Position statement

Preventing hospitalizations for respiratory syncytial virus infection

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Abstract
Respiratory syncytial virus infection is the leading cause of lower respiratory tract infections in young children. Palivizumab has minimal impact on RSV hospitalization rates as it is only practical to offer it to the highest risk groups. The present statement reviews the published literature and provides updated recommendations regarding palivizumab use in children in Canada.

Key Words: At-risk infants; Chronic lung disease; Congenital heart disease; Palivizumab; Prematurity; Prophylaxis; RSV

Epidemiology
Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract infections (LRTIs) in young children worldwide, with almost all experiencing their first RSV infection by two years of age. In developed countries, 1% to 3% of all infants are hospitalized with RSV infection. In Canada, the RSV season typically begins in November or December and persists for four to five months. The present statement replaces four previous position statements from the Canadian Paediatric Society on this topic[1][4] because there is evidence that the risk of RSV hospitalization does not warrant the use of palivizumab in many children for whom it was previously recommended.

Preventing RSV hospitalizations
Instructions for parents
Young infants (and their siblings) should not be in contact with individuals with respiratory tract infections whenever practical. A Cochrane review suggests that hand hygiene in the home decreases the spread of respiratory tract infections in children.[5] Breastfeeding and avoidance of cigarette smoke are also presumed to decrease the incidence and/or severity of viral respiratory tract infections.

Palivizumab
Palivizumab, a humanized murine monoclonal immunoglobulin G-1 directed against an epitope on the F glycoprotein of RSV, is produced by recombinant DNA technology, and has 95% human and 5% murine amino acid sequences. Rare cases of anaphylaxis are the only recognized serious adverse event. Standard dosing is 15 mg/kg administered intramuscularly every 30 days during RSV season for a maximum of five doses. Some Canadian programs administer the second dose 20 days after the first dose to prevent a low trough level.[6][7] However, there are no data showing an increased RSV hospitalization rate before the second dose. Palivizumab is available in 50 mg or 100 mg vials. Drug costs for five doses of palivizumab for an infant with a mean weight of 5 kg are approximately $5,600, assuming no waste.

Palivizumab use in Canada is directed by provincial or territorial programs. When practitioners have questions about eligibility, they should contact their local program; contact information is available through neonatal care units. Some programs routinely begin prophylaxis in November or December. Others use laboratory surveillance from local laboratories or from the National Respiratory Virus Detection Surveillance System (www.phac-aspc.gc.ca/bid-bmi/dsd-dsm/rvdivr/index-eng.php) to determine when to start palivizumab. The latter strategy is more complicated to organize than having a uniform start and stop date, but has been demonstrated to save drug costs in a recent Canadian study.[8]
Efficacy of palivizumab

Table 1 summarizes the results of randomized controlled trials (RCTs) investigating palivizumab, demonstrating a reduction in hospitalizations of approximately 80% in infants with prematurity but without chronic lung disease of prematurity (CLD), of 40% in infants with CLD, and of 45% in children with congenital heart disease (CHD). Efficacy was not demonstrated in the CHD subgroup with cyanotic heart disease.[9]–[11]

Observational studies demonstrate effectiveness in the ‘real world’, where clinicians, in conjunction with parents, decide who should receive palivizumab and where compliance is often lower than in RCTs. A recent systematic review summarized 20 published observational palivizumab studies. Estimates of effectiveness were generally in the range predicted by the RCTs.[12] Exceptions included one study with higher and two with lower efficacy. A study from Korea showed a very high 82% efficacy in children with CLD. [13] A study from Sweden showed no efficacy, with RSV hospitalization in 11 of 151 children (7.3%) with CLD who were given palivizumab versus three of 44 (6.8%) who were not (P=0.91). For infants born at <33 weeks’ gestational age (GA) without CLD, hospitalization rates were two of 75 (2.7%) with palivizumab and 22 of 567 (3.9%) without (P=0.61).[14] A study from Japan also showed no efficacy, with RSV hospitalization rates of 39 of 2806 (1.4%) and 45 of 3496 (1.3%) with and without palivizumab in preterm infants, although testing for RSV was not widely available.[15]

False-negative results for the detection of RSV in the presence of palivizumab have been described;[16] thus, the efficacy of palivizumab may be lower than that demonstrated in studies.

<table>
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<tr>
<th>TABLE 1</th>
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<tr>
<td>A summary of findings on the efficacy of palivizumab for preventing respiratory syncytial virus (RSV) hospitalizations in randomized controlled trials</td>
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<tr>
<th>Risk group</th>
<th>Illustrative comparative risks of RSV hospitalization (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Participants, n (studies, n)</th>
<th>Quality of the evidence (GRADE)*</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>Infants born at &lt;36 weeks' GA with no CLD who are &lt;6 months of age at the start of RSV season – RCT (1998)[9]</td>
<td>81 per 1000</td>
<td>18 per 1000 (8 to 39)</td>
<td>RR 0.22 (0.1 to 0.48)</td>
<td>740 (1 study)</td>
<td>++++ high</td>
</tr>
<tr>
<td>Children with CLD diagnosed clinically and treated with steroids, bronchodilators, diuretics or supplemental oxygen in the past 6 months who are &lt;24 months of age at the start of RSV season – RCT (1998)[9]</td>
<td>128 per 1000</td>
<td>78 per 1000 (51 to 122)</td>
<td>RR 0.62 (0.4 to 0.95)</td>
<td>762 (1 study)</td>
<td>++++ high</td>
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<tr>
<td>Children with hemodynamically significant CHD who are &lt;24 months of age at the start of RSV season – RCT (2003)[10]†</td>
<td>97 per 1000</td>
<td>53 per 1000 (36 to 80)</td>
<td>RR 0.55 (0.37 to 0.82)</td>
<td>1287 (1 study)</td>
<td>++++ high</td>
</tr>
<tr>
<td>Children with CF – RCT (2005)[11]†</td>
<td>11 per 1000</td>
<td>11 per 1000 (1 to 177)</td>
<td>RR 1.02 (0.06 to 16.09)</td>
<td>186 (1 study)</td>
<td>+++-low</td>
</tr>
</tbody>
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*GRADE Working Group grades of evidence: High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate. CF Cystic fibrosis; CHD Congenital heart disease; CLD Chronic lung disease of prematurity; GA Gestational age; NNTI Number needed to vaccinate to prevent one case; RCT Randomized controlled trial; †Only ever published in abstract form, so many details are unclear.

Cost-effectiveness of palivizumab

Reports concerning the cost-effectiveness of palivizumab have varied, owing in large part to
disparate estimates of its short- and long-term benefits. In terms of short-term benefits, there is no evidence that palivizumab prevents mechanical ventilation or death or that breakthrough RSV hospitalizations are less severe than hospitalizations in controls. With regard to longer-term benefits, one RCT showed that palivizumab administered to infants 33 to 35 weeks’ GA without CLD decreased days with parent-reported wheezing in the first year from 4.5% to 1.8% (P<0.001; number needed to treat = 38) and decreased recurrent wheezing from 21% to 11% (P=0.01).

Prophylaxis must be provided to many infants to prevent one hospitalization (Table 1), while the cost to provide prophylaxis to a single infant (approximately $5,600) exceeds that of a typical RSV hospitalization (three or four days). Therefore, given the paucity of evidence that palivizumab prevents severe outcomes, palivizumab is unlikely to be cost-effective in children with prematurity, CLD or CHD, and can only be potentially cost-effective in settings where RSV hospitalizations are exceedingly common and very expensive (such as Inuit infants in rural Baffin Island).

**Challenges of identifying the children at highest risk**

**CHD and CLD**

Higher rates and durations of hospitalization and more intensive care unit admissions occur in RSV-infected children with CHD or CLD compared with healthy term infants. A common recommendation has been to offer palivizumab to children up to 24 months of age at the start of RSV season when they have hemodynamically significant CHD or are still receiving therapy for CLD. A 24-month cut-off applies simply because this age limit was used in the original studies. One study from Switzerland showed that only two of 10 RSV admissions in children with CHD occurred in the second year of life, while a study from Norway showed a mean admission age of 9.5 months in children with CHD. In the original palivizumab CHD trial, RSV admissions in controls declined from 12% in infants <6 months of age to 7% at six to 12 months, and to 4% at 12 to 24 months. Admission rates in one Canadian prospective CHD trial were 16% at <6 months of age (n=42), 0% at six to 12 months of age (n=26), and 1% at 12 to 24 months of age (n=105). A study involving children on Medicaid with CLD showed an estimated RSV admission rate (extrapolated from the incidence of bronchiolitis) of 38.8% in year one (95% CI 30.4% to 49.0%) falling to 7.3% (95% CI 4.2% to 11.9%) in year two, and 1.3% (95% CI 0.2% to 4.6%) in year three.

Figures 1 and 2 summarize the incidence of RSV hospitalization in studies that investigated proven RSV infection in children with CHD or CLD who did not receive palivizumab. They show rates of approximately 10% with CHD and 15% to 20% with CLD. One limitation is that most studies were conducted in the 1990s and very few were population-based. Hospitalized infants were not uniformly tested for RSV and most studies were from the premolecular era of RSV testing; thus, RSV hospitalizations may have been missed. There have been major advances in therapy for CHD and CLD such that children with these conditions now have less severe disease than children born in the 1990s. At the same time, however, increases in infant survival rates mean that there are still medically fragile children with severe CHD and CLD.

**Prematurity without CLD**

Since palivizumab was licensed in 2002, most Canadian infants born before 32 weeks’ GA without CLD were offered prophylaxis if they were <6 months of age at the start of RSV season. Programs have offered prophylaxis to selected infants born up to 35 weeks, 6 days’ GA who were believed to be at higher risk for RSV hospitalization, typically based on a scoring system. Despite the fact that the efficacy of palivizumab is higher in healthy preterm infants than in those with CHD or CLD, use in healthy premature infants has recently come into question based on the following information:

- Although RSV hospitalization rates correlate with GA, the magnitude of difference between preterm infants without CLD and term infants does not warrant routine use of palivizumab, except possibly in very preterm infants. Figure 3 shows RSV hospitalization rates without palivizumab that are significantly lower than for infants with CHD (Figure 1) or CLD (Figure 2). Even in infants born before 30 weeks’ GA, admission rates were <10% in all but one study. The main limitation of Figure 3 is that, as with Figures 1 and 2, case findings were incomplete in some studies, but this proviso should have applied equally to all GAs.
• There have been significant advances in neonatology, such that infants with or without CLD are now healthier and have less residual lung damage than did infants of the same GA in the past.

• The parents of fragile infants are now more aware of the principles of infection transmission than in decades past. Parental leaves are longer and there are fewer young infants in child care settings, where the risk of RSV acquisition is higher.

Figure 1) Percentage of proven respiratory syncytial virus (RSV) hospitalizations in children with congenital heart disease who were not given palivizumab arranged according to the year that data collection ended. At study entry, children were up to 12 months [28], 24 months [19][21][25][27] or 36 months [23] of age. For the study from Sweden [26] the number of children with congenital heart disease was estimated.

Figure 2) Incidence of proven respiratory syncytial virus (RSV) hospitalizations per 1000 children with chronic lung disease of prematurity who were not given palivizumab, presented according to age at the time of the study. The bars represent 95% CIs (except for reference 29, in which raw data were not provided). For the study from Sweden [26] the number of children with chronic lung disease of prematurity was estimated.
**Figure 3** Incidence of proven respiratory syncytial virus (RSV) hospitalizations per 1000 preterm children without chronic lung disease of prematurity who were not given palivizumab, arranged according to gestational age. The bars represent 95% CIs. RSV testing was not performed in 38 of 118 admissions in reference 36. *The upper limit of the 95% CI is 42.9

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**Aboriginal infants**

High rates of hospitalization due to LRTIs have been described in isolated Inuit populations: 484 per 1000 infants <6 months of age in the Qikiqtaaluk (Baffin) region of Nunavut in 1997/1998,\[^44^\] and 202 per 1000 infants <12 months of age in 2009/2010.\[^45^\] Rates were 590 per 1000 infants in the first year of life in the Kitikmeot region of Nunavut between 2000 and 2004\[^46^\] and 389 per 1000 in 2009/2010.\[^45^\]

Approximately one-half of LRTIs are due to RSV. There is a high incidence of complications when infants from remote Northern communities are hospitalized with LRTIs.\[^46^\] Morbidity from LRTIs appears to be far lower in non-Inuit Aboriginal children.

Whether palivizumab should be offered to term Inuit infants in high-incidence communities is controversial. Palivizumab would have saved costs in term infants during the 2002 RSV season in rural Baffin Island Inuit communities, where hospitalization requires air evacuation,\[^20^\] with similar findings from the same communities in the 2009 RSV season.\[^47^\] It appears to be likely that other measures to reduce LRTIs, such as improved housing, prevention of exposure to smoke, and optimal use of influenza and other vaccines, would be more cost-effective than palivizumab in the long term.\[^48^\]

**Immunocompromised children**

There are no population-based data for this population, but severe disease and prolonged viral shedding are well-recognized risks.\[^49^\] A 2010 to 2013 Canadian Paediatric Surveillance Program study estimated an RSV hospitalization rate of five of 488 (1.0%) for hematopoietic stem cell transplant recipients and 13 of 274 (4.7%) for solid organ transplant recipients within two years post-transplant, with two deaths and one child requiring prolonged ventilation.\[^50^\] Under-reporting of cases is suspected and a validation study is ongoing. Lymphopenia, young age, and use of corticosteroids also appear to be risk factors for severe RSV in the immunocompromised child.\[^35^\]
Children with upper airway obstruction or pulmonary disease not related to prematurity
The risk of hospitalization due to RSV is increased but not well quantified in children with neuromuscular disorders, recurrent aspiration, pulmonary malformations, upper airway conditions such as Pierre Robin syndrome, and for conditions requiring a tracheostomy or noninvasive mechanical ventilation. Results of two small,[11][51] and one large[52] study of palivizumab in children with cystic fibrosis were inconclusive. RSV admission rates were low.

Children with Down syndrome
One non-population-based study showed that 39 of 395 children with Down syndrome (9.9%) experienced RSV hospitalization in the first two years of life, at a median age of six months, with the rate being 7.6% for term infants without CHD, 9.4% for preterm infants, and 11.9% for those with CHD.[53] There was no increased risk of recurrent wheezing in individuals hospitalized with RSV infections.[54] Decisions regarding prophylaxis are complicated by the fact that another study showed a much older median age (1.3 years) at the time of RSV hospitalization with Down syndrome.[55] A Canadian study demonstrated only a small number of palivizumab breakthrough infections in children with Down syndrome.[56]

Pharmacokinetics of palivizumab
The level of palivizumab postulated to prevent RSV hospitalization is based on the fact that a trough of 25 mg/mL to 30 mg/mL decreased RSV titres by an average of 99% in the lungs of cotton rats,[57] with all achieving a 99% drop at 40 mg/mL.[58] Lower doses, less frequent doses or a smaller number of total doses have the potential to protect children throughout RSV season,[59] because the trough remains >40 mg/mL for >30 days following the third dose.[60][61] A recent study demonstrated that a presumed therapeutic level of 30 mg/mL to 40 mg/mL can be maintained for the typical duration of the RSV season with only four doses, if doses 2, 3 and 4 are given 38 rather than 30 days apart.[62] Furthermore, a lower trough than 30 mg/mL to 40 mg/mL may be sufficient. Based on these premises, the British Columbia program administers <5 doses. A maximum of three doses are provided to infants born at 29 to 34 weeks’ GA without CLD, and they have reported no RSV admissions >35 days after the third dose in 514 infants over four RSV seasons.[63] A maximum of four doses are provided to higher-risk infants, and they have reported only two admissions >35 days after the fourth dose in 666 infants over two RSV seasons.[64]

Recommendations
Good hand hygiene in the home and avoiding contact of high-risk children with people with RTLS, where practical, remain paramount for RSV prevention. Breastfeeding and avoidance of exposure to cigarette smoke should be encouraged. Given that the efficacy of palivizumab is <50% in the highest-risk groups (CLD or CHD), and that most hospitalizations occur in healthy term infants, more education should be directed at such prevention strategies.

Use of palivizumab in different risk groups
- Children with hemodynamically significant CHD or CLD (defined as a need for oxygen at 36 weeks’ GA) who require ongoing diuretics, bronchodilators, steroids or supplemental oxygen, should receive palivizumab if they are <12 months of age at the start of RSV season. Because the incidence of RSV decreases in the second year of life, palivizumab is not indicated during the second RSV season for infants with CHD or for the vast majority of children with CLD (with the exception of those still on or weaned off of supplemental oxygen in the past three months).

- In preterm infants without CLD born before 30 + 0 weeks’ GA who are <6 months of age at the start of RSV season, it is reasonable (but not essential) to offer palivizumab. Infants born after 30 + 0 weeks’ GA have RSV admission rates that are consistently ≤7% (Figure 3), yielding a minimum number needed to treat of 18 (90 doses of palivizumab to prevent one RSV admission) if one assumes 80% efficacy and five doses per infant. Therefore, palivizumab should not be prescribed for this group.

- Infants in remote communities who would require air transportation for hospitalization born before 36 + 0 weeks’ GA and <6 months of age at the start of RSV season should be offered palivizumab. It is not clear whether this recommendation should apply only to Inuit infants, to all Aboriginal infants or to all infants in remote communities. The incidence of RSV hospitalization in a remote community in previous years should be taken into account when making this decision. A practical issue is that the onset and duration of RSV season is unpredictable in the Far North. A logical option is to delay administering palivizumab until RSV is detected in the Far North. The attendant risk is that significant spread may have already occurred. Consideration
may be given to administering palivizumab during RSV season to **term inuit infants** until they reach six months of age only if they live in communities with documented persistent high rates of RSV hospitalization. However, the first priority should be to provide palivizumab to infants with prematurity, CLD or CHD.

- Children with immunodeficiencies, Down syndrome, cystic fibrosis, upper airway obstruction or a chronic pulmonary disease other than CLD should not routinely be offered palivizumab. However, prophylaxis may be considered for children <24 months of age who are on home oxygen, have had a prolonged hospitalization for severe pulmonary disease or are severely immunocompromised.

- Continuation of monthly palivizumab is not recommended for children hospitalized with **breakthrough RSV infection**. Repeat RSV infections in one season are not common. Although recommended on the product monograph, the number needed to treat is no doubt very high if one continues palivizumab following RSV infection.

### Optimization of program
Each jurisdiction should optimize processes to implement these recommendations in the most cost-effective manner, ensuring that health care providers who administer palivizumab are prepared to monitor for and treat anaphylaxis. Well-organized palivizumab clinics decrease drug wastage.

- For eligible infants being discharged home for the first time during RSV season, palivizumab should be started just before discharge. Use before discharge to prevent nosocomial RSV is an expensive strategy that is not recommended.

- Programs should administer a maximum of three to five doses, with four doses probably being sufficient in all risk groups if palivizumab is started only when there is RSV activity in the community, especially if doses 2, 3, and 4 are given 38 days apart.

- There is no evidence to support giving >5 doses in one RSV season, administration to any child >24 months of age at the start of RSV season, or using palivizumab as RSV therapy.

### Annual program review
A panel of experts should be convened in each province or territory to review annually the palivizumab program guidelines and outcomes. People serving on these panels should not have conflicts of interest, including research funding, participation in a speaker’s bureau or financial links, with the pharmaceutical firm that makes palivizumab.

### Acknowledgements
This position statement has been reviewed by the Acute Care, Community Paediatrics, and Fetus and Newborn Committees of the Canadian Paediatric Society.

### References


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