BlueCross BlueShield of Kansas City

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Immune Prophylaxis for Respiratory Syncitial Virus

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Policy

BCBSKC will provide coverage for RSV immunoprophylaxis when the following criteria are met.

When Policy Topic is covered

Monthly administration of immune prophylaxis for respiratory syncytial virus (RSV) during the RSV season with palivizumab may be considered **medically necessary** in the following infants and children in accordance with current (2014) guidelines from the American Academy of Pediatrics:

1. In the first year of life, ie, younger than 12 months at the start of the RSV season or born during the RSV season:
   - **a**. Infants born before 29 weeks, 0 days' gestation;
   - **b**. Preterm infants with chronic lung disease (CLD) of prematurity, defined as birth at less than 32 weeks, 0 days' gestation and a requirement for more than 21% oxygen for at least the first 28 days after birth;
   - **c**. Certain infants with hemodynamically significant heart disease (eg, infants with acyanotic heart disease who are receiving medication to control congestive heart failure and will require cardiac surgical procedures; infants with moderate to severe pulmonary hypertension; infants with lesions adequately corrected by surgery who continue to require medication for heart failure);
     - **i**. Decisions regarding palivizumab prophylaxis for infants with cyanotic heart defects in the first year of life may be made in consultation with a pediatric cardiologist.
   - **d**. Children with pulmonary abnormality or neuromuscular disease that impairs the ability to clear secretions from the upper airways (eg, ineffective cough, recurrent gastroesophageal tract reflux, pulmonary malformations, tracheoesophageal fistula, upper airway conditions, or conditions requiring tracheostomy);
   - **e**. Children with cystic fibrosis who have at least one of the following conditions:
     - **i**. Clinical evidence of CLD; and/or
     - **ii**. Nutritional compromise.
2. In the second year of life, ie, younger than 24 months at the start of the RSV season:
   - **a**. Children who were born at less than 32 weeks, 0 days' gestation and required at least 28 days of supplemental oxygen after birth and who continue to require medical intervention (supplemental oxygen, chronic corticosteroid, or diuretic therapy) during the 6-month period before the start of the second RSV season.
   - **b**. Children with cystic fibrosis who have either:
     - **i**. Manifestations of severe lung disease (previous hospitalization for pulmonary exacerbation in the first year of life or abnormalities on chest radiography or chest computed tomography that persist when stable); or
     - **ii**. Weight for length less than the 10th percentile.
3. In the first or second year of life:
   - **a.** Children who will be profoundly immunocompromised (eg, will undergo solid organ or hematopoietic stem-cell transplantation or receive chemotherapy) during the RSV season.

4. After surgical procedures that use cardiopulmonary bypass, for children who still require prophylaxis, a postoperative dose of palivizumab may be considered **medically necessary** after cardiac bypass or at the conclusion of extracorporeal membrane oxygenation for infants and children younger than 24 months.

When Policy Topic is not covered

Immunoprophylaxis for respiratory syncytial virus is considered **not medically necessary** in:

1. Infants and children with hemodynamically insignificant heart disease (eg, secundum atrial septal defect, small ventricular septal defect, pulmonic stenosis, uncomplicated aortic stenosis, mild coarctation of the aorta, and patent ductus arteriosus);
2. Infants with lesions adequately corrected by surgery, unless they continue to require medication for heart failure;
3. Infants with mild cardiomyopathy who are not receiving medical therapy for the condition; or
4. Children with congenital heart disease in the second year of life.

Other indications for immune prophylaxis for respiratory syncytial virus are considered **investigational** including, but not limited to, controlling outbreaks of health care-associated disease; or use in children with cystic fibrosis or Down syndrome, unless criteria for medical necessity (outlined above) are satisfied.

Description of Procedure or Service

Dosing and Administration

Palivizumab is administered by intramuscular injection in a dose of 15 mg/kg of body weight per month. The anterolateral aspect of the thigh is the preferred injection site. Routine use of the gluteal muscle for the injection site can cause sciatic nerve damage.

Clinicians may administer up to a maximum of 5 monthly doses of palivizumab (15 mg/kg per dose) during the RSV season to infants who qualify for prophylaxis. Qualifying infants born during the RSV season will require fewer doses. For example, infants born in January would receive their last dose in March (see “Initiation and Termination of Immunoprophylaxis,” next).1

Hospitalized infants who qualify for prophylaxis during the RSV season should receive the first dose of palivizumab 48 to 72 hours before discharge or promptly after discharge.

Breakthrough RSV

If any infant or young child receiving monthly palivizumab prophylaxis experiences a breakthrough RSV hospitalization, monthly prophylaxis should be discontinued because of the extremely low likelihood of a second RSV hospitalization in the same season (<0.5%).1

Prevention of Health Care Associated RSV Disease

RSV is known to be transmitted in the hospital setting and to cause serious disease in high-risk infants. Among hospitalized infants, the major means to reduce RSV transmission is strict observance of infection control practices, including restriction of visitors to the neonatal intensive care unit during respiratory virus season and prompt initiation of precautions for RSV-infected infants. If an RSV outbreak occurs in a highrisk unit (eg, pediatric or neonatal intensive care unit or stem-cell transplantation unit), primary emphasis should be placed on proper infection control practices, especially hand hygiene. No data exist to support palivizumab use in controlling outbreaks of health care–associated disease, and palivizumab use is not recommended for this purpose.

Interactions

Palivizumab does not interfere with response to vaccines.

Palivizumab may interfere with RSV diagnostic tests that are immunologically based (eg, some antigen detection-based assays).

Risk Minimization Techniques
Infants, especially high-risk infants, should never be exposed to tobacco smoke. In published studies, passive household exposure to tobacco smoke has not been associated with an increased risk of RSV hospitalization on a consistent basis. However, exposure to tobacco smoke is a known risk factor for many adverse health-related outcomes. Exposure to tobacco smoke can be controlled by the family of an infant at increased risk of RSV disease, and preventive measures will be less costly than palivizumab prophylaxis.

For all infants, particularly those who are preterm, the environment should be optimized to prevent RSV and other viral respiratory infections by offering breast milk feeds, immunizing household contacts with influenza vaccine, practicing hand and cough hygiene, and by avoiding tobacco or other smoke exposure, and attendance in large group child care during the first winter season, whenever possible.2

Initiation and Termination of Immunoprophylaxis
Initiation of immunoprophylaxis in November and continuation for a total of 5 monthly doses will provide protection into April and is recommended for most areas of the United States. If prophylaxis is initiated in October, the fifth and final dose should be administered in February.

In the temperate climates of North America, peak RSV activity typically occurs between November and March, whereas in equatorial countries, RSV seasonality patterns vary and may occur throughout the year. The inevitability of the RSV season is predictable, but the severity of the season, the time of onset, the peak of activity, and the end of the season cannot be predicted precisely. Substantial variation in timing of community outbreaks of RSV disease from year to year exists in the same community and between communities in the same year, even in the same region. These variations occur within the overall pattern of RSV outbreaks, 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 activity. In recent years, the national duration of the RSV season has been 21 weeks.3

Results from clinical trials indicate that palivizumab trough serum concentrations more than 30 days after the fifth dose will be well above the protective concentration for most infants. Five monthly doses of palivizumab will provide more than 20 weeks of protective serum antibody concentration. In the continental United States, a total of 5 monthly doses for infants and young children with congenital heart disease, CLD of prematurity, or preterm birth before 32 weeks' gestation (31 weeks, 6 days) will provide an optimal balance of benefit and cost, even with variation in season onset and end.

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 should affect the timing of palivizumab administration. Northwest Florida has an onset in mid-November, which is consistent with other areas of the United States. In north central and southwest Florida, the onset of RSV season typically is late September to early October. The RSV season in southeast Florida (Miami-Dade County) typically has its onset in July. Despite varied onsets, the RSV season is of equal duration in the different regions of Florida. Children who receive palivizumab prophylaxis for the entire RSV season should receive palivizumab only during the 5 months after the onset of RSV season in their region (maximum of 5 doses), which should provide coverage during the peak of the season, when prophylaxis is most effective.

BACKGROUND
RSV infections typically occur in the winter months, starting from late October to mid-January and ending from March to May.3 Considerable variation in the timing of community outbreaks is observed year to year. According to CDC, onset of the RSV season occurs when the median percentage of specimens testing positive for RSV is 10% higher over a 2-week period. During 1997 to 2006, an estimated 132,000 to 172,000 children aged younger than 5 years were hospitalized for RSV infection annually in the United States.3

CLD of prematurity (formerly known as bronchopulmonary dysplasia) is a general term for long-term respiratory problems in premature infants. CLD results from lung injury to newborns who, consequently, must use a mechanical ventilator and supplemental oxygen for breathing. With injury, lung tissues become inflamed, and scarring can result. Causes of lung injury include the following: prematurity, low amounts of surfactant, oxygen use, mechanical ventilation. Risk factors for developing CLD include birth at less than 34 weeks' gestation; birth weight less than 2000 grams (4 pounds, 6.5 ounces); hyaline membrane disease; pulmonary interstitial emphysema; patent ductus arteriosus; Caucasian race; male sex; maternal womb infection (chorioamnionitis); and family history of asthma.

In contrast to the well-documented beneficial effect of breastfeeding against many viral illnesses, existing data are conflicting regarding the specific protective effect of breastfeeding against RSV infection. Breastfeeding should be encouraged for all infants in accordance with recommendations of the American Academy of Pediatrics (AAP). High-risk infants should be kept away from crowds and from situations in which exposure to infected individuals cannot be controlled. Participation in group child care should be restricted during the RSV season for high-risk infants whenever feasible. Parents should be instructed on the importance of careful hand hygiene. In addition, all high-risk infants 6 months of age and older and their contacts should receive influenza vaccine, as well, as other recommended age-appropriate immunizations.

This policy does not address therapies to treat RSV infection.

REGULATORY STATUS

In June 1998, the biologic drug, Synagis® (palivizumab; MedImmune Inc., Gaithersburg, MA), was approved for marketing by FDA through the biologics licensing application for use in the prevention of serious lower respiratory tract disease caused by RSV in pediatric patients at high risk of RSV disease. In July 2004, FDA approved a liquid formulation of Synagis®, supplied as a sterile solution ready for injection, thus providing improved convenience for administration. This formulation is used in the physician office or home setting. There are no therapeutic equivalents to this drug. FDA application number: (BLA)103770.

RespiGam® RSV-IVIG for intravenous use was available from 1993 to 2009. It is no longer manufactured.

In August 2010, motavizumab (proposed to be marketed as Rezield™, MedImmune Inc.) received a complete response letter from FDA requesting additional clinical data on its biologics license application. Subsequently, AstraZeneca suspended motavizumab development and on the manufacturer's request, FDA withdrew its biological license application.

Rationale

This policy was created in 1999 and was regularly updated with searches of the MEDLINE database. The most recent literature search was performed for the period through July 7, 2014. The following is a summary of key findings to date.

High-Risk Infants

Systematic Reviews

In 2008, the U.K. Department of Public Health and Epidemiology, University of Birmingham, released a Health Technology Assessment (HTA) on immunoprophylaxis against respiratory syncytial virus (RSV) with palivizumab in children.4 This HTA report was updated in 2011; the update developed the economic model from the first report by cost-effectiveness in different subgroups of children with RSV infection.5 Thirteen studies published through August 2009 were included in this updated analysis. Most studies were small and not powered for outcomes of interest, and the quality of reporting also was frequently poor. In the original HTA report, 2 randomized controlled trials (RCTs) (summarized next) 6,7 were used for establishing the relative risk of hospitalization in children given palivizumab compared

with those not treated with palivizumab. No additional RCTs of palivizumab were found for the HTA update in 2011.5

Randomized Controlled Trials

Several RCTs have demonstrated the success of immune prophylaxis of RSV. In 2013, Blanken et al published the multicenter, double-blind, randomized, placebo-controlled MAKI trial to investigate the potential causal role of RSV infection in the pathogenesis of wheezing illness during the first year of life and the effect of palivizumab prophylaxis.8 The trial randomly assigned 429 otherwise healthy preterm infants born at a gestational age of 33 to 35 weeks to receive either monthly palivizumab injections (214 infants) or placebo (215 infants) during RSV season. The prespecified primary outcome was the total number of parent-reported wheezing days in the first year of life. Premature infants treated with palivizumab had a significant 61% relative decrease in the total number of wheezing days during the first year of life (95% confidence interval [CI], 56 to 65). Moreover, the effect of RSV prevention on the number of wheezing days persisted in the postprophylaxis period (ie, starting at 2 months after the last injection) for a relative reduction of 73% (95% CI, 66 to 80). Additionally, palivizumab treatment reduced hospitalizations related to RSV infection (12.6% in the RSV prevention group compared with 21.9% in the placebo group [p=0.04]).

In the 1998 Impact-RSV Study, prophylaxis with palivizumab for preterm infants with or without chronic lung disease (CLD) resulted in a 55% reduction in RSV hospital admission (4.8% [48/1002] in the palivizumab group and 10.6% [53/500] in the no-prophylaxis group).6 Similar reductions in other measures of RSV severity in breakthrough infections also were reported. In a 2003 double-blind, placebo controlled randomized trial of 1287 children with hemodynamically significant congenital heart disease (CHD), Feltes et al reported that prophylaxis with palivizumab was associated with a 45% reduction in hospitalizations for RSV among children with CHD.7 Hospitalization for RSV occurred in 5.3% (34/639) of the palivizumab group and 9.7% (63/648) of the no prophylaxis group. The authors concluded that prophylaxis with palivizumab is clinically effective for reducing the risk of serious lower respiratory tract infection caused by RSV infection and requiring hospitalization in high-risk children.

In 1997, the PREVENT Study Group reported on a trial that randomly assigned 510 infants with prematurity or CLD to receive either placebo or RSV-intravenous immunoglobulin (IVIg) infusions monthly for 5 months.9 The authors reported a 41% reduction in hospitalization due to RSV infection and reductions in other measures of RSV infection severity when it did occur. Palivizumab eventually became the preferred product over IVIg due to the convenience of intramuscular administration, safety concerns regarding immunoglobulin pooled from multiple donors, and the unlimited supply of a bioengineered product.

In 2008, Cohen et al evaluated the characteristics of patients (N=19,548) enrolled in the Palivizumab Outcomes Registry who had CHD.10 The Palivizumab Outcomes Registry prospectively collected data on patients who received RSV prophylaxis with palivizumab during the 2000 to 2004 RSV seasons. The percentage of registry patients with CHD increased from 4.8% (102/2116) in the first season to 11.4% (688/6050) in the last season. Across all 4 seasons, 1500 patients with CHD were enrolled, 71% of whom had acyanotic CHD. The proportion with cyanotic CHD increased from 19.6% (20/102) in the 2000 to 2001 season to 37.5% (258/688) in the 2003 to 2004 season, while the proportion of all CHD in the registry more than doubled during this time. Cumulative incidence of RSV hospitalization was 1.9% among patients with CHD who received prophylaxis. Among patients with cyanotic and acyanotic CHD, hospitalizations occurred in 2.6% and 1.6%, respectively. As stated by the authors, “Prospective data collected in the Palivizumab Outcomes Registry provide the largest published dataset available on infants with CHD receiving palivizumab and show low hospitalization rates and use consistent with prelicensure clinical trial data and revised American Academy of Pediatrics guidelines.”

A 2008 review article discussed the development of a second-generation humanized monoclonal antibody (mAb), motavizumab, which is no longer under study in Phase 3 clinical trials, and a third generation version of motavizumab, Numax-YTE, which is designed to prolong half-life.11,12 More recently, a randomized trial in 112 children hospitalized for RSV lower respiratory tract infection showed

no effect of motavizumab on RSV viral load, duration of hospitalization, severity of illness, or wheezing episodes during 12-month follow up compared with placebo.13

Cystic Fibrosis

A Cochrane review published in 2010 and updated in 2013 and 2014 assessed the use of palivizumab in children with cystic fibrosis.14-16 Based on a literature search through February 2014, 1 randomized comparative trial met inclusion criteria of all reviews. In the trial, 186 infants younger than 2 years with cystic fibrosis were randomly assigned to receive 5 monthly doses of palivizumab (n=92) or placebo (n=94). One member of each group was hospitalized for RSV within the 6-month follow-up period. The incidence of adverse events was relatively high in both groups, with serious adverse events not significantly different between the palivizumab and placebo groups (20.2% and 17.3%, respectively). Cochrane authors noted that it was not possible to draw conclusions on the safety and tolerability of RSV immune prophylaxis in cystic fibrosis: Although the trial reported similar incidences of adverse events, it did not specify how adverse events were classified, and no clinically meaningful outcome differences were noted at 6-month follow-up. Cochrane authors called for additional randomized studies to establish safety and efficacy of immune prophylaxis in children with cystic fibrosis.

In 2013, Sánchez-Solis et al published a systematic review with meta-analysis of palivizumab prophylaxis for RSV infection in cystic fibrosis patients.17 Literature was searched through November 2012; 4 prospective and retrospective observational studies, a questionnaire, and the randomized trial included in the Cochrane review described earlier were included (total N=617). Historical controls and nonprophylaxed cohorts from 3 other studies also were included. In separate random effects meta-analyses, weighted mean hospitalization rates were 0.018 (95% CI, 0.007 to 0.048) for 354 palivizumab-treated patients and 0.126 (95% CI, 0.086 to 0.182) for 463 controls, a statistically significant difference ($p<0.001$). However, in a meta-analysis of the 3 studies that included treated and untreated patients (ie, contemporaneous controls), the between-group difference was no longer statistically significant (weighted mean hospitalization rate, 0.024 [95% CI, 0.005 to 0.098] for palivizumab-treated patients vs 0.093 [95% CI, 0.037 to 0.218] for controls; $p=0.115$).

Immunodeficiencies

The use of RSV-IVIg or palivizumab in patients with documented immunodeficiencies also has been suggested. AAP guidelines note, "Palivizumab or RSV-IVIg has not been evaluated in randomized trials in immunocompromised children. Although specific recommendations for immunocompromised patients cannot be made, children with severe immunodeficiencies (eg, severe combined immunodeficiency or severe acquired immunodeficiency syndrome) may benefit from prophylaxis. If these infants and children are receiving standard intravenous immune globulin monthly, physicians may consider substituting RSVIVIg during the RSV season."18

Immunocompromised patients undergoing stem-cell transplantation also are at risk for potentially lethal respiratory viral infections. Cortez et al (2002) studied whether RSV-IVIg provided sufficient RSV immune prophylaxis to prevent RSV pneumonia in 54 patients undergoing stem-cell transplantation.19 The authors reported a low incidence of RSV infection in 54 RSV-IVIg patients, as well as in 31 patients not enrolled in the study, and could not determine the preventive effect of RSV-IVIg. In a 2012 literature review, Hynicka and Ensor found that data on RSV prophylaxis in immunocompromised adult patients are limited.20 The only prospective study identified in the review was by Kassis et al (2010)21 who administered intravenous pavilizumab to 16 high-risk stem-cell transplant recipients to prevent nosocomial spread of RSV infection from 5 stem-cell transplant recipients on the same adult inpatient unit. After 1 week, no further RSV cases occurred, but whether controlling the spread of RSV on the stem-cell transplant unit was related to RSV prophylaxis versus implementation of strict quarantine and infection control practices cannot be determined.

Down Syndrome

In 2014, Yi et al published a prospective cohort study of palivizumab prophylaxis for RSV infection in children with Down syndrome who were younger than 2 years of age.22 The primary efficacy outcome was RSV-related hospitalization during the RSV season, defined broadly as September 1 to May 31.

Among 532 palivizumab-treated children with Down syndrome from the Canadian RSV Evaluation Study of Palivizumab registry who were enrolled between 2005 and 2012 (184 patient-years of follow-up), 8 (1.5%) were hospitalized for RSV. Among 233 nonprophylaxed children with Down syndrome from a national Dutch cohort enrolled between 2003 and 2005 (324 patient-years of follow-up), 23 (9.9%) were hospitalized for RSV. The incidence rate ratio for RSV-related hospitalization (adjusted for hemodynamically significant CHD, insignificant CHD, gestational age, and birth weight) in untreated patients compared with treated patients was 3.63 (95% CI, 1.52 to 8.67), indicating an approximately 4-fold risk of RSV-related hospitalization during the RSV season in untreated patients. Use of a noncontemporaneous comparative cohort from a different country introduced potential bias due to different indications for hospitalization and different environmental factors that could affect the severity of RSV infection. Conclusions that can be drawn from this study are therefore limited.

Duration of Prophylaxis

The RSV season typically occurs from November to April. Within the United States, the inevitability of the RSV season is predicable, but the severity of the season and time of onset are variable from year to year and also between geographic areas within a given year. This has led to requests for either earlier or later immunoprophylaxis, or more than 5 monthly doses. Nevertheless, as pointed out by Meissner et al (2004) from the Centers of Disease Control and Prevention (CDC), this yearly and regional variation "occurs within the overall pattern of RSV outbreaks, usually beginning in November or December, peaking in January or February, and ending by March. Communities in the southern region tend to experience the earliest onset of RSV activity, and Midwestern states tend to experience the latest onset, but community to community variation in timing precludes using either national or regional data to precisely predict individual community RSV outbreaks. The duration of the season for western and northeast regions typically occurs between that noted in the South and the Midwest."23 The authors pointed out that the recommendation for 5 monthly doses is derived from randomized trials of palivizumab. A serum palivizumab concentration of greater than 30 µg/mL is the target level for protection, and in randomized trials, trough levels of palivizumab exceeded 30 µg/mL for at least 30 days after the fifth dose. This indicates that 5 monthly doses provide substantially more than 20 weeks of protective serum antibody levels, covering most of the RSV season even with variation in season onset and end.

In a 2014 article sponsored by MedImmune, manufacturer of palivizumab, Makari et al recommended full season RSV prophylaxis with palivizumab for preterm infants of 32 to 34 weeks' gestational age rather than discontinuation of palivizumab at 3 months of age, as is currently recommended.24 The authors reviewed several studies and concluded that elevated risk of RSV-related hospitalization persists through age 6 months. In contrast, Winterstein et al (2013) in a non-industry-sponsored study found support for a 3-month age limit for RSV prophylaxis among preterm infants of 32 to 34 weeks' gestational age.25 The authors compared RSV-related hospitalizations among preterm and term infants with siblings using Medicaid databases in Florida and Texas (total N=247,566). In both databases, the risk of RSV-related hospitalization among preterm infants was similar to that for 1-month-old term infants at approximately 4.4 months of age (4.2 months in Florida [95% CI, 2.5 to 5.7] and 4.5 months in Texas [95% CI, 2.8 to 6.4]). Given palivizumab's 30-day window of effectiveness, prophylaxis to age 3 months would provide coverage until the estimated 4.4-month age threshold. Currently, primary evidence to establish when infants of 32 to 34 weeks' gestational age develop lung function and immunologic responses similar to their term counterparts is lacking. Given emerging and contradictory evidence about RSV prophylaxis duration in these infants, modifications of current guidance cannot be recommended.

Compliance

Frogel et al (2010) reviewed the medical literature on compliance with palivizumab therapy and the relation between hospitalization rates in fully compliant and less compliant groups.26 A total of 25 articles and abstracts were included. Significant heterogeneity was detected due to between-study differences inpatient samples and the definition of compliance used. Incidence of compliance (however defined) ranged from 25% to 100%, compared with incidences reported in licensing studies of 92% to 93%. This led review authors to conclude that compliance in practice is far more variable. Minorities

and patients on Medicaid were less likely to receive the full complement of palivizumab doses, and patients participating in a home health program (defined as nurse-delivered injections performed in the home) tended to have higher compliance and less hospitalization.

Ongoing and Unpublished Clinical Trials
A search of online site ClinicalTrials.gov identified 2 active observational studies addressing palivizumab in infants 2 years or younger (NCT01155193; NCT01269528) and 1 observational study in infants and toddlers (NCT00420966).

Clinical Input Received from Physician Specialty Societies and Academic Medical Centers
In response to requests, input was received through 3 physician specialty societies (7 responders) while this policy was under review in 2009. While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted. Almost all of those providing input agreed with the policy statements approved in October 2009; these statements are in agreement with the 2009 AAP guidelines.

Summary of Evidence
Based on the weight of the clinical evidence from randomized clinical trials, systematic reviews, and strong clinical consensus, immune prophylaxis for respiratory syncytial virus (RSV) has demonstrated reductions in RSV-related hospitalizations in select populations of susceptible infants and children. Therefore, immune prophylaxis for RSV may be considered medically necessary for the patients listed in the previously stated policy statement. For all other uses of immune prophylaxis, clinical evidence has not established that RSV hospitalizations will decrease. Therefore, the policy statements previously stated note indications that are considered investigational or not medically necessary. The policy statements are in agreement with the 2014 American Academy of Pediatrics (AAP) Guidelines. Current evidence for duration of prophylaxis in preterm infants of 32 to 34 weeks' gestational age is inconsistent and insufficient to support deviation from AAP guidelines.

SUPPLEMENTAL INFORMATION
Practice Guidelines and Position Statements
AAP
Since 2003, AAP has released policy statements and guidelines on the use of palivizumab in high-risk infants.18,27-29 AAP's most recent guidance was based on a technical report, and both were published in 2014.1,2 Current recommendations are summarized in the Policy Statements and Policy Guidelines.

American Association for the Study of Liver Diseases and the American Society of Transplantation
In 2013, American Association for the Study of Liver Diseases and American Society of Transplantation published joint practice guidelines for long-term medical management of the pediatric patient after liver transplantation.30 Although the risk of community-acquired infections, such as RSV, is associated with posttransplant immunosuppression, "no guidance exists for RSV prophylaxis" (grade 1 [strong] recommendation based on level B [moderate quality] evidence).

U.S. Preventive Services Task Force Recommendations
The U.S. Preventive Services Task Force (USPSTF) makes the following statement regarding immunizations for children:

> "USPSTF recognizes the importance of immunizations in primary disease prevention. However, USPSTF does not wish to duplicate the significant investment of resources made by others to review new evidence on immunizations in a timely fashion and make recommendations. The USPSTF therefore will not update its 1996 recommendations. The Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (ACIP) publishes recommendations on immunizations for children and adults. The methods used by ACIP to

review evidence on immunizations may differ from the methods used by the USPSTF. For ACIP's current recommendations on immunizations, please refer to the National Immunization Program site at http://www.cdc.gov/vaccines/schedules/index.html."31

ACIP does not specifically address RSV prevention/immunization. Currently, there is no safe and effective RSV vaccine. Scientists at the National Institutes of Health and at 2 pharmaceutical companies are working to develop RSV vaccines.32

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

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Billing Coding/Physician Documentation Information

Codes	Number	Description
CPT	90378	Respiratory syncytial virus, monoclonal antibody, recombinant, for intramuscular use, 50 mg, each
	96365	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
	96366	each additional hour (list separately in addition to code for primary procedure)
	96372	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular
ICD-9 Procedure	99.29	Injection or infusion of other therapeutic or prophylactic substance
ICD-9 Diagnosis	396	Diseases of mitral and aortic valves code range
	417	Other disease of pulmonary circulation code range
	424	Other diseases of endocardium code range
	425	Cardiomyopathy code range
	428	Heart failure code range
	491	Chronic bronchitis code range
	745	Bulbus cordis anomalies and anomalies of cardiac septal closure code range
	746	Other congenital anomalies of the heart code range
	747	Other congenital anomalies of the circulatory system code range
	765.2	Weeks of gestation (5th digit indicates specific weeks of gestation)
	V07.2	Prophylactic immunotherapy
	V46.2	Supplemental oxygen
HCPCS	J1565	Injection, respiratory syncytial virus immune globulin, intravenous, 50 mg (ie, RespiGam) (code deleted 12/31/09)
ICD-10-CM (effective 10/01/14)	I08.0-I08.9	Multiple valve diseases code range
	I28.0-I28.9	Other diseases of pulmonary vessels code range
	I34.0-I34.9	Nonrheumatic mitral valve disorders code range
	I35.0-I35.9	Nonrheumatic aortic valve disorders code range
	I36.0-I36.9	Nonrheumatic tricuspid valve disorders code range
	I37.0-I37.9	Nonrheumatic pulmonary valve disorders code range
	I42.0-I42.9	Cardiomyopathy code range
	I43	Cardiomyopathy in diseases classified elsewhere
	I50.1-I50.9	Heart failure code range
	J41.0-J42	Chronic bronchitis code range
	J44.0-J44.9	Other chronic obstructive pulmonary disease code range
	P07.00-P07.32	Disorders of newborn related to short gestation and low birth weight, not elsewhere classified code range
	P27.0-P27.9	Chronic respiratory disease originating in the perinatal period

		(includes bronchopulmonary dysplasia P27.1)
	P28.0-P28.9	Other respiratory conditions originating in the perinatal period code range
	Q20.0-Q28.9	Congenital malformations of the circulatory system code range
ICD-10-PCS (effective 10/01/14)		ICD-10-PCS codes are only used for inpatient services.
	3E0234Z	Administration, physiological systems and anatomical regions, introduction, muscle, percutaneous, serum, toxoid and vaccine
	3E0334Z	Administration, physiological systems and anatomical regions, introduction, peripheral vein, percutaneous, serum, toxoid and vaccine
Type of Service	Prescription Drug	
Place of Service	Outpatient	

Additional Policy Key Words

N/A

Related Topics

N/A

Policy Implementation/Update Information

10/1999	New policy titled RSV Immunoprophylaxis
10/2000	Reviewed – no changes made
10/2001	Reviewed – no changes made
10/2002	Reviewed – no changes made
10/2003	Updated procedure codes and clinical criteria
10/2004	Updated clinical criteria
10/2005	Updated policy to reflect BCBSA policy 5.01.10
10/2006	Title changed to Immune Prophylaxis for Respiratory Syncitial Virus
10/2007	Reviewed – no changes made
10/2008	Reviewed – no changes made
10/2009	Reviewed – no changes made
10/2010	Updated policy to reflect BCBSA policy 5.01.10
10/2011	Reviewed – no changes made
10/2012	Updated literature search
10/2013	Updated literature search
10/2014	Policy updated with literature review through July 7, 2014; references 1-2, 16-17, 20-22, 25, 27-28, 30, and 32 added; reference 31 updated. Policy statements revised to reflect 2014 updated guidance from AAP.