PEDIATRICS INTERNATIONAL Official Journal of the Japan Pediatric Society

Pediatrics International (2015) **57**, 393–400 doi: 10.1111/ped.12526

Original Article

Impact of time to treatment of oseltamivir on influenza hospitalization cost among Korean children

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Abstract ***Background***: Although oseltamivir is a common influenza treatment, there is a lack of data on the economic benefits of timely oseltamivir treatment.

Methods: From February 2004 through June 2007, 116 hospitalized children ≤15 years of age with laboratory-confirmed influenza who received oseltamivir were identified via retrospective medical chart review. Demographic, clinical, and cost data were abstracted and multivariate linear regression was used to assess the association between oseltamivir time to treatment and treatment-related costs among hospitalized children with laboratory-confirmed influenza.

Results: Overall, 28% ($n = 33$) of patients were treated with oseltamivir ≥day 3 of admission. Rapid influenza diagnostic test was used in a significantly lower proportion of patients treated with oseltamivir ≥day 3 of admission compared with those who received oseltamivir earlier. On multivariate linear regression, initiation of oseltamivir ≥day 3 of admission was associated with a 60.84% increase (95%CI: 32.59–95.11) in treatment-related hospital costs, compared with initiation on admission.

Conclusion: Delayed initiation of oseltamivir was found to be associated with increased treatment-related hospital costs among children hospitalized with laboratory-confirmed influenza.

Key words children, hospital cost, influenza, rapid influenza diagnostic test, oseltamivir.

Influenza viruses cause acute respiratory illness in all ages, and both pandemic and seasonal influenza can lead to excessive respiratory disease-associated hospitalization, mortality, and economic impact.[1–3] Children, especially if they are younger or have underlying medical conditions, often experience a greater influenza burden.[4–6] Pediatric influenza results in substantial morbidity, direct and indirect costs, and excess health-care utilization.[7–9] Furthermore, children can cause secondary illness in the family by transmitting the influenza virus to other household members.[9,10]

Hospitalization with respiratory illness is especially common among younger Korean children during influenza (or other respiratory virus) season given that South Korea's mandatory national insurance system covers a large portion of medical charges incurred during hospitalization. In the USA, a recent study reported the mean cost of influenza-associated hospitalization, as estimated at $US 13 159, and the annual national direct medical cost due to seasonal influenza at $US 10.4bn.[1,8]

Neuraminidase inhibitors are reported to be therapeutically effective and to reduce influenza-associated illness duration, severity, complication risk, influenza-related mortality, and even antibiotic use.[11–15] Oseltamivir is a commonly used antiviral agent, and notably, in the January 2011 issue of the U.S. Centers for Disease Control and Prevention's *Morbidity and Mortality Weekly Report*, oseltamivir was recommended for use in patients hospitalized with suspected or confirmed influenza.[16] It is FDA-approved as influenza treatment for persons aged ≥2 weeks and is recommended to be given within 2 days of symptom onset. Given the year-to-year variation in influenza activity and growing global concern for viral resistance to oseltamivir, the recommendation and treatment guidelines are updated regularly based on influenza surveillance data.[16–18]

The burden of influenza, however, remains high, and in Korea, up to 20% of viral respiratory disease hospitalizations were reported to be due to influenza virus infection despite the national influenza vaccination coverage rate being close to 40%.[19,20] Although oseltamivir is a common influenza treatment, there is no standard treatment regimen for seasonal influenza control in Korea. Although it is well-documented in previous literature that

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Received 25 April 2013; revised 9 August 2014; accepted 2 October 2014.

the prompt initiation of oseltamivir is associated with better clinical outcome,[21–24] there are no studies estimating the economic impact of earlier initiation of oseltamivir in influenza treatment. To help fill the knowledge gaps, we investigated whether there is an economic benefit by evaluating the association of time to oseltamivir treatment with treatment-related hospital cost among hospitalized children with laboratory-confirmed influenza in Korea.

Methods

Nasal aspirate specimens were systematically collected from patients presenting with acute respiratory symptoms at Ansan, Anam, and Guro Hospitals, affiliated with Korea University (KU). These hospitals serve the communities of Ansan city, a neighboring city of Seoul, and the districts of Guro and Anam in Seoul. Nasal aspirate specimens were routinely tested to identify adenovirus, parainfluenza, respiratory syncytial virus (RSV), and influenza A/B on viral culture, using three standard cell lines (HEp-2, MDCK and LLC-MK2). Given that results from viral culture test may take up to 5 days, a subset of patients with clinically suspected influenza was tested for influenza using rapid influenza diagnostic text (RIDT; Directigen EZ Flu A + B Test Kit; Becton-Dickinson, Franklin Lakes, NJ, USA).

At three KU hospitals, 2781 patients who presented with respiratory symptoms were tested for influenza virus, and 1232 hospitalized patients and outpatients were found to have laboratory-confirmed influenza virus. The analysis was limited to hospitalized patients because it was based on treatment prescription information. Among hospitalized children ≤15 years of age with laboratory-confirmed influenza who initially presented with respiratory symptoms at one of the KU hospitals from February 2004 through June 2007, we excluded children with: (i) concurrent respiratory infection with one or more viruses (RSV, parainfluenza virus, or adenovirus); (ii) nosocomial influenza episodes with virus detection ≥7 days after admission; or (iii) recurrent infection returning to hospital within 2 weeks of discharge with the same virus type. Because the analysis was of the association between time to treatment with oseltamivir and hospital costs, the final study group consisted of 116 inpatients treated with oseltamivir during their hospital stay (Fig. 1).

We conducted a retrospective review of medical records for these hospitalized patients with laboratory-confirmed influenza who were treated with oseltamivir. We abstracted the following demographic and clinical data from patient medical records in the KU hospital electronic database: influenza virus type, dates of admission and discharge, diagnosis, signs and symptoms, body temperature, duration of fever, medical history, pre-existing medical conditions, vital signs, hematologic and radiologic test results, and treatment information. Direct hospital medical costs were obtained from the hospital billing/registry office. Study approval was obtained from the Institutional Review Boards of the KU Ansan Hospital and the International Vaccine Institute.

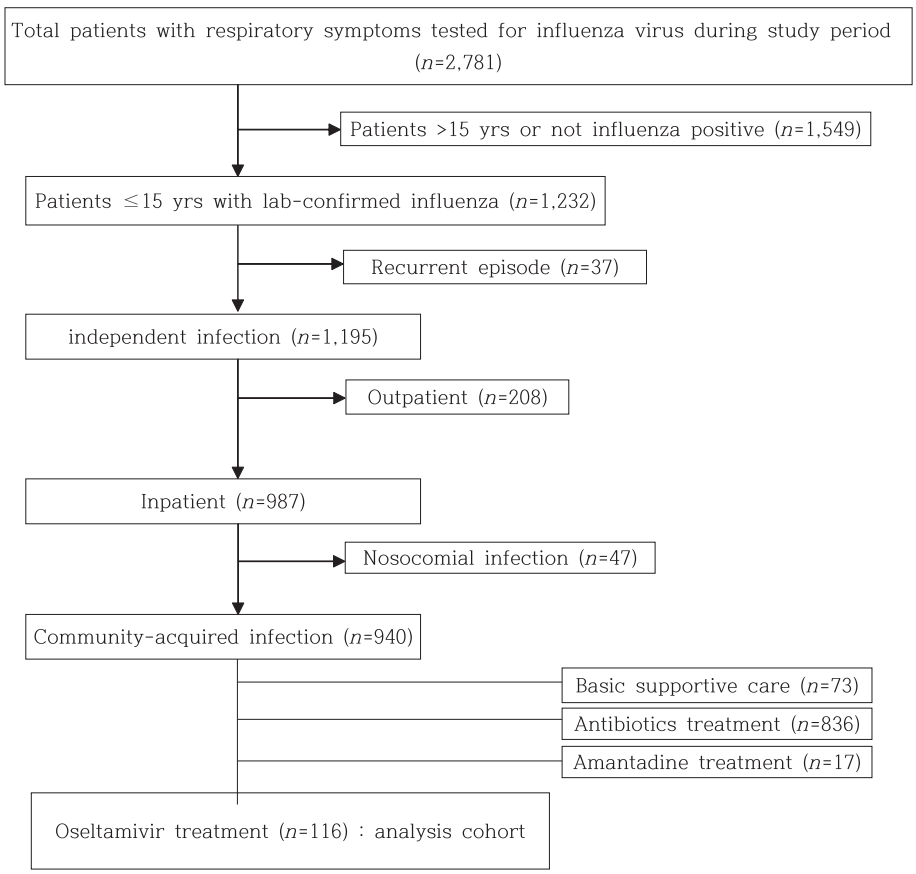

Fig. 1 Patient selection.

Variable for analysis

Time to treatment (in days) was calculated from date of admission to the first oseltamivir (Tamiflu®; Roche Pharmaceuticals, Basel, Switzerland) treatment among hospitalized patients presenting with respiratory symptoms. Time to treatment was measured from admission rather than from onset of fever to avoid possible unreliable reporting of the clinical evolution of the disease by caregivers. Initially derived to reflect the recommended time window for oseltamivir treatment in the hospital setting, the variable constructed allowed reporting on the economic benefit of initiating oseltamivir treatment within 2 days of hospitalization, and was more evidence based and definitive than measuring 2 days from onset of symptoms. Also, there was variation in how the attending physicians measured fever duration: one would count by days while another would count by hours, considering 24 h as 1 day.

Patients were categorized into those given oseltamivir on day 1 of admission, day 2 of admission, and ≥day 3 following admission (outside the recommended 2 day window after onset of symptoms). The patients who receive oseltamivir later in their admission are likely to have the duration of hospitalization extended, at least, by the number of days of the delay. To avoid increase in total hospital cost among these patients due to prolonged hospital stay, we selected treatment-related cost as the outcome of analysis, rather than the total hospital costs which also include test cost, admission-related fees, and treatment costs. Treatment-related cost, consisting of charges for injection, medication, treatment materials, physiotherapy, surgery, anesthesia, and blood infusion, as applicable, would reflect the economic burden due to delayed onset of oseltamivir regardless of changes in the costs due to extension of the duration of hospitalization.

Medical charges were converted from Korean won currency (KRW) to US dollars with the 2004–2007 average exchange rate. Because treatment-related charges had a non-normal distribution (mean, $US115; median, $US105; range, $US24–360), on univariate analysis, we used log-transformed treatment-related charges as the outcome for the linear regression model. The estimates on the natural log scale were back-transformed.

Diagnosis at admission was categorized by primary clinical manifestation. Primary admission diagnoses of pneumonia, bronchitis, croup, and asthma were grouped as lower respiratory tract illness (LRTI), while acute pharyngitis, sinusitis, and laryngitis were grouped as upper respiratory illness. Urinary tract infection, sepsis, and neurologic (e.g. convulsions, febrile seizure, Guillain–Barré syndrome), gastrointestinal (e.g. diarrhea, acute gastroenteritis, stomatitis), and cardiovascular-related conditions were grouped as "non-respiratory" diseases. Axillary temperature ≥37.5°C was defined as fever. The median of the highest temperature recorded during hospitalization, 38.8°C, was used as the cut-off to create a dichotomous variable indicating elevated body temperature. Complications occurring during hospital stay were secondary bacterial pneumonia, other secondary bacterial infection, encephalitis, neurologic problems, exacerbation of pre-existing medical conditions, and so on.

Statistical analysis

A sample of 116 patients hospitalized with community-acquired, laboratory-confirmed influenza treated with oseltamivir was used to examine the relationship between oseltamivir time to treatment from admission and treatment-related cost in the hospital setting. For continuous variables, ANOVA was performed and categorical comparisons were made using chi-squared and Fisher's exact tests with significance at $P < 0.05$. To identify the pattern of geometric mean hospital charges in relation to day of onset of oseltamivir treatment, we used trend tests to identify any significant patterns in the β. Bivariate analysis was used to identify potential confounders and covariates of interest for the regression model, using SAS® version 9.0 (SAS Institute, Cary, NC, USA), and Stat/Transfer 8® (Circle Systems, Seattle, WA, USA).

To adjust for variability in clinical indicators of influenza that may have prompted earlier initiation of oseltamivir, clinical parameters were analyzed as markers of initial illness condition and were included in multivariate analysis. The following parameters were included: temperature measured at admission, selected signs and symptoms, admission diagnosis, previous influenza infection in the past year, influenza circulating season, and presence of underlying disease. Additional clinical characteristics such as laboratory and diagnostic test results, concurrent antibiotic therapy, fever duration, and complications during hospitalization were included as potential confounders to minimize the influence they may have on treatment-related decisions and, hence, on clinical course. Linear regression was performed with the outcome as the log-transformed, treatment-associated hospital costs and the main predictor as oseltamivir time to treatment calculated from admission. The β, percent change in treatment-related costs, and 95%CI, are reported.

Results

Patient characteristics

Among the 116 community-acquired influenza hospitalizations identified, 53% ($n = 62$) and 18% ($n = 21$) were treated with oseltamivir on days 1 and 2 of admission, respectively. Although all study participants underwent testing to confirm influenza on the same day that they were admitted to hospital with respiratory signs and symptoms, 28% ($n = 33$) were given oseltamivir >2 days after admission, that is, outside the recommended 2 day window after the onset of symptoms. Overall, 74% of the 116 oseltamivir-treated patients were ≤5 years of age ($n = 86$; Table 1).

Clinical characteristics

Among the 116 patients, the mean length of hospital stay significantly increased as the oseltamivir time to treatment increased ($P < 0.001$; Table 2). Additionally, the mean peak body temperature also increased as the oseltamivir time to treatment increased ($P = 0.032$). Patients whose oseltamivir therapy began ≥3 days of admission were less likely to undergo influenza antigen detection tests (33% vs 64% and 76% for day 1 and day 2, respectively) and were more likely to receive combined therapy with antibiotics (91% vs 65% and 81% for day 1 and day 2, respectively), compared to those who received oseltamivir from day 1 or day 2 of

Table 1 Patient characteristics vs oseltamivir time to treatment

Oseltamivir time to treatment	*n*	Age (years) Mean ± SD	Female *n* (%)	Influenza virus type, *n* (%)			Clinical impression on admission, *n* (%)		
				A	B	Unidentified	LRTI	URI	Non-respiratory
Day 1 of hospitalization	62	3.81 ± 3.64	30 (48.4)	39 (62.9)	12 (19.4)	11 (17.7)	17 (27.4)	31 (50.0)	14 (22.6)
Day 2	21	2.40 ± 2.07	4 (19.0)	9 (42.9)	4 (19.0)	8 (38.1)	11 (52.4)	5 (23.8)	5 (23.8)
≥Day 3	33	4.05 ± 2.69	19 (57.6)	17 (51.5)	13 (39.4)	3 (9.1)	16 (48.5)	13 (39.4)	4 (12.1)
Total	116	3.59 ± 3.18	53 (45.7)	65 (56.0)	29 (25.0)	22 (18.9)	44 (37.9)	49 (42.2)	23 (19.8)

LRTI, lower respiratory tract illness; URI, upper respiratory illness.

admission. Distribution of episodes by season was significantly different across the oseltamivir time-to-treatment groups, in that patients who received oseltamivir within 2 days of admission were more likely to have influenza viral infection in winter (71% for both groups given oseltamivir on days 1 and 2 of admission), while 55% of the patients given oseltamivir ≥day 3 of admission had influenza hospitalization in spring.

On average, the mean duration from onset of fever to admission was 2.73 days for patients given oseltamivir on day 1 of admission. For those patients treated with oseltamivir on day 2 of admission, the mean duration between fever onset and admission was 1.85 days. For the patients treated with oseltamivir ≥day 3 following admission, the mean interval between fever onset and admission was 2.33 days. There was no statistically significant difference in the period from onset of fever to admission between those treated with oseltamivir within 2 days and those treated ≥day 3 following admission ($P = 0.378$).

Treatment-related hospital costs

The mean total hospital costs and treatment-related costs of the 116 laboratory-confirmed patients treated with oseltamivir during hospitalization increased as the oseltamivir time to treatment

Table 2 Hospitalization and symptoms vs oseltamivir time to treatment

Characteristics	Oseltamivir time to treatment (days)			Total ($n = 116$)	*P*
	Day 1 of hospitalization ($n = 62$)	Day 2 ($n = 21$)	≥Day 3 ($n = 33$)		
Length of hospital stay (days), mean ± SD	3.32 ± 1.48	4.43 ± 2.31	5.70 ± 2.66	4.17 ± 2.26	**<0.001**
Fever duration (days), mean ± SD	4.40 ± 2.50	3.50 ± 1.88	5.03 ± 2.51	4.42 ± 2.45	0.084
Temperature on admission (°C), mean ± SD	37.71 ± 0.85	37.80 ± 0.74	37.78 ± 1.08	37.77 ± 0.92	0.949
Peak temperature during hospitalization (°C), mean ± SD	38.61 ± 0.80	38.99 ± 0.99	39.22 ± 0.74	38.91 ± 0.85	**0.032**
Symptoms, *n* (%)					
Cough	54 (88.5)	16 (76.2)	26 (78.8)	96 (83.5)	0.169
Expectoration	31 (50.8)	11 (52.4)	15 (45.5)	57 (49.6)	0.615
Rhinorrhea	38 (62.3)	10 (47.6)	14 (42.4)	62 (53.9)	**0.045**
Chills	6 (9.8)	2 (9.5)	4 (12.1)	12 (10.4)	0.736
Headache	4 (6.6)	0	1 (3.0)	5 (4.4)	0.285
Diarrhea	1 (1.6)	4 (19.1)	3 (9.1)	8 (7.0)	0.134
Sore throat	2 (3.3)	0	5 (15.2)	7 (6.1)	**0.032**
Signs, *n* (%)					
Pharyngitis	49 (80.3)	16 (76.2)	30 (90.9)	95 (82.6)	0.333
Rales or wheezing	11 (18.0)	9 (42.9)	12 (36.4)	32 (27.8)	**0.030**
Injected tympanic membrane	6 (9.8)	2 (9.5)	5 (15.2)	13 (11.3)	0.457
Rhonchi	3 (4.9)	0	3 (9.1)	6 (5.2)	0.479
Season, *n* (%)					**0.024**
Spring (March–May)	18 (29.5)	6 (28.6)	18 (54.6)	42 (36.5)	
Winter (December–February)	43 (70.5)	15 (71.4)	15 (45.5)	73 (63.5)	
No previous influenza infection in the same year (vs unknown), *n* (%)	25 (41.0)	9 (42.9)	19 (57.6)	53 (46.1)	0.182
Pre-existing conditions, *n* (%)	3 (4.9)	1 (4.8)	4 (12.1)	8 (7.0)	0.209
Complications during hospitalization, *n* (%)	5 (8.2)	1 (4.8)	3 (9.1)	9 (7.8)	0.961
Infiltrate on chest radiograph, *n* (%)	8 (12.9)	6 (28.6)	7 (21.2)	21 (18.1)	0.225
RIDT, *n* (%)	39 (63.9)	16 (76.2)	11 (33.3)	66 (57.4)	**0.022**
Antibiotics during hospitalization, *n* (%)	40 (64.5)	17 (81.0)	30 (90.9)	87 (75.0)	**0.005**
White blood cell count, *n* (%)					0.152
Normal	43 (70.5)	18 (85.7)	27 (81.8)	88 (76.5)	
Abnormal	18 (29.5)	3 (14.3)	6 (18.2)	27 (23.5)	

RIDT, rapid influenza diagnostic test. The bold data showed that the value is under 0.05.

Table 3 Time to treatment vs hospital costs

Hospital day of oseltamivir treatment	No. patients	Hospital costs ($US), mean ± SD			
		Treatment-related***†	Hospital admission***†	Testing(n.s.)†	Total***†
Day 1	62	112.76 ± 1.61	246.63 ± 1.66	302.91 ± 1.59	758.87 ± 1.44
Day 2	21	139.26 ± 1.69	331.52 ± 1.91	276.58 ± 1.35	859.07 ± 1.40
Day 3	11	179.28 ± 1.79	376.11 ± 1.65	319.95 ± 1.51	969.85 ± 1.52
Day 4	9	210.71 ± 1.24	447.90 ± 1.50	301.61 ± 1.28	1060.31 ± 1.26
Day 5	6	212.43 ± 1.32	415.62 ± 1.42	386.61 ± 1.79	1161.49 ± 1.42
Day 6	4	311.99 ± 1.26	632.81 ± 1.24	321.93 ± 1.31	1374.99 ± 1.12
Day 7	3	441.42 ± 1.57	655.10 (1.18)	326.19 ± 2.20	1761.96 ± 1.06

***$P < 0.001$. †Compared by time to oseltamivir treatment.

lengthened (both $P < 0.001$; Table 3). Linear regression analysis was done with treatment-related hospital costs as the outcome and time to oseltamivir treatment as the primary predictor. On unadjusted linear regression, a 98.95% (95%CI: 61.46–145.15) increase in treatment-related hospital costs was associated with initiation of oseltamivir ≥day 3 of admission compared to initiation on the day of admission ($\beta = 0.687$, $P < 0.001$). On multivariate linear regression, adjusting for potential confounders, a 60.84% (95%CI: 32.59–95.11) increase in treatment-related hospital costs was associated with oseltamivir initiated ≥day 3 of admission ($\beta = 0.475$, $P < 0.001$), compared to initiation on day 1 (Table 4). No significant difference was found between those with oseltamivir initiation on days 1 and 2 of hospitalization.

Antibiotic therapy with oseltamivir was associated with a 50.97% (95%CI: 24.74–82.72) increase in treatment-associated hospital costs compared to oseltamivir monotherapy. Conversely, oseltamivir-treated patients with non-respiratory diagnosis at admission were associated with a 43.15% (95%CI: −56.84 to −25.13) decrease in treatment-related hospital costs compared to those diagnosed with LRTI.

Discussion

Using a sample of children with laboratory-confirmed influenza and presenting with respiratory symptoms on admission, we identified a significantly higher treatment-related hospital cost, increased by 60%, associated with oseltamivir treatment on day 3 of admission or thereafter, compared to oseltamivir given on the day of admission. There was no significant difference in treatment-related hospital costs between those treated with oseltamivir on days 1 and 2 of admission. Although half of the present sample of laboratory-confirmed, community-acquired influenza patients was treated with oseltamivir on the day of admission, one-third was given oseltamivir on day 3 of admission or later, outside the recommended 2 day window after the onset of symptoms. Patients whose oseltamivir therapy was initiated after day 3 of admission were half as likely to undergo RIDT and

Table 4 Multivariate predictors of increase in treatment-related costs

Characteristics	β† (% change in treatment charges)	95%CI (% change)	*P*
Oseltamivir time to treatment (reference group: day 1 of hospitalization)			
Day 2	0.209 (23.28)	−0.013 to 0.431 (−1.26–53.92)	0.064
≥day 3	0.475 (60.84)	0.282–0.668 (32.59–95.11)	**<0.0001**
Age	0.039 (3.93)	0.012–0.066 (1.16–3.77)	**0.006**
Presence of pre-existing medical conditions (reference group: absence)	0.717 (104.82)	0.393–1.040 (48.21–183.05)	**<0.0001**
Antibiotics used (reference group none used)	0.412 (50.97)	0.221–0.603 (24.74–82.72)	**<0.0001**
No previous influenza infection in the same year (reference group: unknown)	0.262 (29.93)	0.069–0.455 (7.11–57.61)	**0.001**
Diagnosis (reference group: LRTI)			
URI	−0.092 (−8.75)	−0.286 to 0.102 (−24.84 to 10.78)	0.351
Non-respiratory	−0.565 (−43.15)	−0.840 to −0.289 (−56.84 to −25.13)	**<0.0001**
Clinical attributes at admission			
Presence of infiltrate on chest radiographs (reference group: absent)	−0.259 (−22.84)	−0.489 to −0.029 (−38.71 to −2.86)	**0.028**
Initial body temperature ≤38.9°C (reference group: >38.9°C)	0.256 (29.24)	−0.031 to 0.544 (0.97 to −3.10)	0.080
Normal WBC count (reference group: abnormal)	−0.142 (−13.27)	−0.323 to 0.038 (0.72 to −27.57)	0.120
Fever duration (reference group: 1–2 days)			
3–5 days	0.034 (3.47)	−0.142 to 0.210 (0.868 to −13.22)	0.088
6–7 days	0.184 (20.2)	−0.010 to 0.379 (0.99 to −1.03)	0.063
Influenza antigen detection test (reference group: test not performed)	−0.053 (−5.15)	−0.262 to 0.156 (0.77 to −23.05)	0.616
Presence of complications (reference group: absence)	−0.034 (−3.31)	−0.309 to 0.242 (0.73 to −26.62)	0.139

†Also adjusted for sex, influenza season, presence of signs/symptoms (chills, rales/wheezing, cough, expectoration, rhinorrhea, diarrhea, sore throat, pharyngitis, rhonchi, and headache). LRTI, lower respiratory tract illness; URI, upper respiratory illness; WBC, white blood cells. The bold data showed that the value is under 0.05.

were more likely to be treated with antibiotics in addition to oseltamivir during hospitalization.

Use of day of admission, that is, the first presentation to hospital, for calculating time to oseltamivir treatment, rather than use of onset of symptoms, could be considered a major weakness in the analysis. There was no statistically significant difference in the duration from onset of fever to admission between those treated with oseltamivir within 2 days and those treated ≥day 3 following admission ($P = 0.378$). The increase in treatment-related cost seen in this study could be initially suspected to be due to the longer hospital stay in the patients treated with oseltamivir ≥day 3 following admission. The lack of statistically significant difference in the duration of symptomatic illness prior to admission across the categories of time-to-treatment variable, however, supports the study aim to assess the economic impact of time to (oseltamivir) treatment related to hospitalization, not onset of illness, among Korean children on the economic benefit of initiating oseltamivir within 2 days of admission, even after 2 days of symptom onset as commonly recommended.

Hiba *et al*. reported that there were fewer complications after admission in severe patients hospitalized with 2009 influenza A (H1N1) who had initiation of oseltamivir within 48 h of symptom onset, adjusting for disease severity on admission.[25] Although that retrospective study, also based on hospitalized patients, identified a therapeutic benefit of oseltamivir initiated within the recommended 2 days of symptom onset, the recommendation issued by the US Centers for Disease Control and Prevention (CDC) for the use of antiviral medications in the treatment of influenza for the 2011–2012 season states that antivirals should be considered for children with suspected influenza even past 2 days after symptom onset.[16] Observational studies noted benefits of oseltamivir initiated after 48 h of symptom onset with regard to clinical outcome among patients hospitalized with influenza. Initiation of oseltamivir treatment within 2 days of onset of symptoms is often realistically challenging. With these mixed recommendations, in the present study based on hospital admission in children hospitalized with influenza, we derived a variable to reflect the recommended time window for oseltamivir treatment in order to report on the economic benefit of initiating oseltamivir treatment within 2 days of hospitalization, rather than within 2 days of onset of symptoms. The objective of this analysis was to assess the impact of time to treatment of oseltamivir on hospital costs among the hospitalized children treated with oseltamivir upon first presentation at a health-care facility, rather than upon onset of symptoms reported with varying consistency by caregivers, reflecting clinical promptness in true practical settings.

To assess the difference in treatment cost between the first day and second day for the onset of oseltamivir treatment, the main predictor variable, oseltamivir time to treatment, separated out those who were given oseltamivir on day 1 from those given treatment on day 2 of admission. There was a >50% increase on average in treatment-related cost associated with oseltamivir treatment initiation at ≥3 days of admission, and that as long as oseltamivir is initiated within 2 days of admission (i.e. first presentation at hospital with respiratory symptoms in the present study), there will be no significant changes in treatment cost.

Although we could not identify any study on the economic benefits of earlier initiation of oseltamivir, other studies have explored different time points within the recommended 2 day timeframe of oseltamivir initiation with regard to therapeutic benefits. Kawai *et al*. found that oseltamivir initiation at 24 h was associated with better outcomes in terms of resolution of fever than initiation at 48 or 72 h.[26] In addition, Gillissen and Höffken showed that illness duration was shortened when oseltamivir was started within 12 h after onset of symptoms.[27] Therapeutic benefits of prompt initiation of oseltamivir were found in both children and adults. Heinonen *et al*. reported a significant reduction in the resolution of illness if oseltamivir was initiated within 24 h among children in an outpatient setting,[28] and Shijubo *et al*. noted a trend of slower fever resolution as initiation of therapy was delayed (measured at 0, 1–12, 13–24, and 72 h) in a nursing home setting.[29] Given that better clinical outcome is often associated with lower costs, the present findings seem to be congruent.

We observed that delayed prescription of oseltamivir was associated with a longer mean duration of hospitalization. Although it is impossible to retrospectively determine all the reasons for oseltamivir prescription delay, the pattern of longer hospitalization among patients with respiratory symptoms on admission who were given oseltamivir later during hospitalization was consistent with the data in a multicenter study reported by Aoki *et al*., showing that earlier oseltamivir treatment reduces illness duration.[21] Considering the previous studies reporting therapeutic benefits of oseltamivir initiation within 2 days of symptom onset compared to later in the clinical course,[22–24] and the overall cost-effectiveness of oseltamivir in influenza treatment,[30–32] it is clear that oseltamivir is a first-line treatment choice for influenza patients and its therapeutic benefit is maximized when started as promptly as possible.

In the present study, in which one-third of oseltamivir-treated patients started treatment ≥day 3 of admission, concurrent antibiotic prescription was closely related to initiation of oseltamivir. A significantly higher rate of antibiotic usage was found among patients in whom oseltamivir started on ≥day 3 of admission compared with those with earlier initiation. This may be explained by the fact that these patients may have had clinical indications of bacterial pneumonia or secondary infection, so the decision regarding antibiotic prescription preceded oseltamivir treatment. In the present study, all 33 patients who were treated with oseltamivir ≥day 3 of admission had received antibiotics before oseltamivir prescription, while all 40 patients who received oseltamivir on admission were prescribed with antibiotics at the same time ($n = 33$) or after oseltamivir initiation ($n = 7$). In clinical practice, children hospitalized with mild conditions may be less likely to be treated with antibiotics, while those with more severe findings such as rales/wheezing or chest infiltrate, indicators of bacterial pneumonia, are often treated with antibiotics. The physician decision to prioritize antibiotics due to suspicion of bacterial infection may have led to delayed initiation of oseltamivir.

The timeliness of oseltamivir treatment may also be influenced by the use of RIDT, given that RIDT is known to be cost-effective[33] and can be used to reduce unnecessary antibiotic use in patients with viral infection.[34,35] Although RIDT was not significantly associated with increased treatment-associated cost, the use of RIDT is likely to reflect treatment decisions because they are ordered at clinician discretion. In the present study, twice as many people who had oseltamivir earlier, had RIDT compared to those who had oseltamivir ≥day 3 of admission ($P = 0.022$). Among the patients with LRTI who did not undergo RIDT, 54% of the patients (13/24) were given oseltamivir ≥day 3 of admission while 15% of patients with LRTI who did have RIDT received oseltamivir ≥day 3 of admission. This shows that patients who had RIDT were less likely to have a clinical impression of LRTI. Most of the present cases occurred during the influenza season. Influenza as a differential diagnosis in hospitalized children during the influenza season should be accompanied by prompt use of RIDT for timelier initiation of oseltamivir.

Considering the complexity of treatment decisions related to initiation of oseltamivir treatment, variation in illness condition at admission and during the clinical course was an important confounder. We accordingly used a multivariate model to adjust for the variability that could have influenced timing of oseltamivir initiation during hospitalization and by extension, the relationship of oseltamivir time to treatment and treatment cost. The data abstraction, however, was limited to the information that was available on the medical charts due to the retrospective study design and the small sample size. Other possibly influential confounders may be detection of co-infection due to other viral pathogens during the influenza-related hospitalization and influenza vaccination history, especially given the substantial rate of national influenza vaccination coverage, which was reported to be close to 40%.[19,20] These additional variables were not available for abstraction from medical charts during the data collection phase. Similarly, some other confounding variables that were unable to be measured in this analysis may possibly explain the relationship but the observed relationships and the 95%CI make it unlikely that the present findings are a result of residual confounding not controlled for in the models.

Despite these limitations, three tertiary-level hospitals under the umbrella of KU had a highly uniform standard of patient management and treatment regimen, so the analysis was not affected by variability across clinicians and facilities. Moreover, all study subjects had culture confirmation of influenza virus, in addition to the use of RIDT at the clinician's discretion. In Korea, the predominant circulating strains were A/H3N2 in 2004–2005, A/H1N1 in 2005–2006, and A/H3N2 in 2006–2007 and there were no reported oseltamivir-resistant strains of influenza during the study period of 2004–2007. This approach to diagnosis ensured uniformity in influenza diagnosis. Based on the medical chart data over three complete influenza seasons, the present study provides a realistic illustration of treatment cost according to oseltamivir time to treatment among Korean children hospitalized with laboratory-confirmed influenza.

McNicholl and McNicholl reported that oseltamivir is especially more effective if initiated within 30 h of symptom onset and that this criterion is difficult to meet.[36] This is evident in the present study, in which almost one in three oseltamivir-treated patients was outside the recommended window of oseltamivir treatment. The present data highlight the benefit among hospitalized influenza patients from oseltamivir treatment even if initiated during the hospital stay, possibly outside the recommended 2 day period after symptom onset. Louie *et al*. also reported improved survival with prompt initiation of oseltamivir among children critically ill with influenza, encouraging oseltamivir treatment for critically ill children at an increased risk of death.[37] The present results demonstrate favorable hospitalization-related outcomes and clear benefits from earlier initiation of oseltamivir, especially with regard to the economics. Although the present study is limited by its observational nature, and we cannot definitively conclude that earlier initiation of oseltamivir reduces treatment-related cost among patients hospitalized with influenza, the current study presents a case for cost savings that is consistent with previously published known reductions in morbidity, antibiotic use, and hospitalization time.[21,26–29] Therefore, complemented with routine use of quick and sensitive influenza diagnostics for expeditious clinical decision making, prompt prescription of oseltamivir, even if started outside the recommended 2 day window from onset of symptoms, should be encouraged in clinical treatment practice in children hospitalized with seasonal influenza.

Acknowledgments

We thank the doctors and laboratory staff of Korea University's Ansan Hospitals for their participation in the retrospective pediatric influenza study in Korea. We thank collaborators at Myung Moon Pediatrics for their support, Ms Deborah Hong, as well as the statisticians and administrative staff at the International Vaccine Institute for their helpful comments during the analysis and preparation of this manuscript. This study was supported by funding from the Korean Center for Disease Control and Prevention (grant: 2007-S2-E-003), as well as from the governments of Kuwait, Sweden, and the Republic of Korea. The authors do not have any relevant financial relationships or potential conflicts of interest to disclose regarding the material discussed in this manuscript.

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