NEONATOLOGY TODAY

News and Information for BC/BE Neonatologists and Perinatologists

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Upcoming Medical Meetings

(See www.Neonate.biz for additional meetings)

Hot Topics in Neonatology
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www.psnbm.org.ph

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NEO: The Conference for Neonatology
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2015 Workshop on Perinatal Practice Strategies
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The 26th Annual Meeting of the European Society of Paediatric and Neonatal Intensive Care (ESPNIC 2015)
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Miami Neonatology - 38th Annual International Conference
Nov. 12-15, 2015; Miami, FL USA
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National Perinatal Association 2015 Respiratory Syncytial Virus (RSV) Prevention Guideline

By Mitchell Goldstein, MD; T. Allen Merritt, MD; Raylene Phillips, MD; Gilbert Martin, MD; Sue Hall, MD; Rami Yogev, MD; Alan Spitzer, MD

Peer reviewed

I. Background: Respiratory Syncytial Virus (RSV) is a virus that causes mild, cold-like symptoms in adults, children and most infants born at term. In premature and "at-risk" infants, RSV can cause severe disease and remains a very serious health concern. RSV is the leading cause of hospitalization in babies less than one year of age and causes approximately 90,000 hospitalizations and 4,500 deaths per year in children age five and under.[1-3] 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 certain neonatal and pediatric patients.[4-7] Non-uniform application of RSV prophylaxis over the course of the past several years has increased as providers have endorsed regimens that are not in compliance with Food and Drug Administration (FDA) indication.[8] As recommendations have progressively deviated from the FDA indication, most babies at risk for RSV could now be deemed ineligible for prophylaxis. Parent groups have published recommendations for obtaining coverage for RSV prophylaxis using a number of different techniques including appeals, letter-writing campaigns and engaging insurers. 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/rsv-season-toolkit/.

Whether or not these appeals are successful, the process of appeal has resulted in delays in the administration of immunization. Delays from appeal processes and irregular, sub-optimal dosing regimens have resulted in the reduction of palivizumab levels necessary to prevent illness resulting in hospital admission.[9]

Veering from FDA indications can also lead to provider confusion. Although there is no substitute for clinical practice, recommendations on dosing should be issued in a manner consistent with the broadest FDA indication for dosing to accommodate provider discretion.[8] Although it may be recognized that guidelines do not apply in every condition and for every case and that variation from the guideline is still acceptable practice, the FDA indication provides the most clarity in preventing use of a pharmaceutical product outside of its carefully studied parameters. Following FDA indications is important from a medical-legal perspective as insurers often adopt only the FDA indication for medication administration per se and not the proviso that there can be exceptions due to consensus guidance. Major deviation from the established FDA indication leads to provider disenfranchisement (http://www.nann.org/uploads/RSVGuidelineResponse.pdf) and lack of universal acceptance of a standard of practice.

Of particular public concern has been a de-emphasis on the best available evidence and a focus on adjudicated studies to generate a form of 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 immuno

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prophylaxis of RSV, in an effort to ration therapy and reduce costs, is contrary to published evidence and the FDA-approved product indication for palivizumab.[10] Not dosing according to indication is considered an "off label" use of a medication.[11] Although cost effectiveness is increasingly important, decisions regarding the appropriateness of RSV prophylaxis must be based on the evidence, and not result in harm to the patient at risk.[12-15] Denial of full coverage based on gestational age, without consideration of other risk factors discriminates against certain populations of premature infants and may put other populations at even greater risk due to health and societal disparities.[16,17] Making RSV a reportable disease may be important in documenting the actual extent of RSV prevalence and costs.[16] 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.[8,18]

Even in high-risk infants from 32-35 weeks' gestation, RSV can result in serious morbidities. In one study, Ambrose, et al., evaluated 1642 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 weeks gestation who were <6 months on November 1, 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 week gestation infants eligible under a risk-related criteria, the RSV-related hospitalization rate was 9.1%.[9,19] A recent study by Blanken, et al., supports the original evidence presented in the IMpact RSV trial. In fact, in this study, palivizumab decreased RSV-related hospitalization in 33-35 week gestation infants by 82%, whereas the original IMpact study described a 78% decrease.[20,21] 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).[20,22-24]

Winterstein, et al., evaluated 247,566 patients in Florida and Texas to determine the age at which at-risk infants born from 32-34 weeks gestation 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 equivalent to that of term babies. 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. Increasingly, preterm infants were at higher risk for hospitalization, and the issues pertaining to disparity could not be separately identified in the populations studied.[25] Further, in another at-risk population in Florida, Winterstein, et al., demonstrated that palivizumab prophylaxis was associated with a reduction in severe RSV infection.[26] Analysis of the Kids' Inpatient Database of hospitalizations between 2000-2009 (n=325,494) showed that while the bronchiolitis-related hospitalizations were overall decreased by 17% among all children less than two years of age, bronchiolitis hospitalizations actually increased by 29% in the sub-group where there was an FDA indication for palivizumab prophylaxis.[27,28]

In a study conducted by Hall, et al., RSV-related hospitalizations among preterm and term infants were evaluated in 3 U.S. counties. RSV acute respiratory illness was tallied, and relative risk was identified by age from birth certificate data. Although this study has been used as justification for reduced immunoprophylaxis, the study included an insufficient number of premature infants. Premature infants represented only 10% of the 2,140 subjects studied. Although RSV rates in this study were not found to be significantly different between preterm and term infants, up to 70% of the palivizumab-eligible patients in the study populations may have received palivizumab. Black infants greater than or equal to 6 months of age were hospitalized more often.[17] Previous studies such as that by Boyce, et al., had identified a two-fold higher hospitalization rate for preterm infants.[29] This higher rate of hospitalization might be expected to drop if adequate compliance with prophylaxis guidelines could be assured.[30]

It is well-documented that RSV is associated with a risk of subsequent wheeze and development of reactive lung disease.[31-33] Blanken, et al., demonstrated a significant reduction in wheeze in an at-risk group of infants born at a gestational age of 33 to 35 weeks that received palivizumab prophylaxis. Recurrent wheeze was 10 percentage points lower in patients treated with palivizumab (11% vs. 21%, P=0.01).[21] 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.[34] Subclinical RSV disease that is not identified in the course of a provider interaction may be clinically significant and result in increased morbidity.[13]

Children at high risk for RSV include those with other co-morbidities besides prematurity, including chronic lung disease and congenital heart disease. 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.[35] Actual RSV worldwide fatality data may be useful in determining whether including co-morbidities in evaluating acceptable risk is appropriate.[3,13,36]

II. Financial Considerations: Cost stewardship is important. Patients should receive the best possible care at the lowest possible cost.[10] 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.[13,37,38] 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 weeks gestation.[13,39] 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 from RSV disease 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 justification for prophylaxis.

III. Introduction: RSV is the leading cause of hospitalization for all children less than 12 months of age in the United States.[29,40,41] 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.[42-49] 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 in decreasing hospitalization. The best approach to RSV in at-risk groups is prevention.[20,24,44,50-52] In patients with CLD/BPD and premature infants born at less than 36 weeks' gestational age, prophylaxis decreased hospitalization by 55%; in the subgroup of patients born between 32-35 weeks' gestation, hospitalization rates decreased by 80%.[20] 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.

IV. Respiratory Syncytial Virus Prophylaxis

A. Prophylaxis to prevent RSV is available as intramuscular monoclonal antibody preparation (palivizumab).[53,54]

B. RSV infection is responsible for significant hospitalizations, morbidity, and mortality in infants less than 24 months of age who have chronic lung disease, congenital heart disease, compromised respiratory or immune systems, or impaired nutritional status and growth.[24,50,55]

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., caffeine), supplemental oxygen, bronchodilators, home apnea monitoring, home pulse oximetry, or diuretics.[47,56,57]

2. Infants born at 32 weeks or less without CLD/BPD will also benefit from prophylaxis:[58]

a. Infants born at less than 28 0/7 weeks 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 between 28 0/7 and 32 0/7 weeks of gestation 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 may merit special consideration.[59-61] However, prophylaxis for infants born at 32 1/7 to 35 6/7 weeks gestation 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.[62] 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: child care 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.[33,56,63-66] Correlations exist between air quality and respiratory function.[32,65-75] 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.[32,49] The greater the number of risk factors, the higher the likelihood of RSV hospitalization.[76] A history of maternal smoking during pregnancy may be ameliorated as a risk factor by a history of breastfeeding for greater than 2 months.[69,77-80] These circumstances must be accounted for in the risk assessment.

d. The provider must be aware of risk created by disparity. Minority African American and Hispanic populations who live in blighted inner city neighborhoods are at a higher cumulative risk.[16]

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.[81] 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, fewer than 50% of eligible patients received any prophylaxis, neither prior to nor after discharge.[82] 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.[83-85]

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 the 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 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.[86-89]

4. Infants with congenital heart disease have been shown to benefit from palivizumab.[24,90-92] 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.[24] Infants with complex congenital heart disease are at risk and should be consider as candidates 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 in 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.[90,92] 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.

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.[93] CNS injury prior to, during, or after birth 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.[55,57,93] 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.[94,95]

2. Patients with congenital abnormalities of the airways that compromise respiratory function should receive prophylaxis.[43,96-99] 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.[34] 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. Identification of cystic fibrosis on a newborn screen may merit special consideration.[97,100-102]

4. Immune deficiencies are rare disorders and require collaborative management by pediatricians, infectious disease specialists, and immunologists.[103,104] HIV, SCID, primary or secondary bone marrow depletion, and any defect of humoral or cellular immunity places a patient at-risk of concomitant infection. 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. Special risk circumstances may occur in homes where another individual is at high risk for RSV infection (e.g., an elderly immunocompromised relative), but who may not be able to receive RSV prophylaxis. Providers should determine if it is reasonable to provide prophylaxis to other members of the household.[3,105,106]

E. Administration

1. The National Perinatal Association Guidelines for RSV Prophylaxis are 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.[6,107,108] 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.[109-113] Transport distance of ill infants and resource allocation

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	Less than 12 months at start of RSV season	Monthly during RSV season
Born at 28 0/7-32 0/7 weeks	Less than 6 months at start of RSV season	Monthly during RSV season
Born at 32 1/7-35 6/7 weeks	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	Less than 24 months at start of RSV season	Monthly during RSV season
Immune disorders	Less than 24 months at start of RSV season unless infectious disease or immunology waiver obtained	Monthly during RSV season
Cystic Fibrosis or α1-antitrypsin deficiency	Less than 24 months at start of RSV season; consultation with pediatric pulmonology suggested	Monthly during RSV season

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). The burden of severe RSV disease on healthcare resources is greater than other respiratory viruses.[114] 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.[9,20,108,115] 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.[116]

3. 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. 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 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 877-RX-DDMAC or (877-793-3622), E-Mail: BadAd@fda.gov, by mail: FDA/CDER/DDMAC, 5901-B Ammendale Rd., Beltsville, MD 20705-1266, or Fax: 301-847-8444.[117] However, in the past, 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 law not only provides substantial rewards for whistleblowers, but it includes an action-enforcing mechanism that statutorily requires the government to investigate. If providers want to ensure that the government will consider their concerns, they can file a False Claims Act qui tam action.

4. Once an infant begins RSV prophylaxis for the RSV season, the infant must receive palivizumab monthly through the end of the season.[22]

5. 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.[53] 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.[53]

6. As there is more than one serotype of RSV, RSV disease is not a contraindication to continuing the palivizumab dosing schedule. Infection does not confer lasting immunity. Patients can be re-infected with RSV multiple times during the same RSV season. Thus, monthly dosing should be continued even if the patient is infected with RSV.[53]

7. Fever or other illness including viral syndromes are not contraindications to administration of palivizumab.

8. There are no restrictions on concurrent RSV prophylaxis with any immunization.[118] 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, Diptheria, Tetanus, Pertussis (DTaP) primary immunization schedule, H. Influenza type B (Hib), seasonal influenza vaccination, Pneumococcal Conjugate Vaccine (PCV), or Inactivated Poliovirus Vaccine (IPV).

9. The safety and efficacy of palivizumab have not been demonstrated for treatment of established RSV disease.

10. 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.[53]

b. Fever, irritability and injection site reaction are the most commonly reported adverse events.[119]

V. Nosocomial Infection

A. RSV is 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 stud-

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ies to identify and isolate RSV-infected infants.[40] Proper hand washing is of paramount importance.

C. Cohorting of children with suspected RSV disease is not recommended. Not only are there other viral or bacterial diseases that mimic RSV, but infection with RSV does not preclude co-infection with bacteria, other viruses, or another subtype of RSV. For management of suspected nosocomial outbreaks of RSV occurring within a neonatal intensive care unit, the advice of infectious disease, and infection control experts should be sought.[40,120]

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 locate relevant articles published on Respiratory Syncytial Virus (RSV). The search was restricted to articles published in the English language. Priority, where possible, was given to articles reporting the outcomes of original research. Review articles and commentaries were also consulted where their inclusion was felt to be substantive. Abstracts of research presented at scientific conferences were not included in this document. 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:

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.

III. 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.

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*vs control discontinued Enfamil formulas without DHA and ARA (formula-fed infants) and vs Enfamil powder HMF (breastfed infants)

HMF = human milk fortifier

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