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National Perinatal Association 2018 Respiratory Syncytial Virus (RSV) Prevention Clinical Practice Guideline: An Evidence-Based Interdisciplinary Collaboration

PEER REVIEWED

By Mitchell Goldstein, MD; Raylene Phillips, MD; John P. DeVincenzo, MD; Leonard R. Krilov, MD; T. Allen Merritt, MD; Ram Yogev, MD; Suzanne Staebler, DNP, APRN, NNP-BC, FAANP, FAAN; Munaf Kadri, MD; Jaimie E. Fergie, MD; Michael S. Schechter, MD, MPH; Millicent Gorham, PhD, MBA, FAAN; James D. Cherry, MD, MSc

Background

Respiratory Syncytial Virus (RSV) is a virus that typically causes mild, cold-like symptoms in adults, children and most term infants. In premature and “at-risk” infants, as well as the elderly, RSV can cause severe disease, and is a very serious health concern. RSV is a leading cause of worldwide morbidity, and mortality in children less than five years of age and causes approximately 3.4 million hospitalizations and greater than 66,000 deaths per year in this group.¹ Although 99% of these deaths occur in developing countries, of all infectious diseases affecting children worldwide, only malaria is more deadly.²

A number of different strategies have been studied to reduce the risk from RSV. Although efforts to reduce droplet transmission, good handwashing, and avoidance of known infected patients have been found to be effective, palivizumab is currently the only FDA-approved biologic for RSV prophylaxis. There is a high level of evidence that RSV prophylaxis is effective. The best data available at this time supports the practice of continuing to insure access of RSV prophylaxis for neonatal and pediatric patients at greatest risk.³⁻⁶ Over the course of the past several years, the proportion of infants eligible for RSV prophylaxis who have actually received it has decreased, as providers and insurers have increasingly followed guidelines and policies that are not in compliance with Food and Drug Administration (FDA) indication resulting in needless morbidity and increased hospitalization.^{7, 8} Most babies at risk for RSV are now deemed ineligible for prophylaxis by such guidelines and policies.⁹⁻¹¹ Parent groups, concerned about this trend, have published recommendations for obtaining

FDA-approved coverage for RSV prophylaxis using techniques such as appeals, letter-writing campaigns and political activism. A number of examples are documented on the “preemiebabies101” website <http://www.preemiebabies101.com/2014/08/12-tips-getting-synagis-injections-approved/>, as well as the “Hand to Hold” website <http://handtohold.org/resources/helpful-articles/rsv-101-what-every-nicu-parent-needs-to-know/>. The continued need to appeal what should be covered by FDA indication, delays in the appeals process, and complete denials have all contributed to delays in the administration of immunization to babies at risk resulting in irregular, sub-optimal dosing regimens and a reduction of palivizumab levels necessary to prevent illness. This leads to increased hospital admission as well as increased morbidity.^{8, 12}

Provider confusion is a serious concern. Although there is no substitute for clinical judgement, recommendations on dosing and

“Over the course of the last several years, the proportion of infants eligible for RSV prophylaxis who have actually received palivizumab has decreased as providers and insurers have increasingly followed guidelines that are not in compliance with the Food and Drug Administration indication resulting in needless morbidity and increased hospitalization.”

timing should be issued in a manner consistent with the broadest FDA indication for dosing to accommodate provider discretion.⁷ Guidelines do not apply in every condition and for every case. Variation from the guideline is still acceptable practice; however these guidelines should never deny access. A policy that mandates attenuated palivizumab administration is not reasonable when that policy countermands the FDA indication. The indication provides the most clarity in preventing use of a pharmaceutical product outside of its carefully studied parameters. Following FDA indication is important from a medico-legal perspective as insurers should use the FDA indication to guide remuneration without a *proviso* for denials due to consensus guidance that deviates from the FDA indication. Major deviation from the established FDA indication and insurance reimbursement based on policy statements created from consensus guidance contributes to much confusion for providers as well as parents, may also lead to provider disenfranchisement, and lack of universal acceptance of a standard of practice (<http://www.infanthealth.org/rsv>). This is unfortunate. Despite clear Medicaid regulation, State Medicaid formularies have not met all of the requirements of section 1927(d)(4)(C) of the Social Security Act, since they exclude treatment with an approved therapy despite clear FDA indication. Palivizumab meets all the criteria (significant and clinically meaningful therapeutic advantage, safety profile and effectiveness in clinical outcomes) necessary for coverage by Medicaid programs via the "medically acceptable indication" criteria. The ramifications of a policy for reduced dosing is concerning, as it not only restricts access, but it causes state Medicaid programs to violate their legislative mandate. Under the legal doctrine of "loss of chance," practitioners assume legal liability for not offering and advocating for the use of the only approved pharmaceutical for a specific approved indication.¹³

Of particular public concern has been a de-emphasis on the best available evidence and a focus on adjudicated studies to generate selective expert opinion. Regimens with fewer doses than FDA indication have not been tested in a randomized clinical trial (RCT). Use of an abbreviated dosing schedule for immunoprophylaxis of RSV, in an effort to ration therapy and reduce costs, is contrary to published evidence and the FDA-approved product indication for palivizumab.¹⁴ Not dosing according to indication (under dosing) is considered an "off label" use of a medication.¹⁵ Although cost effectiveness is increasingly important, decisions regarding appropriate RSV prophylaxis must be based on the evidence.¹⁶⁻¹⁹ Denial of full coverage based on gestational age, without consideration of other risk factors, discriminates against certain populations of premature infants and may put certain populations at even greater risk due to health disparities.^{20, 21} Making RSV a reportable disease may be important in documenting the actual extent of RSV prevalence and costs.²⁰ To date, despite widespread efforts to protect infants according to the FDA indications, further restrictions on the use of palivizumab have made prophylaxis potentially unavailable for as many as 75% of the infants in whom it is clearly indicated by FDA guidance.^{7, 22}

Even in high-risk infants from 32-35 wGA (weeks' gestational age), RSV can result in serious morbidities. In one study, Ambrose, et al., evaluated 1,642 subjects across a multitude of outpatient clinics in 38 states and the District of Columbia. In two RSV seasons (2009-2011), ED visits, outpatient respiratory infection, and other clinical factors that place babies at-risk for RSV disease were evaluated. Of the preterm infants 32-35 wGA who were <6 months on November 1st, 4.9% were hospitalized with RSV-related illnesses each season. Pre-school aged siblings and daycare attendance increased the risk of RSV disease. Among the subset of 32-34 wGA infants eligible under a risk-related criteria, the RSV-related hospitalization rate was 9.1%.^{12, 23} A study by Blanken, et al., supports the original evidence presented in the IMPact RSV trial. Palivizumab decreased RSV-related hospitalization in 33-35 wGA infants by 82%, whereas the original IMPact study described a 78% decrease.^{11, 24} A Cochrane review using data from a number of randomized controlled trials found high quality evidence to support the association of palivizumab and reduction in RSV-related hospitalization (RR 0.49, 95% CI 0.37-0.64) as well as high quality evidence to

support an association of palivizumab and reduction in RSV ICU admissions (RR 0.5, 95% CI 0.3-0.81).^{11, 25-27}

Confounding by indication limits the effectiveness of well-designed randomized control studies designed to study the efficacy of palivizumab. Farber et al., described a 38% lower rate of hospitalization for RSV in infants born at 29 to 32 wGA, with ≥ 1 insurance claim for palivizumab.²⁸ However, this group received <50% of the indicated doses. Studies that are retrospective, nonrandomized, and with confounding of the indication should not supersede the data from carefully designed randomized trials.²⁹

Winterstein, et al., evaluated 247,566 patients in Florida and Texas to determine the age at which at-risk infants born from 32-34 wGA experienced a risk of developing RSV equivalent to that of term babies. At one month of age, these babies had a risk of being hospitalized comparable to that of term babies. The RSV-related hospitalization rate of these preterm infants was 3.1% in Florida and 4.5% in Texas. Incomplete coding and testing for RSV was a consistent issue. Increased prematurity was associated with a higher risk for hospitalization, and the issues pertaining to disparity could not be separately identified in the populations studied.³⁰ In another at-risk population in Florida, Winterstein, et al., demonstrated that palivizumab prophylaxis was associated with a reduction in severe RSV infection.³¹ Analysis of the Kids' Inpatient Database of hospitalizations between 2000-2009 (n=325,494) showed that while, overall, the bronchiolitis-related hospitalizations were decreased by 17% among all children less than two years of age, bronchiolitis hospitalizations actually increased by 29% in the sub-group in which there was an FDA indication for palivizumab prophylaxis.^{10, 32}

In a study conducted by Hall, et al., RSV-related hospitalizations among preterm and term infants were evaluated in three United States counties. RSV acute respiratory illnesses were tallied and relative risk was identified by age from birth certificate data. This study has been used as justification for reduced immunoprophylaxis, yet the study included an insufficient number of premature infants to justify generalizing the results to this population. Premature infants represented only 10% of the 2,140 subjects studied. RSV rates in this study were not found to be significantly different between preterm and term infants, an expected result since 70% of the palivizumab-eligible patients in the study populations had received palivizumab (supporting the efficacy of palivizumab in decreasing the rate of RSV infection in preterm infants to be closer to that of term infants). Black infants greater than or equal to 6 months of age were hospitalized more often, documenting ethnic disparities in RSV-related health risks.²¹ Previous studies such as that by Boyce, et al., had identified a two-fold higher hospitalization rate for preterm infants.³³ This higher rate of hospitalization might be expected to drop, if adequate compliance to RSV prophylaxis could be assured.³⁴

Since 2014, more restrictive control over the prescription of palivizumab has resulted in increased morbidity. Zuccotti, et al., demonstrated worse outcomes in the 29-32 wGA group who did not receive prophylaxis as well as increased costs of hospitalization.⁽³⁵⁾ In another study, Capizzi, et al., found a high proportion of admission for the <36 wGA infants, the great majority born at 33 to <36 wGA and a chronological age of <6 months. Of those admitted, a high proportion of preterms were treated with high flow nasal cannula ventilation delivering continuous positive airway pressure. These results suggest the need to re-evaluate the role of prophylaxis in infants up to 36 wGA.³⁶ In a multicenter test case negative control study, palivizumab efficiency for preventing Intensive Care Unit (ICU) admission of infants 29-35 wGA and ≤ 6 months of chronologic age (without chronic lung disease of prematurity or Congenital Heart Disease) was 74% (95% CI 56%-85%).³⁷

SENTINEL1 evaluated 29-35 wGA <12 months old infants hospitalized for confirmed RSV disease who had not received

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Indication

INOMAX is indicated to improve oxygenation and reduce the need for extracorporeal membrane oxygenation in term and near-term (>34 weeks gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension in conjunction with ventilatory support and other appropriate agents.

Important Safety Information

- INOMAX is contraindicated in the treatment of neonates dependent on right-to-left shunting of blood.
- Abrupt discontinuation of INOMAX may lead to increasing pulmonary artery pressure and worsening oxygenation.
- Methemoglobinemia and NO₂ levels are dose dependent. Nitric oxide donor compounds may have an additive effect with INOMAX on the risk of developing methemoglobinemia. Nitrogen dioxide may cause airway inflammation and damage to lung tissues.
- In patients with pre-existing left ventricular dysfunction, INOMAX may increase pulmonary capillary wedge pressure leading to pulmonary edema.
- Monitor for PaO₂, inspired NO₂, and methemoglobin during INOMAX administration.
- INOMAX must be administered using a calibrated INOMax DS_{IR}® Nitric Oxide Delivery System operated by trained personnel. Only validated ventilator systems should be used in conjunction with INOMAX.

Please see Brief Summary of Prescribing Information on adjacent page.

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INOMax® (nitric oxide gas)

Brief Summary of Prescribing Information

INDICATIONS AND USAGE

Treatment of Hypoxic Respiratory Failure

INOMax® is indicated to improve oxygenation and reduce the need for extracorporeal membrane oxygenation in term and near-term (>34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension in conjunction with ventilator support and other appropriate agents.

CONTRAINDICATIONS

INOMax is contraindicated in neonates dependent on right-to-left shunting of blood.

WARNINGS AND PRECAUTIONS

Rebound Pulmonary Hypertension Syndrome following Abrupt Discontinuation

Wean from INOMax. Abrupt discontinuation of INOMax may lead to worsening oxygenation and increasing pulmonary artery pressure, i.e., Rebound Pulmonary Hypertension Syndrome. Signs and symptoms of Rebound Pulmonary Hypertension Syndrome include hypoxemia, systemic hypotension, bradycardia, and decreased cardiac output. If Rebound Pulmonary Hypertension occurs, reinstate INOMax therapy immediately.

Hypoxemia from Methemoglobinemia

Nitric oxide combines with hemoglobin to form methemoglobin, which does not transport oxygen. Methemoglobin levels increase with the dose of INOMax; it can take 8 hours or more before steady-state methemoglobin levels are attained. Monitor methemoglobin and adjust the dose of INOMax to optimize oxygenation.

If methemoglobin levels do not resolve with decrease in dose or discontinuation of INOMax, additional therapy may be warranted to treat methemoglobinemia.

Airway Injury from Nitrogen Dioxide

Nitrogen dioxide (NO₂) forms in gas mixtures containing NO and O₂. Nitrogen dioxide may cause airway inflammation and damage to lung tissues.

If there is an unexpected change in NO₂ concentration, or if the NO₂ concentration reaches 3 ppm when measured in the breathing circuit, then the delivery system should be assessed in accordance with the Nitric Oxide Delivery System O&M Manual troubleshooting section, and the NO₂ analyzer should be recalibrated. The dose of INOMax and/or FiO₂ should be adjusted as appropriate.

Worsening Heart Failure

Patients with left ventricular dysfunction treated with INOMax may experience pulmonary edema, increased pulmonary capillary wedge pressure, worsening of left ventricular dysfunction, systemic hypotension, bradycardia and cardiac arrest. Discontinue INOMax while providing symptomatic care.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from the clinical studies does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Controlled studies have included 325 patients on INOMax doses of 5 to 80 ppm and 251 patients on placebo. Total mortality in the pooled trials was 11% on placebo and 9% on INOMax, a result adequate to exclude INOMax mortality being more than 40% worse than placebo.

In both the NINOS and CINRGI studies, the duration of hospitalization was similar in INOMax and placebo-treated groups.

From all controlled studies, at least 6 months of follow-up is available for 278 patients who received INOMax and 212 patients who received placebo. Among these patients, there was no evidence of an adverse effect of treatment on the need for rehospitalization, special medical services, pulmonary disease, or neurological sequelae.

In the NINOS study, treatment groups were similar with respect to the incidence and severity of intracranial hemorrhage, Grade IV hemorrhage, periventricular leukomalacia, cerebral infarction, seizures requiring anticonvulsant therapy, pulmonary hemorrhage, or gastrointestinal hemorrhage.

In CINRGI, the only adverse reaction (>2% higher incidence on INOMax than on placebo) was hypotension (14% vs. 11%).

Based upon post-marketing experience, accidental exposure to nitric oxide for inhalation in hospital staff has been associated with chest discomfort, dizziness, dry throat, dyspnea, and headache.

DRUG INTERACTIONS

Nitric Oxide Donor Agents

Nitric oxide donor agents such as prilocaine, sodium nitroprusside and nitroglycerine may increase the risk of developing methemoglobinemia.

OVERDOSAGE

Overdosage with INOMax is manifest by elevations in methemoglobin and pulmonary toxicities associated with inspired NO₂. Elevated NO₂ may cause acute lung injury. Elevations in methemoglobin reduce the oxygen delivery capacity of the circulation. In clinical studies, NO₂ levels >3 ppm or methemoglobin levels >7% were treated by reducing the dose of, or discontinuing, INOMax.

Methemoglobinemia that does not resolve after reduction or discontinuation of therapy can be treated with intravenous vitamin C, intravenous methylene blue, or blood transfusion, based upon the clinical situation.

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prophylaxis. Forty-two percent of these were admitted to the ICU, and 20% required intubation and mechanical ventilation. In the younger group, 29-32 wGA and <3 months of age, 68% required ICU admission and 44% required intubation and mechanical ventilation. These results corroborate the original RSV IMPact study, and provide additional information regarding the level of acuity of the hospitalization course.⁸

Following a change in palivizumab dosing patterns for the 2014-2015 season, the TRUVEN database study demonstrated that with a decline in RSV prophylaxis, hospitalization increased among infants born at 29-34 wGA and aged <3 months. Compared with the 2013-2014 season, RSV hospitalization increased by 2.7-fold ($p=0.02$) in the at-risk group. RSV hospitalizations for infants 29-34 wGA were up to seven times higher than normal term infants.³⁸

Increased risk for hospitalization is not the only factor to consider. A number of studies document RSV's association with wheeze and risk of subsequent development of reactive airway disease (39-41). Blanken, et al., demonstrated a significant reduction in wheeze in an at-risk group of infants born at 33-35 wGA that received palivizumab prophylaxis. Recurrent wheeze was 10 percentage points lower in patients treated with palivizumab (11% vs. 21%, $p=0.01$) (24). Yoshihara, et al., demonstrated reduced wheeze in patients who received palivizumab prophylaxis regardless of whether an at-risk patient was documented to have contracted RSV.⁴² Subclinical RSV disease that is not identified in the course of a provider interaction may be clinically significant and result in increased long term morbidity.¹⁷

In an observational case-control prospective multicenter trial of palivizumab prophylaxis, Mochizuki, et al., was able to establish a two-fold increase in the development of recurrent wheezing (15.3% versus 31.6% in the treated and untreated groups, ($p=0.003$)). Although the study did not show a difference in atopic asthma, the risk for subsequent development of asthma and morbidity associated with recurrent wheeze cannot be discounted.⁴³ Feldman, et al., discussed how RSV infection may not be necessary, but is sufficient to increase likelihood of pediatric asthma. Immune mediation and cytokine production common to both conditions may be set into process if RSV infection occurs at a certain point in time.⁴⁴ REGAL (RSV Evidence-a Geographical Archive of the Literature) reviewed 20 years of RSV-related research. Of the 74 prospective, epidemiologic studies qualified by the review, the meta-analysis consistently demonstrated that RSV infection early in life is a significant risk factor for respiratory morbidity characterized by early wheezing and recurrent wheezing as well as asthma within the first decade of life and possibly later.⁴⁵ An expert panel sponsored by the Bill and Melinda Gates Foundation (www.gatesfoundation.org) concluded that the association between early onset RSV and subsequent wheeze as well as asthma has been well defined. The effect of prevention of RSV in infancy on reduction of recurrent wheezing and asthma across multiple gestational ages may ultimately demonstrate a causal link.⁴⁶

Children at high risk for RSV include those with other co-morbidities besides prematurity, including chronic lung disease and Congenital Heart Disease (CHD). Using a structured case analysis of the Medline database, Welliver, et al., described a series of patients with severe underlying comorbidities, as well as those with nosocomial RSV who appear to be at increased risk for death after RSV hospitalization.⁴⁷ Actual RSV worldwide fatality data may be useful in determining whether including co-morbidities in evaluating acceptable risk is appropriate.^{1, 17, 48}

Financial Considerations

Cost stewardship is important. Patients should receive the best possible care at the lowest possible cost.¹⁴ However, any reduction in qualification for RSV prophylaxis must be associated with a model that demonstrates the unequivocal financial benefit without increased attendant morbidity and/or mortality. Further, estimates of cost saving

must incorporate realistic estimates of palivizumab cost, as well as all costs for hospitalization and follow-up care. Included in this consideration must be a risk stratified cost analysis of a patient likely to be hospitalized for RSV-related disease, as well as an estimate of actual prophylaxis cost related to month of birth, extrapolated or actual dosing weight at the time of prophylaxis, and level of discount applied to the list price of palivizumab. An analysis by McLauren, et al., demonstrated modeled costs of 55 to 85% less than list pricing using a blended drug discount of 33% coupled with seasonal and patient weight considerations.^{17, 49, 50} For this model, contemporary hospitalization claim data were used to quantify payer-related costs and cost neutrality was demonstrated in patient groups up to 34 wGA.^{17, 51} Medicaid-related cost discounts were most significant, and prophylaxis of patients in this cohort produced a cost savings. However, physician fee, follow-up costs, parent time off work, and patient factors including "cost" of discomfort were not considered in either commercial or government insurance programs. Extension of this model to include these considerations and dosing according to the full FDA indication may provide additional cost reduction and further tip the balance towards financial justification for prophylaxis. Long-term epidemiologic data from 16 seasons of national palivizumab prophylaxis in Austria reported by Resch, et al., demonstrated an unequivocal seasonal benefit, as well as long-term societal cost savings.⁵²

Introduction

RSV is the leading cause of hospitalization for all children less than 12 months of age in the United States.^{33, 53, 54} The majority of these hospitalizations occur in otherwise healthy infants. Sixty percent of the top five hospital discharge diagnoses are attributable to bronchiolitis. Certain groups of infants and children have higher rates of re-hospitalization, including those with Chronic Lung Disease (CLD)/Bronchopulmonary Dysplasia (BPD), Congenital Heart Disease (CHD), and a history of preterm birth.⁵⁵⁻⁶² Treatment options for RSV are limited. Supportive care is the only medical therapy available. In addition to strategies to minimize exposure to RSV, prophylaxis with RSV monoclonal antibody is effective at decreasing hospitalization. The best approach to RSV in at-risk groups is prevention.^{11, 27, 57, 63-65} In patients with CLD/BPD and premature infants born at less than 36 wGA, prophylaxis decreased hospitalization by 55%; in the subgroup of patients born between 32-35 wGA, hospitalization rates decreased by 80%.¹¹ Although palivizumab may be safe for term infants with no underlying co-morbidities, immunization of otherwise healthy term infants is considered outside of the accepted FDA indication.

Respiratory Syncytial Virus Prophylaxis

- A. Prophylaxis to prevent RSV is available as intramuscular monoclonal antibody preparation (palivizumab).^{66, 67}
- B. RSV infection is responsible for significant hospitalizations, morbidity, and mortality in infants less than 24 months of age who have chronic lung disease, CHD, compromised respiratory or immune systems, or impaired nutritional status and growth.^{27, 63, 68}
- C. Candidates for RSV Prophylaxis: Areas where strong data exist.
  1. Infants with bronchopulmonary dysplasia (BPD) or chronic lung disease (CLD) will benefit from RSV prophylaxis.
    - a. BPD may be defined by oxygen requirement at 36 weeks' corrected gestational age or at 28 days of age regardless of the birth gestational age.
    - b. CLD includes these infants and others who have subsequently developed an oxygen requirement or other pulmonary condition requiring treatment or close medical observation.
    - c. Infants with CLD/BPD who are less than 24 months of age at the start of RSV season who have required intervention or maintenance therapy for their BPD/CLD within 6

months of the start of the RSV season will benefit from RSV prophylaxis. The administration of palivizumab in a previous month may be sufficient to qualify for administration in a subsequent qualified month.

- d. Other interventions for CLD/BPD may include use of corticosteroid preparations, methylxanthines (e.g., aminophylline or caffeine), supplemental oxygen, bronchodilators, home apnea monitoring, home pulse oximetry, or diuretics.^{60, 69, 70}
2. Infants born at 32 wGA or less without CLD/BPD will also benefit from prophylaxis:⁷¹
  - a. Infants born at less than 28 0/7 wGA will benefit from prophylaxis, if they are less than 12 months of age at the start of the RSV season. Infants born during RSV season who are less than 12 months of age at the start of the subsequent RSV season are still candidates for prophylaxis.
  - b. Infants born at 28 0/7-32 0/7 wGA will benefit most from prophylaxis, if they are less than 6 months of age at the start of RSV season.
3. Infants born at a late preterm gestation (34 0/7-36 6/7 wGA) may merit special consideration.⁷²⁻⁷⁴ However, prophylaxis for infants born at 32 1/7-35 6/7 wGA should be reserved for those infants with additional risk factors that increase risk of RSV exposure or morbidity from RSV disease.
  - a. An RSV relative-risk scale has been proposed and may be useful to the practitioner in identifying at-risk patients who may benefit from RSV prophylaxis.⁷⁵ A neonatologist, pediatrician, or other primary care provider is often in the best position to assess and interpret relative risk factors.
  - b. The most consistently identified factors that are associated with increased risk of RSV disease are childcare attendance, school-aged siblings, twin or greater multiple gestation, young chronological age at the start of RSV season and parental smoking; however, exposure to environmental air pollutants, congenital abnormalities of the airways, or severe neuromuscular disease may also justify concern.^{41, 69, 76-79} Correlations exist between air quality and respiratory function.^{40, 78-88} Thus, environmental air quality assessment is important for these patients with special consideration given the unique circumstances of unwarranted air pollution such as residence near a bus station or industrial plant, or use of a wood-burning or coal-burning stove as a primary heat source. Efforts to reduce risk by isolation of the at-risk child, smoking cessation strategies for the parents/caregivers, or relocation to an area with cleaner air may not be practical or workable.
  - c. Certain risk factors may have greater impact based on the level of exposure (i.e., one school-aged sibling versus three school-aged siblings in three different schools); however, no identifiable risk factor has been shown to be unique in its predictive value, and frequently many risk factors may exist simultaneously.^{40, 62} The greater the number of risk factors, the higher the likelihood of RSV hospitalization.⁸⁹ A history of maternal smoking during pregnancy may be ameliorated as a risk factor by a history of breastfeeding for greater than 2 months.^{82, 90-93} These circumstances must be accounted for in the risk assessment.
  - d. The provider must be aware of the risk created and enhanced by disparity. Minority African American and Hispanic populations in blighted inner city neighborhoods are at a higher cumulative risk.⁽²⁰⁾
  - e. After assessment of an individual patient, if a provider determines that the patient is at high risk for RSV disease complicated by hospitalization, prophylaxis should be provided.⁹⁴ Planning for prophylaxis must begin before the time of discharge if the at-risk patient has been

hospitalized for any of the conditions that have a known association for increased risk. In one study, greater than 50% of eligible patients received no prophylaxis, neither prior to nor after discharge.⁹⁵ Lack of parental education, language difficulties, transportation challenges, and issues of potential problems with insurance coverage must be resolved prior to the patient's discharge home.⁹⁶⁻⁹⁸

- f. Cost of prophylaxis should be weighed against the risk of severe RSV disease requiring hospitalization and associated costs to the family as well as potential for long-term sequelae. Direct costs are not the only expenses involved in the long-term care of a child who has had RSV. Costs associated with loss of family income with a parent taking time off for initial hospitalization and later to care for a child with chronic disability, frequent follow-up appointments, and indirect costs involved in providing support for developmental disability as well as loss of academic potential must also be considered.⁹⁹⁻¹⁰²
4. Infants with CHD have been shown to benefit from palivizumab.^{27, 103-105} The degree and severity of the heart disease may factor into the decision to provide RSV prophylaxis. Cyanotic Heart Disease places a patient at considerable risk since oxygen delivery is already compromised. Although Acyanotic Heart Disease has been shown to increase the relative risk for RSV-related hospital admission to even higher than that of cyanotic disease, admission rates of palivizumab-immunized infants are similar in both categories.²⁷ Infants with Complex Congenital Heart Disease (CCHD) are at risk, and should be considered for RSV prophylaxis, including babies with Hypoplastic Left or Right Heart Syndrome, truncus arteriosus, Tetralogy of Fallot, pulmonary atresia, Transposition of the Great Arteries, interrupted aortic arch, Ventricular Septal Defect or Patent Ductus Arteriosus with demonstrated heart failure, cardiomyopathies, arrhythmias capable of causing hemodynamic compromise, and infants who are candidates for potential heart transplant. Children who are post cardiac transplantation are in a particularly high-risk group and should be given RSV prophylaxis.^{103, 105, 106} In order to exclude an infant from receiving palivizumab, the infant must have a documented waiver provided by a board-certified pediatric cardiologist, which documents that their cardiac defect is hemodynamically insignificant, and thereby, poses no additional risk for RSV. During RSV season, children who have received Extracorporeal Membrane Oxygenation (ECMO) or any other form of cardiac bypass should receive monthly prophylaxis. If the baby is receiving palivizumab during the active RSV season, an extra dose of prophylaxis should be considered as soon as the baby comes off bypass support.¹⁰⁷
- D. Candidates for RSV Prophylaxis: Areas where decisions regarding appropriateness of RSV prophylaxis must be individualized.
  1. Infants with severe neuromuscular disease affecting respiratory function (e.g., myotonic or muscular dystrophy) may be candidates for palivizumab prophylaxis, including those with neuromuscular maturational disease common in premature infants.¹⁰⁸ CNS injury prior to, during, or after delivery including, but not limited to, intraventricular hemorrhage (IVH), hypoxic ischemic encephalopathy (HIE), spinal cord injury, disease of the peripheral nervous system, disease of the neuromuscular junction, and periventricular leukomalacia (PVL) are all possible indications for RSV prophylaxis.^{68, 70, 108} IVH, HIE, and PVL may cause cerebral palsy (CP) at a later time. CP alone may qualify an infant for RSV prophylaxis, if there is any association with impaired respiratory function.^{109, 110}
  2. Patients with congenital abnormalities of the airways that compromise respiratory function should receive prophylaxis.^{56, 111-114} Other respiratory viruses may also be

implicated in morbidity, which may include persisting wheeze, symptomatology and/or family history that suggest the possibility of later asthma, or disorders of abnormal lung growth.⁴² Congenital diaphragmatic hernia is included in this category. Although large scale randomized control trials have not been performed, patients with surfactant protein deficiencies may also benefit from prophylaxis, as may infants with childhood interstitial lung diseases such as neuroendocrine hyperplasia of infancy (NEHI) or pulmonary interstitial glycogenosis (PIG).

3. Although large-scale randomized control trials in patients with individual at-risk respiratory disorders have not been performed, patients with cystic fibrosis and other diseases such as α 1-antitrypsin deficiency where there is a genetic basis for changes in the lung milieu may also benefit from prophylaxis.¹¹⁵ As respiratory symptomatology is not generally associated with α 1-antitrypsin deficiency during infancy; based on the degree of pulmonary involvement, palivizumab may be considered only if there is respiratory compromise associated with another qualifier (e.g., prematurity).¹¹⁶ Primary Ciliary Dyskinesia may also be an indication for prophylaxis.¹¹⁷ Identification of cystic fibrosis on a newborn screen may merit special consideration.^{112, 115, 118-120} Cystic fibrosis occurring with transient infantile wheezing has been associated with worse lung function in later life, and RSV is the most common cause of transient infantile wheezing.¹²¹ Certainly, infants who would otherwise qualify for palivizumab based on the indication should be screened for cystic fibrosis if the clinical course and history indicate.
4. Immune deficiencies are rare disorders and require collaborative management by pediatricians, infectious disease specialists, and immunologists.^{122, 123} HIV, SCID, primary or secondary bone marrow depletion, and any defect of humoral or cellular immunity including that occurring with transplantation places a patient at-risk of severe infection. Palivizumab prophylaxis has been associated with improved survival after bone marrow transplantation.¹²⁴ Although there is no conclusive evidence for any particular disease category, because of the understood high risk of any infectious process, RSV prophylaxis is indicated unless a waiver can be obtained from a board certified pediatric immunologist or infectious disease specialist.
5. Certain genetic diseases may place a patient at more cumulative risk for RSV. For the present time, patients should receive prophylaxis to the extent that other qualifiers are met. However, including infants with Down Syndrome in the recommendations for immunoprophylaxis of RSV disease should be considered.¹²⁵
6. Special risk circumstances may occur in homes where another individual is at high risk for RSV infection (e.g., an elderly immunocompromised relative) who may not be able to receive RSV prophylaxis. Although palivizumab does not prevent RSV infection, decreased cough and aerosolization of RSV may provide some degree of protection. Providers should determine if it is reasonable to provide prophylaxis to other members of the household.^{1, 126, 127}

E. Administration

1. The National Perinatal Association Guidelines for RSV Prophylaxis are interdisciplinary peer-reviewed and evidence-based guidelines, but do not represent the sole management criteria for medical care of at-risk infants. Depending on individual case presentations, in selected populations and unique circumstances, these recommendations may not apply. There is no substitute for the clinical judgment of a pediatrician, nurse practitioner, or other licensed provider of pediatric services.
2. RSV prophylaxis should be initiated prior to the onset of the RSV season and terminated at the end of the RSV season.^{5, 128, 129} Although there are regional variations in the United

States, RSV outbreaks begin as early as October and decrease between March and May. Providers should review local historical RSV surveillance data to assist in the decision-making process. Some locales in the Southern United States (e.g., Florida), Hawaii, and Alaska have high enough incidence of RSV to justify initiation in the late summer months and continuation of monthly prophylaxis into the late spring.¹³⁰⁻¹³⁴ Transport distance of ill infants and resource allocation as well as socioeconomic factors (e.g., lack of running water) may be considered in the justification of enhanced RSV prophylaxis coverage where the costs to provide hospitalization for patients at great distance greatly exceed that of most urban locales (e.g., Alaska and Canadian Arctic).¹³⁵ The burden of severe RSV disease on healthcare resources is greater than other respiratory viruses.¹³⁶ Although various cost containment models have been proposed to provide relative risk adjustment based on post-conceptual age at a specific month during RSV season, there is risk that adequate levels of palivizumab will not be achieved or maintained during months when RSV is widespread using this type of model.^{11, 12, 129, 137} Use of an abbreviated schedule of RSV prophylaxis (e.g., based on post conceptual age mid-season) is contrary to published evidence and FDA-approved product indication for palivizumab and is strongly discouraged.¹³⁸

3. Once an infant begins RSV prophylaxis for the RSV season, the infant must receive palivizumab monthly through the end of the season.²⁵
4. Palivizumab 15 mg/kg IM should be given once a month during the RSV season to increase the likelihood of achieving and maintaining appropriate levels for prophylaxis.⁶⁶ A dose should be given 24-48 hours prior to discharge from the hospital if the patient meets criteria. The single-dose vial of palivizumab does not contain a preservative. Administration of palivizumab should occur immediately after dose withdrawal from the vial.⁶⁶
5. Although prophylaxis during active infection will not impact the course of the symptomatology, RSV disease is not a contraindication to continuing palivizumab prophylaxis. Infection does not confer lasting immunity. There is more than one genotype of RSV. Although less common, patients can be re-infected with RSV multiple times during the same RSV season. Thus, monthly dosing should be continued even if the patient has been infected with RSV.⁶⁶
6. Fever or other illness including viral syndromes are not contraindications to administration of palivizumab.
7. There are no restrictions on concurrent RSV prophylaxis with any immunization.¹³⁹ Immunization with Measles-Mumps-Rubella (MMR) and Varicella vaccines need not be deferred in infants receiving RSV prophylaxis. RSV prophylaxis does not interfere with Hepatitis B vaccine, Diphtheria, Tetanus, Pertussis (DTaP) primary immunization schedule, H. Influenza type B (Hib), seasonal influenza vaccination, Pneumococcal Conjugate Vaccine (PCV), or Inactivated Poliovirus Vaccine (IPV).
8. The safety and efficacy of palivizumab have not been demonstrated for treatment of established RSV disease. Palivizumab does not alter the disease severity or course of an active RSV infection.
9. Contraindications and Adverse Reactions
  - a. Palivizumab should not be used in pediatric patients with a history of a severe prior reaction to palivizumab or other components of this product.⁶⁶
  - b. Fever, irritability and injection site reaction are the most commonly reported adverse events.¹⁴⁰

Indication	Chronological Age	Dosing
Areas Where Strong Data Exist		
Chronic lung disease requiring medical management	Less than 24 months at start of RSV season	Monthly during RSV season
Born at <28 0/7 weeks' gestational age (wGA)	Less than 12 months at start of RSV season	Monthly during RSV season
Born at 28 0/7-32 0/7 wGA	Less than 6 months at start of RSV season	Monthly during RSV season
Born at 32 1/7-35 6/7 wGA	Less than 6 months at start of RSV season with significant provider-identified risk factors.	Monthly during RSV season
Hemodynamically Significant Congenital Heart Disease	Less than 24 months at start of RSV season unless cardiology waiver obtained	Monthly during RSV season
Areas Where Individualized Guidance is Indicated		
Neuromuscular Disease affecting respiratory function	Less than 24 months at start of RSV season	Monthly during RSV season
Congenital abnormalities of the airways (e.g., Congenital Diaphragmatic Hernia)	Less than 24 months at start of RSV season	Monthly during RSV season
Immune Disorders (e.g., HIV, SCID, DiGeorge, IgA deficiency, Hypergammaglobulinemia)	Less than 24 months at start of RSV season unless infectious disease or immunology waiver obtained	Monthly during RSV season
Cystic Fibrosis, Primary Ciliary Dyskinesia, or other rare lung disease resulting in chronic respiratory insufficiency	Less than 24 months at start of RSV season; consultation with pediatric pulmonology suggested	Monthly during RSV season

Nosocomial Infection

- A. RSV may be horizontally transmitted in the hospital setting and causes serious disease in high-risk infants and young children.
- B. The best way to prevent RSV disease is strict adherence to infection control practices, as well as the use of in-hospital screening studies to identify and isolate RSV-infected infants.⁵³ Proper hand washing is of paramount importance.
- C. Cohorting of children with suspected RSV disease is not recommended. Not only are there other contagious viral and bacterial diseases that mimic RSV, but infection with RSV does not preclude co-infection with bacteria, other viruses, or another subgroup of RSV. For management of suspected nosocomial outbreaks of RSV occurring within a pediatric ward, pediatric critical care unit, or neonatal intensive care unit, the advice of infectious disease and hospital-based infection control experts should be obtained.^{53, 141}

Use of Palivizumab Outside of the FDA Indications Constitutes Off-Label Use

- A. Off-label use of any medication places the provider at medico-legal risk. The FDA's Center for Drug Evaluation and Research (CDER) has initiated the Bad Ad outreach program with the goal of encouraging health care providers to recognize and report suspected untruthful or misleading drug promotion. "Assuring prescription drug information is truthful, balanced, and accurately communicated" is the intent. Led by the Division of Drug Marketing Advertising and Communications (DDMAC), this effort informs providers about what constitutes misleading promotion and provides a process for reporting suspected violations to the FDA. Violators may include state or professional organizations, those who may profit by modifying FDA-approved dosing or indications for a medication, or individuals who make unrealistic claims about enhanced action of a medication.
- B. Reports can be initiated by contacting the United States Food and Drug Administration's Division of Drug Marketing, Advertising, and Communications at 855-RX-BADAD or (855-792-2323), E-Mail: BadAd@fda.gov, by mail: FDA/CDER/DDMAC, 5901-B Ammendale Rd., Beltsville, MD 20705-1266, or Fax: 301-847-8444.¹⁴² In the past, however, the FDA has not had the resources to act quickly on reports of

wayward drug misinformation. The False Claims Act provides another alternative to the Bad Ad outreach program. This fraud-fighting law not only provides substantial rewards for whistleblowers, but it includes an action-enforcing mechanism that statutorily requires the government to investigate allegations of fraud. If providers want to ensure that the government will consider their concerns, a False Claims Act qui tam action may be filed.

The MEDLINE database, the Cochrane Library, and the National Perinatal Association's own internal resources and documents were used to conduct a literature search to identify relevant articles published on Respiratory Syncytial Virus (RSV). The search was restricted to articles published in the English language. Priority was given to the outcomes of original research. Review articles and commentaries were also consulted when their inclusion added substantively to the guidance. Abstracts of research presented at scientific conference were eligible for inclusion in this document if the abstract was peer reviewed prior to its publication. Guidelines published by other organizations were evaluated for their merit and included where their inclusion was both elucidative and topical. Further, sources from the bibliographies of these guidelines were evaluated and included where appropriate. Expert opinion, while important for the interpretation of the studies, was not judged to be valid independently without substantiation of high level evidence.

Studies were evaluated for quality using the metric provided by the United States Preventive Services Task Force:^{143, 144}

- I. Evidence obtained from at least one properly designed randomized controlled trial.
- II-1. Evidence obtained from well-designed controlled trials without randomization.
- II-2. Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
- II-3. Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.

Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

PediNotes incorporates patient information from all caregivers into a single, easy-to-navigate EMR platform.

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Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

- Level A** – Recommendations based on good and consistent scientific evidence.
- Level B** – Recommendations based on limited or inconsistent scientific evidence.
- Level C** – Recommendations based largely on consensus and expert opinion

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