REVIEW ARTICLE

Immunoprophylaxis of Respiratory Syncytial Virus Infection: Recent Updates

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Abstract

The respiratory syncytial virus (RSV) has been the most prevalent cause of respiratory illness in children and infants. Although the humoral immune response usually produces anti-RSV neutralizing antibodies during an infant's initial infection, they are usually insufficient. Despite the fact that RSV-specific neutralizing antibody production remains effective during infection, humoral immunity declines with time, resulting in frequent reinfection in subsequent seasons. With high prevalence and significant morbidity in young children and older adults, currently available patient care for RSV is based on supportive therapy. RSV prevention strategies have advanced significantly as a result of ongoing studies on the immunopathology, community transmission, and mechanisms underlying the virus replication. Despite the fact that RSV and poliovirus were discovered at the same time, cost-effective vaccinations for the risk groups were unavailable in many countries.

Keywords: Antiviral, Developing countries, Immune response, Respiratory syncytial virus, Vaccine, Viral pathogenesis.

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Introduction

Human respiratory syncytial virus (RSV) is the leading cause of severe lower respiratory infection in infants, older adults, and those with compromised immunity, resulting in bronchiolitis.[1] RSV is a member of the Pneumovirinae subfamily of the Paramyxoviridae family and the *Pneumovirus* genus. It has a single-stranded, nonsegmented, enclosed negative-sense RNA genome that is roughly 15.2 kb long and has 10 genes that code for 11 proteins.[2] The RSV integral membrane proteins comprise the fusion protein, a short hydrophobic protein, and the receptor-binding glycoprotein.[3,4] Variations in the RSV G protein differentiate RSV A and RSV B subtypes. RSV spreads through respiratory droplets and direct contact with an infected person or contaminated surfaces, infecting children under the age of two, as well as more than two-thirds of newborns in the first year of life worldwide.[5] RSV is predicted to cause infection over 3.4 million hospital admissions annually and 66,000–239,000 fatalities in young children around the world.[5] Previous studies demonstrated the global impact of RSV, with approximately thirty million cases of RSV lower respiratory tract infections (LRTI) in adults. China, Indonesia, Nigeria, Pakistan, and India accounted for more than half of the global RSV LRTI burden, with India topping the other nations in RSV LRTI cases.[6,7] RSV-infected persons often have 2–4 days of upper respiratory tract (URT) infection with fever, and if untreated, it spreads to the LRT, resulting in cough, wheezing, and tachypnea.[8] The majority of the RSV-infected people normally recover within 1–2 weeks. However, it is essential to recognize that RSV may be life-threatening, especially in infants and elderly people.[9] RSV is usually managed with supportive care measures that aim to increase the quality of life for patients.[10] In severe cases, patients may require hospitalization for complicated respiratory may be appropriately monitored and treated, as well as intravenous (IV) fluids may be administered.[11] In the case of secondary bacterial LRT, antibiotics may be prescribed. There is currently no defined treatment for RSV infection, and bronchodilators or steroids have not been proven beneficial in treating RSV infection.[10] Palivizumab is an immunoprophylaxis drug that prevents severe RSV infection in infants and children aged below 2 years.[9] It is difficult to differentiate RSV infection from other respiratory infections clinically based on specific clinical signs or symptoms. In developing countries, accurate RSV diagnosis is critical for effectively directing preventive measures. Molecular methods such as polymerase chain reaction have been utilized to differentiate RSV from other respiratory diseases. RSV drugs and vaccinations have been developed as an outcome of the latest advances in medical science and technologies.[12] However, it is vital to emphasize that these drugs are not currently widely accessible in low- and middle-income countries. The interaction between the human immune system and RSV during infection is poorly understood, which is one of the reasons for the delay in developing a safe, efficient, and economical vaccine or antiviral drugs. The frequency and duration of the infection, as well as the host's immune system's response to the RSV infection, contribute to the severity of the disease. The present review will address the complexities associated with RSV host-specific interactions, as well as therapeutic alternatives and the challenges they represent in infection management.

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Pathogenesis of Respiratory Syncytial Virus

Respiratory syncytial virus (RSV) respiratory infection is considered to have a mean incubation period of 3–8 days. Replication occurs in the nasopharynx during the early stages of the disease, and higher viral loads have been found in newborn infants during this time.[7] The most common outcome of RSV infection in infants is LRTI, which includes pneumonia and bronchiolitis, which can lead to respiratory failure and death. RSV is the second leading cause of infant mortality due to respiratory infections.[13] Approximately 2–3% of RSV-infected infants are hospitalized due to RSV LRTI.[5] RSV infection in young children is linked with low levels of proinflammatory cytokines, a low cluster of differentiation (CD) 8^+ T-cell count, and increased natural killer cell activity that is not dependent on the major histocompatibility complex class Ib system.[14]

Respiratory syncytial virus (RSV) pathogenesis varies fairly between adults, the elderly, infants, and children. The virus may be detected for 10–13 days by nasal discharge in RSV-infected individuals, with some cases lasting up to 20 days. The viral titer in nasal samples was found to be lower than that in sputum samples, indicating that viral replication is active in the lower respiratory tract.[15,16] Previous studies reported a significant amount of macrophage inflammatory proteins 1α and interleukin (IL) 6 following RSV infection, indicating an association between the severity of the patient's condition.[17,18] Furthermore, the number of $CD4^+$ memory T-cells, interferon (IFN) γ, and $CD8^+$ memory T-cells decreased with age.[5,18,19]

Respiratory syncytial virus (RSV) spreads through the air from an infected person to a healthy person through a contaminated surface to the nose, mouth, or eye epithelium. RSV interacts with respiratory ciliated epithelial cells using G protein, and the attachment aids in the binding of RSV F protein to nucleolin, which activates the RSV envelope and actin filament, allowing the viral content to penetrate the host cell's cytoplasm.[20] RSV nonstructural protein (NS) 2 viral protein infects respiratory epithelial ciliated cells, causing them to protrude and separate. During RSV infection, cytokines such as IL-33 and thymic stromal lymphopoietin were produced which increases the neutrophil, eosinophil, and mucus production. T-helper 2 (Th2)—induced cytokines such as IL-5 and -13 were also produced to create an inflammatory environment.[5,21,22] Simultaneously, RSV inhibits mucociliary transport, and goblet cell proliferation results in mucus formation in the lumen of the bronchial airway. As a result of these events, bronchiolar constriction develops, along with uneven airway obstruction, compensatory emphysema, and pneumonitis.

Genetics of Respiratory Syncytial Virus

Each segment of the RSV genome is translated into 11 noninvasive mRNAs, which encode the key glycoproteins. The viral membrane comprises three surface proteins: G and F glycoproteins, as well as an SH protein that acts as a viroporin. M protein provides the virion with its filamentous structure and is found in viral particle matrices. M2-2 open reading frame encodes an additional specialized transcription factor that has a unique function. Furthermore, two nonstructural viral products (NS1, NS2) that limit apoptosis and IFN responses develop inside infected cells.[2] RSV is separated into two subgroups based on G protein gene variations: RSV A and B, which have 12 and 20 different genotypes, respectively.[23]

Immunology of Respiratory Syncytial Virus

Humoral Immunity

During RSV infection, infants produce immunoglobulin M (IgM), IgA, and IgG antibodies against the RSV protein in both blood and mucosa. These antibodies increase significantly and aid in the neutralization of the RSV F and G virus proteins after reinfection.[5] Children under 6 months of age have a poor antibody response to the F antigen, causing them to be more susceptible to RSV infection.[5,24] IgM antibody often develops during the incubation period of RSV infection (the first 5–10 days) and can be detected for up to a year, indicating the most common humoral response to the virus. IgG antibody is detected 20–30 days after RSV infection and begins to decline after a year. The level of neutralizing antibodies specific to RSV declines in older adults, placing them at risk of infection.[5,17,24] As maternal antibodies are transmitted transplacentally, all full-term infants have specific RSV-neutralizing antibodies in their serum, which are similar to those of the mother titer, and they decrease gradually in the months after birth. Beyond 7 months of age, natural infection is the primary cause of observable neutralizing antibodies, and breast-fed infants benefit from maternal antibodies present in colostrums.[25] Lower antibody titers in neonates, on the other hand, may be attributed to the inadequate immunity and suppressive characteristics of transplacental maternal antibodies. In an animal study of RSV infection, passively transmitted antibodies were found to have a suppressive effect. Additionally, a study on RSV protein vaccinations contends that RSV-neutralizing antibodies in serum are substantially more crucial than the total titer of anti-F along with anti-G antibodies.[26] Neutralizing and nonneutralizing antibodies control the number of $CD4^+$ and $CD8^+$ T-cells during an RSV infection.[27] RSV additionally triggers unique cellular immunological adaptive responses, such as modifications in lymphocyte proliferation and activation of antibody-dependent cytotoxic T-cells.[28]

Cell-mediated Immunity

Immunocompetent neonates with RSV infection limit virus replication after 21 days; nevertheless, infants with innate immune deficits may shed the virus for several years. Although transient, the underlying mechanisms of an inflammatory response on M2 and N are mediated by cytotoxic T-lymphocytes (CTL). The ineffectiveness of G protein to induce a CTL response has been identified as a potential factor in the pathogenesis of RSV infection.[29]

Respiratory syncytial virus (RSV) clearance is predicted to rely substantially on cellular immune responses. Previous studies have shown that fusion inhibitory RSV (FI-RSV) and Th2-triggered pathology have been associated with the worsening of disease conditions. Early-life viral infections were found to impair $CD4^+$ T-cell differentiation between Th1 and Th2 responses, indicating that immune system modulation could end in a Th2 immune response.[30] In severe combined immunodeficiency cases, bone marrow-reduced $CD8^+$ T-cell counts contributed to mortality. RSV infections could be lethal in the early stages of life due to weakened $CD8^+$ T-cells.[30] In response to RSV infection, Th1 cells induce IFN-γ and neutralizing mucosal antibodies, whereas Th-2 cells induce IL-4, eosinophils, and IgE antibodies. The F protein activates a Th-1 response during RSV infection, whereas the G protein supports a Th-2 response. The protective functions of $CD4^+$ T-follicular helper cells supporting memory B-cells, antibody production, and immune response maintenance were all affected in infants lacking IFN-producing T-cells.[31] Following RSV infection, TNF-α and IFN-γ levels decreased while Il-6 and -17 levels increased in infants.[32] T-cell lymphopenia in young infants and elderly patients with low numbers of T-cells demonstrates the importance of $CD3^+$, $CD4^+$, and $CD8^+$ T-cells during RSV infection.[33]

Roles of Immunity in the Pathogenesis of RSV Diseases

Many of the clinical symptoms associated with RSV infection of the lower respiratory system can be explained by RSV's potential

cytotoxic effects on respiratory epithelial cells. However, there is compelling evidence that changes in RSV pathogenesis are directly influenced by the immune response of the host cell. Even in individuals with strong immune systems, RSV can cause symptomatic reinfection at any time throughout life.[20] Innate and adaptive immune responses provide complete protection against any infection. The physical and metabolic functions of the respiratory system combine to limit pathogen damage to the host. Epithelial cells in the respiratory airway lining secrete mucin, which functions as a physical barrier.[34] In general, innate immune responses are rapid and nonspecific to the pathogen, whereas adaptive immune responses target infection clearance and contain immunological memory, which helps in reinfection. The RSV genome, which codes for 11 proteins, contains multiple methods for restricting host immunity by maintaining replication and modifying immune response following the host immunological response. In response to RSV antigen, mature T-cells, macrophages, and cytokine release drive the cell-mediated immune response. There is also conclusive evidence that prenatally generated anti-RSV Ig has a curative rather than a preventive effect, and the finding of an association between high viral antibody levels in cord blood and severe RSV infection adds to the evidence for maternally generated antibodies having protective benefits.[31] Furthermore, the absence of RSV infection in neonates or children under the age of 6 weeks emphasizes the significance of prenatal antibodies. Parenteral therapy of RSV-neutralizing antibodies prevented rather than exacerbated RSV disease in animal models and, later, in high-risk neonates,[35] indicating that antibodies do not participate in disease immunopathogenesis.

Treatment and Prevention of Respiratory Syncytial Virus Infection

A dearth of literature cannot be blamed for the lack of consensus on how to treat RSV-induced bronchiolitis in children. Bronchodilators have been found to reduce the severity of RSV infection by decreasing viral shedding, strengthening oxygen levels, and improving clinical scores.[36] The World Health Organization emphasizes preventing LRT caused by RSV in young children due to the disease's severe mortality and morbidity.[11,37,38] Supportive treatment for acute RSV infection will be advantageous for lowering comorbidities and hospital stays. Reinfection occurs in both children and adults, requiring adequate long-term vaccination.[39,40] The first formalin-inactivated RSV vaccination had been developed and evaluated in infants; however, it was determined to be ineffective due to safety concerns of the vaccine.[39] Extensive studies on the occurrence of enhanced respiratory disease have led to the hypothetical association between an overactive Th2 memory cell response, insufficient antibody affinity, insufficient signals for toll receptors, and poor response for CD8 T-cell.[41,42] However, as our understanding of RSV structural biology and mechanism of action has advanced, various innovative strategies for preventing RSV infection have been developed.[43–45] Several approaches for RSV prophylaxis have been assessed, including passive immunoprophylaxis with palivizumab, the only approved and successful prophylactic drug usage among extremely susceptible infants, which is given intramuscularly once a month for 5 months.[46] The United States Food and Drug Administration (FDA) recently approved the vaccination (Abrysvo) against RSV for elderly people and pregnant women during the third trimester of pregnancy. Furthermore, the FDA approved nirsevimab for the treatment of RSV in infants.[47] The drugs, including ribavirin, palivizumab, and motavizumab, attempt to give symptomatic relief, lower the severity and duration of the disease, and thereby minimize the risk of transmission. Palivizumab, a recombinant humanized monoclonal antibody that efficiently binds with the RSV fusion protein, has been used for 2 decades to prevent the severity of RSV in high-risk children and infants. Palivizumab has been studied for use in the treatment of acute infections; however, none of these studies demonstrated an effective outcome for RSV infection.[39,48] Furthermore, similar investigations were conducted to determine the therapeutic efficacy of motavizumab, which showed the same results as palivizumab.[39] Ribavirin, a nucleoside analog, prevents viral replication. Patients with hematological diseases, bone marrow transplants, and lung transplants had a better prognosis with ribavirin treatment when compared to RSV infections in infants and children.[39,49–53]

Challenges in Developing Countries

Respiratory syncytial virus (RSV) is a significant etiological agent of respiratory diseases in children throughout the world, particularly in developing countries. There are several challenges associated with managing RSV infection in children. A lack of public awareness about the disease may discourage major pharmaceutical companies from developing RSV drugs.[54] The most common RSV infection preventive measures presently include passive immunization with humanized monoclonal antibodies.[55] Further adverse drug events and a lack of resources to conduct controlled clinical trials for developing novel RSV drugs turned out to be the major barriers to controlling the infection in children.[54,55] In middle and low-income countries, there is a significant and undocumented prevalence of community RSV mortality, with a particular emphasis on infants under 6 months of age.[56] Despite these challenges, there are numerous ongoing projects that aim to combat RSV, such as the development of effective monoclonal antibodies and vaccinations for both maternal and pediatric populations.[12] Current developments in RSV epidemiology, better point-of-care diagnostic methods, and the development of potential antiviral agents provide reassuring evidence that major barriers to drug development will be overcome in the coming years.[54] Comprehensive investigations into disease pathophysiology and the insights gained through systematically conducted controlled clinical trials will be significant to the advancement of our understanding and the development of novel therapeutic treatments. The global health sector requires the development of an RSV vaccine that is affordable, safe, and effective. In the meantime, until a safe and effective RSV vaccine is available, it is necessary to implement immunological prophylaxis measures among specific high-risk populations in low-income countries.[55] It is important to collect precise and up-to-date data on the healthcare resource costs associated with RSV LRTI. This includes inpatient stays, emergency room visits, hospitalization duration, time spent in the intensive care unit, duration of mechanical intervention management in the community, and the subsequent costs of managing respiratory morbidity. This information is essential for conducting pharmacoeconomic analyses of future RSV interventions.

Prospective for Novel Therapies

Sulfated polysaccharides, sulfonic polymers, and synthetically derived dextrans showed anti-RSV activity *in vitro*, most likely

due to their ability to inhibit viral adhesion to host cells. It will be difficult to determine whether these substances interact with RSV receptors unless local or systemic sensors (and/or coreceptors) are identified. New RSV therapies are clearly required for mild to severe infections. Combining aerosolized ritonavir with antibody therapy reduced mortality among patients with respiratory distress and RSV infection,[56] and mixed results were observed in systemic treatment for RSV respiratory infection in bone marrow transplant patients.[55] Animal studies revealed the potential for the use of RSV monoclonal antibodies for future preventative and therapeutic uses. Preliminary findings from human trials assessing the monoclonal-F product's ability to prevent severe RSV sickness in premature infants are promising.[57] Despite the fact that the therapeutic antiviral drugs ribavirin and amantadine benefit children with influenza and RSV, they are rarely used due to their high cost. Passive vaccination for infants is possible by active immunization of pregnant women and has demonstrated promising outcomes in animal models, one of which has already been licensed by the United States FDA but is still not available in much needed regions in underdeveloped countries at an affordable price. RSV can be prevented or reduced by passive immunization with virus-specific antibodies in high-risk populations such as infants and children.[58] Inactivated virus (or its components), recombinant antigen, and live virus have been used to develop immunity against various respiratory viruses, and their safety and efficacy in infants are being investigated thoroughly.[59] In infants and children with congenital heart diseases, RSV causes significant morbidity. RSV IgG neutralizing antibodies could provide protection against severe RSV respiratory tract infection in high-risk patients.[29,60] Palivizumab, the only immunotherapy approved for RSV prophylaxis, must be administered on a regular basis throughout the RSV season.[61]

Recent Updates in Respiratory Syncytial Virus Infection

The disease burden in older children and adults is inadequately documented. Annually, it is estimated that 3–10% of the total population in the United States suffer from respiratory infections caused by RSV, with 1–2% of cases being life-threatening and requiring hospitalization for older people.[62] RSV is an extreme risk to people in this age-group, causing acute LRTI with clinical complications and life-threatening consequences. T-cell responses to RSV tend to decrease in older adults due to impaired immunity, which can potentially aggravate chronic respiratory illness. Seasonal respiratory virus infections have been linked to chronic obstructive pulmonary disease (COPD) hospitalizations, increasing the likelihood of intensive care unit admission by 50% and mechanical ventilation by 90%.[63] The RSV prefusion F (RSVPreF3) vaccine gained initial authorization from the FDA based on clinical trials and safety data, and this vaccine is intended to protect older adults from RSV-related lower respiratory tract disease.[62,64] RSV has been identified as an emerging viral pathogen that is capable of causing acute exacerbations of COPD. The newly approved vaccine candidate (RSVPreF3) has the potential to reduce acute COPD exacerbations. According to the Global Initiative for Chronic Lung Disease report for 2023, COPD patients aged 50 and older may benefit from RSVPreF3 immunization as a prophylactic measure against RSV infection.[63] Researchers are currently working to find a way to get this vaccine to undeveloped countries so that it can provide protection against RSV in vulnerable populations.

Discussion

Respiratory syncytial virus (RSV) is a viral pathogen that causes respiratory tract infections, particularly in infants, the elderly, and people with poor immune function. Pathogenesis of RSV infection is a complex process involving the interaction of viral and host components. In RSV-infected patients, the immune response causes neutrophils to infiltrate the respiratory airways, resulting in respiratory diseases such as bronchiolitis and pneumonia.[29,65] Host risk factors such as an undeveloped immune system, immunologic dysfunction, and aging influence the pathogenesis of severe LRTIs caused by RSV.[5,66] The virus replicates in the URT of young infants during initial infection, leading to an increased amount of virus in nasal discharge.[29] RSV has the ability to cause direct cytopathology of the respiratory epithelium, which results in airway blockage and respiratory distress.[66] Despite an understanding of RSV pathophysiology, many aspects of the etiology remain unclear, necessitating more studies for developing new antivirals.[67] RSV has developed a number of strategies to evade host defense measures, which include blocking IFN signaling pathways and interfering with IFN synthesis.[68] RSV can modulate the function of immune cells, such as dendritic cells and T-cells, to evade the immune response and inhibit apoptosis.[69,70] Understanding the association between RSV and the host immune mechanisms is essential for developing novel therapeutics that target RSV immune evasion mechanisms.[60] Given the limited availability of RSV-specific drugs, the primary focus in managing the disease is on preventative methods. Based on the analysis provided in this review, it is evident that the current preventive measures employed for RSV have demonstrated effectiveness. Furthermore, future strategies hold promise for achieving additional advancements in this regard. However, there is a lack of clinical trials conducted in low and middle-income countries, which is crucial for evaluating their effectiveness in regions with the highest disease burden.[12] Pharmaceutical companies should carefully consider the possibility of conducting future clinical trials in developing countries. Without such trials, it is unlikely that any advancement can be made in reducing global childhood mortality related to RSV. The global severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak has shown the great effectiveness of worldwide preventative measures. The implementation of nonpharmaceutical interventions aimed at mitigating the transmission of SARS-CoV-2 had a notable effect on other respiratory viruses, such as RSV.[68,70] Viral antigens are potential targets for vaccine development and RSV surface antigens (F protein or G protein) may represent significant targets for RSV vaccine development.[71,72] Several RSV vaccine candidates targeting the RSV F protein are being developed, including subunit, live-attenuated, and vector vaccines.[77] Furthermore, the RSV G protein may associate with host factors and modify immunological responses, making it a possible vaccine target.[72] Although certain RSV vaccinations are nearing approval, there are still a number of limitations for widespread availability.[70] Palivizumab monoclonal antibody is the only approved specific treatment for RSV and is limited to use for passive immunoprophylaxis in high-risk infants.[46,73] Globally, supportive and preventive strategies are therapeutic alternatives to address RSV-related illness in newborns. Studies on the pathogenesis of RSV disease have highlighted the role of both humoral and cell-mediated immunity.[29] To reduce the consequences of RSV infection, it is more desirable to focus resources on improving existing conditions in low and middle-income countries. However, novel vaccines for preventing RSV are primarily authorized and

implemented in high-income countries before being evaluated in LMICs. Vaccines such as the *Haemophilus influenzae* type b conjugate vaccine and the rotavirus vaccine, which were available in LMICs, resulted in a significant mortality in children.[74]

Conclusion

Respiratory syncytial virus (RSV) infection poses a significant burden, particularly in young children, with a high mortality rate. RSV replication can be inhibited by B cells that produce antibodies, but T-cells are required to remove the virus from the host system. CTLs may trigger pathological conditions with the help of CD4 Th1 or Th2 cells. Age, malnutrition, premature delivery, and immunocompromised patients possess an impact on the immune response and its ability to prevent infection with minimal damage to body tissues. Due to a weakened or compromised immune system, RSV infection can lead to serious diseases in infants and older adults. Considering there are few options for treatment for RSV-associated respiratory disease, the development of promising new drugs must be the main priority. Vaccine for RSV infection was found to be important in infants and children due to the serious clinical outcome as well as its widespread prevalence and geographic variation. Developing a vaccine for RSV infection involves a number of challenges. The first and most serious challenge is that vaccination can worsen preexisting RSV diseases, such as those observed with the formalin-inactivated vaccine. Second, newborns and young children might not develop a protective immune response due to variable immunological responses or circulating maternal anti-RSV antibodies. The availability of a safe, effective, and affordable RSV treatment is ultimately the most important concern. The ongoing RSV vaccine trials offer a promising and confident indication of preventing diseases in children and infants. Good funding for RSV vaccine research and development could aid poor and middle-income nations in preventing RSV-related deaths in children.

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