REVIEW

A decade of respiratory syncytial virus epidemiology and prophylaxis: Translating evidence into everyday clinical practice

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Respiratory syncytial virus (RSV) is a common infection in infancy, with nearly all children affected by two years of age. Approximately 0.5% to 2.0% of all children are hospitalized with lower respiratory tract disease, of which 50% to 90% have bronchiolitis and 5% to 40% have pneumonia. Morbidity and mortality are highest in children with nosocomial infection and in those with underlying medical illnesses such as cardiac and chronic lung disease. Aboriginal children residing in remote northern regions are specifically considered to be at high risk for hospitalization due to RSV infection. Thorough hand washing and health education are the principal strategies in primary prevention. In the absence of a vaccine, palivizumab prophylaxis is currently the best intervention to reduce the burden of illness and RSV-related hospitalization in high-risk children. Health care professionals should provide palivizumab prophylaxis cost effectively in accordance with recommendations issued by pediatric societies and national advisory bodies.

The present article reviews the epidemiology of RSV infection and the short- and long-term impact of disease in high-risk infants and special populations. Prevention strategies and treatment are discussed based on the existing scientific evidence, and future challenges in the management of RSV infection are addressed.

Key Words: Epidemiology; Prevention; Prophylaxis; Respiratory syncytial virus

Une décennie d'épidémiologie et de prophylaxie du virus respiratoire syncytial : le transfert des données probantes dans la pratique quotidienne

Le virus respiratoire syncytial (VRS) est une infection courante pendant la première enfance, près de tous les enfants en ayant été atteints à l'âge de deux ans. De 0,5 % à 2,0 % de tous les enfants sont hospitalisés en raison d'une atteinte des voies respiratoires inférieures, dont 50 % à 90 % pour une bronchiolite et 5 % à 40 % pour une pneumonie. La morbidité et la mortalité sont plus élevées chez les enfants ayant une infection nosocomiale ou une pathologie sous-jacente telle qu'une maladie cardiaque ou une maladie pulmonaire chronique. Les enfants autochtones qui habitent dans le Grand Nord sont considérés comme particulièrement vulnérables à l'hospitalisation imputable à une infection au VRS. Un lavage des mains minutieux et de l'éducation sur les mesures prophylactiques sont les principales stratégies de prévention primaire. En l'absence d'un vaccin, la prophylaxie au palivizumab est la meilleure intervention pour réduire le fardeau de la maladie et l'hospitalisation attribuable au VRS chez les enfants très vulnérables. Les professionnels de la santé devraient prescrire une prophylaxie au palivizumab efficace sur le plan économique, conformément aux recommandations émises par les sociétés pédiatriques et les organismes consultatifs nationaux.

Le présent article contient une analyse de l'épidémiologie de l'infection au VRS et les répercussions à court et à long terme de la maladie chez les nourrissons très vulnérables et les populations particulières. Les stratégies et les traitements de prévention sont exposés selon les données scientifiques probantes, et les futurs défis dans la prise en charge de l'infection au VRS sont abordés.

CASE PRESENTATION

A 28-year-old gravida 4 mother has labour induced at 34 weeks' gestation on November 20, 2010, because of intrauterine growth restriction. A caesarean section is performed for a nonreassuring fetal heart rate pattern, and a male infant with a birth weight of 1.6 kg (lower than 5th percentile) is delivered with Apgar Scores of 2 (1 min) and 7 (5 min). The infant is hospitalized for three weeks. Breastfeeding proves to be unsuccessful. Both parents smoke two packages of cigarettes per day outside of the home. The mother provides full childcare at home; the father is unemployed. They live in a two-bedroom house with three other children (twins, three years of age in daycare, and a six-year-old in school). The house is heated by wood-burning stoves. The father and the twins have eczema. The family resides 6 h from the nearest small hospital. The grandparents visit regularly; the grandfather has severe chronic obstructive airway disease with recurrent bronchitis. What strategies would you advocate to prevent respiratory syncytial virus (RSV) infection? Does the newborn infant qualify for RSV prophylaxis based on current recommendations? Would it be beneficial?

SEARCH STRATEGY

An electronic PubMed search was performed in May 2010 using the following search terms: Respiratory syncytial virus OR RSV AND Prophylaxis OR Palivizumab, AND Infant-child AND Prevention/Infection Control; Limits: clinical trial and randomized controlled trial. The Cochrane Central Register of Controlled Trials (Cochrane Library issue 5, 2010) was searched without language restriction. The Cochrane Database of Systematic Reviews (Cochrane Library issue 5, 2010) was searched for systematic reviews on RSV and prophylaxis or palivizumab. The references of all identified reports were checked for additional citations of controlled trials on RSV prevention and infection control. Studies in which the treatment allocation was randomized or quasi-randomized were considered for inclusion in the present review, and the best evidence was graded where applicable. The MEsh headings retrieved 91 articles, with seven trials fulfilling the inclusion criteria. Evidence from only four randomized, double-blind, placebo-controlled trials (RCTs) was available (Table 1), upon which worldwide position statements and consensus guidelines for RSV prophylaxis are currently founded.

WHAT IS THE EPIDEMIOLOGY AND IMPACT OF RSV INFECTION?

RSV is the most common cause of lower respiratory tract infection (LRTI) in children younger than two years of age. It usually involves a mild upper respiratory tract illness with fever, nasal congestion,

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TABLE 1
Details of randomized controlled trials of respiratory syncytial virus (RSV) prophylaxis

Study/author (reference)	Therapy	Population	Outcome measures	Length of follow-up	Results	Level of evidence* and quality score† (QS)
IMpact-RSV study group (15), n=1502	Palivizumab vs placebo	Children with prematurity ≤35 weeks' GA or CLD	RSV hospitalization; days in hospital, with supplemental oxygen, or with moderate or severe LRTI; incidence and total days of intensive care or mechanical ventilation; OM, AEs and SAEs	150 days (30 days from last injection)	55% overall reduction in hospitalization (10.6% vs 4.8%; P<0.001) 78% reduction for children with prematurity only (8.1% vs 1.8%; P<0.001); 39% reduction for children with CLD (12.8% vs 7.9%; P=0.038); 80% reduction for infants 32 to 35 weeks' GA (9.8% vs 2.0%; P<0.002) Reduction in days of hospitalization (P<0.001), days of increased oxygen (P<0.001), days with LRTI score ≥3 (P<0.001) and days in ICU (P=0.023); no significant differences in other outcomes	A-I QS 8/8
Feltes et al (16), n=1287	Palivizumab vs placebo	Children ≤2 years of age with hemodynamically significant CHD before operation or partially corrected CHD	Incidence and days of RSV hospitalization, supplemental oxygen, intensive care, and mechanical ventilation; AEs; mortality due to RSV	150 days (30 days from last injection)	45% reduction in RSV hospitalization rate for palivizumab patients (9.7% vs 5.3%; P=0.003); 29% reduction cyanotic group; P=0.003 vs 58% reduction acyanotic group (P=0.003) 56% reduction in hospital days (836 vs 367; P=0.003); 73% reduction in days of supplemental oxygen (658 vs 178; P=0.014); no difference in length of ICU stay or mechanical ventilation	A-I QS 8/8
Cohen et al (109), n=186	Palivizumab vs placebo	Children ≤2 years of age with CF	RSV hospitalization; mortality; AEs; infections with *Pseudomonas aeruginosa;* incidence of wheezing; weight gain; change in pulmonary medications; and duration of steroid use	300 days (180 days from last injection)	No significant difference in RSV hospitalization between groups (n=1 in each) No significant difference between groups in any other outcome	A-I QS 3/8
Carbonell-Estrany et al (147), n=6635	Motavizumab vs palivizumab	Preterm (≤35 weeks' GA) infants ≤6 months at enrollment or children ≤24 months with CLD requiring medical management within 6 months of enrollment	RSV hospitalization or new RSV-related lower respiratory illness while in hospital; outpatient MALRI; frequency and incidence of OM; frequency of prescribed antibiotics for LRTI and OM, AEs and SAEs	150 days	26% relative reduction in RSV hospitalization in motavizumab vs palivizumab patients (1.4% vs 1.9%; RR=0.740 [95% CI 0.503 to 1.083]), achieving noninferiority 50% reduction in RSV MALRI for motavizumab patients (2.0% vs 3.8%; P=0.005) Psychiatric AEs more common in palivizumab recipients (2.9% vs 1.9%; P=0.010); skin AEs more common in motavizumab recipients (7.2% vs 5.1%; P<0.001); fewer motavizumab patients on mechanical ventilation (0.1% vs 0.3%; P=0.012); no significant differences in other outcomes	A-I QS 8/8

*Level of evidence (101): **Strength of Recommendation: A** Good evidence to support a recommendation for use; **B** Moderate evidence to support a recommendation for use; **C** Poor evidence to support a recommendation. **Quality of Evidence: I** Evidence from one or more randomized controlled trial; **II** Evidence from one or more well-designed clinical trial(s) without randomization, cohort or case-controlled studies (preferably from more than one centre), multiple time series or from dramatic results from uncontrolled experiments; **III** Evidence from opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees; †Based on modified Jadad scale (150). AE Adverse event; CF Cystic fibrosis; CHD Congenital heart disease; CLD Chronic lung disease; GA Gestational age; ICU Intensive care unit; LRTI Lower respiratory tract infection; MALRI Medically attended lower respiratory tract infection; OM Otitis media; SAE Serious adverse event; vs Versus*

rhinorrhea and cough. Approximately 40% of all primary RSV infections in infancy result in LRTI, principally bronchiolitis and pneumonia (1,2). Pathologically, the inflammatory process causes edema of the bronchiolar wall, mucus plugging of the airways and necrosis of the respiratory epithelium, which may have short- and long-term effects on lung function (3,4).

While the majority of children younger than five years of age with RSV infection are relatively well, the burden of illness associated with the care of these children is substantial, comprising one of 38 visits to the emergency department, and one of 13 consultations with family practitioners (5). In Canada, RSV is responsible for 5800 to 12,000 hospitalizations annually, with a documented increase in the incidence of admissions for bronchiolitis over the past two decades (6-9). In the United States (US), between 1997 and 2000, RSV bronchiolitis

comprised 77,700 admissions annually and was the leading cause among hospitalized infants younger than one year of age, with an additional 25% increase in hospitalization rate reported between 1997 and 2002 in this age group (10,11). Most children requiring hospitalization are otherwise healthy. However, infants younger than two years of age with pre-existing conditions, such as chromosomal abnormalities, neuromuscular, cardiac or chronic lung disease (CLD), experience significant complications following hospitalization, with a mortality rate ranging from 1% to 4% (12-16). In a cohort study conducted between 1999 and 2007 in a tertiary care hospital in the United Kingdom (13), the mortality rate among patients admitted to the intensive care unit (ICU) was 8.6%; those who died had underlying medical disorders. Based on a model using US national viral surveillance data from 1990 to 1999 (17), investigators concluded that

TABLE 2
Risk scoring tool for infants born at 33 to 35 completed weeks' gestational age in Canada

Risk factor	Yes	No
Birth month November, December or January	25	0
Subject or siblings attend daycare	17	0
>5 individuals in the home, including the subject	13	0
SGA (birth weight <10% for gestational age)	12	0
Family history without eczema	12	0
Male sex	11	0
>1 smoker in the household	10	0
Total score*/100		

*Adapted from reference 115. *Eligible to receive palivizumab if total risk score is from 49 to 100, based on provincial guidelines and expert panels (96): low risk (0 to 48), moderate risk (49 to 64) and high risk (65 to 100). SGA Small for gestational age*

RSV infection was the leading viral cause of infant mortality, with almost nine times the mortality rate of influenza. Mortality rates are highest in underdeveloped countries, with an estimated 66,000 to 199,000 deaths occurring in children younger than five years of age in 2005 (18).

RSV infections in temperate climates usually commence during the winter season, from October to December, and end in March through May. The epidemic curve varies annually and across geographical regions, and infections can be uniformly distributed throughout the year (19,20). Two subtypes of RSV may cocirculate – RSV A is more common than RSV B, and may cause more clinically significant illness (21,22). Reinfection can occur throughout life, but is usually less severe in childhood after a first illness. It is not entirely clear why reinfection occurs. Infants may generate suboptimal antibody titres against infection or titres may wane rapidly. Higher neutralizing antibody titres are associated with greater protection, as is the presence of maternal antibody (23). The virus itself may interfere with efficient innate host immune responses and cell-mediated immunity (24-26).

The direct costs of RSV hospitalization are significant, involving health care resources both in hospital and following discharge (27,28). Hospitalization also takes its toll on parental finances, with lost workdays, costs for travel and consultation visits (29). A prospective cost of illness study conducted by the Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) (6) from 1993 to 1994 estimated that the annual cost of RSV hospitalization for children one to four years of age was $18.5 million. From 1997 to 2002, costs in the US totalled US$1.1 billion (11). In a recent matched-control study in the US (30), first-year health care costs and resource use were 87% higher among premature infants with RSV LRTI than in controls without RSV LRTI (US$19,559 versus US$10,444; P<0.001). Similarly, in a prospective, multicentre, population-based study (31), the annual economic burden in Germany due to LRTI was €66 million, of which the highest cost per hospitalized RSV case was €2,772.

Which infants are considered to be at high risk for severe RSV disease?
Premature infants of all gestational ages (GAs) are at increased risk for severe RSV disease requiring hospitalization. While the general population risk for hospitalization in the first year of life is 1% to 2%, up to 10% of premature infants with RSV infection may require admission for supportive care. Several characteristics may account for this difficulty in coping with respiratory infection. Anatomical and physiological immaturity of the respiratory tract and low IgG levels may increase susceptibility to complicated respiratory infection (32,33). RSV hospitalization rates in preterm infants are also substantially higher than in infants born at term. In the Canadian PICNIC prospective cohort study, which enrolled 1205 moderately premature

infants, RSV admissions ranged from 5.0/1000 to 16.9/1000 infants for those younger than 33 weeks' GA; 9.7/1000 to 25.3/1000 for infants between 33 and 36 weeks' GA, and 1.6/1000 to 3.5/1000 for infants older than 36 weeks' GA (34,35). Premature infants were also more likely to require ICU admissions and ventilation. Low birth weight is considered to be an important predictor of mortality; infants with RSV bronchiolitis weighing less than 1500 g, and 1500 g to 2499 g compared with those weighing more than 2500 g have an OR of 13.9 (95% CI 5.2 to 37.0) and OR of 3.0 (95% CI 1.7 to 5.3) for death, respectively (36). Two retrospective analyses conducted across 10 US hospitals (27,28) demonstrated that preterm infants had longer ICU and hospital lengths of stay, higher intubation and complication rates, and associated health care costs than infants born at term. Notably, 33 to 35 weeks' GA infants incurred morbidities similar to those 32 weeks' GA or younger, but higher than those 36 weeks' GA or older, implying that an RSV LRTI insult during the critical period of lung development between 32 and 35 weeks' GA imposes a greater risk for pulmonary injury (4,27,28,37).

Extremely low-birth-weight premature infants with CLD who acquire RSV infection have an incidence of RSV-associated hospitalization of 12.8% to 13.5% – a rate that is approximately 10-fold higher than children without CLD, even up to three years of age. The risk of ICU admission and mechanical ventilation is almost three- and five-fold higher, respectively, than for healthy infants (12,14,15,38,39).

Moderately premature infants between 33 and 35 completed weeks' GA have been identified as a unique risk group for RSV infection. In multivariate analyses of several cohort studies (40-50), sex, age, birth weight, birth in the first one-half of the RSV season, crowding in the household, subject or siblings attending daycare, preschool-age siblings, passive smoke exposure, breastfeeding and family history of atopy are evidence-rated variables influencing the risk of hospitalization. Knowledge of risk factors in this subgroup have been used to develop robust predictive models both in Canada and Europe to determine which infants are at greatest risk for RSV hospitalization because they constitute 5% to 7.5% of the North American birth cohort (Table 2) (47-52).

Congenital heart disease
RSV infection was first recognized as a threat to infants with congenital heart disease in the 1980s when a case fatality rate of 37% versus 1.5% in controls was observed at one centre (53). More recent multicentre studies (14,16,54) including one RCT of infants with significant cardiac disease before surgery and those with pulmonary hypertension, show a much lower, but important overall mortality rate ranging between 3.4% and 4.2%. Complications are more pronounced in infants who undergo surgery during the course of RSV infection than following disease resolution (55).

WHAT ARE THE OUTCOMES OF RSV INFECTION IN SPECIAL POPULATIONS?

Neuromuscular disease
In a prospective RSV surveillance study of 1541 patients across 14 pediatric hospitals in Germany (56), children with neuromuscular impairments were hospitalized at a median age of 14 months and had a ninefold increased risk of seizures with a fivefold increased risk for ventilation compared with the control group. The attributable mortality was significantly higher in children with neuromuscular disease than controls (5.5% versus 0.2%). Similarly, an observational study (57) confirmed that infants between 29 and 32 weeks' GA with neurological disease were twice as likely to require rehospitalization with RSV than were preterm infants without impairment.

Trisomy 21
Infants with Down syndrome have several risk factors that increase their propensity to do poorly if infected with RSV, namely relative hypotonia, congenital cardiac disease, mid-face hypoplasia with smaller airways, pulmonary abnormalities with a reduced total number of alveoli and corresponding alveolar surface area, increased risk of pulmonary hypertension, and imbalances and alterations in cellular

and humoral immunity. Down syndrome infants without a cardiac defect are more likely to be hospitalized with RSV before two years of age (overall incidence 7.6% versus 0.7% in sibling controls); with significant heart disease, the incidence of hospitalization increases to 11.9% (58,59).

Cystic fibrosis
Patients with cystic fibrosis (CF) develop recurring exacerbations of pulmonary inflammation and infection with a striking propensity for airway colonization with *Pseudomonas* species. Using fluorescent cytometric assays, Van Ewijk et al (60) demonstrated a 1.2-fold to 8.2-fold increased adherence of *Pseudomonas* species to epithelial cells in vitro with previous RSV infection, and a 1.7 fold to 16-fold increased adherence with concurrent addition of RSV to cell monolayers. The authors' hypothesis was that RSV promotes pseudomonal attachment to RSV glycoprotein G. CF patients younger than two years of age who develop RSV infections have more frequent chronic respiratory signs and lower radiographic scores than uninfected infants, and the increased frequency of infections following RSV may cause a decline in lung function (61,62).

Immunodeficiency
Immunocompromised children, particularly those with cell-mediated immune defects, have difficulty clearing RSV infection and demonstrate prolonged viral shedding, increased illness severity, prolonged hospital stays, and morbidity and mortality rates ranging from 1.7% to 40% (14,63-67).

Aboriginal children
Rates of LRTI in Inuit and First Nations children are generally several-fold higher than their non-Aboriginal counterparts (68,69). RSV-specific admission rates for Inuit infants of all GAs are 166/1000 infant-years on Baffin Island (Nunavut) and 328/1000 to 512/1000 infant-years for infants younger than six months of age living in remote communities (70). RSV admission rates for preterm and term Alaska Native infants from the Yukon Delta are 317/1000 and 178/1000, respectively, compared with the average of 25/1000 to 30/1000 US children (71,72). Risk factors implicated in this population worldwide include exposure to smoke and smoking during pregnancy, limited access to medical care, poverty, overcrowding, prematurity and younger age, adoption, lack of breastfeeding and, possibly, a genetic predisposition (73-77).

CONSEQUENCES OF RSV INFECTION
In the short term, RSV LRTI disease may require hospitalization with incumbent morbidity and multisystem complications (12,26-28,56). Premature and term infants with and without pre-existing medical disease may require ICU care and ventilator support depending on illness severity (27,28,78). However, in a nested cohort study involving 2415 preterm infants between 32 and 35 weeks GA with confirmed or probable RSV hospitalizations (79), the overall mortality rate over a mean follow-up period of 2.1 years was 8.1% versus 1.6% in control subjects hospitalized without RSV (P=0.001).

The relationship between RSV infection in infancy, and wheezing and asthma later in life has been the subject of intense debate. In a prospective observational study of children 35 weeks' GA or younger who had or had not received palivizumab (80), those receiving prophylaxis had a significantly lower incidence of recurrent wheezing. Two major prospective studies of infants with RSV LRTI conducted in Sweden (81) and Tucson (Arizona, US) (82) demonstrated that the risk for significant wheeze and asthma symptoms persisted at 13 and 11 years of age, respectively, in children who experienced RSV LRTI in infancy compared with those without LRTI. In a systematic review of 12 longitudinal studies (83), an association of RSV infection with different asthma phenotypes was noted, with progressive disappearance of this association with increasing age. The impact of wheezing following RSV LRTI hospitalization on health-related quality of life at three years of age was also evaluated in a prospective control study involving 136 children over two winter seasons in the Netherlands using a

TABLE 3
Level of evidence* for prevention and treatment of respiratory syncytial virus bronchiolitis

Intervention	Level of evidence; comments
Hand washing with antibacterial soap; alcohol-based hand sanitizers†	BII-2
Avoidance of passive smoke exposure†	BII-2
Breast feeding†	BII-2
Antibiotics‡	A-I; Use short-term only in suspected bacterial infection
Bronchodilators‡	A-I
Chest physiotherapy‡	A-I
Corticosteroids‡	A-I
Deoxyribonuclease (DNase)‡	A-I
Epinephrine and dexamethasone‡	A-I
Fluids and hydration‡	No studies available. Clinically, more benefit than harm
Hypertonic saline and epinephrine‡	A-I
Montelukast‡	A-I
Nebulized hypertonic saline‡	A-I
Ribavarin‡	A-I
Supplemental oxygen‡	No studies available. Benefit if oxygen saturation <90% (C-III)
Vitamin A‡	A-I
Infants with underlying medical disorders (eg, prematurity, CLD and CHD should be closely monitored while oxygen is weaned)‡	C-III; Clinically, more benefit than harm

Adapted from references 40 and 142. *Strength of recommendation and quality of evidence (see Table 1 legend [101]). †Prevention strategies; ‡Treatment strategies. CHD Hemodynamically significant heart disease; CLD Chronic lung disease

validated questionnaire (84). Affected children scored lowest in the lung domain (P<0.01), especially during the winter versus the summer (P<0.01), with scores closely correlated with the number of days of wheezing. RSV-infected patients, together with their families and caregivers, are also reported to have reduced health and functional status during hospitalization and greater stress, poorer health and family health function up to 60 days postdischarge (85).

CAN RSV INFECTION BE PREVENTED?
Infection prevention and control measures can interrupt RSV transmission in the health care setting and have the potential to limit spread in the community. Infection is transmitted through contact with large droplets of nasopharyngeal secretions from infected individuals. The virus gains entry via the mucosal surfaces of the conjunctiva, nose and mouth. It can survive for up to 7 h on nonporous and porous surfaces such as plastic toys and clothes, and can be transferred directly or indirectly by touch (86). The incubation period is two to seven days. Hand washing after patient contact or avoiding contact with persons with respiratory symptoms remain the optimum strategies for primary prevention. Hand washing with soap and water, antimicrobial soap or alcohol-based hand rubs is acceptable depending on the setting (Table 3). Parents or caregivers should be counselled about these measures during the antenatal period and before discharge home. The protective role of breastfeeding in the overall prevention of infections and RSV illness and the avoidance of exposure to cigarette smoke should be actively promoted through education. Infection spreads quickly, both in crowded households and in the hospital setting. Nosocomial RSV infection is associated with higher mortality than community-acquired illness because it tends to occur in children with pre-existing morbidity (87,88). In the presence of an outbreak, control measures include routine admission screening for RSV, extra attention to hand hygiene and cohort nursing with personal protective equipment (gowns, gloves, masks and eye protection) (89,90).

TABLE 4
Current recommendations for respiratory syncytial virus prophylaxis in Canadian children

Indication	Level of evidence*	Comments
Infants born at <32 weeks' and 6 days' GA who are <6 months of age at the start of the RSV season	A-I	–
Infants <2 years of age with CLD who require oxygen, steroids or bronchodilator therapy within 6 months of the preceding RSV season	A-I	–
Infants <2 years with hemodynamically significant cyanotic or acyanotic heart disease	A-I	Infants with moderate/severe cardiomyopathy and pulmonary hypertension are at risk and should receive prophylaxis. Infants with uncomplicated ASD, VSD, PDA or stenotic lesions do not qualify for treatment (100)
Infants born between 33 to 35 completed weeks' GA (33 weeks and 0 days to 35 weeks and 6 days)	B-II	A-I evidence (15) exists for infants born between 33 weeks and 0 days, and 34 weeks' and 6 days' GA. Use of the Risk Scoring Tool is encouraged to make provincial decisions for prophylaxis between 33 weeks' and 0 days', and 35 weeks' and 6 days' GA (see Table 2)
Children <36 completed weeks' GA and <6 months of age at the start of the RSV season, residing in isolated northern or remote, rural communities where air transportation to medical care is required	B-II	Require prophylaxis
All full-term Inuit infants (>37 weeks' GA) and <6 months of age at the start of the RSV season who live in remote, northern communities	B-II	Require prophylaxis
Infants with underlying medical disorders (eg, cystic fibrosis, immunodeficiency, airway anomalies, Down syndrome or neuromuscular impairments)	C-III	Adjudication/approval by provincial panels on a case-by-case basis

Adapted from reference 96. *Strength of recommendation and quality of evidence (see Table 1 legend [101]). ASD Atrial septal defect; CLD Chronic lung disease; GA Gestational age; PDA Patent ductus arteriosus; RSV Respiratory syncytial virus; VSD Ventricular septal defect

What is the evidence in support of prophylaxis? Is it beneficial and cost effective?

Vaccination early in infancy or maternal vaccination would be desirable to prevent the large burden of RSV that occurs in the first year of life. Unfortunately, no infant vaccine candidates are near commercialization. The challenges of infant RSV vaccine development are, in part, related to inadequate attenuation of live viral vaccine candidates, and the hesitancy to explore inactivated vaccines following the safety concerns that arose during clinical trials of a formalin-inactivated F1-RSV vaccine in the 1960s. That vaccine resulted in more severe RSV disease in recipients, and two infants died (91,92). Recently, two live attenuated vaccines have shown preliminary promise and are under evaluation while subunit vaccines are actively being trialed in adults (93,94). The reader is referred to comprehensive reviews of the challenges of RSV vaccine development (93,95).

Passive immunization has proven to be effective for the prevention of RSV hospitalization in infants, but its expense and cumbersome monthly intravenous delivery schedule make it inaccessible to the general population. Palivizumab, a genetically engineered humanized monoclonal antibody, has been available in Canada since 1999 and is routinely given in all provinces to certain high-risk infants. The safety and efficacy of the product was proven in a multicentre RCT (15) (Table 1). Infants received five monthly injections of palivizumab (15 mg/kg) or placebo over the RSV season. A similar, large-scale RCT of palivizumab was conducted in patients with hemodynamically significant heart disease (16), also demonstrating reductions in RSV hospitalization (Table 1). These pivotal trials led to the regulatory approval of palivizumab prophylaxis in North America, with subsequent recommendations made worldwide for routine prophylaxis in high-risk children (Tables 1 and 4) (96-101). The Canadian Paediatric Society also recommends prophylaxis for full-term Inuit infants and all infants younger than 36 weeks GA residing in remote northern rural communities where medical care is inaccessible (70-77,96,102).

Currently, RSV prophylaxis in special patient populations such as Down syndrome, CF, neuromuscular and immunodeficiency disorders is based on adjudication by Hema Quebec and provincial Canadian Ministries of Health (103,104). The use of palivizumab prophylaxis is increasing in these populations as new evidence emerges describing their higher risk of RSV-associated morbidity compared with healthy infants. In the US outcomes registry from 2002 to 2004 (105), 9.1%

(n=12,341) of the infants who received palivizumab had congenital airway anomalies and neuromuscular disorders. In the Canadian Registry for Synagis (CARESS) study from 2005 to 2009 (106), 592 of 5286 infants with underlying medical disorders received palivizumab, the largest groups comprising Down syndrome and congenital airway abnormalities. The proportion of infants prophylaxed for underlying medical disorders increased more than threefold from 4.4% to 14.9% over the time period. Interestingly, the use of prophylaxis in infants with CF has become widespread despite the absence of solid evidence (107-109) and, in a 2007 survey (110), 41% of North American physicians across 83 centres considered prophylaxis as 'standard of care' and, subjectively, physicians in the United Kingdom would prescribe palivizumab if funding was available (111).

Can the cost of palivizumab prophylaxis be justified for use in all populations?

Over the past 10 years, global postmarketing studies and registries suggest that palivizumab is safe and that effectiveness is similar to that shown in the original efficacy trials (112-115). The cost effectiveness of palivizumab has been assessed examining outcomes of cost per quality-adjusted life-years (QALYs) gained (102,116-125), life-years gained (LYG) (126,127) and hospital admissions avoided (HAPs) (70,128-136). With some exceptions (122-124), most studies measuring QALYs found palivizumab to be cost effective within target populations (102,116-121,125). Studies measuring LYGs or HAPs generally found the opposite result (127-130,133-135), although some concluded cost effectiveness in specific subgroups (70,126,131,132). These studies indicate that the benefits of palivizumab related more to quality of life, rather than LYG. This reflects the fact that the clinical trials did not detect differences in mortality – largely because they were not powered to do so – the observation period was short and only stable patients were enrolled. Therefore, the latter groups of analyses have more associated uncertainty in their primary inputs. Besides differences in study design, subgroups and evaluation end points, studies also differed in the assumptions used and whether short- or long-term benefits were considered. Depending on the assumptions and end points used, and evaluations comprising both short- and long-term benefits in QALYs or LYG, palivizumab can be cost effective and its use in specific populations deemed appropriate based on risk factors, local epidemiology and country-specific cut-offs for cost effectiveness

(116-118,137-139). As examples, a Canadian cost evaluation of prophylaxis in infants of 32 to 35 weeks' GA demonstrated cost effectiveness from both the publicly funded health care system and society at large, while in the Canadian Arctic, cost savings were realized for infant prophylaxis in rural communities based on the low numbers needed to treat (n=2.5 to n=3.9) to prevent one hospitalization (Table 5) (102,118). An RCT comparing palivizumab prophylaxis with infection prevention interventions has not been conducted and is awaited.

HOW SHOULD INFANTS WITH RSV BRONCHIOLITIS BE MANAGED?

Several well-conducted RCTs and meta-analyses of therapeutic interventions in the treatment of RSV infection have failed to demonstrate an effective management strategy (Table 3). High-dose vitamin A is not effective in the treatment of children with RSV infection (140,141). Bronchodilators can be tried on an individual basis to determine whether there is benefit. Inhaled and systemic corticosteroids are not recommended, and the use of ribavirin, leukotrienes, DNase, antibiotics and chest physiotherapy do not improve outcomes (142-144). Inhaled hypertonic saline initially appeared promising but a recent RCT (146) showed no benefit in combination with epinephrine. More recently, epinephrine and dexamethasone in combination was shown to be helpful in children with bronchiolitis (145). Such interventions need to be confirmed in other settings before they enter routine practice. In the interim, the mainstay of treatment remains supportive, with maintenance of oxygenation, fluids and nutritional status.

REVIEW OF THE CASE

Using the risk scoring tool (Table 2), this 34 weeks' GA infant scored 88, placing him at high risk for RSV hospitalization compared with a child of the same GA without risk factors. The parents and caregivers should be educated on preventive measures first, including smoking cessation, thorough hand-washing techniques, avoidance of crowded settings such as large party gatherings and individuals with obvious respiratory tract infections. The grandfather with chronic bronchitis should be counselled to avoid contact with his grandson during exacerbations of illness when he could be shedding respiratory viruses or bacterial infection. If the child becomes ill, the parents should seek medical help in a timely fashion. Based on the score, this child would qualify for prophylaxis in most provinces, and application for palivizumab should be made by either the family doctor or pediatrician through the Ministry of Health regional RSV program. Prophylaxis consists of five consecutive monthly injections of palivizumab at 15 mg/kg/dose during the highest risk period of RSV acquisition in the winter season and in the jurisdiction where the infant lives (96-99).

TABLE 5
Cost effectiveness of palivizumab in Canadian subpopulations

Infant category	Direct costs ICER/QALY, $CAN
32 to 35 weeks' GA – including asthma	20,924
32 to 35 weeks' GA – excluding asthma	30,618
Moderate risk (RST* score 49 to 64)	34,215
High risk (RST* score 65 to 100)	5,765
<6 months (<1 year) on Baffin Island (Nunavut)	10,190 (39,435)
<6 months (<1 year) in Iqaluit (Nunavut)	103,325 (152,145)
<6 months (<1 year) in rural regions	Dominant = cost savings (24,750)

*Adapted from references 102 and 118. Decision thresholds for adoption of Canadian interventions (139). *RST Risk scoring tool (see Table 2). Cost per Quality adjusted life-years (QALY): $0 to $20,000 – strong evidence; >$20,000 to $100,000 – moderate evidence; >$100,000 – weak evidence. GA Gestational age; ICER Incremental cost-effective ratio*

FUTURE PROSPECTS

Motavizumab, a more potent monoclonal antibody, was recently shown in an RCT (147) to be noninferior to palivizumab for the prevention of RSV-associated hospitalization and superior in the prevention of medically attended RSV LRTI, with a 50% relative reduction. Active research studies are being conducted on the use of specific viral fusion protein and replication inhibitors and small interfering RNA molecules against RSV (148,149). While awaiting the development of a new vaccine with proven safety and efficacy across the general population, anti-RSV monoclonal antibodies currently offer the best approach to prevention. Further trials of RSV prevention in infants and children with underlying medical conditions are urgently required.

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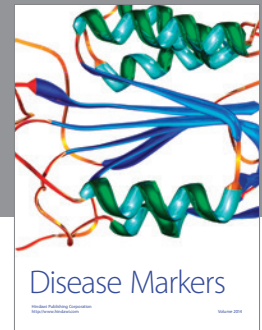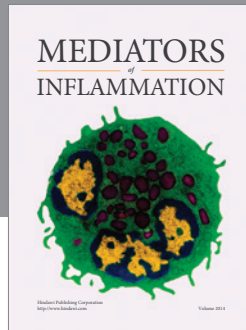
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