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RSV in transplant and immunocompromised patients

ABSTRACT

Respiratory syncytial virus (RSV) is a significant cause of morbidity and mortality in infants, older adults, and patients with weakened immune systems. Disease severity differs by underlying immunologic pathologies, with worse outcomes associated with progression from upper to lower respiratory disease. In this review we address the impact of RSV in immunocompromised populations, and discuss the limited available treatments and the potential impact of newer RSV prevention strategies on immunocompromised adults and children.

KEY POINTS

Prevention, detection, and treatment of select immunocompromised patients are the hallmarks of RSV management; ribavirin is the only drug approved by the US Food and Drug Administration for treatment of RSV.

Among immunocompromised populations, high risk allogeneic hematopoietic stem cell transplant recipients experience the greatest RSV-related morbidity and mortality.

For solid organ transplantation, adult and pediatric lung transplant recipients are the most affected by RSV; prevention and early treatment may aid in preserving longterm lung allograft function.

Nirsevimab, a long-acting monoclonal antibody, was approved for prevention of RSV lower respiratory tract infection in infants and young children; there is an urgent need for well-designed interventional studies with nirsevimab in high-risk children.

Strategies to prevent RSV infection in immunocompromised patients include hand hygiene, masking and inpatient contact/droplet precautions; vaccination may be an important new prevention tool.

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Respiratory syncytial virus (RSV) infection ranges from mild upper respiratory symptoms in healthy children and adults to severe lower respiratory tract bronchiolitis and pneumonia in infants and some immunocompromised hosts. The recent licensure of 2 RSV vaccines for older adults with risk for lower-tract disease and RSV-specific antibody therapies for at-risk infants provide a new landscape to consider preventive and treatment strategies for immunocompromised individuals at risk for significant RSV infection.

PATHOPHYSIOLOGY

RSV is a single-stranded RNA virus and member of the paramyxovirus family with tropism to the respiratory epithelium and type I pneumocytes. RSV uses virally encoded RNA polymerase to replicate its single-stranded RNA genome in the cytoplasm of infected cells. The G glycoprotein mediates viral attachment and the fusion (F) glycoprotein mediates viral penetration and syncytium formation. The F protein in its prefusion form is the major target of recently developed and approved vaccines.[1,2]

RSV is transmitted by contact with virus-containing secretions, or fomites, and self-inoculation of nasal or mucous membranes. It is spread most efficiently from children under age 5 and may be transmitted for 3 days before and 5 to 8 days after symptom onset.[3] Progression from the upper respiratory tract to the lower respiratory epithelium occurs over the course of days and may be more rapid in immunocompromised patients.

During productive infection, virus can be shed for weeks in those with immune impairments,[4] but viral load and duration of shedding do not correlate with disease severity. Postinfection immunoprotection is incomplete and short-lived, mostly due to waning antibodies rather than viral diversification.[5] Thus, reinfections occur in up to 75% of individuals within 2 years, and repeated infections can be expected

through one's lifetime.[6] Of importance to the immunocompromised, the initial cytopathology of lower airway infection can impact mucociliary clearance, increasing the risk for postviral bacterial or fungal infection.[7]

Immunologic control of RSV is mediated primarily by the humoral and T-cell-mediated components of the immune system.[5] Recruitment of the innate immune response occurs early but requires coordinated adaptation to effectively resolve infection and to dampen neutrophil-mediated inflammation. This process is facilitated by gamma-interferon and a growing number of functional virus-specific CD8 T cells that mediate viral clearance. Emergence of RSV-specific nasal immunoglobulin (Ig)A, serum IgG, and serum-neutralizing titers is associated with protection against natural reinfection. The neutrophilic infiltrates in the lower airways during severe disease appear to be more a sign of an immunopathogenic response than key to viral clearance or protection.[8]

Ribavirin is the only drug approved by the US Food and Drug Administration (FDA) for the treatment of RSV. It inhibits viral polymerase and host enzymes that deplete the guanosine triphosphate pool required for viral growth. It is shown to reduce cytopathic effects in infected cells in vitro but has limited effects on established RSV disease. Ribavirin is available in aerosolized and oral formulations in the United States, with the oral formulation now favored in most settings. Other investigative antivirals are in the pipeline. Antibody preparations (intravenous IG [IVIg], palivizumab, nirsevimab) and corticosteroids may act as prophylactic or adjunctive therapies with some potential benefit based on patient type.

IMMUNOCOMPROMISED INFANTS AND CHILDREN

Children with immunocompromising conditions are among those at highest risk for hospitalization for RSV. The first report of the effects of RSV in immunocompromised children was published in 1986.[9] Immunocompromised children were more likely than immunologically competent children to acquire nosocomial RSV, develop lower respiratory tract infections (RTIs), require intensive care, and experience prolonged viral shedding.[4] Subsequent studies demonstrated great variability in outcomes for immunocompromised children.[10]

Primary immunodeficiencies in children

Primary immunodeficiency diseases, a group of more than 400 inherited genetic disorders, differentially affect the immune system and manifest clinically as recurrent infections in children. Children with defects in innate immunity, phagocytosis, combined immunodeficiencies, and low CD4+ and CD8+ subsets are most affected.[11,12] Of those hospitalized in a trial in Spain, 30% required admission to the pediatric intensive care unit, 69% required supplemental oxygen, and 31% needed mechanical ventilation.[12] Similarly, in a Japanese report, RSV accounted for 27% of 54 children with primary immunodeficiency diseases admitted with respiratory virus infections (RVIs); the median age was 2 years and most had combined immunodeficiency syndromes.[13] All patients developed lower RTI, and 20% (3 of 15) required intubation. In both studies, prolonged hospitalizations and coinfections were common with organisms such as *Haemophilus influenzae*, *Staphylococcus aureus*, *Klebsiella*, *Pneumocystis jiroveci* pneumonia, cytomegalovirus, and other RVIs. In both studies, no children died of RSV, though 1 with a dendritic cell disorder and myelodysplastic syndrome died of macrophage activation syndrome possibly triggered by RSV.

HIV: Increased risk for infection

Children infected with human immunodeficiency virus (HIV) or exposed to HIV in utero are at increased risk for infection. Recent research of children from South Africa under 5 years who tested positive for RVIs found that exposure to HIV and HIV infection were associated with increased risk for RSV-associated hospitalization with a relative risk of 1.4 (95% CI 1.3–1.6) and 3.8 (95% CI 3.1–4.8), respectively.[14] Recent data from Kenya demonstrated that the risk of RSV in pregnant women with HIV was twice that of pregnant women without HIV, increasing the risk of morbidity and mortality in mothers and their infants.[15]

Pediatric cancer and HSCT

The incidence of RSV in pediatric hematopoietic stem cell transplant (HSCT) patients ranges from 1% to 17%. The median age of onset is 5 to 7 years and mortality is 5% or less. The largest retrospective multicenter cohort of pediatric RVIs in HSCT reported on 259 children with an RVI; of these, 40 (1.5%) were RSV.[16] Nosocomial transmissions and prolonged viral shedding of more than 200 days are common in this population.[4] The rate of progression in pediatrics is not well established but is associated with adverse outcomes. Children do not adhere as closely to the risk factors elucidated for adults (**Table 1**). St. Jude

TABLE 1
Risk stratification of HSCT recipients for progression from upper to lower RTI: MD Anderson Cancer Center Immunodeficiency Scoring Index

Risk factor at RSV diagnosis	Hazard ratio for progression	Score[a]
Absolute neutrophil count < 500/μL	4.1 (1.4–11.6)	3
Absolute lymphocyte count < 200/μL	2.6 (1.0–6.4)	3
Age > 40 years	2.5 (1.1–5.6)	2
Myeloablative conditioning	1.2 (0.6–2.3)	1
Graft-versus-host disease	1.0 (0.5–2.2)	1
Corticosteroids within 30 days (> 20 mg prednisone)	0.89 (0.4–1.8)	1
Allogeneic HSCT within 30 days (or pre-engraftment)	0.68 (0.2–2.3)	1

[a]Maximum score = 12: Low risk: 0–2, moderate risk 3–6, high risk 7–12

HSCT = hematopoietic stem cell transplant; RSV = respiratory syncytial virus; RTI = respiratory tract infection

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Children's Research Hospital described absolute lymphocyte counts of less than 100 μL and age of 2 years or younger as predictors of lower RTI.[17] Data from a 10-year retrospective study at the University of Texas MD Anderson Cancer Center described RSV predominantly in patients with hematologic malignancies (mainly acute lymphocytic leukemia) and in allogeneic HSCT.[18] No risk factors were identified for progression to lower RTI. Another 6-year study of 450 children from Cincinnati Children's Hospital reported 37 episodes of RSV with 19% being lower RTIs. Coinfections were frequent and significantly associated with lower RTI.[19]

Solid organ transplant in children: Limited data for RSV

Data for RSV in children with solid organ transplants are limited. Like adults, pediatric lung transplant recipients are the most affected with RSV, comprising 6% to 12% of all RVIs. Of 6,980 pediatric solid organ transplant recipients in the largest reported study, 129 (1.8%) were hospitalized due to RSV.[20] The rate of hospitalization for RSV in the first post-transplant year in a recent study was 6 times higher than that of normal children younger than 5 years, and the mortality rate was 53 times greater than that of the general population. Hospitalization was associated with age younger than 2 years and receipt of heart, lung, intestine, or multivisceral transplants. These children experienced longer and more costly length of stay than the general population with RSV.[20] Clinical presentations for nonlung transplant recipients are generally milder, although factors such as use of lymphocyte-depleting agents, hypogammaglobulinemia, time after transplantation, and young age may affect disease severity.[21,22]

RSV in immunocompromised children: Individualized treatment

Supportive care is the mainstay of treatment for RSV in pediatric immunocompetent as well as immunocompromised populations. There are no randomized controlled trials with enough power to establish the efficacy of inhaled or oral ribavirin in treating any pediatric immunocompromised group, including HSCT recipients with lower RTI, or in preventing the progression from upper to lower RTI. Moreover, there are reports of favorable outcomes without the use of ribavirin in hospitalized children with RSV after HSCT. All guidance is based on retrospective studies or meta-analyses and concludes that the routine use of ribavirin in this population cannot be recommended and should be individualized.[19,23] Antiviral treatment approaches therefore vary by center and provider.[24]

Prevention in pediatric patients

Table 2 highlights typical and potential infection prevention strategies for those at risk for RSV.[25–27] Nosocomial infections are common in immunocompromised children, with significant morbidity and mortality.[28] It is estimated that 1 infected child with RSV can generate up to 9 secondary infections, illustrating the high transmissibility of this virus.[28] Infection control measures are the first line of defense against RSV acquisition. Strict adherence to standard and contact and droplet precautions, hand hygiene, and screening of visitors for respiratory illnesses are the cornerstones of prevention in the hospital setting.[29] Importantly, immunocompromised children often require longer periods of isolation due to prolonged viral shedding.[30]

In July 2023, the FDA approved a long-acting monoclonal antibody, nirsevimab, for prevention of RSV lower RTI in infants and children under 24 months of age. The Advisory Committee on Immu-

TABLE 2
Prevention tools for RSV in at-risk immunocompromised patients

	Indication	Method	Efficacy	Cost
Contact	All adult and pediatric immunocompromised patients at risk for RSV	Wash hands Avoid touching face with unclean hands Avoid close contact with others (eg, sharing cups or utensils, handshaking, kissing) Clean frequently touched surfaces	Unknown; during SARS-CoV-2 pandemic, masking and social distancing reduced RSV to 0% until March 2021[25]	Unknown
Isolation	Hospitalized adult and pediatric patients with RSV	Standard and contact and droplet precautions[29] Eyewear for close contact or procedures	Variable: 30% to 50% reduction in transmission in studies[26]	More than $150 per patient per day[27]
Vaccination	Adult patients over age 60, including those with immunocompromising condition	Intramuscular in deltoid region with 1–1.5-inch needle	Not studied, immunocompromised adults not included in trials	$336–$354 per dose
Passive antibody				
Nirsevimab	Children under 8 months during first RSV season; children 8–19 months at risk for second RSV season, including immunocompromised children	Intramuscular	Not studied; preliminary data of 90% efficacy included only 1 RSV infection in immunocompromised patient	Approximately $495 per dose
Palivizumab	Consider in immunocompromised children younger than 24 months	Intramuscular once a month during RSV season up to 5 doses	Limited evidence for support	Up to $15,000 per RSV season

RSV = respiratory syncytial virus

nization Practices (ACIP) recommended that all infants under 8 months of age receive nirsevimab during their first RSV season and that children age 8 to 19 months with risk factors for RSV disease (including severe immunocompromise) receive nirsevimab during their second RSV season. Early reports from the New Vaccine Surveillance Network show 90% protection against RSV hospitalization during part of the RSV season (October 2023 to February 2024) with nirsevimab.[31] Only 1 child in this report was categorized as severely immunocompromised. A more recent French multicenter prospective case control study found an estimated efficacy of 83% in preventing hospitalization.[32] This study did not include immunocompromised children. Prior to the availability of nirsevimab, palivizumab was endorsed by the American Academy of Pediatrics for use in immunocompromised children younger than 2 years, including those with cancer, solid organ transplant, and HSCT, during the RSV season.[30] A recent systematic review, however, found insufficient evidence to support this intervention to prevent severe RSV in this population.[33] Well-designed interventional studies with nirsevimab in high-risk children are urgently needed.

RSV AND IMMUNOCOMPROMISED ADULTS

RSV is among the most common RVI in adult recipients of single-organ transplants or HSCTs; the incidence, 1.5% to 12%, varies by season, local outbreaks, and detection strategies.[34]

Disease severity differs by underlying immunologic

and pulmonary pathologies. Allogeneic HSCT and lung transplant recipients experience the greatest RSV-related morbidity and mortality. This is likely due to the allogeneic mismatch between virus-infected cells and immune effectors that both impair progressive viral control and enhance pathologic inflammation in airway tissue.[35] Most autologous HSCT and nonpulmonary solid organ transplant recipients experience less severe disease but may still require hospitalization for lower respiratory tract symptoms.[36]

Frequency and degree of infection are less well described for other immunocompromised groups. Of adult patients with RSV who presented to clinical care in 2 hospital systems in Switzerland over a 10-year period, 7.4% were in immunocompromised groups. Of 175 adults, most were HSCT (33.7%) or solid organ transplant (33.1%) recipients, with the remainder divided evenly among other immunocompromising conditions, including leukemia/lymphoma, solid tumor, and chronic immunosuppressive therapies for rheumatologic conditions (mostly vasculitis).[10] A quarter of those with other immunocompromising conditions were hospitalized for RSV. Disease severity was associated with older age, chronic immunosuppression for rheumatologic conditions, and solid tumors. Use of corticosteroids, but not tumor necrosis factor-alpha inhibitors, may increase complications of RSV in patients with inflammatory bowel disease.[37]

With the growing body of immunomodulating therapies to treat inflammatory syndromes and malignancies, risk groups may emerge that are not entirely predictable. Notably, patients with adoptive cellular therapies and cellular therapies for malignancy share some risk factors for RSV lower RTI with allogeneic HSCT. However, high incidence of RSV infections has not been observed either in clinical trials of these agents or yet been reported in the clinical literature.[38]

Adult recipients of HSCT: Scoring systems to assess risk

Among HSCT recipients, 2% to 30% are diagnosed with RSV infection, with the greatest disease burden among allogeneic or cord blood transplants.[35,39,40] Mortality rates overall average about 25% to 30% and depend in part on disease at presentation, risk factors, and adequate treatment.

Risk factors for the progression of RSV from upper to lower RTI and mortality in HSCT have been delineated, and scoring systems are now adopted by most transplant centers to stratify the risk. In addition to prognostication, such scores help determine who may benefit from antiviral therapies. **Table 1** characterizes the immunodeficiency scoring index put forth by the University of Texas MD Anderson Cancer Center.[41] The risk criteria mirror the defects in what would ordinarily lead to an effective response to RSV infection, with impairments in effective antigen presentation to an immature, depleted, or impaired allogeneic T-cell population. The severe immunodeficiency scoring system from the University of Basel includes low serum IgG (< 650 mg/dL) as a marker of ineffective helper T-cell function or B-cell depletion and may underscore diminished RSV-specific antibody, important to protection from repeat infection.[7]

Treatment of RSV in HSCT has the clearest benefit in patients with upper RTI at high risk for progression to severe lower RTI. Based on an analysis of mostly retrospective data, early use of any ribavirin formulation appears to reduce the progression of upper to lower RTI and reduce mortality compared to no therapy in at-risk HSCT populations.[42] Randomized or controlled trials establishing the efficacy of oral ribavirin are lacking, but it is generally considered a safer, more pragmatic, and affordable alternative than aerosolized ribavirin. Ribavirin of any kind has no proven efficacy in treating disease that has progressed to severe lower RTI.[41,42] Data are mixed on the addition of antibody preparations like IVIg to ribavirin therapy, but such immunomodulator therapy may provide additional benefit.[42]

Adult lung transplant recipients: Few die of RSV infection

RSV incidence in lung transplantation occurs during seasonal community outbreaks and is spread over the post-transplant course.[35,43] RSV infection can be asymptomatic but typically presents with rhinitis, cough, and, in more than 80% of patients, worsening home spirometry.[44] In studies that include prospective nasopharyngeal screening in lung transplant recipients using molecular assays, RSV is most often symptomatic and progresses to lower tract disease.[45,46] Lower airway involvement may be tracheobronchial or parenchymal with either normal imaging results or interstitial tree-in-bud or alveolar "ground glass" infiltrates.[46] Patients may improve clinically without directed therapy, and few lung transplant recipients die directly of RSV infection.[43–46]

As with other RVIs, symptomatic RSV can cause direct pulmonary cytopathic effects in lung transplant recipients and both immediate and long-term effects on allograft function.[35] Lower respiratory RVIs, including RSV, are associated with chronic allograft

dysfunction (CLAD), evident in a third of patients over months following infection.[47] CLAD is the leading cause of allograft loss and mortality after the first year post transplant. Thus, strategies to prevent RSV infection and the progression of infection to the lower airway are important to preserving allograft function and increasing survival post transplant.

Although no randomized trials demonstrate efficacy of ribavirin in lung transplant recipients, retrospective data appear to demonstrate earlier graft recovery and reduction in CLAD at 6 months.[44] Not all lung transplant programs treat RSV infection when confined to the upper respiratory tract.[24] Treatment of symptomatic upper or lower tract RSV in the setting of lung transplant varies by program but usually includes oral or nebulized ribavirin with or without IVIg. Use of concurrent corticosteroids to ameliorate acute inflammation and the alloimmunity associated with later CLAD may also be employed.[44,48,49]

RSV prevention in adults

Prevention of RSV in immunocompromised at-risk adults has traditionally involved minimizing exposure during seasonal outbreaks. Recommended first-line infection control measures are similar to those advised for children (**Table 2**).

Vaccination is a promising prevention strategy for targeted immunocompromised populations, but the pivotal trials leading to recent vaccine approvals excluded these groups. The data demonstrated significant efficacy for both vaccines at preventing lower tract symptoms in adults over age 60, but the number of RSV infections in the 2021–2022 study periods was low for both the vaccine (11 in 17,215 and 7 in 12,467) and placebo (33 in 17,069 and 40 in 12,449) arms.[1,2] The number needed to vaccinate to prevent both symptomatic lower RTI and severe outcomes was high but may differ in periods of high community prevalence and with patients at highest risk of severe disease. The vaccine is licensed for those 60 and older with high-risk conditions, so observational clinical outcome data in immunocompromised groups in that age range are likely forthcoming.

Given the known effects of compromised immunity on vaccine immunogenicity, optimizing vaccine dosing for these groups is likely to be important.[50] A phase 2b randomized controlled study to compare the immune response and safety of 1 or 2 RSV prefusion F vaccines in adult lung and kidney transplant recipients is underway (NCT05921903). As with the SARS-CoV-2 vaccine, demonstrating RSV-specific vaccine antibody response and clinical efficacy will be paramount, particularly for vaccine-hesitant patients.[51,52]

If data indicate that vaccine immunity is insufficient protection in immunocompromised adult populations (eg, allogeneic HSCT with high Immunodeficiency Scoring Index values or lung transplant recipients with high exposure risk) during RSV season, there may be a role for immunoprophylaxis. Immunoprophylaxis with RSV-specific antibody preparations has long been of interest. RSV-IVIg was removed from the market, and pavilizumab is not approved for use, affordable, or effective at preventing disease in adults.[53] Nirsevimab, a monoclonal antibody targeting the prefusion F protein, was approved in 2023 for use in neonates and high-risk infants during RSV season. Studies are warranted to demonstrate its safety and efficacy at preventing RSV transmission in outbreak situations for the highest-risk immunocompromised patients.

FUTURE DIRECTIONS

Prevention, detection, and treatment of early infection are the hallmarks of RSV management. RSV infection is associated with significant morbidity and mortality in a subset of immunocompromised populations. Unfortunately, ribavirin is a relatively weak antiviral, has unproven benefit in children, and does not reverse the effects of advanced RSV lower RTI in some of the highest-risk adult patients. The vaccines and monoclonal antibody targeting the RSV prefusion F protein approved by the FDA in 2023 have not yet been studied in these populations. However, they could provide important immunologic protection, highlighting the urgent need for clinical outcome studies in these high-risk patients.

DISCLOSURES

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