

Burden of Influenza-Related Hospitalizations and Attributable Mortality in Pediatric Acute Lymphoblastic Leukemia

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Background. Influenza can be severe in patients with underlying malignancy; however, the rate of influenza hospitalizations and attributable mortality in children with cancer is unknown.

Methods. We performed a retrospective cohort study among 10 698 children with new-onset acute lymphoblastic leukemia (ALL) from 41 US children's hospitals between January 1999 and September 2011. Influenza-related hospitalizations were identified using ICD-9 discharge diagnosis codes, excluding hospitalizations during low-prevalence influenza periods. Follow-up was censored at the earliest of 5 events: end of study period, expected end of chemotherapy, last known hospitalization, hematopoietic stem cell transplant, or death. Data were collected on hospitalization characteristics and resource utilization. Hospitalization rates were calculated using season-adjusted person-time. Crude attributable in-hospital mortality was calculated using baseline mortality for noninfluenza hospitalizations during the same period. Subgroup analysis was performed by time from ALL diagnosis and by age category.

Results. The rate of influenza-related hospitalizations was 618.3 per 100 000 person-months. Rates were similar by time from ALL diagnosis and across age categories. Overall attributable in-hospital mortality was 1.0% (95% confidence interval [CI], 0.3%–2.3%) and was highest for children <6 months from diagnosis (1.6%; 95% CI, 0.4%–4.5%) and children <2 years of age (6.7%; 95% CI, 1.3%–22.7%). Total length of stay, days of broad-spectrum antibiotic exposure, and duration of intensive care were significantly greater for influenza-related hospitalizations compared with noninfluenza hospitalizations.

Conclusions. The burden of influenza-related hospitalizations in children with ALL is high and associated with significantly increased resource utilization and attributable mortality.

Key words. epidemiology; hospitalizations; influenza; leukemia; pediatrics.

BACKGROUND

Influenza is an important cause of respiratory illness in childhood, with an increased risk of hospitalization seen in children with underlying medical conditions compared with healthy children [1–3]. Immunocompromised hosts, including children receiving chemotherapy for malignancy, may have decreased ability to control virus replication leading to prolonged viral shedding [4, 5] and increased potential for severe infection. Various complications have been reported in pediatric oncology patients with influenza, including respiratory failure, intensive care unit (ICU)

admission, and death [6–9]. In addition, influenza illness may delay the delivery of cancer therapy, with median chemotherapy interruptions of 7 days or more reported in 40%–60% of infected pediatric oncologic patients [6, 8, 10].

Despite its clinical significance, comprehensive assessments of the burden of influenza in children with cancer are not available. Present data are largely limited to single center studies, case series, and the 2009 H1N1 pandemic, and have included study populations with varied diagnoses and treatment status [6, 8, 10–14]. We aimed to define the

epidemiology, attributable mortality, and outcomes of influenza-related hospitalizations in a multicenter cohort of children with acute lymphoblastic leukemia (ALL), the most common pediatric cancer diagnosis in the United States.

METHODS

Study Design and Data Source

We performed a retrospective multicenter longitudinal cohort study of children ages 0–19 years with new-onset ALL. Data for this study were obtained from the Pediatric Health Information System (PHIS), a comparative administrative database that contains the clinical and billing details from 44 freestanding, not-for-profit, tertiary care US pediatric hospitals affiliated with Children's Hospital Association ([CHA] Overland Park, KS). Data quality and reliability are assured through a joint effort between CHA and participating hospitals. For the purposes of external benchmarking, participating hospitals provide discharge/encounter data including demographics, dates of service, and up to 41 *International Classification of Disease, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis and procedure codes, as well as resource utilization data including pharmaceuticals, imaging, laboratory testing, and clinical services. Actual imaging and laboratory results are not available in PHIS. This study was reviewed and approved by the Institutional Review Board of The Children's Hospital of Philadelphia.

Study Population

The source population was an inception cohort of 10 698 new-onset ALL subjects ages 0–19 years admitted to a PHIS-participating site between January 1, 1999 and September 30, 2011. This cohort was assembled using a previously described and validated 3-step process utilizing ICD-9-CM diagnosis codes and chemotherapy exposure data to identify ALL subjects admitted for induction chemotherapy. Relapsed cases were not included [15]. This approach was previously shown to result in a cohort with demographic characteristics consistent with the National Cancer Institute's Surveillance Epidemiology and End Results program. Follow-up was censored at the earliest of 5 events: study period end-date, anticipated end of ALL treatment (2.5 years for females and 3 years for males) [16, 17], last PHIS hospitalization, hematopoietic stem cell transplant, or death.

Definition of Influenza Hospitalization

Influenza-related hospitalizations during the follow-up period were identified by the presence of an influenza-specific ICD-9-CM diagnosis code (487.x, 488.x). To optimize the positive-predictive value of an influenza diagnosis, only influenza-related hospitalizations during expected periods

of seasonal influenza activity (ie, October–May) or corresponding with the timing of the 2009 novel H1N1 pandemic (ie, April 2009–June 2010) were included.

Data Collection

Clinical and demographic data were collected including age, race, sex, date of ALL diagnosis (defined as day of admission for the hospitalization in which induction chemotherapy was initiated), daily billing data for resource utilization including procedural, clinical, laboratory, and imaging services, and hospitalization characteristics such as length of stay (LOS) and exposure to broad-spectrum antibiotics (defined as antibiotics with *Pseudomonas aeruginosa* or methicillin-resistant *Staphylococcus aureus* spectrum) and neuraminidase inhibitors (NIs), ie. oseltamivir and zanamivir). The presence of chronic comorbidities was identified using a previously derived ICD-9-CM diagnosis code-based classification system for pediatric chronic conditions [18]. Data were also collected on in-hospital death and receipt of ICU-level care, defined using PHIS resource utilization and ICD-9-CM procedure codes consistent with care escalation (eg, mechanical ventilation, administration of vasoactive agents, arterial catheter placement, hemodialysis) [19, 20].

Data Analysis

Influenza-related hospitalization rates were calculated using influenza season-adjusted person-time starting from the date of ALL diagnosis to the end of follow-up and were expressed per 100 000 person-months, with exact 95% confidence intervals (CI). Rates were stratified by age category, defined as less than 2 years, 2 years to less than 5 years, and 5 years or greater. To identify a difference in risk based on intensity of immunosuppression, rates were also stratified by time from ALL diagnosis <6 months or ≥6 months, the time point at which the most intensive chemotherapy typically ends and maintenance chemotherapy begins [16].

In-hospital mortality rates for influenza-related and non-influenza hospitalizations during the season-adjusted period were calculated. Crude attributable mortality was calculated by subtracting the difference between influenza and noninfluenza in-hospital mortality rates and was similarly stratified by age category and time from ALL diagnosis ≥6 months. Pearson χ^2 or Fisher's exact tests and 95% CI using the Wilson score interval were used to evaluate the differences in rates. The number of influenza-related hospitalizations needed to prevent 1 death (NNP) was calculated by taking the inverse of the risk difference in mortality and rounding up to the nearest integer.

Baseline patient characteristics, hospitalization characteristics, and outcomes were summarized as means with standard deviation or medians with interquartile range

(IQR) for continuous variables and as frequencies and percentages for categorical variables. The Wilcoxon rank-sum test was used for continuous variables, and Pearson χ^2 or Fisher's exact tests were used for categorical variables. To account for the skewed distribution of LOS, a generalized linear model with a gamma distribution and log link was used to compare LOS between influenza-related and non-influenza hospitalizations. Days of broad-spectrum antibiotic exposure (defined as each day in which at least 1 dose of broad-spectrum antibiotic was billed) and days of ICU-level care were calculated as a proportion of total hospital days and expressed per 1000 inpatient days with exact binomial 95% CIs. Comparisons for antibiotic use and ICU-level care were made between influenza-related and noninfluenza hospitalizations during the influenza season-adjusted period using the 2-sample test of proportions. All tests were 2-tailed, and $P < .05$ was considered statistically significant. Stata statistical software, version 12.1 (StataCorp, College Station, TX) was used for all analyses.

Sensitivity Analysis

To determine whether the 2009 H1N1 pandemic made a significant impact on estimates of influenza-related hospitalization rates and attributable mortality, repeat analyses were performed after exclusion of influenza-related hospitalizations occurring between April 2009 and June 2010. Analyses were also repeated using an alternate definition of an influenza-related hospitalization that required the additional presence of an inpatient influenza test. This more rigid definition aimed to reduce potential bias in estimated influenza hospitalization rates due to misclassification of noninfluenza hospitalizations based solely on ICD-9-CM codes.

RESULTS

Study Population Characteristics

Influenza Hospitalizations. Of 64 319 hospitalizations during the 13-year study period, 656 had an influenza-specific ICD-9-CM diagnosis code. Of these, 27 hospitalizations

occurred outside of influenza season and were excluded, resulting in 629 influenza-related hospitalizations. These 629 hospitalizations occurred in 577 subjects; 47 subjects had 2 or more influenza-related hospitalizations. Of 52 repeat hospitalizations, 26 occurred within the same season as the initial hospitalization and 26 occurred in a different season. Overall, 5.4% out of the total 10 698 subjects in the ALL cohort had at least 1 influenza-related hospitalization during follow-up.

Demographic characteristics are shown in Table 1. For influenza-related hospitalizations, only the first hospitalization for each subject was included for comparison. The median age at admission was younger for influenza-related versus noninfluenza hospitalizations (5.7 years vs 6.2 years; $P = .04$). There was no significant difference in gender, race, or preexisting chronic comorbid conditions (cardiovascular, pulmonary, neuromuscular, renal). A significantly higher proportion of influenza-related hospitalizations occurred after 6 months from ALL diagnosis compared with noninfluenza hospitalizations (66.7% vs 36.7%; $P < .001$).

Influenza-Related Hospitalization Rates. From 1999 to 2011, children with new-onset ALL experienced an overall rate of 618.3 influenza-related hospitalizations per 100 000 person-months (95% CI, 570.9–668.5 per 100 000 person-months) (Table 2). Rates were similar in children <6 months from ALL diagnosis (582.5 per 100 000 person-months; 95% CI, 505.7–667.7 per 100 000 person-months) and children ≥ 6 months from ALL diagnosis (637.3 per 100 000 person-months; 95% CI, 578.0–701.0 per 100 000 person-months). When stratified by age category, children <2 years of age exhibited the highest rates (737.4 per 100 000 person-months; 95% CI, 486.0–1072.9 per 100 000 person-months); however, this was not statistically significant. Rates declined with increasing age category; however, nonparametric test for trend was nonsignificant ($P = .157$).

When estimates were repeated after excluding all influenza-related hospitalizations occurring during the

Table 1. Admission-Level Demographic and Baseline Characteristics

Characteristic	Influenza-Related Hospitalizations, $n = 577^*$	Noninfluenza Hospitalizations $n = 44\ 095^\dagger$	P Value
Age in years, median (IQR)	5.7 (3.8–9.3)	6.2 (3.6–11.6)	.04
Male, n (%)	326 (56.5)	24 418 (55.4)	.6
Race, n (%)			
White	427 (74.0)	33 992 (77.1)	
Black	40 (6.9)	3168 (7.2)	
Other	93 (16.1)	5808 (13.2)	
Missing	17 (3.0)	1127 (2.6)	.2
Any chronic comorbid condition, n (%) [‡]	81 (14.0)	5414 (12.3)	.2
Time from ALL diagnosis ≥ 6 months, n (%)	385 (66.7)	16 197 (36.7)	<.001

Abbreviations: ALL, acute lymphoblastic leukemia; IQR, interquartile range.

*Only the first influenza-related hospitalization for each subject was included for comparison.

[†]Hospitalizations during the influenza season-adjusted period.

[‡]Chronic pulmonary, cardiac, neuromuscular, or renal condition.

Table 2. Rates of Influenza-Related Hospitalizations Among Children With ALL, 1999–2011

Category	Hospitalizations (<i>n</i>)	Person-Months*	Rate/100 000 Person-Months (95% CI)
Overall	629	101 739	618.3 (570.9–668.5)
Time from ALL diagnosis			
<6 months	206	35 365	582.5 (505.7–667.7)
≥6 months	423	66 374	637.3 (578.0–701.0)
Age category [†]			
0 to <2 years	27	3661	737.4 (486.0–1072.9)
2 to <5 years	232	34 865	665.4 (582.5–756.8)
≥5 years	370	63 212	585.3 (527.2–648.1)

Abbreviations: ALL, acute lymphoblastic leukemia; CI, confidence interval.

*Influenza season-adjusted.

[†]Nonparametric test for trend: $P = .157$.

2009 H1N1 pandemic ($n = 181$), overall rates decreased significantly by 13.1% ($P = .02$). There was no significant difference in rates when stratified by time from ALL diagnosis or by age category (Supplementary Table 1). When analyses were restricted to include only hospitalizations with inpatient influenza testing ($n = 402$), overall rates decreased significantly by 30% ($P < .0001$). However, there remained no significant difference in rates when stratified by time from ALL diagnosis or by age category (Supplementary Table 2). **Attributable Mortality.** Influenza-related hospitalizations were associated with an overall in-hospital mortality rate of 1.4% compared with a noninfluenza hospitalization mortality rate of 0.4% during the same season-adjusted period (Table 3), resulting in a significant attributable in-hospital mortality of 1.0% (95% CI, .3%–2.3%). Attributable mortality was highest in children <6 months from ALL diagnosis (1.6%; 95% CI, .4%–4.5%) and in children <2 years of age (6.7%; 95% CI, 1.3%–22.7%). A significant attributable increase in mortality was seen in children 2 years to <5 years of age (1.1%; 95% CI, .2%–3.5%); no significant attributable mortality was seen in older children. Results were similar when hospitalizations during the 2009 H1N1 pandemic were excluded (Supplementary Table 3). When analyses were repeated after exclusion of hospitalizations without inpatient influenza testing, the attributable mortality in children <6 months from ALL diagnosis remained significant (1.9%; 95% CI, .4%–6.0%) despite a loss of power (Supplementary Table 4).

The decrease in number of influenza-related hospitalizations NNP was 100, overall. For children <6 months from ALL diagnosis the NNP was 63, whereas for those ≥6 months from diagnosis the NNP was 143. When calculated by age category, the NNP ranged from 15 for children <2 years of age to 167 for children ≥5 years (Table 3).

Hospitalization Characteristics. Hospitalization characteristics are summarized in Table 4. Influenza-related hospitalizations were associated with a significantly greater mean LOS compared with noninfluenza hospitalizations (8.9

days vs 7.3 days; $P < .0001$). Administration of any broad-spectrum antibiotic was significantly more common for influenza-related hospitalizations (90.1% vs 57.5%; $P < .0001$). In addition, total days of broad-spectrum antibiotic exposure per 1000 inpatient-days were significantly higher for influenza-related hospitalizations compared with noninfluenza hospitalizations (732 per 1000 inpatient-days vs 546 per 1000 inpatient-days; $P < .0002$). Although the proportion requiring ICU-level care was similar between influenza-related and noninfluenza hospitalizations (10.5% vs 9.5%; $P = .4$), influenza-related hospitalizations were associated with a significantly greater number of days of ICU-level care per 1000 inpatient days (85 per 1000 inpatient-days vs 40 per 1000 inpatient days; $P < .0001$). Neuraminidase inhibitors were administered in 54.5% of influenza-related admissions, with a median day of initiation on Day 1 of hospitalization (IQR, Day 0–Day 2).

DISCUSSION

This multicenter cohort-based longitudinal study yields 3 major findings. First, the burden of influenza-related hospitalizations in children with ALL is significant, with an estimated overall rate of 618.3 episodes per 100 000 person-months. Second, the crude in-hospital mortality rate attributable to an influenza-related hospitalization is highest in children less than 2 years of age (6.7%) and in those within the first 6 months after diagnosis of ALL (1.6%). Third, influenza-related hospitalizations are associated with significantly greater total LOS, broad-spectrum antibiotic exposure, and days of ICU-level care compared with noninfluenza hospitalizations.

To our knowledge, this is the first study to define rates of influenza-related hospitalizations in children with malignancy. The overall rate of influenza-related hospitalizations in our study was higher than that reported by 2 previous population-based studies in otherwise well infants and young children (39–112 per 100 000 person-months) [3, 21] and in children 6–23 months of age with high-risk

Table 3. Crude Attributable Mortality of Influenza-Related Hospitalizations in Children With ALL, 1999–2011

Category	Influenza-Related Hospitalizations (<i>n</i>)	Deaths (<i>n</i>)	Mortality Rate			<i>P</i>	NNP [†]
			Influenza-Related Hospitalizations (95% CI)	Noninfluenza Hospitalizations* (95% CI)	Attributable Increase (95% CI)		
Overall	629	9	1.4% (.7–2.7)	0.4% (.4–0.5)	1.0% (.3–2.3)	.002	100
Time from ALL diagnosis							
<6 months	206	4	1.9% (.5–2.7)	0.4% (.3–.4)	1.6% (.4–4.5)	<.01	63
≥6 months	423	5	1.2% (.4–2.7)	0.6% (.5–.7)	0.7% (–.1 to 2.2)	.10	143
Age category							
0 to <2 years	27	2	7.4% (.9–24.3)	0.7% (.5–1.1)	6.7% (1.3–22.7)	.02	15
2 to <5 years	232	3	1.3% (.3–3.7)	0.2% (.1–.3)	1.1% (.2–3.5)	.01	91
≥5 years	370	4	1.1% (.3–2.7)	0.5% (.5–.6)	0.6% (–.1 to 2.4)	.14	167

Abbreviations: ALL, acute lymphoblastic leukemia; CI, confidence interval; NNP, number needed to prevent.

*Hospitalizations during the influenza season-adjusted period.

[†]Decrease in influenza-related hospitalizations needed to prevent 1 death.

Table 4. Hospitalization Characteristics

Characteristic	Influenza-Related <i>n</i> = 629	Noninfluenza Hospitalization <i>n</i> = 44 095*	<i>P</i>
Length of stay, days			
Median (IQR)	5 (3–8)	5 (3–8)	.3
Mean (SD)	8.9 (13.5)	7.3 (8.6)	<.0001
Day of influenza testing, median (IQR) [†]	0 (0–1)	–	
Neuraminidase-inhibitor, <i>n</i> (%)	343 (54.5)	–	
Day of initiation, median (IQR)	1 (0–2)	–	
Broad-spectrum antibiotics, <i>n</i> (%)	567 (90.1)	25 336 (57.5)	<.0001
Day of initiation, median (IQR)	0 (0–0)	0 (0–1)	.0001
Antibiotic days per 1000 hospital days (95% CI)	732.3 (720.6–743.9)	545.9 (544.1–547.6)	<.0002
Receipt of ICU-level care, <i>n</i> (%)	66 (10.5)	4177 (9.5)	.4
Days of ICU-level care per 1000 hospital days (95% CI)	85.2 (79.4–94.5)	39.5 (38.8–40.1)	<.0002

Abbreviations: ICU, intensive care unit; IQR, interquartile range; SD, standard deviation.

*Hospitalizations during the influenza season-adjusted period.

[†]Median day of influenza testing for those in whom inpatient testing was performed (*n* = 402).

conditions (61 per 100 000 person-months) [21]. Differences in methodology from our study to that of these prior studies including the use of syndrome-based diagnosis codes and statistical models to estimate rates of influenza-related hospitalizations may account for some of the variance. However, it is unlikely that this would fully explain the large increase of influenza-related hospitalizations in ALL patients relative to the general pediatric population that we identified. Similar to these previous studies, our study definition did not distinguish between community-acquired and healthcare-associated influenza.

In contrast to what has been seen in the general pediatric population [3, 22–24], we did not find a significant inverse relationship between rates of influenza-related hospitalizations and age category, suggesting that older children with ALL remain at high risk for influenza-related hospitalization. In addition, we did not find a significant difference in hospitalization rates when analyzed by time from ALL diagnosis, suggesting an equal risk of influenza-related hospitalization during intensive and maintenance chemotherapy treatment phases.

Due to disease- and chemotherapy-related factors impacting immunologic status, children with malignancy are vulnerable to severe influenza-related complications, including death. Despite a low overall mortality rate in our cohort, the crude attributable mortality associated with influenza-related hospitalizations was significant. This finding remained significant even after exclusion of hospitalizations occurring during the 2009 H1N1 pandemic, which had been shown in previous studies to disproportionately impact children with chronic illnesses [25, 26]. Most striking was in children <6 months from ALL diagnosis and in children <2 years of age, in which a decrease in 63 and 15 influenza-related hospitalizations, respectively, would prevent at least 1 death. At a time in which ALL survival rates have surpassed 90% [27], a focus on reducing mortality associated with infections such as influenza is important to further optimize survival rates.

We found a significant increase in days of ICU-level care per 1000 inpatient days for influenza-related hospitalizations, suggesting that influenza in children with ALL is

associated with a comparative increase in ICU-level resource utilization. In addition, we also found a significant association with increased broad-spectrum antibiotic exposure. A high frequency of antibiotic use in children with malignancy who are hospitalized with influenza has previously been reported in single center studies [6, 8, 11], and findings from this cohort suggest that this pattern of utilization is consistent across many pediatric institutions in the United States. Although we were unable to ascertain the indications for antibiotic use in our dataset, complications of bacteremia and pneumonia have been reported in a significant proportion of children with malignancy who are hospitalized with influenza [6, 8–11]. In addition, fever is a common presenting symptom in this population [6, 8, 9, 11, 14], possibly prompting the need for initial empirical antibiotic therapy for fever with neutropenia or suspected central line-associated bloodstream infection. In an era of increasing antimicrobial resistance and limited availability of new antibiotics to treat resistant pathogens, the prevention of influenza-related hospitalizations are a potential means of reducing additional antibiotic exposure in this population. Finally, it is notable that NIs were administered in only 54.5% of influenza-related hospitalizations. Data on the effectiveness of NI to prevent complications in children with high-risk conditions are limited, and recent meta-analyses have called into question the clinical efficacy of NI in adults and children [28, 29]. Future studies are needed to define the effectiveness of NI in immunocompromised children to better define their role in reducing influenza complications.

There are several limitations to our study. Although the use of a large multicenter administrative database such as PHIS permits the generation of influenza-related hospitalizations rates and outcomes reflective of a broad representation of geographic and metropolitan regions across the United States, PHIS data are restricted to freestanding, tertiary care pediatric hospitals that may not be generalizable to all institutions providing pediatric care. However, given the highly specialized nature of pediatric oncology, most children with ALL are likely to be hospitalized at pediatric tertiary care sites similar to those included in PHIS, supporting the generalizability of our results. Administrative data may also be limited due to potential miscoding of discharge diagnoses. Despite our findings of elevated rates of influenza-related hospitalizations in children with ALL, our estimates are likely to be conservative due to our reliance on influenza-specific ICD-9-CM diagnosis codes to identify hospitalizations. Previous studies have demonstrated that the use of influenza diagnosis codes to estimate influenza-related hospitalizations offers only moderate sensitivity and may not fully capture the total burden of

influenza-related hospitalizations [3, 21, 30–32]. Although influenza diagnosis codes are highly specific, misclassification of children diagnosed with other respiratory pathogens may have also occurred [31, 32]. In addition, influenza in hospitalized children may go undiagnosed due to lack of testing or reliance upon rapid influenza antigen tests that have demonstrated limited sensitivity [24, 33–35]. The overall effect of these limitations is likely an underestimation of the full impact of influenza-related hospitalizations in this cohort. Finally, we were unable to determine whether in-hospital mortality and receipt of ICU-level care were directly due to influenza. In addition, we were only able to ascertain deaths associated with influenza-related hospitalizations if they occurred within the hospital. Given that 16% of pediatric influenza deaths occur outside the hospital [36], we may have underestimated the true mortality attributable to influenza.

CONCLUSIONS

In summary, influenza is associated with a substantial burden of hospitalizations, in-hospital attributable mortality, and resource utilization in children with ALL. These findings argue that increased efforts are needed for the prevention of influenza in this population, with a focus not only on immunizing children with ALL but also healthcare workers and household members through contact-based immunization strategies. Guidelines for influenza prevention have been published for high-risk populations such as pediatric ALL [37–40], although data on adherence and clinical effectiveness in immunocompromised populations are limited. Future efforts are needed to optimize the effectiveness of preventive strategies and their implementation in these at-risk populations.

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