

Clinical Performance Guideline
Neonatal Resource Services
Synagis® (palivizumab)

Medical Necessity Guideline

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	<p>Palivizumab is a humanized murine monoclonal immunoglobulin produced by recombinant DNA technology which has neutralizing and fusion-inhibitory activity against RSV.</p> <p>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, chronic lung disease (CLD), or hemodynamically significant congenital heart disease (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.</p> <p>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.</p> <p>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. However, there can be significant year to year variations in the start and stop periods and usage of Synagis should be based on local surveillance. 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 $\geq 10\%$ and RSV season offset is defined as the last of 2 consecutive weeks during which the mean percentage of positive specimens is < 10%.</p> <p>* NREVSS is a laboratory-based system that monitors geographical and temporal trends for various respiratory and enteric viruses, including RSV activity, to the CDC.</p>
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Treatment Criteria	<p><u>Clinical evidence in the medical literature supports the following:</u></p> <p>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)</p> <ul style="list-style-type: none"> • Administered during RSV season as defined by the Centers for Disease and Prevention (CDC) surveillance reports (http://www.cdc.gov/surveillance/nrevss/rsv/index.html) 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”, <ul style="list-style-type: none"> ○ 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. <p style="text-align: center;">AND</p> <ul style="list-style-type: none"> • <u>One</u> of the following clinical situations: <ul style="list-style-type: none"> ○ 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 CLD: <ul style="list-style-type: none"> ▪ <u>Age 0 to < 12 months</u>: 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. ▪ <u>Age ≥ 12 to < 24 months</u>: 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 CHD: <ul style="list-style-type: none"> ▪ <u>Age 0 to < 12 months</u>: Infants born within 12 months of the onset of RSV “season” who will most likely benefit from immunoprophylaxis include: <ul style="list-style-type: none"> • 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
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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.
- 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.
- 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.
- 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 the U.S., based on data from three RSV seasons (2014-2017), the median RSV onset was found to occur in mid-October and last until early May peaking in early February. When the data excluded Florida and Hawaii, the national onset was delayed one week and the duration of the RSV season was one week shorter. The weekly RSV circulation patterns in Florida differ from the national and regional patterns and therefore the Florida statistics are reported separately. The National Respiratory and Enteric Virus Surveillance System (NREVSS) began utilizing PCR lab detections

	<p>(RS10 method) instead of the prior antigen-based methods which has resulted in a relative lengthening of the RSV season. (MMWR, 2018)</p> <ul style="list-style-type: none"> Seasonal variation in the onset of RSV activity is noted in HHS region 4 (Atlanta) and the duration of the season is also longer (37 weeks) than the national average. (MMWR, 2018) 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 Native American populations. However, special consideration may be prudent for Navajo and White Mountain Apache infants in the first year of life. Native American (NA) and Alaska Native (AN) infants living in the Southwest and Alaska regions are at especially high risk for hospitalizations associated with RSV infection. (Holman, 2004) Rates of bronchiolitis-associated hospitalization for NA and AN children are approximately twice that for the general population of U.S. children. (MMWR, 2003) For analysis of NREVSS reports in the CDC Morbidity and Mortality Weekly Report, season onset is defined as the second of two consecutive weeks when the slope (RS10 method), or normalized 5-week moving average of RSV detections between subsequent weeks, is >10 and RSV “season” offset is defined as the last week when the standardized detections exceeded the standardized detections at onset.. Use of specimens to determine the start of the RSV “season” required that the number of specimens tested be statistically significant. (MMWR, 2018)
<p>Clinical Evidence</p>	<ul style="list-style-type: none"> A retrospective observational study by Farber et al (2016) sought to evaluate the efficacy of palivizumab in otherwise healthy infants of 29-36 weeks’ gestational age (GA). The authors included 14,097 premature infants in this study. The rates of hospitalization from RSV bronchiolitis between the 29-32 weeks’ and 33-36 weeks’ gestation groups were identified as equivalent with a relatively low admission rate of 4.2%. The rates of hospitalization and numbers of hospitalization days for RSV were found to be higher in the group of infants 29-32 weeks’ GA who had not received Synagis: 5.0% of infants who had not received palivizumab (n=1186) were hospitalized versus 3.1% in the group that had received prophylaxis. No significant differences were found in the cohort of infants who were 33-35 weeks’ GA. An additional 2.3% of the preterm infants included in this study were hospitalized for bronchiolitis without a diagnosis of RSV. Due to the significant limitations of this study, the authors recommended further evaluation of the cost-effectiveness of palivizumab in this age group. 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 CLD of prematurity, formerly termed bronchopulmonary dysplasia (BPD), infants with a history of premature birth (\leq 35 weeks gestational age), and children with hemodynamically significant CHD. The safety and efficacy of Synagis has not been established for treatment of RSV disease. (Medimmune, LLC, 2014)

- Based on 2014-2017 RSV seasons data reported to NREVSS, median RSV onset occurred mid-October and continued until early May with duration of 31 weeks. The median peak of RSV in the U.S. appeared in early February. The earlier onsets and later offsets of this data as compared to 2012-2014 statistics are due to the analysis of PCR testing results versus antigen testing data. This methodological change resulted in a relative extension of the RSV season. Although the RS10 method of analysis cannot determine seasonal onset and offset in real time, it can identify a large proportion of RSV PCR detections to retrospectively determine RSV seasonality. Prior antigen-based methods expressed conclusions that Florida had an earlier RSV onset than other states in the U.S. but the RS10 methodology did not consistently confirm this observation. (CDC, 2018)
- 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 \leq 24 months of age with BPD or infants with premature birth (\leq 35 weeks gestation) who were \leq 6 months of age at study entry. Trial 2 was conducted over four consecutive seasons among a total of 1287 patients \leq 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. (Blanken, 2013) 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

AAP Policy Statement. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. *Pediatrics* 2014;134:415-420.



AAP Technical Report. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. *Pediatric* 2014;134:e620-638.

American Academy of Pediatrics Committee on Infectious Diseases, Committee on Fetus and Newborn. Respiratory syncytial virus immune globulin intravenous: indications for use. *Pediatrics*. 1997;99(4):645-50.

Andabaka T, Nickerson JW, Rojas-Reyes MX, et al. Monoclonal antibody for reducing the risk of respiratory syncytial virus infection in children. *Cochrane Database Syst Rev*. 2013 Apr 30;4:CD006602.

Blanken MO, Rovers MM, Molenaar JM, et al. Respiratory syncytial virus and recurrent wheeze in healthy preterm infants. *N Engl J Med*. 2013 May 9;368(19):1791-9.

Byington CL & Munoz FM. Palivizumab prophylaxis for healthy preterm infants: More data supporting American Academy of Pediatrics Guidelines. *Pediatrics*. 2016 Aug;138(2). pii:e20161494.

Centers for Disease Control and Prevention. Respiratory Syncytial Virus Seasonality-United States, 2014-2017. *MMWR*. 2018 Jan 19;67(2):71-76.

Centers for Disease Control and Prevention. Bronchiolitis-associated outpatient visits and hospitalizations among American Indian and Alaska Native children- United States, 1990-2000. *MMWR Morb Mortal Wkly Rep*. 2003 Aug 1;52(30):707-10.

Farber H, Buckwold F, Lachman B, et al. Observed effectiveness of palivizumab for 29-36 week gestation infants. *Pediatrics*. 2016;138(2):e20160617.

Feltes TF, Sondheimer HM. Palivizumab and the prevention of respiratory syncytial virus illness in pediatric patients with congenital heart disease. *Expert Opin Biol Ther*. 2007 Sep;7(9):1471-80.

Groothuis JR, Simoes EA, Levin MJ, et al. Prophylactic administration of respiratory syncytial virus immune globulin to high-risk infants and young children. *N Engl J Med*. 1993;329(21):1524-30.

Holman RC, Curns AT, Cheek JE, Bresee JS, et al. Respiratory syncytial virus hospitalizations among American Indian and Alaska Native infants and the general United States infant population. *Pediatrics*. 2004 Oct;114(4):e437-44.

Panozzo CA, Stockman LJ, Cums AT, et al. Use of respiratory syncytial virus surveillance data to optimize the timing of immunoprophylaxis. *Pediatrics*. 2010 Jul;126(1):e116-23.

Resch B. Burden of respiratory syncytial virus infection in young children. *World J Clin Pediatr*. 2012 Oct 8;1(3):8-12.

Simoes E, Groothuis JR, Carbonell-Estrany X, et al. Palivizumab prophylaxis, respiratory syncytial virus, and subsequent recurrent wheezing. *J Pediatr*. 2007;151(1):34-42, 42.e1.

Synagis® (palivizumab) [package insert]. Gaithersburg, MD: Medimmune, LLC., March 2014.

The IMpact-RSV Study Group. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. *Pediatrics*. 1998;102(3):531-7.

Revision History

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

Revision	Date	Description of Change
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1.0	08/28/2014	New medical necessity guideline based on updated 2014 AAP RSV guideline. (CE)
1.0	09/08/2014	Will replace JA2228479 on 10/01/2014. (CE)
1.1	09/07/2015	Annual review with no changes. (CE)
1.2	11/17/2015	Review performed by RS. No changes. (CE)
1.3	05/05/2016	Annual review by RS. No changes to criteria. (CE)
1.4	05/05/2017	Annual review by AJ. Information on seasonal and geographic variation added. (CE)
1.5	05/04/2018	Annual review by AJ. Information on methodology to identify RSV seasons updated. (CE)