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Updated Guidance for Palivizumab Prophylaxis Among Infants and Young Children at Increased Risk of Hospitalization for Respiratory Syncytial Virus Infection

COMMITTEE ON INFECTIOUS DISEASES AND BRONCHIOLITIS
GUIDELINES COMMITTEE

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POLICY STATEMENT

Updated Guidance for Palivizumab Prophylaxis Among Infants and Young Children at Increased Risk of Hospitalization for Respiratory Syncytial Virus Infection

COMMITTEE ON INFECTIOUS DISEASES AND BRONCHIOLITIS
GUIDELINES COMMITTEE**KEY WORDS**

RSV, respiratory syncytial virus, palivizumab, bronchiolitis, infants and young children, chronic lung disease, congenital heart disease

ABBREVIATIONSAAP—American Academy of Pediatrics
CHD—congenital heart disease
CLD—chronic lung disease
COID—Committee on Infectious Diseases
RSV—respiratory syncytial virus

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The guidance in this statement does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

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abstract

FREE

Palivizumab was licensed in June 1998 by the Food and Drug Administration for the reduction of serious lower respiratory tract infection caused by respiratory syncytial virus (RSV) in children at increased risk of severe disease. Since that time, the American Academy of Pediatrics has updated its guidance for the use of palivizumab 4 times as additional data became available to provide a better understanding of infants and young children at greatest risk of hospitalization attributable to RSV infection. The updated recommendations in this policy statement reflect new information regarding the seasonality of RSV circulation, palivizumab pharmacokinetics, the changing incidence of bronchiolitis hospitalizations, the effect of gestational age and other risk factors on RSV hospitalization rates, the mortality of children hospitalized with RSV infection, the effect of prophylaxis on wheezing, and palivizumab-resistant RSV isolates. This policy statement updates and replaces the recommendations found in the 2012 *Red Book. Pediatrics* 2014;134:415–420

Policy statements from the American Academy of Pediatrics (AAP) are designed to provide updated guidance for child health care topics, with an emphasis on evidence-based recommendations whenever possible. Policy statements are reviewed at least every 3 years and updated when appropriate. In following this procedure, the AAP Committee on Infectious Diseases (COID) has undertaken a systematic review of all recent and older peer-reviewed literature relating to the burden of respiratory syncytial virus (RSV) disease in infants and children, focusing on publications that delineate children at greatest risk of serious RSV disease and studies that define pharmacokinetics, safety, and efficacy. Detailed input regarding this guidance has been solicited from 21 committees, councils, sections, and advisory groups within the AAP, as well as organizations outside the AAP. Outside groups include the American College of Chest Physicians, American College of Emergency Physicians, American Thoracic Society, Emergency Nurses Association, National Association of Neonatal Nurses, National Association of Neonatal Nurse Practitioners, and Society of Hospital

Medicine. In addition, this review includes all data presented to the COID by the manufacturer of palivizumab.

As part of this deliberative review of palivizumab use, the COID judged the quality of the available data, as well as the impact of palivizumab prophylaxis to reach a unanimous consensus on guidance for the use of palivizumab in the United States. Cost was considered during deliberations by the COID and Bronchiolitis Guideline Committee, but the final guidance as presented here is driven by the limited clinical benefit derived from palivizumab prophylaxis.^{1–3}

As detailed in the accompanying technical report,⁴ the benefit resulting from this drug is limited. Palivizumab prophylaxis has limited effect on RSV hospitalizations on a population basis, no measurable effect on mortality, and a minimal effect on subsequent wheezing.

This policy statement updates and replaces the most recent AAP recommendations for the use of palivizumab prophylaxis published in 2012 in the 29th edition of the *Red Book*.⁵ This policy statement offers specific guidance for the use of palivizumab on the basis of available evidence, as well as expert opinion. A detailed discussion of the foundation of the updated guidance for each category as well as the references for each section may be found in the accompanying technical report,⁴ and AAP guidelines for the diagnosis and management of bronchiolitis, which were published in 2006⁶ (for which a revision is forthcoming).

The palivizumab package insert states: “Synagis is indicated for the prevention of serious lower respiratory tract disease caused by RSV in children at high risk of RSV disease.”⁷ In the absence of a specific definition of “high risk” by the US Food and Drug Administration, the AAP has endeavored to provide pediatricians and other health care providers with more

precise guidance for determining who is at increased risk since palivizumab was first licensed.^{5,8–11}

The informed opinion of the COID and the Bronchiolitis Guidelines Committee, as well as others participating in the current statement, is that palivizumab use should be restricted to the populations detailed below.

PRETERM INFANTS WITHOUT CHRONIC LUNG DISEASE OF PREMATURITY OR CONGENITAL HEART DISEASE

Palivizumab prophylaxis may be administered to infants born before 29 weeks, 0 days’ gestation who are younger than 12 months at the start of the RSV season. For infants born during the RSV season, fewer than 5 monthly doses will be needed.

Available data for infants born at 29 weeks, 0 days’ gestation or later do not identify a clear gestational age cutoff for which the benefits of prophylaxis are clear. For this reason, infants born at 29 weeks, 0 days’ gestation or later are not universally recommended to receive palivizumab prophylaxis. Infants 29 weeks, 0 days’ gestation or later may qualify to receive prophylaxis on the basis of congenital heart disease (CHD), chronic lung disease (CLD), or another condition.

Palivizumab prophylaxis is not recommended in the second year of life on the basis of a history of prematurity alone.

Some experts believe that on the basis of the data quantifying a small increase in risk of hospitalization, even for infants born earlier than 29 weeks, 0 days’ gestation, palivizumab prophylaxis is not justified.

PRETERM INFANTS WITH CLD

Prophylaxis may be considered during the RSV season during the first year of life for preterm infants who develop

CLD of prematurity defined as gestational age <32 weeks, 0 days and a requirement for >21% oxygen for at least the first 28 days after birth.

During the second year of life, consideration of palivizumab prophylaxis is recommended only for infants who satisfy this definition of CLD of prematurity and continue to require medical support (chronic corticosteroid therapy, diuretic therapy, or supplemental oxygen) during the 6-month period before the start of the second RSV season. For infants with CLD who do not continue to require medical support in the second year of life prophylaxis is not recommended.

INFANTS WITH HEMODYNAMICALLY SIGNIFICANT CHD

Certain children who are 12 months or younger with hemodynamically significant CHD may benefit from palivizumab prophylaxis. Children with hemodynamically significant CHD who are most likely to benefit from immunoprophylaxis include infants with acyanotic heart disease who are receiving medication to control congestive heart failure and will require cardiac surgical procedures and infants with moderate to severe pulmonary hypertension.

Decisions regarding palivizumab prophylaxis for infants with cyanotic heart defects in the first year of life may be made in consultation with a pediatric cardiologist.

These recommendations apply to qualifying infants in the first year of life who are born within 12 months of onset of the RSV season.

The following groups of infants with CHD are not at increased risk of RSV infection and generally should not receive immunoprophylaxis:

- Infants and children with hemodynamically insignificant heart disease (eg, secundum atrial septal

defect, small ventricular septal defect, pulmonic stenosis, uncomplicated aortic stenosis, mild coarctation of the aorta, and patent ductus arteriosus)

- Infants with lesions adequately corrected by surgery, unless they continue to require medication for congestive heart failure
- Infants with mild cardiomyopathy who are not receiving medical therapy for the condition
- Children in the second year of life

Because a mean decrease in palivizumab serum concentration of 58% was observed after surgical procedures that involve cardiopulmonary bypass, for children who are receiving prophylaxis and who continue to require prophylaxis after a surgical procedure, a post-operative dose of palivizumab (15 mg/kg) should be considered after cardiac bypass or at the conclusion of extracorporeal membrane oxygenation for infants and children younger than 24 months.

Children younger than 2 years who undergo cardiac transplantation during the RSV season may be considered for palivizumab prophylaxis.

CHILDREN WITH ANATOMIC PULMONARY ABNORMALITIES OR NEUROMUSCULAR DISORDER

No prospective studies or population-based data are available to define the risk of RSV hospitalization in children with pulmonary abnormalities or neuromuscular disease. Infants with neuromuscular disease or congenital anomaly that impairs the ability to clear secretions from the upper airway because of ineffective cough are known to be at risk for a prolonged hospitalization related to lower respiratory tract infection and, therefore, may be considered for prophylaxis during the first year of life.

IMMUNOCOMPROMISED CHILDREN

No population based data are available on the incidence of RSV hospitalization in children who undergo solid organ or hematopoietic stem cell transplantation. Severe and even fatal disease attributable to RSV is recognized in children receiving chemotherapy or who are immunocompromised because of other conditions, but the efficacy of prophylaxis in this cohort is not known. Prophylaxis may be considered for children younger than 24 months of age who are profoundly immunocompromised during the RSV season.

CHILDREN WITH DOWN SYNDROME

Limited data suggest a slight increase in RSV hospitalization rates among children with Down syndrome. However, data are insufficient to justify a recommendation for routine use of prophylaxis in children with Down syndrome unless qualifying heart disease, CLD, airway clearance issues, or prematurity (<29 weeks, 0 days' gestation) is present.

CHILDREN WITH CYSTIC FIBROSIS

Routine use of palivizumab prophylaxis in patients with cystic fibrosis, including neonates diagnosed with cystic fibrosis by newborn screening, is not recommended unless other indications are present. An infant with cystic fibrosis with clinical evidence of CLD and/or nutritional compromise in the first year of life may be considered for prophylaxis. Continued use of palivizumab prophylaxis in the second year may be considered for infants with manifestations of severe lung disease (previous hospitalization for pulmonary exacerbation in the first year of life or abnormalities on chest radiography or chest computed tomography that persist when stable) or weight for length less than the 10th percentile.

RECOMMENDATIONS FOR TIMING OF PROPHYLAXIS FOR ALASKA NATIVE AND AMERICAN INDIAN INFANTS

On the basis of the epidemiology of RSV in Alaska, particularly in remote regions where the burden of RSV disease is significantly greater than the general US population, the selection of Alaska Native infants eligible for prophylaxis may differ from the remainder of the United States. Clinicians may wish to use RSV surveillance data generated by the state of Alaska to assist in determining onset and end of the RSV season for qualifying infants.

Limited information is available concerning the burden of RSV disease among American Indian populations. However, special consideration may be prudent for Navajo and White Mountain Apache infants in the first year of life.

DISCONTINUATION OF PALIVIZUMAB PROPHYLAXIS AMONG CHILDREN WHO EXPERIENCE BREAKTHROUGH RSV HOSPITALIZATION

If any infant or young child receiving monthly palivizumab prophylaxis experiences a breakthrough RSV hospitalization, monthly prophylaxis should be discontinued because of the extremely low likelihood of a second RSV hospitalization in the same season (<0.5%).

USE OF PALIVIZUMAB IN THE SECOND YEAR OF LIFE

Hospitalization rates attributable to RSV decrease during the second RSV season for all children. A second season of palivizumab prophylaxis is recommended only for preterm infants born at <32 weeks, 0 days' gestation who required at least 28 days of oxygen after birth and who continue to require

supplemental oxygen, chronic systemic corticosteroid therapy, or bronchodilator therapy within 6 months of the start of the second RSV season.

LACK OF THERAPEUTIC EFFICACY OF PALIVIZUMAB

Passive antibody administration is not effective in treatment of RSV disease and is not approved or recommended for this indication.

PREVENTION OF HEALTH CARE-ASSOCIATED RSV DISEASE

No rigorous data exist to support palivizumab use in controlling outbreaks of health care-associated disease, and palivizumab use is not recommended for this purpose. Infants in a neonatal unit who qualify for prophylaxis because of CLD, prematurity, or CHD may receive the first dose 48 to 72 hours before discharge to home or promptly after discharge.

Strict adherence to infection-control practices is the basis for reducing health care-associated RSV disease.

RSV SEASONALITY

Because 5 monthly doses of palivizumab at 15 mg/kg per dose will provide more than 6 months (>24 weeks) of serum palivizumab concentrations above the desired level for most children, administration of more than 5 monthly doses is not recommended within the continental United States. For qualifying infants who require 5 doses, a dose beginning in November and continuation for a total of 5 monthly doses will provide protection for most infants through April and is recommended for most areas of the United States. If prophylaxis is initiated in October, the fifth and final dose should be administered in February, which will provide protection for most infants through March. If

prophylaxis is initiated in December, the fifth and final dose should be administered in April, which will provide protection for most infants through May.

Variation in the onset and offset of the RSV season in different regions of Florida may affect the timing of palivizumab administration. Data from the Florida Department of Health may be used to determine the appropriate timing for administration of the first dose of palivizumab for qualifying infants. Despite varying onset and offset dates of the RSV season in different regions of Florida, a maximum of 5 monthly doses of palivizumab should be adequate for qualifying infants for most RSV seasons in Florida.

Sporadic RSV infections occur throughout the year in most geographic locations. During times of low RSV prevalence (regardless of proportion of positive results), prophylaxis with palivizumab provides the least benefit because of the large number of children who must receive prophylaxis to prevent 1 RSV hospitalization.

EFFECT OF PALIVIZUMAB PROPHYLAXIS ON SUBSEQUENT WHEEZING

Prophylaxis is not recommended for primary asthma prevention or to reduce subsequent episodes of wheezing.

SUMMARY OF GUIDANCE

- In the first year of life, palivizumab prophylaxis is recommended for infants born before 29 weeks, 0 days' gestation.
- Palivizumab prophylaxis is not recommended for otherwise healthy infants born at or after 29 weeks, 0 days' gestation.
- In the first year of life, palivizumab prophylaxis is recommended for preterm infants with CLD of prematurity, defined as birth at <32 weeks, 0 days'

gestation and a requirement for >21% oxygen for at least 28 days after birth.

- Clinicians may administer palivizumab prophylaxis in the first year of life to certain infants with hemodynamically significant heart disease.
- Clinicians may administer up to a maximum of 5 monthly doses of palivizumab (15 mg/kg per dose) during the RSV season to infants who qualify for prophylaxis in the first year of life. Qualifying infants born during the RSV season may require fewer doses. For example, infants born in January would receive their last dose in March.
- Palivizumab prophylaxis is not recommended in the second year of life except for children who required at least 28 days of supplemental oxygen after birth and who continue to require medical intervention (supplemental oxygen, chronic corticosteroid, or diuretic therapy).
- Monthly prophylaxis should be discontinued in any child who experiences a breakthrough RSV hospitalization.
- Children with pulmonary abnormality or neuromuscular disease that impairs the ability to clear secretions from the upper airways may be considered for prophylaxis in the first year of life.
- Children younger than 24 months who will be profoundly immunocompromised during the RSV season may be considered for prophylaxis.
- Insufficient data are available to recommend palivizumab prophylaxis for children with cystic fibrosis or Down syndrome.
- The burden of RSV disease and costs associated with transport from remote locations may result in a broader use of palivizumab for RSV prevention in Alaska Native

populations and possibly in selected other American Indian populations.

- Palivizumab prophylaxis is not recommended for prevention of health care-associated RSV disease.

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