a length of 15.2 kb, encodes 11 proteins: F and G envelope surface glycoproteins, M1, M2-1 and M2-2 matrix proteins, NS1 and NS2 virion proteins, SH protein and N, D, L nucleotide capsule proteins. G (binding) protein is important for binding to the host cell and F (fusion) protein is responsible for fusion of the viral envelope with the cellular plasma membrane. At the same time, F protein promotes fusion of infected cell membranes with those of adjacent cells, leading to the characteristic syncytia formation, which the virus is named after (7). Fusion and G proteins are the main targets of the anti-RSV monoclonal antibody response.

There are two main antigenic groups according to the changes in surface glycoproteins: A and B. Although there are geographic differences, both subgroups are generally in association in RSV epidemic season. Subgroup A infections are more common and have high rates of spread (8).

Infection is transmitted by way of direct or indirect contact with nasal and oral secretion (dirty hands/surface). It is known that the virus can survive for six hours on counters, for 45 minutes on paper, and for 25 minutes on dirty skin surfaces such as hands (9). Infection is limited to the respiratory mucosa, invasion to the other organs generally does not occur except for in immunocompromised patients and infection does not manifest in the blood. Recurrent infection is frequent and it can occur at any age, generally with a lower degree of severity; previous infection does not provide immunity. The virus infects ciliated cells of the upper respiratory tract, and the epithelium of the small bronchioles and type 1 pneumocytes. Nasal discharge and obstruction, fever, and cough develop in the nasopharyngeal epithelium following 4-6-day viral growth (10). Viral spread mostly lasts for 3-8 days, but may last for weeks in immunocompromised patients. It leads to lower respiratory tract infection (LRTI) in 25-40% of patients.

Bronchial narrowing, excessive aeration, and disruption in gas exchange occur as a result of infiltration of the airway by inflammatory cells, necrosis in the respiratory tract epithelium, shedding of necrotic cells, excessive mucus production, decreased ciliary function, and airway edema (11). Both humoral and cellular immunity are involved in the clearing of infection. A strong interleukin-8 (IL-8)-mediated neutrophil response is the first response against RSV infection in the body, which is related with the disease severity. Dendritic cells as antigen-presenting cells reach the lung and viral cleaning occurs by way of a pulmonary CD8 T cell response following systemic T cell lymphopenia. B cell-activating factors in the airway epithelium are important in the production of protective antibodies; interferon gamma (IFN-γ) has a protective role (12).

The cord RSV IgG antibody level is related with disease severity in the first six months. The levels of the IgG type antibodies transferred to the fetus during pregnancy, and especially in the second half of pregnancy, decrease in time in the postnatal period and reach the lowest levels at the age of 2-3 months.

Epidemiology

Respiratory syncytial virus infection occurs most commonly in children aged below 24 months. Its prevalence is 5.2/1000 (26/1000 at the age below 1 month). The first six months is the critical period and the most severe disease is observed during these months. Hospitalization occurs with a 3-fold higher frequency in preterm babies (13). More than 20% of hospitalizations due to RSV occur in the first 2 months, more than 50% occur in the first three months, and more than 70% occur in the first six months (14).

In the study conducted by Hacımustafaoğlu et al. (15) in Turkey, the prevalence of RSV was found as 37.9% in 671 patients aged below 24 months who were hospitalized because of LRTI; babies aged between 0 and three months constituted 38.3% of these patients. In addition, RSV was found to be positive in 41% of the cases of acute bronchiolitis and in 34% of the cases of pneumonia. In a multi-center study conducted by the Turkish Neonatal Society (TNS), RSV was found with a rate of 16.9% in 3464 patients aged below 24 months who had LRTI and were not receiving prophylaxis, and it was observed that RSV peaked in babies aged between 0 and 3 months and between the months of January and March (16). Again, the prevalence of RSV was found as 19.6% in newborns who were hospitalized because of acute LRTI in a study conducted by the TNS TÜRKNİCU-RSV Study Group in 2016 in 44 neonatal

intensive care units; term babies constituted 68.4% of these patients and the RSV-related mortality rate was 1.2% (17).

In China, it was found that RSV constituted 18.7% of LRTI, and RSV infections occurred most commonly in infants (26.5%) and least commonly in children aged 16 years and below (2.8%) (18). In England, respiratory tract infections related with RSV led to 450,158 primary care referrals, 29,160 hospitalizations, and 83 deaths per infection season (most commonly in the first six months) in children and adolescents (19). In the same study, it was found that RSV had a greater share compared with influenza in physician referrals, hospitalizations, and deaths due to respiratory tract diseases in children aged under five years.

It is known that RSV infections lead to 48,000-74,500 deaths yearly in children aged below five years and 99% of the deaths related with RSV occur in developing countries (20). The mortality rate is 2-3% in the neonatal period, 6-7% between the ages of one month and one year, and 1.6% between the ages of one and four years. In developing countries, patients die at younger ages. In developed countries, the mortality rate is lower, severe infections occur in high-risk patients, and a higher number of intensive care unit hospitalizations with longer length of stay occur because of better opportunities (21).

Clinical findings

The majority of infections in early childhood are limited to the upper respiratory tract; they lead to findings of coryza, cough, and hoarse voice. On physical examination, rhinitis and pharyngitis are seen and prominent vessels in the conjunctivae and tympanic membranes accompany frequently. Fever, malaise, and malnutrition are observed together with upper respiratory tract infection. Infection progresses to the lower respiratory tract in one third of patients and findings of respiratory distress including tachypnea, wheezing, nasal flaring, and jugular/intercostal retractions develop. On auscultation of the lungs, prolonged expirium, rales, inspiratory rhonchi, decreased lung sounds, and excessive aeration in the lung periphery may be found (22). Most patients recover in 1-2 weeks. Approximately 20% of infants may present with apnea as the first manifestation of infection (23). The period between six weeks and six months is the most critical period.

Pulmonary dysfunction related with RSV may last for 10 years or longer. Chronic wheezing, asthma, and decreased respiratory functions have been found in babies and in school children with a history of hospitalization because of RSV (24).

Risk factors

Respiratory syncytial virus infections have a severe course in high-risk populations. These include individuals with chronic lung disease, cystic fibrosis, congenital heart disease, nerve and muscle system diseases, primary and secondary immune deficiencies, bronchopulmonary dysplasia, preterms and infants aged below six months in the beginning of RSV season. These patient groups are candidates for immunoprophylaxis with monoclonal antibodies. However, an important part of hospitalized patients does not meet immunoprophylaxis criteria and most patients are previously healthy children who do not carry any risk factor except for young age, which is the strongest risk factor known (25, 26). Therefore, it is thought that genetic predisposition of the host, coinfection with other pathogens, viral phenotype, and viral load affect disease severity (26, 27).

Maternal smoking is an independent risk factor for infection. Low cord blood vitamin D level was found to be associated with a 6-fold increased risk for LRTI caused by RSV in the first year (28). It is believed that breastmilk is the only significant protective factor against respiratory viruses in developing countries. Exclusive breastfeeding reduces the number of hospitalizations related with RSV, the risk of respiratory failure, and the need for oxygen treatment in infants. It is thought that this reduction is related with high levels of interferon (IFN)-gamma, chemotactic cytokines, lactoferrin, and T cells in breastmilk and breastmilk microbiome (29).

Laboratory findings and diagnosis

Laboratory tests show nonspecific results in the diagnosis of RSV infection. Complete blood count is not specific. A mild increase in C-reactive protein (CRP) may be found. Lung imaging may reveal increased aeration, flattening of the diaphragm, infiltrations, patch-type atelectasis, and increased peribronchial shadows. The National Institute for Health and Care Excellence (NICE) recommends that the diagnosis of RSV should be made with a detailed history and physical examination, and laboratory and radiologic tests should be performed in severe cases of bronchiolitis requiring intensive care follow-up or in cases of atypical bronchiolitis (30). Radiologic imaging gains special importance in the differentiation of the other problems included in the differential diagnosis.

Viral bronchiolitis is a mild and self-limiting disease in most infants and tests for RSV and other viruses are generally not needed. Rapid diagnosis of the virus should be made for a definite diagnosis, especially in hospitalized patients, for the discontinuation of empiric antibiotics and for the prevention of nosocomial contamination, isolation, and infection control (31).

Sampling of respiratory tract secretions is made by nasal lavage, nasopharyngeal swab, and aspiration, and examination of throat swab samples. Nasal lavage and nasopharyngeal aspirate samples are more sensitive in detecting viruses compared with the other methods. Bronchoalveolar lavage and tracheal aspirate sampling may be needed in intubated patients because of severe LRTI. For the best results, samples should be obtained 3-4 days after symptom onset, carried with wet ice in the laboratory setting, and kept at 2-8°C in a refregirator, if they are to be studies within 48 hours. If the test will be delayed, they should be kept at –80°C (32).

Viral cell culture was defined as the gold standard in the diagnosis of RSV in the past, but currently, it is not being used frequently because it yields result in 3-7 days. Rapid cell culture (shell-vial) enables the diagnosis in a shorter time (48 hours) compared with classic cell culture. Serologic examination is not helpful in the diagnosis because seroconversion occurs in two weeks, virus-specific antibodies cannot be detected in many infants with RSV infections, and antibodies transmitted from the mother are also present. The direct fluorescence antibody test is a rapid test that yields results in 2-3 hours with a sensitivity and specificity of about 95%, but it requires experience. Rapid antigen tests are used very frequently because they yield results in a very short time (30 minutes). They have a sensitivity of about 80% in children and a specificity of 97%. In patients in whom false-negative results are obtained, retest with more sensitive methods may be needed (33). Reverse transcriptase polymerase chain reaction (RT-PCR) may yield results in hours and is the most commonly preferred method because it has considerably higher sensitivity compared with culture and rapid antigen tests; however, its high cost, and need for experience and equipment limits its use (34).

Treatment

The most important parts of treatment in RSV infections includes close monitoring of the clinical picture, intravenous fluid, and oxygen treatment. Hastiness in treatment of symptoms causes unnecessary use of antibiotics, steroid or inhaled bronchodilator treatment in the majority of patients. According to the guidelines published by the American Academy of Pediatrics (APA) in 2014 and the NICE guidelines, treatment other than nutritional and oxygen support are not effective in the treatment of bronchiolitis (30, 35).

Routine use of bronchodilators (beta 2-agonists and anticholinergics) is not recommended in children with bronchiolitis. Bronchodilators may be tried if a strong personal or familial history of atopy is present; wheezing is the most prominent symptom and wheezing or asthma triggered by virus is considered in the differential diagnosis. They should be discontinued if a marked response is not obtained. Routine use of nebulized adrenaline, systemic or inhaled corticosteroids, leukotriene receptor antagonists and Heliox is not recommended (30, 35). It was found that use of leukotriene receptor antagonists (montelukast) was successful in persistent wheezing following RSV bronchiolitis (36). It was shown that treatment with nebulized hypertonic saline with mucolytic action was effective in the treatment of infants who were hospitalized for longer than 72 hours (37). Hypertonic saline treatment has also been recommended by the AAP as a treatment method to be attempted for patients whose hospitalization period is prolonged rather than as routine treatment (35). Antibiotics should be used in patients with signs of secondary bacterial infection (35). It is recommended that patients with marked respiratory distress, oxygen saturation below 92% at room temperature, severe nutritional deficiency, clinical dehydration, and apnea should be hospitalized (30).

Ribavirin is a synthetic nucleoside analogue that has in vitro action against many DNA and RNA viruses, thereby reducing viral growth. Although it was approved as the only licensed drug in 1993 against severe RSV infections, the AAP does not recommend its routine use because of reasons including necessity of long-term aerosol application and hospitalization, intoxication potential (bone marrow inhibition, carcinogenicity), teratogenic action in pregnancy and high cost (30). It can be used in immunocompromised patients. Adult clinical studies for GS-5806 (Presatovir) and AL-008176, which are the other two RSV inhibitors, are continuing (38).

Respiratory syncytial virus-immunoglobulin (RSV-IVIG) is a hyperimmune polyclonal immunoglobulin obtained from donors with high RSV neutralizing antibodies. These neutralizing antibodies inhibit

the integration of F and G RSV surface glycoproteins with host cells (39). Its efficiency in neutralizing RSV is 5-fold higher compared with standard IVIG treatment. It was observed that RSV-IVIG, which was approved by the Food and Drug Administration (FDA) in 1996 for the first time, reduced hospitalizations in high-risk infants (40). However, its use was abandoned because of factors including necessity for hospitalization and long-term infusion, fluid loading because of high-volume doses, sudden cyanotic adverse effects, risk of blood-borne pathogen, and necessity to avoid live-attenuated vaccines for at least nine months after its use (38).

Prevention and immunoprophylaxis

Standard prevention methods include abiding by hand hygiene and hand washing, supporting breastfeeding, specification of risk groups, and appropriate contact isolation by detecting hospital cases.

The attainment of a better understanding of the structure of RSV and negative effects of RSV-IVIG treatment in 1990s accelerated studies on the development of recombinant monoclonal antibodies against RSV antigens. Palivizumab is a humanized IgG1 monoclonal antibody, which is produced by way of recombinant DNA technology directed to an epitope in the A antigenic part of RSV F protein. It reduces RSV replication by inhibiting adherence of the virus onto respiratory epithelial cells (39). It is the only immunoprophylaxis treatment approved for the prevention of severe LRTIs caused by RSV in high-risk patients. It is administered monthly intramuscularly at a dose of 15 mg/kg in five doses. It is known that this dose maintains the serum concentration above 40 μg/mL (the dose that provided a 99% reduction in pulmonary RSV in mouse experiments) in preterm babies and in babies with bronchopulmonary dysplasia (41).

Palivizumab reduces the frequency of severe RSV-related LRTIs in preterm babies and in children with chronic lung disease or congenital heart disease (42). Again, the MAKI study conducted in Holland showed that use of palivizumab provided a 47% reduction in recurrent wheezing reported by families in moderately preterm babies (24). In the meta-analysis of three randomized, controlled studies encompassing 2831 patients, which compared palivizumab and placebo, it was found that palivizumab provided a statistically significant reduction in RSV hospitalizations and a statistically nonsignificant reduction in mortality rates (43).

According to the guideline of palivizumab prophylaxis in RSV infections updated in 2014 by the AAP, prophylaxis was limited with 29 0/7 gestational age in preterm babies who had no underlying chronic lung disease or congenital heart disease and 32 0/7 weeks of gestation was considered the limit for prophylaxis in babies with chronic lung disease. It was decided to give prophylaxis also in the second year to preterm babies with chronic lung disease who received oxygen treatment for at least 28 days and steroids, bronchodilator or oxygen from the beginning of the second RSV season until 6 months prior. It was concluded that patients aged below 12 months with hemodynamically significant congenital heart disease should receive palivizumab prophylaxis, but prophylaxis should not be continued in the second year in these patients. It was reported that patients who received treatment for congestive heart disease and who had acyanotic heart disease requiring cardiac surgery and pulmonary hypertension would benefit markedly from prophylaxis. Unlike the previous 2012 guidelines, it was reported that prophylaxis should be discontinued in babies who needed to be hospitalized because of RSV while receiving RSV prophylaxis (44).

The Turkish Neonatal Association also updated their recommendations for palivizumab prophylaxis with the guidelines published in 2014. These recommendations are similar to the recommendations of the AAP and are shown in Table 1 (45).

Table 1. The Turkish Neonatal Association recommendations for palivizumab prophylaxis (45)

	Chronologic age at the beginning of the RSV season	
Status months	<12 months	12-24
Preterm <29 weeks	Administer prophylaxis	No
Birth weight <1000 g	Administer prophylaxis	No
CLD**	Administer prophylaxis	No
CLD treatment in the last 6 months***	Administer prophylaxis	Administer prophylaxis
CHD with hemodynamic impairment*	Administer prophylaxis	No

*Congenital heart disease (CHD), pulmonary hypertension, cardiomyopathy creating hemodynamic problem-requiring treatment

**CLD: chronic lung disease <32 weeks >28days 21% O2 requirement

***Baby with CLD who had received steroid, oxygen, bronchodilator, diuretic treatment in the last 6 months should receive prophylaxis in the second season

****Maintenance doses are not administered during the season in candidates with RSV infection

*****Five doses are completed in babies specified as candidates for prophylaxis even if age criteria are exceeded during the season

******Prophylaxis is optional in newborns in the risk group hospitalized in neonatal intensive care unit during outbreak

The patients for which palivizumab prophylaxis is not recommended by the Turkish Neonatal Association because of absence of high risk in terms of RSV infection are as follows:

1) Patients with hemodynamically insignificant heart disease (Secundum ASD, small VSD, pulmonary stenosis, uncomplicated aortic stenosis, mild coarctation of the aorta and patent ductus arteriosus).
2) Cases corrected surgically, if treatment for congestive heart disease is not needed.
3) Patients with mild cardiomyopathy not necessitating medical treatment.
4) After turning one year of age in babies with congenital heart disease who received prophylaxis in the first year of life.
5) In babies who need hospitalization because of RSV while receiving RSV prophylaxis, prophylaxis is discontinued because the probability of hospitalization due to multiple RSV infections in the same season is very low (<0.5%) (45).

Motavizumab (Medi-524) was produced as another monoclonal antibody and is specific for part A of the RSV F protein like palivizumab. Its neutralizing action has been investigated in in vitro and animal models and it was observed that motavizumab had a 70-fold higher affinity for F protein compared with palivizumab and provided 20-fold greater viral neutralization. An application for an FDA license for motavizumab was made in 2008 and the application was rejected in 2010 because it was found to be similar to palivizumab in terms of safety, efficacy, and tolerability (46, 47).

Vaccination

Currently, an effective vaccine against RSV infection is not yet available. The development of a vaccine that could protect infants in particular from RSV infections is an important public health priority. Vaccination is the most effective and economic way to provide protective immunity against RSV. The first formalin-inactivated candidate RSV vaccine in the 1960s did not provide protective immunity. On the contrary, it exacerbated natural RSV infection and led to an excessive Th2 response and symptoms (48). Subsequently, vaccination studies were interrupted and then accelerated again in recent years.

Currently, more than 50 vaccine development programs (live-attenuated, whole-inactive, particle containing, subunit, nucleic acid, gene-based vectors, and combined with immunoprophylaxis) are continuing in different stages. The target population of vaccines includes babies aged below 6 months, infants aged between 6 months and 2 years, pregnant women, and the elderly (49). Vaccination in the late stages of pregnancy and protection of infants with transplacental antibodies is also very important because the median age for hospitalization due to RSV bronchiolitis is three months and the peak age is one month (50).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - Y.P., M.Ö.; Design - Y.P., M.Ö.; Supervision - Y.P., M.Ö.; Funding - Y.P., M.Ö.; Materials - Y.P., M.Ö.; Data Collection and/or Processing - Y.P., M.Ö.; Analysis and/or Interpretation - Y.P., M.Ö.; Literature Review - Y.P., M.Ö.; Writing - Y.P., M.Ö.; Critical Review - Y.P., M.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012; 380: 2095-128. [CrossRef]
2. Borchers AT, Chang C, Gershwin ME, Gershwin LJ. Respiratory syncytial virus-a comprehensive review. Clin Rev Allergy Immunol 2013; 45: 331-79. [CrossRef]
3. Nair H, Nokes DJ, Gessner BD, et al. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. Lancet 2010; 375: 1545-55. [CrossRef]
4. Hall CB, Weinberg GA, Iwane MK, et al. The burden of respiratory syncytial virus infection in young children. N Engl J Med 2009; 360: 588-98. [CrossRef]
5. Chanock R, Roızman B, Myers R. Recovery from infants with respiratory illness of a virus related to chimpanzee coryza agent (CCA). I. Isolation, properties and characterization. Am J Hyg 1957; 66: 281-90.
6. Afonso CL, Amarasinghe GK, Bányai K, et al. Taxonomy of the order Mononegavirales: update 2016. Arch Virol 2016; 161: 2351-60. [CrossRef]
7. Johansson C. Respiratory syncytial virus infection: an innate perspective. F1000Res 2016; 5: 2898. [CrossRef]
8. White LJ, Waris M, Cane PA, Nokes DJ, Medley GF. The transmission dynamics of groups A and B human respiratory syncytial virus (hRSV) in England & Wales and Finland: seasonality and cross-protection. Epidemiol Infect 2005; 133: 279-89. [CrossRef]

9. Hall CB, Douglas RG Jr, Geiman JM. Possible transmission by fomites of respiratory syncytial virus. J Infect Dis 1980; 141: 98-102. [CrossRef]
10. Rezaee F, Linfield DT, Harford TJ, Piedimonte G. Ongoing developments in RSV prophylaxis: a clinician's analysis. Curr Opin Virol 2017; 24: 70-8. [CrossRef]
11. Lambert L, Sagfors AM, Openshaw PJ, Culley FJ. Immunity to RSV in Early-Life. Front Immunol 2014; 5: 466. [CrossRef]
12. Russell CD, Unger SA, Walton M, Schwarze J. The Human Immune Response to Respiratory Syncytial Virus Infection. Clin Microbiol Rev 2017; 30: 481-502. [CrossRef]
13. Hall CB, Weinberg GA, Blumkin AK, et al.Respiratory syncytial virus-associated hospitalizations among children less than 24 months of age. Pediatrics 2013; 132: 341-8. [CrossRef]
14. Parikh RC, McLaurin KK, Margulis AV, et al. Chronologic Age at hospitalization for respiratory syncytial virus among preterm and term ınfants in the United States. Infect Dis Ther 2017; 6: 477-86. [CrossRef]
15. Hacımustafaoğlu M, Celebi S, Bozdemir SE, et al. RSV frequency in children below 2 years hospitalized for lower respiratory tract infections. Turk J Pediatr 2013; 55: 130-9.
16. Turkish Neonatal Society. The seasonal variations of respiratory syncytial virus infections in Turkey: a 2-year epidemiological study. Turk J Pediatr 2012; 54: 216-22.
17. Alan S, Erdeve O, Cakir U, et al. Outcome of the respiratory syncytial virus related acute lower respiratory tract infection among hospitalized newborns: a prospective multicenter study. J Matern Fetal Neonatal Med 2016; 29: 2186-93. [CrossRef]
18. Zhang Y, Yuan L, Zhang Y, Zhang X, Zheng M, Kyaw MH. Burden of respiratory syncytial virus infections in China: Systematic review and meta-analysis. J Glob Health 2015; 5: 020417. [CrossRef]
19. Taylor S, Taylor RJ, Lustig RL, et al. Modelling estimates of the burden of respiratory syncytial virus infection in children in the UK. BMJ Open 2016; 6: e009337. [CrossRef]
20. Shi T, McAllister DA, O'Brien KL, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. Lancet 2017; 390: 946-58. [CrossRef]
21. Scheltema NM, Gentile A, Lucion F,et al. Global respiratory syncytial virus-associated mortality in young children (RSV GOLD): a retrospective case series. Lancet Glob Health 2017; 5: 984-91. [CrossRef]
22. Tregoning JS, Schwarze J. Respiratory viral infections in infants: causes, clinical symptoms, virology, and immunology. Clin Microbiol Rev 2010; 23: 74-98. [CrossRef]
23. Sabogal C, Auais A, Napchan G, et al. Effect of respiratory syncytial virus on apnea in weanling rats. Pediatr Res 2005; 57: 819-25. [CrossRef]
24. Blanken MO, Rovers MM, Bont L; Dutch RSV Neonatal Network. Respiratory syncytial virus and recurrent wheeze. N Engl J Med 2013; 369: 782-3. [CrossRef]
25. Vandini S, Biagi C, Lanari M. Respiratory Syncytial Virus: The Influence of Serotype and Genotype Variability on Clinical Course of Infection. Int J Mol Sci 2017; 18: 1717. [CrossRef]
26. Murray J, Bottle A, Sharland M, et al. Medicines for Neonates Investigator Group. Risk factors for hospital admission with RSV bronchiolitis in England: a population-based birth cohort study. PLoS One 2014; 9: e89186. [CrossRef]
27. Hervás D, Reina J, Ya-ez A, del Valle JM, Figuerola J, Hervás JA. Epidemiology of hospitalization for acute bronchiolitis in children: differences between RSV and non-RSV bronchiolitis. Eur J Clin Microbiol Infect Dis 2012; 31: 1975-81. [CrossRef]
28. Belderbos ME, Houben ML, Wilbrink B, et al. Cord blood vitamin D deficiency is associated with respiratory syncytial virus bronchiolitis. Pediatrics 2011; 127: 1513-20. [CrossRef]
29. Dixon DL. The role of human milk immunomodulators in protecting against viral bronchiolitis and development of chronic wheezing illness. Children (Basel) 2015; 2: 289-304. [CrossRef]
30. National Institute for Health and Care Excellence (NICE) (2015) Bronchiolitis: diagnosis and management of bronchiolitis in children. Clinical Guideline 9, London: NICE.
31. Drysdale SB, Green CA, Sande CJ. Best practice in the prevention Best practice in the prevention and management of paediatric respiratory syncytial virus infection. Ther Adv Infect Dis 2016; 3: 63-71. [CrossRef]
32. Ginocchio CC, McAdam AJ. Current Best Practices for Respiratory Virus Testing J Clin Microbiol 2011; 49: 44-8. [CrossRef]
33. Chartrand C, Tremblay N, Renaud C, Papenburg J. Diagnostic accuracy of rapid antigen detection tests for respiratory syncytial virus infection: systematic review and meta-analysis. J Clin Microbiol 2015; 53: 3738-49. [CrossRef]
34. Somerville LK, Ratnamohan VM, Dwyer DE, Kok J. Molecular diagnosis of respiratory viruses. Pathology 2015; 47: 243-9. [CrossRef]
35. Ralston SL, Lieberthal AS, Meissner HC, et al. Clinical Practice Guideline: The Diagnosis, Management, and prevention of bronchiolitis. Pediatrics 2014; 134: 1474-502. [CrossRef]
36. Bisgaard H, Flores-Nunez A, Goh A, et al. Study of montelukast for the treatment of respiratory symptoms of post-respiratory syncytial virus bronchiolitis in children. Am J Respir Crit Care Med 2008; 178: 854-60. [CrossRef]
37. Zhang L, Mendoza-Sassi RA, Klassen TP, Wainwright C. Nebulized Hypertonic Saline for Acute Bronchiolitis: A Systematic Review. Pediatrics 2015; 136: 687-701. [CrossRef]

38. Ruckwardt TJ, Morabito KM, Graham BS. Determinants of early life immune responses to RSV infection. Curr Opin Virol 2016; 16: 151-7. [CrossRef]
39. Huang K, Wu H. Prevention of respiratory syncytial virus infection: from vaccine to antibody. Microbiol Spectrum 2014; 2: AID-0014. [CrossRef]
40. The PREVENT Study Group. Reduction of respiratory syncytial virus hospitalization among premature infants and infants with bronchopulmonary dysplasia using respiratory syncytial virus immune globulin prophylaxis. Pediatrics 1997; 99: 93-9. [CrossRef]
41. Johnson S, Oliver C, Prince GA, et al. Development of a humanized monoclonal antibody (MEDI-493) with potent in vitro and in vivo activity against respiratory syncytial virus. J Infect Dis 1997; 176: 1215-24. [CrossRef]
42. The IMpact-RSV Study Group. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. Pediatrics 1998; 102: 531-7. [CrossRef]
43. Andabaka T, Nickerson JW, Rojas-Reyes MX, et al. Monoclonal antibody for reducing the risk of respiratory syncytial virus infection in children. Cochrane Database Syst Rev 2013: CD006602. [CrossRef]
44. American Academy of Pediatrics, Committee On Infectıous Dıseases And Bronchıolıtıs Guıdelınes Commıttee. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. Pediatrics 2014; 134: 415-20. [CrossRef]
45. Türk Neonatoloji Derneği Palivizumab ile RSV Proflaksisi Çalışma Grubu. Türk Neonatoloji Derneği Palivizumab Proflaksisi Önerileri. 2014.
46. Mejias A, Chávez-Bueno S, Ríos AM, et al. Comparative effects of two neutralizing anti-respiratory syncytial virus (RSV) monoclonal antibodies in the RSV murine model: time versus potency. Antimicrob Agents Chemother 2005; 49: 4700-7. [CrossRef]
47. Carbonell-Estrany X, Simões EAF, Dagan R, et al. Motavizumab Study Group. Motavizumab versus palivizumab for the prophylaxis of serious respiratory syncytial virus disease in high-risk children: A randomized controlled noninferiority trial. Pediatrics 2010; 125: 35-51. [CrossRef]
48. Kapikian AZ, Mitchell RH, Chanock RM, Shvedoff RA, Stewart CE. An epidemiologic study of altered clinical reactivity to respiratory syncytial (RS) virus infection in children previously vaccinated with an inactivated RS virus vaccine. Am J Epidemiol 1969; 89: 405-21. [CrossRef]
49. Neuzil KM. Progress toward a Respiratory Syncytial Virus Vaccine. Clin Vaccine Immunol 2016; 23: 186-8. [CrossRef]
50. Jorquera PA, Anderson L, Tripp RA. Understanding respiratory syncytial virus (RSV) vaccine development and aspects of disease pathogenesis. Expert Rev Vaccines 2016; 15: 173-87. [CrossRef]