Palivizumab
Newborn use only

2020

Alert	Cost effectiveness is unclear. Use of this drug should be done in conjunction with local hospital guidelines. Use should consider the infant's susceptibility to severe RSV disease, RSV prevalence and seasonality, risk of exposure including siblings and social factors, and parental preference.
Indication	Prophylaxis against RSV infection in at risk infants (see practice points section).
Action	Humanised monoclonal antibody that neutralises and inhibits fusion of respiratory syncytial virus (RSV) with the host cell, preventing its replication.
Drug type	Humanised monoclonal antibody
Trade name	Synagis solution for injection. [1]
Presentation	100 mg/mL; 0.5 mL (50 mg), 1 mL (100 mg)
Dose	Administer 15 mg/kg via intra-muscular injection once per month during periods of RSV risk (e.g. May to August in Southern Australia). Preferably administer first dose before RSV season (e.g. April in southern Australia). It may not be cost-effective to use beyond 12 months corrected age.
Dose adjustment	Therapeutic hypothermia: not applicable. ECMO: after cardiopulmonary bypass surgery, give a dose once child is stable (serum concentration markedly reduced after these procedures). Renal: not applicable. Hepatic: not applicable.
Maximum dose	Monthly doses of 15 mg/kg to maximum 5 doses. Infants discharged during RSV season may receive fewer doses.
Total cumulative dose	
Route	IM
Preparation	Do not dilute or mix with any other medications Do not shake the vial
Administration	Administration immediately by IMI into anterolateral thigh. The gluteal muscle should not be used as a routine site of injection due to the risk of damage to the sciatic nerve. Give injection volumes >1 mL as divided doses. To administer, remove the tab portion of the vial cap, clean the stopper with alcohol.
Monitoring	Hypersensitivity including anaphylaxis.
Contraindications	Palivizumab is contraindicated in patients with hypersensitivity to the active substance or other humanized monoclonal antibodies. [1]
Precautions	Keep all equipment needed for the treatment of severe hypersensitivity reactions ready before the administration of palivizumab.
Drug interactions	
Adverse reactions	These did not occur more commonly than in the placebo arm of a trial. [2]. Common (>1%): fever, rash, rhinitis, wheeze, cough, diarrhoea, injection site reaction, cyanosis (in children with congenital heart disease); Infrequent (0.1–1%) anaemia, elevated liver enzymes; Rare (<0.1%) hypersensitivity (including anaphylaxis). [3]
Compatibility	Not applicable. Do not reconstitute palivizumab with any other diluents or medicinal components.
Incompatibility	Do not reconstitute palivizumab with any other diluents or medicinal components.
Stability	Administer immediately.
Storage	Palivizumab vials should be stored in a refrigerator at 2^{O} to $8\,^{O}$C. Do not freeze. [1]
Excipients	Palivizumab contains histidine and glycine and the active ingredient, palivizumab, at a concentration of 100 milligrams per mL. [1]
Special comments	Educate the parents regarding adverse effects such as fever, irritability and diarrhoea.
Evidence	Palivizumab is a humanised monoclonal antibody (comprised of 95% human and 5% murine amino acid sequences) which exhibits neutralising and fusion-inhibitory activity against RSV. Palivizumab is registered in Australia for prevention of serious lower respiratory tract disease caused by RSV in children at high risk of RSV disease. There is no consensus regarding the use of palivizumab in Australia. [4] **Seasonality of RSV illness:** The peak in RSV-coded hospitalizations in NSW, Australia 2001-2010 was between May and August with 81% of the total RSV-coded hospitalizations recorded between these months. [5]

Efficacy

Palivizumab for prevention of respiratory syncytial virus infection in children: Systematic review found 3 RCTs in a total of 2831 patients that compared palivizumab with placebo. [2] The doses of palivizumab varied across studies from 3 to 6 doses at 15 mg/kg per dose. Palivizumab reduced hospitalisation for RSV infection [3 trials, 2831 infants; RR 0.49, 95%CI 0.37, 0.64] and admission to ICU [2 trials, 2789 infants; RR 0.50, 95%CI 0.30, 0.81]. There was no difference in mortality [3 trials, 2831 infants; RR 0.69, 95%CI 0.42, 1.15] or use of mechanical ventilation [2 trials, 2789 infants; RR 1.10, 95%CI 0.20, 6.09].

Palivizumab versus motavizumab for prevention of respiratory syncytial virus infection in children: When compared to motavizumab, palivizumab recipients showed no significant difference in risk of RSV hospitalisation [2 trials, 7870 infants; RR 1.36, 95%CI 0.97, 1.90] and all-cause mortality [4 trials, 8265 infants; RR 0.74, 95%CI 0.38, 1.43]. In both cases, the proportion of children with any adverse events (AE) or any AE related to the study drug was similar between the two groups. [2] No studies were found for children with immunodeficiency, chronic neuromuscular disease or congenital anomalies. [2]

Immunoglobulin treatment for hospitalised infants and young children with respiratory syncytial virus infection: Systematic review found no difference in mortality [3 trials, 196 infants; RR 0.87, 95%CI 0.14, 5.27] or days hospitalisation [5 trials, 324 infants; MD -0.70; 95%CI -1.83, 0.42] from use of palivizumab or motavizumab for infants and children under 3 years of age with RSV infection. [6]

Palivizumab for prophylaxis against respiratory syncytial virus infection in children with cystic fibrosis: One RCT with 186 infants with cystic fibrosis. One admission in each arm and the incidence of adverse events was similar in both groups. There is insufficient evidence to determine efficacy of palivizumab for prophylaxis against respiratory syncytial virus infection in children with cystic fibrosis. [7]

Safety

A single trial [2, 8] that included 1287 infants comparing palivizumab with placebo reported no difference in the number of children with an adverse event [RR 0.99, 95%CI 0.97, 1.01], a reduction in the number with a serious adverse event [1 trial, 1287 infants; RR 0.88, 95%CI 0.80, 0.96], and no difference in related serious adverse events [1 trial, 1287 infants; RR 0.14 [0.01, 2.80]. Two cases of anaphylaxis (<1 case per 100,000 patients) have been reported to the FDA. [9]

Palivizumab does not interfere with the immune response to live or inactivated vaccines. The childhood immunization schedule should be followed for all children, regardless of palivizumab use. [10]

Pharmacokinetics

A modelled pharmacokinetic study [11] of palivizumab data from 22 clinical studies reported Palivizumab clearance increased slightly from 10.2 ml/day to 11.9 ml/day as a function of postnatal age ranging from 7 to 18 months. Covariate analysis indicated 20% higher clearance in children with chronic lung disease and in children with antidrug antibody titer values >80. Body weight-based dosing of 15 mg/kg yielded similar palivizumab concentrations in children of different gestational and postnatal ages. There was little difference in palivizumab PK between healthy term and premature infants. Simulations found the 5 monthly palivizumab doses of 15 mg/kg, used in 2 RCTs, provided greater and more prolonged palivizumab exposure than did an abbreviated dosing regimen of 3 monthly doses.

Cost

Results from economic evaluations of palivizumab prophylaxis are inconsistent across studies, ranging from highly cost-effective to not cost-effective, implying that economic findings must be interpreted with caution. [2]

The average cost of 5 doses of palivizumab for a full term male infant < 1 year, based on the 50th centile for weight, is likely to be approximately $9,323 (drug cost only, excluding outpatient clinic costs), and $14,560 for a patient between 1-2 years. For a patient on the 3rd centile, the average estimated cost is $8,385 < 1 year, and $11,806 between 1-2 years. [9] Estimated bed saving for infant

age <1 year age is 3.4 days and for an infant 1 to 2 years age is 2.5 days. If bed cost is assumed to be a maximum average $3500 per day, then one admission saved results in a $11900 to $8750 hospital cost saving. Estimated pharmaceutical only cost of treatment is below:

Population	RSV related admission rate per 100000	NNT to prevent one RSV related admission	Cost palivizumab per admission averted 50th centile <1 year $9,323; 1-2 years $14,560 [9]	Cost palivizumab per admission averted 3rd centile <1 year $8,385; 1-2 years$11,806 [9]
Infants with CLD 0 to <6 months age [9]	56250	4	37292	33540
Infants with CLD 6 to <12 months age [9]	21430	9	83907	75465
Infants with CLD 12 to <24 months age [9]	7340	27	393120	318762
≤26 weeks gestation [9]	13900	14	130522	117390
Infants with CHD 0 to <6 months [9]	12080	17	158491	142545
Infants with CHD 6 to <12 months [9]	6350	32	298336	268320
Other condition* 0 to <6 months [9]	2230	16	149168	134160

Colour coding: Orange <$150000 per treatment course; green <$100000 per treatment course
* Asthma, cystic fibrosis, cancer, HIV infection, immunodeficiency, steroid therapy, chronic renal disease, diabetes mellitus, congenital anomalies of the respiratory tract, or respiratory distress syndrome.

Practice points

Palivizumab for prevention of respiratory syncytial virus infection in children: Palivizumab prophylaxis is effective in reducing the frequency of hospitalisations including admissions to ICU due to RSV infection in children with chronic lung disease, congenital heart disease, or those born preterm. There is insufficient data to determine if Palivizumab prophylaxis reduces need for mechanical ventilation or mortality. [2] [LOE I GOR B]

It is reasonable to consider use in Australia of palivizumab 15 mg/kg/dose from April to August (5 doses) in the following infants:

- Ex-preterm infants with chronic lung disease (oxygen or respiratory support at 36 weeks post menstrual age);
- Preterm infants born ≤26 weeks gestation;
- Infants with haemodynamically significant congenital heart disease between 0 to <6 months age; and
- Infants at risk of severe RSV bronchiolitis including infants with moderate to severe pulmonary conditions particularly those requiring continued respiratory and/or oxygen support.
- Children with severe pulmonary abnormality or neuromuscular disease that impairs the ability to clear secretions from the upper airways may be considered for prophylaxis in the first year of life.
- Children younger than 24 months who will be profoundly immunocompromised during the RSV season may be considered for prophylaxis.
- Insufficient data are available to recommend palivizumab prophylaxis for children with cystic fibrosis or Down syndrome.

Additional practice points:

- Infants born during the RSV season may require fewer doses. [10, 12]
- Prophylaxis should be discontinued in any child who experiences a breakthrough RSV hospitalization. [10, 12]
- Prophylaxis is not required in congenital heart disease where there is mild cardiomyopathy or surgically corrected disease (unless medication required for heart failure). [3]

	• After cardiopulmonary bypass surgery, give a dose once child is stable (serum concentration markedly reduced after these procedures); resume doses each month if prophylaxis still required. [3]
References	1. MIMS Online, Palivizumab ;Accessed 24/03/2020. 2. 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:CD006602. 3. Australian Medicines Handbook. Palivizumab ; Accessed 24/03/2020. 4. The Australian Immunisation Handbook. Respiratory syncytial virus monoclonal antibodies. 10th Edition 2013 (updated January 2014). 5. Homaira N, Oei JL, Mallitt KA, Abdel-Latif ME, Hilder L, Bajuk B, Lui K, Ferson M, Nurkic A, Chambers GM, Rawlinson W, Snelling T, Jaffe A. High burden of RSV hospitalization in very young children: a data linkage study. Epidemiol Infect. 2016;144:1612-21. 6. Sanders SL, Agwan S, Hassan M, van Driel ML, Del Mar CB. Immunoglobulin treatment for hospitalised infants and young children with respiratory syncytial virus infection. Cochrane Database Syst Rev. 2019;8:CD009417. 7. Robinson KA, Odelola OA, Saldanha IJ. Palivizumab for prophylaxis against respiratory syncytial virus infection in children with cystic fibrosis. Cochrane Database Syst Rev. 2016;7:CD007743. 8. Feltes TF, Cabalka AK, Meissner HC, Piazza FM, Carlin DA, Top FH, Jr., Connor EM, Sondheimer HM, Cardiac Synagis Study G. Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. J Pediatr. 2003;143:532-40. 9. Evaluation summary. Palivizumab for prevention of serious lower respiratory tract disease caused by Respiratory Syncytial Virus (RSV) in infants at high risk of RSV disease. South Australian Medicines Evaluation Panel. 2015. 10. American Academy of Pediatrics Committee on Infectious D, American Academy of Pediatrics Bronchiolitis Guidelines C. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. Pediatrics. 2014;134:415-20. 11. Robbie GJ, Zhao L, Mondick J, Losonsky G, Roskos LK. Population pharmacokinetics of palivizumab, a humanized anti-respiratory syncytial virus monoclonal antibody, in adults and children. Antimicrob Agents Chemother. 2012;56:4927-36. 12. American Academy of Pediatrics Committee on Infectious D, American Academy of Pediatrics Bronchiolitis Guidelines C. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. Pediatrics. 2014;134:e620-38.

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