Respiratory Syncytial Virus Prophylaxis in Infants With Congenital Diaphragmatic Hernia in the Canadian Respiratory Syncytial Virus Evaluation Study of Palivizumab, 2005–2017

Doyoung Kim,[1] Mahwesh Saleem,[1] Bosco Paes,[2] Ian Mitchell,[3] and Krista L. Lanctôt[1]

[1]Medical Outcomes and Research in Economics Research Group, Sunnybrook Health Sciences Centre, University of Toronto, and [2]Department of Pediatrics, McMaster University, Hamilton, Ontario and [3]Department of Pediatrics, University of Calgary, Alberta, Canada

Background. Infants with congenital diaphragmatic hernia (CDH) are at an increased risk of respiratory morbidity from recurrent respiratory tract infections including those from respiratory syncytial virus (RSV). Prospective studies on RSV prophylaxis in CDH infants are limited. We determined the risk of respiratory illness– and RSV-related hospitalizations (RIH and RSVH, respectively) among infants prophylaxed for CDH, standard indications (SIs) and those without increased risk (NR).

Methods. The prospective Canadian Respiratory Syncytial Virus Evaluation Study of Palivizumab (CARESS) registry was searched for infants who received palivizumab during 12 RSV seasons (2005–2017) in Canada. Cox proportional hazards analyses were conducted to compare RIH and RSVH risks across the groups adjusted for potential confounders.

Results. In total, 21 107 infants (201 CDH, 389 NR, and 20 517 SI) were included. RIH incidences were 10.0% (CDH), 2.1% (NR), and 6.2% (SI). CDH patients had a significantly higher RIH hazard compared with NR (hazard ratio [HR], 3.6 [95% confidence interval {CI}, 1.5–8.8]; $P = .005$) but not SI (HR, 1.2 [95% CI, .8–2.0]; $P = .379$). RSVH incidences were 0.6%, 0.3%, and 1.5% for CDH, NR, and SI, respectively. RSVH risk was similar across groups (SI: HR, 0.0, $P = .922$; NR: HR, 0.0, $P = .934$).

Conclusions. CDH infants had a 3-fold increased risk of RIH compared to NR but not SI infants. RSVH risk was similar with low RSVH incidences across all groups, implying that CDH infants may benefit from palivizumab during the RSV season, similar to other high-risk groups.

Clinical Trials Registration. NCT00420966.

Keywords. palivizumab; respiratory syncytial virus; RSV; congenital diaphragmatic hernia; outcome.

Respiratory syncytial virus (RSV) is a viral pathogen causing acute lower respiratory tract illness and affects nearly 90% of children by the age of 2 years [1]. RSV lower respiratory tract infections are associated with increased subsequent healthcare resource utilization, morbidity, and mortality [2–4], especially in premature infants and those with chronic lung disease and significant congenital heart disease [5–7]. Furthermore, infants with preexisting medical conditions have the highest case fatality rates [5, 6].

Congenital diaphragmatic hernia (CDH) occurs when the diaphragm fails to close during prenatal development, causing the abdominal organs to migrate into the chest. Consequently, fetal lung development and maturation are compromised, resulting in pulmonary hypoplasia [8]. Approximately 1 in 2000–3000 infants [8–10] is born with CDH and these infants are at high risk for respiratory morbidity. Accordingly, infants with CDH have been reported to be at an increased risk for recurrent respiratory tract infections, including severe RSV infection, because of preexisting pulmonary hypoplasia, persistent pulmonary hypertension, and obstructive lung function after neonatal discharge [5, 11–16].

Palivizumab is a humanized monoclonal antibody that has been approved for prophylaxis against RSV in high-risk infants [6, 7]. The Canadian Paediatric Society [7] states that children with chronic pulmonary disease other than chronic lung disease should not be routinely offered prophylaxis. However, prophylaxis may be considered for children <2 years of age who are on home oxygen, have had a prolonged hospitalization for severe pulmonary disease, or are severely immunocompromised. While limited evidence

suggests that palivizumab may be beneficial in reducing the severity of RSV illness and RSV-related hospitalization (RSVH) [14, 17], the impact of RSV prophylaxis in CDH in early infancy remains unclear. Therefore, the primary objective of this article was to determine the risk of respiratory illness–related hospitalization (RIH) and RSVH in infants with CDH who received RSV prophylaxis with palivizumab during the RSV season compared to infants prophylaxed for standard indications (SIs) and those who received prophylaxis but were considered not at increased risk (NR).

METHODS

The Canadian Respiratory Syncytial Virus Evaluation Study of Palivizumab (CARESS) was a prospective, longitudinal, observational cohort study of high-risk infants prophylaxed with palivizumab between the 2005 and 2017 RSV seasons across 32 participating sites. On a monthly basis, the registry tracked palivizumab usage and adherence to monthly injections during the RSV season (November–March) and evaluated respiratory illness–related events that led to hospitalization. These events included apnea, bronchiolitis, decreased oxygen saturation, pneumonia, respiratory distress, and respiratory arrest. Prior to enrollment, written informed consent forms in English or French, outlining the use and disclosure of the patient's personal and health data, were collected from the parents or legal guardian. Any infant who received at least 1 dose of palivizumab during the RSV season was eligible for enrollment. Infants were excluded if they were receiving palivizumab or any other monoclonal antibody as part of a clinical trial during the study period, or if their parents or legal guardian could not communicate in English or French. Eligible children were enrolled after the first injection and before the third injection to facilitate data collection. Patient demographics, neonatal course events, prior medical history, and details of palivizumab administration were obtained at baseline. Follow-up telephone interviews were conducted monthly to collect data on palivizumab utilization and adherence, changes in baseline data, adverse and respiratory illness events, and related complications.

Following a hospitalization, details of the hospital stay were extracted from the patient's medical record after parental or legal guardian approval. These details included diagnoses at the time of admission, duration of hospital stay, requirement for respiratory support (invasive and noninvasive), oxygen therapy, intubation, mechanical ventilation, and laboratory confirmation of RSV. RSV diagnosis was determined using polymerase chain reaction, enzyme or immunofluorescent assay, or viral culture on nasopharyngeal swabs, aspirates, or washes obtained from the patients during their hospital stay. An RIH with a positive RSV test was categorized as an RSVH.

Study Definitions

CDH was defined as the presence of abdominal organs in the thoracic cavity requiring surgery. Subjects presenting with CDH were selected from the CARESS database, regardless of any other coexisting medical disorders. In keeping with pediatric advisory guidelines, only children aged <2 years were included. The SI category comprised of infants with indications currently approved for palivizumab by the majority of international consensus guidelines (premature infants ≤35 completed weeks gestational age, children with bronchopulmonary dysplasia [chronic lung disease], and those with hemodynamically significant congenital heart disease) [6, 7, 18]. Infants in the NR group had no comorbidity and received RSV prophylaxis as part of multiple births of which 1 sibling qualified for prophylaxis. RSV prophylaxis was provided to healthy NR infants as a protective strategy to reduce RSV transmission to high-risk, multiple-birth siblings [19].

Adherence to palivizumab was defined as receipt of ≥5 or at least the expected number of injections during the RSV season, and within the recommended time intervals between doses [20]. Expected number of injections was calculated as 1 injection per month from the first injection to the last month of the RSV season. The accepted time intervals for palivizumab administration were 16–35 days between the first and second injection and 25–35 days between the remaining injections.

Statistical Analysis

All statistical analyses were conducted using SPSS version 25.0 software (IBM Corporation, Armonk, New York). Baseline demographic and neonatal characteristics were compared between the CDH, SI, and NR groups using the Pearson χ^2 test for categorical variables and analysis of variance for continuous variables. Additionally, nonparametric continuous demographic variables are reported using median and interquartile range, and Kruskal-Wallis tests were performed to compare these variables between groups. A P value < .05 was considered to be statistically significant for all analyses.

RIH and RSVH rates were calculated for descriptive purposes. Cox proportional hazards analyses using a backwards conditional method were conducted to compare RIH and RSVH risks between children with CDH vs the SI and NR groups, respectively. Hazards for RIH and RSVH were estimated by the number of days from enrollment to the patient's first RIH or RSVH. Results for each individual regression are reported as hazard ratios (HRs) with 95% confidence intervals (95% CI), and P values.

RESULTS

A total of 21 107 infants were included (201 CDH, 389 NR, and 20 517 SI infants). Overall, infants received 4.3 ± 1.4 injections, which differed across groups; the mean number of injections ± standard deviation for CDH, NR, and SI was

4.6 ± 1.2, 4.6 ± 1.1, and 4.3 ± 1.4, respectively (χ^2 = 13.2, degrees of freedom [df] = 2; P < .0005). Cumulatively, 13 583 (64.4%) of children were perfectly adherent, meeting criteria for both interinjection interval and expected number of injections. Perfect adherence was different across the study groups: 63.2%, 74.6%, and 64.2%, for CDH, NR, and SI, respectively (χ^2 = 18.0, df = 2; P < .0005). Table 1 depicts the demographic comparisons between the groups, where all of the variables, except school-aged siblings or siblings in daycare and family history of atopy, were statistically significant (P < .05). These variables were therefore, adjusted for in subsequent Cox proportional hazards analyses. Higher proportions of CDH children were male, in day care, and of older gestational age, and had a higher birth weight compared to the NR and SI groups.

The neonatal characteristics of the CDH, NR, and SI groups are described in Table 2. Greater proportions of CDH infants required respiratory support and oxygen therapy than the other subpopulations. They also experienced longer duration of hospital stay and episodes of sepsis.

Table 3 describes RIH and RSVH incidences across the study populations. A total of 1292 children were hospitalized 1538 times. Children were hospitalized from 1 to 6 times. Cox proportional hazard analyses were conducted to compare the risk of RIH and RSVH across groups while controlling for potential confounders listed in Table 1 along with adherence and number of injections. The RIH hazard of CDH patients was significantly higher compared to NR but similar to SI, as shown in Figure 1 (NR: HR, 3.6 [95% CI, 1.5–8.8], P = .005; SI: HR, 1.2 [95% CI, .8–2.0], P = .379). On the other hand, CDH infants were at a similar risk for RSVH as those prophylaxed for SIs (HR, 0.0; P = .922) and NR infants (HR, 0.0; P = .934) (Figure 2).

Gestational age was a significant predictor of risk for RSVH (HR, 0.96 [95% CI, .9–1.0], P = .007); the risk of RSVH was reduced by 4% with each week increment in gestational age.

DISCUSSION

In the present study, CDH infants had an approximately 4-fold increased risk of RIH compared to nonrisk infants but not those with SI. RSVH risk was similar across all groups, suggesting that prophylaxis is beneficial for risk reduction in CDH.

Infants with CDH generally present with complications including pulmonary hypoplasia and pulmonary hypertension [8, 10, 16, 17] as well as chronic lung disease, neurological, gastrointestinal, and musculoskeletal sequelae, which places them at a higher risk for respiratory illness during infancy and early childhood [8, 17, 21]. Koziarkiewicz et al [16] reported that 34% of children with CDH repair experienced an average of 6–8 recurrent respiratory tract infections a year, which they attributed to lower perfusion of the ipsilateral lung. Overall, the incidence of respiratory symptoms coupled with recurrent infections has been estimated to range from 24% to 60% [15, 21–23]. Our study definitively confirms that infants with CDH have an increased hazard for RIH in the first 2 years of life compared with healthy infants, but the risk is similar to that of SI infants.

Survivors with CDH are likely prone to RSV infection and subsequent hospitalization because of both preexisting and incurred pulmonary morbidity during the neonatal course. This study also identified lower gestational age as a predictor of increased risk for RSVH, which was expected as gestational age is an independent risk factor for RSVH [2]. However, information regarding the true incidence of RSVH in infants

Table 1. Demographical Comparisons Across Groups

Characteristic	CDH (n = 201)	NR (n = 389)	Standard Indication (n = 20 517)	χ^2 or H Test	P Value
Male sex[a]	126 (62.7)	158 (40.6)	11 638 (56.8)	43.7	**< .0005**
White[a]	147 (73.1)	298 (76.6)	13 892 (67.7)	16.4	**< .0005**
Aboriginal[a]	4 (2.0)	2 (0.5)	851 (4.1)	15.2	**.001**
Day care attendance[a]	17 (8.5)	23 (5.9)	536 (2.6)	40.6	**< .0005**
With siblings[a]	110 (54.7)	371 (95.4)	13 044 (63.6)	175.4	**< .0005**
With siblings in day care or school-aged[a]	54 (41.5)	123 (46.1)	6135 (44.1)	0.8	.683
Exposure to smoking[a]	36 (17.9)	86 (22.1)	6029 (29.4)	22.2	**< .0005**
Household crowding[a]	31 (15.4)	140 (36.0)	5101 (24.9)	35.1	**< .0005**
Family history of atopy	80 (40.0)	151 (39.2)	8138 (39.8)	0.1	.968
Multiple birth[a]	11 (5.5)	386 (99.2)	6234 (30.4)	903.1	**< .0005**
Enrollment age, mo, median (IQR)[a]	5.4 (2.3–12.6)	6.4 (1.6–11.8)	3.1 (1.5–5.7)	113.4	**< .0005**
Gestational age, wk, median (IQR)[a]	39.0 (37.9–40.0)	34.1 (32.0–35.7)	31.9 (29.1–34.1)	496.9	**< .0005**
Birth weight, g, median (IQR)[a]	3150.0 (2743.0–3458.3)	2035.0 (1568.0–2450.0)	1636.0 (1165.0–2160.0)	420.9	**< .0005**
Enrollment weight, g, median (IQR)[a]	6280.0 (4522.5–8320.0)	6800.0 (3550.0–8860.0)	4000.0 (2800.0–6000.0)	281.0	**< .0005**

Data are presented as no. (%) unless otherwise indicated. All variables had degrees of freedom = 2. Boldface values indicate statistical significance (P < .05).

Abbreviations: CDH, congenital diaphragmatic hernia; IQR, interquartile range; NR, not at increased risk.

[a]Variables adjusted for in the Cox regression analyses.

Table 2. Neonatal Characteristics Across Groups During the Hospital Course

Characteristic	CDH (n = 201)	NR (n = 389)	Standard Indication (n = 20 517)	χ² or F test	P Value
Days of neonatal stay, mean ± SD	57.0 ± 67.1	33.9 ± 48.1	50.0 ± 64.3	12.6	**< .0005**
Respiratory support	189 (94.0)	151 (38.8)	13 170 (64.2)	186.1	**< .0005**
Duration, d, mean ± SD	23.3 ± 31.9	19.8 ± 25.5	23.1 ± 33.0	0.7	.481
Received oxygen therapy	169 (84.1)	116 (29.8)	10 344 (50.4)	157.1	**< .0005**
Duration, d, mean ± SD	40.6 ± 66.6	28.1 ± 43.7	34.6 ± 60.4	1.5	.222
Documented necrotizing enterocolitis	1 (0.5)	4 (1.0)	634 (3.1)	10	**.007**
Surgery for patent ductus arteriosus	6 (3.0)	7 (1.8)	1036 (5.0)	10.2	**.006**
Documented sepsis	47 (23.4)	29 (7.5)	2804 (13.7)	28.8	**< .0005**

Data are presented as no. (%) unless otherwise indicated. All variables had degrees of freedom = 2. Boldface values indicate statistical significance ($P < .05$).

Abbreviations: CDH, congenital diaphragmatic hernia; NR, not at increased risk; SD, standard deviation.

with CDH is limited. In a large Danish RSV database study of children aged 0–23 months, 9 (11.1%) children with CDH were identified with an incidence rate ratio of 1.41 (95% CI, .66–3.01) for RSVH ($P = .38$) [24]. In a recent study, 6.9% of the CDH study population (n = 19) was hospitalized with RSV infection with an RSVH rate of 13.7% for the first RSV season and 20.7% over 2 seasons [14]. This RSVH rate was similar to the study by Masumoto et al [12], who reported a rate of 23.8%. In comparison, this study found an RSVH rate of 0.6% in infants with CDH who received prophylaxis, similar to rates of RSVH risk in unprophylaxed healthy term infants (0.8%–2.0%) [25–29]. Unfortunately, no studies to date have examined the role of palivizumab in healthy term infants. However, the motavizumab randomized trial conducted in healthy term Native American infants indicated that there was an 87% relative reduction in RSVH (11% placebo; 2% motavizumab) [30]. Assuming that palivizumab may have an equal efficacy in CDH, our study may indicate a possible 94.5% reduction in RSVH in children with CDH (11% placebo; 0.6% palivizumab). These findings suggest that RSV prophylaxis in infants with CDH may be warranted. Prophylaxis may also be beneficial in attenuating the risk of RSV-induced recurrence of the hernia postsurgical repair in up to 40% of infants with CDH [12].

While palivizumab was associated with a lower rate of RSVH in this study, adherence was lower in infants with CDH compared

Table 3. Hospitalizations due to Respiratory Illness or Respiratory Syncytial Virus in Patients With Congenital Diaphragmatic Hernia Versus Other Groups

Characteristic	CDH (n = 201)	NR (n = 389)	Standard Indication (n = 20 517)
No. of RIHs	20	8	1267
RIH incidence, %	10.0	2.1	6.2
RSV tested, no.	18	7	1074
No. of RSVHs	1	1	266
RSVH incidence, %	0.6	0.3	1.5

Abbreviations: CDH, congenital diaphragmatic hernia; NR, not at increased risk; RIH, respiratory illness–related hospitalization; RSV, respiratory syncytial virus; RSVH, respiratory syncytial virus–related hospitalization.
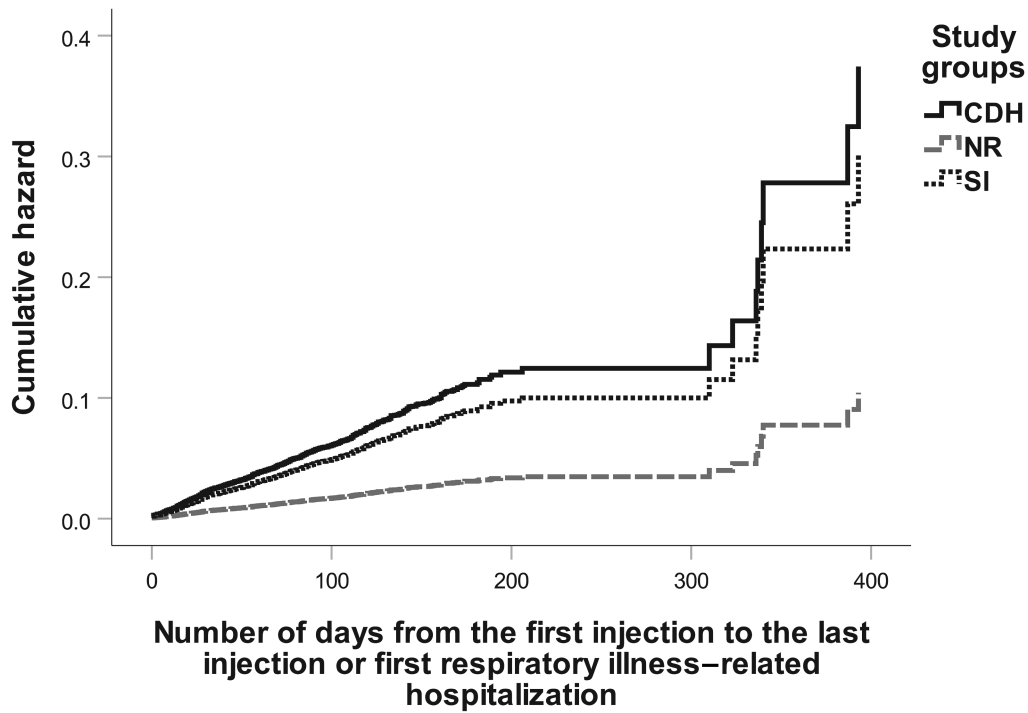
with NR infants. Scheduled visits to multidisciplinary healthcare professionals during follow-up may have compromised the parents' ability to maintain the recommended interdose injection schedule for prophylaxis. It is also possible that parents with twins (NR category) are more likely to maintain their scheduled visits, recognizing that RSV has a broader impact on the whole family. However, this is speculative and should be explored in future studies.

The incidence of off-label use of palivizumab in CDH is unclear and limited to a few case series without a control group [14, 17]. Muratore et al [17] documented that prior to the use of palivizumab, 2 patients with CDH (25%) required admission to intensive care but, following the adoption of prophylaxis in 1997, 36% (8/22) patients aged <3 years were seen in the emergency room with respiratory distress and were discharged. RSV positivity in the affected subjects was not stated. Resch et al showed no differences in hospitalizations due to RSV in infants who received palivizumab (0%) compared to those without prophylaxis (5%) [14]. However, the Italian neonatal society indicated that the evidence for the use of palivizumab in CDH infants is low (level of evidence, V; strength of recommendation, B) but should be carefully considered for patients with severe disease during the RSV epidemic season [18]. The definition of severe disease was not specified. In addition, a Delphi study [31] and recommendations by the Section on Surgery and Fetus Newborn Committee in the United States [23], indicate that palivizumab should be used for the prevention of RSV in infants <2 years of age with CDH and associated chronic respiratory insufficiency or chronic lung disease. In line with these recommendations, our study indicates that infants with CDH remain at risk for RSVH in the first 2 years of life. Canadian pediatricians currently target infants for RSV prophylaxis at a provincial level, on a case-by-case basis based on operative repair performed at <6 months rather than 12 months prior to the onset of the RSV season [31], to minimize the potential risk of CDH recurrence. In some provinces, the request for prophylaxis for children with CDH also requires a referral letter from a pulmonologist to indicate that the child has residual respiratory compromise postsurgery.

Figure 1. Cox proportional hazards analysis of respiratory illness–related hospitalizations. CDH vs NR: hazard ratio (HR), 3.6 (95% confidence interval [CI], 1.5–8.8; *P* = .005); CDH vs SI: HR, 1.2 (95% CI, 0.8–2.0; *P* = .379). Analysis was adjusted for appropriate demographic variables (see Table 1). Abbreviations: CDH, congenital diaphragmatic hernia; NR, not at increased risk; SI, standard indication.
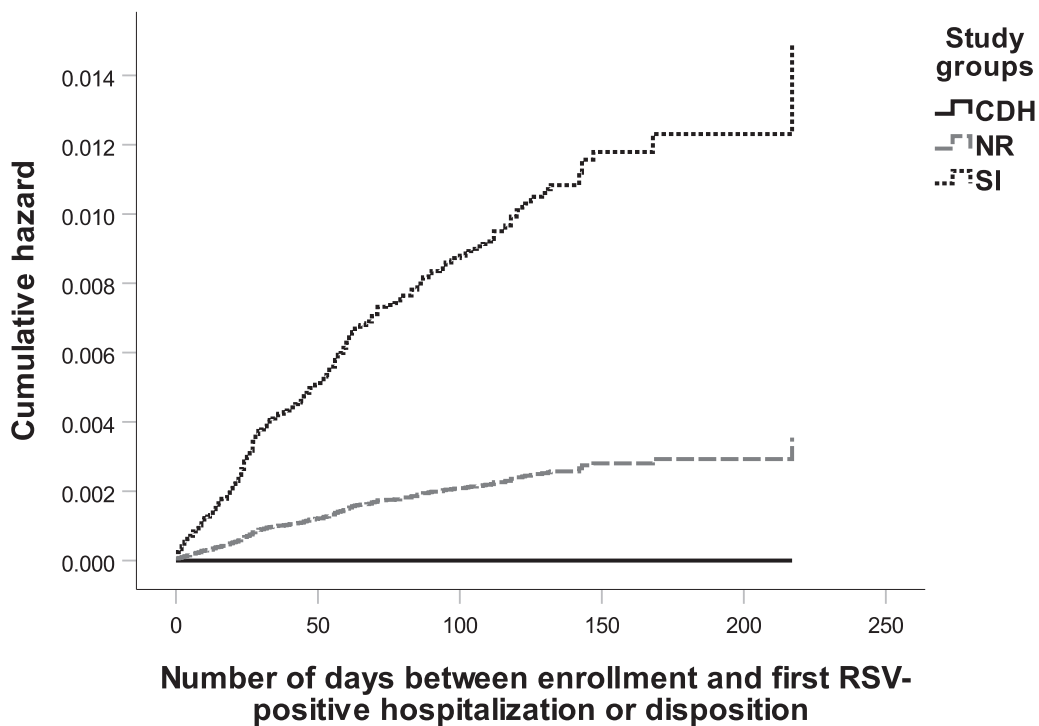
Figure 2. Cox proportional hazards analysis of respiratory syncytial virus–related hospitalization. CDH vs SI: hazard ratio (HR), 0.0; *P* = .922. CDH vs NR: HR, 0.0; *P* = .934. Analysis was adjusted for appropriate demographic variables (see Table 1). Abbreviations: CDH, congenital diaphragmatic hernia; NR, not at increased risk; SI, standard indication.

Our study has several limitations that merit consideration. First, not all patients with CDH were captured, as enrollment was voluntary. Overall, during the 2016–2017 season in the CARESS registry, 1369 of 1406 (97.4%) potential subjects were enrolled. RSV incidence was likely underestimated as not all patients were tested for RSV. In addition, while RIH risk may not be directly related to the value of palivizumab prophylaxis, it is an important outcome since children with CDH are at an increased risk for RIH. Also, despite the CDH sample size in this study being the largest in the published literature, it was still relatively small compared to the other groups, which could have limited our ability to accurately compare the risk of RSVH across the groups. Furthermore, in the absence of antenatal ultrasound data on the lung-thoracic transverse area ratio, other prenatal indicators and postnatal oxygenation and oxygen saturation indices that may be reflective of the degree of pulmonary hypoplasia in infants with CDH [32, 33], we are unable to recommend prophylaxis based on CDH severity. However, in a cohort of 100 infants with CDH, pulmonary problems constituted a source of morbidity, particularly in the first 2 years of life, even with mild CDH treated with gentler ventilation strategies [17]. Future studies should explore the efficacy of prophylaxis in relation to CDH severity to inform clinical practice. Last, the CARESS registry is an observational prospective study, without a control group. As in other groups of children sharing uncommon or rare diagnoses, a randomized double-blind, multicenter, placebo-controlled trial may be difficult to execute. Given the consequences of RSV infection in an already vulnerable group of children, even if a randomized controlled trial was feasible, clinicians may have ethical concerns about the use of placebo. Despite the absence of a control group, our prospective, multicenter study was rigorously conducted and showed a low incidence of RSVH compared to the other 2, relatively small retrospective, single-center studies [14, 17], suggesting that palivizumab worked effectively in these infants.

CONCLUSIONS

Infants with CDH in the CARESS registry who received palivizumab had an increased RIH hazard compared with the NR prophylaxed group. Similar RSVH hazard between CDH, NR, and the SI groups, coupled with low RSVH incidences, suggests that infants with CDH may benefit from palivizumab by reducing RSVH during the RSV season. This may consequently result in improved obstructive lung disease and restrictive lung function, but this remains to be determined sequentially through childhood, adolescence, and adulthood. Further large, prospective, long-term studies are awaited on the use of RSV prophylaxis in this population to confirm our findings.

Notes

References

1. Collins PL, Graham BS. Viral and host factors in human respiratory syncytial virus pathogenesis. J Virol **2008**; 82:2040–55.
2. Sampalis JS. Morbidity and mortality after RSV-associated hospitalizations among premature Canadian infants. J Pediatr **2003**; 143:S150–6.
3. Bont L, Checchia PA, Fauroux B, et al. Defining the epidemiology and burden of severe respiratory syncytial virus infection among infants and children in Western countries. Infect Dis Ther **2016**; 5:271–98.
4. Fauroux B, Simões EAF, Checchia PA, et al. The burden and long-term respiratory morbidity associated with respiratory syncytial virus infection in early childhood. Infect Dis Ther **2017**; 6:173–97.
5. Manzoni P, Paes B, Resch B, et al. High risk for RSV bronchiolitis in late preterms and selected infants affected by rare disorders: a dilemma of specific prevention. Early Hum Dev **2012**; 88(Suppl 2):S34–41.
6. American Academy of Pediatrics Committee on Infectious Diseases, American Academy of Pediatrics Bronchiolitis Guidelines Committee. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. Pediatrics **2014**; 134:415–20.
7. Robinson JL, Le Saux N; Canadian Paediatric Society, Infectious Diseases and Immunization Committee. Preventing hospitalizations for respiratory syncytial virus infection. Paediatr Child Health **2015**; 20:321–33.
8. Gabra HOS, Wilkinson DJ, Losty PD. Management of congenital diaphragmatic hernia. Paediatr Child Health **2018**; 28:18–21.
9. Russo FM, De Coppi P, Allegaert K, et al. Current and future antenatal management of isolated congenital diaphragmatic hernia. Semin Fetal Neonatal Med **2017**; 22:383–90.
10. Ameis D, Khoshgoo N, Keijzer R. Abnormal lung development in congenital diaphragmatic hernia. Semin Pediatr Surg **2017**; 26:123–8.
11. Bagolan P, Morini F. Long-term follow up of infants with congenital diaphragmatic hernia. Semin Pediatr Surg **2007**; 16:134–44.
12. Masumoto K, Nagata K, Uesugi T, et al. Risk of respiratory syncytial virus in survivors with severe congenital diaphragmatic hernia. Pediatr Int **2008**; 50:459–63.

13. Kamata S, Usui N, Kamiyama M, et al. Long-term follow-up of patients with high-risk congenital diaphragmatic hernia. J Pediatr Surg 2005; 40:1833–8.

14. Resch B, Liziczai K, Reiterer F, Freidl T, Haim M, Urlesberger B. Respiratory syncytial virus associated hospitalizations in children with congenital diaphragmatic hernia. Pediatr Neonatol 2018; 59:184–8.

15. Gischler SJ, van der Cammen-van Zijp MH, Mazer P, et al. A prospective comparative evaluation of persistent respiratory morbidity in esophageal atresia and congenital diaphragmatic hernia survivors. J Pediatr Surg 2009; 44:1683–90.

16. Koziarkiewicz M, Taczalska A, Piaseczna-Piotrowska A. Long-term follow-up of children with congenital diaphragmatic hernia—observations from a single institution. Eur J Pediatr Surg 2014; 24:500–7.

17. Muratore CS, Kharasch V, Lund DP, et al. Pulmonary morbidity in 100 survivors of congenital diaphragmatic hernia monitored in a multidisciplinary clinic. J Pediatr Surg 2001; 36:133–40.

18. Bollani L, Baraldi E, Chirico G, et al; Italian Society of Neonatology. Revised recommendations concerning palivizumab prophylaxis for respiratory syncytial virus (RSV). Ital J Pediatr 2015; 41:97.

19. Dotan M, Ashkenazi-Hoffnung L, Samra Z, et al. Hospitalization for respiratory syncytial virus bronchiolitis and disease severity in twins. Isr Med Assoc J 2013; 15:701–4.

20. Chan P, Li A, Paes B, Abraha H, Mitchell I, Lanctôt KL; CARESS Investigators. Adherence to palivizumab for respiratory syncytial virus prevention in the Canadian registry of palivizumab. Pediatr Infect Dis J 2015; 34:e290–7.

21. Peetsold MG, Heij HA, Kneepkens CM, Nagelkerke AF, Huisman J, Gemke RJ. The long-term follow-up of patients with a congenital diaphragmatic hernia: a broad spectrum of morbidity. Pediatr Surg Int 2009; 25:1–17.

22. Wischermann A, Holschneider AM, Hübner U. Long-term follow-up of children with diaphragmatic hernia. Eur J Pediatr Surg 1995; 5:13–8.

23. American Academy of Pediatrics Section on Surgery, American Academy of Pediatrics Committee on Fetus and Newborn; Lally KP, Engle W. Postdischarge follow-up of infants with congenital diaphragmatic hernia. Pediatrics 2008; 121:627–32.

24. Kristensen K, Hjuler T, Ravn H, Simões EA, Stensballe LG. Chronic diseases, chromosomal abnormalities, and congenital malformations as risk factors for respiratory syncytial virus hospitalization: a population-based cohort study. Clin Infect Dis 2012; 54:810–7.

25. Helfrich AM, Nylund CM, Eberly MD, Eide MB, Stagliano DR. Healthy late-preterm infants born 33-36 + 6 weeks gestational age have higher risk for respiratory syncytial virus hospitalization. Early Hum Dev 2015; 91:541–6.

26. Eriksson M, Bennet R, Rotzén-Ostlund M, von Sydow M, Wirgart BZ. Population-based rates of severe respiratory syncytial virus infection in children with and without risk factors, and outcome in a tertiary care setting. Acta Paediatr 2002; 91:593–8.

27. Gouyon JB, Rozé JC, Guillermet-Fromentin C, et al. Hospitalizations for respiratory syncytial virus bronchiolitis in preterm infants at <33 weeks gestation without bronchopulmonary dysplasia: the CASTOR study. Epidemiol Infect 2013; 141:816–26.

28. Gijtenbeek RG, Kerstjens JM, Reijneveld SA, Duiverman EJ, Bos AF, Vrijlandt EJ. RSV infection among children born moderately preterm in a community-based cohort. Eur J Pediatr 2015; 174:435–42.

29. Hall CB, Weinberg GA, Blumkin AK, et al. Respiratory syncytial virus–associated hospitalizations among children less than 24 months of age. Pediatrics 2013; 132:e341–8.

30. O'Brien KL, Chandran A, Weatherholtz R, et al; Respiratory Syncytial Virus (RSV) Prevention Study Group. Efficacy of motavizumab for the prevention of respiratory syncytial virus disease in healthy Native American infants: a phase 3 randomised double-blind placebo-controlled trial. Lancet Infect Dis 2015; 15:1398–408.

31. Gaboli M, de la Cruz ÒA, de Agüero MI, Moreno-Galdó A, Pérez GP, de Querol MS. Use of palivizumab in infants and young children with severe respiratory disease: a Delphi study. Pediatr Pulmonol 2014; 49:490–502.

32. Coughlin MA, Werner NL, Gajarski R, et al. Prenatally diagnosed severe CDH: mortality and morbidity remain high. J Pediatr Surg 2016; 51:1091–5.

33. Lakshminrusimha S, Keszler M, Kirpalani H, et al. Milrinone in congenital diaphragmatic hernia—a randomized pilot trial: study protocol, review of literature and survey of current practices. Matern Health Neonatol Perinatol 2017; 3:27.