

# The impact of prophylaxis on paediatric intensive care unit admissions for RSV infection: a retrospective, single-centre study

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**Abstract** Respiratory syncytial virus (RSV) is the leading cause of lower respiratory tract infections and hospitalizations in children aged <2 years. The aim of this retrospective, single-centre study was to examine the characteristics of patients admitted to a paediatric intensive care unit (PICU) with RSV infection following the implementation of a RSV prophylaxis programme. Electronic hospital medical records of all PICU admissions for RSV infection were searched from 2003 to 2009. Data on baseline demographics, underlying disease, criteria for hospitalization, respiratory diagnosis and management, complications and palivizumab prophylaxis were collected. A total of 181 patients were admitted with RSV infection, accounting for 5.7% of all admissions. Eighty-four percent were ≤2 years of age. Majority (70.2%) had no underlying medical illness, and 79.6% received antibiotics as part of their medical treatment. Comparison of children aged ≤2 years and those >2 years revealed that fewer of the younger cohort (20.4% versus 79.3%;  $p < 0.001$ ) had an underlying medical condition. RSV infection occurred in 3.3% ( $n=6$ ) children who had received palivizumab prophylaxis, and

there were two deaths. The results indicate that >88% of all PICU admissions would not qualify for RSV prophylaxis under our established guidelines and 66% of the children aged ≤2 years were >36 weeks gestation and are not currently targeted for prophylaxis. The number of high-risk infants admitted to PICU with RSV infection has likely plateaued, and further reductions in admission rates may only be realised with the use of universal, vaccine immunization programmes.

**Keywords** RSV · PICU · Admissions · Prophylaxis

## Introduction

Respiratory syncytial virus (RSV) is the leading cause of lower respiratory tract viral infections (LRTI) in children less than 2 years of age. In 2005, the estimated global impact of RSV-associated LRTI was approximately 3.4 million hospitalizations [26]. In the USA, 20% of hospitalizations and 18% of emergency department visits for children under the age of 5 years were as a result of RSV infection [15]. In Canada, 10% of all hospital admissions of children with a respiratory aetiology can be attributed to RSV infection, and hospitalization rates are the highest in infants <6 months of age at 2,000 per 100,000 infants [43].

The majority of children who are hospitalized with a LRTI secondary to RSV infection are healthy. However, there are a number of groups that are at a higher risk of requiring hospitalization than the general population. Premature infants with or without chronic lung disease and infants with hemodynamically significant congenital heart disease comprise these high-risk groups [52]. Other special populations that have been found to be at an

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increased risk of significant RSV-associated LRTI are patients with neuromuscular disease, Down syndrome, immunodeficiency and cystic fibrosis [1, 7, 17, 25, 39, 53].

The incidence of RSV infections has seasonal variations. In temperate regions, RSV infections usually appear in October/November and end in March/April. Geographic variations of the impact of RSV infection on a population also exist. Rates of LRTI in Inuit children in the Canadian Arctic have been reported to be as high as 484 per 1,000 infant-years in infants less than 6 months of age [4]. The environmental factors that place these children at risk include smoking in pregnancy, overcrowding, breastfeeding and living in isolated communities [5].

Active immunization against the virus is not available, but passive immunization using palivizumab, a genetically engineered humanized monoclonal antibody, has been shown to be safe and effective [11, 46]. Palivizumab was licensed for use in the USA in 1998 and in Canada in 2002. The Canadian Paediatric Society (CPS) and other international paediatric position statements recommend RSV prophylaxis for premature infants born before 32 weeks gestation, infants with chronic lung (CLD) and congenital heart disease and those born between 32 and 35 completed weeks gestation that are considered at moderate to high risk for RSV hospitalization based on risk factors [8, 12, 13, 18, 38, 41, 42, 44].

Since the introduction of RSV prophylaxis therapy, the burden of illness secondary to RSV-associated LRTI has been reduced in the targeted high-risk populations [14]. However, healthy children, who are not currently eligible for RSV prophylaxis, still become infected during the first few years of life [15, 33]. Over a decade has elapsed since the introduction of RSV prophylaxis and a closer look at the infants with severe RSV-associated LRTI, who require admission to intensive care units, is warranted to describe the population that utilizes the healthcare resources.

The aim of this study was to examine the characteristics of patients admitted to a paediatric intensive care unit (PICU) with RSV infection following the implementation of a RSV prophylaxis programme. Specifically, the objectives were (a) to determine if the patients admitted to PICU with RSV infection have unique demographic characteristics which may target them as potential candidates for prophylaxis, apart from currently delineated criteria; (b) to identify the incidence of RSV infection in patients receiving palivizumab and (c) to examine infant co-morbidities following PICU admission for RSV infection.

## Methods

A retrospective, single-centre study was conducted at McMaster Children's Hospital, a major tertiary care

hospital in Hamilton, ON, Canada, which services a community of 2.3 million people from the south-central region of the province.

Electronic hospital medical records of all PICU admissions for RSV infection were searched over a 7-year period from January 1, 2003 to December 31, 2009. Patients who are hospitalized with RSV LRTI are admitted to the general paediatric ward. Indications for transfer to the PICU include apnoea, infants who require >50% oxygen supplementation to maintain oxygen saturation (SaO<sub>2</sub>) levels >92%, severe respiratory distress with a respiratory rate >70 breaths per minute, those who appear ill or “toxic” with reduced vascular perfusion and infants with underlying medical illnesses who merit close observation such as complex heart or chronic lung disease. The primary diagnosis of RSV infection (bronchiolitis or pneumonia or viral pneumonia unspecified) was identified by the 10th revision of the International Classification of Diseases and Related Health Problems codes. RSV cases were confirmed by direct-fluorescent antibody staining, culture or nucleic acid sequence-based amplification polymerase chain reaction on nasopharyngeal swabs or aspirates. All cases from 0 to 18 years of age were included; there were no exclusion criteria. Data were extracted from the medical records by members of the research team, and any queries arising from the data collection were verified by a single, pre-assigned investigator. Data on baseline demographics, underlying disease, criteria for hospitalization, respiratory diagnosis and management, complications and palivizumab prophylaxis were collected using a standardized data collection form.

All analyses were performed using the statistical software package SPSS<sup>®</sup> Statistics 17. Descriptive statistics were conducted on the variables extracted. Cases were classified into two age groups for sub-analyses: group 1—children ≤2 years of age and group 2—children >2 years of age. Differences in demographic and co-morbidity variables between the two groups were analysed using chi-square test for categorical data and the Mann–Whitney *U* test for non-normally distributed continuous variables. A *p* value <0.05 was considered statistically significant. The study was granted ethics approval by the institutional research ethics board prior to commencement.

## Results

A total of 181 patients were admitted to PICU with RSV infection over the 7 years. The majority of these admissions (86.2%) occurred during the months of December through to March; 51.9% of the cases were male, and the majority (59.7%) were ≥37 weeks gestational age. The patients ranged in age from 0 to 15.4 years (mean=12.73 months; SD=25.98), and 84% of the cases were ≤2 years of age,

14.4% were >2–10 years of age and only 1.6% older than 10 years of age. Admissions were the highest in the 0–3-month age category, with rates ranging from 21.6 to 52.9 per 1,000 admissions during the 7 years (Table 1). Overall, RSV hospitalizations requiring intensive care accounted for 5.7% of all PICU admissions.

Majority of the children (70.2%) did not have an underlying medical illness. At the time of hospitalization, 96.7% of the patients had respiratory distress, 76.8% decreased oxygen saturation and 70.7% could not maintain oral intake. The primary documented respiratory diagnosis was bronchiolitis (79.6%), pneumonia (11.0%), RSV infection undefined (7.7%) and nosocomial acquired RSV (1.7%).

During the course of illness, approximately half of the children (47.5%) required conventional mode mechanical ventilation, 19.9% required continuous positive airway pressure and 27.6% received supplemental oxygen alone. Two children (1.1%) required mechanical ventilation with nitric oxide for persistent pulmonary hypertension. Three children (1.7%) developed a pneumothorax, and two (0.12%) required surfactant for adult respiratory distress syndrome. As part of their PICU medical treatment, more than three quarters of the children (79.6%) received antibiotics. The median number of days in PICU was 5 days (range 1–73 days), while the median length of hospital stay was 9 days (range 1–113 days).

Almost all of the children (96.7%;  $n=175$ ) admitted to PICU with RSV infection had not received prophylaxis, and this is also reflected in Table 2 showing the annual RSV PICU hospitalizations based on the CPS criteria for prophylaxis. The incidence of RSV infection in children who had received palivizumab was 3.3% ( $n=6$ ). The respective cases had a mean age of 4.3 months ( $SD=4.18$ ) at time of admission to PICU; four were preterm (range 27–32 weeks gestational age), whereas two were term; 66.7% had one or more underlying medical conditions, including cyanotic congenital heart disease, chronic lung disease, neurological disorder or a genetic syndrome. Five (83.3%) had a primary diagnosis of RSV bronchiolitis; one child

had nosocomial acquired RSV. All six cases were managed with conventional mode mechanical ventilation and treated with antibiotics.

Few complications occurred, with bacterial infections (9.4%) and respiratory complications (2.8%) being the most frequent. Cerebrospinal fluid and blood cultures were positive in 5.5% of all patients while 3.9% had positive urine and endotracheal specimen cultures. There were two deaths among the study population: one directly attributed to RSV infection and one was related to previous underlying medical illness which included chronic lung disease, atrial septal defect, patent ductus arteriosus and factor V Leiden deficiency.

### Comparison of young and older children with RSV

Infants  $\leq 2$  years of age were compared to the cohort of children >2 to 18 years of age (Table 3). Significantly fewer of the younger infants in comparison to older children (20.4% versus 79.3%;  $p<0.001$ ) had an underlying medical condition. The two groups also differed in the proportion of children presenting with clinical signs and symptoms that prompted admission to PICU. A significantly greater proportion of the children in the younger age group compared to the older age group, not unexpectedly, presented with apnoea (30.9% versus 6.9%,  $p=0.008$ ), inability to maintain oral intake (75.7% versus 44.8%,  $p=0.001$ ) and were diagnosed with bronchiolitis (88.8% versus 55.2%;  $p<0.001$ ) upon admission. In contrast, more of the older (72.4%) than the younger (40.1%) children presented with fever ( $p=0.001$ ). There was a significant difference between the groups in relation to the final primary diagnosis at the time of discharge ( $p<0.001$ ), with most of the younger group (85.5%) classified as RSV bronchiolitis compared to 48.3% of the older infants.

During their hospitalization in PICU, the level of respiratory support needed (ranging from no support to high-frequency oscillation with nitric oxide) differed between the two age groups ( $p=0.001$ ). Significantly more of the young children (73.7% versus 41.3%;  $p<0.001$ ) required some level of respiratory support. The two groups were similar in relation to the proportion of children that received IV antibiotics as part of their treatment. The median number of days in PICU did not differ between the groups; however, the median length of hospitalization was significantly longer for younger children than for older children (9 days versus 7 days;  $p=0.03$ ). RSV infections following palivizumab occurred only in the younger group, since the current prophylaxis guidelines pertain in the majority to infants  $\leq 2$  years of age.

There were no significant differences between the two age groups in relation to the proportion of children who

**Table 1** Rate per 1,000 patients admitted to PICU with RSV infection

Year	Age in months					
	0–3	4–6	7–12	13–24	25–60	>61
2003	52.9	13.9	0	8.4	2.8	2.8
2004	26.1	11.8	2.4	7.1	4.7	7.1
2005	34.1	4.9	4.9	0	4.9	0
2006	37.6	10.0	7.5	5.0	7.5	5.0
2007	21.6	0	2.2	4.3	4.3	4.3
2008	40	0	5.5	5.5	3.6	9.1
2009	27.4	3.4	3.4	3.4	6.9	0

**Table 2** Annual RSV PICU hospitalizations based on Canadian Paediatric Society criteria

Year	≤32 weeks GA	33–35 weeks GA	>36 weeks GA <sup>c</sup>	Significant heart disease	BPD/CLD	All other medical illnesses <sup>d</sup>
2003	4	5 <sup>a</sup>	18	1	2	3
2004	2	4 <sup>a</sup>	13	0	0	3
2005	1	1 <sup>b</sup>	16	0	0	2
2006	4	1 <sup>b</sup>	16	1	1	5
2007	2	2 <sup>b</sup>	9	0	0	1
2008	1	3 <sup>b</sup>	23	0	0	2
2009	3	3 <sup>b</sup>	16	0	0	6

<sup>a</sup> Guidelines for prophylaxis not available for this cohort of infants prior to 2005

<sup>b</sup> All low risk and do not qualify for prophylaxis based on the Canadian risk assessment tool [41]; Canadian Paediatric Society criteria [42]

<sup>c</sup> Do not qualify for prophylaxis

<sup>d</sup> Includes neurological, complex syndromes, infants with multiple system disorders

experienced complications from the RSV infection. Of the two deaths in the study population, the case attributed directly to RSV infection was 3 years of age.

## Discussion

In the USA, RSV bronchiolitis is the leading cause of hospitalizations in infants less than 1 year of age, numbering over 311,000 admissions from 1977 to 2000

[20]. RSV hospitalization rates increased further by 25% from 1997 to 2002 with a corresponding 39% increase in hospital costs [23]. In our study, the number of admissions to PICU for RSV infection comprised 5.7% of all intensive care admissions over the 7-year study period. This is lower than the 10.8% rate for children <3 years of age reported by Berger et al. [6] from Switzerland between 2001 and 2005 and the 6.1–12.2% rate documented by Purcell and Fergie from Texas from 1991 to 2002 [34].

**Table 3** Comparison of demographic characteristics of RSV cases by age group

Variable	Children ≤2 years (n=152)	Children >2 years (n=29)	p value
Gender: M/F (%)	52:48	52:48	NS
Age at admission (months): mean (SD)	3.7 (5.65)	59.9 (37.71)	<0.001
Respiratory diagnosis at admission: n (%)			
RSV bronchiolitis	130 (85.5%)	14 (48.3%)	
RSV pneumonia	13 (8.6%)	7 (24.1%)	
RSV infection undefined	6 (3.9%)	8 (27.6%)	
RSV nosocomial acquired	3 (2.0%)	0 (0%)	<0.001
Underlying medical disorders: n (%)			
Cyanotic congenital heart disease	2 (1.3%)	0 (0%)	
Acyanotic congenital heart disease	4 (2.6%)	1 (3.4%)	
Bronchopulmonary dysplasia/chronic lung disease	3 (2.0%)	1 (3.4%)	
Neurological	2 (1.3%)	6 (20.7%)	
Diagnosed syndrome	1 (0.7%)	0 (0%)	
Other <sup>a</sup>	6 (3.9%)	5 (17.2%)	
Two or more disorders	13 (8.6%)	10 (34.5%)	
No underlying diagnosis	121 (79.6%)	6 (20.7%)	<0.001
Mechanical ventilation	112 (73.7%)	12 (41.4%)	<0.001
Length of PICU stay: median (range)	5 (1–73)	2 (1–36)	NS
Total length of hospital stay: median (range)	9 (1–113)	7 (1–64)	0.03

NS not significant

<sup>a</sup> Includes disorders such as biliary atresia with failure to thrive, severe gastro-oesophageal reflux disease and chylothorax

The months of admission encompassed the typical RSV season from November to April, with most admissions occurring between December and March. Consistent with the population known to be most susceptible to the virus, most of the cases (84%) were  $\leq 2$  years of age. Within this age group, infants 0–3 months had the highest rate of admissions (21.6 to 52.9 per 1,000 over the study period; Table 1) which is in agreement with the chronological data from McLaurin and Leader [23] where the highest overall comparative hospitalization rates for RSV were 45.3 per 1,000. The high rate of PICU admissions among the youngest children is not surprising since RSV infection acquired at less than 6 months of age correlates closely with hospitalization and admissions to intensive care [6, 9, 16, 22, 34, 45, 48].

Overall, the demographic characteristics of the children admitted to PICU for RSV infection in this study resemble similar cohorts described in the literature. Most (>70%) of the children with RSV infection necessitating PICU admission were healthy with no underlying medical conditions [6, 15, 33]. However, comparing children  $\leq 2$  years of age to those >2 years, it is evident that older children with RSV are more likely to have an underlying medical problem requiring intensive care. Clinical signs and symptoms such as apnoea, severe bronchiolitis and inability to maintain intake at time of admission to intensive care were more prevalent for children aged  $\leq 2$  years than for older children, and younger children were more likely to need respiratory support. These findings indicate that infants who are premature and are of younger chronological age are most vulnerable to RSV infection and are likely to need more aggressive clinical intervention with longer durations of hospital stay [16, 24, 35, 37].

An interesting finding of this study was the proportion of children with RSV that were initially treated with IV antibiotics prior to receipt of culture results. More than three quarters of all RSV cases were treated with antibiotics despite less than 10% being diagnosed with a bacterial infection. The American Academy of Pediatrics recommends that antibiotics should only be used with RSV infection when bacterial co-infection is present [2]. However, the reported incidence of bacterial co-infections in RSV patients admitted to the PICU ranges from 0.6% to 44% [10, 36, 49, 50] compared to a rate of 1.9% for infants not requiring intensive care [40]. Since majority of the patients are critically ill and face the additional risk of multi-system morbidities posed by bacterial infections in this setting, the use of empirical antibiotics is perhaps justifiably greater than 80% pending the results of bacteriological cultures and appears to be minimally influenced by even the rapid availability of positive RSV detection tests [21, 36, 47].

While the demographic characteristics of our studied population over 7 years post-licensure of palivizumab in

2002 seem similar to other studies, there has been a significant change in the number of children admitted to the PICU and the overall spectrum of disorders. The Pediatric Investigators Collaborative Network in Canada (PICNIC) conducted a prospective, multi-centre study of 1,516 children hospitalized with RSV LRTI from January 1993 to June 1994 [19]. Of 1,205 healthy children, 64 were <33 weeks gestation, 155 between 33 and 36 weeks and 986 >36 weeks gestational age; 31.2%, 28.4% and 11% required PICU admission, respectively, and 21.9%, 12.2% and 4.6% received mechanical ventilation. In the same study, a sub-group analysis of underlying medical conditions such as CLD, upper airway and pulmonary malformations, cystic fibrosis and neuromuscular disorders warranted PICU admission, the incidence of ICU admission ranged from 12% to 50% and 0–33% required ventilator support [3]. In another multi-centre study conducted by the PICNIC group involving 689 RSV hospitalizations between January to April 1993, the incidence of PICU admission was 16% ( $n=110$ ) and 9.1% ( $n=63$ ) needed mechanical ventilation [51]. One hundred forty-eight patients were <37 weeks gestation and 156 patients had underlying illness. The proportion of patients with underlying illness who were admitted to intensive care and required ventilation were higher than the group of infants without risk factors. In a cohort study involving 406 infants admitted to the PICU over eight consecutive RSV seasons from 1999 to 2007, 46% ( $n=187/406$ ) had pre-existing medical disorders, 98.5% required mechanical ventilation and 35 children died (PICU mortality rate of 8.6%). All of the 18 RSV-related deaths had underlying medical illnesses [48]. This contrasts with our study where 70.2% ( $n=127/181$ ) of the infants had no previous medical conditions (Table 2) because the proportion of infants across Canada receiving RSV prophylaxis in this category has increased two-fold from 2006 (5.6%) to 2009 (12.2%) [31].

Six (3.3%) children who received palivizumab were admitted with RSV infection and were in agreement with the range of 1.3–5.3% in published reports on the efficacy of palivizumab from randomized controlled trials and registries [11, 14, 27, 28, 32, 46]. The CPS has issued national guidelines for RSV prophylaxis which have been adopted uniformly across all provinces [42]. A Canadian Registry of patients receiving palivizumab prophylaxis (CARESS) from 2005 to 2009 across 27 Canadian sites indicates that the RSV hospitalization rate for 5,286 enrolled infants has decreased to 1.38% (range 0.3–1.94%) [28]. Additionally, in our region from 2005 to 2008, the majority of moderate- to high-risk infants between 33 and 35 completed weeks gestational age received prophylaxis in accordance with provincial guidelines and only low-risk infants (Table 2) appear to be hospitalized with RSV LRTI [29].

The retrospective analysis of our case series is subject to several biases, and the results are in part dependent on accurate documentation of the interventions instituted by healthcare providers in the care of RSV-positive hospitalized patients. Although this is a single-centre study involving a relatively small sample size, it was conducted in a defined geographical region which captured all patients who either received or did not receive RSV prophylaxis and required paediatric intensive care. The results are therefore generalizable to similar tertiary PICU centres that provide centralized RSV prophylaxis clinics with efficient surveillance to overshadow the problem of referral-filter bias.

In summary, the profile of patients admitted to the PICU with RSV infection at our centre has changed over the past 7 years with majority of the admissions  $\leq 2$  years of age comprising term infants and only 20% of this group had pre-existing medical disorders. This may in part be due to active community education programmes on the prevention of RSV, but there has been a concomitant overall decrease in RSV hospitalizations across the high-risk groups of infants in our annual surveillance with the rising use of RSV prophylaxis in patients with medical illnesses and those who meet defined eligibility criteria [31, 42]. Based on national and provincial guidelines, 88% of the admissions to PICU in our study would not have qualified for RSV prophylaxis. Moreover, 66% of all admissions aged  $\leq 2$  years were greater than 36 weeks gestation, and currently none of the risk factors in the Canadian risk assessment tool effectively target a sub-group of patients among this cohort that would cost-effectively benefit from prophylaxis [30]. The incidence of RSV infection in those who received palivizumab prophylaxis was 3.3% and is within the range of similar reports from the scientific literature.

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