Palivizumab (Synagis®) Criteria for Respiratory Syncytial Virus (RSV) Infection

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BACKGROUND

Palivizumab (Synagis) is a respiratory syncytial virus (RSV) F protein inhibitor monoclonal antibody indicated for the prevention of serious lower respiratory tract disease caused by RSV in children at high risk of RSV disease.[1] In 2014, the American Academy of Pediatrics (AAP) issued an updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for RSV.[2,3] In 2017, and subsequently in 2019, the Committee on Infectious Diseases and the Subcommittee on Bronchiolitis reviewed and reaffirmed the guideline.[4,5] The AAP policy statements are reviewed at least every 3 years and updated when appropriate. The palivizumab criteria below reflect the latest AAP guidance.

Nonpharmacologic public health precautions (e.g., use of face masks, social distancing) taken during 2020 and 2021 to control the spread of the coronavirus infection 2019 (COVID-19) may have resulted in an unusual decrease in circulating RSV during the Fall and Winter of 2020-2021. Subsequently, in the Spring of 2021, parts of the Southern United States (US) experienced an *interseasonal* increase in RSV cases, which may be due to relaxing COVID-19 precautions throughout the country. During this atypical spike in RSV activity, a corresponding increase in emergency department (ED) visits and hospitalizations of infants and children occurred. In June 2021, the Centers for Disease Control and Prevention (CDC) released a health advisory recommending broader RSV testing in patients presenting with acute respiratory illness who test negative for the SARS-CoV-2 virus that causes COVID-19.[6] In addition, in August 2021, the AAP issued an *interim* guidance and strongly supports consideration for use of palivizumab in patients who would be candidates per current eligibility recommendations.[7] The AAP recognizes the need for flexible approaches that may include early initiation of palivizumab for the RSV prior to the typically Fall onset. Clinicians should evaluate the need for palivizumab at least monthly and children eligible for palivizumab therapy who received fewer than 5 doses during the first half of 2021 could receive additional doses. This *interim* guidance does not replace AAP's guidance for the typical RSV season and is expected to expire on June 30, 2022 unless otherwise specified by the AAP.[8,9]

In December 2021, the AAP released new information regarding RSV prophylaxis.[10] According to the AAP, the 2021-2022 Fall/Winter RSV season is considered a new season, rather than a continuation of the interseason spread observed in the Spring and Summer of 2021. For the typical 2021-2022 Fall/Winter season, the AAP recommends initiating palivizumab prophylaxis in all regions of the country at the usual time, regardless of whether an area experienced unusual interseasonal RSV activity. Prescribing of palivizumab prophylaxis in eligible infants should be

similar to a typical winter season. The AAP acknowledges that these considerations could allow eligible children to receive greater than 5 consecutive doses of palivizumab in some regions and less than 5 dose doses in other areas during the 2021-2022 Fall/Winter season. Although data is lacking on the use of greater than 5 consecutive doses, the AAP advises that there is no evidence of increased frequency or severity of adverse events with later doses in a 5-dose series nor with treatment beyond 5 doses. Therefore, the AAP recommends consideration of greater than 5 consecutive doses from the atypical interseason period through the 2021-2022 Fall/Winter season.

In a 2018 Morbidity and Mortality Weekly Report (MMWR), the CDC advised that data regarding RSV seasonality can guide diagnostic testing and inform policy decisions on the administration of immunoprophylaxis products, when indicated.[11] The CDC and AAP state that season onset can be determined in real time by identifying the first week of 2 consecutive weeks that RSV real-time polymerase chain reaction (RT-PCR) test positivity is 3% or greater or antigen detection positivity is 10% or greater.[12,13]

RSV SEASON – TYPICAL SEASONALITY ACTIVITY

There is variability in the onset and offset of the *typical* RSV season. Generally, it runs from November to April* within the continental US.[14,15]

A *typical* RSV season is determined when both the following are met:

- Timeframe: November to April*
- RSV is detected at high rates, defined by statewide or local positivity rates of:
  - ≥ 3% polymerase chain reaction (PCR) positivity rate average over 2 consecutive weeks *AND/OR*
  - ≥ 10% antigen test positivity rate average over 2 consecutive weeks[16,17]

The AAP recommends a maximum of 5 doses of palivizumab during the *typical* RSV season, which provides 6 months of RSV prophylaxis.[18,19]

A total of 5 monthly doses beginning in November* and the last dose given in March* will provide protection for most infants through April* and is recommended for most areas in the US.[20,21] However, according to the AAP, if the first dose is given in October, the fifth and final dose should be given in February, which will provide protection through March. Similarly, if the first dose is given in December, the fifth and final dose should be administered in April, which will provide protection for most infants through May.

Alaska – Due to the varied epidemiology of RSV infection, clinicians can use RSV surveillance data by the state of Alaska to determine the onset and offset of the local RSV season.

Florida – Data from the Florida Department of Health can be used to determine the onset and offset of the RSV season in the different regions of Florida.

Native American Indian infants – There is limited information about the burden of RSV infection among American Indian populations. Prophylaxis can be considered for Navajo and White Mountain Apache infants in the first year of life.

Despite differences in onset and offset of RSV infection in some states or regions, only a maximum of 5 doses will be approved during the *typical* RSV season. If prophylaxis is initiated later in the RSV season, the infant or child will receive less than 5 doses.

** The typical RSV season may not be applicable in all locations for the reasons above.*

RSV INTERSEASONAL ACTIVITY

Interseasonal spike in RSV activity may occur outside the usual timeframe for the typical RSV season when RSV is detected at high rates.

An *atypical RSV* season is determined when both the following are met:

- Timeframe: May to October
- RSV is detected at high rates, defined by statewide or local positivity rates of:
  - ≥ 3% polymerase chain reaction (PCR) positivity rate average over 2 consecutive weeks *AND/OR*
  - ≥ 10% antigen test positivity rate average over 2 consecutive weeks[22,23]

After a *typical* RSV season, a new *atypical* season can be distinguished from an extension of the previous RSV season by a distinct period of decreased RSV activity to < 3% PCR positivity and/or < 10% antigen positivity for > 2 consecutive weeks.

The AAP recommends consideration of greater than 5 consecutive doses from the atypical interseason period through the 2021-2022 Winter RSV season.[24]

LENGTH OF AUTHORIZATION

- During the *typica*l RSV season, authorize for a maximum of 5 doses during RSV season (5 monthly doses of 15 mg/kg intramuscularly).
- In infants and children < 24 months, already on prophylaxis and eligible, 1 post-op dose can be approved after cardiac bypass or after extracorporeal membrane oxygenation (ECMO).
- In regions experiencing high rates of RSV circulation, consistent with a *typical* Fall-Winter season, coverage may be provided if surveillance data from the CDC indicate a high percent positivity rate for RSV testing in the area.
- In regions experiencing *interseasonal* RSV circulation, based on surveillance data from the CDC indicating a high percent positivity rate (as defined above) for their area, the AAP recommends consideration of greater than 5 consecutive doses from the *atypical interseason* period through the 2021-2022 Winter RSV season.[25]

APPROVAL CRITERIA

Palivizumab will be approved in the following scenarios.

Infant/Child Age at Start of RSV Season	Criteria
< 12 months (1st year of life)	▪ GA < 29 wks, 0 d (otherwise healthy) ▪ Profoundly immunocompromised
≤ 12 months (1st year of life)	▪ CHD (hemodynamically *significant*) with *acyanotic* HD on CHF medications and will require cardiac surgery or with moderate to severe PH. For *cyanotic* heart defects consult a pediatric cardiologist ▪ CLD of prematurity (GA < 32 wks, 0 d and > 21% O_2 x first 28 d after birth) ▪ Anatomic pulmonary abnormalities, or neuromuscular disorder, or congenital anomaly that impairs the ability to clear upper airway secretions ▪ CF with CLD and/or nutritional compromise
> 12 months (2nd year of life)	▪ CLD of prematurity (GA < 32 wks, 0 d and > 21% O_2 x first 28 d after birth) and medical support (chronic steroids, diuretic therapy, or supplemental O_2) within 6 months before start of 2nd RSV season ▪ CF with severe lung disease* or weight for length < 10th percentile
< 24 months (2nd year of life)	▪ Cardiac transplant during RSV season ▪ Already on prophylaxis and eligible: give post-op dose after cardiac bypass or after ECMO ▪ Profoundly immunocompromised

GA=gestational age; d=day; CF=cystic fibrosis; CHD=congenital heart disease; CHF=congestive heart failure; CLD=chronic lung disease; ECMO=extracorporeal membrane oxygenation; HD=heart disease; O_2=oxygen; PH=pulmonary hypertension; wks=weeks

*Examples of severe lung disease: previous hospitalization for pulmonary exacerbation in the first year of life, abnormalities on chest radiography (chest X-ray), or chest computed tomography (chest CT) that persist when stable.

DENIAL CRITERIA

If a patient meets approval criteria in the above table, palivizumab will be approved. Palivizumab will NOT be approved in the following scenarios.

Infant/Child Age at Start of RSV Season	Deny
> 12 months (2nd year of life)	▪ Based on prematurity alone ▪ CLD *without* medical support (chronic steroids, diuretic therapy, or supplemental O_2) ▪ CHD ▪ Otherwise healthy children in 2nd year of life
Any age	▪ Outpatient RSV infection or breakthrough RSV hospitalization** ▪ Hemodynamically *insignificant* CHD*** ▪ CHD lesions corrected by surgery (unless on CHF meds) ▪ CHD and mild cardiomyopathy not on medical therapy ▪ CHD in 2nd year of life
No specific age defined	▪ GA ≥ 29 wks, 0 d (otherwise healthy) ▪ Asthma prevention ▪ Reduce wheezing episodes ▪ Down Syndrome ▪ CF (otherwise healthy) ▪ Healthcare-associated RSV disease****

CF=cystic fibrosis; CHF=congestive heart failure; CHD=congenital heart disease; CLD=chronic lung disease; GA=gestational age

**If any infant or child is receiving palivizumab prophylaxis and experiences an outpatient RSV infection of breakthrough RSV hospitalization, discontinue palivizumab, because the likelihood of a second RSV hospitalization in the same season is extremely low.

***Examples of hemodynamically *insignificant* CHD: secundum atrial septal defect, small ventricular septal defect, pulmonic stenosis, uncomplicated aortic stenosis, mild coarctation of the aorta, patent ductus arteriosus.

**** No rigorous data exist to support palivizumab use in controlling outbreaks of health care-associated disease; palivizumab use is not recommended for this purpose.

REFERENCES

1 Synagis [package insert]. Waltham MA; Sobi; November 2020.

2 American Academy of Pediatrics. Policy Statement. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. Reaffirmed February 2019. Pediatrics. 2014; 134(2); 415-420. DOI: 10.1542/peds.2014-1665. Available at: http://www.aappublications.org/search/palivizumab%20numresults%3A10%20sort%3Arelevance-rank%20format_result%3Astandard?facet%5Bseries-name%5D%5B0%5D=Policy%20Statement. Accessed February 1,2022.

3 American Academy of Pediatrics. Technical Report. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. Reaffirmed February 2019. DOI: 10.1542/peds.2014-1666. Available at: http://www.aappublications.org/search/palivizumab%20numresults%3A10%20sort%3Arelevance-rank%20format_result%3Astandard?facet%5Bseries-name%5D%5B0%5D=Technical%20Report. Accessed February 1, 2022.

4 Munoz FM, Ralston SL, Meissner HC. RSV recommendations unchanged after review of new data. AAP News. October 19, 2017. Available at: https://publications.aap.org/aapnews/news/13439. Accessed February 1, 2022.

5 AAP publications reaffirmed. Pediatrics. 2019; 144(2) e20191767. DOI: 10.1542/peds.2019-1767. Available at: https://pediatrics.aappublications.org/content/144/2/e20191767. Accessed February 1, 2022.

6 CDC. Emergency Preparedness and Response. Increased interseasonal respiratory syncytial virus (RSV) activity in parts of the southern United States. June 10, 2021. Available at: https://emergency.cdc.gov/han/2021/han00443.asp. Accessed February 1, 2022.
7 Interim guidance for use of palivizumab prophylaxis to prevent hospitalization from severe respiratory syncytial virus infection during the current atypical interseasonal RSV spread. Available at: https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/interim-guidance-for-use-of-palivizumab-prophylaxis-to-prevent-hospitalization/. Accessed February 1, 2022.
8 Updated Guidance: Use of Palivizumab Prophylaxis to Prevent Hospitalization From Severe Respiratory Syncytial Virus Infection During the 2021-2022 RSV Season. December 17, 2021. Available at: https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/interim-guidance-for-use-of-palivizumab-prophylaxis-to-prevent-hospitalization/. Accessed February 1, 2022.
9 AAP News. AAP releases interim guidance on preventing RSV during delayed season. August 10, 2021. Available at: https://www.aappublications.org/news/2021/08/10/rsv-palivizumab-interim-guidance-081021. Accessed February 1, 2022.
10 Updated Guidance: Use of Palivizumab Prophylaxis to Prevent Hospitalization From Severe Respiratory Syncytial Virus Infection During the 2021-2022 RSV Season. December 17, 2021. Available at: https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/interim-guidance-for-use-of-palivizumab-prophylaxis-to-prevent-hospitalization/. Accessed February 1, 2022.
11 Respiratory Syncytial Virus Seasonality — United States, 2014–2017. January 19, 2018. Available at: https://www.cdc.gov/mmwr/volumes/67/wr/mm6702a4.htm?s_cid=mm6702a4_w. Accessed February 23, 2022.
12 Respiratory Syncytial Virus Seasonality — United States, 2014–2017. January 19, 2018. Available at: https://www.cdc.gov/mmwr/volumes/67/wr/mm6702a4.htm?s_cid=mm6702a4_w. Accessed February 23, 2022.
13 Kimberlin DW, Barnett ED, Lynfield R, et al. Red Book: 2021–2024 Report of the Committee on Infectious Diseases (32nd edition). Available at: https://publications.aap.org/redbook/book/347/Red-Book-2021-2024-Report-of-the-Committee-on. Accessed February 24, 2022.
14 American Academy of Pediatrics. Policy Statement. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. Reaffirmed February 2019. Pediatrics. 2014; 134(2); 415-420. DOI: 10.1542/peds.2014-1665. Available at: http://www.aappublications.org/search/palivizumab%20numresults%3A10%20sort%3Arelevance-rank%20format_result%3Astandard?facet%5Bseries-name%5D%5B0%5D=Policy%20Statement. Accessed February 1,2022.
15 American Academy of Pediatrics. Technical Report. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. Reaffirmed February 2019. DOI: 10.1542/peds.2014-1666. Available at: http://www.aappublications.org/search/palivizumab%20numresults%3A10%20sort%3Arelevance-rank%20format_result%3Astandard?facet%5Bseries-name%5D%5B0%5D=Technical%20Report. Accessed February 1, 2022.
16 Midgley CM, Haynes AK, Baumgardner JL, et al. Determining the seasonality of respiratory syncytial virus in the United States: The impact of increased molecular testing. J Infect Dis. 2017;216(3):345-355. DOI: 10.1093/infdis/jix275.
17 Respiratory syncytial virus seasonality — United States, 2014–2017. Available at: https://www.cdc.gov/surveillance/nrevss/rsv/reports.html. Accessed February 1, 2022.
18 American Academy of Pediatrics. Policy Statement. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. Reaffirmed February 2019. Pediatrics. 2014; 134(2); 415-420. DOI: 10.1542/peds.2014-1665. Available at: http://www.aappublications.org/search/palivizumab%20numresults%3A10%20sort%3Arelevance-rank%20format_result%3Astandard?facet%5Bseries-name%5D%5B0%5D=Policy%20Statement. Accessed February 1,2022.
19 American Academy of Pediatrics. Technical Report. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. Reaffirmed February 2019. DOI: 10.1542/peds.2014-1666. Available at: http://www.aappublications.org/search/palivizumab%20numresults%3A10%20sort%3Arelevance-rank%20format_result%3Astandard?facet%5Bseries-name%5D%5B0%5D=Technical%20Report. Accessed February 1, 2022.
20 American Academy of Pediatrics. Policy Statement. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. Reaffirmed February 2019. Pediatrics. 2014; 134(2); 415-420. DOI: 10.1542/peds.2014-1665. Available at: http://www.aappublications.org/search/palivizumab%20numresults%3A10%20sort%3Arelevance-rank%20format_result%3Astandard?facet%5Bseries-name%5D%5B0%5D=Policy%20Statement. Accessed February 1,2022.
21 American Academy of Pediatrics. Technical Report. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. Reaffirmed February 2019. DOI: 10.1542/peds.2014-1666. Available at: http://www.aappublications.org/search/palivizumab%20numresults%3A10%20sort%3Arelevance-rank%20format_result%3Astandard?facet%5Bseries-name%5D%5B0%5D=Technical%20Report. Accessed February 1, 2022.
22 CDC advises broader testing for RSV due to regional spikes. June 10, 2021. Available at: https://publications.aap.org/aapnews/news/17156. Accessed February 1, 2022.
23 RSV National Trends. August 25, 2021. Available at: https://www.cdc.gov/surveillance/nrevss/rsv/natl-trend.html. Accessed February 1, 2022.
24 Updated Guidance: Use of Palivizumab Prophylaxis to Prevent Hospitalization From Severe Respiratory Syncytial Virus Infection During the 2021-2022 RSV Season. December 17, 2021. Available at: https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/interim-guidance-for-use-of-palivizumab-prophylaxis-to-prevent-hospitalization/. Accessed February 1, 2022.
25 Updated Guidance: Use of Palivizumab Prophylaxis to Prevent Hospitalization From Severe Respiratory Syncytial Virus Infection During the 2021-2022 RSV Season. December 17, 2021. Available at: https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/interim-guidance-for-use-of-palivizumab-prophylaxis-to-prevent-hospitalization/. Accessed February 1, 2022.