

Time to Asthma-Related Readmission in Children Admitted to the ICU for Asthma

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Objectives: To compare the time to asthma-related readmissions between children with a previous ICU hospitalization for asthma and those with a non-ICU hospitalization and to explore predictors of time to readmission in children admitted to the ICU.

Design: Retrospective cohort study using a pan-Canadian administrative inpatient database from April 1, 2008, to March 31, 2014.

Setting: All adult and pediatric Canadian hospitals.

Subjects: Children 2–17 years old with a hospitalization for asthma.

Interventions: None.

Measurements and Main Results: A total of 26,168 children were hospitalized 33,304 times during the study period. The time to readmission was shorter in the ICU group compared with the non-ICU group (median time to readmission 27 mo in ICU vs 35 mo in non-ICU group). Preschool-aged children (hazard ratio, 1.48; 95% CI, 1.02–2.14) and increased length of stay (hazard ratio, 1.63; 95% CI, 1.17–2.27) were associated with a shorter time to readmission.

Conclusions: Children previously admitted to the ICU for asthma had a shorter time to asthma-related readmission, compared with children who did not require intensive care, underlining the importance of targeted long-term postdischarge follow-up of these children. Children of preschool age and who have a lengthier hospital stay are particularly at risk for future morbidity. (*Pediatr Crit Care Med* 2017; XX:00–00)

Key Words: asthma; intensive care; pediatrics; readmission; status asthmaticus

Asthma is a chronic inflammatory condition affecting approximately 10% of Canadian children (1, 2). In Canada, which has an universal healthcare system, asthma-related hospitalizations account for 10% and 8% of all hospitalizations in children 0–4 years old and 5–14 years old, respectively (1). Based on American and Australian studies, of all hospitalizations for asthma, 6–12% of children are admitted to the ICU (3, 4). However, no recent Canadian data on asthma-related ICU hospitalizations are available.

Although the Global Initiative for Asthma specifically identifies ICU admission as a risk factor for adverse asthma outcomes (5) and evidence suggests that children with severe exacerbations may represent a distinct asthma phenotype (6, 7), few studies have examined the long-term outcomes of children admitted to the ICU for asthma, and findings have been controversial. In a single-center Australian study, 67% of children admitted to the ICU for asthma were readmitted over a follow-up period of 10 years, 17% of whom were readmitted to the ICU (3). Although no direct comparison was made with children not admitted to the ICU, this suggests significant long-term morbidity and mortality among these children. Several smaller studies corroborate this observation, documenting a higher asthma-related readmission rate in ICU patients over follow-up periods ranging from 30 days to 1 year (8, 9). Interestingly, using a large U.S. administrative database, Kenyon et al (4) found a lower asthma-related readmission rate at 1 year in children admitted to the ICU for asthma, compared with those not admitted to the ICU, when adjusted for comorbidities. The authors suggest that this may result from targeted outpatient interventions to ICU patients. Methodological differences between these studies and differences in healthcare systems may explain the differential findings. Thus, country-specific data would be informative, although no such data are available for Canadian children.

Although studies have identified risk factors for asthma-related readmissions among all children hospitalized for asthma (4, 10, 11), it is unknown whether these same risk factors apply to children with the most severe exacerbations. Only

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one study focused on the subgroup of children admitted to the ICU and found that being overweight, having public insurance, and being non-Caucasian were associated with higher odds of asthma-related readmission (12). Again, these risk factors may be country specific given differences in population composition and healthcare systems.

The primary objective of this study is to compare the time to first asthma-related readmission between children with a history of asthma-related ICU hospitalization and those with a history of asthma-related non-ICU hospitalization in Canadian children, using a country-wide inpatient administrative database. Furthermore, we explored the predictors of asthma-related readmissions among children admitted to the ICU for asthma.

MATERIALS AND METHODS

Data Source

Data for this retrospective cohort study were obtained from the Canadian Institute for Health Information's (CIHI) Discharge Abstract Database (DAD) for the period of April 1, 2008, to March 31, 2014. This administrative database contains deidentified information abstracted from discharge summaries, which is mandatorily reported to CIHI. Data in the DAD include the most responsible diagnosis (MRD), defined as the diagnosis that is the most responsible for the patient's hospital stay, basic patient demographics, and details about a patient's hospitalization. A unique identification number is assigned to each subject to allow the identification of readmissions from the same individual. Diagnoses and procedures are coded using the *International Classification of Diseases* version 10 with Canadian Enhancement (ICD-10-CA) (13) and the Canadian Classification of Health Interventions (14), respectively. This study has obtained approval from the Sainte-Justine University Hospital Center Research Ethics Board and from Québec's "Commission d'accès à l'information."

Subjects

We included children 2–17 years old inclusively who had an asthma-related hospitalization during the study period, defined using the ICD-10-CA code J45 as the MRD of a hospital stay. We excluded children less than 2 years old for the purpose of reducing confounding by common wheezing disorders such as bronchiolitis.

Ascertainment of Asthma-Related Hospitalizations and Time to Asthma-Related Readmissions

We considered a patient's first asthma-related hospitalization during the study period as the index hospitalization. If a patient was discharged from one facility and readmitted to another facility the same day, this was considered as the same hospitalization. An admission to the ICU was defined as an ICU stay at any time during a hospitalization. The primary outcome of interest in this study was time to first asthma-related readmission following the index hospitalization. We also assessed asthma-related readmission rates within 30, 90, 180 days, and 1, 3, and 5 years of the index hospitalization's discharge date.

Other Measures

In addition to demographic and clinical variables related to the hospitalization, we assessed other relevant comorbidities and interventions, including prematurity (P07), bronchopulmonary dysplasia (P27.1), atopic dermatitis (L20), allergic rhinitis (J30.1, J30.3–4), endotracheal intubation (1.GZ.31.CA-ND), noninvasive ventilation (1.GZ.31.CB-ND), and usage of a chest tube (1.GV.52).

Statistical Analyses

We evaluated the number of ICU and non-ICU asthma-related hospitalizations in Canada by study year and sex and performed a descriptive analysis of the patient characteristics at the time of the index hospitalization. We used the log-rank test to test for differences in our primary outcome, the time to readmission, between the ICU and non-ICU groups. Subjects were censored if they had not been readmitted as of March 31, 2014. Cox proportional hazard models were used to evaluate the effect of patient and clinical characteristics at the time of index hospitalization on time to readmission. Variables considered include age category, sex, year of index hospitalization, ICU stay, total and ICU length of stay, number of comorbidities, prematurity, bronchopulmonary dysplasia, atopic dermatitis, allergic rhinitis, endotracheal intubation, and noninvasive ventilation. Age was divided into three categories (preschool: 2–5 yr; school-aged: 6–11 yr; adolescents: 12–17 yr), consistent with current management guidelines in pediatric asthma (5, 15, 16). In addition to age and sex, any variables with a *p* value of less than 0.2 in bivariate analysis were included in the multivariate model. In addition to time to asthma-related readmission, we also described readmissions rates within 30, 90, 180 days, and 1, 3, and 5 years of the index hospitalization discharge. *p* values are two sided. All analyses were performed with R software, version 3.2.1 (www.r-project.org).

RESULTS

Between April 1, 2008, and March 31, 2014, 26,168 children were hospitalized 33,304 times for asthma, 1,490 of which were ICU admissions (4.5%). While the overall number of asthma-related hospitalizations was decreasing over the study period (**Fig. 1A**), the number of asthma-related ICU admissions was trending up with time (**Fig. 1B**). The longitudinal patterns of hospitalizations were similar between males and females.

A total of 1,055 children required intensive care during their index hospitalization. Baseline characteristics of the entire study cohort and stratified by ICU admission at the index hospitalization are presented in **Table 1**. The mean (SD) age of children who were admitted to the ICU was 7.1 (4.5), compared with 5.6 (3.8) for the children in the non-ICU group. The proportion of females was higher in the ICU group. The median (interquartile range [IQR]) length of stay for all index hospitalizations was 2 days (1–2 d), compared with 3 days (2–5 d) for those admitted to the ICU. Approximately 9% of ICU subjects were intubated. There were only a total of five in-hospital deaths in the entire cohort.

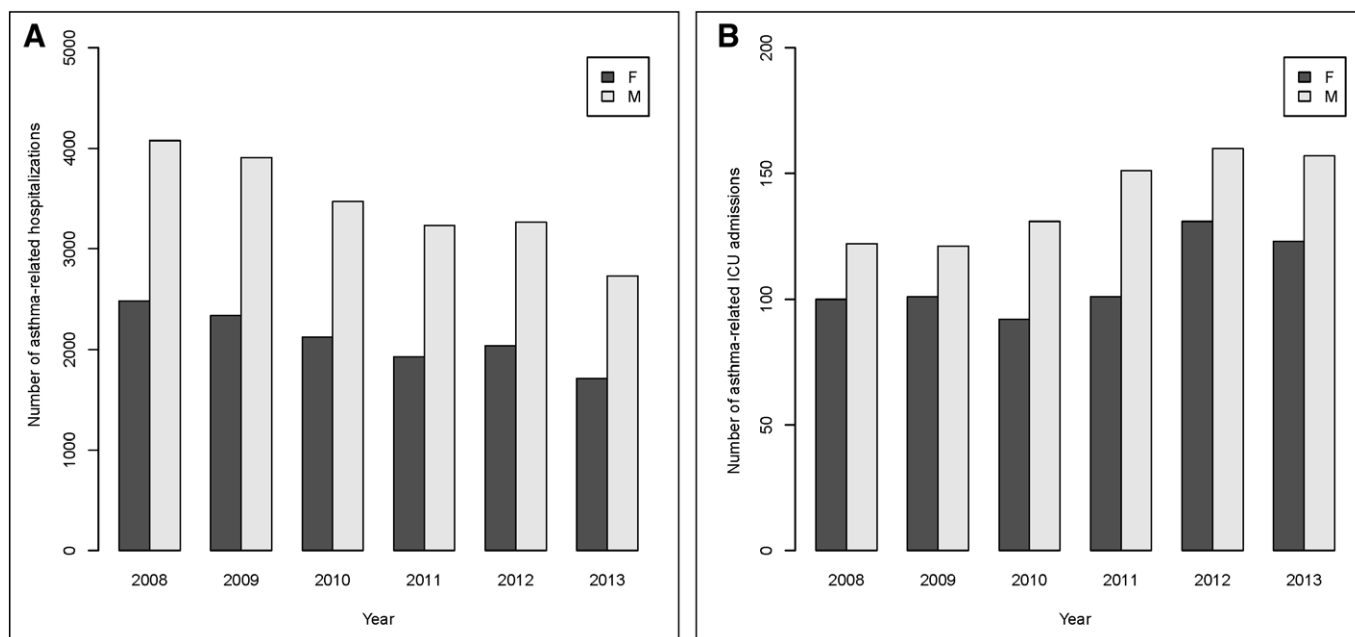


Figure 1. A, Asthma-related hospitalization by Canadian children 2–17 years old, stratified by sex. **B,** Asthma-related ICU hospitalizations by Canadian children 2–17 years old, stratified by sex. F = female, M = male.

Time to Asthma-Related Readmissions

The readmission rate for the entire cohort was 10.6% at 1 year and 23.0% at 5 years. Of the 2,429 children who were readmitted at least once within 1 year of their index hospitalization, 81.2% were readmitted once, 13.9% were readmitted twice, and 4.9% were readmitted three or more times. Of those readmitted once, twice, and three or more times within 1 year, 4.5%, 6.2%, and 9.3% had an index ICU admission, suggesting a higher frequency of readmissions among children initially admitted to the ICU. The time to readmission was significantly lower in the index ICU group compared with the non-ICU group (median [IQR] time to readmission of 27.0 mo [10.5–47.8 mo] and 34.6 mo [15.0–54.1 mo] in the ICU and non-ICU group, respectively, $p < 0.001$) (Fig. 2). When looking over specific follow-up periods, children with an index ICU admission were more likely to be readmitted within 180 days, 1 year, and 3 years of discharge, compared with the non-ICU group (Table 2). Strikingly, among children who were readmitted within 1 year of discharge, 47% of those with an index ICU admission were readmitted to the ICU, compared with only 4.6% in the non-ICU group. The significantly higher proportion of ICU readmission among children with an index ICU admission was observed for all time points.

Predictors of Time to Asthma-Related Readmission in Children Admitted to the ICU

In bivariate analyses, we found that an increased length of stay was associated with asthma-related readmission while intubation was a protective factor (Supplemental Table 1, Supplemental Digital Content 1, <http://links.lww.com/PCC/A532>). These variables remained significantly associated with time to readmission in the multivariate analysis, in addition to preschool age which was a risk factor for time to readmission (Table 3):

preschool-aged children (hazard ratio [HR], 1.48; 95% CI, 1.02–2.14), length of stay (HR, 1.63 for each additional day; 95% CI, 1.17–2.27), and intubation (HR, 0.51; 95% CI, 0.28–0.94).

DISCUSSION

Using a pan-Canadian administrative database, we found that children with an asthma-related ICU hospitalization had a shorter time to asthma-related readmission compared with those who were not admitted to the ICU. We identified preschool age and increased length of stay as risk factors for a shorter time to readmission while intubation during the index hospitalization was a protective factor. Additionally, although the number of asthma-related hospitalizations among Canadian decreased from 2008 to 2014, the number of asthma-related ICU hospitalizations trended up.

Children with a previous asthma-related ICU hospitalization had shorter times to asthma-related readmissions compared with those who were not in the ICU. Although previous studies did not examine time to readmission (3, 4, 8, 9), our finding corroborate the previous literature by emphasizing the increased morbidity of children admitted to the ICU for asthma in Canadian children. Furthermore, when looking at specific follow-up periods, we found that these children were at higher risk for readmission up to 3 years post discharge. However, they were more likely to be readmitted to the ICU independent of the follow-up period of up to 5 years. Although previous studies have mostly reported readmission rates at 1 year post discharge, our findings suggests that this increased morbidity is persistent for several years after the index ICU hospitalization. Thus, a long-term follow-up with targeted management of children admitted to the ICU for asthma is warranted.

TABLE 1. Characteristics of Study Cohort at the Index Hospitalization in Subjects With an ICU and a Non-ICU Admission

Characteristics	ICU, <i>n</i> = 1,055	Non-ICU, <i>n</i> = 25,113	Total, <i>n</i> = 26,168
Age, yr, mean (sd)	7.1 (4.5)	5.6 (3.8)	5.7 (3.8)
Age categories, yr, <i>n</i> (%)			
2–5	508 (48.2)	15,459 (61.5)	15,967 (61.0)
6–11	329 (31.2)	7,248 (28.9)	7,577 (29.0)
12–17	217 (20.6)	2,406 (9.6)	2,623 (10.0)
Male, <i>n</i> (%)	602 (57.1)	15,695 (62.5)	16,297 (62.3)
Region/province of origin, <i>n</i> (%)			
Atlantic provinces (Nova Scotia, New Brunswick, Newfoundland, Prince Edward Island)	106 (10.1)	1,876 (7.5)	1,982 (7.6)
Quebec	242 (22.9)	6,006 (23.9)	6,248 (23.9)
Ontario	356 (33.7)	10,095 (40.2)	10,451 (39.9)
Prairies (Manitoba, Saskatchewan, Alberta)	233 (22.1)	4,744 (18.9)	4,977 (19.0)
British Columbia	115 (10.9)	2,308 (9.2)	2,423 (9.3)
Northern Canada (Yukon Territory, Northwest Territories, Nunavut Territory)	3 (0.3)	84 (0.3)	87 (0.3)
Length of stay, d, median (IQR)	3 (2–5)	1 (1–2)	2 (1–2)
Length of stay in ICU, d, median (IQR)	1 (1–2)	NA	NA
Prematurity, <i>n</i> (%)	6 (0.6)	37 (0.1)	43 (0.2)
Bronchopulmonary dysplasia, <i>n</i> (%)	7 (0.7)	31 (0.1)	38 (0.1)
Atopic dermatitis, <i>n</i> (%)	20 (2.0)	228 (0.9)	248 (1.0)
Allergic rhinitis, <i>n</i> (%)	9 (0.9)	141 (0.6)	150 (0.6)
Endotracheal intubation, <i>n</i> (%)	97 (9.2)	6 (0.0)	103 (0.4)
Noninvasive ventilation, <i>n</i> (%)	48 (4.5)	9 (0.0)	57 (0.2)
Chest tube, <i>n</i> (%)	4 (0.4)	0 (0.0)	4 (0.0)
Death, <i>n</i> (%)	4 (0.4)	1 (0.0)	5 (0.0)

IQR = interquartile range, NA = not applicable.

Although we had limited sociodemographic information given the administrative nature of the database, we identified preschool age and increased length of stay during the index hospitalization as risk factors for time to asthma-related readmission. Previous studies have reported that younger children were at higher risk of asthma-related readmissions (10, 11), likely reflecting their higher frequency of asthma exacerbations compared with other age groups (16–18). The median length of hospital stay among our ICU patients was relatively short (2 d) but comparable to other cohorts (4, 19). Although further studies are required to clarify the mechanisms underlying the association between a lengthier index hospital stay and a shorter time to readmission, our hypotheses include the increased severity of baseline disease, presence of comorbid factors such as complex chronic conditions (20, 21), environmental exposures such as secondhand smoke (22, 23), and

decreased treatment responses to acute and chronic asthma therapy (24). Interestingly, we found that intubation during the index hospitalization was associated with a longer time to readmission, although it remained an infrequent event overall (0.4% of all asthma-related hospitalization and 9.2% of those admitted to the ICU). We hypothesize that given the near-fatal nature of their exacerbation, intubated children may receive targeted outpatient care to prevent subsequent adverse outcomes.

Despite an increasing prevalence in physician-diagnosed asthma (25, 26), most countries report decreasing (27–31) or stable (32, 33) rates of childhood asthma-related hospitalizations. Our findings demonstrate a similar decreasing trend in the absolute numbers of hospitalizations for asthma from 2008 to 2014 in Canada. This may reflect improved diagnosis of asthma and management of disease in the

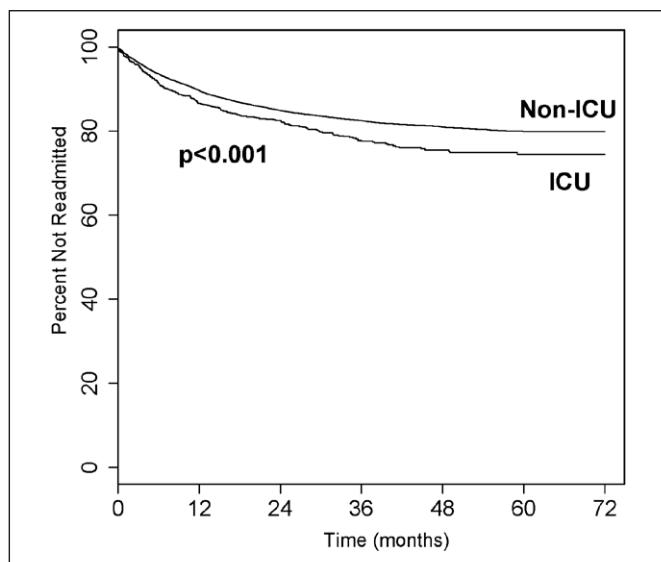


Figure 2. Kaplan-Meier curve for time to readmission over the study period, stratified by ICU admission during the index hospitalization.

outpatient setting, including in the emergency department, resulting in milder exacerbations. A decrease in the availability of inpatient beds due to hospital sector downsizing in Canada has also been linked to the decrease in hospitalization rates (25).

While the absolute asthma-related hospitalizations decreased, the number of asthma-related ICU hospitalizations trended up. Consistent with our findings, while the rate of asthma-related hospitalizations decreased, the rate of asthma-related ICU admissions in hospitals with PICUs more than tripled (34) in New Jersey from 1992 to 2006. Thus, children with severe asthma exacerbations represent an increasing proportion of all asthma-related hospitalizations, and they need targeted management given their increased long-term morbidity.

Interestingly, although we documented an asthma-related ICU admission rate of 4.5% in Canada, this number varies from 12% to 34% in the United States (4, 19). This observed discrepancy in ICU admissions between Canada and the United States may reflect differences in several aspects of asthma management, including healthcare access issues, threshold for ICU admission, or true differences in asthma severity. However, no study compared the epidemiology of pediatric asthma between the two countries using comparable criteria and study periods, which would help elucidate country-specific issues that might be of public health relevance.

This study has several strengths. First, we included all asthma-related hospitalizations in Canada over a 6-year period. Given Canada's universal healthcare system and that all hospitals are publicly operated, our findings are generalizable to all Canadian children and provide an up-to-date picture of asthma morbidity among Canadian children. The availability of well-accepted,

TABLE 2. Asthma-Related Readmissions in Subjects With an ICU and a Non-ICU Index Hospitalization by Follow-Up Period

Asthma-Related Readmissions	ICU	Non-ICU	<i>p</i>
Subjects with 30 d follow-up, <i>n</i>	1,041	24,922	
Readmission within 30 days, <i>n</i> (%)	23 (2.2)	385 (1.5)	0.12
Readmission to the ICU within 30 d, <i>n</i> (% of those readmitted)	12 (52.2)	4 (1.0)	< 0.001
Subjects with 90 d follow-up, <i>n</i>	1,015	24,584	
Readmission within 90 d, <i>n</i> (%)	44 (4.3)	909 (3.7)	0.33
Readmission to the ICU within 90 d, <i>n</i> (% of those readmitted)	16 (36.4)	49 (5.4)	< 0.001
Subjects with 180 d follow-up, <i>n</i>	967	23,781	
Readmission within 180 d, <i>n</i> (%)	85 (8.8)	1,537 (6.5)	0.005
Readmission to the ICU within 180 d, <i>n</i> (% of those readmitted)	36 (42.4)	69 (4.5)	< 0.001
Subjects with 1-yr follow-up, <i>n</i>	874	22,102	
Readmission within 1 yr, <i>n</i> (%)	121 (13.8)	2,308 (10.4)	0.002
Readmission to the ICU within 1 yr, <i>n</i> (% of those readmitted)	57 (47.1)	107 (4.6)	< 0.001
Subjects with 3-yr follow-up, <i>n</i>	522	14,823	
Readmission within 3 yr, <i>n</i> (%)	126 (24.1)	2,690 (18.1)	< 0.001
Readmission to the ICU within 3 yr, <i>n</i> (% of those readmitted)	58 (46.0)	155 (5.8)	< 0.001
Subjects with 5-yr follow-up, <i>n</i>	191	5,802	
Readmission within 5 yr, <i>n</i> (%)	54 (28.3)	1,323 (22.8)	0.09
Readmission to the ICU within 5 yr, <i>n</i> (% of those readmitted)	23 (42.6)	88 (6.7)	< 0.001

TABLE 3. Multivariate Analysis of Determinants of Time to Asthma-Related Readmission in Children Admitted to the ICU for Asthma ($n = 1,055$)

Characteristics	Hazard Ratio (95% CI)	<i>p</i>
Age category vs 12–17 yr (yr)		
6–11	1.02 (0.67–1.54)	0.92
2–5	1.48 (1.02–2.14)	0.04
Female vs male		
Female	0.90 (0.68–1.18)	0.44
Length of stay of index hospitalization, per additional day	1.63 (1.17–2.27)	0.004
Atopic dermatitis	1.51 (0.67–3.42)	0.32
Endotracheal intubation during index hospitalization	0.51 (0.28–0.94)	0.03

standard Canadian guidelines in the management of acute childhood asthma also minimizes heterogeneity in ICU admission (35). Second, in addition to examining time to readmission, we assessed asthma-related readmissions over six different periods of time following the index hospital discharge, allowing us to determine the persistence of the differences in readmissions between the ICU and non-ICU group over time.

Several limitations to this study are noteworthy. First, we assumed that each child had coverage for the duration of the study period. Although we can account for interprovincial migration, we could not account for emigrated children who were hospitalized, nor for children who died outside of a hospitalization for asthma. However, these factors account for a very small number of children in Canada (36, 37). Second, we had limited data on sociodemographic variables and comorbidities, the latter likely because of incomplete documentation on hospital discharge summaries. Given the administrative nature of the database, we did not have objective measures of atopic comorbidities, the chronicity and control of asthma symptoms, data on environmental exposures, nor some risk factors that can influence readmission risk, including posthospitalization follow-up and medication adherence. Furthermore, genotypic differences, which may help explain interindividual variability in asthma pharmacotherapy response, can also influence the risk of readmission. These factors can only be optimally examined in a prospective study. Finally, in order to minimize misclassification and to be consistent with previous literature in this field (19, 31, 38), we included only hospitalizations with asthma as the principal diagnosis, which may have slightly underestimated the number of asthma-related hospitalizations.

CONCLUSIONS

In conclusion, this study highlighted the significant morbidity of Canadian children previously admitted to the ICU for asthma. Specifically, compared with children who had not

been admitted to the ICU, they have a shorter time to asthma-related readmission, underlining the importance of following these children post discharge. A particular focus on preschool age children and those with longer length of hospital stays may be warranted, as these were associated with a shorter time to readmission among all children admitted to the ICU.

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