Clinical Performance Guideline
Neonatal Resource Services
Synagis® (palivizumab)

Purpose: To provide an evidence-based guideline for utilization of Synagis in infants and young children.

Goal: Immunization of select high risk infants with Synagis provides immunity against Respiratory Syncytial Virus (RSV) infections which can cause significant clinical illness resulting in readmission to the hospital.

Target Client Population: Infants and young children less than 24 months who are at high risk for contracting respiratory syncytial virus (RSV).

Background
Palivizumab is a humanized murine monoclonal immunoglobulin produced by recombinant DNA technology which has neutralizing and fusion-inhibitory activity against RSV.

Children with certain co-morbidities are at increased risk of severe RSV disease relative to children without these co-morbidities. Chronologic age is the single most important risk factor for RSV hospitalization on the basis of the observation that more than 58% to 64% of pediatric RSV hospitalizations occur in the first 5 months after birth. Most of these hospitalizations occur in the first 90 days after birth. Certain subgroups of infants with co-morbidities such as prematurity, CLD, or hemodynamically significant CHD have increased risks for RSV hospitalization. Infants in the second month after birth experience the highest RSV hospitalization rate, a rate that is almost twice that of the next highest risk group (infants in the first month after birth). Most host and environmental factors increase the risk for RSV hospitalization by only a small magnitude, so their contribution to overall disease burden is limited.

Among children under the age of 5 in the United States, RSV infection accounted for 24% of an estimated 5.5 million hospitalizations for lower respiratory tract illness among children <5 years of age during the 10 study years from 1997-2006. It has been estimated that 132,000 to 172,000 RSV-associated hospitalizations occurred annually in this population. Although the rate of hospitalization is greatest in children < 3 months of age, more than 40 percent of total hospitalizations in the < 5 years of age group occur in children > 1 year of age.

From July 2007 to January 2013 the median duration of the RSV “season” ranged from 13 to 23 weeks with the median peak activity from mid-December to early February, with the exception of Florida and Alaska. For analysis of National Respiratory and Enteric Virus Surveillance System (NREVSS)* reports in the CDC Morbidity and Mortality Weekly Report, season onset is defined as the first of 2 consecutive weeks during which the mean percentage of specimens testing positive for RSV antigen is ≥ 10% and RSV season offset is defined as the last of 2 consecutive weeks during which the mean percentage of positive specimens is ≥ 10%.

* NREVSS is a laboratory-based system that monitors geographical and temporal trends for various respiratory and enteric viruses, including RSV activity, to the CDC.

Treatment Criteria
Clinical evidence in the medical literature supports the following:
Palivizumab (Synagis®) is medically necessary to prevent serious respiratory syncytial
virus disease (RSV) in high risk infants and young children when **all** of the following are met: (AAP, 2014; Perrin, 2014)

- Administered during RSV season as defined by the Centers for Disease and Prevention (CDC) surveillance reports ([http://www.cdc.gov/surveillance/nrevss/rsv/](http://www.cdc.gov/surveillance/nrevss/rsv/)) or state or local health departments to confirm the start of the respiratory syncytial virus (RSV) “season”, **AND**
- Monthly dose of palivizumab does not exceed 15 mg/kg per dose, **AND**
- Monthly doses of palivizumab do not exceed 5 doses per single RSV “season”;
  - Infants in a neonatal intensive care unit who qualify for prophylaxis may receive the first dose 48 to 72 hours before discharge to home or promptly after discharge. If the first dose is administered in the hospital, this dose will be considered the first dose of the maximum 5 dose series for the season. Any subsequent doses received in the hospital setting are also considered as part of the maximum 5 dose series. For infants born during the RSV “season” fewer than 5 monthly doses will be needed.
  - **AND**
  - **One** of the following clinical situations:
    - Infants born prematurely before 29 weeks, 0 days gestation who are < 12 months of age at the start of RSV “season”.
    - Infants and young children with **chronic lung disease (CLD)***:
      - Age 0 to < 12 months: 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.
      - Age ≥ 12 to < 24 months: Palivizumab is proven for use in preterm infants born at < 32 weeks, 0 days gestation who are ≥ 12 to < 24 months of age who required at least 28 days of oxygen after birth and who continue to require supplemental oxygen, diuretics or chronic systemic corticosteroid therapy within 6 months of the start of the second RSV season.
    - Infants and young children with **hemodynamically significant congenital heart disease (CHD)***:
      - Age 0 to < 12 months: Infants born within 12 months of the onset of RSV “season” who will most likely benefit from immunoprophylaxis include:
        - Infants with acyanotic heart disease that are receiving medication to control congestive heart failure and will require cardiac surgical procedures.
        - Infants with moderate to severe pulmonary
hypertension.

- Documentation that decisions regarding palivizumab prophylaxis for infants with cyanotic heart defects in the first year of life were made in consultation with a pediatric cardiologist.

- **Age < 24 months:** A post-operative dose for young children who still require prophylaxis and who have undergone surgical procedures should be administered palivizumab prophylaxis after cardiac bypass or at the conclusion of extracorporeal membrane oxygenation.

- Children who undergo cardiac transplantation during the RSV “season” may be considered for palivizumab prophylaxis.

  o **Infants with congenital abnormalities of the airway or neuromuscular disease:**

    - **Age 0 to < 12 months:** Infants with neuromuscular disease or congenital anomaly that impairs the ability to clear secretions from the lower airway because of an ineffective cough may be considered for prophylaxis during the first year of life.

  o **Young children < 24 months of age who are immunocompromised:**

    - Palivizumab may be administered for prophylaxis in young children who are receiving cancer chemotherapy or are severely immunocompromised. The efficacy of prophylaxis in this population (e.g., children receiving chemotherapy, undergoing hematopoietic stem cell transplantation or solid organ transplantation) is unknown however.

  o **Infants and young children with cystic fibrosis (CF) who have the following qualifying indications:**

    - **Age 0 to < 12 months:** Infants with CF with clinical evidence of CLD and/or nutritional compromise in the first year of life may be considered for prophylaxis
      - Failure to thrive is defined as weight for length less than the 10th percentile on a pediatric growth chart.

    - **Age ≥ 12 to < 24 months:** Continued use of palivizumab prophylaxis in the second year of life may be considered for young children with manifestations of severe lung disease including:
      - Previous hospitalization for pulmonary exacerbation in the first year of life
      - Abnormalities on chest radiography or chest computed tomography that persist when stable
      - Weight for length less than the 10th percentile on a pediatric growth chart.
There is insufficient clinical evidence to support the use of palivizumab for:

(AAP, 2014; Perrin, 2014)

- Infants with CLD who do not continue to require medical support in the second year of life.
- Infants and children with hemodynamically insignificant heart disease (e.g., secundum atrial septal defect, small ventricular septal defect, pulmonic stenosis, uncomplicated aortic stenosis, mild coarctation of the aorta, and patent ductus arteriosus).
- Infants with cardiac lesions adequately corrected by surgery, unless they continue to require medication for congestive heart failure.
- Infants with cardiomyopathy sufficiently mild that they do not require pharmacotherapy.
- Children in the second year of life unless otherwise indicated as medically necessary above.
- Routine use of prophylaxis in children with Down syndrome [unless qualifying heart disease, CLD, airway clearance issues (the inability to clear secretions from the upper airway because of ineffective cough or prematurity (<29 weeks, 0 days gestation) is present].
- Routine use of prophylaxis in children with CF (unless noted in medically necessary indications above.
- Administration of monthly palivizumab prophylaxis after an infant or child who had met the criteria for palivizumab experienced a breakthrough RSV hospitalization during the current season.
- Prophylaxis for primary asthma prevention or to reduce subsequent episodes of wheezing in infants and children.
- Prophylaxis for prevention of nosocomial disease.
- Prophylaxis administered in any of the following scenarios:
  - Outside of the RSV “season”
  - In doses greater than needed to provide protection in the RSV “season”
  - In excess of 5 doses per single RSV “season”
  - To persons other than those at defined high risk as specified above
- Treatment of symptomatic RSV disease

Additional Information:

In most of North America the peak RSV activity typically occurs between November and March, usually beginning in November or December, peaking in January or February, and ending by the end of March or sometime in April. Communities in the southern United States, particularly some communities in the state of Florida, tend to experience the earliest onset of RSV. Data from the Centers for Disease Control and Prevention (CDC) have identified variations in the onset and offset of the RSV
“season” in the state of Florida that could affect the timing of palivizumab administration.

- Despite varied onsets, the RSV “season” is of the same duration (5 months) in the different regions of Florida.
- 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 U.S. 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 the onset and end of the RSV season for qualifying infants.
- Limited information is available concerning the burden of RSV disease among the American Indian populations. However, special consideration may be prudent for Navajo and White Mountain Apache infants in the first year of life.
- For analysis of National Respiratory and Enteric Virus Surveillance System (NREVSS) reports in the CDC Morbidity and Mortality Weekly Report, season onset is defined as the first of two consecutive weeks during which the mean percentage of specimens testing positive for RSV antigen is ≥ 10% and RSV “season” offset is defined as the last of two consecutive weeks during which the mean percentage of positive specimens is ≥ 10%. Use of specimens to determine the start of the RSV “season” required that the number of specimens tested be statistically significant.

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- Synagis (palivizumab) is FDA-approved for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients at high risk of RSV disease. Safety and efficacy were established in infants with chronic lung disease of prematurity, formerly termed bronchopulmonary dysplasia (BPD), infants with a history of premature birth (≤ 35 weeks gestational age), and children with hemodynamically significant congenital heart disease (CHD). The safety and efficacy of Synagis has not been established for treatment of RSV disease. (Medimmune, LLC, 2014)

- For the 2012–13 RSV season, onset analysis is limited to laboratories that reported results for at least 1 week of the NREVSS season and at least one antigen test on average per week during the NREVSS season. Preliminary analysis of these data included a total of 135,849 RSV antigen tests and 19,903 (14.7%) positive results reported by 462 laboratories from 50 states and the District of Columbia. The season onset occurred in nine of the 10 HHS regions by December 15, 2012. Nationally, the onset of RSV season occurred the week ending October 27, 2012; however, when Florida is excluded from analysis, the national onset occurred November 10, 2012 (1 week later). (CDC, 2013)

- During July 2011–June 2012, national and regional RSV trends were similar to patterns previously reported for RSV season from 2010 to 2011. Collected data from 174 (33.3%) laboratories in 42 states during the NREVSS season was analyzed. Laboratories reported a total of 270,441 tests, of which 41,299 (15.3%) were positive. The onset of the national RSV season occurred the week ending November 19, 2011, and lasted 21 weeks, until the week ending April 7, 2012. The proportion of laboratory specimens positive for RSV by antigen detection reached a season high of 26.2% during the week ending January 28, 2012. With the exclusion of Florida, the national onset occurred 1 week later (November 27,
2011), and the season duration decreased by 1 week. Onset for the 10 U.S. Department of Health and Human Services (HHS) regions (HHS) regions (excluding Florida) ranged from late October to mid-January, and season offset ranged from early March to early May. The RSV season peak ranged from mid-January to mid-March, and the duration ranged from 14 to 23 weeks (median = 19 weeks). The season onset for Florida occurred the week ending August 13, 2011, and the season continued through the week ending March 3, 2012. Florida's season onset occurred 5 weeks earlier than the previous season, and each HHS region differed in onset, offset, and duration. Florida's earlier onset has been well documented, as having differences in activity from year-to-year in the same geographic location possibly due to social and demographic factors, population density, pollution, and climate. (CDC, 2013)

- Researchers in The Cochrane Collaboration conducted a literature review to assess the effectiveness and safety of palivizumab prophylaxis compared with placebo, or another type of prophylaxis, in reducing the risk of complications (hospitalization due to RSV infection) in high-risk infants and children. Additionally they assessed the cost-utility of palivizumab prophylaxis compared with no prophylaxis in infants and children in different risk groups. A literature search was conducted and randomized, controlled trial (RCTs) comparing palivizumab prophylaxis with a placebo, no prophylaxis or another type of prophylaxis in preventing serious lower respiratory tract disease caused by RSV in pediatric patients at high risk were included in the evaluation along with cost-effectiveness analyses and cost-utility analyses comparing palivizumab prophylaxis with no prophylaxis. Of the 7 available RCTs, 3 compared palivizumab with a placebo in a total of 2831 patients, and 4 compared palivizumab with motavizumab in a total of 8265 patients. All RCTs were sponsored by the drug manufacturing company. A statistically significant reduction in RSV hospitalizations (RR 0.49, 95% CI 0.37 to 0.64) was found with palivizumab prophylaxis compared to placebo. When compared to motavizumab, palivizumab recipients showed a non-significant increase in the risk of RSV hospitalizations (RR 1.36, 95% CI 0.97 to 1.90). Adverse events (AE) related to the study drug was similar in both cases. In regards to economic evidence (EE), researchers included 34 studies that reported cost-effectiveness and/or cost-utility data for palivizumab prophylaxis compared with no prophylaxis, in high-risk children with different underlying medical conditions. The overall quality of EEs found was good, but the variations in modeling approaches were considerable across the studies, leading to big differences in cost-effectiveness results. Cost-effectiveness of palivizumab prophylaxis depended on the consumption of resources taken into account by the study authors; and on the cost-effectiveness threshold set by the healthcare sector in each country. Researchers concluded that there is evidence that palivizumab prophylaxis is effective in reducing the frequency of hospitalizations due to RSV infection in children who are at higher risk (such as children with chronic lung disease, congenital heart disease or those born preterm) of acquiring severe RSV infections, when compared to placebo. Additionally, results from economic evaluations of palivizumab prophylaxis are inconsistent, implying that economic findings must be interpreted with caution. The incremental cost-effectiveness ratio (ICER) values varied considerably across studies, from highly cost-effective to not cost-effective. (Andabaka et al, 2013)

- Two randomized, double-blind placebo-controlled trials of prophylaxis against RSV infection in pediatric patients at high risk of an RSV-related hospitalization were
assessed. Trial 1 was conducted during a single RSV season and studied a total of 1502 patients ≤ 24 months of age with bronchopulmonary dysplasia (BPD) or infants with premature birth (≤ 35 weeks gestation) who were ≤ 6 months of age at study entry. Trial 2 was conducted over four consecutive seasons among a total of 1287 patients ≤ 24 months of age with hemodynamically significant congenital heart disease. In both trials participants received 15 mg/kg palivizumab or an equivalent volume of placebo IM monthly for five injections and were followed for 150 days from randomization. In Trial 1, 99% of all subjects completed the study and 93% completed all five injections. In Trial 2, 96% of all subjects completed the study and 92% completed all five injections. In trial 1, the reduction of RSV hospitalization was observed both in patients with BPD - (34/266 [12.8%] placebo vs. 39/496 [7.9%] palivizumab), and in premature infants without BPD (19/234 [8.1%] placebo vs. 9/506 [1.8%] palivizumab). In Trial 2, reductions were observed in acyanotic (36/305 [11.8%] placebo vs. 15/300 [5.0%] palivizumab) and cyanotic (27/343 [7.9%] placebo vs. 19/339 [5.6%] palivizumab) children. (Impact-RSV Study Group, 1998; Feltes et al, 2003)

- **MAKI** was a multicenter, double-blind, placebo controlled trial to explore the causal role of RSV infection in the pathogenesis of wheezing during the first year of life using palivizumab. Healthy preterm infants (n=429) born at a gestational age of 33 to 35 weeks were randomized in a 1:1 ratio to receive either monthly palivizumab (dose = 15 mg/kg) injections (n=214) or placebo (n=215) during the RSV season. The primary outcome evaluated was number of parent reported wheezing days in the first year of life. Secondary outcomes assessed included were the number of days with bronchodilator use, the number of RSV infections confirmed by means of a nasopharyngeal swab positive for RSV RNA with or without medical attention, the number of hospitalizations for laboratory-proven RSV infection, the number of wheezing episodes, and the prevalence of recurrent wheeze. Researchers reported that treatment with palivizumab (median number of injections was 4) resulted in a relative reduction of 61% (95% confidence interval, 56 to 65) in the total number of wheezing days during the first year of life (930 of 53,075 days in the RSV-prevention group [1.8%] vs. 2309 of 51,726 days [4.5%] in the placebo group). Additionally, the proportion of infants with recurrent wheezing was lower in the RSV-prevention group than in the placebo group (11.2% vs. 20.9%, p=0.005). More co-infections during non-wheezing episodes were reported in the RSV-prevention group than in the placebo group (114 of 291 swabs [39%] vs. 70 of 233 swabs [30%], p=0.03). Researchers concluded that in otherwise healthy preterm infants, prophylactic treatment with palivizumab reduced the total number of wheezing days in the first year of life among preterm infants with a gestational age of 33 to 35 weeks. These findings implicate RSV infection as an important mechanism of recurrent wheeze during the first year of life in this population. (Blanken et al, 2013) The significance of these conclusions must be validated in additional randomized, controlled trials in order to be considered for inclusion into the recommendations of the Committee on Infectious Diseases (COID) of the American Academy of Pediatrics (AAP) on palivizumab prophylaxis of infants and young children.

**Bibliography**


Perrin JM, Meissner HC, and Ralstonh SL. Updated AAP guidance for palivizumab prophylaxis among infants and young children at increased risk of RSV hospitalization [webinar]. July 28, 2014.


Revision History
The following are approved changes incorporated into the revision numbers indicated below.

<table>
<thead>
<tr>
<th>Revision</th>
<th>Date</th>
<th>Description of Change</th>
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<tr>
<td>1.0</td>
<td>08/28/2014</td>
<td>New medical necessity guideline based on updated 2014 AAP RSV guideline. (CE)</td>
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<tr>
<td>1.1</td>
<td>09/07/2015</td>
<td>Annual review with no changes. (CE)</td>
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<td>1.2</td>
<td>11/17/2015</td>
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<td>1.3</td>
<td>05/05/2016</td>
<td>Annual review by RS. No changes to criteria. (CE)</td>
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