Oseltamivir Shortens Hospital Stays of Critically Ill Children Hospitalized With Seasonal Influenza

A Retrospective Cohort Study

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Background: Antiviral therapy reduces symptom duration and hospitalization risk among previously healthy and chronically ill children infected with seasonal influenza. The effect of oseltamivir on outcomes of hospitalized children is unknown. The primary objective of this study was to determine whether oseltamivir improves outcomes of critically ill children hospitalized with influenza.

Methods: We performed a retrospective cohort study of children with influenza infection admitted to a pediatric intensive care unit during 6 consecutive winter seasons (2001–2007). We used the Pediatric Health Information System database, which contains resource utilization data from 41 children's hospitals. We matched oseltamivir-treated patients with oseltamivir-nontreated patients by the probability of oseltamivir exposure using a propensity score we derived from patient and hospital characteristics. We subsequently compared the outcomes of critically ill children treated with oseltamivir within 24 hours of admission with propensity score matched children who were not treated with oseltamivir.

Results: We identified 1257 children with influenza infection, 264 of whom were treated with oseltamivir within 24 hours of hospital admission. Multivariable analysis of 252 oseltamivir-treated patients and 252 propensity score-matched untreated patients demonstrated that patients treated with oseltamivir experienced an 18% reduction in total hospital days (time ratio: 0.82, $P = 0.02$), whereas intensive care unit stay, in-hospital mortality, and readmission rates did not differ.

Conclusion: For critically ill children infected with seasonal influenza, treatment with oseltamivir within 24 hours of hospitalization was associated with a shorter duration of hospital stay. Additional study is needed to determine the effect of delayed initiation of oseltamivir on clinical outcomes.

Key Words: influenza, child, treatment, epidemiology, oseltamivir

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Each year in the United States, 1 in every 100 children <5 years of age is hospitalized with influenza or influenza-related complications.[1] During the past 5 years, researchers have shown the potential severity of influenza. In 2004, pediatric influenza-related deaths became nationally reportable; since that time 43 to 88 deaths have been reported each year.[2,3] Although children with chronic conditions are at increased risk of influenza-related complications,[4] approximately half of fatal pediatric infections occur in previously healthy children.[5–7]

In 2009, the emergence and rapid spread of a novel pandemic influenza strain underscored the urgent need for a better understanding of the effectiveness of antiviral medications in the treatment of patients infected with influenza. More than 10 clinical trials of anti-influenza medications have been conducted in nonhospitalized patients. The majority of these trials demonstrated that antiviral medications, including oseltamivir and amantadine, shortened the duration of fever and influenza symptoms when initiated within 48 hours of symptom onset.[8–15] In addition, antiviral therapy reduced the rate of influenza-related respiratory complications and hospitalizations in both previously healthy and chronically ill ambulatory patients.[8,11,13,16–18] Antiviral therapy has also been shown to reduce mortality among hospitalized adults.[19,20] Although influenza is a common cause of pediatric hospitalization, little is known about the impact of antiviral medications on the course of illness among children with influenza. We undertook this study to examine the effectiveness of oseltamivir to alter outcomes of critically ill children hospitalized with influenza.

MATERIALS AND METHODS

Study Design

We performed a retrospective cohort study of children admitted to an intensive care unit (ICU) for treatment of influenza at one of 41 children's hospitals in the United States. We compared the outcomes of critically ill children treated with oseltamivir with propensity score-matched children who did not receive oseltamivir.

Data Sources and Quality

Data for this study were obtained from the Pediatric Health Information System (PHIS). PHIS is a national administrative database containing resource utilization data from 41 freestanding, tertiary care children's hospitals. PHIS-participating hospitals account for 20% of all tertiary care general (rather than subspecialty) children's hospitals. They are located in 23 different states plus the District of Columbia; no more than 1 participating hospital is present in a specific metropolitan area. These hospitals are affiliated with the Child Health Corporation of America (Shawnee Mission, KS), a business alliance of children's hospitals. Data quality and reliability are assured through a combined effort between the Child Health Corporation of America and participating hospitals. For the purposes of external benchmarking, participating hospitals provide discharge data, including patient demographics, diagnoses, and procedures. Billing data are also available on a daily basis, which detail all the drugs, radiologic imaging studies, laboratory tests, and supply charged to each patient. Daily

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room charges allow for determination of patient location (eg, neonatal ICU, pediatric ICU, medical/surgical ward). Systematic monitoring, including bimonthly coding consensus meetings, coding consistency reviews, and quarterly data quality reports, occurs on an ongoing basis to ensure data quality. Analyses of PHIS data have been published in many peer-reviewed journals studying research topics spanning a wide variety of pediatric and pediatric subspecialty disciplines.[21–26]

Selection of the Cohort

The study sample consisted of patients aged 0 to 21 years who (1) had an International Classification of Diseases, ninth revision, Clinical Modification (ICD-9-CM) discharge diagnosis code of influenza (487.0, 487.1, or 487.8 in any position on discharge); (2) were discharged from any of the 41 participating hospitals between October and April during the years 2001 to 2007 (limited to patients discharged from hospitals with billing data during the time period); (3) had a charge for an influenza test within the first 48 hours of admission (test results are not currently available in PHIS); and (4) were directly admitted to an ICU from home or were transferred from another institution. We excluded patients who received an influenza antiviral medication other than oseltamivir (ie, zanamivir, amantadine, or rimantadine; N = 989) or who had been hospitalized in the preceding 14 days (N = 295). Only the first influenza encounter was included for all patients who had multiple influenza-related admissions during the same season. Patients hospitalized at PHIS hospitals with significant data issues (eg, inaccurate day of service) identified by PHIS during regularly scheduled data quality checks were also excluded (N = 236).

Exposures

The primary exposure of interest was treatment with oseltamivir within the first 24-hour calendar day of hospital admission, as defined by a charge for oseltamivir on the calendar day of hospital admission (hospital day 0) or the first 24-hour calendar day of hospitalization (hospital day 1). Untreated patients were defined by the absence of a charge for oseltamivir at any time during the hospitalization or a charge for oseltamivir on hospital day 2 or greater.

Outcomes

The primary outcome was length of hospital stay (measured in days). Secondary outcomes included (1) length of ICU stay, (2) in-hospital mortality, and (3) readmission within 7 days from hospital discharge.

Clinical and Demographic Data

We collected information about patient age, gender, race, influenza season, and census region. The presence of a comorbid condition was assessed using an ICD-9-CM-based diagnostic classification system for pediatric complex chronic conditions.[27] The categories include neuromuscular, cardiovascular, respiratory, renal, gastrointestinal, hematologic or immunologic, malignancy, and other congenital defect conditions. Information regarding influenza vaccination status is not included in this database and could not be assessed. We also collected information on supportive therapies on hospital day 0 (defined as at least 1 hospital charge in the billing record). Supportive therapies included mechanical ventilation, high-frequency ventilation, other assisted ventilation (including continuous positive airway pressure, Bi-Pap, and any noninvasive ventilation support), use of vasoactive medications, nitric oxide, and supplemental oxygen.

Statistical Methods

Propensity-matched Analysis

To account for potential confounding by observed baseline covariates, we matched treated patients with untreated one using a propensity score we derived to estimate the likelihood of receiving oseltamivir (ie, clinically eligible to receive oseltamivir) based on the presence or absence of baseline covariates. This approach can balance covariates between the treated and untreated groups better than other strategies such as conventional multivariable methods.[28–30] Propensity scores were calculated from a multivariable logistic regression that modeled receipt of the drug by the following covariates: age, sex, race, season, supportive therapies at admission, and the presence of individual complex chronic conditions. Two additional variables were included in the propensity score model to adjust for the severity of illness. First, we included the PHIS expected mortality variable (risk of mortality), a risk adjustment measure based on the risk of mortality derived from Thomson Reuter's national database and the 3M All Patient Refined Diagnosis Related Group classification system. Second, we derived a variable to indirectly assess the intensity of care delivered during the first 24-hour hospital calendar day (hospital day 1). Hospital bills from hospital day 1 were reviewed, and all unique charges (ie, medications, radiology, laboratory tests) were counted for each patient, with the assumption that the severity of illness would be directly associated with the number of unique charges.

We matched oseltamivir-treated patients with untreated one within each hospital. We chose to match by hospital to account for the between hospital variability in the utilization rate of oseltamivir.[31] Each treated patient was matched with 1 untreated control patient using nearest-neighbor matching with a caliper set at one-quarter of the standard deviation of the logit of the propensity scores.[32] To make within hospital contrasts between the matched sets, only hospitals with a $\geq$10% oseltamivir utilization rate were included in the analysis. To determine whether the propensity score was successful in balancing the covariates between cases and matched controls, we performed pairwise comparisons. We used accelerated failure time models to compare ICU length of stay and total hospital length of stay between treated and untreated patients.[33] Death was included in the model as a covariate to distinguish between 2 groups with a priori different length of stays. To account for unobserved heterogeneity among patients, we added a frailty term with gamma distribution to the model. For binomial outcomes, we used logistic link models to determine the difference in outcomes while adjusting for covariates. Covariates that were determined to be well balanced were not included in the models. To further explore the effect of death on our primary outcome, length of stay, we excluded all patients who died of the dataset, rematched treated and untreated patients, and repeated the analysis. All statistical analyses were performed using the statistical software SAS 9.1 (SAS Institute, Inc., Cary, NC) and Stata 10.0 (Stata Corp., College Station, TX), and $P < 0.05$ was considered statistically significant.

Human Subjects Protections

The protocol for the conduct of this study was reviewed and approved by The Children's Hospital of Philadelphia Committee for the Protection of Human Subjects with a waiver of informed consent.

RESULTS

Patient Characteristics

We identified a total of 17,072 children with influenza during the study period (Fig. 1). After exclusions (because of treatment with influenza antiviral medications other than oseltamivir, hospitalization in the preceding 14 days, and admission to a non-ICU hospital ward), a total of 1257 children were included in our study cohort. The median age of patients was 1.7 years

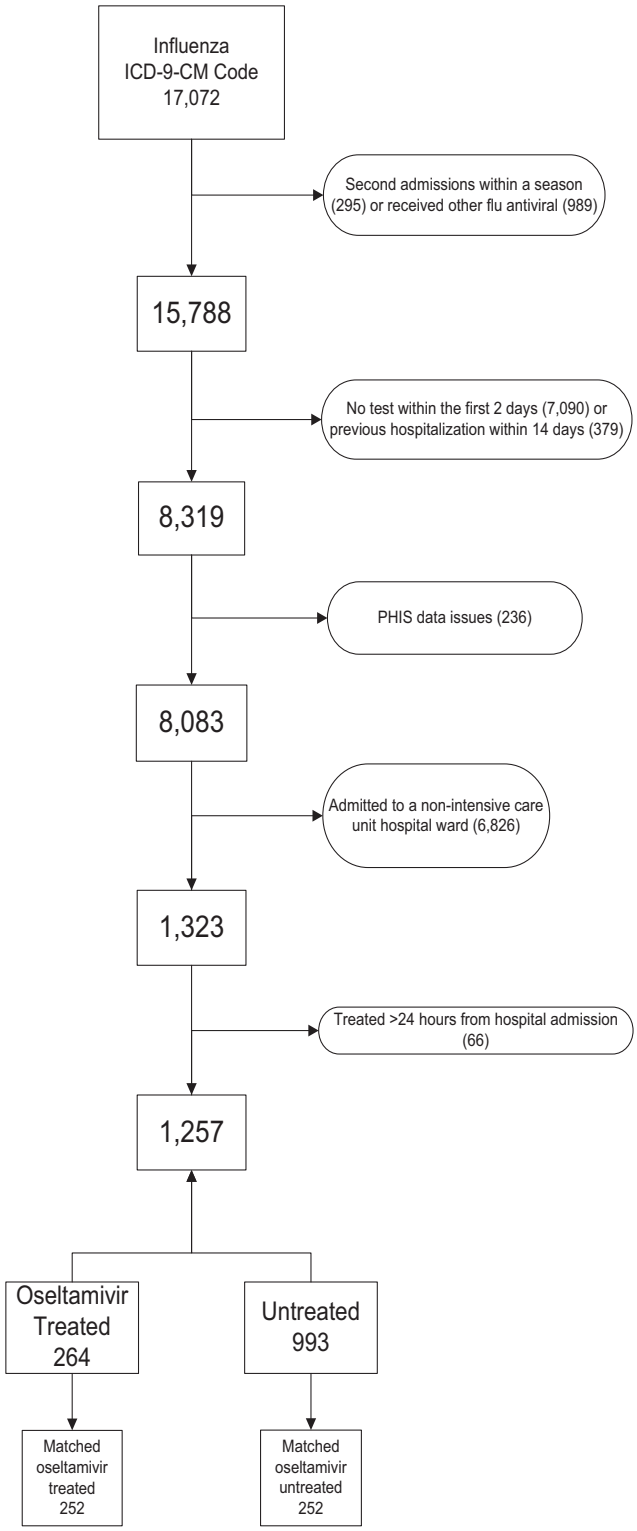

FIGURE 1. Assembly of the study cohort.

(interquartile range, 0.45–5.6), and 39% had one or more complex chronic conditions.

Overall, 264 of 1257 patients (21%) were treated with 1 or more doses of oseltamivir within the first 24-hour calendar day of hospital admission. The age distribution of treated and untreated patients differed; younger patients (<2 years) were less likely to have received oseltamivir ($P < 0.001$) (Table 1). Oseltamivir utilization also varied by year; 2% of treated patients received the drug in 2001–2002, whereas 36% of treated patients received the drug in 2006–2007 ($P < 0.001$). There were fewer treated patients located in the Western region of the United States (9%) as compared with the Northeast (22%), South (35%), and North Central U.S. (34%) ($P < 0.001$; data not shown).

Patients treated with oseltamivir were more likely to have a neuromuscular condition (25% vs. 16%, $P < 0.001$), metabolic condition (5% vs. 2%, $P = 0.038$), or other congenital or genetic defect (9% vs. 6%, $P = 0.049$) than untreated patients and were more likely to require mechanical ventilation (11% vs. 5%, $P < 0.001$) or vasoactive medications (23% vs. 13%, $P < 0.001$) on hospital day 0. As compared with untreated patients, patients treated with oseltamivir had a greater predicted risk of mortality (0.43% vs. 0.02%) and a greater total number of unique charges (28.5 vs. 20) on hospital day 1 ($P < 0.001$).

Patient Outcomes in Propensity Score-matched Analysis

In the propensity score matched analysis, 95% of treated patients were matched with appropriate untreated patients. From 1 hospital, 1 patient was excluded because of a low oseltamivir utilization rate (<10%), whereas 11 treated patients from 6 hospitals failed to match with appropriate control patients and were excluded. After successfully matching 95% of the treated patients, there was 1 statistically significant difference between matched treated and untreated patients (Table 1) in contrast to the unmatched analysis described earlier. Patient age was significantly different between the treated and untreated patients and was included in the final model. In addition, the variable neuromuscular comorbid condition was considered for inclusion in the model. In the propensity matched analysis, we found that treatment with oseltamivir was associated with a shorter length of hospital stay (Table 2). Length of stay (in days) for treated patients was 18% shorter than propensity score matched untreated patients while controlling for death (time ratio: 0.82, 95% confidence interval: 0.69–0.97, $P = 0.02$). The addition of death to the model had no impact on the time ratio or P value. We excluded patients who died of this analysis; our finding persisted with an 18% shorter length of stay for treated patients (time ratio: 0.82, 95% confidence interval: 0.71–0.95, $P = 0.007$). There was no difference between treated and untreated patients in length of ICU stay ($P = 0.51$), the in-hospital mortality rate ($P = 0.67$), or readmission rate within 7 days from discharge ($P = 0.42$).

DISCUSSION

We found that critically ill children treated with oseltamivir had a shorter duration of total hospital stay when compared with matched patients who did not receive oseltamivir treatment within 24 hours of hospital admission. The duration of hospital stay was approximately 18% shorter for critically ill children treated with oseltamivir within 24 hours of hospitalization as compared with those whom were either untreated or received oseltamivir >24 hours after hospital admission. This is the first study that demonstrated a benefit of oseltamivir in critically ill children hospitalized with influenza.

Prior studies have demonstrated improved outcomes for nonhospitalized patients who received antiviral therapy. Oseltamivir treatment has been associated with reduced duration of illness, rates of influenza-related complications, and subsequent hospitalization among previously healthy, influenza-infected children[8] and

TABLE 1. Demographic and Clinical Characteristics of Patients With Influenza Infection Admitted to Intensive Care Units*

	Unmatched Analysis		Propensity-matched Analysis	
	No Oseltamivir Treatment (N = 993)	Oseltamivir Treatment (N = 264)	No Oseltamivir Treatment (N = 252)	Oseltamivir Treatment (N = 252)
Age, y (median, IQR)†	1.33 (0.35–4.47)	4.59 (1.87–11.90)	1.68 (0.48–7.13)	4.45 (1.87–10.94)
Gender				
Males	559 (56%)	150 (57%)	139 (55%)	144 (57%)
Females	434 (44%)	114 (43%)	113 (45%)	108 (43%)
Race				
White	401 (40%)	99 (38%)	90 (36%)	96 (38%)
Non–white	530 (53%)	157 (59%)	153 (61%)	148 (59%)
Unknown	62 (6%)	8 (3%)	9 (3%)	8 (3%)
Season				
2001–2002	52 (5%)	4 (2%)	5 (2%)	4 (2%)
2002–2003	60 (6%)	7 (3%)	8 (3%)	7 (3%)
2003–2004	283 (29%)	42 (16%)	33 (13%)	41 (16%)
2004–2005	185 (19%)	34 (13%)	42 (17%)	32 (13%)
2005–2006	212 (21%)	82 (31%)	84 (33%)	77 (31%)
2006–2007	201 (20%)	95 (36%)	80 (32%)	91 (36%)
Comorbid conditions‡				
Neuromuscular	160 (16%)	67 (25%)	46 (18%)	64 (25%)
Cardiovascular	121 (12%)	40 (15%)	45 (18%)	37 (15%)
Respiratory§	51 (5%)	16 (6%)	21 (8%)	15 (6%)
Renal	8 (1%)	2 (1%)	2 (<1%)	2 (<1%)
Gastrointestinal	9 (1%)	2 (1%)	1 (<1%)	2 (<1%)
Hematology and immunodeficiency	18 (2%)	4 (2%)	4 (2%)	4 (2%)
Metabolic	22 (2%)	12 (5%)	11 (4%)	11 (4%)
Other congenital or genetic defect	57 (6%)	24 (9%)	23 (9%)	24 (10%)
Malignancy	18 (2%)	7 (3%)	8 (3%)	7 (3%)
Clinical support at admission				
Oxygen support	275 (28%)	73 (28%)	76 (30%)	69 (27%)
Mechanical ventilation	54 (5%)	30 (11%)	24 (10%)	29 (12%)
High–frequency ventilation	25 (3%)	13 (5%)	16 (6%)	13 (5%)
Other assisted ventilation	301 (30%)	86 (33%)	82 (33%)	82 (33%)
Use of vasoactive medications	125 (13%)	62 (23%)	48 (19%)	56 (22%)
Nitric oxide	7 (1%)	5 (2%)	3 (1%)	5 (2%)
Severity of illness measures				
Total no. unique charges on hospital day 1 (median, IQR)	20 (11–31)	28.5 (19.0–46.5)	27 (17–42)	28 (19–44)
Risk of mortality (median, IQR)	0.0002 (0–0.031)	0.0043 (0–0.067)	0.0041 (0–0.057)	0.0043 (0–0.058)

*All variables are expressed as frequency and percent unless otherwise specified.
†Age in years remained statistically significant after the propensity score match ($P < 0.001$).
‡As defined by CCC's.[17]
§Excludes asthma.
IQR indicates interquartile range; ICU, intensive care unit.

TABLE 2. Results of the Propensity Score-matched Analysis Comparing Differences in Length of Hospital Stay (in Days) Between Oseltamivir-treated and -untreated Patients With Influenza Infection

Outcome	Oseltamivir Treatment Within 24 h	Median (IQR)	Time Ratio (95% CI)	*P*
Total length of hospital stay	Yes	6 (3–11)	0.82 (0.69–0.97)	0.02
	vs.			
	No	9 (4–17)		
Total length of intensive care unit stay	Yes	4 (2–8)	1.07 (0.88–1.29)	0.51
	vs.			
	No	4 (2–10)		

Both statistical models were adjusted for age and propensity score.
IQR indicates interquartile range; CI, confidence interval.

adults.[17,34] Using health insurance claims data, Piedra et al[35] recently demonstrated that oseltamivir therapy improved the outcomes of influenza-infected children with chronic medical conditions. Chronically ill outpatients who received oseltamivir within 1 day of influenza diagnosis had lower rates of respiratory complications, otitis media, and all-cause hospitalizations as compared with untreated children. Recently published data suggest that initiation of antiviral therapy within 48 hours of symptom onset, as compared with either delayed or no antiviral therapy, was associated with better clinical outcomes among adults hospitalized 2009 H1N1 influenza.[18]

Although children treated with oseltamivir had a shorter total length of hospital stay, we did not find a difference in the secondary outcomes examined such as duration of ICU stay, mortality, or readmission within 7 days. We did not power the study to detect a difference in mortality, as the mortality rate among children hospitalized with influenza has historically been relatively low.[5] Because the median duration of ICU stay was 4 days for both treated and untreated patients and ICU stay was measured in days, we suspect that we were also underpowered to detect modest differences in this outcome. Because oseltamivir prevents viral replication, we hypothesize that the drug may have minimal effect in altering the course of acute inflammatory reaction associated with severe influenza. Oseltamivir may hasten the time for resolution of other symptoms, and thereby shortening the duration of non-ICU hospital stay. It is unclear why there was no difference between treated and untreated patients in the readmission rate.

Our study had several limitations. First, the use of administrative data might have led to misclassification of the principal

exposure of interest (oseltamivir treatment) and important covariates (such as severity of illness measures); however, we believe this bias would be nondifferential. We recognize that we might not have fully adjusted for all differences in severity of illness. However, any residual confounding by indication would have biased our findings toward oseltamivir having less effect on the outcome of interest; thus, we believe that the difference in length of stay would be even greater in favor of the oseltamivir-treated group. Selection bias (eg, the use of ICD-9 codes for identifying influenza-infected patients) might have led to under-ascertainment of influenza-infected patients; however, this bias would have also led to a reduction in the difference in the duration of hospital stay among treated and untreated patients. Finally, we were unable to determine whether the time interval between symptom onset and initiation of oseltamivir influenced the effect of antiviral therapy on patient outcomes. Prior reports have suggested that antiviral medications may have negligible effect if begun greater than 48 hours after symptom onset.[36] However, it is unlikely that all patients had symptoms for only 24 hours, and therefore the effect size is likely to have been greater had treatment been initiated prior to hospital admission.

In summary, oseltamivir treatment reduced the duration of hospital stay among critically ill children with influenza infection when begun within 24 hours of hospital admission. This finding can assist clinical decision making to improve patient outcomes. In the event of critical shortages, our results suggest that severely ill children should be given priority to receive antiviral treatment. Future studies are needed to assess the effectiveness of antiviral medications upon specific populations of critically ill patients and less seriously ill hospitalized children.

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