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Drug Policy Update: RSV Antivirals - Palivizumab

Date of Review: February 2022

Date of Last Review: September 2014
Dates of Literature Search: 06/01/2014 - 10/20/2021

Purpose for Class Update:
To identify new literature since the last update in 2014. Evidence related to the impact of the coronavirus disease 2019 (COVID-19) pandemic on seasonality of respiratory syncytial virus (RSV) onset will be sought, as well as data for the use of palivizumab in children over the age of 24 months who might not have acquired immunity due to lack of exposure to RSV.

Research Questions:
1. Is there any new evidence on the effectiveness of palivizumab on important outcomes such as mortality and hospitalizations due to RSV?
2. Is there any new evidence about harms associated with palivizumab treatment?
3. Are there subpopulations of patients who benefit more from palivizumab prophylaxis?
4. Is there any evidence on the impact of the COVID-19 pandemic on RSV seasonality onset/offset?
5. Is there any evidence to support the use of palivizumab in high-risk children over the age of 24 months?
6. Is there any evidence to support the use of more than 5 doses per RSV season of palivizumab because of differences in seasonality of RSV?

Conclusions:
- New evidence for use of palivizumab for RSV prophylaxis in infants and children does not suggest current Oregon Health Plan (OHP) policy changes are necessary.
- Mitigation measures implemented to curb the spread of COVID-19 virus has led to variances in the typical RSV season. Guidance to address these changes are limited, but the American Academy of Pediatrics (AAP) recommends to monitor interseasonal RSV activity and identify high risk infants who would qualify for palivizumab prophylaxis outside of the traditional RSV season.[1]
- In 2019 AAP reaffirmed their 2014 guidance on use of palivizumab prophylaxis in children, ages 1 month up to 24 months of age, who are at increased risk of hospitalization due to RSV.[2]
- A Cochrane review found no evidence that use of palivizumab for treatment of RSV reduced mortality or length of hospital stay in hospitalized infants and children up to the age of 24 months.[3]
- A second Cochrane review found palivizumab, compared to placebo or no intervention, to reduce hospitalizations due to RSV infections in children at high-risk of RSV infection, based on high quality of evidence (relative risk [RR] 0.44 (95% confidence interval [CI], 0.30 to 0.64).[4] High quality evidence found a reduction in wheezing in children treated with palivizumab compared to placebo or no intervention (RR 0.39; 95% CI, 0.30 to 0.64).[4]
- There is insufficient evidence for the use of palivizumab in high-risk children over the age of 24 months.

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- There is insufficient evidence for the use of more than 5 doses of palivizumab per RSV season to accommodate for variations in the RSV season.

Recommendations:
- Recommend revising the prior authorization (PA) criteria to correlate with state guidance on season onset.

Summary of Prior Reviews and Current Policy:
- Palivizumab prophylaxis is directed by PA criteria which follows the AAP guidelines for palivizumab use in infants and children that are at high risk of hospitalization from RSV.
- There were 63 pre-covid claims for palivizumab within a 12-month timespan and 38 claims during the 2020-2021 RSV season. Cost per claim for palivizumab prophylaxis represents a substantial cost to Oregon Health Authority (OHA).

Background:
Respiratory syncytial virus is a common cause of lower respiratory infection in infants and children and is the most common cause of bronchiolitis.[5] Approximately 1% to 3% of infections become severe enough to result in hospitalizations and annually there are 59,600 deaths due to RSV worldwide in children under 5 years.[6] Risk factors for the development of severe disease due to RSV include: preterm infants born before 29 weeks gestation, infants with hemodynamically significant congenital heart disease, preterm infants with chronic lung disease, diseases that affect the ability to clear secretions from the upper airway, and immunocompromised children.[7] The AAP published recommendations for the use of palivizumab for prophylaxis of RSV in infants and children at risk of hospitalization in 2014 and reaffirmed these recommendations in a 2019.[2,7]

Palivizumab is a humanized mouse immunoglobulin (IgG1) monoclonal antibody which is indicated for prevention of serious lower respiratory tract disease caused by RSV in children, up to the age of 24 months, at high risk for RSV disease.[7] Data demonstrating reduced RSV hospitalizations with palivizumab immunoprophylaxis comes from two randomized controlled trials.[8,9] The Impact-RSV trial included children born prematurely (≤35 weeks) or with bronchopulmonary dysplasia (BPD).[8] Palivizumab prophylaxis demonstrated reduction in risk of RSV hospitalizations compared to placebo (4.8% vs. 10.6%, respectively).[8] In a second study, the Cardiac Synagis Study Group found that in children with hemodynamically significant CHD, palivizumab prophylaxis reduced RSV hospitalization rates compared to placebo (5.3% vs. 9.7%, respectively).[9] Mortality reduction from RSV due to palivizumab prophylaxis are inconclusive.[7,10,11]

RSV prophylaxis is initiated during high RSV activity. Surveillance data tracks patterns of RSV activity. Generally, the RSV season onset occurs in October or November with an offset in April or May. RSV infection rates were historically monitored via antigen testing. In 2014, the Centers for Disease Control and Prevention (CDC), which provides guidance on RSV testing, incorporated the use of polymerase chain reaction (PCR) laboratory detection.[12] These PCR detections are reported to the National Respiratory and Enteric Virus Surveillance System (NREVSS). The CDC recommends antigen or PCR testing as ways to determine season onset and offset.[13] Season onset occurs when 2 consecutive weeks of mean percentage of specimen testing positive for RSV by antigen tests are at least 10% positive or RSV by PCR tests are at least 3% positive, whichever occurs first.[12,13] In Oregon laboratories report to the OHA/Public Health Division for determination of season onset and offset based on the definition provided by the CDC.

During the COVID-19 pandemic, risk mitigation strategies applied to limit the spread of the COVID-19 virus resulted in variability of the typical seasonal RSV onset, with cases reported in the spring and early summer.[14,2] In June of 2021, the southern region of the U.S. saw an increase in RSV cases prompting the CDC to recommend broader testing.[15] A large RSV resurgence was reported in Tokyo, Japan, with 10,327 cases documented through week 28 of 2021 compared to a

total number of cases in 2020 of 520.[16] Western Australian also reported an unexpected summer RSV surge in late 2020 and hospital admissions occurred in children who were older, median age of 16.4 months compared to 8.1 months in 2019.[17]

The OHA determined the start of the onset of the 2021 RSV season in Oregon was October 2, 2021. RSV rates are reported to the OHA for four regions throughout Oregon and SW Washington and are designated as: northwest Oregon and southwest Washington, central Oregon, the Gorge/northeast Oregon, and southern Oregon. Season onset and offset is determined for the state as a whole, although there is often regional variability in RSV rates.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 1**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

<u>Cochrane – Immunoglobulin Treatment for Hospitalized Infants and Young Children with Respiratory Syncytial Virus Infection</u>
A 2019 Cochrane review evaluated the use of immunoglobulins for the treatment of RSV.[3] The anti-RSV immunoglobulin and the monoclonal antibody included in the analysis were palivizumab and motavizumab (not available in the U.S.). Trials included children and infants hospitalized for pneumonia, bronchiolitis, or other lower respiratory tract infection. Seven trials were included in the review, which included children up to 24 months of age (n=486).[3] Only 2 trials evaluated IV palivizumab (1 dose) for the treatment of RSV compared to control (e.g., saline). The main outcomes of interest were mortality, length of hospital stay, and adverse events. Trials were at unclear or high risk of bias for 3 domains and evidence quality was graded as very low to low.

Results were pooled for 5 trials, 2 of which studied palivizumab. For the outcome of mortality there was very low quality evidence that there was no difference between immunoglobulins and control (RR 0.87; 95% CI, 0.14 to 5.27; p=0.88).[3] There was low quality evidence that the length of hospital stay was similar between groups with no benefit demonstrated for immunoglobulins (MD -0.7; 95% CI, -1.83 to 0.42; P=0.66).[3] There was also no statistical difference in adverse event rates or serious adverse event rates.

Overall, there is no evidence that treatment of RSV with palivizumab reduces mortality or length of hospitalization in children 24 months of age or younger.

After review, 5 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses or failure to meet AMSTAR criteria), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[18–22]

<u>Cochrane – Palivizumab for Preventing Severe Respiratory Syncytial Virus (RSV) Infection in Children</u>

A 2021 systematic review and meta-analysis of RCTs evaluated palivizumab use for prevention of RSV in children (maximum 5 doses and ages up to 24 months) compared to placebo or no intervention.[4] Five studies (n=3343) in children at high-risk of RSV infection were included. Participants were infants with a gestational age of 35 weeks or less, diagnosis of bronchopulmonary dysplasia (BPD) or hemodynamically significant congenital heart disease (CHD). All studies evaluated monthly intramuscular (IM) doses of palivizumab 15 mg/kg. Outpatient use of palivizumab was used in all studies and one study also enrolled hospitalized patients. The risk of bias of all five studies was determined by the authors to be low.

A summary of findings with moderate to high quality of evidence are presented in **Table 1**. All outcome results were based on a follow-up period of 2 years. There was low quality evidence that the use of palivizumab resulted in a lower rate of RSV infection compared to placebo or no intervention, 64 per 1000 vs. 195 per 1000.[4]

Table 1. Prevention of RSV Infection in Children Treated with Palivizumab Compared to Placebo or No Intervention[4]

Outcome	Results	Relative Effect	Quality of Evidence
Hospitalizations due to RSV infection	Palivizumab: 43 per 1000 Placebo or no intervention: 98 per 1000	RR 0.44 (95% CI, 0.30 to 0.64)	High
Mortality	Palivizumab: 16 per 1000 Placebo or no intervention: 23 per 1000	RR 0.69 (95% CI, 0.42 to 1.15)	Moderate
Hospitalization due respiratory-related illness	Palivizumab: 274 per 1000 Placebo or no intervention: 341 per 1000	RR 0.78 (95% CI, 0.62 to 0.97)	Moderate
Number of wheezing days	Palivizumab: 18 per 1000 Placebo or no intervention: 45 per 1000	RR 0.39 (95% CI, 0.30 to 0.64)	High
Adverse Events	Palivizumab: 91 per 1000 Placebo or no intervention: 84 per 1000	RR 1.09 (95% CI, 0.85 to 1.39)	Moderate

Palivizumab reduced hospitalizations but mortality benefits at 2 years of follow-up were not demonstrated. The number of respiratory-related illness hospitalizations and number of wheezing days were also reduced with the use of palivizumab.[4]

New Guidelines:
High Quality Guidelines:

American Academy of Pediatrics – Clinical Practice Guideline: The Diagnosis, Management and Prevention of Bronchiolitis
In 2019 the AAP reaffirmed the 2014 guidelines on managing and preventing bronchiolitis in children, ages 1 through 23 months.[5] No data was provided on the reaffirmation process. The AAP guideline was previously presented September 2014 in a Drug Use Research and Management (DURM) RSV Policy Update. A brief review of recommendations for prevention, as it relates to palivizumab, are presented in **Table 2**.[5]

Table 2. Recommendations for the Use of Palivizumab for Prevention of Bronchiolitis[5]

Recommendation	Evidence Quality	Recommendation Strength

Palivizumab should not be administered to otherwise healthy infants with a gestational age of 29 weeks, 0 days or greater	B	Strong
Palivizumab should be administered during the first year of life to infants with hemodynamically significant heart disease or chronic lung disease of prematurity defined as preterm infants <32 weeks, 0 days' gestation who require >21% oxygen for at least the first 28 days of life	B	Moderate
A maximum of 5 monthly doses (15 mg/kg/dose) of palivizumab should be given in the first year of life to infants who qualify* for palivizumab during the RSV season	B	Moderate
Key: * Detailed guidance on the infants who qualify is described in the AAP guidance on palivizumab prophylaxis which was detailed in the 2014 policy update, including those children up to 24 months of age who would be candidates for prophylaxis		

Additional Guidelines for Clinical Context:

American Academy of Pediatrics – Interim Guidance for Use of Palivizumab Prophylaxis to Prevent Hospitalization from Severe Respiratory Syncytial Virus Infection During the Current Atypical Interseasonal RSV Spread

The traditional RSV season onset and offset was altered due to nonpharmacological measures (i.e., masking, social distancing) used to prevent the spread of COVID-19.[1] The rates of RSV were dramatically lower starting in March of 2020 and activity remained low during the normal fall-winter RSV season of 2020-2021. In the Spring of 2021, there was an interseasonal increase in RSV activity. This increase was thought to be due to relaxation of nonpharmacological measures at around the same time.

Previously published recommendations from AAP for the prophylaxis use of palivizumab for high-risk patients has been used as guidance for identifying the most appropriate candidates for palivizumab use. With evidence of a delayed onset of the 2020-2021 RSV season, AAP supports the use of palivizumab for those patients who have already been identified as appropriate candidates per previous guidance.[1] Early initiation of palivizumab is recommended during the atypical interseasonal variations seen in RSV epidemiology in 2021 for regions that are experiencing high RSV circulation. There was no recommendation for additional doses beyond previous guidance for the use of 5 doses, which continues to provide protection for up to one month after injection. AAP recommends providers assess RSV rates at least monthly and identify eligible infants that may benefit from palivizumab administration.[1]

After review, one guideline was excluded due to poor quality.[23]

New Formulations or Indications:
None identified.

New FDA Safety Alerts:

Table 3. Description of new FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Palivizumab[24]	Synagis	5/2017	Use in specific populations	Palivizumab should not be used in females of reproductive potential

Randomized Controlled Trials:

A total of 123 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical).

References:

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Appendix 1: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to October 18, 2021
Search Strategy:

#	Searches	Results
1	Palivizumab/ or palivizumab.mp.	1184
2	respiratory syncytial virus.mp. or Respiratory Syncytial Viruses/	16722
3	1 or 2	16799
4	limit 3 to (english language and humans and yr="2014 -Current")	4217
5	limit 4 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	123

Appendix 2: Key Inclusion Criteria

Population	Infants and children 24 months and younger at high risk of hospitalization
Intervention	Palivizumab prophylaxis
Comparator	No prophylaxis, placebo
Outcomes	Hospitalizations, mortality, recurrent wheeze, asthma
Timing	Prophylaxis during peak RSV activity
Setting	Outpatient or inpatient

Palivizumab (Synagis®)

Goal(s):

- Promote safe and effective use of palivizumab in high-risk infants and children. Prophylaxis against RSV should cover up to 5 months during high viral activity season, usually spanning from November through March in Oregon.

Length of Authorization:

- Based on individual factors; may extend up to 5 months (5 total doses)

Requires PA:

- Synagis (Palivizumab) pharmacy and physician-administered claims

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Has the patient been receiving monthly palivizumab prophylaxis and been hospitalized for a breakthrough RSV infection?	**Yes:** Pass to RPh; deny for medical appropriateness.	**No:** Go to #3
3. Is the request for RSV prophylaxis to be administered during the typical high viral activity season from November through March?	**Yes:** Go to #5	**No:** Go to #4
4. Is the request for prophylaxis starting in October due to interseasonal increase in RSV activity with season onset designated by the OHA*? * Data provided by the Oregon's Weekly Respiratory Syncytial Virus Surveillance Report from the Oregon Public Health Division based on regions. Weekly updates are found at: https://public.health.oregon.gov/DiseasesConditions/DiseasesAZ/Pages/disease.aspx?did=40)	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness. Prophylaxis is indicated only during high viral activity.

Approval Criteria		
5. Is the current age of the patient < 24 months at start of RSV season?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness. Not recommended for patients ≥24 months old.
6. **GROUP A** Does the patient have the CLD (chronic lung disease) of prematurity ICD10 Q331through Q339 **and** in the past 6 months has required medical treatment with at least one of the following: a. diuretics b. chronic corticosteroid therapy c. supplemental oxygen therapy	**Yes:** Go to #18	**No:** Go to #7
7. **GROUP B** Has the patient received a cardiac transplant during the RSV season?	**Yes:** Go to #18	**No:** Go to #8
8. **GROUP C** Is the child profoundly immunocompromised during the RSV season (i.e. solid organ transplant or hematopoietic stem cell transplantation)?	**Yes:** Go to #18	**No:** Go to #9
9. **GROUP D** Does the infant have cystic fibrosis and manifestations of severe lung disease or weight or length less than the 10th percentile?	**Yes:** Go to #18	**No:** Go to #10

Approval Criteria		
10. **GROUP E** Is the request for a second season of palivizumab prophylaxis for a child born <32 weeks, 0 days gestation who required at least 28 days of oxygen, chronic systemic corticosteroid therapy, or bronchodilator therapy within 6 months of start of second RSV season?	**Yes:** Go to #18	**No:** Go to #11
11. Will the patient be <12 months at start of RSV season?	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness.
12. **GROUP F** Was the infant born before 29 weeks, 0 days gestation?	**Yes:** Go to #18	**No:** Go to #13
13. **GROUP G** Does the infant have pulmonary abnormalities of the airway or neuromuscular disease compromising handling of secretions?	**Yes:** Go to #18	**No:** Go to #14

Approval Criteria		
14. **GROUP H** Does the patient have hemodynamically significant congenital heart disease (CHD) ICD10: P293, Q209, Q220-Q223, Q225, Q229-Q234, Q238, Q240-Q246, Q248-Q249, Q250-Q256, Q278-Q279,Q282-Q283,Q288-Q289, Q2560-Q2565,Q2568-Q2569, Q2570-Q2572, Q2579,Q2731-Q2732 and at least one of the following: a. Acyanotic heart disease who are receiving treatment to control congestive heart failure and will require cardiac surgical procedures; OR b. Have moderate to severe pulmonary hypertension; OR c. History of lesions adequately corrected by surgery AND still requiring medication for congestive heart failure?	**Yes:** Go to #18	**No:** Go to #15
15. **GROUP I** Does the patient have chronic lung disease (CLD) of prematurity defined as gestational age <32 weeks, 0 days and requirement for >21% oxygen for at least the first 28 days after birth?	**Yes:** Go to #18	**No:** Go to #16
16. **GROUP J** Does the patient have cyanotic heart defects and immunoprophylaxis is recommended?	**Yes:** Go to #18	**No:** Go to #17
17. **GROUP K** Does the patient have cystic fibrosis with clinical evidence of CLD and/or nutritional compromise?	**Yes:** Go to #18	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
18. Is the request for more than 5 doses within the same RSV season or for dosing <28 days apart?	**Yes:** Pass to RPh. Deny; medical appropriateness. Prophylaxis is indicated for 5 months maximum and doses should be administered ≥28 days apart. May approve for the following on a case-by-case basis: a. >5 doses; b. Prophylaxis for a second / subsequent RSV season	**No:** Go to #19
19. Has the patient had a weight taken within the last 30 days?	**Yes:** Document weight and date and go to #20 Weight:_____ Date:_____	**No:** Pass to RPh. Obtain recent weight so accurate dose can be calculated.
20. Approve palivizumab for a dose of 15 mg/kg. Document number of doses received in hospital and total number approved according to month of birth (refer to Table 1): Total number of doses approved for RSV season:_____ Number of doses received in the hospital:_____ Prior to each refill, the patient's parent/caregiver and prescriber must comply with all case management services, including obtaining current weight for accurate dosing purposes throughout the approved treatment period as required by the Oregon Health Authority.		

Table 1. Maximum Number of Doses for RSV Prophylaxis

MONTH OF BIRTH	ALL GROUPS
April	5
May	5
June	5
July	5
August	5
September	5
October	5
November	5
December	4
January	3
February	2
March	1

* Infant may require less doses than listed based on age at the time of discharge from the hospital. Subtract number of doses given in hospital from total number of approved doses.

Notes:

- Dose: 15 mg/kg via intramuscular injection once monthly throughout RSV season.
- The start date for Synagis® is November 1 each year (or sooner when the Oregon Public Health Division has determined that RSV season onset has occurred) for a total of up to 5 doses.
- Approval for more than 5 doses or additional doses after March 31 will be considered on a case-by-case basis. Results from clinical trials indicate that Synagis® trough concentrations greater than 30 days after the 5th dose are well above the protective concentration. Therefore, 5 doses will provide more than 20 weeks of protection.

P&T/DUR Review: *2/22 (KS); 11/16 (DE); 9/14; 5/11; 5/12*
Implementation: *4/1/22; 1/1/17; 3/30/12*