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Respiratory Syncytial Virus Infections in Neonates: A Persisting Problem

Srijan Singh[1,2], **Akhil Maheshwari**[2,3], **Ilhama Namazova**[2,4], **John T Benjamin**[2,5], **Yuping Wang**[6]

[1]Neonatologist, Kailash Hospital, Noida, Uttar Pradesh, India

[2]Global Newborn Society (https://www.globalnewbornsociety.org/)

[3]Department of Pediatrics, Louisiana State University, Shreveport, Louisiana, United States of America

[4]Department of Pediatrics, Azerbaijan Tibb Universiteti, Baku, Azerbaijan

[5]Department of Pediatrics, Vanderbilt University Medical Center, Nashville, Tennessee, United States of America

[6]Department of Obstetrics and Gynaecology, Louisiana State University, Shreveport, Louisiana, United States of America

Abstract

Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract infections in young infants. It is an enveloped, single-stranded, nonsegmented, negative-strand RNA virus, a member of the family Pneumoviridae. Globally, RSV is responsible for 2.3% of deaths among neonates 0–27 days of age. Respiratory syncytial virus infection is most common in children aged below 24 months. Neonates present with cough and fever. Respiratory syncytial virus-associated wheezing is seen in 20% infants during the first year of life of which 2–3% require hospitalization. Reverse transcriptase polymerase chain reaction (RT-PCR) gives fast results and has higher sensitivity compared with culture and rapid antigen tests and are not affected by passively administered antibody to RSV. Therapy for RSV infection of the LRT is mainly supportive, and preventive measures like good hygiene and isolation are the mainstay of management. Standard precautions, hand hygiene, breastfeeding and contact isolation should be followed for RSV-infected newborns. Recent AAP guidelines do not recommend pavilizumab prophylaxis for preterm infants born at 29–35 weeks without chronic lung disease, hemodynamically significant

Corresponding Author: Srijan Singh, Neonatologist, Kailash Hospital, Noida, Uttar Pradesh, India; Global Newborn Society (https://www.globalnewbornsociety.org/), Phone: +91 7011033174, srijanstar89@gmail.com.

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congenital heart disease and coexisting conditions. RSV can lead to long-term sequelae such as wheezing and asthma, associated with increased healthcare costs and reduced quality of life.

Keywords

Arexvy; Bronchiolitis; Lower respiratory tract infection; Neonate; Nerve growth factor/TrkA receptor axis; Newborn; Nirsevimab; Palivizumab; Perinatal RSV infection; Pneumoviridae

Introduction

Respiratory syncytial virus was isolated from primate carriers in 1956.[1] Despite major advances in our ability to prevent, diagnose, and treat RSV infections, this virus continues to be the most common cause of lower respiratory tract (LRT) infections in infants less than 1 year of age.[2] In this article, we present a review of the virus structure, epidemiology, clinical features, and management of infants infected with these viruses.

Pathogenesis

Viral Structure—Respiratory syncytial virus is an enveloped, single-stranded, nonsegmented, negative-strand RNA virus (Fig. 1), a member of the family *Pneumoviridae* and order Mononegalevirales.[3] It is a pleiomorphic virus with an average diameter of 50–250 nm. The viral genome is 15.2 kb in size, has 10 genes and 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. The F protein promotes fusion of infected cell membranes with adjacent cells, leading to the formation of the eponymous syncytia.[4] The anti-RSV monoclonal antibody response mainly targets Fusion and G proteins. Two antigenic subgroups exist differing in the surface glycoproteins: A and B. Subgroup A infections are more common, severe, and contagious.[5–10] Table 1 outlines the major viral components.

Epidemiology

In a systematic review, the global annual rate of RSV hospitalization among children <5 years was 4.4 per 1000 with highest rates among children aged less than 6 months and preterm neonates.[11] Globally, RSV is responsible for 2.3% of deaths among neonates 0–27 days of age, 6.7% among infants 28–364 days, and 1.6% among children 1–4 years of age.[12] The mode of transmission is nasal and oral secretions.[13] The incubation period is 4–6 days (range 2–8 days).[14] Viremia typically lasts around 3–8 days, although it might be longer in the immunocompromised. The average duration of viral shedding is 11 days.[15] Viral shedding may last up to 4 weeks in young infants and several months in children with HIV infection.[16] Recurrent infections are seen frequently.

Respiratory syncytial virus infection is seen most frequently in children aged less than 24 months; the prevalence is 5.2/1000 (26/1000 in neonates during the first month after birth). Hospitalization rates are highest during the first 6 months.[17] Nearly, 80% of RSV infections are seen in infants because they have lower IgG levels approaching nadir at 3–6 months.

Prematurity is a risk factor in view of lower IgG antibody titers and an immature neonatal immune system.

In the Northern Hemisphere, seasonal outbreaks of RSV occur from October to April, with a peak in January or February.[2,18,19] In contrast, wintertime epidemics are seen in the Southern Hemisphere from May to September, peaking in May or June. In tropical and semitropical climates, the seasonal outbreaks usually are seen during the rainy season, whereas the epidemic peaks are not as sharp in temperate climates. The COVID-19 pandemic was associated with marked reduction in RSV infections in children and were attributed to mitigation measures, such as the use of masks, social distancing, and temporary closure of schools.[20–27]

Patients at the highest risk for severe LRT disease include:

- Infants under 6 months of age,[28] attending daycare,[29,30] and those with older siblings who may harbour asymptomatic RSV.[31,32]
- Infants and children with chronic lung disease (bronchopulmonary dysplasia, cystic fibrosis)[33–35]
- Preterm infants less than 35 weeks gestational age.[28,32,36–38]
- Infants with congenital heart disease.[39]
- Infants exposed to second-hand smoke.[40–42]
- Human immunodeficiency virus (HIV)-exposed, uninfected infants.[43–45]
- Infants with Down syndrome.[34,46]

In a meta-analysis, 8 risk factors were identified to be associated with RSV-associated acute lower respiratory infection: prematurity, low birth weight, male gender, siblings, maternal smoking, history of atopy, and no breastfeeding and crowding.[47] A Risk Scoring Tool (RST) has been developed using three risk factor variables: (a) birth between 3 months before and 2 months after season start date; (b) smokers in the household and/or maternal smoking while pregnant; and (c) siblings and/or daycare attendance to accurately and reliably predict RSV hospitalization. It is a useful tool when opting for RSV prophylaxis; it helps determine the likely risk severity of infection and guide therapy in a cost-effective manner. Smoking in the household and daycare are modifiable risk factors. The chronological age at the beginning of RSV season, low birth weight, and birth order are neonatal risk factors for RSV LRT requiring hospitalization.[48]

Polymorphisms in cytokine and chemokine-related genes, namely, the interleukin (IL)-4, IL-8, IL-10, IL-13, and the chemokine receptor (CCR)5 predispose to severe RSV disease.[49–54] Severe disease is also predisposed by cell surface interactions or cell signaling genes, such as toll-like receptor (TL)-4, chemokine receptor 1 (CX3CR1), surfactant protein (SP)-A, and SP-D.[55–60]

The Canadian RST and the International RST are both validated, reliable, and show a similar level of good predictive accuracy (both show Area Under Curve–Receiver Operator Characteristic, AUC-ROC >0.75; as significant ($p < 0.001$) correlations apparent

for risk scores and risk categories.[76] The RST used data from six prospective, observational studies – the: "Risk Factors Linked to Respiratory Syncytial Virus Infection Requiring Hospitalization in Premature Infants Study" (FLIP-2, Spain);[77] "RISK" (the Netherlands);[78] "Pediatric Investigators Collaborative Network on Infections in Canada" (PICNIC, Canada);[79] "Italian National Birth Cohort" (IBC, Italy);[80] "Respiratory Syncytial Virus (RSV) Respiratory Events Among Preterm Infants Outcomes and Risk Tracking Study" (REPORT, USA);[32] and "Predictors Associated with RSV Hospitalization in Nonprophylaxed, Premature Infants" (PONI, multinational).[81]

The RST predicts the risk of RSV hospitalization in 32–35^{+6} weeks' gestational age preterm infants. The RST can facilitate decision-making for clinicians, parents, and policy-makers regarding RSV prophylaxis. Two out of the five identified risk factors, including smoking in the household and daycare, are modifiable and can be used to educate parents.[82] The scoring is performed on a scale between 0 and 56; ≤19 is considered low, 20–45 is perceived as moderate and ≥50 as high-risk. The cumulative RSV hospitalization risk was 3.6% (484/13,475) in the pooled dataset. The combined moderate- and high-risk groups showed a score of 6.3%. The high-risk group had a score of 9.5%, and the very high-risk group showed a score of 11.9%.[82] The IMpact randomized controlled trial showed that prophylaxis with palivizumab reduced RSV hospitalization in 32–35-week gestational age infants by 80–85%. The number needed to treat was 12.[83,84]

The RST is an efficient way for deciding for selective prophylaxis, targeting only 18% of any birth cohort. The financial constraints make it difficult to provide prophylaxis to all infants. Notably, 41% of all LRT infection hospitalizations are in infants who did not receive RSV prophylaxis. RSV-infected children account for 40–60% of the total number of children hospitalized for LRT infections. Only 16% of the total number of hospitalizations due to LRT infections occur in those who have received RSV prophylaxis.[27]

Maternal-fetal Transmission—Respiratory syncytial virus spreads from the respiratory tract of the mother first to the placenta, and then to the developing fetal lungs during transient RSV viremia (Flowchart 1). It is detected postnatally in the lungs.[85] Vertical RSV infection is associated with dysregulation of critical neurotrophic pathways – the nerve growth factor (NGF)/TrkA receptor axis during fetal development, leading to aberrant cholinergic innervation of the respiratory tract and increased airway reactivity after postnatal reinfection with RSV.[86]

Respiratory syncytial virus does not induce persistent immunity in humans, reinfection of adult healthy humans causes community-acquired respiratory infections and seasonal epidemics; hence, post-infection of pregnant mothers, immune response is inadequate to prevent viremia and transplacental transmission. Prenatal RSV infection interferes with the NGF promoter via suppression of specific miRNAs (especially miR-221) and selective demethylation, which also manifests postnatally.

Intrauterine fetal RSV infections, before the establishment of immunological self-tolerance, induce selective tolerance toward viral antigens. Therefore, exposed newborns do not regard

RSV as pathogenic and non-self during an early-life reinfection, in view of weak anti-RSV Th1 immunity and persistent post-RSV airway dysfunction in childhood.[86]

Respiratory syncytial virus-exposed fetal lungs display changes in critical molecular alterations with persistent functional consequences. Viral transmission and replication in the growing fetal lung tissues modulate expression of ion channels and receptors, predisposing to airway hyperreactivity in later life, supporting Barker's Fetal Programming hypothesis of the Developmental Origins of Health and Disease (DOHaD).

Perinatal RSV persists as an immunologically privileged sanctuary by causing latent infection in cells.[87] It is associated with dysregulation of neurotrophins, involved in neuronal survival and function.[88] The NGF controls the release and expression of major neurotransmitters from the peripheral neurons.[89] It is also associated with innate and adaptive immunity, and allergic inflammation.[90,91] NGF also increases the expression of the antiapoptotic Bcl-2 family and promotes the longevity of infected bronchial epithelium to support viral replication.[92] Prenatal RSV infection interferes with the NGF promoter via suppression of specific miRNAs (such as miR-221) and selective demethylation.

Pathophysiology—Respiratory syncytial virus infects ciliated cells, epithelium of the small bronchioles and type 1 pneumocytes with infection being confined to the respiratory mucosa. Bronchial narrowing and interference in gas exchange occurs as a result of infiltration of the airway by inflammatory cells, necrosis of the respiratory tract epithelium, shedding of necrotic cells and impaired ciliary function.[93] Infection clearance is dependent on both humoral and cellular immunity. IL-8-mediated neutrophil response is the first response against RSV infection in the body, and correlates with disease severity. Viral clearance occurs by pulmonary $CD8^+$ T-cell response following systemic T-cell lymphopenia. B-cell-activating factors in the airway epithelium and interferon-gamma (IFN-γ) have a protective role.[94] Previous RSV infections do not appear to protect against reinfection.[95]

Humoral immunity reduces the severity of RSV infection, thereby making recurrent infections milder.[96] Higher transplacentally acquired RSV antibody titers are associated with milder symptoms restricted to the upper respiratory tract.[97] Lower antibody titers in cord blood are associated with increased risk of RSV hospitalization before 6 months of age.[98] RSV reaches the small bronchiolar epithelium from the nasopharynx, progressing to type 1 and 2 alveolar pneumocytes.[99,100]

Histopathologic findings of RSV are epithelial cell necrosis, bronchiolar epithelium proliferation, infiltration of monocytes, T-cells and neutrophils.[100,101] This leads to airway obstruction, air trapping and neutrophilia in bronchoalveolar lavage.[102] RSV is generally restricted to the respiratory epithelium, although it may be occasionally recovered from extrapulmonary tissues, such as the liver,[103] cerebrospinal fluid,[104] or pericardial fluid.[105] IL-8, IL-6, tumor necrosis factor (TNF)-α, and IL-1β can be detected in RSV-infected airways.[106–108] IL-6 levels correlate with severity of the disease. Chemokines in respiratory tract secretions include chemokine ligand (CCL) 3 (macrophage inflammatory protein-1 alpha [MIP1α]), CCL2 (monocyte chemoattractant protein-1 [MCP-1]), CCL11 (eotaxin),

and CCL5 (RANTES [regulated on activation, normal T cell expressed and secreted]),[109,110] but only the β-chemokines, especially MIP-1α, are associated with severe disease.[109–111]

Respiratory syncytial virus infections can lead to endoplasmic reticulum (ER) dysfunction or ER stress in airway cells resulting in the UPR response to restore homeostasis by activating three transmembrane ER stress sensors: activated transcription factor 6 (ATF6), PKR-like ER kinase (PERK) and inositol-requiring enzyme 1 (IRE1). UPR response switches from being pro-survival to being proapoptotic if homeostasis is not achieved. Manipulation of the UPR response is used by many viruses to promote their translation. ER stress activation by RSV has been demonstrated in primary human tracheobronchial epithelial (HTBE) cells and in the A549 cell line.[74]

Clinical Presentations

Neonates present with cough and fever. On examination, rhinitis and pharyngitis, congestion of conjunctivae and tympanic membranes, tachypnea, wheezing, nasal flaring, and retractions are seen. On auscultation of the lungs, prolonged expiration, rales, inspiratory rhonchi, decreased lung sounds, and excessive aeration in the lung periphery may be found.[112] Apnea may be the presenting symptom in one-fifth of the cases hospitalized with RSV.[113–118] One cause of reflex apnea may be altered sensitivity of laryngeal chemoreceptors.[119] In a systematic review, the incidence of apnea in hospitalized infants with RSV was found to be between 1.2 and 23.8%. The risk of apnea was <5% in children without serious underlying disease. Overall, the incidence was higher in preterm than in term neonates.[113]

Infants are most susceptible between the ages of 6 weeks and 6 months. Genetic predisposition of the host, co-infection with other pathogens, viral phenotype, and viral load affect disease severity.[120,121]

Respiratory syncytial virus causes severe LRT disease, including bronchiolitis, bronchospasm, and pneumonia.[122] Primary infection usually causes LRT disease, while it is seen in around 50% of secondary infections.[96,123] Disease severity reduces with subsequent infections.[124] RSV-associated wheezing is seen in 20% infants during the first year of life of which 2–3% require hospitalization.[28,123] Some infants who require assisted ventilation may develop inappropriate secretion of antidiuretic hormone, which results in hyponatremia.[125–127] However, in most cases, RSV infection is a self-limited process without any long-term pulmonary sequelae. A few cases may show decreased pulmonary function and chronic obstructive pulmonary disease persisting into adulthood.[128]

Laboratory Diagnosis

Laboratory diagnosis is required in severe or atypical bronchiolitis or to decide for palivizumab prophylaxis, infection control, and additional clinical/laboratory evaluation.[129] Complete blood count is not specific, with a mild increase in C-reactive protein (CRP). Chest X-ray shows hyperinflation with flattening of the diaphragm, infiltrations, atelectasis, and increased peribronchial shadows; helps to rule out other differentials.

Nasal lavage, nasopharyngeal swab, throat swab can be used. Nasal lavage and nasopharyngeal aspirate samples are more sensitive in detecting viruses. Bronchoalveolar lavage and tracheal aspirate sampling is required in intubated patients because of severe LRT infections. Samples are obtained 3–4 days after symptom onset, carried on wet ice, and kept at 2–8°C in a refrigerator. Processing should be done within 48 hours; in case of delay, samples should be kept at −80°C.[130] 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 LRT infections. 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 refrigerator, if they are to be studies within 48 hours. If the test will be delayed, they should be kept at −80°C.[130]

Reverse Transcriptase Polymerase Chain Reaction—Reverse transcriptase polymerase chain reaction (RT-PCR) gives rapid, reliable results with higher sensitivity compared with culture and rapid antigen tests and are not affected by passively administered antibody to RSV.[131,132] Drawbacks are high cost and the needs for maintenance of equipment and training of personnel.[133]

PCR-based assays typically are included as part of a multiplex PCR assay that can detect multiple respiratory pathogens.[134] Multiplex PCR-based assays are more expensive than rapid antigen diagnostic tests (RADT). They also usually have a longer turnaround time than RADT, but some commercially available PCR-based assays provide results in <3 hours.[135] In a prospective study, RSV was noted to be more prevalent in children with community-acquired pneumonia (CAP) than in asymptomatic controls (26.6 vs. 1.9%). Similarly, in a multicenter case-control study, RSV was isolated from 36% of 1–11-month-old infants and 17% of 1–4 year-old children who were hospitalized with severe pneumonia compared with 3% of asymptomatic controls.[122]

Serology—The cord RSV IgG antibody levels correlate with disease severity in the first 6 months. IgG antibodies transferred to the fetus during pregnancy decrease as time progresses reaching a nadir at the age of 2–3 months.

Serology has limitations as a diagnostic tool because seroconversion occurs in 2 weeks, and virus-specific antibodies cannot be detected in infants with RSV infections, and antibodies transmitted from the mother are also present. The direct fluorescence antibody test provides results in 2–3 hours with a sensitivity and specificity of about 95%, but it warrants expertise. Diagnostic serology is also not helpful in the evaluation and management of RSV infection because of maternal antibody in infants and a stable and sustained level of RSV-specific antibody in older children.[136]

Antigen Testing—Rapid antigen diagnostic tests provide results in the shortest time of less than 30 minutes. Sensitivity is 80% in children and specificity is 97%. Retesting may be required in patients with false-negative results.[132] The RADT can be used to screen and negative results can be confirmed with PCR.[137] It is less sensitive than PCR-based assays.[137] Palivizumab prophylaxis may interfere with RADT, leading to false-negative results.[131] In

a meta-analysis of 71 studies, the sensitivity of RADT was 80% and the specificity was 97%.[132]

Viral Culture—Viral cell culture is gold-standard in the diagnosis of RSV but results take around 3–7 days. Rapid cell culture (shell-vial) yields result in 48 hours compared with classic cell culture. Definitive diagnosis can be made by viral isolation from human epithelial type 2 (HEp-2) cells demonstrating characteristic plaque morphology with syncytium formation.

Treatment—Therapy for RSV infection of the LRT is mainly supportive, and preventive measures like good hygiene and isolation are the mainstay of management (Flowchart 2).[138,139] Supportive care includes monitoring of clinical status; fluids, paracetamol, and respiratory support as required. Inhaled bronchodilators, hypertonic saline, inhaled and systemic steroids are not proven to be effective. Mechanical ventilation may be required in patients with severe respiratory symptoms or apnea due to RSV.

Ribavirin—Ribavirin is a synthetic nucleoside analog with good *in vitro* activity against RSV and is approved by the US Food and Drug Administration (FDA) for the treatment of RSV infection. But it is not routinely recommended for infants and children with RSV LRT infection because its efficacy has not been proven.[140,141] It is expensive and must be given early in the course to be effective with concerns about occupational exposure.[140] It is contraindicated in pregnant females because of teratogenic risk. Adverse effects include hemolytic anemia, leukopenia, cough, bronchospasm, rash, and conjunctival irritation.[142–145] Studies in rodents have shown teratogenicity although the risk in human pregnancy is uncertain.[146] It is also associated with bronchoconstriction and warrants caution in asthma or chronic obstructive pulmonary disease.[142] National Institute of Occupational Safety and Health has recommended to reduce the ambient air concentrations of ribavirin and limit occupational exposure to hospital personnel.[147]

Randomized controlled trials comparing ribavirin with placebo in children with RSV LRTI are inconclusive with some reporting decreased severity of illness; decreased duration of mechanical ventilation, oxygen therapy, and hospital stay; and decreased viral shedding,[148–151] whereas others have reported no benefit.[152–154] A 2004 systematic review comparing ribavirin with placebo in infants and children with RSV LRTI found that trials of ribavirin lack sufficient power to provide reliable estimates of the effects.[140]

The American Academy of Pediatrics recommends against the routine use of ribavirin because of long-term aerosol application and hospitalization, intoxication potential (bone marrow inhibition, carcinogenicity), teratogenicity and high cost.[129,155] Ribavirin should be reserved for immunosuppressed patients with severe RSV infection, with opinion of an infectious disease's specialist being required before its use.

Palivizumab—Palivizumab is an RSV-specific humanized IgG1 monoclonal antibody against an epitope in the A antigenic part of the RSV F-glycoprotein, which is highly conserved among various isolates. It prevents viral replication by inhibiting its adherence to the respiratory epithelium.[156] It is produced by recombinant DNA technology and was

licensed in 1998 for the prevention of serious RSV LRT disease in high-risk children.[152] It is given intramuscularly at a dose of 15 mg/kg monthly for a total of five doses to maintain a serum concentration above 40 μg/mL in preterms with bronchopulmonary dysplasia (BPD).[157]

Palivizumab is administered intramuscularly and does not interfere with response to live virus vaccines.[153] Existing literature does not show any benefit of palivizumab in RSV bronchiolitis.[158, 159] Adverse reactions are manifested by fever, rash, and formation of antibodies. In a meta-analysis comparing palivizumab prophylaxis with placebo in BPD, preterm infants ≤35 weeks' gestation and congenital heart disease; palivizumab reduced RSV hospitalizations without increase in adverse events.[154] Palivizumab prophylaxis can be used for infants with BPD who are younger than 1 year of age at the start of RSV season,[143,160] or between the ages of 12–23 months in infants requiring medical management for BPD.[83,161] Recent AAP guidelines do not recommend pavlizumab prophylaxis for preterm infants born at 29–35 weeks without chronic lung disease, hemodynamically significant congenital heart disease and coexisting conditions. But healthy preterms born at more than 32 gestational weeks may also have increased RSV-associated hospitalization.

RSV-IVIG—Intravenous immune globulin with a high neutralizing activity against RSV (RSV-IVIG) is a hyperimmune polyclonal immunoglobulin obtained from donors with high RSV neutralizing antibodies and prevents integration of F and G RSV surface glycoproteins with host.[156] It has five-fold greater efficiency in neutralizing RSV as compared with IVIG. It was approved by the FDA in 1996 for reduced hospitalizations in high-risk infants.[162] It is no longer available because RCTs showed no benefit.[163] Other disadvantages are necessity for hospitalization, long-term infusion, fluid loading because of high-volume doses, sudden cyanotic episodes and necessity to avoid live-attenuated vaccines for at least nine months after treatment with RSV-IVIG.[164] Other monoclonal antibodies against RSV are still under research.[165]

Nirsevimab—Nirsevimab is a monoclonal antibody with a long half-life, high neutralizing activity. It targets the prefusion-conformation of the RSV F-glycoprotein. In a multi-center, placebo-controlled RCTs in healthy infants born at ≥29 weeks' gestation, a single injection of nirsevimab effectively prevented RSV LRT infections and hospitalization for 150 days.[165,166] It was recently approved for clinical use.[167]

Breastfeeding—Exclusive breastfeeding reduces hospitalizations, risk of respiratory failure, and the need for oxygen treatment in neonatal RSV infection, attributed to high levels of interferon (IFN)-gamma, cytokines, lactoferrin, and T-cells in human milk and its microbiota.[168]

Outcomes

RSV can lead to long-term sequelae such as wheezing and asthma, associated with increased healthcare costs and reduced quality of life. Transplacental transmission of RSV leads to

persistence of vertically transmitted virus in lungs postnatally, culminating in dysregulation of neurotrophic pathways and airway hyperreactivity.[85]

Prevention—Standard precautions, hand hygiene, breastfeeding, and contact isolation should be followed for RSV-infected newborns. The Centers for Disease Control and Prevention (CDC) recommends standard and contact precautions for the prevention of RSV.[169,170] Measures for healthcare providers include hand washing, appropriate use of gloves, surgical mask, eye protection, and disposable gowns.

In inpatient settings, infected patients should be isolated with standard and contact precautions in private rooms or cohorted in rooms with other RSV-infected patients.[169,171–173] During outbreaks, cohorting of healthcare personnels caring for RSV patients is also recommended. Healthcare personnel should have continued education about the symptoms, epidemiology, diagnosis, and transmission of RSV.

Vaccine Development

A new RSV vaccine, Arexvy, was recently approved in the US to prevent LRT disease caused by RSV in individuals 60 years of age and older.[174,175] Tests are needed in infants. Several other candidate vaccines are also being evaluated in clinical trials.[176] Live-attenuated vaccines, including molecular clones,[177–179] gene-based vector vaccines,[180] subunit vaccines,[181] or prefusion-conformations of RSV F-glycoproteins[182] are under evaluation. A variety of gene-based vector vaccines, nucleic acid vaccines, particle-based approaches, and novel adjuvants for candidate RSV vaccines are also in preclinical and early phase clinical development.[176] Challenges to development of an RSV vaccine for infants are immature immunity, suppression of immune response by maternal antibodies and antigenically divergent strains.[176,183,184]

Future Directions

We still need major, consolidated efforts to develop effective vaccines and monoclonal antibodies.

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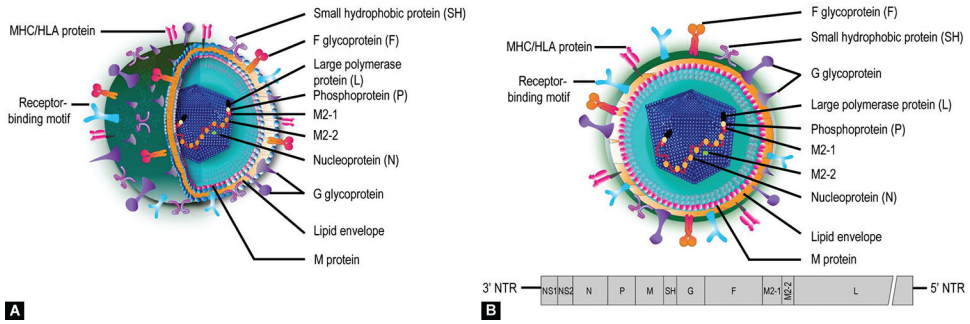
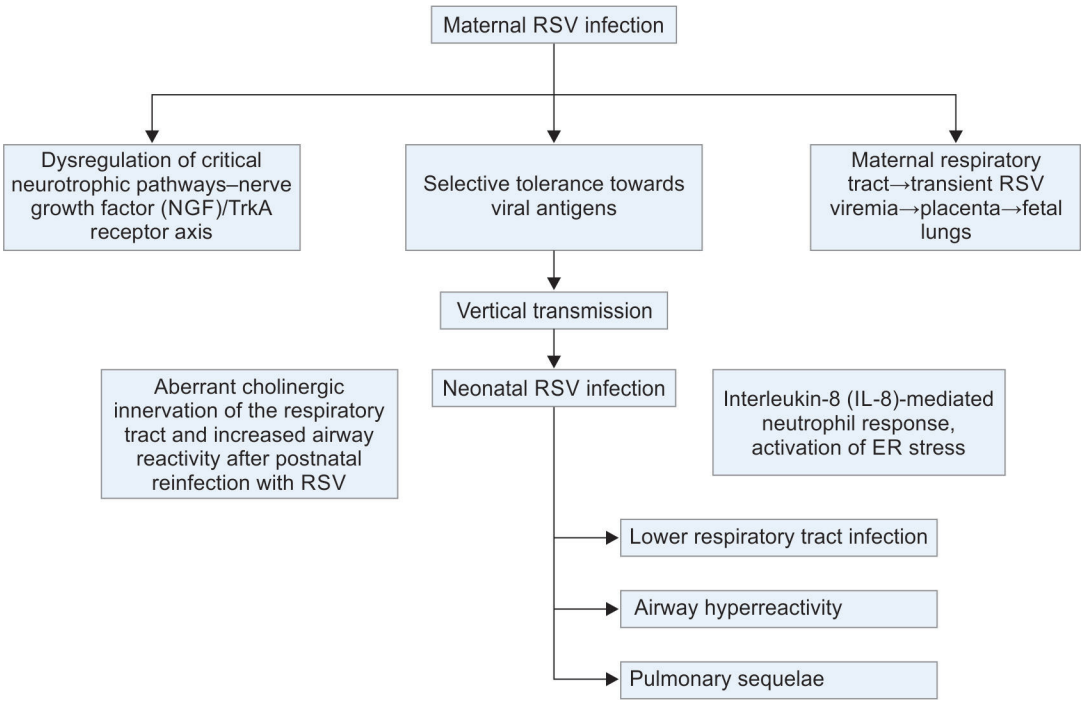
Keypoints

- Respiratory syncytial virus (RSV) is transmitted by nasal and oral secretions; the incubation period is 4–6-days.
- Seasonal outbreaks of RSV in the Northern Hemisphere occur from October to April, with a peak in January or February. In the Southern Hemisphere, epidemics occur during the May–September wintertime, peaking in May or June.
- A Risk Scoring Tool (RST) has been developed. It includes three risk factors: (a) birth between 3 months before and 2 months after the aforementioned season start dates; (b) presence of smokers in the household and/or maternal smoking whil pregnant; and (c) having young siblings in the family and/or daycare attendance to accurately and reliably predict RSV hospitalization.
- Vertical RSV infection is associated with dysregulation of critical neurotrophic pathways, including the nerve growth factor (NGF)/TrkA receptor axis during fetal development, which promotes aberrant cholinergic innervation of the respiratory tract and increases airway reactivity after postnatal reinfection with RSV.
- Rapid antigen diagnostic tests (RADT) provide results in less than 30 minutes, but these are less sensitive than PCR.
- The American Academy of Pediatrics does not recommend routine use of ribavirin because of the possibility of (a) long-term need for aerosols and hospitalization; (b) potential for intoxication (bone marrow suppression); and of (c) high costs.
- A new RSV vaccine was recently approved for use in adults, which has brought new excitement about the possibilities for testing in infants.

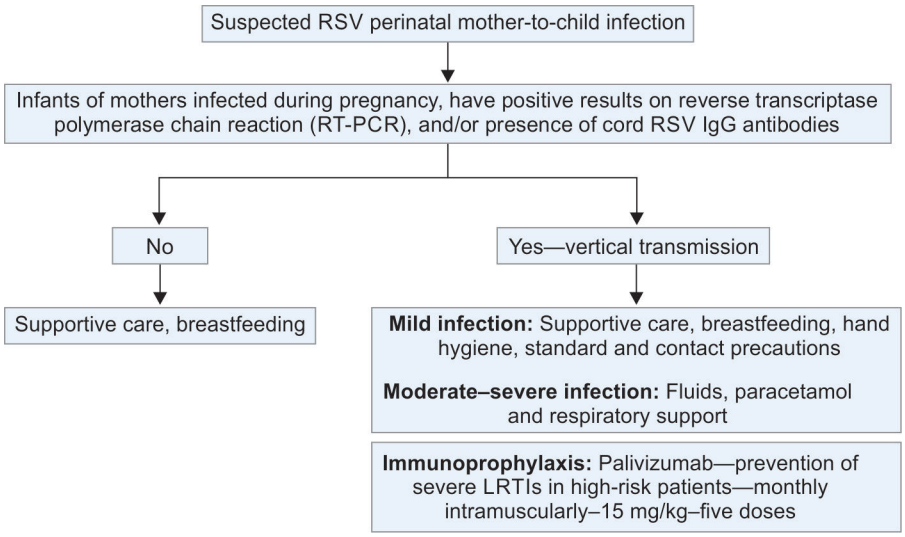


Figs 1A and B:

Schematic diagrams showing (A) Surface and side dissection; and (B) Cross-section of the respiratory syncytial virus



Flowchart 1:
Pathogenesis of perinatal RSV infection



Flowchart 2:
Management of perinatal RSV infections

Table 1:

Major structural components of RSV

Structure	Available information
Lipid envelope	The nucleocapsid is surrounded by a lipoprotein envelope derived from the nuclear membrane of the infected host cell.[61] The RSV virions are pleomorphic consisting of both irregular spherical shape with sizes of 150–300 nm and also filamentous forms of the virions that are 60–100 nm in diameter and up to 10 μm in length.[62]
Glycoproteins	Viral glycoprotein spikes are attached to the lipid envelope and bind specific host receptors to facilitate attachment and entry of the virus. There are three transmembrane surface glycoproteins. The attachment glycoprotein (G) and the fusion (F) glycoprotein control the initial phases of infection. G glycoprotein targets the ciliated cells of the airways, and F-glycoprotein facilitates fusion of the virion membrane and target cell membrane. The F protein is pertinent to antiviral drug development, and G and F-glycoproteins are targeted by neutralizing antibodies induced by infection.[63] 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.
Receptor-binding motifs	Receptor-binding motifs are involved in virion attachment to cell surface receptors. RSV attachment (G) glycoprotein targets CX3CR1 receptor on primary human airway epithelial (HAE) cultures. The G protein contains a CX3C motif which is critical for its role in infection of HAE cultures.[64]
Envelope protein	RSV has three envelope proteins, namely, the small hydrophobic protein (SH), G protein, and F protein. The G protein facilitates binding of RSV to target cells while the function of SH is not known. F protein mediates virus-to-cell and cell-to-cell fusion, resulting in syncytia formation, after which the virus is named.[65]
Membrane protein	The F gene encodes a type I integral membrane protein, which is synthesized as a 574 amino acid inactive precursor, F_0. Three F_0 monomers assemble into a trimer and, while passing through the Golgi apparatus, these monomers get activated by a host protease.[63]
MHC or HLA proteins	RSV infection of lung epithelium induces RIG-I expression, leading to induction of a class I MHC transactivator, NLRC5, and subsequent upregulation of MHC-I. Suppression of RIG-I induction leads to blockage of RSV-induced NLRC5 expression and MHC-I upregulation. Increased MHC-I expression may exacerbate RSV infection by immunopathologic damage.[66]
Spike protein	Specific receptor binding is achieved by the RSV F protein, a spike protein required for attachment to specific receptors and membrane fusion.[67]
Surface tubules	RSV exploits cytoskeletal components to complete its life cycle, such as actin, affecting its entry into the host cell, formation of cell-associated virus, virus escape, and exacerbation of the infection and syncytium formation. The cell membranes of the RSV-infected cells lost their characteristic shape and the cytoskeleton was reduced and elongated.[68]
Palisade layer	Either not expressed or relevance unclear fetal/infantile disease.
Viral tegument	Either not expressed or relevance unclear fetal/infantile disease.
Lateral bodies	Either not expressed or relevance unclear fetal/infantile disease.
Capsid	RSV has a capsid which forms viral particles and packages the viral genomic RNA, leading to the rapid assembly of nucleocapsid cores in the cytoplasm. The RNA nucleocapsid of RSV is enclosed in a bilayer lipid sphere and the genome is a single strand of RNA encoding for 10 viral proteins.[69] The RSV genome encodes 11 proteins and is tightly encapsidated with the nucleocapsid, consisting of the nucleocapsid (N) protein, RNA polymerase (L) and its cofactor phosphoprotein (P) and M2–1 protein. The genome also encodes the envelope glycoproteins fusion protein (F), glycoprotein (G) and small hydrophobic protein (SH), two non-structural proteins (NS1 and NS2), the M2–2 protein, and the matrix protein (M).
Capsomeres	The proteins that compose the structural unit of the capsid may form three-dimensional structures known as capsomeres that are visible in an electron micrograph.
Core membrane	Either not expressed or relevance unclear fetal/infantile disease.
Protein core	The non-structural proteins help with viral replication within the infected host cell. The structural proteins have three functional groups. The HRSV protein core forms a trimer-of-hairpins structure. The complex is a six-helix bundle in which the HR-N peptides form a three-stranded, central coiled coil, and the HR-C peptides pack in an antiparallel manner into hydrophobic grooves on the coiled-coil surface.[70]
Core fibrils	Either not expressed or relevance unclear fetal/infantile disease.
Matrix	The matrix consists of two membrane-associated proteins. The matrix (M) protein, a non-glycosylated phosphorylated protein located external to the nucleocapsid layer, acts as a bridge between the lipid bilayer envelope and the nucleocapsid. It drives the viral structural components to facilitate viral assembly. The RSV M also facilitates the transportation

Structure	Available information
	of newly synthesized ribonucleoprotein complexes (RNPs) to assembly sites, thereby leading to assembly at the cell surface. M protein associates with the RNPs to inhibit viral transcription and, thereby facilitating viral assembly.[71] The matrix protein (M) lays between the RNP and the envelope, acting as the cushion.[72]
Enzymes	The L protein contains a polymerase domain associated with a polyribonucleotidyl transferase domain in its N-terminus, and a methyltransferase (MTase) domain followed by the C-terminal domain (CTD) enriched in basic amino acids at its C-terminus. These enzymatic activities are essential for efficient viral mRNA translation into proteins, and to prevent the recognition of viral RNA by innate immunity.[73]
RNA elements	Transcription and replication of RSV genome generate RNA intermediates that constitute pathogen-associated molecular patterns (PAMPs), which are sensed by pattern recognition receptors (PRRs) to trigger the interferon (IFN)-mediated antiviral response and the expression of proinflammatory cytokines.[74] RSV participates in viral RNA synthesis by RNA synthesis RNP complex, comprising four proteins, the nucleoprotein (N), the large protein (L), the phosphoprotein (P), and the M2–1 protein.[72]
Nucleus	Either not expressed or relevance unclear fetal/infantile disease.
Nucleosome	Either not expressed or relevance unclear fetal/infantile disease.
DNA	No DNA genome exists.
RNA	Respiratory syncytial virus (RSV) is a negative-sense (−) nonsegmented RNA virus and its RNA synthesis occurs by viral gene transcription and genome replication. Gene transcription includes the positive-sense (+) viral mRNA synthesis, 5’-RNA capping and methylation, and 3’ end polyadenylation. Genome replication includes positive-sense RNA antigenome and negative-sense RNA genome synthesis.[72]
Genome-associated polyprotein	Each RSV gene encodes an mRNA with the 5’ methylated cap and 3’ polyA tail to be translated into a single corresponding protein, except the M2 gene, which has two slightly overlapped open reading frames (ORFs) encoding two proteins: M2–1 and M2–2. RSV initiates viral infection by a virus-specific RNA synthesis RNP required for replication of the full-length genome along with transcription of individual genes.[75]
DNA polymerase	Either not expressed or relevance unclear fetal/infantile disease.
RNA polymerase	Transcription by the RNA-dependent-RNA-polymerase composed of L and P proceeds directly from the negative-sense (3’-5’) genome through the production of capped/polyA monocistronic mRNAs.[74] RNA synthesis is carried out by the RNA-dependent RNA polymerase (RdRp) complex, which consists of the catalytic core L and the cofactor P. L is a 250 kDa polypeptide facilitating synthesis of viral genomic or antigenomic RNAs and mRNA. It also catalyzes ribonucleotide polymerization, mRNA 5’ cap addition and cap methylation.[72]
Reverse transcriptase	Either not expressed or relevance unclear fetal/infantile disease.
Head	Either not expressed or relevance unclear fetal/infantile disease.
Base plate	Either not expressed or relevance unclear fetal/infantile disease.
Integrase	Either not expressed or relevance unclear fetal/infantile disease.
Tail	Either not expressed or relevance unclear fetal/infantile disease.
Tail fiber	Either not expressed or relevance unclear fetal/infantile disease.
Neck	Either not expressed or relevance unclear fetal/infantile disease.