Respiratory Syncytial Virus (RSV) Prevention

ISSUE: There is a high level of evidence that RSV prophylaxis is effective. NPA proposes expanding access for certain neonatal and pediatric patients, consistent with the evidence available at this time.1-3

BACKGROUND: RSV is the leading cause of hospitalization in all children less than 12 months of age for the United States.4-6 The majority of these hospitalizations occur in otherwise healthy infants. 60% of the top five hospital discharge diagnoses are attributable to bronchiolitis. Certain groups of infants and children have higher rates of re-hospitalization including children with Chronic Lung Disease (CLD)/Bronchopulmonary Dysplasia (BPD), Congenital Heart Disease (CHD), and premature infants.7-14 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.9,15-19 In patients with CLD/BPD and premature infants born at less than 36 weeks gestational age, prophylaxis decreased hospitalization by 55%; in the patients born between 32-35 weeks gestation, hospitalization rates decreased by 80%.15

Respiratory Syncytial Virus Prophylaxis:

A. Prophylaxis to prevent RSV is available as intramuscular monoclonal antibody preparation (palivizumab).20,21

B. RSV infection is responsible for significant hospitalizations, morbidity, and mortality in infants less than 24 months of age who have CLD/BPD, Congenital Heart Disease, compromised respiratory or immune systems or who have impaired nutritional status and growth.16,17,22

C. Candidates for RSV Prophylaxis: Decisions regarding appropriateness of RSV prophylaxis must be individualized.

1. Infants or children 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 CLD/BPD within 6 months of the start of the RSV season will benefit from RSV prophylaxis. Other interventions for CLD/BPD may include use of corticosteroid preparations, methylxanthines, supplemental oxygen, bronchodilators, home apnea monitoring, home pulse oximetry, or diuretics.12,23,24

2. Infants born at 32 weeks or less without CLD/BPD will also benefit from prophylaxis:25
   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. Birth at a late preterm gestation may merit special consideration.26-28 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. 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. 29The 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 consequences. 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 developmental disability as well as loss of academic potential must also be considered.30-33 A neonatologist, pediatrician, or other primary care provider is often in the best position to assess and interpret relative risk factors. 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 maternal smoking; however, exposure to environmental air pollutants, congenital abnormalities of the airways, or severe neuromuscular disease may also justify concern.23,34-38 Correlations exist between air quality and respiratory function.37-48 Thus, environmental air quality assessment is important for these patients with special consideration given to unique circumstances of unwarranted air pollution such as residence near a bus station or industrial plant, or use of a wood 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 for the immediate term. 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 particular risk factor has been shown to be unique in its predictive value, and frequently many risk factors may exist simultaneously.14,46 The greater the number of risk factors, the higher the likelihood of RSV hospitalization.49 A history of maternal smoking during pregnancy may be augmented as a risk factor by a history of breastfeeding for less than 2 months.41,50-53 These circumstances must be accounted for in the risk assessment. The provider must be aware of risk created by disparity. Minority African American and Hispanic populations in blighted inner city neighborhoods are at a higher cumulative risk.54 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.55 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 prophylaxis.56 Lack of parental education, language difficulties, transportation challenges, and issues of potential problems with insurance coverage must be resolved prior to discharge home. 57-59

4. Palivizumab has been shown to be of benefit to patients with congenital heart disease.16,60-62 The degree and severity of the heart disease may factor into the decision to provide RSV prophylaxis. In order to exclude an infant from receiving palivizumab, the infant must have a documented waiver provided by a board certified pediatric cardiologist that their cardiac defect is hemodynamically insignificant and thereby poses no additional risk for RSV. Children who are in need of or status post cardiac transplantation are in a particularly high risk group and should be given RSV prophylaxis.60,62 During RSV season, children who have received Extracorporeal Membrane Oxygenation (ECMO) management or any other form of cardiac bypass should receive monthly prophylaxis.5

5. Infants with severe neuromuscular disease affecting respiratory function may be candidates for palivizumab prophylaxis, including those with neuromuscular maturational disease common in premature infants.63 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) all are considerations for RSV prophylaxis. IVH, HIE, and PVL may cause cerebral palsy (CP) at a later time. CP alone may be a qualifier for RSV prophylaxis if there is any association with impaired respiratory function.

6. Patients with congenital abnormalities of the airways that compromise respiratory function should receive prophylaxis. This may include persisting wheeze, or disorders of abnormal lung growth. Congenital diaphragmatic hernia is included in this category.

7. 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.

8. Immune deficiencies are rare disorders and require collaborative management by pediatricians, infectious disease specialists, and immunologists. Although there is no conclusive evidence for a 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.

9. Special risk circumstances may occur in homes where another individual is at high risk for RSV infection 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.

D. Administration

1. RSV prophylaxis should be initiated prior to the onset of the RSV season and terminated at the end of the RSV season. 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, 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. The burden of severe RSV disease on healthcare resources is greater than other respiratory viruses. 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. Use of an abbreviated schedule of RSV prophylaxis (e.g., based on post conceptual age mid season) is contrary to published evidence and Food and Drug Association (FDA) approved product indication for palivizumab and is strongly discouraged.

2. Non-adherence to FDA approved dosing regimens is considered an off label use of a medication. 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 (e.g., 3 doses are as effective as 5). 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. 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 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, they can file a False Claims Act qui tam action.

3. Once a child begins RSV prophylaxis for the RSV season, the child must receive palivizumab monthly through the end of the season.86

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.20 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. The vial should not be re-entered.20

5. 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.20

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

7. At present, there are no restrictions on concurrent RSV prophylaxis with any immunization.87 Immunization with Measles-Mumps-Rubella (MMR) and Varicella vaccines need not be deferred in infants receiving RSV prophylaxis. RSV prophylaxis should 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.

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.20
   b. Fever, irritability and injection site reaction are the most commonly reported adverse events.88

IV. 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 practice, the use of in hospital screening studies to identify and cohort RSV-infected infants.4 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 these viruses or bacteria, or for that matter, another subtype of RSV.4,89
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<thead>
<tr>
<th>Indication</th>
<th>Age of Child</th>
<th>Dosing</th>
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<tr>
<td>Chronic Lung Disease requiring medical management</td>
<td>Less than 24 months at start of RSV season</td>
<td>Monthly during RSV season</td>
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<tr>
<td>Born at &lt; 28 0/7 weeks</td>
<td>Less than 12 months at start of RSV season</td>
<td>Monthly during RSV season</td>
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<td>Born at 28 0/7-32 0/7 weeks</td>
<td>Less than 6 months at start of RSV season</td>
<td>Monthly during RSV season</td>
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<tr>
<td>Born at 32 1/7-35 6/7 weeks</td>
<td>Less than 6 months at start of RSV season with provider determined significant risk</td>
<td>Monthly during RSV season</td>
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<tr>
<td>Congenital Heart Disease</td>
<td>Less than 24 months at start of RSV season unless cardiology waiver obtained</td>
<td>Monthly during RSV season</td>
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<tr>
<td>Neuromuscular Disease</td>
<td>Less than 24 months at start of RSV season</td>
<td>Monthly during RSV season</td>
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<tr>
<td>Congenital Abnormalities of the Airways</td>
<td>Less than 24 months at start of RSV season</td>
<td>Monthly during RSV season</td>
</tr>
<tr>
<td>Immune Disorders</td>
<td>Less than 24 months at start of RSV season unless infectious disease or immunology waiver obtained</td>
<td>Monthly during RSV season</td>
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26. Engle WA. A recommendation for the definition of "late preterm" (near-term) and the birth weight-gestational age classification system. Semin Perinatol 2006;30:2-7.

50. Cunningham J, Dockery DW, Speizer FE. Maternal smoking during pregnancy as a predictor of lu