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ORIGINAL ARTICLE

Respiratory syncytial virus (RSV) infection in children with medical complexity

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Abstract

Children with medical complexity (CMC) are vulnerable to respiratory illness hospitalization (RIH) and respiratory syncytial virus (RSV)-related hospitalization (RSVH) due to multisystem disorders and compromised airways. It is unknown whether RSV prophylaxis is effective, or if RSVH is associated with significant morbidities in CMC. The study objectives were to (1) determine the incidence of RSV-related infection in prophylaxed CMC during the first 3 years of life and (2) assess the burden of illness following RSVH. A single tertiary center, retrospective study, was conducted of CMC who received palivizumab during the 2012–2016 RSV seasons. Fifty-four subjects were enrolled; most received one (38.9%, $n = 21$) or two (57.4%, $n = 31$) seasons of prophylaxis (mean = 4.2 [SD = 1.24], palivizumab doses per season). The cohort comprised children with multiple medical conditions ($n = 22$, 40.8%), tracheostomy ($n = 18$, 33.3%), and invasive ($n = 10$, 18.5%) or non-invasive ($n = 4$, 7.4%) ventilation. Of the CMC, 24 were hospitalized 47 times for a viral-related respiratory illness. RSV incidence in the first 3 years of life was 7.4%. Viral-related RIH and RSVH rates were 44.4% ($n = 24/54$) and 1.9% ($n = 1/54$), respectively. Of the four RSV-positive children, one was ventilated for 9 days, two acquired nosocomial RSV that was managed on the ward, and one was discharged home under close complex care supervision. All four RSV-positive cases required additional oxygen during their illness. CMC experience a high viral-related RIH rate and palivizumab likely minimizes RSV-related events and associated morbidities. The efficacy of palivizumab in CMC, especially in those ≤ 3 years, should be prospectively evaluated.

Keywords Medical complexity · Children · Respiratory syncytial virus · Palivizumab · Outcomes

Introduction

Children with medical complexity (CMC) are a unique group that can be characterized by four essential domains, namely, family identified service needs associated with increased financial expenditure, potential lifelong chronic conditions associated with medical fragility that necessitate care and are accompanied by significant morbidity and mortality, substantial functional limitations which may involve technological assistance, and health care use that is dependent on multiple subspecialty services [1, 2]. CMC are especially vulnerable to respiratory illness (RI) and respiratory syncytial virus (RSV)-related infection due to multisystem disorders, compromised respiratory status, and medical fragility [3, 4]. RSV-related infection is common in children ≤ 2 years, and the incidence gradually declines in childhood with increasing age [5, 6]. The burden of RSV illness in children with general chronic medical conditions is significant and results in both morbidity and mortality [7]. In a systematic review conducted from 1995 to 2015 across 98 articles, RSV was associated with 12–63% of all acute respiratory infections and 19–81% of all viral-related hospitalizations in children. Overall length of hospital stay ranged from 2 to 11 days, and 2–12% of cases were admitted to intensive care with an estimated case-fatality rate of < 0.5% in industrialized countries [6]. Children with general chronic medical conditions experience the highest morbidity rates, and data indicate that in RSV-related deaths, comorbidities are present in approximately 28%, 47%, and 70% of children from low-income, lower middle-income, and upper middle-income countries, respectively. Children with pre-existing cardiac conditions, chronic lung disease, neurological impairment, and genetic or chromosomal disorders experience the

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highest RSV-related mortality rates [8–11]. Scheltema et al. noted that the median age for RSV-related deaths, majority of which occurred during the RSV season, was 5·0 months, 4 years, and 7 years in low and lower middle-income, upper middle-income, and high-income countries, respectively [11].

Palivizumab has been proven to be safe and efficacious in the reduction of RSV-related hospitalization (RSVH) in preterm infants and children with bronchopulmonary dysplasia and congenital heart disease [12–14]. However, its use for CMC is considered off-label and approval is country dependent and usually granted individually on a case-by-case basis. Several descriptive reports have confirmed that palivizumab can be utilized for RSV prevention in high-risk children with pre-existing medical conditions without serious adverse events [15–18]. Although RSV prophylaxis is prescribed for children with general complex medical disorders, it is unknown whether palivizumab is effective, or if RSV-related infection is associated with significant morbidities, in a well-defined CMC population. The objectives of this study were to (1) determine the incidence of RSV-related illness in CMC who received RSV prophylaxis during the first 3 years of life and (2) assess the burden of illness following RSVH.

Materials and methods

A retrospective chart review was conducted of CMC enrolled in the complex care program at a tertiary-care pediatric center in the central-west region of Ontario, Canada. CMC with tracheostomies, home mechanical ventilation (invasive and non-invasive) and other complex multisystem disorders, who had received palivizumab during the 2012–2016 RSV seasons (November 1–March 31) were included. Subjects with single, unique disorders such as cystic fibrosis and immunodeficiency were excluded since they do not meet the stringent criteria for CMC [1, 2].

Following enrollment, demographic data on each child who visited the clinic or was seen in the emergency room for a RI-related event was collected through the electronic medical records by two investigators. RSV positivity and the presence of other viral pathogens were confirmed on nasopharyngeal swabs, washes, or tracheal aspirates by enzyme, immunofluorescent assay, or polymerase chain reaction. If the child was hospitalized, data were assembled on length of hospital stay in the ward or intensive care unit, days on oxygen and respiratory support, and outcomes. Similar data was also recorded if an RSV-positive child was discharged to home care following a medical assessment. If the child's basic support included invasive or non-invasive ventilation, the time taken to return to baseline parameters either in the hospital or home was documented as being related to the respective viral illness. A viral-related RIH was categorized as one associated with a positive test for any viral pathogen detected by any of the laboratory methods. Similarly, a RSVH was classified as an admission to hospital with a RSV-positive test.

Data on the frequency of palivizumab injections, adherence to the monthly administration protocol, and any other complications associated with a respiratory infection event were excerpted from the clinic visits. Monthly follow-up visits to the clinic were continued until 1 month after the end of the relevant RSV season. Study subjects were considered adherent to the RSV prophylaxis protocol if they received either ≥ 5 or at least the expected number of palivizumab injections within the recommended time intervals between injections. This definition accounts for the full duration of the RSV season and the therapeutically effective inter-dose interval based on published pharmacokinetic studies [19–21]. The recommended time intervals for the study were 16–35 days between the first and second injections and 25–35 days between subsequent injections.

The study protocol was reviewed by the research ethics board of the hospital, and approval was granted with a waiver of patient consent.

Statistical analysis

Data were entered into the statistical software program IBM SPSS 25.0 and analyzed using descriptive statistics (frequencies for categorical data and mean [with standard deviation] as measures of central tendency and dispersion, respectively, for continuous data).

Results

Of the CMC who received RSV prophylaxis, 54 were enrolled out of the total cohort of 66 subjects followed by the Complex Care program at a tertiary center. The demographic characteristics of the enrolled subjects and those who were not enrolled are shown in Table 1. The two largest groups who received prophylaxis were those with multisystem disorders ($n = 22$, 40.8%) and children with a tracheostomy ($n = 18$, 33.3%), followed by those on invasive and non-invasive home ventilation ($n = 10$, 18.5%; $n = 4$, 7.4%), respectively. Most CMC received one (38.9%, $n = 21$) or two (57.4%, $n = 31$) seasons of prophylaxis based on the severity of the medical status at the start of the RSV season. Each child received a mean of 4.2 [SD = 1.24] doses of palivizumab per season and 78.7% received all of their expected injections within the appropriate time intervals.

Twelve children did not receive prophylaxis during the study period, and the reasons included parents declined treatment ($n = 2$), not meeting prophylaxis eligibility at time of enrollment in the complex care clinic ($n = 2$), transferred to another region ($n = 1$), no parent follow-up on acceptance of RSV prophylaxis ($n = 1$), and prophylaxis not offered due to

Table 1 Demographic characteristics of the prophylaxed ($n = 54$) versus unprophylaxed ($n = 12$) children with medical complexity

Characteristic	Treated with palivizumab	Not treated with palivizumab
Gender (male), *n* (%)	31 (57.4)	8 (66.7)
Gestational age (weeks)[a]	34.9 (5.58), 23–41	36.8 (3.19), 32–42
Birth weight (g)[a]	2307.4 (1017.70), 570–3770	2695.0 (850.46), 1170–3855
Chronological age at first time of prophylaxis (months)[a]	6.4 (7.36), 0–36	Not applicable

[a] Mean (SD), range

provider oversight, failure to prioritize need for RSV prophylaxis, or lack of coordination with RSV community clinics ($n = 6$). The outcomes of these children versus the CMC cohort who received prophylaxis ($n = 54$) are reported in Table 2.

Of the CMC who received prophylaxis, 24 were hospitalized 42 times for a viral-related RI. The types of viruses isolated at the time of hospital admission are shown in Fig. 1. The majority of all viruses identified were comprised of rhinovirus (41.7%, $n = 30$) and enterovirus (40.3%, $n = 29$). The hospitalization rates for any viral-related RI were 44.4% ($n = 24/54$) and the RSVH rate was 1.9% ($n = 1/54$). The overall RSV incidence in the first 3 years of life was 7.4% ($n = 4/54$). This included three breakthrough infections during prophylaxis (one in the first season and two during the second season) and one infection during the season following prophylaxis. Of the four RSV-positive children, one was admitted to the pediatric intensive care unit and ventilated for 9 days, two acquired nosocomial RSV while in hospital (one was transferred to intensive care for 3 days for high-flow oxygen and Bilevel Positive Airway Pressure and one was managed on the ward), and one was seen in the complex care clinic and successfully managed at home with close monitoring by the complex care team (Subject had DiGeorge syndrome, Tetralogy of Fallot, tracheostomy with home mechanical ventilation). All four subjects required additional supplemental oxygen during the RSV illness episode. The total length of hospital stay for the child who required intensive care was 213 days and was due to the initial RSV illness combined with family-identified service needs that arose successively because of the child's pre-existing chromosomal anomaly and multisystem complications. Similarly of the two children who acquired nosocomial RSV infection, one was hospitalized for 112 days and the other for 90 days. The latter child was admitted to intensive care for 5 days for high-flow oxygen and non-invasive ventilation. Overall, both children required prolonged hospitalization because of significant medical problems that necessitated multiple hospital-based and community service health care providers.

Discussion

There is growing awareness that the use of a non-standardized definition for CMC impacts comparison and reproducibility of data across studies. Cohen et al. developed a framework that incorporates the four domains which collectively defines CMC [1, 2]. Our study encompasses all four domains and was specifically designed to assess RSV-related outcomes in a well-defined CMC population both within and extern to the RSV season in the first 3 years of life, following RSV prophylaxis.

Children aged < 2 years with general complex medical conditions are prone to acute RI. Jama-Alol et al. found that the incident (incidence) rate ratios for respiratory infection were much higher in children with birth defects compared to those without defects, and was 3-fold greater in children with multiple compared to single birth defects [22]. In our study, after prophylaxis, the hospitalization rate for viral-related RI was 44.4% and 33.3% in the untreated subjects, which supports the findings in the literature [3, 22]. However, the rate is 3.7–4.9-fold higher than the rate (9%) reported among children with general chronic diseases who received prophylaxis, in the Canadian registry of palivizumab [16].

In a large Danish database study, Kristensen et al. reported that children with multisystem malformations, neuromuscular disorders, and acquired chronic diseases had an increased propensity for RSVH [4]. In a case-control study, Onoyama et al. indicated that children with severe motor and intellectual disabilities infected with RSV were at increased risk for ventilation and required oxygen for a longer duration (> 7 days; OR 5.3, $p = 0.03$) [23]. Similarly, children with neuromuscular impairments sustain major morbidities and mortality following RSV infection. Wilkesmann et al. found that 56% of their cohort with neuromuscular disorders had additional risk

Table 2 RIH and RSVH incidences among the prophylaxed versus unprophylaxed CMC cohort

	Treated ($n = 54$)	Untreated ($n = 12$)
Hospitalized (*n*)	24	4
RIH incidence (%)	44.4 (24/54)	33.3 ($n = 4/12$)
RSV tested (*n*)	24	4
RSV-positive (*n*)	4[a]	2
RSVH incidence (%)	1.9 (1/54)	16.7 (2/12)

CMC children with medical complexity, RIH respiratory illness-related hospitalization, RSVH respiratory syncytial virus-related hospitalization

[a] One hospitalized, two hospital acquired nosocomial infections, one managed at home (not hospitalized)

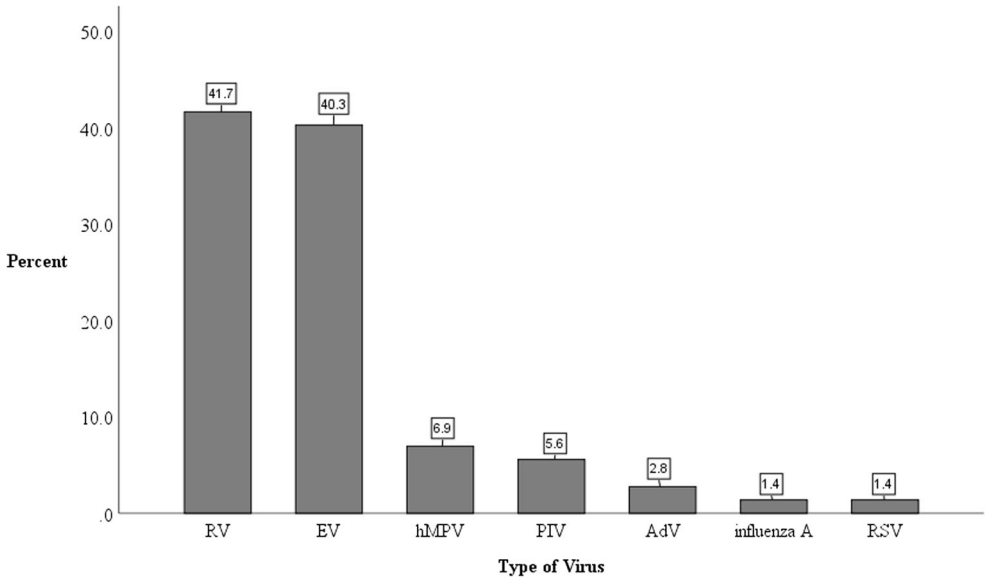

Fig. 1 Types of virus as proportion of all viruses identified on hospital admission ($n = 24$). AdV adenovirus, EV enterovirus, hMPV human metapneumovirus, PIV parainfluenza, RV rhinovirus, RSV respiratory syncytial virus. Note that some of the patients had multiple viruses detected which are included in the percentages as shown

factors for RSV such as congenital heart and chronic lung disease, prematurity, and immunodeficiency [24]. Following hospitalization at a median age of 14 months, the patients experienced a statistically significant higher rate of seizures and a higher proportion required intensive care admission and mechanical ventilation compared to the control group. The overall mortality rate was also significantly higher in the group with neuromuscular disease (5.5% versus 0.2%; $p < 0.001$). Manzoni et al. conducted a systematic review of 58 articles from 1995 to 2015, of the risk and burden of RSV infection in children with chronic diseases, some of whom had neurologic and neuromuscular impairments, cancer, congenital malformations, and chromosomal and non-chromosomal aberrations that may in part meet the definition of CMC [7]. The authors concluded that RSV caused a significant health care burden, but the quality and strength of evidence was deemed low because of the relatively small sample size in majority of the studies. The overall case fatality rate attributed to RSV infection in children with pre-existing disease in developed Western countries is < 1% (RR 2.4, 95% CI 2.0–2.8) [7]. The age of RSV-related death in upper and high-income countries ranges between 4 and 7 years, which indicates that some CMC aged ≥ 2 years remain at risk for both morbidity and mortality [11]. With the increasing use of palivizumab and influenza vaccine in young CMC, the predominant viruses causing hospitalization in our study were rhinovirus and enterovirus followed by lower proportions of other viral pathogens commonly associated with severe lower respiratory tract illness [25, 26].

The true incidence of RSVH in CMC is difficult to estimate since there are no specific reports that pertain to this population. In children with general chronic diseases who do not fulfill all of the criteria for CMC, RSVH rates independent of prophylaxis range from 7 to 19% in children with Down syndrome, 1.1–18.7% in immunocompromised children, and 6.4–18.1% in those with cystic fibrosis [7]. There are very few reports of RSVH rates among children with general chronic diseases who received prophylaxis, and they range from 2.4% ($n = 952$) [16] to 4.3% ($n = 4856$) [15] compared to the lower rate of 1.9% ($n = 54$) in our CMC study. Of note, only 3.7% ($n = 2$) of our CMC cohort received prophylaxis for three RSV seasons, and this is in keeping with the epidemiological pattern and severity of RSV illness that steadily declines after 2 years [5, 27–29]. However, in our study, the RSV incidence rate of 7.4% in CMC aged ≤ 3 years indicates that this cohort may remain at risk beyond 2 years of age and palivizumab may reduce the severity of illness since the RSVH rate overall was 8.8-fold lower compared to the untreated subjects. Our findings also suggest that if CMC do acquire RSV following prophylaxis that the severity of illness may be ameliorated since the majority of children only required additional oxygen and one was managed at home. CMC are also at risk for nosocomial infection, and such acquisition in children with pre-existing medical disorders is significantly associated with greater morbidity and independent mortality [9, 30–32].

There are several limitations of our study to be noted. First, not all CMC subjects were captured since prophylaxis is governed by severity of disease and is in the majority age limited to < 2 years based on the Ministry of Health and long-term care RSV guidelines in Ontario. Second, the retrospective, descriptive study design limited the amount of retrievable data for analysis. Third, although all the subjects were tested for RSV, the diagnostic yield may have been underestimated based on the sensitivity and specificity of the RSV diagnostic test conducted. Fourth, the overall sample size is relatively small, which limited our ability to assess RSVH rates in sub-populations such as those with tracheostomies and invasive versus non-invasive mechanical ventilation.

Last, the absence of a well-defined control group a priori makes it difficult to accurately determine the efficacy of palivizumab in CMC, although the low RSVH rate with treatment aligns with the reduced RSVH rates published in other studies [15, 16] and the randomized trials [12, 13].

Conclusion

This is the first study to report on the incidence of RI events, and RSV infection in hospitalized CMC aged < 3 years. The findings indicate that CMC experience very high rates of viral-related RI which necessitate hospitalization and that RSV prophylaxis may be of benefit in reducing RSVH and its attendant morbidities. Larger prospective studies of CMC are necessary to accurately estimate the effect of palivizumab on RSVH in this population and to target which sub-groups of infants among this wide spectrum of disorders will benefit most from prophylaxis, cost-effectively.

Author's contribution AL, JD, LE, MLB, BP: conception and design, analysis and interpretation of data, drafting of article;
MLB, BP, AL: analysis and interpretation of data;
All: reviewed manuscript and facilitated revisions;
All: final approval of manuscript and assume public responsibility for the content.

Compliance with ethical standards

Conflict of interest BP has received investigator initiated research funding and compensation as advisor or lecturer from AbbVie Corporation. The rest of the authors have no conflicts of interest to declare. No honorarium, grant, or other form of payment was received by any of the authors to produce the manuscript.

Ethical approval The study was approved by The Hamilton Integrated Research Ethics Board, and patient consent was waived because of the anonymized, retrospective database study design.

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