

Prevention of respiratory syncytial virus infection



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Parent handout: [Respiratory Syncytial Virus: RSV](#)

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ABSTRACT

Respiratory syncytial virus (RSV) infection is the leading cause of lower respiratory tract infection in young children, with significant numbers of premature infants and those with other risk factors requiring hospitalization in Canada each year. Palivizumab, an RSV-specific monoclonal antibody, can reduce the hospitalization rate and severity of illness for a small group of high-risk or premature infants during their first RSV season. The present statement reviews the published literature and provides recommendations regarding its use in premature and other at-risk infants, for Canadian physicians.

Key Words: *At-risk infants; Palivizumab; Prematurity; Prophylaxis; RSV*

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The present statement replaces the 1999 (1) and 2003 (2) position statements, and aims to summarize the available information regarding the prevention of respiratory syncytial virus (RSV) infection in infants. In June 2002, Health Canada approved a monoclonal anti-RSV antibody, palivizumab, for the prevention of serious lower respiratory tract disease caused by RSV in paediatric patients at high risk of RSV disease. The present statement includes revised recommendations regarding the use of palivizumab in the Canadian context, including those infants born between 32 and 35 weeks' gestation. RSV immune globulin intravenous (RSV-IGIV) is no longer available in Canada. Each jurisdiction should optimize processes to implement these recommendations in the most cost-effective manner.

EPIDEMIOLOGY OF RSV INFECTION

RSV is the most common cause of lower respiratory tract infection (LRTI) in young children worldwide, infecting almost all children by age two years. In Canada, RSV is responsible for the majority of the approximately 12,000 hospitalizations for bronchiolitis in children younger than two years of age each year (3). In Canada, there are subpopulations, specific risk factors and/or geographic vulnerabilities associated with hospitalization that have been identified. Annualized incident admission rates of 484 per 1000 Inuit infants younger than six months of age in the Qikiqtaaluk (Baffin) Region of Nunavut, and bronchiolitis

attack rates of up to 57% in a central Canadian Inuit population, represent some of the highest reported rates in the world (4-6). Approximately 1% of children hospitalized with RSV bronchiolitis die, with an increase in mortality to 3% in those with pre-existing cardiac or lung disease.

In Canada, RSV has seasonal variation, with most of the country experiencing annual epidemics between December and March except in our northern regions where this variation is less marked. Primary infection does not confer protective immunity, and reinfection can occur within a single season or in sequential seasons (7,8). The Canadian RSV season usually begins between November and January, resolving by the end of April (4,9-11).

RISK FACTORS ASSOCIATED WITH HOSPITALIZATION AND SEVERE RSV INFECTION

Previously healthy infants younger than six weeks of age, premature infants in the first six months of life, children with underlying cardiac or pulmonary disease in the first two years of life, and the immunocompromised (particularly transplant patients) are at highest risk of severe RSV infection. In the Canadian context, these children have prolonged hospital stays and are more likely to require admission to an intensive care unit and need mechanical ventilation (9,12-16). In addition, infants with chronic lung disease (CLD) of prematurity have high rates of rehospitalization for LRTI (17,18). Children with other symptomatic lung diseases not associated with prematurity (eg, recurrent aspiration pneumonitis, cystic fibrosis, pulmonary malformation), as well as those with Down syndrome, are also at risk for hospitalization with severe RSV LRTI in the first two years of life (19,20). Insufficient data exist regarding the risk of RSV LRTI for healthy infants genetically diagnosed with cystic fibrosis through newborn screening programs.

Prematurity (less than 36 weeks' gestation) alone is a significant risk factor for RSV-related hospitalization and severe disease, with 2% to 9.8% of those born between 33 and 35 weeks' gestation and 7% of those born at less than 33 weeks' gestation requiring admission (13,21-25).

Children with hemodynamically significant cardiac disease, especially if pulmonary hypertension is present, are also at significant risk of severe RSV infection (10,26,27), with those requiring admission to hospital having increased mortality rates (3.4%), intensive care admission rates (33.4%) and need for mechanical ventilation (18%).

Additional risk factors that have been inconsistently associated with hospitalization in the first year of life include birth between October and December, low birth weight (less than 2500 g), male sex, young age (younger than 12 months), low socioeconomic status, attendance at daycare, school-aged siblings, exposure to air pollutants including second-hand smoke, congenital abnormalities of airways and severe neuromuscular disease. For infants born between 33 and 35 weeks' gestational age, particular attention has been given to identifying additional factors associated with severe disease and the development and validation of risk assessment tools (21,24,28).

A Canadian RSV risk scoring tool has been developed using prospectively identified factors associated with RSV hospitalization in 1758 infants born at 33 to 35 weeks' gestational age at 16 Canadian centres. The tool weighs seven risk factors to develop low (0 to 48), moderate (49 to 64) and high (greater than 65) risk scores ([Table 1](#)). The risk factors are birth between November and January, male sex, small size for gestational age (smaller than 10%), subject or sibling attendance at daycare, more than two smokers in the household, more than five individuals in the home and lack of eczema in a first-degree relative (22). Each risk is identified as being either present or absent, with a positive answer being assigned a pre-determined score between 10 and 25.

The risk scoring tool has been retrospectively validated using a study among Spanish infants at the same gestational ages (22). Several provinces have started to use either this tool or other risk-based strategies to identify eligibility for palivizumab among infants born between 33 and 35 weeks' gestational age.

TABLE 1
Canadian respiratory syncytial virus risk scoring tool for infants born between 33 and 35 weeks gestation

Risk factor	Score	
	Yes	No
Birth month is November, December or January	25	0
Infant to attend daycare OR siblings attend daycare	17	0
More than five individuals in the home including the infant (ie, six or more)	13	0
Small for gestational age (birth weight less than the 10th percentile for gestational age)	12	0
Immediate family (mother, father, sibling) history without eczema (without eczema = Yes)	12	0
Sex is male	11	0
Two or more smokers in the household	10	0

A total score from 0 to 48 means low risk, from 49 to 64 means moderate risk, and from 65 to 100 means high risk. Adapted from reference 22

Given the high rates of severe RSV LRTI among infants in northern and remote Canadian communities, the risks associated with hospitalization in these children must be explored. A case-control study (29) in Nunavut revealed that factors other than prematurity were more significantly associated with LRTI hospitalization. These included maternal smoking in pregnancy, residing in communities outside of Iqaluit, full Inuit race and overcrowding. Breastfeeding was found to be protective in this study.

PREVENTION OF RSV INFECTION

RSV Education

An important factor in preventing RSV transmission to young infants remains the education of parents/caregivers and health care providers. Targeted education initiatives should include information about how to avoid RSV exposure and acquisition. Information on the modes of transmission of RSV, the importance of hand hygiene measures in preventing RSV transmission, risk factors for RSV-related hospitalizations, the importance of avoiding modifiable risk factors (eg, cigarette smoking) and the important role of breastfeeding should be highlighted.

Immunization

Passive immunization has been the mainstay of disease prevention because of difficulties in developing a vaccine for RSV.

Two passive immunization agents have been developed to date: RSV-IGIV and palivizumab. RSV-IGIV, a poly-clonal immunoglobulin product from pooled blood donors, is no longer available.

Palivizumab, a humanized monoclonal immunoglobulin G-1 directed against an epitope on the F glycoprotein of RSV, is produced by recombinant DNA technology and approved for use in Canada since 2002. Palivizumab consists of 95% human and 5% murine amino acid sequences. Palivizumab is not derived from human immune globulin. It is highly active in vitro against type A and type B RSV isolates, where it was 50 to 100 times more potent than similar concentrations of RSV-IGIV (30).

EFFICACY OF PALIVIZUMAB

Two randomized controlled clinical trials (31,32) have demonstrated that palivizumab results in significant reductions in the incidence of RSV hospitalizations. A 55% (95% CI 38% to 72%) relative risk (RR) reduction in hospitalizations was seen in premature infants younger than 32 weeks' gestational age (31). The palivizumab group also had a shorter duration of moderate to severe respiratory illness than the placebo group (22). An RR reduction of 45% (95% CI 23% to 67%) was observed in hospitalizations for infants with hemodynamically significant congenital heart disease (32). Reductions were also observed in the number of days of hospitalization and number of hospital days when oxygen supplementation was required (32). Neither study observed changes in mortality rates; however, they were not powered to detect differences in this relatively rare outcome. Canadian sites were used in both studies. Decreased hospitalizations have also been seen among infants younger than six months of age and born at less than 35 weeks' gestation, those younger than 24 months of age with a clinical diagnosis of CLD requiring ongoing medical treatment, and in those with either cyanotic or acyanotic heart disease (24-28). Subgroup analyses demonstrated reductions in RSV-related hospitalizations for infants with or without CLD, those born before 32 weeks' gestation and those born between 32 and 35 weeks' gestation.

Using current guidelines, most children will be eligible for monthly palivizumab prophylaxis for only one winter season during the first year of life. Two small observational studies have investigated the safety and immunological effect of repeated prophylaxis with palivizumab for a second year in children with high-risk conditions other than cardiac disease. No adverse clinical or immune effects were identified (34,35).

Since publication of the initial trials, there have been many subsequent 'real-life' analyses of the efficacy of palivizumab. In Alberta, a comparison of RSV hospitalization rates among moderate- and high-risk premature infants at two tertiary care paediatric centres with differing approaches to RSV prophylaxis was undertaken (36). There was a significant reduction in hospitalization for high-risk infants in the centre that adopted an RSV prophylaxis program. High-risk premature infants were 2.6 times more likely to be hospitalized for RSV in the centre that did not undertake an RSV prophylaxis program than the centre that adopted a prophylaxis program with palivizumab. These differences were not seen in moderate-risk infants who were not offered a prophylaxis in either centre. When palivizumab was administered to premature Alaskan native infants, the RSV hospitalization rates declined from 439 hospitalizations per 1000 infants per year to 150 hospitalizations per 1000 infants per year (37).

DOSE AND ADMINISTRATION

Palivizumab is administered monthly at a dose of 15 mg/kg of body weight intramuscularly. This dose maintained mean trough serum concentrations above 40 µg/mL, a level that resulted in a 99% reduction of pulmonary RSV in an animal model (2,5,7).

Palivizumab is administered monthly during the period in which the patient is expected to be at high risk of exposure to RSV. This period of exposure has been assumed to be five months during the winter season beginning in November or December, with the last dose given in March or April (31,32). The first dose of palivizumab should be given before the onset of the period of highest risk to provide sufficient serum concentration of antibody to confer protection. For neonates being discharged home for the first time during this period, palivizumab immunization should be started just before discharge. In hospital-based studies (15) carried out by Pediatric Investigators Collaborative Network on Infections in Canada, the occurrence of two admissions to hospital in one week was used to indicate that there was a sufficient amount of local community RSV illness to initiate active hospital surveillance, and this seemed to occur before the annual epidemic had become established. This end point used with local surveillance activities can assist local decision making about the appropriate time to begin monthly palivizumab prophylaxis programs. Selected Canadian laboratories report RSV isolates to Health Canada weekly as part of the Respiratory Virus Detection Surveillance System; this collated information is available on the Public Health Agency of Canada Web site at <<http://www.phac-aspc.gc.ca/bid-bmi/dsd-dsm/rvdi-divr/index-eng.php>>. Because infection with RSV does not confer protective immunity (7), it is recommended that children who become infected with RSV continue to receive monthly doses of palivizumab throughout the RSV season.

ADVERSE EFFECTS AND INTERACTIONS

The most common reported side effects (1% to 3% of study patients) are local erythema, pain at the injection site, fever and rash (31). Very rare cases of anaphylaxis have been reported following re-exposure to palivizumab. Adverse events among infants with cardiac disease did not differ between treatment and placebo groups (32).

Palivizumab is a recombinant product and, thus, has no potential for transmitting blood-borne infectious diseases. It does not affect the measles-mumps-rubella or other live virus immunization schedules. Anti-palivizumab binding has been observed in the context of clinical trials, in both placebo and treatment groups, but was not associated with increased adverse events or lower palivizumab concentrations (31).

ECONOMIC CONSIDERATIONS

While hospitalization is believed to account for the majority of the economic burden of RSV in children, estimating the total costs associated with infection is complex. One must consider the costs of the palivizumab itself, the resources required to administer an immunization program, all of the health care costs associated with RSV infection, societal costs related to RSV illness and the RR reduction associated with immunization. These considerations make it difficult to truly assess the economic impact of palivizumab. In addition, a meta-analysis demonstrated a statistically significant difference in outcome between studies that received pharmaceutical industry support and those that did not. Multiple economic analyses undertaken, to date, have yielded conflicting results (33,38,39). Even in the highest risk groups, costs per hospitalization averted are high (38). Only when long-term costs are considered do the incremental associated costs of treatment fall within acceptable Canadian health prevention standards (eg, a cost of \$20,924 per quality-adjusted life year) (33,38-40). In one Canadian study (40) examining the long-term direct and indirect costs in infants born between 32 and 35 weeks' gestational age, palivizumab was most likely to be cost effective for moderate- to high-risk infants when the Canadian risk scoring tool was used.

A comparative cost analysis in full-term Inuit children living in Nunavut (41), which examined only the direct medical costs associated with RSV hospitalization, found that only 3.9 infants younger than six months of age from rural communities needed to be treated to avoid one admission. The number needed to treat was lowest (2.5) among infants from the highest risk communities, defined as those where infant LRTI admission rates were 500 or more per 1000 births a year. For infants younger than one year of age living in the town of Iqaluit, the actual cost per admission avoided was \$162,551. However, for infants less than six

months of age living in communities outside of Iqaluit, there was actually a cost savings of \$633 per admission averted. This cost saving was even greater (\$8,118 per admission avoided) for infants younger than six months of age living in the highest risk communities (41).

RECOMMENDATIONS

The levels of evidence reported in the recommendations have been described using the evaluation of evidence criteria outlined by the Canadian Task Force on Preventive Health Care (42).

- Given that the prevention of RSV and its associated hospitalizations by palivizumab is not complete, other preventive measures remain paramount and need to be emphasized. These include eliminating exposure to tobacco smoke, limiting exposure to contagious settings such as child care centres, as well as education regarding handwashing when siblings or adult contacts have respiratory infections (A-III).
- The use of palivizumab for preventing the spread of RSV among otherwise healthy patients in paediatric wards or intensive care settings has not been evaluated, and is not routinely recommended (D-III).
 - Among hospitalized patients, the observance of strict infection prevention and control measures, such as hand hygiene and the cohorting and isolation of infants infected with RSV, remains a major step in preventing the spread of the disease.
- Priority for RSV prophylaxis should be given to patients at highest risk of developing severe RSV infection. Children younger than 24 months of age with CLD of prematurity who require ongoing medical therapy (such as oxygen dependence, ongoing steroids or daily bronchodilator therapy) within the six months preceding the RSV season, should receive RSV prophylaxis (A-I).
- Children younger than 24 months of age with hemodynamically significant cyanotic and acyanotic heart disease should be given RSV prophylaxis. It is not expected that children with uncomplicated small atrial or ventricular septal defects or hemodynamically insignificant lesions, such as patent ductus arteriosus, without other risk factors would be at high risk of severe pulmonary RSV. Therefore, palivizumab prophylaxis is not recommended for this population (A-I).
 - Children receiving RSV prophylaxis, who undergo cardiopulmonary bypass have demonstrated a 58% decrease in serum antibody levels. Because this post-bypass concentration may be significantly below the serum concentration at which protection is achieved (greater than 40 µg/mL), repeat dosing of palivizumab should be given as soon as the patient is stable, if the child continues to have risk factors requiring prophylaxis, once the cardiac lesion has been corrected.
- Infants born at 32 weeks 0 days' gestation or earlier who are six months of age or younger (with or without CLD) at the start of the RSV season should be given RSV prophylaxis (A-I).
- An independent panel of experts should be convened in each province or territory to establish policy with regard to administering palivizumab to infants born between 32 weeks 1 day and 35 weeks 6 days' gestational age. If this expertise is not available locally, consultation with experts in other jurisdictions should be considered. The panel of experts should take into account known risk factors and may want to use the Canadian risk assessment tool to identify moderate- and high-risk infants in this cohort for whom RSV prophylaxis should be considered (B-II).
 - This recommendation differs from the American Academy of Pediatrics given differences in our epidemiology, geography and practice settings.
- Children in isolated northern or rural remote communities (for example, children who require air transportation to hospital facilities), born before 36 weeks' gestation, should be given RSV prophylaxis if they are younger than six months of age at the onset of RSV season given the increased incidence and severity of RSV and the costs associated with hospitalization (B-II).
- Consideration should be given to administering RSV prophylaxis to all full-term Inuit infants younger than six months of age at the onset of the RSV season in northern remote communities (for example, children who require air transportation to hospital facilities), regardless of gestational age (B-II).
 - There are insufficient data at this time to make recommendations for other First Nations and Métis full-term infants living in remote communities. This is identified as an urgent research priority, and in the interim, some experts may recommend prophylaxis in these populations based on local epidemiology (C-III).
- Limited data have not demonstrated adverse consequences following administration of palivizumab over a second viral season. Patients with severe CLD or congenital heart disease, who require ongoing medical therapy, may benefit from prophylaxis during a second RSV season (C-III).
- There are no data to support or refute the routine use of palivizumab for the prevention of severe RSV disease in children with severe immunodeficiency diseases. Consideration should be given to using palivizumab in these children and in those with other rare conditions at high risk of developing severe disease with RSV, such as Down syndrome, in the first year of life depending on the degree of immunodeficiency and pulmonary disease, in consultation with paediatric infectious diseases experts, immunologists and other members of paediatric transplant teams, if appropriate. Replacement

intravenous immunoglobulin therapy is not an appropriate alternative because it has variable amounts of RSV-specific antibody, and expert opinion recommends that it is not protective against RSV (C-III).

- Palivizumab is not indicated for the routine inpatient treatment of established RSV infection (D-II).

An application for the use of palivizumab in patients who do not fulfill these criteria will be considered on a case-by-case basis by the Canadian Blood Services, Héma Québec or the appropriate provincial or territorial bodies. Contact the individual product distributors for further information.

RESEARCH PRIORITIES INCLUDE BUT ARE NOT LIMITED TO:

- Further prospective validation of the clinical assessment tools used to identify those infants born between 32 and 35 weeks' gestational age, who are at increased risk of hospitalization with RSV, is required.
- Further cost-effectiveness studies of the use of RSV prophylaxis in the Canadian setting among different high-risk groups, including differing gestational ages, should be undertaken.
- The impact of substandard housing including but not limited to First Nations and Inuit communities on respiratory illnesses, such as RSV, needs to be further defined.
- Further studies are urgently needed to assess the cost-effectiveness of palivizumab in full-term infants from all First Nations, Métis and other specific populations living in remote communities.
- Further studies to assess the safety and efficacy of a second season of prophylaxis should be conducted.

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