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Committee Approvals:
UW Health Clinic Administered Medications Policy (CAMP) Subcommittee (September 2014, September 2017)
UW Health Pharmacy and Therapeutics Committee (October 2014, November 2015, November 2017)
Introduction
Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract infections in infants and children.\(^1\) It generally occurs in the fall, winter, and early spring and usually presents as upper respiratory tract infection in healthy infants and children. In infants and children at risk, including premature infants, children with chronic lung disease (CLD), congenital heart disease (CHD), and congenital or acquired immunodeficiency, it can progress to bronchiolitis, pneumonia, and, occasionally, respiratory failure. In the United States, over 90,000 children are hospitalized each year due to RSV disease and 4500 die. The best method to prevent RSV disease is to prevent person-to-person transmission through good hand hygiene and isolation procedures. The RSV season in Wisconsin generally runs from November through April, but varies slightly from year to year.

Palivizumab is indicated for the prevention of serious lower respiratory tract infection caused by RSV in children younger than 24 months of age with CLD or CHD and in infants with a history of premature birth (fewer than 29 weeks gestation).

Palivizumab has been shown to reduce hospitalizations due to RSV by 45% to 55%. Palivizumab is an intramuscular injection administered monthly for up to a maximum of five injections throughout the RSV season. Palivizumab is dosed 15 mg/kg. The recommendations in this guideline are based on the guidelines published by the American Academy of Pediatrics in 2014.\(^2\) The policy statement replaces the recommendations found in the 2012 Red Book.\(^3\) Systematic review supports the palivizumab recommendations from the American Academy or Pediatrics.\(^4,5\)

Scope
Intended Users: Physicians, Advanced Practice Providers, Pharmacists, Nurses

Objective: To outline those infants that would derive the most benefit from the use of palivizumab RSV prophylaxis to reduce hospitalizations due to RSV infection.

Target Population:
Pediatric and neonatal patients identified as at high risk for hospitalization from RSV infection.

Infants and children eligible for palivizumab prophylaxis:
- Preterm infants born before 29 weeks, 0 days gestation who are younger than 12 months old at the start of RSV season (November);
- Infants with CLD of prematurity in the first year of life;
- Infants and children who are 12 months or younger at the start of RSV season and have hemodynamically significant congenital heart disease; and
- Other infants in the first year of life as identified at high-risk from complications of RSV infection.

Definitions
- **Respiratory syncytial virus (RSV) season in Wisconsin**: based on viral circulation patterns, the season typically runs from November to April/May in Wisconsin.
- **Gestational age**: 32 weeks gestation refers to an infant born on or before the 32\(^{nd}\) week of gestation (32 weeks, 0 days).
- **Chronic lung disease (CLD) of prematurity**: birth at less than 32 weeks, 0 days gestation and a requirement for greater than 21% oxygen for at least 28 days after birth.
- **Hemodynamically significant congenital heart disease**: includes infants with acyanotic heart disease who are receiving medication to control congestive heart failure or infants with moderate to severe pulmonary hypertension.
- **Hemodynamically insignificant heart disease**: examples include secundum atrial septal defect, small ventricular septal defect, pulmonic stenosis, uncomplicated aortic stenosis, mild coarctation of the aorta, or patent ductus arteriosus.

**Recommendations**

**Palivizumab Use Recommendations**

1. RSV prophylaxis with the use of palivizumab is recommended in the following situations:
   1.1. In the first year of life, for infants born before 29 weeks, 0 days gestation.6,7 (*UW Health Strong Recommendation, Low Quality of Evidence*)
   1.2. In the first year of life, preterm infants who develop chronic lung disease (CLD) of prematurity, defined as gestational age younger than 32 weeks, 0 days at birth and a requirement for greater than 21% oxygen for at least the first 28 days after birth.6,8,9 (*UW Health Strong Recommendation, Moderate Quality of Evidence*)
   1.3. In the second year of life, for infants with CLD of prematurity who continue to require medical support (e.g. chronic corticosteroid therapy, diuretic therapy, or supplemental oxygen) during the six-month period before the start of the second RSV season (May 1).6 (*UW Health Strong Recommendation, Very Low Quality of Evidence*)
   1.4. In the first year of life, children 12 months or younger with hemodynamically significant congenital heart disease (CHD) such as congestive heart failure requiring medications, moderate to severe pulmonary hypertension or acyanotic heart disease on medications.6,10,11 (*UW Health Strong Recommendation, Low Quality of Evidence*)

2. RSV prophylaxis with the use of palivizumab is NOT recommended in the following situations:
   2.1. In the first year of life for otherwise healthy infants born at or after 29 weeks, 0 days gestation.6-8 (*UW Health Strong Recommendation, Moderate Quality of Evidence*)
   2.2. In the second year of life for otherwise healthy infants born before 29 weeks, 0 days gestation.6,7 (*UW Health Strong Recommendation, Moderate Quality of Evidence*)
   2.3. In the second year of life, for infants with CLD of prematurity who do not require medical support (e.g. chronic corticosteroid therapy, diuretic therapy, or supplemental oxygen) during the six-month period preceding the start of the second RSV season (May 1).6 (*UW Health Strong Recommendation, Low Quality of Evidence*)
   2.4. Infants with hemodynamically insignificant CHD such as secundum atrial septal defect, small ventricular septal defect, pulmonic stenosis, uncomplicated aortic stenosis, mild coarctation of the aorta, or patent ductus arteriosus.6 (*UW Health Strong Recommendation, Low Quality of Evidence*)
   2.5. Infants with cardiac lesions adequately corrected by surgery, unless they continue to require medication for congestive heart failure.6 (*UW Health Strong Recommendation, Low Quality of Evidence*)
   2.6. Infants with mild cardiomyopathy who are not receiving medical therapy for the condition.6 (*UW Health Strong Recommendation, Low Quality of Evidence*)
   2.7. Infants diagnosed with cystic fibrosis by newborn screening unless other indications for use are present.12-17 (*UW Health Strong Recommendation, Moderate Quality of Evidence*)
   2.8. Infants with Down syndrome unless other indications for use are present.6,18 (*UW Health Strong Recommendation, Low Quality of Evidence*)
   2.9. For infants and children as primary asthma prevention or to reduce subsequent episodes of wheezing.6,19,20 (*UW Health Weak/Conditional Recommendation, Low Quality of Evidence*)
2.10. For infants and children with contracted RSV for treatment of current illness.\textsuperscript{6,21,22} \textit{(UW Health Strong Recommendation, Low Quality of Evidence)}

2.11. No available data support the use of palivizumab in effort to control health-care associated outbreak of RSV disease, therefore, palivizumab is not recommended for this indication.\textsuperscript{6} \textit{(UW Health Strong Recommendation, Low Quality of Evidence)}.

3. RSV prophylaxis with the use of palivizumab \textbf{MAY be considered} in the following situations\textsuperscript{6}: \textit{(UW Health Weak/Conditional Recommendation, Very Low Quality of Evidence)}

3.1. Children younger than two years who are undergoing cardiopulmonary bypass and are receiving palivizumab and will continue to require prophylaxis may receive a post-operative dose of palivizumab (15 mg/kg) at the conclusion of extracorporeal membrane oxygenation.

3.2. Children younger than two years who undergo cardiac transplantation during the RSV season.

3.3. Children younger than two years who are profoundly immunocompromised (e.g. solid organ or hematopoietic stem cell transplantation, severe combined immunodeficiency (SCID), or severe acquired immunodeficiency syndromes (AIDS)), during the RSV season.

3.4. In the first year of life, infants with pulmonary abnormalities or neuromuscular disease that impairs the ability to clear secretions from the upper airway because of ineffective cough.

3.5. In the second year of life for infants with cystic fibrosis diagnosis with manifestations of severe lung disease (previous hospitalization for pulmonary exacerbation in the first year of life, abnormal chest radiograph, abnormal chest CT, or weight for length below the tenth percentile).

3.6. Children younger than 2 years old with interstitial lung disease.

3.7. Children in the second year of life with chronic ventilation.

\textbf{Palivizumab Dosing, Administration, and Duration Recommendations}

4. The dose of palivizumab is 15 mg/kg once a month during the RSV season. A maximum of five doses should be given during any single RSV season.\textsuperscript{6,8} \textit{(UW Health Strong Recommendation, Moderate Quality of Evidence)} In Wisconsin, the RSV season is usually considered to be November through April.

4.1. Administration of more than five monthly doses of palivizumab is not recommended. \textit{(UW Health Strong Recommendation, Low Quality of Evidence)}\textsuperscript{6,8}

5. Administration of more than five monthly doses of palivizumab is not recommended. \textit{(UW Health Strong Recommendation, Low Quality of Evidence)}\textsuperscript{6,8}

6. If an infant or young child develops a breakthrough RSV hospitalization while on palivizumab prophylaxis, palivizumab prophylaxis discontinuation is reasonable as the likelihood of a second RSV hospitalization in the same RSV season is extremely low (less than 0.5%).\textsuperscript{6} \textit{(UW Health Strong Recommendation, Very Low Quality of Evidence)}

7. Children who are hospitalized during RSV season and who qualify for palivizumab for whom a long hospital stay is anticipated, palivizumab given 24 to 48 hours prior to discharge may be considered. \textit{(UW Health Strong Recommendation, Low Quality of Evidence)}

8. The dose should be administered intramuscularly in the anterolateral aspect of the thigh. Do not use the gluteal muscle routinely because of the risk of damage to the sciatic nerve.\textsuperscript{23} \textit{(UW Health Strong Recommendation, High Quality of Evidence)}

9. Volumes greater than 1 mL should be divided and administered in separate sites as divided doses.\textsuperscript{23} \textit{(UW Health Strong Recommendation, High Quality of Evidence)}
Additional RSV Prevention Methods\textsuperscript{6,8}

1. Prevention during hospitalization
   1.1. The first dose of palivizumab for hospitalized infants who qualify may be considered for administration 48 to 72 hours before discharge or directly after discharge. (UW Health Weak/Conditional Recommendation, Very Low Quality of Evidence)
   1.2. For infants receiving palivizumab prophylaxis who are hospitalized within five days of the date when the next monthly dose is due, their next monthly scheduled dose may be considered for administration while in the hospital. (UW Health Weak/Conditional Recommendation, Very Low Quality of Evidence)
   1.3. Proper hand hygiene and infection control protocols should be followed, especially if an RSV outbreak occurs in a high-risk unit.\textsuperscript{24-26} (UW Health Strong Recommendation, High Quality of Evidence)
   1.4. No data are available to support prophylactic use of palivizumab to control a hospital outbreak of RSV.\textsuperscript{6} (UW Health Strong Recommendation, Low Quality of Evidence)

2. Home prevention
   2.1. Tobacco smoke exposure should be avoided in high-risk infants. (UW Health Strong Recommendation, High Quality of Evidence) Environmental tobacco smoke has been shown to increase risk of hospitalization and disease severity of acquired RSV.\textsuperscript{27}
   2.2. Families should be educated about the importance of decreasing exposure to and transmission of RSV for high-risk infants. Prevention measures include limiting, where feasible, exposure to contagious settings (e.g. child care centers).\textsuperscript{6} (UW Health Strong Recommendation, Low Quality of Evidence)
   2.3. Families should also be taught the importance of good hand hygiene in all settings, including the home, especially during periods when contacts of high-risk children have respiratory tract infections.\textsuperscript{6} (UW Health Strong Recommendation, High Quality of Evidence)

Disclaimer
Clinical practice guidelines assist clinicians by providing a framework for the evaluation and treatment of patients. This guideline outlines the preferred approach for most patients. It is not intended to replace a clinician’s judgment or to establish a protocol for all patients. It is understood that some patients will not fit the clinical condition contemplated by a guideline and that a guideline will rarely establish the only appropriate approach to a problem.
Methodology
Development Process
Each guideline is reviewed and updated a minimum of every 3 years. All guidelines are developed using the guiding principles, standard processes, and styling outlined in the UW Health Clinical Practice Guideline Resource Guide. This includes expectations for workgroup composition and recruitment strategies, disclosure and management of conflict of interest for participating workgroup members, literature review techniques, evidence grading resources, required approval bodies, and suggestions for communication and implementation.

Methods Used to Collect the Evidence:
- AAP Guideline
- Electronic database search (PUBMED)
- Database of systematic reviews (Cochrane Library)
- Hand-searching journals, external guidelines, and conference publications

Time period: 2014 to 2017

Methods Used to Select the Evidence:
Published literature other than randomized, clinical trials or any clinical trials preceding the 2014 AAP Guideline were excluded. References from the articles were also searched. Finally, the personal libraries of the authors were queried. The 2017 revision evaluated new clinical evidence published between 2014 and 2017.

Methods Used to Formulate the Recommendations:
The workgroup members agreed to adopt recommendations developed by external organizations and/or created recommendations internally via a consensus process using discussion of the literature and expert experience/opinion. If issues or controversies arose where consensus could not be reached, the topic was escalated appropriately per the guiding principles outlined in the UW Health Clinical Practice Guideline Resource Guide.

Methods Used to Assess the Quality of the Evidence/Strength of the Recommendations:
Recommendations developed by external organizations maintained the evidence grade assigned within the original source document and were adopted for use at UW Health.

Internally developed recommendations, or those adopted from external sources without an assigned evidence grade, were evaluated by the guideline workgroup using an algorithm adapted from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (see Figure 1).
Figure 1. GRADE Methodology adapted by UW Health

<table>
<thead>
<tr>
<th>GRADE Ranking of Evidence</th>
<th>Description</th>
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<tbody>
<tr>
<td>High</td>
<td>We are confident that the effect in the study reflects the actual effect.</td>
</tr>
<tr>
<td>Moderate</td>
<td>We are quite confident that the effect in the study is close to the true effect, but it is also possible it is substantially different.</td>
</tr>
<tr>
<td>Low</td>
<td>The true effect may differ significantly from the estimate.</td>
</tr>
<tr>
<td>Very Low</td>
<td>The true effect is likely to be substantially different from the estimated effect.</td>
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<thead>
<tr>
<th>GRADE Ratings for Recommendations For or Against Practice</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Strong</td>
<td>The net benefit of the treatment is clear, patient values and circumstances are unlikely to affect the decision.</td>
</tr>
<tr>
<td>Weak/conditional</td>
<td>Recommendation may be conditional upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented.</td>
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Recognition of Potential Health Care Disparities
None identified.
Collateral Tools and Resources

Metrics
- Proportion of patients receiving palivizumab who were screened appropriately.
- Proportion of patients receiving palivizumab who meet guideline criteria.
- Proportion of patients receiving palivizumab who do not develop RSV.

Patient Resources
1. Health Facts For You #4319: RSV
2. Health Facts For You #7301: Bronchiolitis
3. Health Facts For You: #7343: RSV (Spanish)
4. Health Facts For You: #7342: Bronchiolitis (Spanish)

Policies
1. UW Health Clinical Policy #6.1.9: Restricted Primarily Ambulatory Administered Medications in Hospitalized Patients
2. UWMF Policy - MF Clinic Administered Mediations with Prior Authorization

Companion Documents
- Palivizumab (Synagis) Toolkit
- Palivizumab (Synagis) Clinic Memo for 2015-2016
- UW Health Palivizumab Referral and Order Form (301361-DT)
- Forward Health Prior Authorization Form for Synagis
- American Academy of Pediatrics Updated Guidance for Palivizumab Prophylaxis among Infants and Young Children at Increased Risk of Hospitalization for Respiratory Syncytial Virus Infection Policy Statement
- UW Health Diagnosis, Management and Prevention of Bronchiolitis – Pediatric – Emergency Department/Inpatient Clinical Practice Guideline
References


