NEONATOLOGY TODAY

News and Information for BC/BE Neonatologists and Perinatologists

Volume 12 / Issue 10
October 2017

In This Issue

NEONATOLOGY TODAY

ISSN: 1932-7137 (online)

Editorial and Subscription Offices
16 Cove Rd., Ste. 200
Westerly, RI 02891 USA
www.NeonatologyToday.net
Twitter: www.Twitter.com/NeoToday

Recruitment ad: page 21

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 polices.[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," practicioners 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).1[1, 25-27]

Confoundation by indication limits the effectiveness of well-designed randomized control studies designed to study the efficancy 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, demonatrated 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

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 wheese 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 consider 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 Ddefect 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 α1-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 α1-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 Downs 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.

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

References

1. Nair H, Nokes DJ, Gessner BD, Dherani M, Madhi SA, Singleton RJ, et al. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. Lancet. 2010;375(9725):1545-55. Level II-2 (A).
2. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2095-128. Level II-2 (A).
3. From the American Academy of Pediatrics: Policy statements--Modified recommendations for use of palivizumab for prevention of respiratory syncytial virus infections. Pediatrics. 2009;124(6):1694-701. Level II-1 (A).
4. Revised indications for the use of palivizumab and respiratory syncytial virus immune globulin intravenous for the prevention of respiratory syncytial virus infections. Pediatrics. 2003;112(6 Pt 1):1442-6. Level II-2 (A).
5. Krilov LR, Weiner LB, Yogev R, Fergie J, Katz BZ, Henrickson KJ, et al. The 2009 COID recommendations for RSV prophylaxis: issues of efficacy, cost, and evidence-based medicine. Pediatrics. 2009;124(6):1682-4. Level II-3 (A).
6. Wang D, Bayliss S, Meads C. Palivizumab for immunoprophylaxis of respiratory syncytial virus (RSV) bronchiolitis in high-risk infants and young children: a systematic review and additional economic modelling of subgroup analyses. Health Technol Assess. 2011;15(5):iii-iv, 1-124. Level II-1 (A).
7. American Academy of Pediatrics Committee On Infectious Disease, Bronchiolitis Guidelines C, Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. Pediatrics. 2014;134(2):415-20. Level III (C).
8. Anderson EJ, Krilov LR, DeVincenzo JP, Checchia PA, Halasa N, Simoes EA, et al. SENTINEL1: An Observational Study of Respiratory Syncytial Virus Hospitalizations among U.S. Infants Born at 29 to 35 Weeks' Gestational Age Not Receiving Immunoprophylaxis. Am J Perinatol. 2017;34(1):51-61. Level II-2 (A).
9. Wong PC, Parimi PS, Domachowske JB, Friedman DM, Marcus MG, Garcia DF, et al. The Logistics and Coordination of Respiratory Syncytial Virus Immunoprophylaxis Use Among US Pediatric Specialists. Clin Pediatr (Phila). 2016;55(13):1230-41. Level II-2 (A).
10. Hasegawa K, Tsugawa Y, Brown DF, Mansbach JM, Camargo CA, Jr. Trends in bronchiolitis hospitalizations in the United States, 2000-2009. Pediatrics. 2013;132(1):28-36. Level II-2 (A).
11. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. The IMpact-RSV Study Group. Pediatrics. 1998;102(3 Pt 1):531-7. Level I (A).
12. Forbes M, Kumar V, Yogev R, Wu X, Robbie G, Ambrose CS. Serum palivizumab level is associated with decreased severity of respiratory syncytial virus disease in high-risk infants. Human vaccines & immunotherapeutics. 2014;10(10). Level II-2 (A).
13. Boylan M. A practical guide to medical negligence litigation. Haywards Health, West Sussex: Bloomsbury Professional; 2016. xxix, 355 pages p. Level III (C).
14. AAP. NeoReviewsPLUS October 2014 Question #2. NeoReviewsPlus [Internet]. 2014 10/20/2014; (October 2014):[2 p.]. Level III (C).
15. Caliskan M, Bochkov YA, Kreiner-Moller E, Bonnelykke K, Stein MM, Du G, et al. Rhinovirus wheezing illness and genetic risk of childhood-onset asthma. The New England journal of medicine. 2013;368(15):1398-407. Level II-2 (A).
16. Bentley A, Filipovic I, Gooch K, Busch K. A cost-effectiveness analysis of respiratory syncytial virus (RSV) prophylaxis in infants in the United Kingdom. Health economics review. 2013;3(1):18. Level III (B).
17. Meissner HC, Kimberlin DW. RSV immunoprophylaxis: does the benefit justify the cost? Pediatrics. 2013;132(5):915-8. Level III (C).
18. Pockett RD, Campbell D, Carroll S, Rajoriya F, Adlard N. A comparison of healthcare resource use for rotavirus and RSV between vulnerable children with co-morbidities and healthy children: a case control study. J Med Econ. 2013;16(4):560-5. Level II-2 (A).
19. Sullivan C, Morgan C. PC.74 The importance of testing for Respiratory Syncytial Virus (RSV) in infants presenting with bronchiolitis who are receiving palivizumab. Archives of disease in childhood Fetal and neonatal edition. 2014;99 Suppl 1:A61. Level II-2 (A).
20. Panel NMAC. Respiratory Syncytial Virus and African Americans. Journal of the National Medical Association. 2010:46. Level I (A).
21. Hall CB, Weinberg GA, Blumkin AK, Edwards KM, Staat MA, Schultz AF, et al. Respiratory syncytial virus-associated hospitalizations among children less than 24 months of age. Pediatrics. 2013;132(2):e341-8. Level II-2 (A)
22. Gijtenbeek RG, Kerstjens JM, Reijneveld SA, Duiverman EJ, Bos AF, Vrijlandt EJ. RSV infection among children born moderately preterm in a community-based cohort. Eur J Pediatr. 2014. Level II-2 (A).
23. Ambrose CS, Anderson EJ, Simoes EA, Wu X, Elhefni H, Park CL, et al. Respiratory syncytial virus disease in preterm infants in the U.S. born at 32-35 weeks gestation not receiving immunoprophylaxis. Pediatr Infect Dis J. 2014;33(6):576-82. Level II-2 (A).
24. Blanken MO, Rovers MM, Molenaar JM, Winkler-Seinstra PL, Meijer A, Kimpen JL, et al. Respiratory syncytial virus and recurrent wheeze in healthy preterm infants. The New England journal of medicine. 2013;368(19):1791-9. Level I (A).
25. Subramanian KN, Weisman LE, Rhodes T, Ariagno R, Sanchez PJ, Steichen J, et al. Safety, tolerance and pharmacokinetics of a humanized monoclonal antibody to respiratory syncytial virus in premature infants and infants with bronchopulmonary dysplasia. MEDI-493 Study Group. Pediatr Infect Dis J. 1998;17(2):110-5. Level I (A).
26. Andabaka T, Nickerson JW, Rojas-Reyes MX, Rueda JD, Bacic Vrca V, Barsic B. Monoclonal antibody for reducing the risk of respiratory syncytial virus infection in children. Cochrane Database Syst Rev. 2013;4:CD006602. Level I (A).
27. Feltes TF, Cabalka AK, Meissner HC, Piazza FM, Carlin DA, Top FH, et al. Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. J Pediatr. 2003;143(4):532-40. Level I (A).
28. Farber HJ, Buckwold FJ, Lachman B, Simpson JS, Buck E, Arun M, et al. Observed Effectiveness of Palivizumab for 29-36-Week Gestation Infants. Pediatrics. 2016;138(2). Level II-2 (A).
29. Boyce TG, Yogev R, DeVincenzo JP, Krilov LR. Confounding by Indication Limits Conclusions of Study of Palivizumab Effectiveness. Pediatrics. 2017;139(3). Level I (A).
30. Winterstein AG, Knox CA, Kubilis P, Hampp C. Appropriateness of age thresholds for respiratory syncytial virus

immunoprophylaxis in moderate-preterm infants: a cohort study. JAMA pediatrics. 2013;167(12):1118-24. Level II-2 (A).
31. Winterstein AG, Hampp C, Saidi A. Effectiveness of palivizumab prophylaxis in infants and children in Florida. Pharmacoepidemiology and drug safety. 2012;21(1):53-60. Level II-2 (A).
32. McLaurin K, Ambrose CS. Clarifying costs and benefits of respiratory syncytial virus immunoprophylaxis. Pediatrics. 2014;133(4):e1101. Level II-2 (A).
33. Boyce TG, Mellen BG, Mitchel EF, Jr., Wright PF, Griffin MR. Rates of hospitalization for respiratory syncytial virus infection among children in medicaid. J Pediatr. 2000;137(6):865-70. Level II-2 (A).
34. Carroll KN, Griffin MR, Edwards KM, Ali A, Zhu Y, Iwane MK, et al. Adherence to guidelines for respiratory syncytial virus immunoprophylaxis among infants with prematurity or chronic lung disease in three United States counties. Pediatr Infect Dis J. 2012;31(11):e229-31. Level II-2 (A).
35. Zuccotti G, Fabiano V. Indications to respiratory syncytial virus immunoprophylaxis in the 29-32 wGA group: is there still room for debating? Ital J Pediatr. 2017;43(1):17. Level II-3 (A).
36. Capizzi A, Silvestri M, Orsi A, Cutrera R, Rossi GA, Sacco O. The impact of the recent AAP changes in palivizumab authorization on RSV-induced bronchiolitis severity and incidence. Ital J Pediatr. 2017;43(1):71. Level II-2 (A).
37. Anderson EJ, Carosone-Link P, Yogev R, Yi J, Simoes EAF. Effectiveness of Palivizumab in High-risk Infants and Children: A Propensity Score Weighted Regression Analysis. Pediatr Infect Dis J. 2017;36(8):699-704. Level II-1 (A).
38. Kong AM, Krilov LR, Fergie J, Goldstein M, Diakun D, Wade SW, et al. The 2014-2015 National Impact of the 2014 American Academy of Pediatrics Guidance for Respiratory Syncytial Virus Immunoprophylaxis on Preterm Infants Born in the United States. Am J Perinatol. 2017. Level II-1 (A).
39. Sigurs N, Aljassim F, Kjellman B, Robinson PD, Sigurbergsson F, Bjarnason R, et al. Asthma and allergy patterns over 18 years after severe RSV bronchiolitis in the first year of life. Thorax. 2010;65(12):1045-52. Level II-2 (A).
40. McConnochie KM, Roghmann KJ. Parental smoking, presence of older siblings, and family history of asthma increase risk of bronchiolitis. Am J Dis Child. 1986;140(8):806-12. Level II-2 (A).
41. Celedon JC, Litonjua AA, Weiss ST, Gold DR. Day care attendance in the first year of life and illnesses of the upper and lower respiratory tract in children with a familial history of atopy. Pediatrics. 1999;104(3 Pt 1):495-500. Level II-2 (A).
42. Yoshihara S, Kusuda S, Mochizuki H, Okada K, Nishima S, Simoes EA, et al. Effect of palivizumab prophylaxis on subsequent recurrent wheezing in preterm infants. Pediatrics. 2013;132(5):811-8. Level I (A).
43. Mochizuki H, Kusuda S, Okada K, Yoshihara S, Furuya H, Simoes EAF, et al. Palivizumab Prophylaxis in Preterm Infants and Subsequent Recurrent Wheezing. Six-Year Follow-up Study. Am J Respir Crit Care Med. 2017;196(1):29-38. Level I (A).
44. Feldman AS, He Y, Moore ML, Hershenson MB, Hartert TV. Toward primary prevention of asthma. Reviewing the evidence for early-life respiratory viral infections as modifiable risk factors to prevent childhood asthma. Am J Respir Crit Care Med. 2015;191(1):34-44. Level II-2 (A).
45. Fauroux B, Simoes EAF, Checchia PA, Paes B, Figueras-Aloy J, Manzoni P, et al. The Burden and Long-term Respiratory Morbidity Associated with Respiratory Syncytial Virus Infection in Early Childhood. Infect Dis Ther. 2017;6(2):173-97.Level II-2 (A)
46. Caballero MT, Jones MH, Karron RA, Hartert TV, Simoes EA, Stein RT, et al. The Impact of Respiratory Syncytial Virus Disease Prevention on Pediatric Asthma. Pediatr Infect Dis J. 2016;35(7):820-2. Level II-2 (A).
47. Welliver RC, Sr., Checchia PA, Bauman JH, Fernandes AW, Mahadevia PJ, Hall CB. Fatality rates in published reports of RSV hospitalizations among high-risk and otherwise healthy children. Curr Med Res Opin. 2010;26(9):2175-81. Level II-3 (A).
48. Matias G, Taylor R, Haguinet F, Schuck-Paim C, Lustig R, Shinde V. Estimates of mortality attributable to influenza and RSV in the United States during 1997-2009 by influenza type or subtype, age, cause of death, and risk status. Influenza Other Respir Viruses. 2014;8(5):507-15. Level II-2 (A).
49. Fenton TR, Nasser R, Eliasziw M, Kim JH, Bilan D, Sauve R. Validating the weight gain of preterm infants between the reference growth curve of the fetus and the term infant. BMC Pediatr. 2013;13:92. Level II-2 (A).
50. Smart KA, Paes BA, Lanctot KL. Changing costs and the impact on RSV prophylaxis. J Med Econ. 2010;13(4):705-8. Level II-3 (B).
51. Shi N, Palmer L, Chu B-C, Katkin JP, Hall CB, Masaquel AS, et al. Association of RSV lower respiratory tract infection and subsequent healthcare use and costs: a Medicaid claims analysis in early-preterm, late-preterm, and full-term infants. J Med Econ. 2011;14(3):335-40. Level II-2 (A).
52. Resch B, Sommer C, Nuijten MJ, Seidinger S, Walter E, Schoellbauer V, et al. Cost-effectiveness of palivizumab for respiratory syncytial virus infection in high-risk children, based on long-term epidemiologic data from Austria. Pediatr Infect Dis J. 2012;31(1):e1-8. Level II-2 (A).
53. Bont L. Nosocomial RSV infection control and outbreak management. Paediatr Respir Rev. 2009;10 Suppl 1:16-7. Level III (C).
54. Boron ML, Edelman L, Groothuis JR, Malinoski FJ. A novel active respiratory syncytial virus surveillance system in the United States: variability in the local and regional incidence of infection. Pediatr Infect Dis J. 2008;27(12):1095-8. Level II-2 (A).
55. Ballow M, Cates KL, Rowe JC, Goetz C, Desbonnet C. Development of the immune system in very low birth weight (less than 1500 g) premature infants: concentrations of plasma immunoglobulins and patterns of infections. Pediatr Res. 1986;20(9):899-904. Level II-3 (B).
56. Fanos V, Scarcella A, Puddu M, Gallini F, Tuminelli F, Bragetti P, et al. Respiratory disorders and hospitalization rates during the second RSV season in preterm infants who received palivizumab prophylaxis during their first RSV season. J Chemother. 2009;21(3):302-10. Level II-2 (A).
57. Fitzgerald DA. Preventing RSV bronchiolitis in vulnerable infants: the role of palivizumab. Paediatr Respir Rev. 2009;10(3):143-7. Level III (B).
58. Groothuis J, Bauman J, Malinoski F, Eggleston M. Strategies for prevention of RSV nosocomial infection. J Perinatol. 2008;28(5):319-23. Level II-2 (B).
59. Kramer MS, Demissie K, Yang H, Platt RW, Sauve R, Liston R. The contribution of mild and moderate preterm birth to infant mortality. Fetal and Infant Health Study Group of the Canadian Perinatal Surveillance System. Jama. 2000;284(7):843-9. Level II-2 (A).
60. Liese JG, Grill E, Fischer B, Roeckl-Wiedmann I, Carr D, Belohradsky BH. Incidence and risk factors of respiratory syncytial virus-related hospitalizations in premature infants in Germany. Eur J Pediatr. 2003;162(4):230-6. Level II-2 (A)
61. Okoko JB, Wesumperuma HL, Hart CA. The influence of prematurity and low birthweight on transplacental antibody transfer in a rural West African population. Trop Med Int Health. 2001;6(7):529-34. Level II-2 (A).
62. Simoes EA, King SJ, Lehr MV, Groothuis JR. Preterm twins and triplets. A high-risk group for severe respiratory syncytial virus infection. Am J Dis Child. 1993;147(3):303-6. Level II-3 (B).
63. Geskey JM, Thomas NJ, Brummel GL. Palivizumab: a review of its use in the protection of high risk infants against respiratory syncytial virus (RSV). Biologics. 2007;1(1):33-43. Level III (B).
64. Goddard NL, Cooke MC, Gupta RK, Nguyen-Van-Tam JS. Timing of monoclonal antibody for seasonal RSV prophylaxis in the United Kingdom. Epidemiol Infect. 2007;135(1):159-62. Level II-3 (A).

65. Meissner HC, Welliver RC, Chartrand SA, Law BJ, Weisman LE, Dorkin HL, et al. Immunoprophylaxis with palivizumab, a humanized respiratory syncytial virus monoclonal antibody, for prevention of respiratory syncytial virus infection in high risk infants: a consensus opinion. Pediatr Infect Dis J. 1999;18(3):223-31. Level III (C).
66. MedImmune L. Synagis (Palivizumab). Package insert. Package insert (2009). Level 1 (A).
67. Wu H, Pfarr DS, Losonsky GA, Kiener PA. Immunoprophylaxis of RSV infection: advancing from RSV-IGIV to palivizumab and motavizumab. Curr Top Microbiol Immunol. 2008;317:103-23. Level III (C).
68. Resch B, Manzoni P, Lanari M. Severe respiratory syncytial virus (RSV) infection in infants with neuromuscular diseases and immune deficiency syndromes. Paediatr Respir Rev. 2009;10(3):148-53. Level II-3 (B).
69. Greenough A, Alexander J, Burgess S, Bytham J, Chetcuti PAJ, Hagan J, et al. Health care utilisation of prematurely born, preschool children related to hospitalisation for RSV infection. Arch Dis Child. 2004;89(7):673-8. Level II-2 (A).
70. Wilkesmann A, Ammann RA, Schildgen O, Eis-Hubinger AM, Muller A, Seidenberg J, et al. Hospitalized children with respiratory syncytial virus infection and neuromuscular impairment face an increased risk of a complicated course. Pediatr Infect Dis J. 2007;26(6):485-91. Level II-3 (B).
71. Horn SD, Smout RJ. Effect of prematurity on respiratory syncytial virus hospital resource use and outcomes. J Pediatr. 2003;143(5 Suppl):S133-41. Level II-2 (A).
72. Engle WA. A recommendation for the definition of "late preterm" (near-term) and the birth weight-gestational age classification system. Semin Perinatol. 2006;30(1):2-7. Level III (B).
73. Engle WA, Tomashek KM, Wallman C. "Late-preterm" infants: a population at risk. Pediatrics. 2007;120(6):1390-401. Level III (A)
74. Coffman S. Late preterm infants and risk for RSV. MCN Am J Matern Child Nurs. 2009;34(6):378-84; quiz 85-6. Level III (C).
75. Sampalis JS, Langley J, Carbonell-Estrany X, Paes B, O'Brien K, Allen U, et al. Development and validation of a risk scoring tool to predict respiratory syncytial virus hospitalization in premature infants born at 33 through 35 completed weeks of gestation. Med Decis Making. 2008;28(4):471-80. Level II-1 (A).
76. Borell M, Myers J, Rineair S. Preventing RSV in pediatric patients: improving the outcome at home. Caring. 2007;26(9):34-7. Level III (C).
77. Dales RE, Cakmak S, Brand K, Judek S. Respiratory illness in children attending daycare. Pediatr Pulmonol. 2004;38(1):64-9. Level II-2 (A)
78. Holberg CJ, Wright AL, Martinez FD, Morgan WJ, Taussig LM. Child day care, smoking by caregivers, and lower respiratory tract illness in the first 3 years of life. Group Health Medical Associates. Pediatrics. 1993;91(5):885-92. Level II-3 (B).
79. Koch A, Molbak K, Homoe P, Sorensen P, Hjuler T, Olesen ME, et al. Risk factors for acute respiratory tract infections in young Greenlandic children. Am J Epidemiol. 2003;158(4):374-84. Level II-2 (A).
80. Bradley JP, Bacharier LB, Bonfiglio J, Schechtman KB, Strunk R, Storch G, et al. Severity of respiratory syncytial virus bronchiolitis is affected by cigarette smoke exposure and atopy. Pediatrics. 2005;115(1):e7-14. Level II-2 (A).
81. Gurkan F, Kiral A, Dagli E, Karakoc F. The effect of passive smoking on the development of respiratory syncytial virus bronchiolitis. Eur J Epidemiol. 2000;16(5):465-8. Level II-2 (A).
82. Hanrahan JP, Tager IB, Segal MR, Tosteson TD, Castile RG, Van Vunakis H, et al. The effect of maternal smoking during pregnancy on early infant lung function. Am Rev Respir Dis. 1992;145(5):1129-35. Level II-2 (A).
83. Jaakkola JJK, Jaakkola MS. Effects of environmental tobacco smoke on the respiratory health of children. Scand J Work Environ Health. 2002;28 Suppl 2:71-83. Level III (C)
84. Karr CJ, Rudra CB, Miller KA, Gould TR, Larson T, Sathyanarayana S, et al. Infant exposure to fine particulate matter and traffic and risk of hospitalization for RSV bronchiolitis in a region with lower ambient air pollution. Environ Res. 2009;109(3):321-7. Level II-2 (A).
85. Leung GM, Ho L-M, Lam T-H. Secondhand smoke exposure, smoking hygiene, and hospitalization in the first 18 months of life. Arch Pediatr Adolesc Med. 2004;158(7):687-93. Level II-2 (A).
86. Li JS, Peat JK, Xuan W, Berry G. Meta-analysis on the association between environmental tobacco smoke (ETS) exposure and the prevalence of lower respiratory tract infection in early childhood. Pediatr Pulmonol. 1999;27(1):5-13. Level II-1 (A).
87. Tepper RS, Williams-Nkomo T, Martinez T, Kisling J, Coates C, Daggy J. Parental smoking and airway reactivity in healthy infants. Am J Respir Crit Care Med. 2005;171(1):78-82. Level II-2 (A).
88. Young S, Sherrill DL, Arnott J, Diepeveen D, LeSouef PN, Landau LI. Parental factors affecting respiratory function during the first year of life. Pediatr Pulmonol. 2000;29(5):331-40. Level II-2 (A).
89. Figueras-Aloy J, Carbonell-Estrany X, Quero-Jimenez J, Fernandez-Colomer B, Guzman-Cabanas J, Echaniz-Urcelay I, et al. FLIP-2 Study: risk factors linked to respiratory syncytial virus infection requiring hospitalization in premature infants born in Spain at a gestational age of 32 to 35 weeks. Pediatr Infect Dis J. 2008;27(9):788-93. Level II-2 (A).
90. Cunningham J, Dockery DW, Speizer FE. Maternal smoking during pregnancy as a predictor of lung function in children. Am J Epidemiol. 1994;139(12):1139-52. Level II-3 (B).
91. Fingerhut LA, Kleinman JC, Kendrick JS. Smoking before, during, and after pregnancy. Am J Public Health. 1990;80(5):541-4. Level II-3 (B).
92. Bachrach VRG, Schwarz E, Bachrach LR. Breastfeeding and the risk of hospitalization for respiratory disease in infancy: a meta-analysis. Arch Pediatr Adolesc Med. 2003;157(3):237-43. Level II-3 (B).
93. Kramer MS, Chalmers B, Hodnett ED, Sevkovskaya Z, Dzikovich I, Shapiro S, et al. Promotion of Breastfeeding Intervention Trial (PROBIT): a randomized trial in the Republic of Belarus. Jama. 2001;285(4):413-20. Level I (A)
94. Elhassan NO, Stevens TP, Sorbero ME, Dick AW, Guillet R, Hall CB. Guidelines for palivizumab prophylaxis: are they based on infant's risk of hospitalization for respiratory syncytial viral disease? Pediatr Infect Dis J. 2003;22(11):939-43. Level 3 (C).
95. Hampp C, Kauf TL, Winterstein AG. Small budget impact is a result of flawed assumptions and ignores questionable cost-effectiveness for RSV prophylaxis. Value Health. 2010;13(5):684. Level III (C).
96. Frogel M, Nerwen C, Cohen A, VanVeldhuisen P, Harrington M, Boron M, et al. Prevention of hospitalization due to respiratory syncytial virus: results from the Palivizumab Outcomes Registry. J Perinatol. 2008;28(7):511-7. Level II-2 (A).
97. Frogel MP, Stewart DL, Hoopes M, Fernandes AW, Mahadevia PJ. A systematic review of compliance with palivizumab administration for RSV immunoprophylaxis. J Manag Care Pharm. 2010;16(1):46-58. Level II-2 (A)
98. Hand IL, Noble L, Geiss D, Shotkin A. Respiratory syncytial virus immunoprophylaxis in an urban population: a comparison of delivery strategies and outcomes. Pediatr Infect Dis J. 2008;27(2):175-6. Level II-2 (A).
99. Leader S, Kohlhase K. Respiratory syncytial virus-coded pediatric hospitalizations, 1997 to 1999. Pediatr Infect Dis J. 2002;21(7):629-32. Level II-2 (A)
100. Leader S, Kohlhase K. Recent trends in severe respiratory syncytial virus (RSV) among US infants, 1997 to 2000. J Pediatr. 2003;143(5 Suppl):S127-32. Level II-2 (A).
101. Leader S, Yang H, DeVincenzo J, Jacobson P, Marcin JP, Murray DL. Time and out-of-pocket costs associated with respiratory

syncytial virus hospitalization of infants. Value Health. 2003;6(2):100-6. Level II-2 (A).
102. McLaurin KK, Hall CB, Jackson EA, Owens OV, Mahadevia PJ. Persistence of morbidity and cost differences between late-preterm and term infants during the first year of life. Pediatrics. 2009;123(2):653-9. Level II-2 (A).
103. Boyer KM. RSV and the timing of surgery for congenital heart disease. Crit Care Med. 1999;27(9):2065-6. Level II-2 (A).
104. Eriksson M, Bennet R, Rotzen-Ostlund M, von Sydow M, Wirgart BZ. Population-based rates of severe respiratory syncytial virus infection in children with and without risk factors, and outcome in a tertiary care setting. Acta Paediatr. 2002;91(5):593-8. Level II-3 (B).
105. Lanari M, Rossi GA, Merolla R, di Luzio Paparatti U. High risk of nosocomial-acquired RSV infection in children with congenital heart disease. J Pediatr. 2004;145(1):140. Level II-3 (B).
106. Li A, Wang DY, Lanctot KL, Mitchell I, Paes BA, Investigators C. Comparing First- and Second-year Palivizumab Prophylaxis in Patients With Hemodynamically Significant Congenital Heart Disease in the CARESS Database (2005-2015). Pediatr Infect Dis J. 2017;36(5):445-50. Level II-1 (A).
107. Shekar K, Roberts JA, McDonald CI, Ghassabian S, Anstey C, Wallis SC, et al. Protein-bound drugs are prone to sequestration in the extracorporeal membrane oxygenation circuit: results from an ex vivo study. Crit Care. 2015;19:164. Level II-2 (A).
108. Panitch HB. Viral respiratory infections in children with technology dependence and neuromuscular disorders. Pediatr Infect Dis J. 2004;23(11 Suppl):S222-7. Level III (C).
109. Fitzgerald DA, Follett J, Van Asperen PP. Assessing and managing lung disease and sleep disordered breathing in children with cerebral palsy. Paediatr Respir Rev. 2009;10(1):18-24. Level III (C).
110. Skidmore MD, Rivers A, Hack M. Increased risk of cerebral palsy among very low-birthweight infants with chronic lung disease. Dev Med Child Neurol. 1990;32(4):325-32. Level II-2 (A).
111. Hoo A-F, Dezateux C, Henschen M, Costeloe K, Stocks J. Development of airway function in infancy after preterm delivery. J Pediatr. 2002;141(5):652-8. Level II-2 (A).
112. Hiatt PW, Grace SC, Kozinetz CA, Raboudi SH, Treece DG, Taber LH, et al. Effects of viral lower respiratory tract infection on lung function in infants with cystic fibrosis. Pediatrics. 1999;103(3):619-26. Level II-2 (A).
113. Langston C, Kida K, Reed M, Thurlbeck WM. Human lung growth in late gestation and in the neonate. Am Rev Respir Dis. 1984;129(4):607-13. Level II-3 (B).
114. Simoes EAF. Environmental and demographic risk factors for respiratory syncytial virus lower respiratory tract disease. J Pediatr. 2003;143(5 Suppl):S118-26. Level II-2 (A).
115. Kua KP, Lee SWH. Systematic Review of the Safety and Efficacy of Palivizumab among Infants and Young Children with Cystic Fibrosis. Pharmacotherapy. 2017;37(6):755-69. Level II-2 (A).
116. Strange C, Stoller JK, Sandhaus RA, Dickson R, Turino G. Results of a survey of patients with alpha-1 antitrypsin deficiency. Respiration. 2006;73(2):185-90. Level II-3 (B).
117. Mullowney T, Manson D, Kim R, Stephens D, Shah V, Dell S. Primary ciliary dyskinesia and neonatal respiratory distress. Pediatrics. 2014;134(6):1160-6. Level II-2 (B).
118. Arnold SR, Wang EE, Law BJ, Boucher FD, Stephens D, Robinson JL, et al. Variable morbidity of respiratory syncytial virus infection in patients with underlying lung disease: a review of the PICNIC RSV database. Pediatric Investigators Collaborative Network on Infections in Canada. Pediatr Infect Dis J. 1999;18(10):866-9. Level II-2 (A).
119. Wadsworth MEJ, Vinall LE, Jones AL, Hardy RJ, Whitehouse DB, Butterworth SL, et al. Alpha1-antitrypsin as a risk for infant and adult respiratory outcomes in a national birth cohort. Am J Respir Cell Mol Biol. 2004;31(5):559-64. Level II-2 (A).
120. Winterstein AG, Eworuke E, Xu D, Schuler P. Palivizumab immunoprophylaxis effectiveness in children with cystic fibrosis. Pediatr Pulmonol. 2013;48(9):874-84. Level II-2 (A).
121. Ren CL, Konstan MW, Rosenfeld M, Pasta DJ, Millar SJ, Morgan WJ, et al. Early childhood wheezing is associated with lower lung function in cystic fibrosis. Pediatr Pulmonol. 2014;49(8):745-50. Level II-2 (A).
122. Boeckh M, Berrey MM, Bowden RA, Crawford SW, Balsley J, Corey L. Phase 1 evaluation of the respiratory syncytial virus-specific monoclonal antibody palivizumab in recipients of hematopoietic stem cell transplants. J Infect Dis. 2001;184(3):350-4. Level II-1 (A).
123. Ottolini MG, Curtis SR, Mathews A, Ottolini SR, Prince GA. Palivizumab is highly effective in suppressing respiratory syncytial virus in an immunosuppressed animal model. Bone Marrow Transplant. 2002;29(2):117-20. Level I (A).
124. Thomas NJ, Hollenbeak CS, Ceneviva GD, Geskey JM, Young MJ. Palivizumab prophylaxis to prevent respiratory syncytial virus mortality after pediatric bone marrow transplantation: a decision analysis model. J Pediatr Hematol Oncol. 2007;29(4):227-32. Level II-2 (A).
125. Sanchez-Luna M, Medrano C, Lirio J, Group R-S. Down syndrome as risk factor for respiratory syncytial virus hospitalization: A prospective multicenter epidemiological study. Influenza Other Respir Viruses. 2017;11(2):157-64. Level 1 (B).
126. Schildgen O. The lack of protective immunity against RSV in the elderly. Epidemiol Infect. 2009;137(12):1687-90. Level III (C).
127. Cunha BA, Syed U, Hage JE. Respiratory syncytial virus (RSV) community-acquired pneumonia (CAP) ina hospitalized adult with human immunodeficiency virus (HIV) mimicking influenza A and Pneumocystis (carinii) jiroveci pneumonia (PCP). Heart Lung. 2012;41(1):76-82. Level II-3 (B).
128. edraz C, Carbonell-Estrany X, Figueras-Aloy J, Quero J. Effect of palivizumab prophylaxis in decreasing respiratory syncytial virus hospitalizations in premature infants. Pediatr Infect Dis J. 2003;22(9):823-7. Level II-2 (A).
129. Fenton C, Scott LJ, Plosker GL. Palivizumab: a review of its use as prophylaxis for serious respiratory syncytial virus infection. Paediatr Drugs. 2004;6(3):177-97. Level III (B).
130. Centers for Disease Control, Prevention. Respiratory syncytial virus activity - United States, July 2008-December 2009. MMWR Morb Mortal Wkly Rep. 2010;59(8):230-3. Level II-3 (B).
131. Bulkow LR, Singleton RJ, Karron RA, Harrison LH. Risk factors for severe respiratory syncytial virus infection among Alaska native children. Pediatrics. 2002;109(2):210-6. Level II-2 (A).
132. Bauman J, Eggleston M, Oquist N, Malinoski F. Respiratory syncytial virus: seasonal data for regions of Florida and implications for palivizumab. South Med J. 2007;100(7):669-76. Level II-3 (B).
133. Light M, Bauman J, Mavunda K, Malinoski F, Eggleston M. Correlation between respiratory syncytial virus (RSV) test data and hospitalization of children for RSV lower respiratory tract illness in Florida. Pediatr Infect Dis J. 2008;27(6):512-8. Level II-3 (B).
134. Yorita KL, Holman RC, Steiner CA, Effler PV, Miyamura J, Forbes S, et al. Severe bronchiolitis and respiratory syncytial virus among young children in Hawaii. Pediatr Infect Dis J. 2007;26(12):1081-8. Level II-2 (A).
135. Banerji A, Ng K, Moraes TJ, Panzov V, Robinson J, Lee BE. Cost-effectiveness of palivizumab compared to no prophylaxis in term infants residing in the Canadian Arctic. CMAJ Open. 2016;4(4):E623-E33. Level II-2 (A).
136. Suryadevara M, Cummings E, Bonville CA, Bartholoma N, Riddell S, Kiska D, et al. Viral etiology of acute febrile respiratory illnesses in hospitalized children younger than 24 months. Clin Pediatr (Phila). 2011;50(6):513-7. Level II-2 (A).
137. Tang JW, Loh TP. Correlations between climate factors and incidence--a contributor to RSV seasonality. Reviews in medical virology. 2014;24(1):15-34. Level III (C).

138. Krilov LR. Palivizumab in the prevention of respiratory syncytial virus disease. Expert Opin Biol Ther. 2002;2(7):763-9. Level III (C).
139. Groothuis JR, Nishida H. Prevention of respiratory syncytial virus infections in high-risk infants by monoclonal antibody (palivizumab). Pediatr Int. 2002;44(3):235-41. Level III (C).
140. Scott LJ, Lamb HM. Palivizumab. Drugs. 1999;58(2):305-11; discussion 12-3. Level III (C).
141. Zhang Z-Y, Du L-N, Chen X, Zhao Y, Liu E-M, Yang X-Q, et al. Genetic variability of respiratory syncytial viruses (RSV) prevalent in Southwestern China from 2006 to 2009: emergence of subgroup B and A RSV as dominant strains. J Clin Microbiol. 2010;48(4):1201-7. Level II-2 (A).
142. U.S. Food and Drug Administration's Division of Drug Marketing A, and Communications. TRUTHFUL PRESCRIPTION DRUG ADVERTISING AND PROMOTION: THE PRESCRIBER'S ROLE 2010 [cited 2011 1/20/2012]. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/PrescriptionDrugAdvertisingandPromotionalLabeling/UCM209847.pdf. Level III (C).
143. Barton MB, Miller T, Wolff T, Petitti D, LeFevre M, Sawaya G, et al. How to read the new recommendation statement: methods update from the U.S. Preventive Services Task Force. Annals of internal medicine. 2007;147(2):123-7. Level III (C).
144. Guirguis-Blake J, Calonge N, Miller T, Siu A, Teutsch S, Whitlock E, et al. Current processes of the U.S. Preventive Services Task Force: refining evidence-based recommendation development. Annals of internal medicine. 2007;147(2):117-22. Level III (C).

NT

Corresponding Author

Mitchell Goldstein, MD
Chair, 2018 Respiratory Syncytial Virus (RSV) Prevention Guideline Committee
Past President, Emeritus Board
National Perinatal Association
Lonedell, MO
Professor of Pediatrics, Loma Linda University School of Medicine
Division of Neonatology
Loma Linda University Children's Hospital
Loma Linda, CA USA
Office 909-558-7448
Fax: 909-558-0298

MGoldstein@llu.edu

Raylene Phillips, MD
Immediate Past President, Executive Board
National Perinatal Association
Lonedell, MO
Associate Professor of Pediatrics, Loma Linda University School of Medicine
Division of Neonatology
Loma Linda University Children's Hospital
Loma Linda, CA USA

John P. DeVincenzo, MD
Children's Foundation Professor of Pediatrics
Division of Pediatric Infectious Diseases
Professor of Microbiology, Immunology, and Biochemistry
Director Molecular and Virology Diagnostics Laboratories
University of Tennessee Center for Health Sciences
Memphis, TN USA

Leonard R. Krilov, MD
Chairman, Department of Pediatrics
Chief, Pediatric Infectious Disease
NYU Winthrop and Professor of Pediatrics
SUNY Stony Brook School of Medicine
Stony Brook, NY USA

T. Allen Merritt, MD
Executive Board
National Perinatal Association
Lonedell, MO
Professor of Pediatrics, Loma Linda University School of Medicine
Division of Neonatology
Loma Linda University Children's Hospital
Loma Linda, CA USA

Ram Yogev, MD
Director, Pediatric and Maternal HIV Infection;
Susan B. DePree Founders' Board Professor of Pediatrics, Northwestern University Feinberg School of Medicine
Ann & Robert H. Lurie Children's Hospital
Chicago, IL USA

Suzanne Staebler, DNP, APRN, NNP-BC, FAANP, FAAN
Associate Professor, Clinical Track
Specialty Program Director, NNP Program
Nell Hodgson Woodruff School of Nursing at Emory University
Atlanta, GA USA

Munaf Kadri, MD
Chair of Quality Assurance and Quality Improvement
Founding Board Member
Umma Community Clinic
Los Angeles, CA
Assistant Professor of Pediatrics, Loma Linda School of Medicine
Division of Neonatology
Loma Linda University Children's Hospital
Loma Linda, CA USA

Jaime E. Fergie, MD
Director Infectious Diseases
Driscoll Children's Hospital
Corpus Cristi, TX
Professor of Pediatrics
Texas A&M College of Medicine
Bryan, TX USA

Michael S. Schechter, MD, MPH
Professor and Chief
Division of Pulmonary Medicine
Department of Pediatrics
Virginia Commonwealth University
Children's Hospital of Richmond at VCU
Richmond, VA USA

Millicent Gorham, PhD, MBA, FAAN
Executive Director
National Black Nurses Association
Silver Spring, MD USA

James D. Cherry, MD, MSc
Distinguished Professor of Pediatrics, David Geffen School of Medicine at the University of California, Los Angeles
Division of Infectious Diseases
University of California, Los Angeles
Mattel Children's Hospital
Los Angeles, CA USA