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Respiratory syncytial virus:
an overview of clinical manifestations and management in the Indian pediatric population

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Abstract

Respiratory syncytial virus (RSV) plays a major part in causing lower respiratory tract infections in younger populations, especially in infants and pediatric patients, causing a higher rate of morbidity and mortality in the respective population, affecting 60% of the population globally. Typically, identifying the virus in the patient's respiratory secretions is important for laboratory validation of a clinically suspected RSV infection. Unfortunately, the only available preventive measure to lower the incidence for infants who are at high risk of RSV-induced hospitalization is palivizumab prophylaxis. Treatment strategies to manage RSV involve using an antiviral drug that is Ribavirin along with bronchodilators, nebulized adrenaline (epinephrine), and nebulized hypertonic saline. Providing patients with alternative treatment options like vitamin D-cathelicidin as well as probiotics and prebiotics can help reduce the intensity of the infection. This review article focuses on the epidemiology, clinical manifestation, prophylaxis, and available treatment options for RSV infections in infants, children, and young adults.

Key words: respiratory syncytial virus, rhinorrhoea, RSV-associated acute lower respiratory infection, RSV glycoprotein, bronchiolitis, probiotic and prebiotic, Vitamin D-cathelicidin.

Introduction

Respiratory syncytial virus (RSV) is a non-segmented single-stranded, negative-sense, enveloped ribonuclease (RNA) virus that is a part of the pneumovirus genus and subfamily of the paramyxoviridae family of viruses [1]. The two primary viral antigens on the surface, the G (attachment glycoprotein) and the F (fusion) protein, are essential to the pathogenicity of RSV [2,3].

Premature newborns, infants with chronic lung diseases such as interstitial lung disorders, bronchopulmonary dysplasia, and cystic fibrosis, and infants with hemodynamically severe congenital heart disease all have greater rates of RSV disease morbidity and mortality [3]. RSV is known to be one of the main causes of lower respiratory disease among young children. RSV causes respiratory illness in young children under 5 years and presents a significant global health burden, due to which most of all patients before the age of 2 got infected before, and bronchitis is the primary medical cause of neonatal hospitalization [1]. It is the most significant cause of LRTI's in pediatrics all over the world, globally, with over 33 million scenarios and roughly 160,000–190,000 causalities yearly, or 6.7% of all deaths among babies aged <1 year. Katherine M. Begley et al the prevelamce of RSV among adults was significant among patients of age group between 18 to 45 as well as patients above 65

In developing countries, the majority of the deaths of approximately 118,200 children annually are associated with RSV, with almost 50% of the deaths occurring in younger children who are below 6 months of age and infants [4]. RSV-ALRI (RSV -associated acute lower respiratory infection) will result in approximately 100,000 RSV-ALRI (RSV -associated acute lower respiratory infection) deaths in LMICs in 2019. RSV infection affects 60-70% of newborns in their initial year of life and most of all pediatrics aged two; of these, 2-3% require hospitalization for RSV-induced bronchiolitis [4]. It is said that RSV has become one of the most common reasons for infant hospitalization [5]. And an increasing number of experts acknowledge that RSV has a significant role in adult severe respiratory diseases. In the US, there are an estimated 60,000 to 160.000 hospitalizations linked to RSV and 6,000 to 10,000 deaths per year among persons 65 and older.

According to estimates from the WHO, RSV causes < 60% of acute respiratory infections among kids globally and <80% of them in babies under 1 year old during the height of the viral season. RSV is thus by far the most common reason for pediatric bronchiolitis and pneumonia [6].

There is a widespread notion in industrialized nations that RSV is predominantly a significant agent in newborns and that the illness is typically less prevalent and severe in older children [7]. Similar to other respiratory viruses, RSV infections typically rise in colder climates, during rainy seasons, and during low temperatures [8].

Clinical manifestation

Clinical criteria are very different enough to accurately distinguish RSV -associated from other, non -RSV related RTI's because of the high number of possible bacteria that can cause comparable symptoms referring to respiratory illness. The signs and symptoms of RSV infection among premature newborns are typically atypical and may include,adjustments to feeding and breathing [4].

Symptoms

The initial symptoms typically upper respiratory tract manifestations such as mucosal inflammation and sneezing, congestion, and rhinorrhoea; gradually, the symptoms evolve to lower respiratory tract manifestations like cough and increased airway obstruction. All of these mentioned clinical manifestations are induced by the immune response of the body rather than cytotoxicity and viral replication, and therefore symptoms of bronchiolitis like wheezing are generally absent or not observed [9]. Table 1 shows the clinical manifestation and description of RSV.

Diagnosis

RSV infection affects 60-70% of newborn babies in their initial year and almost every child by the age of two; of these, 2-3% require hospitalization for RSV-induced bronchiolitis [4]. Rapid diagnostic testing is necessary to influence clinical decision making since clinical illnesses usually have a brief duration. The detection of virus-specific nucleic acid sequences or viral antigens or virus in respiratory secretions is the accurate diagnosis of RSV infection [10]. The detection of virus-specific nucleic acid sequences, viral antigens, or viruses in respiratory secretions is an accurate diagnosis of RSV infection [10].

If we look into the pathophysiology of RSV in humans, the initiation of viral attachment to the host cell is done by the RSV-G (RSV glycoprotein) and the RSV-F (RSV fusion protein), which is crucial to the RSV viral life cycle, mediates viral cell membrane fusion [11].

Respiratory syncytial virus (RSV) is a common respiratory pathogen that can cause severe respiratory illness, especially in infants, young children, and older adults. Diagnostic tests play a crucial role in identifying RSV infections, guiding treatment decisions, and implementing infection control measures. Several diagnostic methods are available for detecting RSV, each with its advantages and limitations.

1. **Viral testing:** This conventional technique entails gathering respiratory specimens, such as throat swabs or nasal secretions, and cultivating them in a lab in order to separate and identify the virus. Although viral culture has a high degree of specificity, its

turnaround time (several days) may restrict its therapeutic value, particularly in acute care settings [12].

2. **Immunofluorescence assay:** IFA uses antibodies that have been fluorescently tagged to identify RSV antigens in respiratory specimens. Rapid results are usually obtained in a matter of hours, which makes it appropriate for prompt clinical decision-making. The sensitivity of IFA, however, can differ based on how well specimens are collected and processed, which could result in false-negative results [12].
3. **Polymerase chain reaction:** RSV RNA is amplified in respiratory samples by PCR, which has a high specificity and sensitivity. It is able to distinguish between RSV subtypes (A and B) and identify low virus levels. Quick results from rapid PCR assays, including point-of-care tests, help with timely clinical treatment and infection control [13].
4. **Antigen detection test:** RSV antigens are directly detected in respiratory specimens by quick antigen assays like lateral flow immunoassays. These tests are quick (typically within15–30minutes) and convenient. They might, however, not be as sensitive as PCR, which could occasionally result in false-negative results [13].
5. **Serological testing:** RSV-specific antibodies are found in blood samples by serological assays, which can reveal viral infection in the past or present. These assays have use in population immunity assessments and epidemiological research. However, because antibody formation takes time, serological testing is not frequently employed for acute RSV diagnosis [14].

Who is at risk

It is crucial to identify children who should be taken into consideration for severe and deadly RSV infection as the potential for treatment of prophylaxis against RSV infection increases. Groups who are at high risk for severe RSV infection are infants with having a history of premature delivery, with or without chronic lung illness [15], pediatrics with cystic fibrosis [16], with congenital heart disease [17], immune compromised patients, or patients with immunodeficiency [18]. According to a study done by ERICA. F. SIMOES there are certain independent risk factors that can influence in development of RSV infection [15]. Table 2 shows the highrisk groups and their independent risk factors for RSV infection.

Prophylaxis

It is imperative to prevent infections with the respiratory syncytial virus (RSV), particularly in high-risk groups such newborns, young children, elderly people, and people with underlying medical disorders. Reducing hospitalizations and problems associated to RSV can be achieved through effective preventative initiatives.

The most potent, affordable, and successful way to prevent infectious diseases is vaccination. By granting passive protection through placental antibody transfer, RSV vaccination during pregnancy is likely to improve serum neutralizing antibody responses established by prior natural infections and may lower the prevalence of RSV-associated LRTI in young newborns [16]. Prevention of RSV diseases in all newborn babies is a top public health priority. In clinical studies, passive RSV antibody methods have been successful [17].Previous research on an RSV fusion (F) protein vaccination given to expectant mothers showed that the mother's RSV-specific antibodies were effectively passed on to the child [18].

1. **Vaccination Programs:** Vaccination is still one of the best ways to avoid contracting RSV. Even though there isn't a licensed RSV vaccine available for general public usage just yet, research is still being done to create safe and efficient vaccinations. Specifically, vaccination of the mother during pregnancy has demonstrated potential in preventing severe RSV disease in the first few months of life in the infant [19].
   In India, several vaccines for respiratory syncytial virus (RSV) are available, including:
   - Synflorix (Pfizer)
   - Prevenar 13 (Pfizer)
   - Rotarix (GSK)

   These vaccines offer indirect protection against RSV by targeting related pathogens or boosting immune responses. However, specific RSV vaccines designed solely for RSV prevention are still in development or limited in availability in India [20].
2. **Palivizumab Prophylaxis:** In order to prevent severe RSV infections, prophylaxis with the monoclonal antibody palivizumab is advised for a few high-risk newborns. Updated guidelines on palivizumab use are provided by the American Academy of Pediatrics, which emphasizes the drug's efficiency in lowering hospitalizations linked to RSV in eligible newborns [20].
3. **Hand hygiene and Respiratory Etiquette:** Using alcohol-based hand sanitizers or encouraging frequent hand washing with soap and water are two effective ways to help prevent the spread of respiratory swine fever. Furthermore, promoting respiratory etiquette helps stop the spread of virus-containing respiratory droplets. Examples of this include concealing sneezes and coughs with tissues or elbows [21].
4. **Environmental Hygiene and Disinfection:** Preventing RSV outbreaks requires maintaining clean and sanitary conditions, particularly in healthcare and childcare settings. Toys and high-touch surfaces should be regularly disinfected to help limit the virus's survival and spread [22].

5. **Refraining from Close Contact with Sick People:** People should stay away from people who are sick with respiratory ailments, especially if they are more likely to get a severe RSV infection. To stop the transmission of RSV and other respiratory infections, this also entails remaining at home while exhibiting respiratory symptoms [22].
6. **Education and Awareness about Public Health:** Educating the public about RSV, its symptoms, transmission channels, and preventive measures is essential to encouraging adherence to prevention protocols. Healthcare professionals are essential in teaching communities, caregivers, and patients about RSV preventive techniques [11].

Treatment

Guidelines on RSV and bronchiolitis have been created by the AAP, and they emphasize both prevention and therapeutic approaches (Table 3) [23].

Therapeutic approaches

1. Antiviral Drugs: Antiviral medications work by preventing the spread of viruses and lessening the severity of RSV infections. One such drug that has been used to treat severe RSV infections, particularly in patients with impaired immune systems, is ribavirin. Its effectiveness is still debatable, though, and its serious adverse effects prevent it from being used widely [24].
2. Monoclonal antibodies (mAbs): Specifically designed to target RSV proteins, such as the fusion (F) protein, mAbs have demonstrated potential in preventing severe RSV infections in high-risk populations, such as preterm infants and individuals with chronic lung disease. One FDA-approved mAb that is used prophylactically to lower RSV-related hospitalizations in high-risk infants is palivizumab [25].
3. Immunomodulatory Therapies: The ability of immunomodulatory drugs to alter immune responses and lessen inflammation linked to severe RSV infections has been investigated. Examples of these drugs include corticosteroids and monoclonal antibodies that target immunological pathways. However, more research is needed to determine their effectiveness and safety in managing RSVs [26].
4. Vaccines: A number of vaccines, including live attenuated, subunit, and viral vector-based vaccinations, are being developed to combat RSV. By boosting immune responses to RSV, these vaccinations seek to lessen transmission and avert serious disease. However, the complicated biology of the virus and the possibility of vaccine-enhanced illness have made the development of a safe and effective RSV vaccine difficult [27].

Non therapeutic approaches

1. Infection Prevention and Control: In communities and hospital settings, non-pharmacological treatments are essential for reducing the spread of RSV. Hand hygiene, respiratory etiquette (such as cough etiquette), ambient disinfection, and isolation precautions for afflicted persons are some of these methods. Strong infection control procedures can help stop the spread of RSV and safeguard susceptible groups [28].
2. Supportive Care: The cornerstone of managing RSV, particularly in mild to moderate cases, is supportive care. This covers proper diet and hydration, oxygen therapy for respiratory distress, and symptomatic treatment (such as bronchodilators for wheezing, antipyretics for fever). The goals of supportive care are to reduce symptoms and enhance patient outcomes [29].
3. Public Health Interventions: In order to manage RSV infections at the community level, public health methods are crucial. These include surveillance systems, outbreak investigations, and immunization programs (such as palivizumab prophylaxis in high-risk newborns). To lessen the burden of sickness, these treatments assist in tracking RSV trends, identifying risk factors, and putting targeted interventions into action [30]
4. Prebiotics and probiotics: In a randomized experiment, probiotic and prebiotic treatment in preterm infants (32 to 36 weeks) decreased the prevalence of viral RTI's in comparison to placebo [30].
5. Vit. D-Cathelicidin: Innate immunity is heavily dependent on cationic host defence peptides called cathelicidins, which have bactericidal properties [30]. and recently discovered antiviral qualities, particularly those against influenza [31]. In a previous trial done by Currie et al. [32]. In addition to reducing the bronchial epithelial cells' sensitivity towards infection, the simultaneous exposure of the virus and Human Cathelicidin LL-37 resulted in a considerable dose-related reduction in infectivity. This reduction was partially caused by a direct effect on the viral particles. Furthermore, c-reactive protein (c-rep) expression was significantly reduced after RSV-infected human epithelial cells were continuously treated with LL-37, suggesting that LL-37 possesses immunomodulatory actions against RSV.

Discussion and Conclusions

Given the substantial morbidity and death that respiratory syncytial virus (RSV) infections are linked to, particularly in high-risk populations like newborns, young children, and people with underlying medical disorders, prevention and control of RSV infections are imperative. Aiming

to lower complications associated with RSV and enhance patient outcomes, the aforementioned treatments cover both therapeutic and non-therapeutic approaches.

Therapeutic approaches

Antiviral Pharmaceuticals: In patients with immunocompromised conditions, ribavirin, an antiviral drug, has been used to treat severe RSV infections. But there is still disagreement over its effectiveness, and using it widely is hampered by its negative effects. New antiviral drugs with better safety and efficacy profiles are still being researched.

Monoclonal Antibodies (mAbs): In high-risk newborns, palivizumab, a monoclonal antibody that targets RSV, has shown promise in avoiding severe RSV infections. Future therapeutic treatments could benefit from the investigation of other monoclonal antibodies (mAbs) that target RSV proteins, such as the fusion (F) protein.

Immunostimulatory Medication: Immunomodulatory drugs are being investigated to control immune responses and lessen inflammation linked to severe RSV infections. These drugs include corticosteroids and monoclonal antibodies that target immunological pathways. To ascertain their efficacy and safety in RSV management, more research is required.

Vaccines: Research is concentrated on developing vaccines against RSV; many types of vaccines are being developed with the goal of stimulating immune responses against RSV, limiting severe sickness, and minimizing transmission. Vaccine design must take challenges like vaccine-enhanced disease into account.

Non-therapeutic approaches

Infection Prevention and Control: In order to stop the spread of RSV in clinical and community settings, non-pharmacological measures like hand washing, respiratory etiquette, environmental cleaning, and isolation precautions are essential. Sturdy infection control procedures can stop the spread of RSV and safeguard susceptible groups. Supportive Care: When treating RSV infections, especially in mild to moderate cases, supportive care is essential. Symptomatic relief, oxygen therapy, proper diet, and hydration all contribute to symptom alleviation and better patient outcomes. Public Health Interventions: To prevent RSV infections at the community level, public health initiatives such as surveillance systems, outbreak investigations, and immunization programs (such palivizumab prophylaxis) are crucial. In order to lessen the burden of sickness, these programs track RSV trends, pinpoint risk factors, and put specific actions into action.

New approaches

What are probiotics and prebiotics? Prebiotics and probiotics may lessen the frequency of viral respiratory tract illnesses, such as RSV, according to research. By altering the gut microbiome, these therapies strengthen the body's defenses against respiratory infections.

Research has looked into the function of cathelicidin and vitamin D in innate immunity against RSV. Supplementing with vitamin D may increase the production of cathelicidin, which has antiviral qualities and regulates immunological responses. New Antiviral medications: Research is still being done to create new antiviral medications that specifically target RSV proteins or viral replication pathways. These medications may be more widely applicable, more effective, and have fewer adverse effects while treating RSV infections.

In conclusion, an all-encompassing strategy that incorporates therapeutic interventions, non-therapeutic measures, and cutting-edge tactics is necessary to successfully prevent and treat RSV infections. To create novel therapies and preventative measures to lessen the effects of RSV on public health, interdisciplinary research and cooperation are required. A rising infectious condition called RSV infection will have serious repercussions, such as a higher hospitalization rate for infants. In order to determine the best preventive measures and concentrate on efficient infection control, it is crucial to carry out additional research.

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Table 1. Clinical manifestation and description of respiratory syncytial virus.

Clinical manifestation	Description
Upper Respiratory Tract Manifestations	- Mucosal inflammation - Sneezing - Congestion - Rhinorrhoea
Lower Respiratory Tract Manifestations	- Cough - Increased airway obstruction
Absence of Bronchiolitis-like Symptoms	- Symptoms of bronchiolitis, such as wheezing, are generally absent or not observed
Induced by Immune Response	- These clinical manifestations are induced by the immune response of the body rather than cytotoxicity and viral replication

Table 2. High-risk groups and their independent risk factors for respiratory syncytial virus infection.

High-risk groups	Independent risk factors for RSV infection
Infants with a history of premature delivery	Male gender
	Multiple gestations
	Young maternal age
	Exposure to environmental tobacco smoke
	Breastfeeding for less than 3 months
	Exposure to older siblings
	Crowded living conditions
	Low socioeconomic status
Infants with or without chronic lung illness	Exposure to environmental tobacco smoke
Pediatrics with cystic fibrosis	Exposure to environmental tobacco smoke
Pediatrics with congenital heart disease	Exposure to environmental tobacco smoke
Immune-compromised patients	Immunodeficiency or compromised immune system

RSV, respiratory syncytial virus.

Table 3. Guidelines from the American Academy of Paediatrics about bronchiolitis.

Therapy	AAP recommendation	Evidence level
Inhaled bronchodilators (ie, albuterol, nebulized epinephrine)	Should not be routinely used; Can consider trial and continue only if clinical response	B
Corticosteroids	Should not be routinely used	B
Ribavirin	Should not be routinely used	B
Palivizumab prophylaxis	Should not be given to select infants (premature infants <35 weeks gestation, children with congenital lung or heart disease)	A
Antibacterial medication	Should not be used in children with comorbid bacterial infection	B
Oral pr IV fluids	Should asses hydration status and provide fluids accordingly	X
Chest therapy	Should not be routinely used	B
Oxygen	Indicated if oxygen saturations are persistently <90 percent in room air	D

Guidelines on RSV and bronchiolitis have been created by the AAP, and they emphasize both prevention and therapeutic approaches [23].