ORIGINAL ARTICLE

Respiratory illness and respiratory syncytial virus hospitalization in infants with a tracheostomy following prophylaxis with palivizumab

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Abstract

Data on respiratory-related illness and respiratory syncytial virus (RSV) infection in children with a tracheostomy are sparse. We determined respiratory illness hospitalization (RIH) and RSV-related hospitalization (RSVH) hazard ratios in children with a tracheostomy following prophylaxis compared with infants' prophylaxed for standard indications (prematurity ≤ 35 weeks' gestational age, bronchopulmonary dysplasia, and significant congenital heart disease) and children with complex medical disorders. Children who received ≥ 1 injection of palivizumab were prospectively enrolled across 32 Canadian sites during the RSV season. Respiratory illness event data were collected monthly. Data were analyzed using t tests, chi-square tests, and Cox proportional hazards adjusted for confounders. A total of 23,597 infants were enrolled; 220 tracheostomy, 19,402 standard indications, 3975 complex medical disorders. Of the 220 tracheostomy infants, 30 had bronchopulmonary dysplasia, 18 were premature, 12 had congenital heart disease, and 160 had other medical complexities. RIH and RSVH incidences (tracheostomy, standard indications, complex medical disorders) were 24.5%, 6.2%, and 9.8% and 2.0%, 1.5%, and 1.8% respectively. RIH hazard was significantly higher in tracheostomy infants compared with standard indications (HR = 1.8, 95% CI 1.1–3.0, $p = 0.02$) but was similar between the tracheostomy and complex medical disorders groups (HR = 1.3, 95% CI 0.7–2.2, $p = 0.37$). RSVH hazard was also similar in tracheostomy infants relative to standard indications and complex medical disorders (both $p > 0.75$). Children with tracheostomies who received palivizumab had an increased RIH hazard compared with the standard indications group. Similar RSVH hazard between tracheostomy, standard indications, and complex medical disorders groups suggests that children with tracheostomies may benefit from palivizumab by reducing RSVH during the RSV season.

Keywords Hospitalization · Palivizumab · Respiratory illness · Respiratory syncytial virus · Tracheostomy

Introduction

Children with a tracheostomy comprise a diverse population that spans those who require the procedure to resolve upper airway obstruction primarily due to congenital anomalies to those who require respiratory support for long-term chronic respiratory and neuromuscular disease. In a recent review, the largest percentage of children with a tracheostomy was aged < 1 year (range 4–78%) with a statistically significant increase in the respective cohort from 41.3 to 63% between 1985–1994 and 1995–2004, respectively [1]. Over the last 30 years, several investigators have reported an evolution in the indications for a tracheostomy in children from principally infectious causes to predominantly those who require respiratory support for neurologic impairment and traumatic injury [2–5].

Complication rates resulting from pediatric tracheostomy vary by time, namely intra, early, and late postoperative and the inclusion or exclusion of serious events such as air leak syndrome, erosive wound infection, tube obstruction, accidental decannulation, respiratory arrest, and death [1, 3, 5–7].

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Overall, adverse event rates range between 10 and 63% among published reports and the frequency of complications is dependent on the study duration and severity of illness [3, 6–8]. Similarly, mortality rates in the pediatric population are influenced by age at the time of death, the underlying medical condition governing the indication for tracheostomy (range 2–59%) and direct association with the procedure (range 0–5.9%) [1–3, 6, 9–14]. Important predictors of mortality are prematurity, young age, cardiopulmonary and acquired neurologic disease, cancer, and children with medical complexity [1, 2, 9–14].

The literature regarding the contribution of respiratory-related illness, especially respiratory syncytial virus (RSV) to the morbidity incurred by children with a tracheostomy is extremely sparse and not clearly defined. Schweiger et al. briefly reported that among 123 children with a tracheostomy, 38 (31%) died. Pneumonia of undefined etiology and clinical complications resulted in the death of 11 children [6]. Yaneza et al. documented that respiratory tract infection occurred in 35.6% ($n = 85/239$) outpatient visits among children with a tracheostomy, but none of the patients were hospitalized [5]. Furthermore, the majority of the focus in regard to lower respiratory tract infections in children with a tracheostomy is on pathogenic bacteria [15, 16].

RSV is the main viral organism responsible for lower respiratory tract illness in children < 2 years of age worldwide and is associated with significant morbidity and mortality especially in children with complex medical conditions [17, 18]. In randomized clinical trials, palivizumab, a humanized monoclonal antibody, has been proven to be safe and effective in reducing RSV-related hospitalization (RSVH) in premature children and those with bronchopulmonary dysplasia and congenital heart disease [19, 20]. The objective of our study was to determine respiratory illness hospitalization (RIH) and RSVH hazard ratios in children with a tracheostomy compared with children prophylaxed for standard indications (SI; prematurity ≤ 35 weeks gestational age, bronchopulmonary dysplasia, and hemodynamically significant congenital heart disease) and complex medical disorders (CMD) in the Canadian RSV Evaluation Study of Palivizumab (CARESS).

Materials and methods

CARESS is a prospective, observational registry of children who received ≥ 1 dose of palivizumab from 2005 to 2017 in 32 Canadian sites [21]. The study was reviewed and approved independently, by each site's respective research ethics board. Informed consent was obtained from parents or legal guardians prior to patient enrollment. Baseline data were collected at the time of recruitment on patient demographics, prior medical history, neonatal course, and details of palivizumab administration. Interviews were subsequently conducted at

monthly time intervals with the subjects' primary caregivers during the respective RSV season. At each interview information regarding palivizumab administration, changes in baseline data, hospitalization for respiratory illness, diagnostic tests for RSV-related infection, reasons for discontinuation of prophylaxis, and incurred adverse events were recorded. In the event of a hospitalization, the relevant hospital records of the subject were reviewed by the site's research nurse for the indication for hospitalization, length of stay (regular ward versus intensive care), days on respiratory support and/or intubation, RSV diagnostic test results, and clinical diagnosis, as documented in the discharge summary.

Subjects, definitions, and outcomes

Any child who received ≥ 1 injection of palivizumab during the respective RSV season was eligible and was enrolled at the start of the RSV season following the first dose of palivizumab and preferably before the third injection, in order to secure sequential data collection and analysis. Children were excluded if they were receiving any other similar monoclonal antibody within a clinical trial, or if their parents or caregivers were unable to communicate in English or French.

All children with a tracheostomy, aged < 2 years, were eligible irrespective of the indication and underlying medical condition. The SI group comprised children currently approved for RSV prophylaxis by the majority of international consensus guidelines (premature infants ≤ 35 completed weeks gestational age, children with bronchopulmonary dysplasia, or hemodynamically significant congenital heart disease) [22–25]. Children with a CMD included those with serious medical conditions such as airway anomalies, pulmonary disorders, neuromuscular impairment, and immunodeficiency who were approved for off-label prophylaxis provincially on a case-by-case basis [26–28].

Adherence with the monthly protocol of injections was defined as an infant who received ≥ 5 or at least the expected number of palivizumab injections within the recommended time intervals between injections, during the respective RSV season [29]. Dosing intervals for palivizumab were defined as 16 to 35 days between the first and second injection and 30 ± 5 days for subsequent injections [29–31]. Children hospitalized with a symptomatic lower respiratory tract infection during the RSV season were tested for the presence of RSV infection. RSV positivity was confirmed by enzyme or immunofluorescent assay, real-time PCR or a positive viral culture from a posterior nasopharyngeal swab, wash or tracheal secretions. RIH was defined as all patients admitted with a respiratory tract illness that had both positive and negative RSV test results. The primary endpoints of this study were the hazard for first RIH and RSVH across the groups (tracheostomy, SI, and CMD).

Statistical analysis

Data were analyzed by standard descriptive methods, comparative statistics (chi-square, analysis of variance (ANOVA), and Student's t tests), and regression analysis using IBM SPSS Statistics 20 (IBM, Armonk, NY). Demographic comparisons between the tracheostomy, SI, and CMD groups were performed using ANOVA for continuous variables and chi-square tests for categorical variables. A p value < 0.05 was considered statistically significant.

RIH and RSVH rates were calculated for descriptive purposes. The RIH rate was determined by the number of children hospitalized for a respiratory illness divided by the total number of children. The RSVH rate was calculated as the incidence of RIH, multiplied by the number of RSV-positive subjects, and divided by the number of patients tested for RSV. Cox proportional hazards analyses were conducted to compare RIH and RSVH risks across groups and were adjusted for potential confounders (demographic and neonatal variables that were significantly different between the groups [$p < 0.05$]) that correlated to time to hospitalization using a backward conditional method. A sensitivity analysis was also conducted excluding all patients in the SI category (prematurity, bronchopulmonary dysplasia, and significant congenital heart disease) and those with pulmonary hypertension. This was performed to control for any known risk factors that enhance the risk for RSVH and to estimate the true risk of RIH or RSVH in the subjects with a tracheostomy.

Results

A total of 23,597 children were included between the 2005 and 2016 RSV seasons (n); tracheostomy (220), SI (19402), and CMD (3975). Of the 220 children with a tracheostomy who received prophylaxis in the SI group, 18 were premature, 30 had bronchopulmonary dysplasia, and 12 had significant congenital heart disease. One-hundred and sixty children with a tracheostomy had CMD.

Across the groups, children received on average, 4.4 ± 1.3 palivizumab injections per RSV season and 58.6% with a tracheostomy were perfectly adherent to the protocol (received ≥ 5 injections or at least the expected number of palivizumab injections within the recommended time intervals between injections per season) compared with 63.5% and 68.3% of the SI and CMD groups respectively. The overall perfect adherence rate among the three groups was 64.2%. The demographic and neonatal characteristics are shown in Tables 1 and 2. All the variables were significantly different between the study groups ($p < 0.05$). A greater proportion of tracheostomy infants were male, Caucasian, and had a family history of atopy compared with the SI and CMD groups. During the neonatal course, a higher proportion of children with a tracheostomy required respiratory support, oxygen therapy, and had surgery for patent ductus arteriosus and documented necrotizing enterocolitis and sepsis, than the SI and CMD groups. Children with a tracheostomy were older and bigger at enrollment and required longer durations of hospital stay, respiratory support, and oxygen therapy than the other sub-populations. Respiratory illness and RSV-related hospitalizations are described in Table 3. A total of 1655 children were hospitalized for 1970 respiratory-related events. Of the 220 subjects with a tracheostomy, 54 were hospitalized for a total of 74 respiratory illness events. 19.1% (316/1655) hospitalized children were RSV-positive; 4 (tracheostomy), 250 (SI), and 62 (CMD).

The characteristics of RSVHs among the recruited subjects are shown in Table 4. All 4 RSVHs in the children with a tracheostomy, who received prophylaxis, occurred in the second year of life. Of the RSV-positive children, there were significant group differences in the proportion who were admitted with apnea (tracheostomy, 25.0%; SI, 16.4%; and CMD, 4.8% [$\chi^2 = 6.5$, $p = 0.038$]) and bronchiolitis (tracheostomy, 50.0%; SI, 77.6%; and CMD, 69.4% [$\chi^2 = 6.3$, $p = 0.042$]) (Table 4). A higher proportion of RSV-positive children with a tracheostomy (25.0%) were hospitalized with respiratory arrest, compared with the SI (1.6%) and CMD groups (3.2%) [$\chi^2 = 10.1$, $p = 0.006$] (Table 4).

Cox proportional hazard analyses were adjusted for potential confounders as shown in Tables 1 and 2. The hazard plot for RIH is shown in Fig. 1. The RIH hazard of children with a tracheostomy was significantly higher compared with the SI group (HR = 1.8, 95% CI 1.1–3.0, $p = 0.022$). The RIH hazard was similar between the tracheostomy and CMD groups (HR = 1.3, 95% CI 0.7–2.2, $p = 0.369$). No significant difference in RSVH hazard was observed in children with a tracheostomy relative to the SI and CMD groups (tracheostomy versus SI: HR = 1.2, 95% CI 0.4–3.6, $p = 0.803$; tracheostomy versus CMD: HR = 1.2, 95% CI 0.4–3.9, $p = 0.751$).

A sub-analysis of the tracheostomy group was conducted to determine whether there were differences in the risk of RIH and RSVH after excluding children with established risk factors for RSVH (prematurity, bronchopulmonary dysplasia and congenital heart disease [$n = 60$], and those with pulmonary hypertension [$n = 7$]). The analysis was performed controlling for neonatal respiratory support, oxygen therapy, documented sepsis, enrollment age and weight, and gestational age. Tracheostomy subjects with risk factors ($n = 67$) had similar RIH and RSVH hazards relative to those without risk factors ($n = 153$) (RIH: HR = 1.3, 95% CI 0.7–2.5, $p = 0.361$; RSVH: HR = 8.2, 95% CI 0.5–130.2, $p = 0.136$).

Table 1 Demographic characteristics of the enrolled subjects

Demographic characteristics

	Trach ($n = 220$)	SI ($n = 19,402$)	CMD ($n = 3975$)	X^2 or H	p value
Male, n (%)	138 (62.7)	10,996 (56.7)	2164 (54.6)	9.8	0.008
Caucasian, n (%)	120 (74.5)	269 (68.0)	13,916 (72.0)	42.5	< 0.0005
Aboriginal, n (%)	7 (3.2)	796 (4.1)	123 (3.1)	0.2	0.010
Daycare attendance, n (%)	4 (1.8)	531 (2.7)	395 (10.0)	455.4	< 0.0005
Multiple birth, n (%)	26 (11.8)	5870 (30.3)	640 (16.1)	358.0	< 0.0005
Exposure to smoking, n (%)	55 (25.0)	5732 (29.5)	968 (24.4)	45.0	< 0.0005
Siblings, n (%)	143 (65.0)	12,261 (63.2)	2601 (65.4)	7.4	0.026
Siblings in daycare or school-aged, n (%)	76 (49.4)	5715 (44.6)	1328 (51.0)	36.6	< 0.0005
≥ 5 people in the household, n (%)	43 (19.5)	4860 (25.0)	842 (21.2)	29.6	< 0.0005
Family history of atopy, n (%)	99 (45.4)	7702 (39.8)	1688 (42.8)	13.9	0.001
Median enrollment age (months [IQR])	13.7 [6.9–21.9]	3.2 [1.5–5.8]	7.6 [3.1–14.2]	1812.8	< 0.0005
Median gestational age (week [IQR])	36.2 [31.3–38.1]	31.9 [29.1–34.1]	38.0 [35.0–39.1]	3665.4	< 0.0005
Median enrollment weight (g [IQR])	8405.0 [6335.0–10,257.5]	4020.0 [2820.0–6042.0]	7140.0 [4900.0–9250.0]	2826.6	< 0.0005

CMD, complex medical disorders; *IQR*, interquartile range; *SI*, standard indications; *Trach*, tracheostomy

All variables were significantly different between the groups ($p < 0.05$) and adjusted for in subsequent analyses

Discussion

Published reports on respiratory tract infections with specific etiology causing hospitalization in children with a tracheostomy have been limited [5, 6]. More recently, Shay et al. [32] noted that upper respiratory disease featured among the top ten admission diagnosis in children with a pediatric tracheotomy ($n = 14/373$; 3.8%) among which 43 (11.5%) had pneumonia and 43 (11.4%) were classified as other lower respiratory disease but the pathogenic organisms were not reported. Akangire et al. [33] conducted a retrospective cohort study on 110 infants aged < 2 years with a tracheostomy who were ventilator dependent. Tracheostomies were performed principally for bronchopulmonary dysplasia (28%) and other

acquired chronic pulmonary disease (23%). The main cause for re-hospitalization in the total cohort who received RSV prophylaxis was viral-related respiratory tract infections (26%). Rhinovirus/enterovirus was the most common virus isolated (37%), followed by RSV (9%). Tan et al. [34] reviewed 90 children from 2002 to 2016 with a tracheostomy among which 42 (46.7%) were hospitalized in a tertiary care center in Taiwan with 141 episodes of respiratory tract infections. Of this cohort, 125 (88.7%) had definite or possible bacterial pneumonia and 12 (8.5%) were classified as nonbacterial pneumonia, during a median follow-up of 3.15 years. A total of 20 viral episodes were identified among the cases of non-bacterial pneumonia, at a median age of 1.24 years, and the majority ($n = 12$; 60%) were due to RSV. The median age

Table 2 Neonatal characteristics of the enrolled subjects

Neonatal characteristics

	Trach ($n = 220$)	SI ($n = 19,402$)	CMD ($n = 3975$)	X^2 or F	p value
Days of neonatal stay (mean ± SD)	157.9 (± 149.6)	49.8 (± 65.1)	40.2 (± 71.4)	283.1	< 0.0005
Respiratory support, n (%)	180 (81.8)	12,342 (63.6)	1535 (38.6)	901.7	< 0.0005
Duration in days (mean ± SD)	112.2 (± 136.9)	23.0 (± 32.1)	24.3 (± 49.6)	494.7	< 0.0005
Oxygen therapy, n (%)	161 (73.2)	9913 (51.1)	1640 (41.3)	176.9	< 0.0005
Duration in days (mean ± SD)	113.4 (± 143.0)	34.8 (± 60.6)	28.4 (± 55.9)	132.6	< 0.0005
Documented necrotizing enterocolitis	11 (5.0)	617 (3.2)	77 (1.9)	20.7	< 0.0005
Surgery for patent ductus Arteriosus, n (%)	21 (9.5)	1000 (5.2)	95 (2.4)	67.4	< 0.0005
Documented sepsis, n (%)	70 (32.1)	2702 (14.0)	411 (10.3)	102.3	< 0.0005

CMD, complex medical disorders; *SI*, standard indications; *Trach*, tracheostomy

All variables were significantly different between the groups ($p < 0.05$) and adjusted for in subsequent analyses

Table 3 Unadjusted RIH and RSVH incidences

	Trach ($n = 220$)	SI ($n = 19{,}042$)	CMD ($n = 3975$)	Total ($n = 23{,}597$)
RIH	54	1212	389	1655
RIH incidence	24.5%	6.2%	9.8%	7.0%
Tested for RSV	49	1025	337	1411
RSVH	4	250	62	316
RSVH incidence	2.0%	1.5%	1.8%	1.6%

CMD, complex medical disorders; RIH, respiratory illness-related hospitalization; RSV, respiratory syncytial virus; RSVH, respiratory syncytial virus-related hospitalization; SI, standard indications; Trach, tracheostomy

for tracheostomy was 3.05 months and the median duration from tracheostomy to infection was 0.57 years. Cerebral palsy and gastroesophageal reflux disease were independently associated with the occurrence of respiratory tract infections. In our study, the mean gestational age of the subjects was 34.7 weeks and enrollment for RSV prophylaxis occurred at a mean chronological age of 16.2 months. All of the children who underwent a tracheostomy had a more complex neonatal course with a 3.6-fold longer duration of hospital stay and higher morbidities in terms of oxygen and respiratory support requirement, sepsis, necrotizing enterocolitis, and surgical intervention for patent ductus arteriosus. The higher proportional morbidity in the children with a tracheostomy compared with the SI and CMD groups and the accompanying prematurity place them at greater risk for RSVH.

The overall RIH incidence in the Taiwan study [34] was 46.7% and the RSVH incidence of presumed untreated patients was 8.8% (12/137) compared with 24.5% and 2% respectively in the prophylaxed subjects in the CARESS study.

Since the demographics of the underlying conditions that necessitated a tracheostomy were similar to our study and the rest of the published, scientific literature, RSV prophylaxis during the RSV season (November to March in temperate climates) may possibly achieve an approximately 77% reduction in RSVH, but this needs to be validated in further prospective, well-designed clinical trials. Akangire. et al. reported an RSVH rate of 4% in a smaller sample size of infants with a tracheostomy who received palivizumab ($n = 100$) but adherence with the protocol was not delineated [33]. This would result in a corresponding reduction in RSVH of 54.5%, compared with 77% in our study but the former finding is similar to the overall reductions in RSVH reported in the randomized, placebo controlled IMpact study (55%) and the cardiac controlled trial (45%).

It is difficult to extrapolate the precise morbidities experienced by patients following RSVH in the Tan et al. [34] study since the data were broadly grouped under the umbrella of non-bacterial pneumonia. Based on the latter

Table 4 Characteristics of respiratory syncytial virus hospitalizations among the recruited subjects (total $n = 316$ RSV hospitalizations)

n = Number of RSV hospitalizations	Trach ($n = 4$)	SI ($n = 250$)	CMD ($n = 62$)	X^2 or F	p value
Apnea, n (%)	1 (25.0)	41 (16.4)	3 (4.8)	6.5	0.038
Bronchiolitis, n (%)	2 (50.0)	194 (77.6)	43 (69.4)	6.3	0.042
Decreased oxygen saturation, n (%)	3 (75.0)	106 (44.9)	34 (54.8)	2.6	0.268
Inability to maintain oral intake, n (%)	1 (25.0)	106 (42.4)	29 (46.8)	0.6	0.744
Pneumonia, n (%)	1 (25.0)	48 (19.2)	21 (33.9)	4.8	0.090
Respiratory arrest, n (%)	1 (25.0)	4 (1.6)	2 (3.2)	10.1	0.006
Respiratory distress, n (%)	3 (75.0)	170 (68.0)	52 (83.9)	2.6	0.274
Respiratory support required, n (%)	1 (25.0)	83 (33.2)	25 (40.3)	0.7	0.705
Days on respiratory support (mean ± SD)	0.3 ± 0.6	2.6 ± 6.8	2.0 ± 3.8	0.4	0.679
Length of hospital stay in days (mean ± SD)	5.0 ± 5.5	8.2 ± 11.0	7.1 ± 5.6	0.5	0.626
ICU admission, n (%)	2 (50.0)	71 (28.4)	15 (24.2)	1.8	0.404
ICU length of stay in days (mean ± SD)	1.5 ± 2.4	2.5 ± 7.0	1.4 ± 3.4	0.8	0.450
Intubation required, n (%)	1 (25.0)	30 (12.0)	7 (11.3)	0.7	0.692
Days on intubation (mean ± SD)	0.3 ± 0.5	1.4 ± 6.1	0.7 ± 2.7	0.5	0.621

$df = 2$; $p < 0.05$ is statistically significant

CMD, complex medical disorders; ICU, intensive care unit; RSV, respiratory syncytial virus; SI, standard indications; Trach, tracheostomy
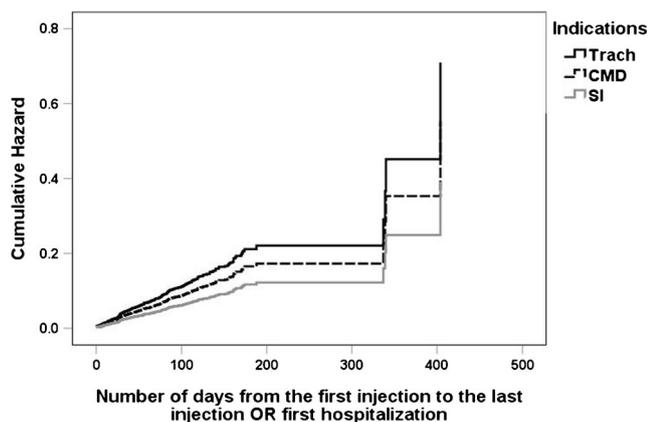
Fig. 1 Cox proportional hazard analysis of respiratory-illness hospitalization. RIH hazard of children with a tracheostomy was significantly higher compared with SI (HR = 1.8, 95% CI 1.1–3.0, p = 0.022). RIH hazard was similar between the tracheostomy and CMD groups (HR = 1.3, 95% CI 0.7–2.2, p = 0.369). CMD, complex medical disorders; RIH, respiratory illness hospitalization; SI, standard indications; Trach, tracheostomy

categorization, three patients (25%) required ventilator support; four (25%) were admitted to intensive care and the total duration of hospital stay was 5.67 ± 2.55 days. In our study, the children with a tracheostomy who received prophylaxis and were hospitalized with RSV were more commonly admitted with apnea. Of note, a significantly higher proportion presented with respiratory arrest (25%, p = 0.006). Morbidities incurred during the hospital course included higher but statistically insignificant admission to intensive care and intubation compared with the SI and CMD groups. The overall hazard for RIH was significantly higher in the children with tracheostomies compared with those who received prophylaxis for standard, approved indications and the RIH rate (24%) aligns with the rate reported by Akangire et al. [33] but was much lower than the almost 50% RIH rate documented by Tan et al. [34]. The RSVH rate in the tracheostomy group in this study was similar to the SI and CMD group suggesting that prophylaxis with palivizumab may have dampened the severity of RSV infection and corresponding related hospitalization.

It is important to emphasize that at the time of RSVH, all the children with tracheostomies enrolled in the CARESS study were symptomatic. With regard to bacterial infections, there are no established, evidence-based guidelines for the diagnosis of respiratory infections in children with tracheostomies. Multicenter studies indicate significant variation in the approach to diagnosis, care, and outcomes of these children following hospitalization [15, 16, 35–37]. Drysdale et al. [38] in a recent report on the interpretation of viral tests in children indicated that the detection of a virus especially by PCR in association with respiratory disease progression signifies that the virus is the cause of clinical disease. In our study, real-time

PCR has evolved as the diagnostic test of choice in recent years and has superseded other tests for RSV and other viral detection when indicated.

This is the largest, prospective, comprehensive study of RIH and RSVH in children with tracheostomies who received prophylaxis during the RSV season over a period of 11 years. The prospective design and close surveillance of the subjects for specific outcomes of interest across 32 sites affords generalizability across the population in Canada and is applicable to similar cohorts in other countries worldwide. The association of tracheostomies with apnea and respiratory arrest, albeit a small sample size due to the positive treatment effect of palivizumab, should raise awareness that when these children present with bronchiolitis and lower respiratory tract infection in the emergency room, local causes such as accidental decannulation and pre-existing pathology should first be excluded. A rapid screen for RSV should be performed and hospitalization should be considered for a child who is RSV-positive and clinically symptomatic.

There are several limitations that merit consideration. First, the absence of a control arm restricts an estimate of the true efficacy and benefit of palivizumab in the reduction of RSVH in this population. Second, although the majority of subjects with a tracheostomy were evaluated for RSV following hospitalization (91%), the absence of testing in 5 children, and the range of diagnostic tests conducted with varying sensitivity and specificity, may have resulted in an underestimate of the incidence of RSVH [38]. Third, the registry focuses on RSV-related illness following hospitalization, and data on other viral pathogens causing respiratory tract illness were not systematically collected. Fourth, children were enrolled in the CARESS registry at different time points which may have influenced the RSVH rate relative to the use of prophylaxis. However, this was accounted for by the Cox proportional analysis of either the number of days from the first to the last injection or time to first RIH and RSVH. There was a lack of homogeneity across the groups but the differences were adjusted in the Cox proportional hazards analysis. The heterogeneity illustrates real-world evidence of children with medical complexity who receive palivizumab. Of note, children with a tracheostomy are not indifferent to those with CMDs. Last, the sample size of the tracheostomy group was relatively small compared with the SI and CMD groups but is consistent with other published studies [3, 5, 6]. This may have compromised our ability to detect statistically significant differences in morbidities following RSVH between the groups.

Conclusion

This study involves the largest cohort of children with a tracheostomy who have received RSV prophylaxis. Children enrolled in the CARESS registry, who received

palivizumab during the RSV season, had an increased RIH hazard compared with those who received prophylaxis for SI. The finding of a similar RSVH hazard between the tracheostomy, SI, and CMD groups suggests that infants with a tracheostomy, independent of documented risk factors for RSVH, may benefit from palivizumab by reducing RSVH and attendant morbidities during the RSV season.

Compliance with ethical standards

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