

Palivizumab for the prevention of respiratory syncytial virus infection

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ABSTRACT

QUESTION Palivizumab, a specific monoclonal antibody for respiratory syncytial virus (RSV), is available for prevention of pediatric respiratory tract infections. What are the indications for its use and can it be used for treatment of RSV infections?

ANSWER Most infants should not be considered for RSV prophylaxis with palivizumab. The drug is approved for use for different indications in different Canadian provinces. The drug should be administered only in the context of infants most vulnerable to severe RSV illness with a high likelihood of hospital admission, particularly in the first 6 months of life. It is not effective in the treatment of RSV disease and it is not approved or recommended for this indication.

RÉSUMÉ

QUESTION Le palivizumab, un anticorps monoclonal spécifique contre le virus respiratoire syncytial (VRS), est accessible pour la prévention des infections des voies respiratoires chez l'enfant. Quelles sont les utilisations indiquées et peut-il être utilisé pour traiter les infections au VRS?

RÉPONSE On ne devrait pas envisager de prophylaxie avec du palivizumab pour le VRS chez la plupart des nourrissons. Le médicament est homologué pour différentes indications selon la province canadienne. Le médicament ne devrait être administré qu'aux nourrissons les plus vulnérables à une grave infection au VRS chez qui il y a une forte probabilité d'être admis à l'hôpital, en particulier durant les 6 premiers mois de la vie. Il n'est pas efficace dans le traitement d'une maladie causée par le VRS et il n'est ni approuvé ni recommandé pour cet usage.

Respiratory syncytial virus (RSV) is the most common cause of bronchiolitis in young children worldwide, affecting almost all children by 2 years of age. Respiratory syncytial virus infection is the most common reason for admission to hospital in the first year of life and is responsible for most of the approximately 12 000 hospitalizations per year in children younger than 2 years of age in Canada.¹ The RSV season lasts about 5 months in Canada, from December to April.²

Premature infants in their first 6 months, children with underlying cardiac or pulmonary disease in their first 2 years, immunocompromised children (particularly transplant patients), and healthy infants younger than 6 weeks of age are at the highest risk of severe RSV infection. These children are likely to have prolonged hospital stays, and are more likely to require admission to the intensive care unit (ICU) and to need mechanical ventilation.² In older children and adults, RSV infection usually manifests as upper respiratory tract illness.

The absence of a vaccine to prevent RSV infection narrows preventive measures to a combination

of public health advice and the use of passive immunization with palivizumab, the only licensed product available for prevention of RSV lower respiratory tract disease in high-risk infants and children during the RSV season. A previously used hyperimmune polyclonal RSV intravenous immunoglobulin, prepared from the plasma of donors selected for high serum titres of an RSV-neutralizing antibody, is no longer available.

Variability in indications

Respiratory syncytial virus is an RNA virus of the Paramyxoviridae family. The virus uses surface glycoproteins G and F, which lack neuraminidase and hemagglutinin activity, to infect cells. Palivizumab is a humanized mouse monoclonal immunoglobulin G1, comprising 95% human and 5% murine amino acid sequences. It is produced by recombinant DNA technology and directed against an epitope of the F glycoprotein of RSV. Palivizumab binds to this glycoprotein and prevents viral invasion of the host cells in the airway. This reduces viral activity and cell-to-cell transmission, and blocks the fusion of infected cells.³

Palivizumab has been approved for use in Canada since 2002. It is effective against both RSV subtypes (A and B). Palivizumab is administered intramuscularly at



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a dose of 15 mg/kg once every 30 days in a series of 5 monthly intramuscular injections to infants and children during the RSV season. The half-life for palivizumab is in the range of 18 to 21 days; therefore, monthly administration during the RSV season is enough for palivizumab to maintain its serum concentration at a protective level.³ The American Academy of Pediatrics recommends administering palivizumab for 5 consecutive months, covering the peak of the local RSV season.⁴

Clinical trials

The efficacy of palivizumab has been evaluated in 2 multicentre randomized controlled trials (RCTs), both of which used a primary end point of reduction in hospitalization owing to RSV infection.^{5,6} One RCT was conducted at 139 centres in the United States, the United Kingdom, and Canada. A total of 1502 children who were premature (ie, gestation for less than or equal to 35 weeks) or who had bronchopulmonary dysplasia (BPD) were randomized to receive injections of either palivizumab (15 mg/kg) or an equivalent volume of placebo by intramuscular injection every 30 days for 5 months.⁵ Palivizumab prophylaxis resulted in a 5.8% absolute reduction in hospitalization for RSV (10.6% placebo vs 4.8% palivizumab, number needed to treat [NNT] = 17). Children born premature but without BPD had a 6.3% reduction in RSV hospitalization (NNT = 16), while children with BPD had a 4.9% reduction (NNT = 20).⁵ The palivizumab group also had fewer total RSV hospital days and a lower incidence of ICU admissions, although ICU admission duration was significantly longer in the palivizumab group ($P = .02$, NNT = 37). There were no significant differences in adverse events between the 2 groups. Reactions at the site of injection were uncommon (1.8% placebo vs 2.7% palivizumab); the most frequent reaction was mild and transient erythema.⁵

In another RCT, 1287 children with hemodynamically significant congenital heart disease (CHD) received 5 monthly intramuscular injections of 15 mg/kg palivizumab or placebo.⁶ Palivizumab recipients had a 4.4% reduction in RSV hospitalizations (NNT = 23), a 56% reduction in total days of RSV hospitalization per 100 children, and a 73% reduction in total RSV hospital days with increased supplemental oxygen per 100 children. Adverse events were similar between the treatment groups and no child had the drug discontinued for a related adverse event.⁶ Therefore, monthly intramuscular injections of palivizumab (15 mg/kg per month) are well tolerated and effective for prophylaxis of serious RSV disease in young children with CHD or BPD.

The IMPact trial suggested an NNT of 16 to 20 infants treated with palivizumab to prevent 1 hospitalization, based on treating all infants born after less than 35 weeks' gestation; a subsequent study of children with CHD suggested a similar NNT for children younger than

6 months of age. For children older than 6 months of age the NNT was 83.^{5,6}

In general, cost-benefit analyses of palivizumab have found that because of its high cost there are no savings to be gained in health care dollars if all at-risk infants are offered prophylaxis, although some studies have yielded conflicting results.⁷⁻¹⁰ A recent systematic review and economic evaluation¹¹ has shown that although palivizumab is clinically effective for reducing the risk of serious lower respiratory tract infection requiring hospitalization in high-risk children, if used unselectively in preterm infants without chronic lung disease (CLD) or children with CLD or CHD, the incremental cost-effectiveness ratio is double that which is considered to represent good value for money. However, prophylaxis with palivizumab might be cost-effective for premature children with CLD when they have 2 or more additional risks (male sex, intrauterine growth retardation, low birth weight, maternal smoking, rural residence, breastfeeding for 2 months or less, a birthday in November, December, and January, etc).¹¹

Adverse effects

The most common reported adverse effects of palivizumab are local erythema, pain at the injection site, fever, and rash (1% to 3% of patients).⁵ In 2 small observational studies investigating the safety and immunological effects of repeated prophylaxis with palivizumab for a second year, no adverse clinical or immune effects were identified, although very rare cases of anaphylaxis have been reported following re-exposure to palivizumab.^{12,13} In a clinical trial, adverse events in infants with cardiac disease did not differ between treatment and placebo groups.⁶

Palivizumab is a recombinant product and has no potential for transmitting blood-borne infectious diseases. Moreover, it does not interfere with response to vaccines and does not affect the measles-mumps-rubella or other live virus immunization schedules.

Indications

Most infants should not be considered for RSV prophylaxis with palivizumab. Further, according to the American Academy of Pediatrics, palivizumab is not effective in the treatment of RSV infection and is not approved or recommended for this indication.⁴

Prophylaxis with palivizumab is only available for high-risk infants during the RSV season. Canadian indications for administration of palivizumab are shown in Table 1.¹⁴ According to the American Academy of Pediatrics, children eligible for a maximum of 5 doses include infants younger than 2 years of age who require medical therapy for CLD or CHD, premature infants born before 31 weeks' gestation, and certain infants with neuromuscular disease or congenital abnormalities of the airways.⁴ Premature infants with a gestational age of 32 to 35 weeks with at

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Table 1. Indications for administering palivizumab for RSV prophylaxis

PALIVIZUMAB USE	CRITERIA
Routine	<p>Children younger than 2 years of age with CLD due to prematurity who require ongoing medical therapy (oxygen, steroids, or daily bronchodilator therapy) within the 6 months preceding the RSV season</p> <p>Children younger than 2 years of age with hemodynamically significant cyanotic and acyanotic heart disease</p> <p>Infants born at 32 weeks' gestation or earlier who are 6 months of age or younger (with or without CLD) at the start of the RSV season</p> <p>Children in isolated northern or rural remote communities (eg, children who require air transportation to hospital facilities), born before 36 weeks' gestation, if they are younger than 6 months of age at the onset of RSV season</p>
Discretionary	<p>Full-term Inuit infants younger than 6 months of age at the onset of the RSV season in northern remote communities (eg, children who require air transportation to hospital facilities), regardless of gestational age</p> <p>Some patients with severe CLD or congenital heart disease, who require ongoing medical therapy</p> <p>Children with severe immunodeficiency diseases and those with other rare conditions, such as Down syndrome, at high risk of developing severe disease with RSV in the first year of life</p>

CLD—chronic lung disease, RSV—respiratory syncytial virus.

Data from Samson et al.¹⁴

least 1 risk factor and born 3 months before or during RSV season are eligible for a maximum of 3 doses.⁴

Conclusion

Palivizumab should only be considered for infants most vulnerable to severe RSV illness with a high likelihood of hospitalization, particularly in the first 6 months of life. Palivizumab is not effective in the treatment of RSV disease and is not approved or recommended for this indication.



Competing interests

None declared

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References

- Mitchell I, Tough S, Gillis L, Majaesic C. Beyond randomized controlled trials: a "real life" experience of respiratory syncytial virus infection prevention in infancy with and without palivizumab. *Pediatr Pulmonol* 2006;41(12):1167-74.
- Wang EE, Law BJ, Boucher FD, Stephens D, Robinson JL, Dobson S, et al. Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) study of admission and management variation in patients hospitalized with respiratory syncytial viral lower respiratory tract infection. *J Pediatr* 1996;129(3):390-5.
- Johnson S, Oliver C, Prince GA, Hemming VG, Pfarr DS, Wang SC, et al. Development of a humanized monoclonal antibody (MEDI-493) with potent in vitro and in vivo activity against respiratory syncytial virus. *J Infect Dis* 1997;176(5):1215-24.
- Committee on Infectious Diseases; Bocchini JA Jr, Bernstein HH, Bradley JS, Brady MT, Byington CL, Fisher MC, et al. From the American Academy of Pediatrics: policy statements—modified recommendations for use of palivizumab for prevention of respiratory syncytial virus infections. *Pediatrics* 2009;124(6):1694-701. Epub 2009 Sep 7.
- The IMPact-RSV Study Group. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. *Pediatrics* 1998;102(3 Pt 1):531-7.
- 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;143(4):532-40.
- Fitzgerald DA. Preventing RSV bronchiolitis in vulnerable infants: the role of palivizumab. *Paediatr Respir Rev* 2009;10(3):143-7. Epub 2009 Jul 15.
- Elhassan NO, Sorbero ME, Hall CB, Stevens TP, Dick AW. Cost-effectiveness analysis of palivizumab in premature infants without chronic lung disease. *Arch Pediatr Adolesc Med* 2006;160(10):1070-6.
- Reeve CA, Whitehall JS, Buettner PG, Norton R, Reeve DM, Francis F. Cost-effectiveness of respiratory syncytial virus prophylaxis with palivizumab. *J Paediatr Child Health* 2006;42(5):253-8.
- Nuijten MJ, Wittenberg W, Lebmeier M. Cost effectiveness of palivizumab for respiratory syncytial virus prophylaxis in high-risk children: a UK analysis. *Pharmacoeconomics* 2007;25(1):55-71.
- Wang D, Cummins C, Bayliss S, Sandercock J, Burls A. Immunoprophylaxis against respiratory syncytial virus (RSV) with palivizumab in children: a systematic review and economic evaluation. *Health Technol Assess* 2008;12(36):iii, ix-x, 1-86.
- Lacaze-Masmonteil T, Seidenberg J, Mitchell I, Cossey V, Cihar M, Csader M, et al. Evaluation of the safety of palivizumab in the second season of exposure in young children at risk for severe respiratory syncytial virus infection. *Drug Saf* 2003;26(4):283-91.
- Null D Jr, Pollara B, Dennehy PH, Steichen J, Sánchez PJ, Givner LB, et al. Safety and immunogenicity of palivizumab (Synagis) administered for two seasons. *Pediatr Infect Dis J* 2005;24(11):1021-3.
- Samson L; Canadian Paediatric Society, Infectious Diseases and Immunization Committee. Prevention of respiratory syncytial virus infection. *Paediatr Child Health* (Oxford) 2009;14(8):521-6.



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