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Guidance Update for Prophylaxis of Respiratory Syncytial Virus

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The American Academy of Pediatrics (AAP) Committee on Infectious Disease (COID) has published a new policy statement and accompanying technical report for palivizumab (Synagis™) prophylaxis among infants and children at increased risk of hospitalization for respiratory syncytial (RSV) infection.[1,2] The guidance refines the definition of high risk and allows health care providers to better identify patients most likely to benefit from RSV prophylaxis. This newsletter will highlight the changes to the guidance for best use of palivizumab.

Background: RSV infection occurs primarily among young infants.[3] It is estimated that 100% of infants have been infected with RSV by 2 years of age, although infants greater than 2 years of age, as well as adults, may become re-infected following initial exposure. Illness from RSV typically begins 4 – 6 days post-exposure, and manifests similarly to the common cold (i.e. runny nose, decreased appetite, cough, sneezing, fever, etc.). In most cases, symptom resolution takes 1 – 2 weeks, but may take longer in higher-risk infants. Furthermore, symptomatology (i.e. pneumonia or bronchiolitis) secondary to RSV infection may necessitate hospitalization. Average hospitalization rates for children younger than 24 months (regardless of gestational age) with RSV were found to be 5.2/1000 (95% CI 4.8 to 5.7) in one study.[1]

Palivizumab is a humanized monoclonal antibody that acts by binding the RSV F protein on the surface of the virus.[4] In doing so, palivizumab blocks a critical step in the membrane fusion process, prevents cell-to-cell fusion of RSV infected cells (i.e. formation of syncytia), and is felt to decrease the rate of hospitalization among infants and children whose immune system are not adequately equipped to fight infection.

In June 1998, the Food and Drug Administration (FDA) approved palivizumab for use in humans.[4] Safety and efficacy data was based on the results from Impact-RSV trial, a randomized, double-blind, placebo-controlled trial of palivizumab administered to infants at a high risk of RSV infection.[5] This trial included infants ≤24 months of age with chronic lung disease (CLD), or infants ≤6 months of age at study entry and born before 36 weeks gestation. RSV prophylaxis with palivizumab resulted in a statistically significant absolute risk reduction (ARR) of 5.8% in RSV-related hospitalizations compared to placebo. In 2003, another randomized, double-blind, placebo-controlled trial was published, which included infants with hemodynamically significant congenital heart disease (CHD).[6] Palivizumab prophylaxis was associated with an ARR of 4.4% in RSV-related hospitalizations compared to placebo. At this time, no evidence is available from high quality studies demonstrating a statistically significant reduction in mortality among children or infants receiving RSV prophylaxis with palivizumab.[1]

AAP 2014 Guidance Update: AAP guidance originally followed FDA labeled indications for RSV prophylaxis, but has since evolved as new data has become available. According to AAP 2014 guidance, palivizumab immunoprophylaxis may be considered in infants and children when the following criteria are met:

Preterm Infants Without Chronic Lung Disease of Prematurity or Congenital Heart Disease: Whereas the AAP 2012 guidance recommended RSV prophylaxis for infants born before 32 weeks gestation without the requirement of other qualifying condition, palivizumab is now only recommended during the first year of life to infants born before 29 weeks gestation. The decrease in gestational age and elimination of risk factors was based on data from retrospective analyses comparing gestational age and hospitalization rates,[5–7] as well as multiple logistic-regression analyses from a prospective, population-based study.[8,9] Hospitalization for RSV infection in moderately preterm infants occurs in 2.5% to 4.9% of infants based on large cohort studies.[1] The data indicate that infants born before 29 weeks gestation are at the highest risk for hospitalization, with a significant (P = 0.007) inverse relationship between hospitalization rate and gestational age at 27-28 weeks gestation.[6] The data also revealed that risk factors for RSV infection (i.e. daycare attendance, sibling in the home, young chronological age) are not correlated with those at highest risk for complications, and are therefore invalid characteristics for determining eligibility for palivizumab immunoprophylaxis.

Preterm Infants with Chronic Lung Disease (CLD): Whereas the AAP 2012 guidance recommended palivizumab immunoprophylaxis for infants <24 months of age during RSV season with CLD who received medical therapy (i.e. supplemental oxygen, bronchodilator, diuretic or chronic corticosteroid therapy) within 6 months before the start of RSV season, the AAP 2014 guidance has limited palivizumab immunoprophylaxis to infants <12 months of age at the start of RSV season who satisfy the definition for CLD of prematurity (i.e. gestational age <32 weeks, 0 days' and a requirement for >21% oxygen for at least the first 28 days after birth). Although the updated guidance does not require that infants receive medical therapy for CLD that was present within 6 months prior to the start of RSV season, the new guidance is more restrictive than the previous guidance because infants are now required to satisfy the definition of CLD of prematurity. The AAP 2014 states that infants in the second year of life (>12 and ≤24 months of age) may also receive palivizumab prophylaxis as long as they satisfy the definition of CLD of prematurity and require medical support (i.e. chronic corticosteroid therapy, diuretic therapy, or supplemental oxygen) for CLD within 6 months before the start of RSV season. The updated guidance does not recommend palivizumab immunoprophylaxis for infants if they do not continue to require medical support during the second year of life.

Hemodynamically Significant Congenital Heart Disease (HS-CHD): The AAP 2014 guidance recommends palivizumab immunoprophylaxis for infants ≤12 months of age at the start of RSV season with HS-CHD, but specifies that treatment decisions should be based on degree of cardiovascular compromise. The guidance states that infants who are most likely to benefit from palivizumab immunoprophylaxis are those with acyanotic heart disease who will require cardiac surgical procedures and are receiving medication to control congestive heart failure, and have moderate to severe pulmonary hypertension.[6] Because there are limited data to support palivizumab immunoprophylaxis among infants with cyanotic heart disease, the AAP 2014 advises that health care providers make treatment decisions in consultation with a pediatric cardiologist. If infants and children <24 months of age require a cardiac transplantation, palivizumab prophylaxis is recommended by the AAP 2014, as well as a post-operative dose following cardiopulmonary bypass.[11] RSV prophylaxis is no longer recommended for infants and children with HS-CHD who are between one to two years of age because the hospitalization rate is nearly identical to infants <12 months of age who are at low-risk of RSV infection.[7]

Anatomic Pulmonary Abnormalities or Neuromuscular Disease: The AAP 2014 guidance states that palivizumab prophylaxis may be considered in infants <12 months of age at start of RSV season with anatomic pulmonary abnormalities or neuromuscular disease that impairs the ability to clear secretions from upper airway. There is no change in guidance regarding infants with these conditions.

Immunocompromised: Severely immunocompromised infants and children <24 months of age during RSV season may receive palivizumab

immunoprophylaxis. Age eligibility is now defined by the AAP 2014 guidance, but a definition for severely immunocompromised is not provided. Nevertheless, the AAP 2012 guidance defined severe immunodeficiency as "severe combined immunodeficiency or advanced AIDS."[12]

Down syndrome and Cystic Fibrosis: While Down syndrome was not addressed in the AAP 2012 guidance and no recommendation was made for cystic fibrosis, the AAP 2014 guidance provides treatment recommendations for appropriate use of palivizumab prophylaxis among these patient populations. Infants with cystic fibrosis who are <12 months of age during RSV season and have clinical evidence of CLD or nutritional compromise, or are in the second year of life and have severe lung manifestations or weight for length <10th percentile may receive palivizumab immunoprophylaxis.[17,18] Among infants with Down syndrome, insufficient data is available to justify treatment unless an other qualifying condition is present (i.e. CLDP, airway clearance issues, HS-CHD, and birth prior to 29 weeks gestation).

Breakthrough RSV Hospitalizations: While the AAP 2012 guidance recommended continued monthly RSV prophylaxis based on re-hospitalization data and data documenting co-occurrence of several RSV strains within communities, the AAP 2014 guidance does not endorse the same recommendation. Instead, the AAP 2014 guidance advises that palivizumab prophylaxis be discontinued following a breakthrough RSV hospitalization. This recommendation is based on data demonstrating a low incidence of re-hospitalization for RSV infection within the same RSV season (<0.5%),[10] as well as data demonstrating that a subsequent RSV infection within the same RSV season is associated with less severe clinical illness than the initial RSV infection.[8,13,14]

Wheezing: The most compelling data for use of palivizumab prophylaxis to reduce wheezing episodes among infants comes from a double-blind, placebo-controlled, randomized controlled trial.[15] In this trial, infants ≤6 months of age at start of RSV season and born between 33 to 35 weeks gestation were assigned to receive monthly palivizumab injections or placebo. The primary outcome was the number of parent-reported wheezing days. Compared to placebo, palivizumab prophylaxis was associated with an ARR of 2.7% in wheeze days during the first year of life, as well as an ARR of 2.8% in wheeze days during the post-prophylaxis period, which started two months after the last injection. Limitations of this study are reliance on parent-reported wheezing days, exclusion of high-risk, young gestational age infants, absence of association between wheeze and symptom severity, and the disproportional number of infants at baseline who were using bronchodilators in the placebo group (23%) versus the palivizumab group (13%). Additional data to support palivizumab prophylaxis for wheezing reduction is still needed and currently prophylaxis is not recommended by the AAP 2014 guidance for primary asthma prevention or to reduce subsequent episodes of wheezing.

Seasonality of RSV: The AAP 2014 guidance states that infants who qualify for 5 monthly doses of palivizumab should receive the first dose at the time of RSV season onset, which historically has been set as November for region 10 (Oregon, Washington, Idaho). However, over the past three RSV seasons, season onset has begun in December for the 2011 – 2012 and 2012 – 2013 season and January for the 2013 – 2014 season.[17,18] Therefore, consideration for allowing prophylactic coverage to begin in December may more appropriately align with this regional RSV season.

Limitations of the guidelines: The AAP 2014 guidance did not include a grading system to assess strength of recommendation and quality of evidence. Other limitations of the guidance are that much of the new data comes from trials using study designs that have the potential for a high degree of bias.

Quick Reference Guide: RSV surveillance data: http://www.cdc.gov/surveillance/nrevss/rsv/.

Conclusion: The AAP 2014 guidance further defines those infants that would benefit most from RSV prophylaxis with palivizumab based on limited high-quality efficacy.

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