Therapeutic Class Overview
Palivizumab

Therapeutic Class

- **Overview/Summary:** Respiratory syncytial virus (RSV) causes seasonal outbreaks throughout the world with usual occurrence from November to April in the northern hemisphere. RSV causes acute respiratory tract illness in individuals of all ages with almost all children infected by two years of age.[1] In the United States, 75,000 to 125,000 children under one year of age are hospitalized due to RSV every year. Most healthy individuals recover from RSV infection in one to two weeks; however, the infection can be severe in certain high-risk individuals.[2] The only agent that is approved by the Food and Drug Administration for the prevention of serious lower respiratory tract infection caused by RSV in pediatric patients at high risk of RSV infection is palivizumab (Synagis®). Safety and efficacy of palivizumab were established in infants with a history of premature birth (≤35 weeks gestational age), children with bronchopulmonary dysplasia or hemodynamically significant congenital heart disease. Safety and efficacy of palivizumab have not been established for treatment of RSV disease. Palivizumab is a recombinant humanized monoclonal antibody with anti-RSV activity. Palivizumab acts by binding the RSV envelope fusion protein on the surface of the virus and blocking a critical step in the membrane fusion process; palivizumab also prevents cell-to-cell fusion of RSV-infected cells. The recommended dose of palivizumab is 15 mg/kg of body weight injected intramuscularly once monthly throughout the RSV season.[3] According to available clinical evidence, palivizumab therapy reduces hospital and intensive care unit admission rates, but it does not effectively reduce either the incidence of RSV or RSV mortality.[4-7] This review only includes the clinical evidence evaluating the safety and efficacy of palivizumab in high-risk individuals.

  The most recent consensus guidelines are published by the American Academy of Pediatrics (AAP) for the prevention of RSV infections with palivizumab in certain high-risk groups. The AAP recommends that palivizumab be administered once monthly beginning in November, up to a maximum of five doses for infants and young children with congenital heart disease, chronic lung disease of prematurity, neuromuscular disease/congenital abnormalities of the airway or preterm birth before 31 weeks, six days of gestation. Due to a cumulative effect on serum concentration, the fifth palivizumab dose administered in March should provide immunologic protection through April. Furthermore, according to the AAP guidelines, infants born between 32 and 35 weeks of gestation should receive palivizumab prophylaxis only until they reach three months of age or up to a maximum of three doses. This was a change from the 2006 AAP guideline, which allowed five doses in infants of this gestational age category until their 6th month birthday.[8]

Table 1. Current Medications Available in the Therapeutic Class[3]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Palivizumab (Synagis®)	Prevention of serious lower respiratory tract disease caused by respiratory syncytial virus in children with high risk of respiratory syncytial virus disease	Single-dose solution vials for injection: 50 mg/0.5 mL 100 mg/1 mL	-

Evidence-based Medicine

- Placebo-controlled, randomized controlled clinical trials have demonstrated that palivizumab prophylaxis is effective in reducing hospitalizations due to respiratory syncytial virus (RSV).[4,5]
- Meta-analyses and systematic reviews also concluded effectiveness of palivizumab prophylaxis in reducing RSV-related hospitalizations; however, there was no difference in relative risk reduction in all-cause mortality with monthly prophylaxis with palivizumab compared to placebo.[6,7]

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Key Points within the Medication Class

- According to the American Academy of Pediatrics consensus guidelines for the prevention of respiratory syncytial virus (RSV) infections, it is appropriate to provide palivizumab prophylaxis in the following high-risk groups:[8]
    - Patients 24 months of age and younger with hemodynamically significant cyanotic or acyanotic congenital heart disease;
    - Patients younger than 24 months of age with bronchopulmonary dysplasia or chronic lung disease of prematurity who require medical therapy within six months before the start of the RSV season;
    - Patients younger than six months of age, born prematurely between 29 weeks, 0 days through 31 weeks, six days of gestation;
    - Patients in their first 12 months of age, born prematurely at or before 28 weeks, six days of gestation;
    - Patients in their first three months of age born prematurely between 32 weeks, 0 days and 34 weeks, six days of gestation with one of the following risk factors: one or more older siblings less than five years of age living in the same household or child care attendance; and
    - Patients one year of age or younger with congenital abnormalities of the airway or neuromuscular disease (compromising handling of respiratory tract secretions).
- Other Key Facts:
    - The most frequently occurring adverse events in clinical trials in patients using palivizumab were fever and rash.[3-7]
    - Currently, palivizumab is only available as a branded agent and is associated with significant acquisition costs.

References

1. Barr FE, Graham BS. Respiratory syncytial virus infection: Clinical features and diagnosis. In: Basow DS (Ed). UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2014 [cited 2014 Feb 26]. Available from: http://www.uptodate.com/contents/respiratory-syncytial-virus-infection-clinical-features-and-diagnosis?source=search_result&search=RSV&selectedTitle=1~144.
2. Centers for Disease Control and Prevention. Respiratory Syncytial Virus (RSV), 2013 [cited 2014 Feb 24]. Available from: http://www.cdc.gov/rsv/index.html.
3. Synagis® [package insert]. Gaithersburg (MD): MedImmune, LLC; 2013 Apr.
4. The IMpact-RSV Study Group: Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in infants at high risk. Pediatrics. 1998 Sep;102(3 Pt 1):531-7.
5. Feltes TF, Cabalka AK, Meissner HC, Piazza FM, Carlin DA, Top FH Jr, et al. Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. J Pediatr. 2003 Oct;143(4):532-40.
6. Checchia PA, Nalysnyk L, Fernandes AW, Mahadevia PJ, Xu Y, Fahrbach K, et al. Mortality and morbidity among infants at high risk for severe respiratory syncytial virus infection receiving prophylaxis with palivizumab: a systematic literature review and meta-analysis. Pediatr Crit Care Med. 2011 Sep;12(5):580-8.
7. Andabaka T, Nickerson JW, Rojas-Reyes MX, Rueda JD, Bacic Vrca V, Barsic B. Monoclonal antibody for reducing the risk of respiratory syncytial virus infection in children. Cochrane Database Syst Rev. 2013 Apr 30;4:CD006602.
8. American Academy of Pediatrics. Respiratory syncytial virus, 2012. In: Red Book: 2012 Report of the Committee on Infectious Diseases, 29th, Pickering LK (Ed), American Academy of Pediatrics, Elk Grove Village (IL) 2012 p.609-12.

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Therapeutic Class Review
Palivizumab

Overview/Summary

Respiratory syncytial virus (RSV) causes seasonal outbreaks throughout the world and has usual occurrence from November to April in the northern hemisphere. RSV causes acute respiratory tract illness in individuals of all ages with almost all children infected by two years of age.[1] In the United States, 75,000 to 125,000 children under one year of age are hospitalized due to RSV every year. Most healthy individuals recover from RSV infection in one to two weeks; however, the infection can be severe in certain high-risk individuals.[2] The only medication that is approved by the Food and Drug Administration for the prevention of serious lower respiratory tract infection caused by RSV in pediatric patients at high risk of RSV infection is palivizumab (Synagis®). Safety and efficacy of palivizumab were established in infants with a history of premature birth (≤35 weeks gestational age), children with bronchopulmonary dysplasia or hemodynamically significant congenital heart disease. Safety and efficacy of palivizumab have not been established for treatment of RSV disease. Palivizumab is a recombinant humanized monoclonal antibody with anti-RSV activity. Palivizumab acts by binding the RSV envelope fusion protein on the surface of the virus and blocking a critical step in the membrane fusion process; palivizumab also prevents cell-to-cell fusion of RSV-infected cells. The recommended dose of palivizumab is 15 mg/kg of body weight injected intramuscularly once monthly throughout the RSV season.[3] According to available clinical evidence, palivizumab therapy reduces hospital and intensive care unit admission rates, but it does not effectively reduce either the incidence of RSV or RSV mortality.[4-7] This review only includes the clinical evidence evaluating the safety and efficacy of palivizumab in high-risk infants and children. Given the limitations in comparing one cost-effectiveness study to another cost-utility evaluation, pharmacoeconomic analyses were not included as part of this review. Nonetheless, palivizumab therapy is associated with significant acquisition costs.

The most recent consensus guidelines are published by the American Academy of Pediatrics (AAP) for the prevention of RSV infections with palivizumab. According to the AAP recommendations, palivizumab prophylaxis is appropriate in the following high-risk groups: 1) patients 24 months of age and younger with hemodynamically significant cyanotic or acyanotic congenital heart disease; 2) patients younger than 24 months of age with bronchopulmonary dysplasia or chronic lung disease of prematurity who require medical therapy within six months before the start of the RSV season; 3) patients younger than six months of age, born prematurely between 29 weeks, 0 days through 31 weeks, six days of gestation; 4) patients in their first 12 months of age, born prematurely at or before 28 weeks, six days of gestation; 5) patients in their first three months of age born prematurely between 32 weeks, 0 days and 34 weeks, six days of gestation with one of the following risk factors: one or more older siblings less than five years of age living in the same household or child care attendance; and 6) patients one year of age or younger with congenital abnormalities of the airway or neuromuscular disease (compromising handling of respiratory tract secretions). The AAP recommends that palivizumab be administered once monthly beginning in November, up to a maximum of five doses for infants and young children with congenital heart disease, chronic lung disease of prematurity, neuromuscular disease/congenital abnormalities of the airway or preterm birth before 31 weeks, six days of gestation. Due to a cumulative effect on serum concentration, the fifth palivizumab dose administered in March should provide immunologic protection through April. Furthermore, according to the AAP guidelines, infants born between 32 and 35 weeks of gestation should receive palivizumab prophylaxis only until they reach three months of age or up to a maximum of three doses. This was a change from the 2006 AAP guideline, which allowed five doses in infants of this gestational age category until their 6th month birthday.[8]

Medications

Table 1. Medications Included Within Class Review[3,9]

Generic Name (Trade name)	Medication Class	Generic Availability
Palivizumab (Synagis®)	Monoclonal antibody	-

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Indications

Table 2. Food and Drug Administration-Approved Indications[3]

Generic Name	Prevention of Serious Lower Respiratory Tract Disease caused by Respiratory Syncytial Virus in Children with High Risk of Respiratory Syncytial Virus Disease
Palivizumab	✔

Pharmacokinetics

Table 3. Pharmacokinetics[3]

Generic Name	Serum Half-Life (days)
Palivizumab	18 (adults); 20 (children <24 months old)

Clinical Trials

The safety and efficacy of palivizumab was evaluated in two randomized, double-blind, placebo-controlled trials (N=2,789) of respiratory syncytial virus (RSV) infection prophylaxis in children at high-risk of an RSV-related hospitalization. In both studies, patients received palivizumab 15 mg/kg or placebo intramuscularly every month for five total doses. The patients were followed for 150 days from randomization.[3-5] The study by Connor et al (N=1,502) was conducted in children less than or equal to 24 months of age with bronchopulmonary dysplasia or infants less than or equal to six months of age with premature birth at less than or equal to 35 weeks gestation during one RSV season. Palivizumab therapy was associated with 55% reduction in hospitalization (4.8% children in palivizumab group vs 10.6% children in placebo group; 95% confidence interval [CI], 38 to 72; *P*=0.00004). Significant reductions were observed in both, children with bronchopulmonary dysplasia and premature children without bronchopulmonary dysplasia. Palivizumab was associated with significant reduction in RSV hospitalizations in infants >5 kg (51%; *P*=0.014) and ≤5 kg (57%; *P*=0.001) and in infants <32 weeks gestational age (47%; *P*=0.003) and 32 through 35 weeks gestational age (80%; *P*=0.002).[4] The study by Feltes et al (N=1,287) was conducted in children less than or equal to 24 months of age with hemodynamically significant congenital heart disease over four consecutive seasons. RSV hospitalization rates was 5.3% in the palivizumab group compared to 9.7% in the placebo group (*P*=0.003).[5]

Meta-analysis and systematic literature review conducted by Checchia et al evaluated the impact of palivizumab prophylaxis on all-cause mortality and RSV-related mortality in infants at high-risk such as ≤35 weeks of gestation, chronic lung disease or congenital heart disease. All-cause mortality during the RSV season occurred in 0.19% of infants with prophylaxis compared to 0.53% of infants without prophylaxis (Peto odds ratio, 0.30; 95% CI, 0.17 to 0.55). Majority of the studies did not report RSV-related deaths. The number needed to treat with palivizumab to prevent one all-cause death for the various subgroups ranged from 113 to 1,736.[6] A Cochrane review by Andabaka et al included seven clinical trials evaluating effectiveness and safety of palivizumab prophylaxis against placebo, no prophylaxis or motavizumab (agent not available in the United States). The authors found that children receiving palivizumab had a statistically significant 51% relative risk reduction in RSV hospitalizations compared to patients receiving placebo (relative risk [RR], 0.49; 95% CI, 0.37 to 0.64). There was no difference in relative risk reduction in all-cause mortality with monthly prophylaxis with palivizumab compared to placebo (RR, 0.69; 95% CI, 0.42 to 1.15). Patients in the palivizumab group had a statistically non-significant 36% relative increase in the risk of hospitalization due to RSV infection, when compared to motavizumab group (RR, 1.36; 95% CI, 0.97 to 1.90). Patients receiving palivizumab had a statistically non-significant 26% relative risk reduction in all-cause mortality compared to motavizumab patients (RR, 0.74; 95% CI, 0.38 to 1.43). This systematic review also included 34 studies evaluating cost-effectiveness or cost-utility and the authors concluded that the cost-effectiveness of palivizumab prophylaxis depends on threshold set by each country's healthcare sector as well as consumption of resources taken into account in each study.[7]

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Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Andabaka et al[7] Palivizumab 15 mg/kg prophylaxis vs placebo or no prophylaxis or another type of prophylaxis in reducing the risk of complications in high-risk infants and children (motavizumab*)	SR RCTs comparing palivizumab prophylaxis with a placebo, no prophylaxis or another type of prophylaxis in preventing serious lower respiratory tract disease caused by RSV in high-risk infants and children were included (children with cystic fibrosis were excluded); cost-effectiveness analyses and cost-utility analyses comparing palivizumab prophylaxis with no prophylaxis were included	7 trials for effectiveness and safety; 34 trials for cost-effectiveness (or cost-utility) 150 days after randomization (30 days after last dose)	Primary: Effectiveness and safety of palivizumab prophylaxis compared to placebo, or another type of prophylaxis, in reducing the risk of complications (hospitalization due to RSV infection); assess cost-effectiveness (or cost-utility) of palivizumab prophylaxis compared to no prophylaxis in infants and children in different risk groups Secondary: Not reported	Primary: Of the seven trials included in the review, three RCTs compared palivizumab to placebo and four compared motavizumab to palivizumab. Thirty-four economic evaluation studies were included. Patients receiving palivizumab had a statistically significant 51% RR reduction in RSV hospitalizations compared to patients receiving placebo (RR, 0.49; 95% CI, 0.37 to 0.64). Patients receiving palivizumab also had a statistically significant 50% RR reduction in admissions to the ICU (RR, 0.50; 95% CI, 0.30 to 0.81). The number of patients requiring mechanical ventilation for RSV infection seemed similar between the two groups (RR, 1.10; 95% CI, 0.20 to 6.09). There was no difference in RR reduction in all-cause mortality with monthly prophylaxis with palivizumab compared to placebo (RR, 0.69; 95% CI, 0.42 to 1.15). Patients in the palivizumab group had a 12% RR reduction in any serious adverse event compared to placebo (RR, 0.88; 95% CI, 0.80 to 0.96) and had a statistically non-significant risk reduction in serious adverse event related to study drug (RR, 0.14; 95% CI, 0.01 to 2.80). Patients in the palivizumab group had a statistically non-significant 36% relative increase in the risk of hospitalization due to RSV infection, when compared to motavizumab recipients (RR, 1.36; 95% CI, 0.97 to 1.90). The risk of outpatient medically attended lower respiratory tract infections specific for RSV infection in the palivizumab group was twice that of the motavizumab group (RR, 1.98; 95% CI, 1.25 to 3.13). Patients receiving palivizumab had a statistically non-significant 68% RR increase in admission to the ICU compared to motavizumab patients (RR, 1.68; 95% CI, 0.89 to 3.19), as well as a statistically non-significant 49% RR increase in incidence of supplemental oxygen therapy for RSV infection (RR, 1.49; 95% CI, 0.98 to 2.26). The risk of mechanical ventilation in the palivizumab group was almost four times that of the motavizumab group (RR,

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				3.79; 95% CI, 1.26 to 11.42). Patients receiving palivizumab had a statistically non-significant 26% RR reduction in all-cause mortality compared to motavizumab patients (RR, 0.74; 95% CI, 0.38 to 1.43). No significant differences were found in the proportion of children with any adverse event (RR, 1.00; 95% CI, 0.99 to 1.02), with adverse event related to study drug (RR, 0.98; 95% CI, 0.73 to 1.32), with any serious adverse event (RR, 1.04; 95% CI, 0.96 to 1.13), or with serious adverse event related to study drug (RR, 0.88; 95% CI, 0.32 to 2.43) between patients receiving palivizumab and motavizumab. The overall quality of economic evaluations was good. There were considerable variations in modelling approaches across the studies and this resulted in differences in cost-effectiveness results. The cost-effectiveness of palivizumab prophylaxis depends on threshold set by each country's healthcare sector as well as consumption of resources taken into account in each study. Secondary: Not reported
Checchia et al[6] Palivizumab prophylaxis vs placebo (no prophylaxis)	MA, SR Included trials had to report ten or more patients per study group, age up to 24 months at enrollment and noting any of the following outcomes: all-cause mortality and RSV-related	N=~15,000 (10 trials) Duration varied	Primary: All-cause mortality and RSV-related mortality Secondary: RSV hospitalizations, emergency department and ICU admissions, hospital and ICU length of stay,	Primary: Seven out of ten trials reported mortality outcomes. The mortality rate for all causes occurring during the first RSV season for the preterm group with prophylaxis was 0.19% and for the preterm group without prophylaxis was 0.53% (Peto OR, 0.30; 95% CI, 0.17 to 0.55). Mortality rates for the different subgroups of the preterm cohort were 1) CLD: prophylaxis, 0.22%; with no prophylaxis, 0.34% (Peto OR, 0.83; 95% CI, 0.13 to 5.25); 2) preterm ≤32 weeks gestational age with prophylaxis, 0.23%; preterm ≤32 weeks gestational age with no prophylaxis, 0.99% (Peto OR, 0.25; 95% CI, 0.13 to 0.49); 3) preterm 32 to 35 weeks gestational age with prophylaxis, 0.09%; preterm 32 to 35 weeks gestational age with no prophylaxis, 0.13% (Peto OR, 0.22; 95% CI, 0.03 to 1.89); 4) CHD with

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	mortality, RSV hospitalizations, emergency department and ICU admissions, hospital and ICU length of stay, oxygen requirements, apnea episodes, outpatient visits, and use of mechanical ventilation		oxygen requirements, apnea episodes, outpatient visits, and use of mechanical ventilation	prophylaxis, 3.29%; and CHD with no prophylaxis, 4.17% (Peto OR, 0.78; 95% CI, 0.44 to 1.39). A sensitivity analysis comparing RCTs vs non RCTs showed that all-cause mortality in the premature cohort was similarly reduced, non RCT had an OR of 0.32 (95% CI, 0.15 to 0.58) and RCT had an OR of 0.32 (95% CI, 0.09 to 1.20). The results were not statistically significant for the RCT groups. The number needed to treat with palivizumab to prevent one all-cause death for the various subgroups were as follows: 1) all preterm, 270; 2) CLD, 1,736; 3) preterm ≤32 weeks gestational age, 136; 4) preterm 32 to 35 weeks gestational age, 987; 5) mixed preterm gestational categories, not available; 6) CHD, 113. Secondary: Emergency department and ICU admissions, hospital and ICU length of stay, oxygen requirements, apnea episodes, outpatient visits, and use of mechanical ventilation were not included in the MA as not all studies had this information and as a result, a formal MA was not conducted for these endpoints. In the two RCTs of preterm infants in which hospitalizations were the primary end points, palivizumab resulted in a significant reduction of RSV hospitalizations (OR, 0.42; 95% CI, 0.27 to 0.64). The results were similar when RCTs were excluded from analyses (OR, 0.33; 95% CI, 0.22 to 0.48). The number needed to treat with palivizumab to prevent one RSV hospitalization for the various subgroups were as follows: 1) all preterm, 16; 2) CLD, 11; 3) preterm ≤32 weeks gestational age, 14; 4) preterm 32 to 35 weeks gestational age, 18; 5) mixed preterm gestational categories, 24; 6) CHD, 23.
Connor et al[4] Impact-RSV Palivizumab 15 mg/kg	DB, MC, PC, RCT Children six months of age or	N=1,502 (1,002 in the palivizumab group and 500	Primary: Hospitalization with confirmed RSV infection; safety	Primary: Palivizumab therapy was associated with 55% reduction in hospitalization (4.8% children in palivizumab group vs 10.6% children in placebo group; 95% CI, 38% to 72%; *P*=0.00004). Significant reductions were observed in both,

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
intramuscularly every 30 days for five doses vs placebo 15 mg/kg intramuscularly every 30 days for five doses	younger with prematurity (≤ 35 weeks of gestation) or ≤24 months old with a clinical diagnosis of bronchopulmonary dysplasia (or chronic lung disease of prematurity) requiring ongoing medical treatment (i.e., supplemental oxygen, steroids, bronchodilators, or diuretics within the past six months); children with CHD were excluded, except for those with a patent ductus arteriosus or a septal defect that was uncomplicated and hemodynamically insignificant	in the placebo group) 150 days (30 days after the last scheduled study injection)	Secondary: Compare the effect of monthly palivizumab prophylaxis with placebo on characteristics of RSV hospitalization: total RSV days with supplemental oxygen, incidence and total RSV-associated days in the ICU, and incidence and total days of RSV-associated mechanical ventilation; compare the effect of monthly palivizumab prophylaxis with placebo on the incidence and total days of hospitalization for non-RSV respiratory disease and respiratory disease and hospitalizations for any cause;	children with bronchopulmonary dysplasia (7.9% children in palivizumab group vs 12.8% children in placebo group; 39% reduction, 95% CI, 20 to 58; *P*=0.038), and premature children without bronchopulmonary dysplasia (1.8% children in palivizumab group vs 8.1% children in placebo group; 78% reduction, 95% CI, 66 to 90; *P*<0.001). Palivizumab was associated with significant reduction in RSV hospitalizations in infants >5 kg (51%; *P*=0.014) and ≤5 kg (57%; *P*=0.001) and in infants <32 weeks gestational age (47%; *P*=0.003) and 32 through 35 weeks gestational age (80%; *P*=0.002). When included in the logistic regression analysis, gestational age was not a significant predictor of RSV hospitalization and the palivizumab effect remained statistically significant (*P*<0.001). The proportion of children with adverse events judged by the blinded investigator to be related to the study drug was similar between the two groups. Overall, 1.8% of the placebo group and 2.7% of the palivizumab group reported adverse events related to the injection site. Secondary: Children randomized to palivizumab had significantly fewer total days (per 100 children) of RSV hospitalization (62.6 placebo days vs 36.4 palivizumab days; *P*<0.001), days with increased oxygen (50.6 days vs 30.3 days; *P*<0.001), and days with an lower respiratory infection score of 3 or greater (47.4 days vs 29.6 days; *P*<0.001). Three percent of placebo patients and 1.3% of palivizumab recipients had RSV ICU admissions (*P*=0.026); total days were 12.7 and 13.3, respectively (*P*=0.023). There was no significant differences in incidence of mechanical ventilation (0.2 vs 0.7%; *P*=0.280) or total days of mechanical ventilation (1.7 vs 8.4 days; *P*=0.210) between the two groups. Palivizumab recipients had significant reductions in the incidence (31 vs 24%; *P*=0.011) and total days per 100 children (242 vs 191 days; *P*=0.005) of all hospitalizations and the incidence (22 vs 16%; *P*=0.008) and total days per 100 children (180 vs 124 days; *P*=0.004) of respiratory hospitalizations.

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			compare the effect of palivizumab prophylaxis with placebo on the incidence of otitis media	These differences were attributable to the observed reduction of RSV hospitalizations, because no significant differences were observed in the incidence (14 vs 13%; *P*=0.470) or total days per 100 children (118 vs 88 days; *P*=0.369) of respiratory hospitalizations unrelated to RSV. The proportion of children with at least one episode of otitis media was similar in both placebo and palivizumab group (40 vs 42%; *P*=0.505).
Feltes et al[5] Palivizumab 15 mg/kg intramuscularly every 30 days for five doses vs placebo 15 mg/kg intramuscularly every 30 days for five doses	DB, MC, PC, RCT Children ≤24 months of age at time of randomization with documented hemodynamically significant unoperated or partially corrected CHD as determined by clinical (e.g., prescriptions for cardiac medications) and echocardiographic assessment by the investigator; patients were excluded if they had simple atrial septal defects, ventricular septal defects, patent ductus arteriosus, or unstable cardiac	N=1,287 150 days (30 days after the last scheduled study injection)	Primary: Compare the safety, tolerance, and efficacy of palivizumab with placebo for the reduction of the incidence of RSV hospitalization among children with hemodynamically significant CHD Secondary: Compare the effects of treatment on RSV hospitalization outcomes as measured by total days of RSV hospitalization, total RSV hospital days with increased oxygen requirement,	Primary: RSV hospitalization rates was 5.3% in the palivizumab group compared to 9.7% in the placebo group (*P*=0.003). Treatment with palivizumab remained significant when logistic regression analysis was performed with predefined variables of age, sex and cardiac strata (*P*=0.004). The proportion of children with adverse events, adverse events that required medical intervention and adverse events judged by the blinded investigator to be related to the study drug was similar between the two groups. There were some adverse events that were reported at an absolute incidence ≥1% higher in the palivizumab group compared to the placebo group including fever (27.1% in palivizumab group vs 23.9% in placebo group), infection (5.6% in palivizumab group vs 2.9% in placebo group), study drug injection site reaction (3.4% in palivizumab group vs 2.2% in placebo group), upper respiratory infection (47.4% in palivizumab group vs 46.1% in placebo group), conjunctivitis (11.3% in palivizumab group vs 9.3% in placebo group), arrhythmia (3.1% in palivizumab group vs 1.7% in placebo group), and cyanosis (9.1% in palivizumab group vs 6.9% in placebo group). The most common injection site reactions were redness, swelling and bruising and none were serious. The incidence of serious adverse events was significantly lower in the palivizumab group compared to the placebo group (55.4 vs 63.1%; *P*=0.005). Secondary: Children randomly assigned to palivizumab had significantly fewer total days of RSV hospitalization per 100 children (56% reduction; 57.4 days in

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	or respiratory status		incidence and total days of RSV-associated intensive care, and incidence and total days of RSV-associated mechanical ventilation; to describe the effect of cardiac bypass on serum palivizumab concentrations; and to determine palivizumab trough concentrations before the second and fifth doses	palivizumab group vs 129.0 days in placebo group; *P*=0.003). Children randomly assigned to palivizumab had significantly fewer RSV hospital days with increased oxygen requirement per 100 children (73% reduction; 27.9 days in palivizumab group vs 101.5 days in placebo group; *P*=0.014). The incidence of RSV-associated intensive care was lower in the palivizumab group (46% reduction; 13 children in palivizumab group vs 24 children in placebo group; *P*=0.094). The total number of days of RSV-associated intensive care per 100 children was also lower in the palivizumab group (78% reduction; 15.9 days in palivizumab group vs 71.2 days in placebo group; *P*=0.080). The incidence of RSV-associated mechanical ventilation was lower in the palivizumab group (41% reduction; eight children in palivizumab group vs 14 children in placebo group; *P*=0.282), and days of RSV-associated mechanical ventilation per 100 children was also lower in the palivizumab group (88% reduction; 6.5 days in palivizumab group vs 54.7 days in placebo group; *P*=0.224). Prolonged RSV hospitalization (≥14 days) occurred in five children in the palivizumab group compared to 16 children in the placebo group. Paired serum was available before and after cardiac bypass for 139 children who had received palivizumab. Before and after cardiopulmonary bypass, the mean ± SD serum palivizumab concentrations were 98.0 ± 52 µg/mL and 41.4 ± 33 µg/mL, respectively (58% reduction in serum palivizumab concentration after bypass; *P*=0.0001). Mean ± SD serum palivizumab concentrations before the second and fifth doses were 55.5 ± 19 µg/mL and 90.8 ± 35 µg/mL in the palivizumab group and 0.4 ± 5 µg/mL and 0.1 ± 2 µg/mL in the placebo group.

*Drug not available in the United States.
Study abbreviations: DB=double-blind, MA=meta-analysis, MC=multicenter, PC=placebo-controlled, RCT=randomized controlled trial, SR=systematic review
Miscellaneous: CHD=congenital heart disease, CI=confidence interval, CLD=chronic lung disease of maturity, ICU=intensive care unit, OR=odds ratio, RR=relative risk, RSV=respiratory syncytial virus, SD=standard deviation

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Special Populations

Table 5. Special Populations[3]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Palivizumab	Safety and efficacy in children greater than 24 months of age at the start of dosing have not been established.	Safety and efficacy in patients with renal dysfunction have not been established.	Safety and efficacy in patients with hepatic dysfunction have not been established.	C	Unknown; not indicated for adult use.

Adverse Drug Events

Table 6. Adverse Drug Events[3]

Adverse Event	Palivizumab
Acute hypersensitivity reactions	✔
Anaphylaxis	✔
Fever	✔
Injection site reactions*	✔
Rash	✔
Severe thrombocytopenia*	✔

*Postmarketing experience.

Contraindications/Precautions

Table 7. Contraindications[3]

Contraindication(s)	Palivizumab
Previous significant hypersensitivity reaction to palivizumab	✔

Table 8. Warnings and Precuations[3]

Warning(s)/Precaution(s)	Palivizumab
Anaphylactoid/hypersensitivity reactions: there have been reports of very rare cases of anaphylaxis; rare cases of severe acute hypersensitivity reactions have also been reported; caution is recommended with mild hypersensitivity reaction and for severe hypersensitivity reaction, the medication should be permanently discontinued	✔
Appropriate use: the single-dose vial does not contain a preservative; administration should occur immediately after dose withdrawal from the vial; the vial should not be re-entered and any unused portion should be discarded	✔
Bleeding disorders: use with caution in patients with a history of bleeding disorders (including thrombocytopenia); bleeding/hematoma may occur from intramuscular administration.	✔
Respiratory syncytial virus: safety and efficacy have not been demonstrated in the treatment of established respiratory syncytial virus disease	✔
Respiratory syncytial virus diagnostic test interference: interference (false negatives) with immunological-based respiratory syncytial virus diagnostic tests (antigen detection) and viral culture assays has been reported; reverse-transcriptase-polymerase chain reaction-based assays and clinical findings should be relied upon	✔

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Drug Interactions

There are no formal drug-drug interaction studies conducted with palivizumab. In one of the clinical trials, there was no incremental increase in adverse reactions seen in patients who also received routine childhood vaccines, influenza vaccine, bronchodilators or corticosteroids.[3,10]

Dosage and Administration

Table 9. Dosing and Administration[3]

Generic Name	Adult Dose	Pediatric Dose	Availability
Palivizumab	Safety and efficacy in adults have not been established.	Prevention of serious lower respiratory tract disease caused by RSV in children with high risk of RSV disease: Injection: 15 mg/kg of body weight intramuscularly prior to commencement of the RSV season and remaining doses administered monthly throughout the RSV season*	Single-dose solution vials for injection: 50 mg/0.5 mL 100 mg/1 mL

RSV=respiratory syncytial virus
*Children undergoing cardio-pulmonary bypass should receive an additional dose of palivizumab as soon as possible after the cardio-pulmonary bypass procedure (even if sooner than a month from the previous dose). Thereafter, doses should be administered monthly as scheduled.

Clinical Guidelines

Table 10. Clinical Guidelines

Clinical Guideline	Recommendations
American Academy of Pediatrics: **Respiratory Syncytial Virus (2012)**[8]	Prevention of respiratory syncytial virus (RSV) infections: • Palivizumab is the only licensed product available to reduce the risk of RSV lower respiratory tract disease in infants and children with chronic lung disease of prematurity, with a history of preterm birth (less than 35 weeks' gestation), or with congenital heart disease. • Palivizumab is administered intramuscularly at a dose of 15 mg/kg once every 30 days. • Maintaining compliance with monthly administration of palivizumab is important. • Additional doses of palivizumab should not be given to any patient with a history of a severe allergic reaction following a previous dose. • Palivizumab is not effective in treatment of RSV disease and is not recommended for this indication. Cost considerations: • Immunoprophylaxis with palivizumab is an effective, although costly, intervention that reduces RSV hospitalization rates by 39 to 82% among high-risk infants. • Optimal cost benefit from palivizumab immunoprophylaxis is achieved during peak outbreak months when most RSV hospitalizations occur. • No prospective, randomized clinical trial has demonstrated a significant decrease in the rate of mortality attributable to RSV or in the rate of recurrent wheezing following RSV infection among infants who receive prophylaxis with palivizumab. Initiation and termination of immunoprophylaxis: • Peak RSV activity in North America typically occurs between November and March.

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Clinical Guideline	Recommendations
	• 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 five monthly doses for infants and young children with congenital heart disease, chronic lung disease of prematurity, or preterm birth before 32 weeks' gestation (31 weeks, six days and younger) will provide an optimal balance of benefit and cost, even with variation in season onset and end. • For infants who qualify for five doses, initiation of immunoprophylaxis in November and continuation for a total of five 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. • Infants and children with congenital heart disease or chronic lung disease of prematurity or preterm infants born at or before 31 weeks, six days' gestation who initiate palivizumab prophylaxis after start of the RSV season will not require all five doses. <u>Eligibility criteria for prophylaxis of high-risk infants and young children:</u> • Infants with chronic lung disease of prematurity: palivizumab prophylaxis may be considered for infants and children <24 months of age who receive medical therapy (supplemental oxygen, bronchodilator, diuretic or chronic corticosteroid therapy) for chronic lung disease of prematurity within six months before the start of the RSV season. These infants and young children should receive a maximum of five doses. Patients with the most severe chronic lung disease of prematurity who continue to require medical therapy may benefit from prophylaxis during a second RSV season. Data are limited regarding the effectiveness of palivizumab during the second year of life. Individual patients may benefit from decisions made in consultation with neonatologists, pediatric intensivists, pulmonologists, or infectious disease specialists. • Infants born before 32 weeks' gestation (at or before 31 weeks, six days of gestation): infants in this category may benefit from RSV prophylaxis, even if they do not have chronic lung disease of prematurity. For these infants, major risk factors to consider include gestational age and chronologic age at the start of the RSV season. Infants born at or before 28 weeks, six days' gestation may benefit from prophylaxis during the RSV season, whenever that occurs during the first 12 months of life. Infants born at 29 weeks, 0 days through 31 weeks, six days of gestation may benefit most from prophylaxis up to six months of age. However, once an infant qualifies for initiation of prophylaxis at the start of the RSV season, administration should continue throughout the season and should not stop when the infant reaches either six months or 12 months of age. A maximum of five monthly doses is recommended for infants in this category. • Infants born at 32 to less than 35 weeks' gestation (defined as 32 weeks, 0 days through 34 weeks, six days of gestation): Numerous factors have been proposed as increasing the risk of acquiring RSV infection among infants in this gestational age group. Other factors have been associated with an increased risk of severe disease and hospitalization. Certain

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Clinical Guideline	Recommendations
	factors (congenital heart disease, prematurity, chronic lung disease of prematurity) are well-established risk factors for hospitalization, because they consistently are present across numerous studies. In contrast, other reported risk factors either are found inconsistently, even in studies by the same authors, or increase the risk of hospitalization by a relatively small factor (less than twofold to threefold). A risk-scoring tool developed from a Canadian prospective study of infants born at 33 through 35 weeks' gestation revealed that multiple risk factors needed to be present before a significant increase in hospitalization risk was seen. Available data do not allow for definition of a subgroup of infants who are at risk of prolonged hospitalization and admission to the intensive care unit. Therefore, although current recommendations were designed to be consistent with the United States Food and Drug Administration's approval for marketing of palivizumab for the prevention of serious RSV lower respiratory tract disease, they specifically target infants in this group with consistently identified risk factors for RSV hospitalization during the period of greatest risk, which is the first three months of life. Palivizumab prophylaxis should be limited to infants in this group at greatest risk of hospitalization attributable to RSV infection, namely infants younger than three months of age at the start of the RSV season or who are born during the RSV season and who are likely to have an increased risk of exposure to RSV. Epidemiologic data suggest that RSV infection is more likely to occur and more likely to lead to hospitalization for infants in this gestational age group when one of the following two risk factors is present: o The infant attends child care, defined as a home or facility where care is provided for any number of infants or young toddlers; or o One or more older siblings younger than five years of age or other children younger than five years of age lives permanently in the same household. Multiple births younger than one year of age do not qualify as fulfilling this risk factor. Prophylaxis may be considered for infants born at 32 through less than 35 weeks' gestation (defined as 32 weeks, 0 days through 34 weeks, six days of gestation) who are born less than three months before the onset of or during the RSV season and for whom at least one of the two risk factors is present. Infants in this gestational age category should receive prophylaxis only until they reach three months of age and should receive a maximum of three monthly doses; many will receive only one or two doses before they reach three months of age. Once an infant has passed 90 days of age, the risk of hospitalization attributable to RSV lower respiratory tract disease is reduced. Administration of palivizumab is not recommended after three months of age for patients in this category. • Additional preventive measures for all high-risk infants: Infants, especially those at high risk, never should be exposed to tobacco smoke. Tobacco smoke is a known risk factor for many adverse health-related outcomes. However, in published studies, passive household exposure to tobacco smoke has not been associated with an increased risk of RSV hospitalization on a consistent basis. Exposure to tobacco smoke must be controlled by families with infants, especially with infants who are at increased risk of RSV disease. Such preventive measures will be far less costly than palivizumab prophylaxis. In contrast to the well-documented beneficial effect of breastfeeding against many viral

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Clinical Guideline	Recommendations
	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. High-risk infants should be kept away from crowds and from situations in which exposure to infected people 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 infants (beginning at six months of age) and their contacts (beginning when the child is born) should receive influenza vaccine as well as other recommended age-appropriate immunizations. • Infants with congenital abnormalities of the airway or neuromuscular disease: Immunoprophylaxis may be considered for infants who have either congenital abnormalities of the airway or a neuromuscular condition that compromises handling of respiratory secretions. Infants and young children in this category should receive a maximum of five doses of palivizumab during the first year of life. • Infants and children with congenital heart disease: Children who are ≤24 months of age with hemodynamically significant cyanotic or acyanotic congenital heart disease may benefit from palivizumab prophylaxis. Decisions regarding prophylaxis with palivizumab in children with congenital heart disease should be made on the basis of the degree of physiologic cardiovascular compromise. Children ≤24 months of age with congenital heart disease who are most likely to benefit from immunoprophylaxis include: o Infants who are receiving medication to control congestive heart failure; o Infants with moderate to severe pulmonary hypertension; and o Infants with cyanotic heart disease. Because a mean decrease in palivizumab serum concentration of 58% was observed after surgical procedures that use cardiopulmonary bypass, for children who still require prophylaxis, a postoperative dose of palivizumab (15 mg/kg) should be considered as soon as the patient is medically stable. The following groups of infants are not at increased risk of RSV and generally should not receive immunoprophylaxis: o Infants and children with hemodynamically insignificant heart disease (e.g., secundum atrial septal defect, small ventricular septal defect, pulmonic stenosis, uncomplicated aortic stenosis, mild coarctation of the aorta, and patent ductus arteriosus). o Infants with lesions adequately corrected by surgery, unless they continue to require medication for congestive heart failure. o Infants with mild cardiomyopathy who are not receiving medical therapy for the condition. Dates for initiation and termination of prophylaxis should be based on the same considerations as for high-risk infants with chronic lung disease of prematurity. • Immunocompromised children: palivizumab prophylaxis has not been evaluated in randomized trials in immunocompromised children. Although specific recommendations for immunocompromised patients cannot be made, infants and young children with severe immunodeficiencies (e.g., severe combined immunodeficiency or advanced acquired immunodeficiency syndrome) may benefit from

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Clinical Guideline	Recommendations
	prophylaxis. • Patients with cystic fibrosis: Limited studies suggest that some patients with cystic fibrosis may be at an increased risk of RSV infection. Whether RSV infection exacerbates the chronic lung disease of cystic fibrosis is not known. In addition, insufficient data exist to determine the effectiveness of palivizumab use in this patient population and a recommendation for routine prophylaxis in patients with cystic fibrosis cannot be made. • Special situations: o If an infant or child who is receiving palivizumab immunoprophylaxis experiences a breakthrough RSV infection, monthly prophylaxis should continue until a maximum of three doses have been administered to infants in the 32 weeks, 0 days' through 34 weeks, six days' gestation group, or until a maximum of five doses have been administered to infants with congenital heart disease, chronic lung disease of prematurity, or preterm birth before 32 weeks' gestation. This recommendation is based on the observation that high-risk infants may be hospitalized more than once in the same season with RSV lower respiratory tract disease and the fact that more than one RSV strain often co-circulates in a community. o 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. o Infants who have begun palivizumab prophylaxis earlier in the season and are hospitalized on the date when the next monthly dose is due should receive that dose as scheduled while they remain in the hospital. o No data exist to support palivizumab use in controlling outbreaks of health care-associated disease, and palivizumab use is not recommended for this purpose. Palivizumab does not interfere with response to vaccines.

Conclusions

Respiratory syncytial virus (RSV) causes acute respiratory tract illness in individuals of all ages and the infection can be severe in certain high-risk individuals.[2] Currently, one agent, palivizumab (Synagis®), has been approved by the Food and Drug Administration and is commercially available in the United States for the prevention of serious lower respiratory tract infection caused by RSV in pediatric patients at high risk of RSV infection. Safety and efficacy of palivizumab were established in infants with a history of premature birth (≤35 weeks gestational age), children with bronchopulmonary dysplasia or hemodynamically significant congenital heart disease. Palivizumab is not approved for the treatment of RSV disease. The recommended dose of palivizumab is 15 mg/kg of body weight injected intramuscularly once monthly throughout the RSV season.[3] The most frequently occurring adverse events in clinical trials in patients using palivizumab were fever and rash.[3-7] According to available clinical evidence, palivizumab therapy reduces hospital and intensive care unit admission rates, but it does not effectively reduce either the incidence of RSV or RSV mortality.[4-7] The consensus guidelines published by the American Academy of Pediatrics establishes eligibility criteria for prophylaxis of high-risk infants and young children for the prevention of RSV infections with palivizumab.[8] Currently, palivizumab is only available as a branded agent.

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References

1. Barr FE, Graham BS. Respiratory syncytial virus infection: Clinical features and diagnosis. In: Basow DS (Ed). UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2014 [cited 2014 Feb 26]. Available from: http://www.uptodate.com/contents/respiratory-syncytial-virus-infection-clinical-features-and-diagnosis?source=search_result&search=RSV&selectedTitle=1~144.
2. Centers for Disease Control and Prevention. Respiratory Syncytial Virus (RSV), 2013 [cited 2014 Feb 24]. Available from: http://www.cdc.gov/rsv/index.html.
3. Synagis® [package insert]. Gaithersburg (MD): MedImmune, LLC; 2013 Apr.
4. The IMpact-RSV Study Group: Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in infants at high risk. Pediatrics. 1998 Sep;102(3 Pt 1):531-7.
5. Feltes TF, Cabalka AK, Meissner HC, Piazza FM, Carlin DA, Top FH Jr, et al. Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. J Pediatr. 2003 Oct;143(4):532-40.
6. Checchia PA, Nalysnyk L, Fernandes AW, Mahadevia PJ, Xu Y, Fahrbach K, et al. Mortality and morbidity among infants at high risk for severe respiratory syncytial virus infection receiving prophylaxis with palivizumab: a systematic literature review and meta-analysis. Pediatr Crit Care Med. 2011 Sep;12(5):580-8.
7. Andabaka T, Nickerson JW, Rojas-Reyes MX, Rueda JD, Bacic Vrca V, Barsic B. Monoclonal antibody for reducing the risk of respiratory syncytial virus infection in children. Cochrane Database Syst Rev. 2013 Apr 30;4:CD006602.
8. American Academy of Pediatrics. Respiratory syncytial virus, 2012. In: Red Book: 2012 Report of the Committee on Infectious Diseases, 29th, Pickering LK (Ed), American Academy of Pediatrics, Elk Grove Village (IL) 2012 p.609-12.
9. Anti-infective Agents 8:00, Antivirals 8:18, Monoclonal Antibodies 8:18.24. In: McEvoy GK, editor; American Hospital Formulary Service. AHFS drug information 2014 [monograph on the Internet]. Bethesda (MD): American Society of Health-System Pharmacists; 2014 [cited 2014 Feb 26]. Available from: http://online.statref.com.
10. Facts and Comparisons® eAnswers [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2013 [cited 2013 Feb 26]. Available from: http://online.factsandcomparisons.com.

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